Sleep disorders in immune-mediated synaptic encephalopathies

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Doctoral thesis dissertation presented by Amaia Muñoz Lopetegi to apply for the degree of doctor at the University of Barcelona

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ABBREVIATIONS

AIE: autoimmune encephalitis

AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

Caspr2: contactin-associated protein-like 2

CNS: central nervous system

CSF: cerebrospinal fluid

D2R: dopamine receptor type 2

DNER: delta/notch-like epidermal growth factor-related receptor

DPPX: dipeptidyl-peptidase-like protein 6

EEG: electroencephalography

EMG: electromyography

FBDS: facio-brachial dystonic seizures

GABAbR: gamma-aminobutiric acid type B receptor

GAD65: glutamic acid decarboxylase 65

GlyR: glycine receptor

LGI1: leucine-rich glioma-inactivated protein 1

mGluR: metabotropic glutamate receptor

NMDAR: N-methyl-d-aspartate receptor

NMOSD: neuromyelitis optica spectrum disorder

NREM: non-rapid-eye-movement sleep

RBD: REM sleep behavior disorder

REM: rapid-eye-movement sleep

SWS: slow-wave sleep

VGCC: voltage-gated calcium channel

VGKC: voltage-gated potassium channel

V-PSG: video-polysomnography

LIST OF ARTICLES IN THE THESIS

Thesis in compendium of publications format.

The thesis consists of 4 objectives and 2 articles:

Article 1:

Helena Ariño, **Amaia Muñoz-Lopetegi**, Eugenia Martínez-Hernández, Thaís Armangué, Mireia Rosa-Justicia, Domingo Escudero, Nuria Matos, Francesc Graus, Gisela Sugrenyes, Josefina Castro-Fornieles, Albert Compte, Josep Dalmau, Joan Santamaria. **Sleep disorders in anti-NMDAR encephalitis**, Neurology, 2020, 19, 1010:1022

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Article 2:

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Impact factor: 46.5

Quartile: Q1

ABSTRACT

RESUM DE LA TESI EN CATALÀ

Títol: Trastorns de son en les encefalitis sinàptiques immunomediades

Introducció: Les encefalitis autoimmunitàries (EAI) són malalties inflamatòries del sistema nerviós central, causades per anticossos específics contra proteïnes sinàptiques o de la superfície neural. Se n'han descrit més de vint en les últimes dues dècades, amb anticossos i síndromes clíniques específiques. Produeixen una gran varietat de símptomes, incloent alteracions cognitives, psiquiàtriques, trastorns del moviment o crisis epilèptiques. Els trastorns de son en les EAI han rebut poca atenció, probablement eclipsats per símptomes més destacats, però l'escassa literatura disponible suggereix que són freqüents, sovint greus i en alguns casos persistents. L'encefalitis anti-NMDAR i l'encefalitis anti-LG1 són les dues EAI més freqüents i els trastorns de son, tot i descrits en ambdues, no han estat sistemàticament estudiats ni caracteritzats i se'n desconeixen la freqüència, la intensitat i l'evolució.

Hipòtesis: 1) Els trastorns de son en l'encefalitis anti-NMDAR s'han descrit poc freqüentment en la literatura, però una avaluació sistemàtica revelaria una prevalença major que la descrita. 2) Els trastorns de son persisteixen en la fase post-aguda de l'encefalitis anti-NMDAR. 3) L'estudi vídeo-polisomnogràfic sistemàtic en la fase post-aguda de l'encefalitis anti-NMDAR pot revelar trastorns de son prèviament no descrits. 4) Els trastorns de son en la fase aguda de l'encefalitis anti-LGI1 no han estat ben caracteritzats i una avaluació sistemàtica podria revelar que són més prevalents i diversos del que s'ha descrit prèviament. 5) Els trastorns de son persisteixen en la fase post-aguda de l'encefalitis antiLGI1. 6) L'estudi sistemàtic i longitudinal amb vídeo-polisomnografia en la fase post-aguda de l'encefalitis anti-LGI1 podria desemmascarar trastorns de son prèviament no descrits en aquesta fase de la malaltia. 7) Les crisis epilèptiques poden persistir en la fase post-aguda de l'encefalitis anti-LGI1 i l'estudi sistemàtic amb electroencefalograma nocturn i diürn podria ajudar a identificar crisis subclíniques o a determinar el risc de desenvolupar epilèpsia crònica.

Objectius: 1) Determinar la freqüència i caracteritzar el tipus de trastorns de son que ocorren en la fase aguda i post-aguda de l'encefalitis anti-NMDAR. 2) Caracteritzar vídeo-polisomnogràficament el son en la fase post-aguda de l'encefalitis anti-NMDAR.

3) Descriure el perfil de símptomes neurològics i els trastorns de son en la fase aguda i post-aguda de l'encefalitis anti-LGI1. 4) Caracteritzar vídeo-polisomnogràficament i electroencefalogràficament el son en la fase post-aguda de l'encefalitis anti-LGI1.

Mètodes: aquesta tesi la conformen dos estudis prospectius, longitudinals i observacionals en què es van incloure pacients amb encefalitis anti-NMDAR (objectius 1 i 2) i anti-LGI1 (objectius 3 i 4) en la fase post-aguda de la malaltia, reclutats de diferents centres d'Espanya, i controls sans. Es va contactar els pacients, diagnosticats i tractats als centres locals, després de l'alta hospitalària. Cada estudi va consistir en 3 visites (inclusió, 6 mesos i 12 mesos) de 2 dies i una nit d'hospitalització, en què es van realitzar avaluacions neurològiques, cognitives, psiquiàtriques i de son, un estudi vídeo-polisomnogràfic (V-PSG) amb electroencefalograma (EEG) nocturn, un EEG diürn i una ressonància magnètica cerebral. La fase aguda es va explorar retrospectivament mitjançant la revisió d'històries clíniques i una anamnesi estructurada amb el pacient i un acompanyant, investigant tots els símptomes de les malalties. En cada visita es van recollir prospectivament els símptomes residuals. L'estudi de son va incloure una anamnesi específica, diversos qüestionaris i una avaluació detallada del vídeo-polisomnograma i l'electroencefalograma.

Resultats: **El primer estudi (objectius 1 i 2)** va incloure 18 pacients amb encefalitis anti-NMDAR i 21 controls. En la fase aguda, tots els pacients van patir alteracions del son, el 89% insomni. En la fase post-aguda, el 78% van desenvolupar hipersòmnia, que persistia en el moment de la inclusió a l'estudi en el 44%. El canvi en el patró de son es va associar amb un canvi concomitant del patró d'alteracions conductuals, amb apatia, hiperfàgia i hipersexualitat freqüents. Per V-PSG l'estructura i l'eficiència de son van ser normals, però el 39% van tenir despertars confusos durant el son NREM. **El segon estudi (objectius 3 i 4)** va incloure 24 pacients amb encefalitis anti-LGI1 i 20 controls. Durant la fase aguda, el 71% van tenir símptomes de son, a més de símptomes cognitius (100%), psiquiàtrics (88%), crisis epilèptiques focals (88%) i crisis facio-braquio-distòniques (FBD) (54%). A la visita d'inclusió, el 58% van reportar insomni i 4 (17%) i 5 (21%) pacients, respectivament, crisis focals i FBD. Els estudis de V-PSG i EEG nocturn van revelar crisis focals o FBD que havien passat desapercebudes en 5 i 4 pacients més, respectivament. El 50% tenien un trastorn de conducta del son REM

(reportat només pel 8%). A més, en comparació als controls, el 79% dels pacients tenien una baixa qualitat de son. Als canals d'electromiografia de la V-PSG, es va detectar en el 63% dels pacients mioclonus fragmentari excessiu i en el 38% descàrregues mioquímiques, signes suggestius d'hiperexcitabilitat nerviosa perifèrica, prèviament no descrits. Arran de totes aquestes troballes, el 63% va rebre immunoteràpia addicional. Tot i millorar, a l'any de seguiment el 65% dels pacients seguien amb dèficits cognitius. La presència de REM sense atonia i d'anticossos en sèrum a la primera visita, i no haver rebut rituximab precoçment van ser els factors associats a la persistència dels dèficits cognitius.

Conclusions: Els trastorns de son són freqüents, però substancialment diferents, en l'encefalitis anti-NMDAR i anti-LGI1. En l'encefalitis anti-NMDAR, els símptomes de son són greus i intensos en la fase aguda i clínicament més discrets en la fase post-aguda. Hi ha un patró temporal característic (amb insomni en la fase aguda i hipersòmnia en la fase post-aguda), que coincideix amb els canvis en el patró conductual. A més, hi ha despertars confusos en la fase post-aguda, prèviament no descrits. En l'encefalitis anti-LGI1, el tipus i nombre de troballes, moltes inesperades i indetectables en absència d'estudis dirigits (especialment les crisis epilèptiques i facio-braquio-distòniques; però també la persistència de REM sense atonia), tenen implicacions clíniques rellevants i representen un canvi de paradigma en aquesta malaltia. Globalment, aquests resultats reflecteixen que l'estudi del son pot contribuir al diagnòstic, pronòstic, monitorització i comprensió de les diferents EAI.

RESUMEN DE LA TESIS EN CASTELLANO

Título: Trastornos del sueño en las encefalitis sinápticas inmunomediadas.

Introducción: Las encefalitis autoinmunes (EAI) son enfermedades inflamatorias del sistema nervioso central, causades por anticuerpos específicos contra proteínas sinápticas o de la superficie neural. Se han descrito más de veinte en las últimas dos décadas, con anticuerpos y síndromes clínicos específicos. Producen una gran variedad de síntomas, incluyendo alteraciones cognitives, psiquiátricas, trastornos del movimiento o crisis epilépticas. Los trastornos del sueño en las EAI han recibido poca atención, probablemente eclipsados por síntomas más llamativos, pero la escasa literatura disponible sugiere que son frecuentes, a menudo graves y en algunos casos persistentes. La encefalitis anti-NMDAR y la encefalitis anti-LG1 son las dos EAI más frecuentes y los trastornos del sueño, aunque se han descrito en ambas, no han sido sistemáticamente estudiados ni caracterizados y se desconoce su frecuencia, intensidad y evolución.

Hipótesis: 1) Los trastornos de sueño en la encefalitis anti-NMDAR se han descrito poco frecuentemente en la literatura, pero una evaluación sistemática revelaría una prevalencia mayor que la descrita. 2) Los trastornos de sueño persisten en la fase post-aguda de la encefalitis anti-NMDAR. 3) El estudio vídeo-polisomnográfico sistemático en la fase post-aguda de la encefalitis anti-NMDAR puede revelar trastornos de sueño previamente no descritos. 4) Los trastornos de sueño en la fase aguda de la encefalitis anti-LGI1 no han sido bien caracterizados y una evaluación sistemática podría revelar que son más frecuentes y diversos de lo que se ha descrito previamente. 5) Los trastornos de sueño persisten en la fase post-aguda de la encefalitis anti-LGI1. 6) El estudio sistemático y longitudinal con vídeo-polisomnografía en la fase post-aguda de la encefalitis anti-LGI1 podría desenmascarar trastornos de sueño previamente no descritos en esta fase de la enfermedad. 7) Las crisis epilépticas pueden persistir en la fase post-aguda de la encefalitis anti-LGI1 y el estudio sistemático con electroencefalograma nocturno y diurno podría ayudar a identificar crisis subclínicas o a determinar el riesgo de desarrollar epilepsia crónica.

Objetivos: 1) Determinar la frecuencia i caracterizar el tipo de trastornos de sueño que ocurren en la fase aguda i post-aguda de la encefalitis anti-NMDAR. 2) Caracterizar vídeo-polisomnográficamente el sueño en la fase post-aguda de la encefalitis anti-NMDAR. 3) Describir el perfil de síntomas neurológicos i los trastornos de sueño en la fase aguda i post-aguda de la encefalitis anti-LGI1. 4) Caracterizar vídeo-polisomnográficamente y electroencefalográficamente el sueño en la fase post-aguda de la encefalitis anti-LGI1.

Métodos: esta tesis la conforman dos estudios prospectivos, longitudinales y observacionales en los que se incluyeron pacientes con encefalitis anti-NMDAR (objetivos 1 y 2) y anti-LGI1 (objetivos 3 y 4) en la fase post-aguda de la enfermedad, reclutados en diferentes centros de España, y controles sanos. Se contactó con los pacientes, diagnosticados y tratados en sus centros locales, después del alta hospitalaria. Cada estudio consistió en 3 visitas (inclusión, 6 meses y 12 meses) de 2 días y una noche de hospitalización, en que se realizaron evaluaciones neurológicas, cognitivas, psiquiátricas y de sueño, un estudio vídeo-polisomnográfico (V-PSG) con electroencefalograma (EEG) nocturno, un EEG diurno y una resonancia magnética cerebral. La fase aguda se exploró retrospectivamente mediante la revisión de historias clínicas y una anamnesis estructurada con el paciente y un acompañante, investigando todos los síntomas relacionados con las enfermedades. En cada visita se recogieron prospectivamente los síntomas residuales. El estudio de sueño incluyó una anamnesis específica, varios cuestionarios y una evaluación detallada del V-PSG y el EEG.

Resultados: **El primer estudio (objetivos 1 i 2)** incluyó 18 pacientes con encefalitis anti-NMDAR y 21 controles. En la fase aguda, todos los pacientes sufrieron alteraciones de sueño, el 89% insomnio. En la fase post-aguda, el 78% desarrollaron hipersomnia, que persistía en el momento de la inclusión al estudio en el 44%. El cambio en el patrón de sueño ocurrió de manera concomitante con un cambio en el patrón de alteraciones conductuales, con apatía, hiperfagia e hipersexualidad frecuentes. Por V-PSG la estructura y eficiencia del sueño fueron normales, pero el 39% presentaron despertares confusos durante el sueño NREM. **El segundo estudio (objetivos 3 i 4)** incluyó 24 pacientes con encefalitis anti-LGI1 y 20 controles. Durante la fase aguda, el 71% tuvieron síntomas de sueño, además de síntomas cognitivos (100%), psiquiátricos

(88%), crisis epilépticas focales (88%) y crisis facio-braquio-distónicas (FBD) (54%). En la visita de inclusión, el 58% reportaron insomnio y 4 (17%) y 5 (21%) pacientes, respectivamente, crisis focales i FBD. Los estudios de V-PSG y EEG nocturno revelaron crisis focales o FBD que habían pasado desapercibidas en 5 y 4 pacientes más, respectivamente. El 50% presentaron un trastorno de conducta del sueño REM (reportado solo por el 8%). Además, en comparación con los controles, el 79% de los pacientes tenían una baja calidad de sueño. En los canales de EMG del V-PSG, se detectaron en el 63% de los pacientes mioclono fragmentario excesivo y en el 38% descargas mioquímicas, signos sugestivos de hiperexcitabilidad nerviosa periférica, previamente no descritos. A raíz de todos estos hallazgos, el 63% recibieron inmunoterapia adicional. Aunque todos mejoraron, al año de seguimiento el 65% de los pacientes seguía con déficits cognitivos. La presencia de REM sin atonía y de anticuerpos en suero en la primera visita, y no haber recibido rituximab de forma precoz, fueron los factores asociados a la persistencia de déficits cognitivos.

Conclusiones: Los trastornos de sueño son frecuentes, aunque sustancialmente diferentes, en las encefalitis anti-NMDAR i anti-LGI1. En la encefalitis anti-NMDAR, los síntomas de sueño son graves e intensos en la fase aguda y clínicamente más discretos en la fase post-aguda. Hay un patrón temporal característico (con insomnio en la fase aguda e hipersomnia en la fase post-aguda), coincidente con cambios en el patrón conductual. Además, hay despertares confusos en la fase post-aguda, previamente no descritos. En la encefalitis anti-LGI1, el tipo y número de hallazgos, muchos inesperados e indetectables en ausencia de estudios dirigidos (especialmente las crisis epilépticas y Facio-braquio-distónicas, pero también la persistencia de REM sin atonía), tienen implicaciones clínicas relevantes y representan un cambio de paradigma en esta enfermedad. Globalmente, estos resultados reflejan que el estudio del sueño puede contribuir al diagnóstico, pronóstico, monitorización y comprensión de las diferentes EAI.

INTRODUCTION

Antibody-associated diseases of the central nervous system: Historical background

Autoimmune encephalitides (AIE) are immune-mediated inflammatory diseases of the central nervous system (CNS). In the early 2000s, specific antibodies against neural surface antigens were found in the serum and cerebrospinal fluid (CSF) of patients with different types of encephalitis, yielding a new category of diseases of the CNS. This includes an extensive and heterogeneous group of diseases with compelling evidence that the associated brain-specific antibodies have a direct pathogenic effect resulting in patients' symptoms [1]. In the last two decades, more than twenty antibodies have been described, that are associated with specific clinical syndromes and usually respond to prompt immunotherapy [2].

Decades before the breakthrough of neural surface antibodies, immune-mediated mechanisms were known to be involved in the development of certain CNS diseases that manifest as remote effects of cancer. The first evidence was provided in 1965 by Wilkinson and Zeromski, who identified antibodies against neuronal antigens in the serum of four patients with sensory neuronopathy and small-cell lung carcinoma [3]. Technical improvements in the field of neuroimmunology and increased awareness of cancer-related neurological syndromes led during the late 70s up to the 90s to identify numerous neuronal paraneoplastic antibodies in serum and CSF of patients with several neurological syndromes, including paraneoplastic cerebellar degeneration, encephalomyelitis, or limbic encephalitis [4–7]. Most of the antigens were also identified in the tumor tissue, supporting the hypothesis of their paraneoplastic nature, so that the tumor expression of these neuronal proteins (named onconeuronal antigens) would trigger an immune response that cross-reacted with the same proteins expressed in the brain [6,8].

The existence of a pathophysiologic explanation brought about the possibility to treat previously untreatable, disabling or even fatal diseases. However, despite the initial enthusiasm, immunotherapies often were ineffective [9–11]. All these antibodies had in common that they targeted antigens expressed intracellularly in the neurons, thus being unreachable by circulating antibodies, while neuropathological studies showed lymphocytic infiltrates, gliosis, and T-cell mediated neuronal death in the CNS [12–14].

These findings suggested that the antibodies against intracellular neuronal proteins were not pathogenic by themselves, but just disease markers.

There was some evidence, though, that antibodies could be direct effectors of the immune attack and responsible for the symptoms in some diseases of the peripheral nervous system, such as myasthenia gravis (mediated by antibodies against the acetyl choline receptor in the neuromuscular plate) and Issacs´ syndrome or acquired neuromyotonia (associated with antibodies supposedly directed against voltage-gated potassium channels) [15,16]. These diseases responded to immune therapies like plasma exchange and immunosuppression, further supporting the antibody-mediated pathogenesis.

In 1996, Madrid and colleagues reported complete symptom resolution in two patients with Morvan fibrillary chorea after plasma exchange [17]. This is a rare neurological disease described in 1890 by Augustine Marie Morvan, and had been attributed until Madrid's findings to viral infections, mercury intoxication, crysotherapy, and thymoma. Morvan syndrome manifests with central, peripheral, and autonomic nervous system dysfunction, including encephalopathy with hallucinations, neuromyotonia, and severe insomnia [18]. Plasma exchange improved neuromyotonia symptoms as well as mental and dysautonomic dysfunction in Madrid's patients. The authors did not find specific serum or CSF antibodies, but Lee and colleagues did two years later, in another patient with Morvan syndrome and thymoma, who had acetyl choline receptor antibodies and voltage-gated potassium channel (VGKC) antibodies [19]. By the same time, patients with limbic encephalitis also harboring VGKC antibodies were reported, who improved after treatment with intravenous steroids, intravenous immunoglobulins, or plasma exchange [20,21].

The confirmation that antibodies against neuronal surface proteins or ion channels could be responsible for at least part of the limbic encephalitis, led to a dichotomization of this syndrome: limbic encephalitis with intracellular or onconeuronal antibodies were cancer-associated and had a poor prognosis, while limbic encephalitis mediated by VGKC antibodies responded to immunotherapy and had a better prognosis. This classification was proved to be oversimplified in 2005,

when Ances et al. reported a series of 7 patients with suspected immune-mediated encephalitis that showed a variety of immunostaining patterns of the neuropil of rat brain, suggesting that VGKC would not be the only target antigen [22]. In addition, some of these patients had clinical manifestations diffusely involving the CNS, not restricted to the limbic system. However, regardless of the clinical picture and immunostaining pattern, the distinction remained between disorders associated to antibodies against neuronal surface proteins, which responded to immunotherapy, and those with antibodies against intracellular antigens, that did not or showed very poor responses.

The same year, Dalmau and colleagues identified four young women who developed a form of encephalitis with prominent psychiatric symptoms and rapid addition of severe neurological alterations, decreased level of consciousness and central hypoventilation: All four patients had ovarian teratomas and three of them showed substantial improvement after immunotherapy and tumor removal. The four patients harbored antibodies in CSF and serum that showed an identical pattern of immunostaining of the neuropil of the hippocampus and cerebellum of rat brain, and also reacted with the surface of live neurons [23]. Two years later the target antigen was characterized as the N-methyl-d-aspartate receptor and the disorder, the first autoimmune encephalitis in which the target antigen was molecularly characterized, was named anti-NMDAR encephalitis [24]. A series of 100 patients was published by the same group the year after [25], indicating a far from negligible incidence of the disease. A few years later, similar techniques of antigen isolation (immunoprecipitation and mass spectrometry characterization of the antigen) served to establish that the antibodies reported against VGKC in patients with several autoimmune neurological disorders were instead directed against different proteins that closely interact with the VGKC (leucine-rich glioma-inactivated protein 1 -LGI1- and contactin-associated protein-like 2 –Caspr2–) [26,27].

In the two decades following the discovery of anti-NMDAR encephalitis, this new category of disorders of the CNS that occur in association with antibodies against neuronal surface and synaptic proteins (the AIE) experienced an unprecedented expansion, with more than 20 different antibodies and clinical syndromes described by

the time this PhD thesis was written [2]. As opposed to the encephalitis associated with intracellular antibodies, and despite similar clinical presentations in some instances, AIE respond well to immunotherapy and symptoms are totally or partially reversible after appropriate treatment.

Clinical manifestations of autoimmune encephalitis

AIE produce a wide variety of symptoms, often severe and in some instances potentially lethal, especially if they are not recognized and treated timely. The associated syndromes are different for each antibody and, with a few exceptions, the presentation is acute or subacute (within three months) with diverse neurological symptoms progressively appearing throughout days or weeks. The chronic type of presentation (more than 3 months) is less frequent but is often the case of anti-dipeptidyl-peptidase-like protein 6 (DPPX) encephalitis or anti-IgLON5 disease and can occur with anti-LGI1 encephalitis, as in the non-paraneoplastic syndromes associated with antibodies against intracellular proteins (e.g., glutamic acid decarboxylase 65 –GAD65– antibody-associated encephalitis).

Overall, an AIE should be suspected in patients presenting with subacute-onset of cognitive deficits, encephalopathy, and psychiatric or behavioral alterations, together with focal neurological deficits, new-onset epileptic seizures, CSF pleocytosis, or a neuroimaging study showing inflammatory changes. Other frequent symptoms include movement disorders (dyskinesia, chorea, myoclonus, stiffness), brainstem or cerebellar symptoms, autonomic dysfunction, and often sleep dysfunction [1].

Within the spectrum of AIE, some diseases present with distinctive and well-identifiable clinical syndromes, which already allow to suspect one specific autoantibody (like anti-NMDAR encephalitis), whereas others have more unspecific manifestations or present with clinical syndromes that may be similar for various autoantibodies (like limbic encephalitis, which can be driven by LGI1, gamma-aminobutiric acid type B receptor –GABAbR–, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor –AMPAR–, Caspr2, and others). The main clinical and paraclinical characteristics of the most frequent AIE are shown in table [1].

Antibody	Main presenting symptoms	Main syndrome	MRI FLAIR/T2 sequences	Frequency of cancer	Types of cancer
NMDAR	Psychiatric (adults); seizures, dyskinesia (children)	NMDA receptor encephalitis	Normal or transient non-region-specific changes	Overall, 40%; 18-45 y.o. women, 58%	Teratoma*
AMPAR	Memory loss	Limbic encephalitis	Hyperintense signal restricted to medial temporal lobes	65%	Thymoma, SCLC, other
GABAbR	Memory loss, seizures	Limbic encephalitis; early, prominent seizures	Hyperintense signal restricted to medial temporal lobes	50%	SCLC
LGI1	Memory loss, FBDS	Limbic encephalitis	Hyperintense signal restricted to medial temporal lobes	5-10%	Thymoma
CASPR2	Sleep disorder, neuromyotonia	Morvan; limbic encephalitis	Normal or hyperintense signal in medial temporal lobes	Overall, 20%; Morvan 50%	Thymoma
GABAaR	Seizures	Encephalitis, refractory seizures, status epilepticus	Hyperintense signal in cortical and subcortical areas	25%	Thymoma, other
DPPX	Confusion, diarrhea, hyperekplexia	Encephalitis, hyperekplexia	Normal or non-region-specific changes	<10%	Lymphoma
D2R	Lethargy, psychiatric, abnormal movements and gait	Basal ganglia encephalitis	Hyperintense signal in basal ganglia	0%	n/a
mGluR5	Memory loss	Encephalitis	Normal or hyperintense signal in various regions	A few cases described	Hodgkin
Neurexin-3α	Confusion, seizures	Encephalitis	Normal	0%	n/a
IgLON5	Sleep disorder	NREM & REM sleep disorder, brainstem symptoms	Normal	0%	n/a
DNER (Tr)	Gait instability	Cerebellar ataxia	Normal or cerebellar atrophy	>90%	Hodgkin disease
P/Q-type VGCC	Gait instability	Cerebellar ataxia	Normal or cerebellar atrophy	>90%‡	SCLC
mGluR1	Gait instability	Cerebellar ataxia	Normal or cerebellar atrophy	A few cases described	Hodgkin
GlyR	Muscle rigidity, spasms	PERM, stiff-person syndrome	Normal or non-region-specific changes	<5%	Thymoma, lung, Hodgkin
Amphiphysin	Muscle rigidity, spasms	Stiff-person encephalomyelitis	Normal or non-region-specific changes	>90%	Breast, SCLC

Table 1. Main clinical features associated with antibodies to neuronal cell surface proteins and synaptic receptors. NMDAR: N-methyl-D-aspartate receptor; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GABAbR: gamma-aminobutyric acid type B receptor; LGI1: leucine-rich glioma inactivated 1; CASPR2: contactin-associated protein-like 2; GABAaR: gamma-aminobutyric acid type A receptor; DPPX: dipeptidyl-peptidase-like protein-6; D2R: dopamine receptor type 2; mGluR: metabotropic glutamate receptor; DNER: delta/notch-like epidermal growth factor-related receptor; VGCC: voltage-gated calcium channel; GlyR: glycine receptor; REM: rapid-eye-movement sleep; NREM: non-rapid-eye-movement sleep; PERM: progressive encephalomyelitis with rigidity and myoclonus; MRI FLAIR: magnetic resonance imaging fluid-attenuated inversion recovery; y.o: year old; SCLC: small-cell lung cancer; n/a: not applicable. *The association with teratoma is sex- and age-dependent (uncommon in children or young adult males). ‡Refers to paraneoplastic cerebellar degeneration (in Lambert-Eaton myasthenic syndrome, SCLC affects 50–60%). Adapted from [1].

An overview of anti-NMDAR encephalitis

Anti-NMDAR encephalitis is the most frequent AIE, with an approximate annual incidence of 1,5 cases per million of persons [28]. It mainly affects young women (4:1 female to male ratio) and children of any gender, with a median age at presentation of 21 years. The female predominance is age-related and almost circumscribed to the

young adulthood, while being less evident below the age of 12 and above the age of 45 years [29]. About 45% of the young women with anti-NMDAR encephalitis have an underlying ovarian teratoma triggering the production of the NMDAR antibodies. The association with other tumors is very rare and is most often seen in older patients. Approximately 5% of the cases of anti-NMDAR encephalitis occur after herpes simplex encephalitis, which is the only other known trigger of anti-NMDAR encephalitis. Approximately 25% of patients with herpes simplex encephalitis develop autoimmune encephalitis a few weeks after the viral encephalitis; in most of these patients the autoimmune encephalitis is mediated by NMDAR antibodies [30].

Anti-NMDAR encephalitis manifests as a complex neuropsychiatric syndrome with severe behavioral, cognitive, and speech alterations, insomnia (further discussed in a separate section), seizures, abnormal movements, decreased level of consciousness, dysautonomia, and central hypoventilation appearing in a rapid progression over days or weeks. Even though the typical initial presentation varies between children (seizures, abnormal movements, insomnia, and irritability predominate) and adults (with a predominantly psychiatric profile with psychosis and bizarre behaviors), in most cases the multistage progression of symptoms finally evolves into a similar and recognizable syndrome. Especially in teenagers and young adults, due to the prominent psychiatric manifestations that predominate at the initial stages of the encephalitis, it can be easily misdiagnosed as a primary psychiatric disorder presenting with a first episode of psychosis [31].

In more than half of the patients a flu-like prodrome with fever, headache, or respiratory or gastrointestinal symptoms may precede the onset of neurological or psychiatric manifestations[32]. The CSF of patients with anti-NMDAR encephalitis harbours mild to moderate pleocytosis or elevated protein concentration in about 85% of the cases but it may be normal. In about 70% of patients, the magnetic resonance imaging (MRI) is normal or may show non-specific or transient changes, such as T2/FLAIR hyperintensities, particularly involving cortical, subcortical, or cerebellar regions [25].

A definite diagnosis of anti-NMDAR encephalitis can be established in patients who develop any symptom of the disease along with the detection of antibodies against the GluN1 subunit of the NMDAR in CSF [33]. However, early treatment of anti-NMDAR encephalitis is crucial for improving outcomes, and a set of clinical and paraclinical criteria have been proposed (Table 2) so that in patients with "probable anti-NMDAR encephalitis" immunotherapy is started as soon as possible.

Probable anti-NMDAR encephalitis*
Diagnosis can be made when all three of the following criteria have been met: • Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms: • Abnormal (psychiatric) behavior or cognitive dysfunction • Speech dysfunction (pressured speech, verbal reduction, mutism) • Seizures • Movement disorder, dyskinesias, or rigidity/abnormal postures • Decreased level of consciousness • Autonomic dysfunction or central hypoventilation • At least one of the following laboratory study results: • Abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush) • CSF with pleocytosis or oligoclonal bands • Reasonable exclusion of other disorders **Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma**
Definite anti-NMDAR encephalitis*
Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies, after reasonable exclusion of other disorders

Table 2: Diagnostic criteria for anti-NMDAR encephalitis Adapted from [33].

The treatment of anti-NMDAR encephalitis consists of tumour removal, which is critical when there is one, and immunotherapy, starting with first-line therapies (intravenous steroids, intravenous immunoglobulins, or plasma exchange) and escalating to second-line therapies, like rituximab or cyclophosphamide in patients who do not respond adequately or sufficiently to initial therapy [29].

Long-term outcomes for patients with anti-NMDA receptor encephalitis vary. While many patients experience substantial or complete recovery (often after months or years) other patients may have persistent cognitive and functional deficits. The evolution after initial immunotherapy of symptoms other than cognition, are largely unexplored and are part of the aims of this PhD thesis.

An overview of anti-LGI1 encephalitis

Anti-LGI1 encephalitis is the second most common of the AIE, with an estimated annual incidence of about 0.7 cases per million persons [34]. It mainly affects people over 50 years (median age of about 65 years), with a mild male predominance (65% of the cases), and low cancer association (similar to the general population) [35].

Anti-LGI1 encephalitis usually presents as a limbic encephalitis with seizures and cognitive impairment being the core symptoms. Usually, seizures precede the development of cognitive deficits by days or weeks and can be of diverse types. The most characteristic are the faciobrachial dystonic seizures (FBDS), considered to be specific for this AIE. These consist of a sudden, very brief, one-sided, tonic contraction of the upper limb and the ipsilateral face (less frequently the leg), that usually occur frequently during the day (up to dozens of times), and can be unilateral or bilateral asynchronous. These patients also develop focal onset seizures of the temporal lobes, including pilomotor seizures, which are suggestive, but not specific, of anti-LGI1 encephalitis. Episodes of bradycardia have been reported in up to 20% of the patients in a short series [36] and are likely ictal autonomic manifestation of temporal lobe seizures that probably went underrecognized in larger series. Cognitive symptoms are primarily short-term memory deficits, confusion, and disorientation. In neuropsychological testing, episodic verbal memory, as well as visuospatial memory and working memory are impaired in most of the patients and executive functions are often altered too [37].

Other frequent symptoms are behavioral and psychiatric alterations (especially depression, anxiety, irritability, and personality changes), sleep disorders (insomnia, REM sleep behavior disorder), dizzy spells (episodic dizziness lasting a few seconds, not proved to be epileptic in origin), and symptoms of peripheral nerve involvement (leg pain and cramps, feet dysesthesia) [35,38].

Hyponatremia is a common finding (up to 75% of the patients in some series) [39] and should rise the suspicion of an anti-LGI1 encephalitis in patients with new-onset seizures or subacute short-term memory loss. CSF is usually normal or shows mild pleocytosis (20%) [38], while brain MRI shows unilateral or bilateral alterations (mainly

seen in FLAIR-T2 sequences) involving the medial aspect of the temporal lobes in more than 65% of the patients [38,39]. Hyponatremia and MRI changes may be absent in the initial stages of the disease or in patients with isolated seizures and no evident cognitive symptoms [40].

The diagnosis is confirmed by the detection of LGI1 antibodies in serum or CSF; however, as in anti-NMDAR encephalitis, early treatment associates with better clinical outcomes and immunotherapy should be initiated as soon the diagnosis is suspected without need to wait for antibody results. Anti-LGI1 encephalitis usually responds well and promptly to intravenous steroids. Maintenance steroid therapy and slow taper of oral steroids is advisable for some weeks after initial improvement. However, symptom rebound is not rare during steroid tapper or after steroid withdrawal [35] and second-line immunotherapies, especially rituximab, are increasingly used to avoid relapses [41].

Cognitive and functional outcomes in patients with anti-LGI1 encephalitis are variable. About 70% of patients return to their previous functional status after two-year follow-up. Further improvement after a two-year period is rare, with main deficits involving memory, executive function, and verbal fluency [42]. Besides cognition, patients may also develop chronic epilepsy, which is typically related to mesial temporal lobe sclerosis [38,43,44].

Studies of sleep disorders in AIE

Sleep is a complex function resulting from the coordinated activity of many neural centers and networks in the brain and not surprisingly, it is also affected in many of the AIE. In some of them, such as Morvan syndrome, sleep dysfunction is one of the cardinal symptoms of the disease, and was described decades before recognizing the autoimmune etiology of the disease [18,26]. Similarly, anti-IgLON5 disease was discovered because of the unique characteristics of the sleep disorder, which eventually led to identify the antibody and the target antigen [45]. However, overall, sleep disorders have received little attention in most AIE. For instance, in anti-NMDAR encephalitis, the associated syndrome was thoroughly characterized during the first

years following the initial description of the disease: psychiatric and behavioral symptoms could include anxiety, delusion, hallucination, or catatonia; seizure disorders may be focal or generalized, with or without convulsive or non-convulsive status epilepticus, and even a distinctive EEG pattern (of extreme delta brushes) was soon described; movement disorders were further subdivided into dyskinetic, choreic, or dystonic; or the profile of cognitive dysfunction was established as predominantly affecting executive and memory functions [29,46]. However, sleep problems, despite the high frequency and their severity, that were patent since the initial descriptions, have been studied much more superficially [24,47] or are disregarded in most publications.

A review of the literature about sleep disorders in autoimmune encephalitis carried by our group during the process of this PhD thesis [48] revealed that most of the current evidence about sleep disturbances came mainly from case reports rarely focused on sleep. Details were lacking in most cases; however, it was evident that all major types of sleep disorders may occur in AIE, including insomnia, hypersomnia, parasomnia, and sleep breathing disorders. There are a few potential reasons why sleep symptoms are more easily disregarded in AIE. The first one is that they are overshadowed by other more prominent, more severe, and more disrupting neurological and psychiatric symptoms, such as cognitive deficits, severe psychotic or behavioral symptoms, abnormal movements, or seizures. Moreover, sleep symptoms predominantly occur during the night, having less direct impact in daytime activity and more easily going unnoticed in the absence of testimonies. Not only do they occur at night, but they also occur during sleep, so that patients' recall may be absent.

Despite that, sleep symptoms are usually severe and often persist beyond the acute phase of the disease, affecting the process of recovery and quality of life of patients [47,57,58]. A summary of the sleep symptoms and disorders described in different types of AIE up to date are shown in table 3.

		Sleep symptom			V-PSG findings					
	N. of reported cases; % sleep symptoms	Insomnia	Abnormal sleep behavior	EDS/ Hyper-somnia	NREM Sleep: spindles / K complexes and N3 sleep stage	REM sleep	Quasi-purposeful behaviors	PLMS or other NREM movements	OSA#	Stridor
NMDAR	>2000; 21-100% [47,49]	Almost universal at onset; can be severe	Reported in 30% in one series (confusional arousals)	Frequent in the recovery phase	Normal	Normal	Absent	Absent	Absent	Absent
LGI1*	>500; 65%[38]	Frequent. Can be severe.	Reported (RBD)	Reported	Normal	RBD reported (acute phase)	Absent	Unknown	Absent	Absent
CASPR2*	200; 55% In series of MS: 60; 93% [50,51]	Almost universal	Very frequent (quasi-purposeful behaviors, hallucinations)	Reported	Decreased or absent	Decreased; brief periods of REM with and without atonia	Very frequent, eyes open or closed. Dream recall.	Frequent jerks, motor hyper-activation	Absent	Absent
DPPX	50; 45%[52]	Frequent	Reported (RBD, jerks)	Reported	"Ambiguous sleep" reported	RBD reported	Reported	Frequent (PLMS)	Reported	Absent
AMPAR	80; 22%	Reported	Unknown	Reported	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Ma2*	120; 30-45% [53,54]	Absent	Reported (RBD)	Frequent, can be severe (with cataplexy)	Normal	RBD reported (within secondary narcolepsy)	Absent	Absent	Absent	Absent
IgLON5	>100; > 80% [55,56]	Frequent, rarely severe	Very frequent (quasi-purposeful behaviors, jerks)	Frequent, can be severe, improves with CPAP	Absent in some parts of the night, normal in others	RBD frequent	Very frequent, eyes always closed (mainly UNREM). No dream recall	Very frequent (rapid PLMS, jerks)	Very frequent	Frequent

Table 3: Sleep symptoms and V-PSG findings in the different AIE. The global percentage of sleep symptoms in each AIE and frequencies displayed for particular symptoms are estimates based on currently published data. Reported: described in single cases or in small series where the symptom has not been systematically assessed, so the frequency is unknown; Frequent: reported in >50% of the patients; Very frequent: reported in >75%; Almost universal: reported in >90% of the patients; PLMS: periodic limb movements during sleep; OSA: obstructive sleep apnea; RBD: REM sleep behavior disorder. MS: Morvan Syndrome; Ambiguous sleep: sleep stages cannot be differentiated; CPAP: continuous positive airway pressure therapy; UNREM: undifferentiated NREM sleep. For other abbreviations see Table 1 legend. *Symptoms refer to anti-LGI1 associated limbic encephalitis phenotype, anti-Caspr2 associated Morvan syndrome and anti-Ma2 with hypothalamic involvement. #Please, understand absent OSA as frequency not different from general population. Adapted from [48].

Potential mechanisms of sleep dysfunction in the different AIE

As for the other neurologic and psychiatric symptoms occurring in AIE, the frequency, type, and intensity of sleep disorders vary according to the specific disease and are likely a manifestation of the effects of the antibodies or associated immune responses on their specific targets. As indicated, disease mechanisms differ depending on whether the antibodies target cell-surface antigens, in which case they are directly pathogenic, or intracellular antigens, in which case they are biomarkers of immune-

mechanisms probably mediated by cytotoxic T cells [1]. These cell-mediated mechanisms cause neuronal loss at specific brain regions (that vary according to the syndrome) and may allow tracing the pathophysiological mechanisms of sleep dysfunction, whenever present. For instance, hypothalamic lesions may cause secondary narcolepsy in anti-Ma2 encephalitis, whereas brainstem damage can cause central hypoventilation, more prominent during sleep, in anti-Hu encephalitis. However, the exact mechanisms of how cell surface antibodies cause sleep dysfunction in most AIE are currently unknown. The pathogenicity of these antibodies has been shown in experimental studies using cultured neurons and animal models and cause multiple symptoms (memory deficit, anhedonia, depressive-like behavior, psychotic features, seizures or decrease in seizure-threshold), but the effects on sleep function have not been assessed [38,47,49,51–56,59]. Table 4 summarizes the mechanisms by which specific antibodies alter the normal function of the target protein and the potential association with the sleep disorders described in each of the AIE (adapted from [48]).

Antigen/ Epitope	Main sleep symptoms	Normal function of protein	Antibody effects	Additional information related to sleep
NMDAR/ GluN1	Insomnia (acute phase), hypersomnia (recovery), confusional arousals (at least during recovery)	Ionotropic glutamate receptors; essential for excitatory synaptic transmission.	Internalization of NMDAR; decreased NMDAR-mediated currents. Disruption of crosstalk between NMDAR and dopamine receptors [60,61]. In animal models, the antibodies cause decrease of memory, depressive-like behavior, anhedonia, psychotic features, and decrease threshold for seizures [62]. Sleep studies not performed.	In mice, selective NMDAR antagonists produce total inhibition of sleep for 3 hours, with rebound enhancement of SWS [63]. Sleep deprivation in mice causes cumulative phosphorylation of NMDAR, reverted with sleep. Dopamine D1 and D2 are involved in the induction of hyperarousal [64]
AMPAR/ GluA1, GluA2	Insomnia, hypersomnia (information very limited)	Ionotropic glutamate receptors; mediate fast excitatory synaptic transmission.	Internalization of AMPARs; replacement of GluA2-containing receptors for GluA1 homomeric receptors, increasing synaptic excitability. In an animal model the antibodies caused impaired memory. Sleep studies not performed.	GRIA1 (coding for GluA1) knockout mice: increased sleep latency with normal total sleep time, absence of sleep spindles, reduced efficiency of initial SWS after sleep deprivation (non-restorative sleep)
LGI1/ Epitempin, leucine-reach repeat	Insomnia, RBD	Neuronal secreted protein that interacts with presynaptic ADAM23 and Kv1.1 potassium channel, and post-synaptic ADAM22 and AMPA receptor. Regulates synaptic transmission and excitability	Inhibition of LGI1 interaction with ADAM22 and 23. Decrease of levels of Kv1.1 and AMPAR along with neuronal hyperexcitability [65,66]. In an animal models the antibodies caused memory impairment [66]. Sleep studies not performed.	Human mutations of LGI1 cause inherited epilepsy; sleep has not been studied. Antibodies bind hypothalamic neurons [67] and hypothalamic dysfunction may explain hyponatremia (ADH-neurons), episodes of hypothermia and sleep dysregulation. In RBD models of cats with brainstem lesions, further lesion of the amygdala produces intensification of aggressive behaviors during REM sleep [68]
Caspr2/ Discoidin-like and lamininG1 domains	Insomnia, Morvan syndrome	Interacts with Kv1.1/Kv1.2 (VGKC) in myelinated axons facilitating nerve conduction. In the CNS, cell-recognition molecule in inhibitory synapses [51]	In cultures of neurons: alter gephyrin clusters in inhibitory synapses, resulting in central hyperexcitability [69]	KNAC2 (coding for Kv1.2) knockout mice have increased wake time with decreased NREM time [70]. In Drosophila point mutations at VGKC-Shaker genes (Kv1 and others) relate to short-sleeping phenotypes with shorter lifespam [71]
DPPX/ N-terminus of DPPX protein	Insomnia, PLMS, RBD, hypersomnia, OSA	Modulates gating of VGCK type Kv4.2 (attenuates propagation of action potential)	In cultures of neurons: decrease density of surface DPPX and Kv4.2 [72]	KCND2 (coding for Kv4) mutations in Drosophila fly: delayed sleep onset rescued by restoring Kv4 expression (has a role in sleep-wake transition [73])
IgLON5/ Ig-like domain 2	Insomnia, NREM parasomnia, RBD, OSA. stridor, EDS	Unknown	In cultures of neurons: irreversible internalization of IgLON5. Neuronal loss, deposits of tau (unclear mechanism) [45]	Autopsy studies in human show neuronal loss in brainstem medulla likely affecting: 1) Parafacial zone* (center for NREM sleep initiation); 2) Nucleus ambiguous (respiratory centers and vocal cord control); 3) Ventral medulla (generator of REM sleep atonia) [74]
Ma2	Symptomatic narcolepsy	Unknown	Unknown; pathogenic effects related to cytotoxic T-cell mechanisms [53,75]	Human autopsies show loss of hypothalamic (including hypocretin) neurons, in patients with secondary narcolepsy and Ma2 antibodies [76]
AQP4	Symptomatic narcolepsy	Water channel protein; expressed in astrocytes.	In animal models: antibody-mediated complement cytotoxicity in areas of expression of AQP4 [77]	MRI studies show hypothalamic lesions in patients with secondary narcolepsy and AQP4 antibodies [78]
Hu	Central hypoventilation/ Ondine's course	RNA-binding protein	Unknown; pathogenic effects related to cytotoxic T-cell mechanisms [75,79]	Autopsy studies in human show loss of brainstem neurons, likely affecting respiratory centers [80]

Table 4. Protein targets of AIE, antibody effects, and potential involvement of the antigens in sleep disorders. SWS: slow wave sleep; AQP4: aquaporin 4; VGKC: voltage gated potassium channels; RBD: REM sleep behavior disorder; ADLTE: autosomal dominant lateral temporal epilepsy; ADH: antidiuretic hormone; CNS: central nervous system; PNS: peripheral nervous system; PLMS: periodic limb movements during sleep; OSA: obstructive sleep apnea; EDS: excessive daytime sleepiness. For other abbreviations see Table 1 legend. *Parafacial zone is a GABAergic NREM sleep inducing center in rats and an analogous center is probably present in humans; and damaged in anti-IgLON5 disease. However, there is no information about this nucleus in autopsy studies of this disease. Adapted from [48].

Assessment of sleep disorders in AIE

The best way to adequately characterize sleep disorders, especially in AIE, is a combined clinical and neurophysiological evaluation.

Clinically, sleep symptoms in AIE can be similar to those of well-known conventional sleep disorders, but in the context of encephalitis they develop more rapidly and rarely are the main reason for consultation. Even if they are often overshadowed by other neurologic and psychiatric symptoms, and self-report may be absent, patients and families readily describe sleep symptoms when specifically asked. In addition, sleep disorders in AIE can have unusual features, like the presence of combined symptoms (e.g., insomnia and parasomnia) in the same patient [58,81].

There are some important considerations for the clinical evaluation of sleep in AIE: 1) whenever possible, information should be obtained from both the patient and the bedpartner or caregiver using a structured anamnesis; 2) questions should cover the four major problems: insomnia, parasomnia, sleep disordered breathing and hypersomnolence and other daytime symptoms, and 3) a major effort should be made in obtaining comparisons between the current and premorbid sleep characteristics.

Insomnia designates any difficulty to initiate or maintain sleep. The review of literature reveals that AIE-related insomnia has three distinguishing characteristics: it is severe, often described as less than 3 hours of sleep in a day, or even total absence, that may last for several days or weeks (depending on the AIE); it has an acute onset, so that patients are able to point to a particular day or week of onset; and often it associates with other nocturnal symptoms (hallucinations, abnormal behaviors) [82,83].

Parasomnias and movement disorders during sleep are also frequently reported. Sleep is normally a placid, quiet, relaxed state but this may be completely altered in AIE. The differential diagnosis of nocturnal movements and behaviors in these patients is complex, ranging from voluntary movements to parasomnia, hallucinations, or even seizures. Epileptic seizures usually have a stereotyped presentation that facilitates their recognition but may be oligosymptomatic or subclinical in some instances [84].

Hallucinations occurring throughout the 24-hours are typical of Morvan syndrome and may occur in anti-NMDAR encephalitis. The state of the eyes is an important clinical clue here, because movements, vocalizations or gesticulations that are displayed with the eyes open are more likely hallucinations while awake than sleep-related behaviors. Thus, complex, quasi-purposeful (or finalistic), nonviolent movements, seeming to manipulate imaginary objects and imitating daytime activities (eating, sewing), which are characteristic of anti-IgLON5 disease and Morvan syndrome [55,82,85–88], occur always with the eyes closed in the former, but have been described with the eyes open in the latter. In disorders of arousal, like confusional arousals or sleepwalking, the eyes suddenly open at the onset of the event, but the patient was clearly and typically deeply asleep just before the event.

Vigorous, more violent, jerky movements of dream-enactment, with vocalizations (mumbling, talking, shouting), suggest REM sleep behavior disorder (RBD) and can be seen in several different AIE (anti-LGI1, anti-Caspr2, anti-IgLON5, anti-Ma2) [83,89,90]. In RBD there is a loss of the physiological atonia of REM sleep and patients act out their dreams, typically nightmares containing discussions, fights, or chasing among other manifestations. Patients also have their eyes closed during episodes of RBD.

Other movements described in AIE are irregular body or limb jerks, or periodic limb movements occurring during awake or asleep, affecting any sleep-stage or period of the night, which are typical of anti-IgLON5 disease and also occur in anti-DPPX encephalitis [52,83].

On the other hand, respiration during sleep can be seriously altered in AIE. Obstructive sleep apnea and associated stridor, caused by laryngeal obstruction due to vocal cord palsy, are frequent in anti-IgLON5 disease. Stridor is an inspiratory high-pitched sound produced by the narrowing of the glottic space at the larynx and can be confused with snoring, which usually has a pharyngeal origin. Central hypoventilation syndromes can result from brainstem dysfunction, like in anti-Hu encephalitis [80,91].

Finally, hypersomnolence and other related daytime symptoms may also occur. Hypersomnia and excessive daytime sleepiness are two different forms of hypersomnolence that sometimes coexist [92]. Hypersomnia is defined as an excessive

need for sleep (beyond 10 hours per day), while excessive daytime sleepiness is the inability to stay awake and alert in relaxed situations. In extreme cases, patients may fall asleep unintendedly (sleep attack). In case of hypersomnolence, one should actively search for cataplexy. Cataplexy is almost pathognomonic of hypocretin-deficient narcolepsy, which can be primary or secondary, as in anti-Ma2 encephalitis or neuromyelitis optica spectrum disorders (NMOSD) with anti-aquaporin 4 antibodies [53] and is characterized by sudden bilateral loss of muscle tone (with preserved awareness) involving the face, neck or legs (buckling knees), with or without involvement of the arms, typically triggered by intense emotions, particularly of a positive nature related to laughter [93].

Video-polysomnography is the gold standard physiological assessment of sleep

The gold standard for physiological assessment and behavioral observation of sleep is video-polysomnography (V-PSG). A V-PSG comprises a series of biological parameters that are recorded during a whole night, usually in a dedicated sleep-lab, aimed to identify wake-sleep stages and see how they are distributed across the night. It also includes the evaluation of sleep-associated events such as disordered breathing, cardiac events, and abnormal movements and behaviors.

The standardized rules for scoring wake-sleep stages and sleep-associated events, as well as the technical requirements and recommendations are provided in the American Association of Sleep Medicine (AASM) manual [94]. The minimal signals to be recorded are 6-derivation electroencephalogram (EEG; with surface electrodes placed at positions F3, F4, C3, C4, O1, and O2 of the international 10-20 system [95] and referenced to contralateral mastoid -M1 or M2-), right and left electrooculogram (EOG), chin electromyogram (EMG), 1-derivation electrocardiogram (ECG), airflow (with a pressure cannula, a thermal sensor, or both), thoracic and abdominal movements (with gauges), lower limb EMG (at the anterior tibialis muscle bilaterally), and synchronized video and audio recording (for body movements, abnormal behaviors, vocalizations, and respiratory sounds among other features).

For sleep scoring purposes, the one-night recording is divided into sequential 30-second periods (named epochs) and each epoch is assigned one wake-sleep stage. The whole sequence is then represented in a hypnogram (Figure 1). There are five stages to score: wake, non-rapid eye movement (non-REM; NREM) stage 1 (N1), NREM stage 2 (N2), NREM stage 3 (N3), and REM. In normal circumstances, sleep onset occurs with NREM sleep and progressively deepens from N1 to N3 before the first REM sleep period occurs. This cycle repeats 3-5 times over the night, usually with a greater presence of NREM N3 in the initial cycles and REM sleep predominating in later cycles.

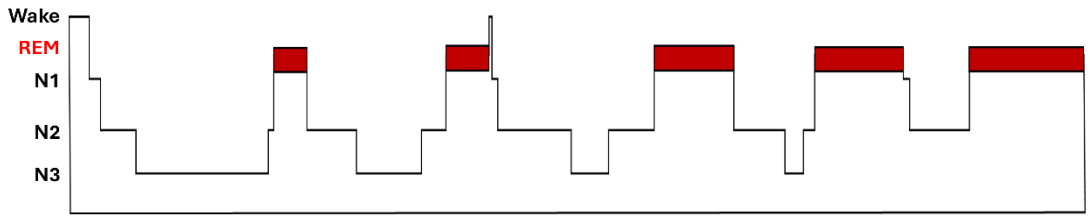

Figure 1: One-night hypnogram showing the normal distribution and cyclic repetition of sleep stages. Periods of stage N3 are longer in the initial cycles, while periods of REM become longer towards the end. Occasional, brief awakenings, like the one represented after the second REM period, are normal. REM: rapid eye movement; N1: stage N1 of non-REM (NREM); N2: stage N2 of NREM; N3: stage of N3 NREM.

This sequence can be altered in many different ways. For instance, sleep time may be reduced due to long sleep-onset latencies, to fragmented sleep, or to early awakenings; some sleep stages may be absent or reduced, while others are consequently increased; or REM sleep may abnormally occur at sleep onset (typically seen in narcolepsy). V-PSG is the best way to identify these abnormal sleep patterns and to look for potential causes (e.g. severe sleep apnea causing sleep fragmentation and producing a reduction of total sleep time and of deeper sleep stages). Besides the sequence and percentage of wake-sleep stages (sleep macrostructure) the features of each stage (sleep microstructure) may also be altered. Sometimes, altered sleep may be restricted to particular sleep stages, like in isolated REM sleep behavior disorder (RBD) which affects only REM sleep. This is in contrast with Morvan syndrome or anti-IgLON5 disease, in which the structure of sleep is more extensively affected, with loss of sleep spindles, K complexes, and slow wave sleep characteristic of stages N2 and N3 NREM, and lack of REM-sleep atonia. Thus, V-PSG is necessary to recognize disordered sleep microstructure, and synchronized video and audio during V-PSG is critical to

detect and interpret abnormal behaviors and sounds and establish whether they occur with the patient awake or asleep and if so, in which sleep stage.

Considerations for VPSG assessment in neurological diseases

The parameters that are necessary and sufficient for the identification of wake-sleep stages include electroencephalogram (EEG), electrooculogram (EOG), and chin electromyogram (EMG). Each stage has distinctive features, and the combination of these three biological parameters allows specific identification of each of the stages. Briefly, wakefulness is characterized by posterior alpha activity in the EEG, rapid eye movements and blinking in the EOG, and high chin EMG tone; N1 is scored when posterior alpha rhythm vanishes or, in the absence of awake alpha, when vertex waves or slow eye movements appear; K complexes and sleep spindles define stage N2, and slow, synchronized, high-voltage delta activity defines stage N3, regardless of the eye movements and EMG tone in both cases; finally, REM sleep is characterized by lower-amplitude EEG activity, bursts of rapid eye movements (that may remind those of wakefulness), and EMG atonia (or the lowest EMG tone of the whole recording).

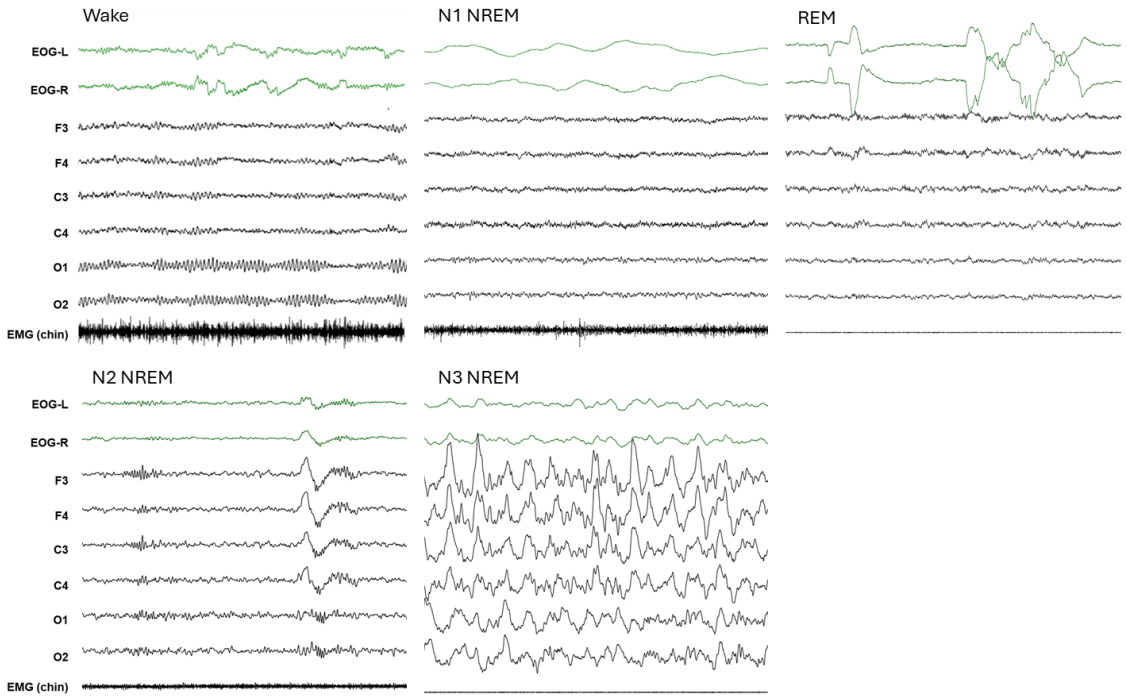

Figure 2: Differing polysomnographic features of normal wake-sleep stages. EOG-L: left electrooculogram; EOG-R: right electrooculogram; EMG: electromyogram; NREM: non-rapid eye movement; REM: rapid eye movement

Despite the utility and worldwide applicability of the standardized criteria for scoring sleep [94], there are important limitations in many neurological diseases. Any of the EEG, EOG, or EMG signals may be abnormal in diseases causing brain dysfunction; often to a point where identifying wake-sleep stages based on conventional sleep-scoring criteria is hindered, even not feasible. In some instances, especially if awake EEG is already pathologically slow (without normal posterior alpha rhythm), determining if the patient is awake or asleep may already be challenging [96–98]. In some conditions alpha or "subalpha" frequencies abnormally persist during the onset of NREM sleep, what also makes it difficult to establish sleep onset [96,97]. In such cases, deciding whether the patient is awake or asleep needs to rely on behavioral aspects from the video and audio (e.g. closed eyes, open mouth, or snoring usually indicate sleep). Brain dysfunction may also cause the loss of the physiological markers of NREM sleep, like spindles and K complexes, so that scoring stage NREM N2 becomes impossible [83,98]. Finally, the most common presentation of disordered REM sleep is that of the loss of normal muscle atonia in the chin and limbs. Even though chin atonia is a requirement to score REM sleep, if the remaining features of REM sleep are present (i.e. low-amplitude, mixed-frequency EEG background and rapid eye movements), a high EMG tone rarely prevents from identifying REM sleep (it would be abnormal REM sleep, but easily identifiable as REM sleep). However, in some neurodegenerative diseases abnormal delta slowing may be part of the background EEG during REM sleep, or eye movements may be markedly reduced [99], and if in addition the EMG tone is high, it may be difficult to differentiate REM sleep from NREM N1 sleep or even wakefulness.

There are some classical neurological diseases, like fatal familial insomnia (FFI) or Morvan syndrome, that are well-known to cause a severe loss of the normal features of sleep (REFS). However, these have been considered in the field of sleep as rare exceptions; indeed, the literature is scarce, descriptions heterogeneous, and a thorough characterization of these disorders is lacking. Interest for how sleep is disordered in neurological diseases has emerged recently among neurologists who are not sleep-specialists, particularly those focused on neurodegenerative diseases. Schenck described RBD in 1986 [100] and was the first to report that some of these

patients may develop symptoms of parkinsonism in the future [101]. More recent research has confirmed that the actual percentage of patients with isolated RBD who eventually develop overt symptoms of alpha-synucleinopathy (e.g., Parkinson's disease, dementia with Lewy bodies or, less frequently multiple system atrophy) is greater than 90% [102]. This has positioned sleep as an important biological marker of early neurodegeneration and patients with isolated RBD as potential candidates for future neuroprotective trials. Similarly, the recent description of anti-IgLON5 disease as an antibody-mediated encephalopathy manifesting with prominent sleep disturbances and sleep-microstructure abnormalities, has drawn the attention of neuroimmunologists to sleep investigations as well.

Whether the disturbances of sleep microstructure may have diagnostic or prognostic value or whether these could be used as markers of response to different treatments (neuroprotective trials, immunotherapy) are relevant clinical questions. Towards this end, however, there is a clear need to develop specific criteria, adapted rules, and a homogeneous terminology to characterize these disturbances in order to avoid inaccuracy and inconsistency in the results [103]. These goals have long been pursued by us and others [104] but have not yet been achieved. In the last decade, the group from Hospital Clinic de Barcelona has thoroughly characterized sleep in a series of neurological disorders by applying a novel scoring system which includes a series of additional wake-sleep stages aimed to overcome the limitations of the conventional system [94]. Firstly, when anti-IgLON5 disease was discovered, authors found it necessary to adopt new terms such as "Undifferentiated NREM" or "Poorly structured N2" to refer to different periods of the night where NREM sleep was altered. A similar terminology was used to characterize sleep disturbances other than REM sleep without atonia in patients with Lewy body dementia, where the "Undifferentiated NREM" was also present [98].

Finally, in parallel with the work included in this PhD thesis, I participated in the characterization of the sleep architecture and sleep-disordered breathing in fatal insomnia [96], which allowed me to acquire experience with challenging scoring o sleep alterations. For the work with fatal familial insomnia, additional wake-sleep stages were required to reflect the abnormal transition between wake and NREM

sleep, namely subwake 1 and subwake 2. These included persistent alpha or subalpha frequencies at sleep onset, that prevented from scoring NREM sleep in behaviorally sleeping patients, as had been previously noted, but not comprehensively described, by other investigators [105,106]. In all instances, the novel stages received names that intended to be descriptive, and easy to apply by other centers and specialists. In the same line of work, a novel scoring system has been proposed for groups of patients with different alpha-synucleinopathies (Parkinson's disease, Lewy body dementia, and multisystem atrophy) [97].

In addition, our studies on fatal insomnia highlighted the importance of sleep-related respiratory alterations and central apneas in neurological diseases. For example, an enhanced attention to respiratory events (beyond conventional obstructive sleep apnea) during analysis of V-PSG, helped us to later identify seizure disorders that manifested with ictal central apnea in anti-LGI1 encephalitis (shown in results).

Proposed steps for V-PSG assessment in AIE

Based on the experience with anti-IgLON5 disease and reports on other AIE [83], we reported a series of steps to assess sleep studies in AIE (Figure 3; Figure 2 of the review included at the end of this introduction [48]).

The first step is to determine if there are sleep spindles and K-complexes, which along with high-amplitude delta slowing are the best markers of a normal NREM sleep. In Morvan's syndrome, for instance, all normal features of NREM sleep are completely lost, while in anti-IgLON5 disease they are absent only in parts of the night [82,83].

The next step is to examine REM sleep. This can be reduced, absent, or manifest abnormalities typical of RBD, including lack of EMG atonia, with excessive intermittent (phasic) or continuous (tonic) activity, associated with jerky, vigorous movements.

A synchronized video recording is crucial to characterize the different movements occurring along the night, distinguishing awake movements from sleep related ones, and within the latter, the presence of quasi-purposeful movements typical of

undifferentiated NREM or poorly structured N2 sleep from the more vigorous movements that are characteristic of RBD.

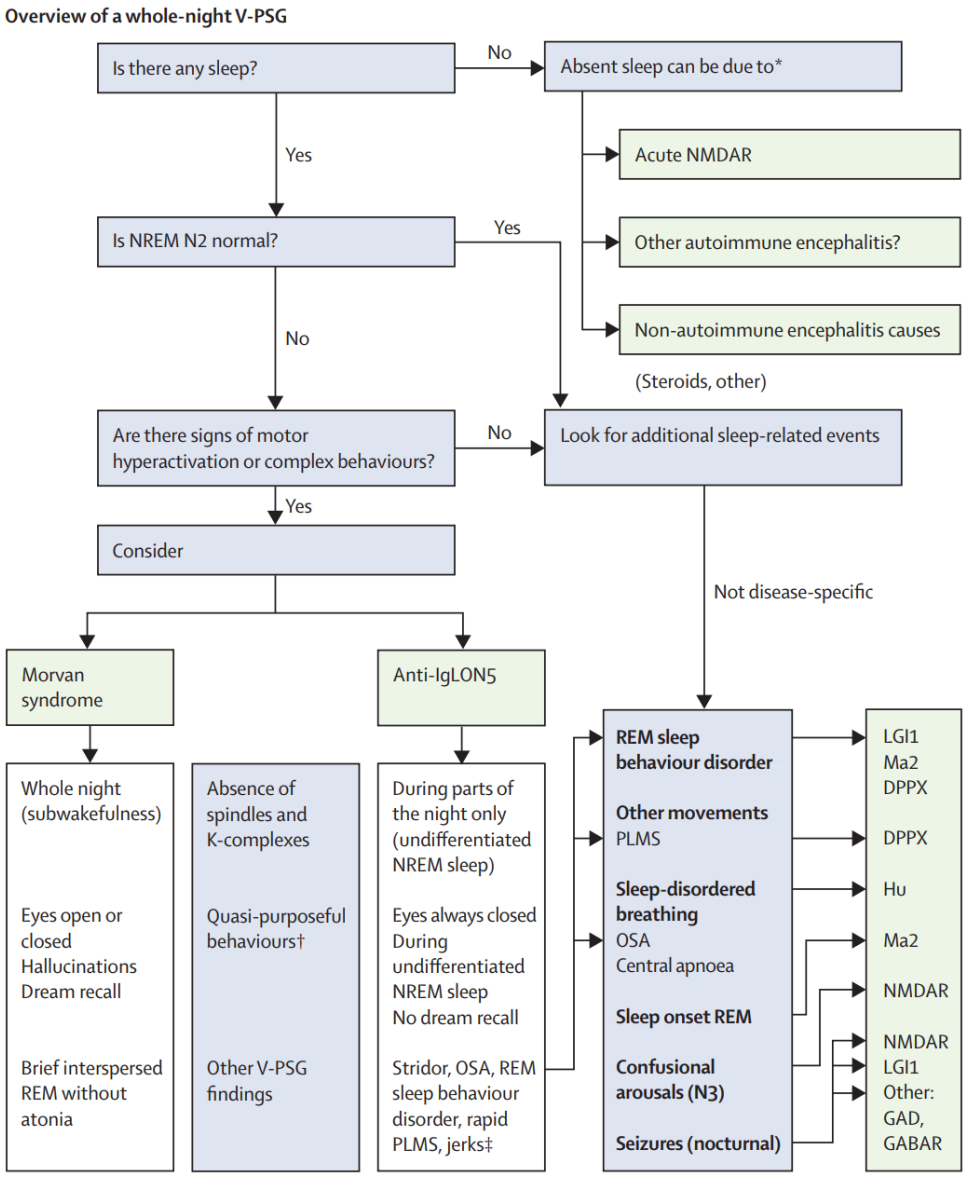

Figure 3: Stepwise evaluation of nocturnal V-PSG in patients with suspected autoimmune encephalitis. The V-PSG assessment should start with a general overview of the whole recording, looking for periods of sleep along with associated behaviors in the video. The lack of sleep spindles and K complexes associated with behavioral and motor abnormalities is highly suggestive of AIE. However, if behavior is normal, it is less specific. Note that Morvan syndrome and anti-IgLON5 disease share the combination of absent sleep spindles and K complexes with quasi-purposeful behaviors but these are associated with the indicated differing features. In all clinical scenarios where sleep is present, several sleep-related V-PSG events should be explored, such as RBD, other movements, sleep disordered breathing, sleep onset REM, confusional arousals, and seizures. These events can occur in isolation in AIE and non-AIE diseases, but it is the combination of different sleep symptoms and association with other daytime symptoms (cognitive, behavioral, psychotic, epileptic) what finally outlines the specific clinical picture. (#)Complete absence of sleep is frequent in the acute phase of anti-NMDAR encephalitis; severely reduced sleep has been reported in isolated cases of anti-LGI1 and anti-DPPX. (*)In Morvan syndrome, lack of recognizable features of NREM combined with subwakefulness and motor hyperactivation is known as *agrypnia excitata*. Quasi-purposeful behaviors with dream recall are also described as oneiric stupor. From [48].

Sleep tests other than V-PSG may also help in the setting of AIE. A multiple sleep latency test, recording consecutive naps during daytime, may serve to confirm daytime sleepiness and identify episodes of sleep-onset REM, which occur in the secondary narcolepsy of patients with anti-Ma2 encephalitis and NMOSD [89,107]. On the other hand, wrist-actigraphy is used to study circadian-rhythm abnormalities. It is a watch-like accelerometer that patients wear at home for several days or a few weeks and provides a continuous recording of motion. From the amount of movement recorded, it allows tracking the periods of wake and sleep during the whole recording time. A few studies have shown that actigraphy may also be useful to detect nocturnal motor activities, like REM sleep behavior disorder or epileptic seizures [108,109].

AIE-related seizures and epilepsy

A big concern for the long-term outcome of AIE is the risk of developing chronic epilepsy. When neural-surface antibodies were discovered, epileptologists immediately saw in autoimmunity a plausible cause of many chronic and often drug-resistant focal epilepsies of unknown etiology [110,111]. Indeed, in 2017 the International League Against Epilepsy (ILAE) included the “immune etiology” alongside structural, genetic, infectious, and metabolic etiologies, and was deemed to have a particular value as a group of patients that may benefit from etiology-targeted treatments [112].

Studies searching for the presence of autoantibodies in the serum and CSF of patients with chronic temporal lobe epilepsy have yielded positive results in 3-5%, most frequently involving GAD65 autoimmunity [113–115]. These percentages increase in studies that include participants with new-onset seizures, not only chronic epilepsies [110,111]. However, the term epilepsy implies an enduring predisposition to have unprovoked epileptic seizures [112], which needs to be differentiated from the acute symptomatic seizures that occur during the active stage of encephalitis. Studies with long-term follow-up are scarce, but overall have shown that most patients suffering an AIE achieve complete seizure freedom after the acute phase of the encephalitis is treated, and often antiseizure medications can eventually be discontinued [116–119]. Percentages vary among studies, with many potential explanations. For instance, no

specific timeline has been recommended to make the distinction between autoimmune associated epilepsy and acute symptomatic seizures related to autoimmune encephalitis. Moreover, the type of immunotherapy and intensity of treatment may vary considerably among centers and series (e.g., older series in which the treatment approach to AIE was less well-established than more recent series). In some instances, patients may still have active encephalitis by the time of determining whether seizures are symptomatic, in which case the diagnosis of epilepsy cannot be established, or alternatively the patient no longer has active disease, in which case the seizures can be classified as epilepsy. Table 5 [116] shows the estimated risk of epilepsy in different AIE with neural surface antibodies.

Antigen	Seizures	Risk of epilepsy	General outcome
NMDAR	~75% of patients develop seizures, often the first symptom in children [29]. 11-30% of adults and 6% of children have a characteristic EEG pattern (extreme delta brush) associated with higher severity [46,120]. Diffuse or focal slowing are the most frequent EEG findings [25]. Normal posterior rhythm on the first EEG predicts a favorable outcome; severely abnormal EEG predicts poor outcome [120].	Low (<5%)	Good. ~80%–85% of patients with substantial or full recovery. Relapses in ~15%–20%
AMPAR	~30–40% of patients develop seizures in the context of limbic encephalitis.	Low (5%)	Depends on the control of the tumor. Otherwise, ~70% partial or full recovery. Relapses in ~16%
GABAbR	90-95% of patients have limbic encephalitis with early and prominent seizures. Can present with status epilepticus.	Low (<5%)	Depends on the control of the tumor. Otherwise, ~70% partial or full recovery. Relapses occur.
LGI1	~40%–50% of patients present with faciobrachial dystonic seizures (FBDS). EEG is often normal in patients with isolated FBDS [40]; some have MRI T1 and T2 basal ganglia hyperintensity [121]. At the stage of encephalitis, multiple types of seizures (temporal lobe, focal, tonic-clonic, or autonomic) can occur [38,122,123]. Low chance of seizure control unless immunotherapy is used.	~15% (some with hippocampal sclerosis)	~70%–80% partial or complete recovery, but only ~35% able to return to work. Relapses in 27%–34% [38,39]
CASPR2	24% of patients present with seizures. Overall, 54% develop seizures during the course of the disease [59].	Exact risk of epilepsy unknown; probably low (<10%) [124]	48% full response to treatment, 44% partial response, 7% no response. Relapses in 25% [59]
GABAaR	Seizures occurred in 88% of patients (48% developed status epilepticus). Compared with adults, children were more likely to have generalized seizures [125].	probably moderate (20%–30%) [126]	23% complete recovery, 64% partial recovery, 13% death (status epilepticus or sepsis) [125].
mGluR5	6 of 11 patients presented with seizures. Compared with adults, children were more prone to develop generalized seizures and status epilepticus [127]	Low (5%)	6 of 11 patients had complete recovery and 5 partial recovery. None developed epilepsy [127]
D2R	2 of 12 patients developed seizures [128].	Low (5%)	5 of 12 patients had full recovery. None developed epilepsy. Relapses in 3 of 12 cases [128].
DPPX	Seizures in 10%–22% of patients [52,72].	Not available (small number of patients)	60% substantial or moderate improvement, 23% none (most not treated), 17% died [52,72]. Relapses 23% [72]
GlyR	At disease onset, 13% of had seizures. 5 of 45 patients developed only encephalopathy with seizures [129].	Not available	Most had substantial or partial improvement; 11% died. 14% relapsed [129]

Table 5: Antibody-mediated encephalitis, seizures, and estimated risk of epilepsy. For abbreviations see Table 1 legend. Adapted from [116]

In anti-NMDAR encephalitis, which is the most frequent AIE, epileptic seizures are common in the acute stage (70-80% of patients) and usually appear early in the disease course [25,29,130,131]. EEG is abnormal in more than 90% of patients, however epileptogenic abnormalities or seizures are not as frequent (10-60%) [29,131–134]. The most common finding in the acute stage is diffuse, frontal predominant slowing, and about 1/3 of patients develop an EEG pattern named extreme delta brush, which is highly characteristic of this disorder and its presence associates with prolonged hospitalization [46]. In the long term, the risk of persistent seizures is overall low in anti-NMDAR encephalitis [135] and EEG slowing improves alongside with other symptoms. However, most long-term follow-up studies do not include EEG data.

In anti-LGI1 encephalitis, the second most prevalent AIE, seizures occur in up to 90% in the acute stage. The most characteristic are the faciobrachial dystonic seizures (FBDS), which are specific to anti-LGI1 encephalitis. FBDS present in approximately half of the patients with anti-LGI1 encephalitis and are characterized by a sudden, very brief, one-sided, tonic contraction of the upper limb and the ipsilateral face (less frequently the leg), that appears up to dozens of times a day, and can be unilateral or bilateral asynchronous. It is still debated whether the nature of these episodes is epileptic or a paroxysmal movement disorder and whether the origin is cortical or subcortical. The most consistently described scalp EEG findings related to FBDS include diffuse electrodecrement and a contralateral frontal infraslow wave immediately preceding the movement [122,136,137]. Moreover, in some patients FBDS may precede or follow focal temporal lobe epileptic seizures. These arguments favor the hypothesis of a cortical origin. However, FBDS respond poorly to antiseizure medications and functional neuroimaging studies with positron emission tomography show basal ganglia hypermetabolism, but not cortical involvement, rather supporting the paroxysmal movement disorder hypothesis. Likely, a combination of both mechanisms is responsible for the generation of FBDS, due to the impairment of a cortico-subcortical network involving the basal ganglia and the frontal ant temporal cortices [138].

Although less disease-specific, focal onset seizures are one of the main manifestations of anti-LGI1 encephalitis, occurring in 70-90% of patients [38,39,139]. Seizures in anti-

LGI1 encephalitis typically originate in temporal lobes and clinically manifest as impaired awareness with oral and manual automatisms, some with epigastric rising sensation, or as autonomic seizures with episodic piloerection, and secondary generalization may occur. However, seizures are often subclinical and underreported and patients may have up to dozens in a day, also during sleep. In anti-LGI1 encephalitis a distinct EEG pattern has also been described during these subclinical seizures, consisting of periodic lateralized sharp or slow-sharp waves preceding or following the rhythmic ictal discharges, which are always confined to the temporal lobes [84,140]. As FBDS, focal seizures do not respond well to antiseizure medications, but readily respond to immunotherapy. Long-term follow-up studies are scarce, but overall show that anti-LGI1 encephalitis is among the AIE with higher risk for developing chronic epilepsy (15-35% depending on the series), often showing a high number of seizures during the acute stage and eventually developing hippocampal sclerosis [38,43,44,141]. However, EEG follow-up is missing in most studies and given that seizures in anti-LGI1 are often not clinically manifest, the real long-term prevalence of seizures is unknown.

Epilepsy and sleep have a bidirectional relationship

The relationship between epilepsy and sleep is bidirectional and intricate. Some epileptic seizures are more frequent during sleep or even restricted to sleep, which highlights the profound interaction between sleep and epilepsy. For instance, certain types of epilepsy, such as nocturnal frontal lobe epilepsy and benign epilepsy with centrotemporal spikes, are particularly known for their association with sleep [142,143]. Moreover, seizures occur mainly during NREM sleep, which is characterized by widespread cortical neuronal synchronization that facilitates the generation of physiological sleep features such as sleep spindles, K-complexes, and slow-wave sleep. However, this synchronized neuronal firing also results in increased cortical excitability and renders the brain more susceptible to epileptic discharges and their propagation into epileptic seizures [144,145]. In contrast, during REM sleep, the brain is in a more desynchronized state, reducing the likelihood of synchronous epileptiform activity.[146]

Sleep deprivation is a well-known precipitant of epileptic seizures. Both experimental and clinical studies have demonstrated that lack of sleep can lower the seizure threshold and increase the likelihood of seizure occurrence in individuals with epilepsy. This phenomenon is partly due to the impact of sleep deprivation on the stability of neuronal networks, leading to increased excitability and synchronization of neuronal firing, which are critical factors in the initiation of seizures [147,148].

Conversely, epileptic seizures themselves, as well as antiseizure medications, can significantly alter sleep architecture and reduce sleep quality. Seizures can disrupt sleep continuity, leading to increased wake time and reduced slow-wave sleep and REM sleep time [149,150]. Antiseizure medications can also have varying effects on sleep. The impact of these medications on sleep is multifaceted and can depend on the type of drug, dosage, and patient idiosyncrasy [151].

The probability of finding epileptiform activity in a routine EEG strongly increases if sleep periods are included in the recording. Especially stages N1 and N2 of NREM sleep and unstable phases of sleep with increased arousal frequency [152,153] are predominantly involved in the occurrence of seizures in many focal and generalized epilepsies. Moreover, medial temporal regions are more prone than other brain regions to spike production or propagation during NREM sleep [154]**.**

In AIE that present with seizures, these can occur either during wakefulness or sleep. However, most studies do not include sleep EEG investigations during the acute stage of the disease; moreover, the post-acute stage has been even more unexplored. For the works conforming this PhD thesis, V-PSGs were recorded with EEG including all brain regions [95] instead of the standard 6-derivation EEG necessary for sleep-staging purposes only, allowing the simultaneous assessment of sleep disorders and epileptic phenomena.

In summary, there is preliminary evidence that sleep can be altered in many different ways in AIE, however this field is largely unexplored. Specifically, there are no studies that systematically assess sleep disorders in anti-NMDAR encephalitis and anti-LGI1 encephalitis, which are by far the most common neuronal antibody-mediated encephalitis. The complexity of the sleep function, added to the complexity and

uniqueness of the different types of AIE, underscore the importance of a combined clinical and neurophysiological approach for assessing sleep disorders in these diseases. V-PSG could potentially show alterations that are specific for a disease and could assist in the characterization of nocturnal symptoms or even uncover clinically silent manifestations. The EEG can provide additional information to help in the interpretation of V-PSG, which can be challenging in neurological disorders, and is essential to monitor seizure activity, especially in the post-acute stage, where systematic studies are lacking.

Review published during the PhD process

Sleep disorders in autoimmune encephalitis

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Sleep disorders in people with autoimmune encephalitis have received little attention, probably overshadowed by the presence of other neurological and psychiatric symptoms in this group of conditions. However, sleep disorders are frequent, often severe, and usually persist beyond the acute disease stage, interfering with patients' recovery and quality of life. Because autoimmune encephalitis can affect any brain network involved in sleep initiation and regulation, all types of sleep disorders can occur, with varying distinct associations, frequency, and intensity. Anti-IgLON5 and anti-NMDA receptor encephalitis exemplify two diseases in which sleep disorders are prominent. In anti-IgLON5 disease, sleep disorders were the core symptoms that led to the description of this disease, whereas in anti-NMDA receptor encephalitis, sleep disorders vary according to the disease stage along with other neuropsychiatric symptoms. Comprehensive, systematic, multicentre studies are needed to characterise sleep disorders and their mechanisms in autoimmune encephalitis.

Introduction

Sleep is a complex function resulting from the coordinated activity of many neural centres and brain networks.[1] Not surprisingly, sleep is altered in neurological diseases, such as Parkinson's disease, fatal familial insomnia, or Alzheimer's disease, that damage these structures, with clinical implications that are increasingly recognised.[2–4] Sleep disorders also occur in many of the antibody-associated diseases of the CNS, also known as autoimmune encephalitis, but these disorders have received little attention. In some instances, such as Morvan syndrome, the sleep dysfunction was described decades before recognising its autoimmune biological cause.[5] By contrast, in anti-NMDA receptor encephalitis, the associated syndrome and immune-mediated mechanisms were described first, whereas the frequency and severity of sleep problems have been under-recognised until this past year.[6] Moreover, anti-IgLON5 disease was discovered because of the unique characteristics of the sleep disorder, which eventually led to the identification of the antibody and target antigen.[7] This diversity of scenarios, the absence of a standardised assessment of sleep, and the scarce number of studies (mostly based on case reports not focused on sleep) complicate the assessment of sleep disorders in autoimmune encephalitis. Moreover, sleep disorders in autoimmune encephalitis are usually severe and persist beyond the acute phase of the disease, affecting the process of recovery and quality of life.[6,8] Thus, the prompt recognition and adequate management of sleep symptoms might not only help in diagnosing autoimmune encephalitis but also in accelerating the overall recovery.

All major types of sleep disorders can occur in autoimmune encephalitis—eg, insomnia, parasomnia, hypersomnia, and sleep-disordered breathing. In this Review, we discuss their specific symptoms and potential pathophysiological mechanisms, propose a clinical and neurophysiological approach highlighting the particularities of sleep symptoms in autoimmune encephalitis, and provide a comprehensive review of each of the autoimmune conditions in which sleep disorders have been reported.

Assessment of sleep disorders in autoimmune encephalitis

The mechanisms of the sleep–wake control involve localised neuronal groups with different neurotransmitters and neural circuits distributed in the entire brain, which regulate the transition between wakefulness, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep, in oscillations also modulated by the circadian clock (panel[9–11]).

Sleep can be altered in many ways in patients with autoimmune encephalitis, resulting in a wide variety of symptoms. The best way to characterise these sleep disorders is by the use of a combined clinical and video-polysomnography (V-PSG) evaluation.

V-PSG is the gold standard for physiological assessment and behavioural observation of sleep. On the basis of distinctive EEG, electrooculogram, and electromyogram features, sleep stages can be identified sequentially over the night (figure 1A–C). Sleep onset occurs in NREM sleep, in which three progressively deepening sleep stages (N1, N2, and N3) can be differentiated, each with characteristic features. Stage N1 can be defined by disappearance of awake alpha rhythm slow eye movements and vertex waves. Stage N2 can be defined by K-complexes and sleep spindles. Stage N3 (slow-wave sleep) can be defined by high-voltage delta activity. Finally, REM sleep is characterised by low amplitude EEG activity and bursts of rapid eye movements (reminding of wakefulness), with complete electromyogram atonia. Sleep-related events can be identified with specific sensors (eg, airflow, respiratory effort, limb electromyogram) and synchronised video and audio recordings (crucial to interpret behaviours and sounds).[12]

Clinical assessment

Although sleep symptoms are rarely the main reason for consultation in patients with autoimmune encephalitis and are often overshadowed by other neurological and psychiatric symptoms, they are readily recognisable when specifically asked.[8,13] In many aspects, these symptoms are similar to those of well known conventional sleep disorders, but in patients with autoimmune encephalitis,

they have a better defined onset that can be pointed to a particular day or week, and several sleep disorders can coexist in the same patient.

There are several considerations for sleep evaluation in patients with autoimmune encephalitis. First, information should be obtained from both the patient and the bedpartner or caregiver using a structured anamnesis. Second, questions should cover the four major problems: insomnia, parasomnia, sleep-disordered breathing, and hypersomnolence and other daytime symptoms. Finally, comparisons should be established between current and premorbid sleep characteristics.

Insomnia

Insomnia is a broad term that designates any difficulty to initiate or maintain sleep. Relevant information includes timing, regularity, and duration of the major sleep episode (usually nocturnal), sleep onset latency, the number of times sleep is interrupted, why, and for how long, and the time and type of morning awakening. Daily sleep–wake patterns can be assessed with an actimeter or alternatively, patients can keep a sleep–wake diary.[14]

Autoimmune encephalitis-related insomnia (eg, anti-NMDA receptor, anti-Caspr2, and occasionally anti-LGI1 encephalitis), is usually acute and severe, with reduced or absent sleep for days or weeks, and usually associated with hallucinations or abnormal behaviours.[3,8,15]

Parasomnias and movement disorders during sleep

Sleep is normally a placid, relaxed state but can be completely altered in patients with autoimmune encephalitis. The differential diagnosis of nocturnal movements and behaviours in these patients is complex, ranging from voluntary movements to parasomnias, hallucinations, or seizures. Seizures usually have a stereotyped presentation that facilitates their recognition. For the rest of the symptoms (ie, abnormal movements or behaviours), the state of the eyes and the type of behaviours provide important clinical clues.

Open eyes are irrefutable indicators of wakefulness, so behaviours or vocalisations displayed with the eyes open are most likely hallucinations while awake than parasomnias. Hallucinations typically occur throughout the 24 h in patients with Morvan syndrome and are frequent in patients with anti-NMDA receptor encephalitis. Instead, in patients with anti-IgLON5 disease (in whom hallucinations are rare), the eyes remain closed during the behaviours (video 1). The same applies to episodes of REM sleep behaviour disorder. Sudden opening of the eyes at the onset of an event can also be seen in disorders of arousal, such as confusional arousals.

Voluntary movements to change body position when lying in bed awake, although normal, can occur incessantly, especially in insomnia, and must be differentiated from sleep-related movements. Involuntary movements and behaviours of autoimmune encephalitis can be classified into four groups. First, irregular body or limb jerks, or periodic limb movements awake or during sleep (at any sleep stage and period of the night), are typical of anti-IgLON5 disease and also occur in patients with anti-DPPX encephalitis.[16,17] Second, complex, quasi-purposeful (or finalistic), non-violent movements, with the eyes closed, seeming to manipulate imaginary objects and imitating daytime activities (eg, eating, sewing) are characteristic of anti-IgLON5 disease and Morvan syndrome (also reported with the eyes opened, making the distinction from hallucinations difficult).[3,18–20] Third, vigorous, more violent, jerky movements of dream enactment, with vocalisations (mumbling, talking, shouting), suggest REM sleep behaviour disorder and can be seen in several different autoimmune encephalitis (eg, anti-LGI1, anti-Caspr2, anti-IgLON5, anti-Ma2).[16,21,22] Last, confusional arousals, in which patients suddenly wake up from sleep, open the eyes, look around disoriented, sit up, or talk, occur in anti-NMDA receptor encephalitis.[6,23] In contrast to conventional parasomnias in which behaviours are episodic, but can be very vigorous, autoimmune encephalitis-related parasomnias are frequently prolonged (lasting several minutes or hours), recur throughout the night and across many nights, and rarely result in injuries.

See online for video 1

Sleep breathing disorders

Respiration during sleep can be seriously altered in patients with autoimmune encephalitis. Obstructive sleep

Panel: Brain centres, circuits, and neurotransmitters involved in sleep-regulation

Wake-promoting centres are located at the rostral brainstem, lateral hypothalamus, and basal forebrain and involve cholinergic, noradrenergic, serotonergic, histaminergic, dopaminergic, and hypocretinergic neurotransmission.[9] Non-rapid eye movement sleep is promoted by GABAergic and glycinergic neurotransmission at the anterior hypothalamus and medullary parafacial zone. Rapid eye movement sleep is modulated by hypothalamic melanin-concentrating hormone and GABAergic neurons, and has its main centre at the pontine tegmentum, which induces muscle atonia (via inhibitory ventro-medullar neurons) and cortical and paralimbic activation, through glutamatergic–GABAergic and cholinergic neurotransmission.[9,10]

The thalamus gets afferences from most sleep centres and plays important roles in arousal promotion as well as sleep onset and consolidation, through thalamocortical interaction.[11] Cortical activation and desynchronisation (ie, low-voltage, fast EEG activity) is characteristic of wakefulness and rapid eye movement sleep, whereas non-rapid eye movement sleep associates with cortical synchronisation and slow waves (ie, high-voltage, slow EEG activity). A key concept is that promoters of arousal and sleep, and of non-rapid and rapid eye movement sleep, antagonise each other and cannot be maximally active at the same time.[10]

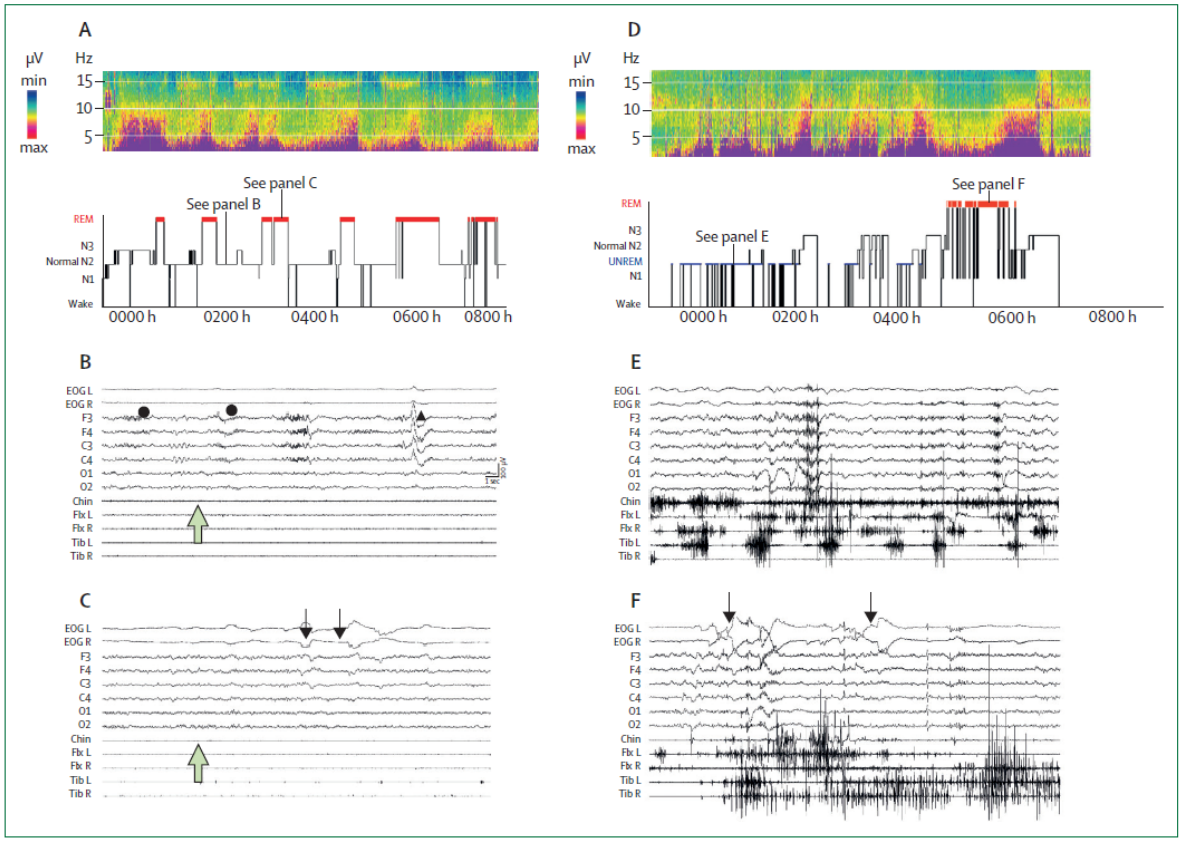

Figure 1: **Normal features of V-PSG and some of the abnormalities found in patients with autoimmune encephalitis**
(A) Normal hypnogram and spectrogram by time (in hour): normal sleep latency (<30 min), sleep onset in NREM (usually a brief N1, longer N2, and reaching N3 within the first 60–90 min). The first REM sleep period occurs 60–90 min after sleep onset, and cyclical alternations between NREM and REM sleep occur every 60–90 min throughout the rest of the night. Interspersed arousals or brief awake periods occur throughout the night (eg, posture change, going to bathroom). The density spectral array (top panel) shows the power spectrum of electroencephalographic frequencies (0–17 Hz); warmer colours indicate higher power in the corresponding frequency. (B) 30 s epoch of normal NREM N2 showing frequent sleep spindles (circle) and well formed K-complexes (triangle), with background electromyogram of variable amplitude, usually lower than awake (upward arrow). (C) 30 s epoch of normal REM sleep showing rapid eye movements (downward arrows), low-amplitude mixed-frequency EEG without sleep spindles or K-complexes, and electromyogram atonia (lowest background electromyogram of the recording; upward arrow). (D) Hypnogram from a patient with anti-IgLON5 disease showing low sleep efficiency with fragmented sleep, an awake period after sleep onset (around 0230 h), and early awakening (around 0630 h). Sleep onset occurs with undifferentiated NREM, which predominates during the first half of the night (see E); in the second half there is normal NREM sleep (with stages N1, N2, and N3). There is detectable REM sleep, although sleep stages are abnormal (detail in F). (E) 30 s epoch of undifferentiated NREM sleep (awake alpha disappeared): there are no vertex waves, sleep spindles or K-complexes, and there is intense motor hyperactivation as shown by electromyogram activity in electromyogram and EEG channels, with rapid periodic limb movements recorded with the left tibial electrode. The reading belongs to a patient with anti-IgLON5 disease, although in a patient with Morvan syndrome with altered NREM sleep and motor hyperactivation (designed agrypnia excitata) the alterations shown in this panel would be similar. (F) 30 s epoch of REM sleep: characteristic REM and EEG but with excessive phasic electromyogram activity in the chin and limb muscles indicating REM sleep behaviour disorder. Chin=mentalis muscle. EOG=electrooculogram. Flx L=flexor digitorum superficialis muscle left. Flx R=flexor digitorum superficialis muscle right. Max=maximum. Min=minimum. NREM=non-rapid eye movement. REM=rapid eye movement. Tib L=anterior tibialis muscle left. Tib R=anterior tibialis muscle right. UNREM=undifferentiated non-rapid eye movement. V-PSG=video-polysomnography.

apnoea in patients with anti-IgLON5 disease is frequently caused by laryngeal obstruction with associated stridor,[18] which is different from conventional pharyngeal obstruction that produces snoring, a more familiar sound. Both problems, stridor and snoring, might concur, and both might respond to continuous positive airway pressure (CPAP) treatment, further complicating their recognition. However, a correct diagnosis is important because stridor usually suggests brainstem damage and has been associated with increased risk of sudden death (eg, in multiple system atrophy).[24] Conventional (pharyngeal) obstructive apnoeas and respiratory pauses ending with a gasp can also occur and are easily recognised by partners sharing a bed. Brainstem dysfunction also produces central hypoventilation syndromes, like in anti-Hu encephalitis.[25]

Hypersomnolence and other daytime symptoms

Hypersomnia and excessive daytime sleepiness are two different forms of hypersomnolence that sometimes coexist.[14] Hypersomnia is defined as an excessive need for sleep (beyond 10 h per day), whereas excessive daytime sleepiness is the inability to stay awake and alert in relaxed situations, with unintended lapses into sleep (sleep attacks) in extreme cases. In patients with autoimmune

encephalitis, hypersomnolence is usually under-reported, and scales such as the Epworth Sleepiness Scale[26] or the Barcelona Sleepiness Index[27] are useful for detection and quantification. In patients with hypersomnolence, clinicians should actively search for cataplexy. Cataplexy is almost pathognomonic of hypocretin-deficient narcolepsy (either primary or secondary, as in anti-Ma2 encephalitis)[28] and is characterised by sudden bilateral loss of muscle tone (with preserved awareness) involving the face, neck, or legs (buckling knees), with or without involvement of the arms, typically triggered by intense emotions, particularly of a positive nature related to mirth.[29]

V-PSG

Complex sleep alterations of suspected autoimmune encephalitis are best evaluated in a stepwise approach with V-PSG (figure 2). Sleep recordings might objectively confirm the absence or reduction of sleep and aid in determining sleep patterns. Sleep time might be reduced due to long sleep-latencies, fragmented sleep, or early awakenings, and potential causes (eg, sleep apnoeas fragmenting sleep) can be recorded too. Sometimes, altered sleep patterns might be restricted to particular sleep stages.

The absence of normal NREM sleep features (ie, spindles, K-complexes, and high-amplitude delta slowing), are sensitive disease markers in patients with autoimmune encephalitis. In patients with Morvan syndrome, for instance, all normal features of NREM sleep are completely lost, whereas in patients with anti-IgLON5 disease they are absent only during parts of the night (figure 2).[3,16] These unconventional sleep patterns have been described by different authors with different terms including ambiguous sleep, status dissociatus, subwakefulness, or undifferentiated NREM sleep, but the actual differences among them need to be ascertained.[7,17,31,32]

REM sleep can be reduced or absent, or manifest abnormalities such as the absence of normal electromyogram atonia, with excessive intermittent (phasic) or continuous (tonic) electromyogram activity, and associated jerky, vigorous movements (ie, REM sleep behaviour disorder). Synchronised video recording is crucial to characterise the different movements occurring along the night, distinguishing awake movements from sleep-related movements and distinguishing quasi-purposeful movements typical of oneiric stupor or undifferentiated NREM sleep from the more vigorous movements characteristic of REM sleep behaviour disorder (figure 2). Finally, daytime sleep assessment (with a multiple sleep latency test), serves to measure daytime sleepiness objectively and identify episodes of sleep onset in REM, which can occur in patients with anti-Ma2 encephalitis and secondary narcolepsy.

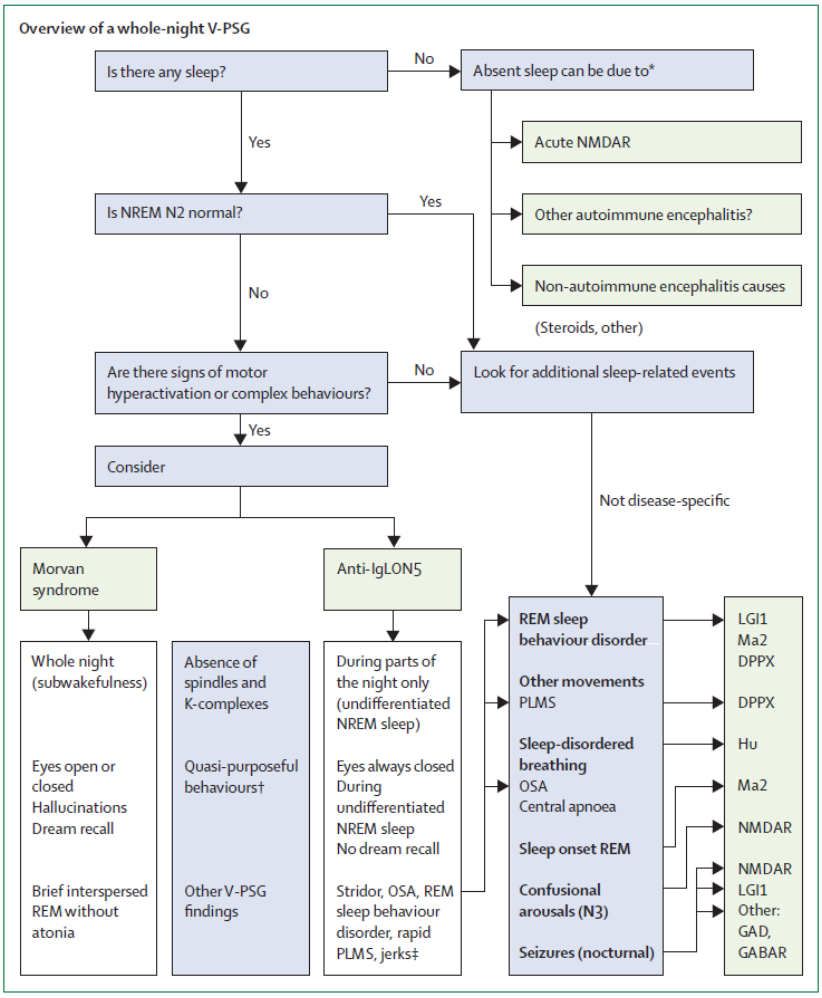

Figure 2: **Stepwise evaluation of nocturnal V-PSG in patients with suspected autoimmune encephalitis**
V-PSG assessment should start with an overview of the whole-night recording, looking for periods of sleep along with associated behaviours. In sleep periods, it is crucial to identify the presence of normal features of NREM N2. Absent sleep spindles and K-complexes with accompanying behavioural and motor abnormalities (eg, quasi-purposeful behaviours) should raise suspicion of autoimmune encephalitis. These combined features can be seen in Morvan syndrome and anti-IgLON5 disease, with some differing features, as indicated. In all clinical scenarios in which sleep is present, other sleep-related V-PSG events should be explored, such as REM sleep behaviour disorder, other movements, sleep-disordered breathing, sleep-onset REM, confusional arousals, and seizures. These events can occur in isolation in autoimmune encephalitis and in non-autoimmune conditions. What finally outlines the specific clinical picture is the combination of the different sleep symptoms in association with other daytime symptoms (eg, cognitive, behavioural, psychotic, and epileptic). GABAR=GABAa and GABAb receptor encephalitis. GAD=glutamic acid decarboxylase encephalitis. NREM=non-rapid eye movement. OSA=obstructive sleep apnoea. PLMS=periodic limb movements during sleep. REM=rapid eye movement. V-PSG=video-polysomnography. *Complete absence of sleep is frequent in the acute phase of anti-NMDA receptor encephalitis; severely reduced sleep (but with scarce V-PSG) has been reported in isolated cases of anti-LGI1 and anti-DPPX. †In Morvan syndrome, the absence of recognisable features of NREM combined with subwakefulness and motor hyperactivation is known as agrypnia excitata. Quasi-purposeful behaviours with dream recall are also described as oneiric stupor[30] (video 1). ‡See video 2.

Sleep disorders in specific autoimmune encephalitis

There is evidence that the frequency, type, and intensity of sleep disorders vary according to the specific autoimmune encephalitis and are most likely a manifestation of the effects of the antibodies or associated immune responses on their specific targets. Different mechanisms of disease have been identified depending on whether the antibodies target cell surface antigens, in which case the antibodies are directly pathogenic, or intracellular antigens, in which case the antibodies are biomarkers of immune mechanisms, probably mediated by cytotoxic T cells.[33] These

See online for video 2

	Main sleep symptoms in patients	Protein function	Antibody effects	Additional information related to sleep
NMDAR (GluN1)	Insomnia (acute phase), hypersomnia (recovery), confusional arousals (at least during recovery)	Ionotropic glutamate receptors; essential for excitatory synaptic transmission	Internalisation of NMDAR; reduction of NMDAR-mediated currents; disruption of crosstalk between NMDAR and dopamine receptors;[34,35] in animal models, the antibodies cause decrease of memory, depressive-like behaviour, anhedonia, psychotic features, and decrease threshold for seizures;[36] sleep studies not done yet	In mice, selective NMDAR antagonists produce total inhibition of sleep for 3 h, followed by rebound enhancement of slow-wave sleep;[37] sleep deprivation in mice causes cumulative phosphorylation of NMDAR, reverted with sleep;[38] dopamine D1 and D2 are involved in the induction of hyperarousal[39]
AMPAR (GluA1, GluA2)	Insomnia, hypersomnia (information very limited)	Ionotropic glutamate receptors; mediate fast excitatory synaptic transmission	Internalisation of AMPA receptors; replacement of GluA2-containing receptors for GluA1 homomeric receptors, which increase synaptic excitability;[40–42] in an animal model the antibodies caused impairment of memory, sleep studies not done yet	*GRIA1* (coding for GluA1) knockout mice: increased sleep latency with normal total sleep time, absence of sleep spindles, reduced efficiency of initial slow-wave sleep after sleep deprivation (non-restorative sleep)[43]
LGI1 (epitempin, leucine-reach repeat)	Insomnia, REM sleep behaviour disorder	Neuronal secreted protein that interacts with the presynaptic proteins ADAM23 and Kv1·1 potassium channel, and the postsynaptic proteins ADAM22 and AMPA receptor; regulates synaptic transmission and excitability	Inhibition of LGI1 interaction with ADAM22 and ADAM23; decrease of levels of Kv1·1 and AMPAR along with neuronal hyperexcitability;[44,45] in an animal model the antibodies caused memory impairment,[45] sleep studies not done yet	In humans, mutations of LGI1 cause inherited epilepsy; sleep has not been studied; antibodies bind hypothalamic neurons,[46] and hypothalamic dysfunction might explain hyponatremia (antidiuretic hormone neurons), episodes of hypothermia, and sleep dysregulation; in REM sleep behaviour disorder cat models with brainstem lesions, further lesion of the amygdala produces intensification of aggressive behaviours during REM sleep[47]
Caspr2 (discoidin-like and laminin G1 domains)	Insomnia, Morvan syndrome	Interacts with Kv1·1/Kv1·2 (voltage-gated potassium channels) in myelinated axons (CNS, peripheral nervous system) facilitating nerve conduction; in the CNS, it operates as a cell-recognition molecule in inhibitory synapses[21]	In cultures of neurons: the antibodies alter the levels of gephyrin clusters in inhibitory synapses, resulting in central hyperexcitability[48]	*KNAC2* (coding for Kv1·2) knockout mice have increased wake time with decreased NREM sleep time;[49] point mutations at voltage-gated potassium channels–Shaker family genes (Kv1 and others) relate to short-sleeping phenotypes with shorter lifespan in *Drosophila melanogaster*[50]
DPPX (N-terminus of DPPX protein)	Insomnia, periodic limb movements during sleep, REM sleep behaviour disorder, hypersomnia, obstructive sleep apnoea	Modulates gating of VGCK type Kv4·2 (attenuate back-propagation of action potential)	In cultures of neurons: the antibodies cause a decrease of density of surface DPPX and Kv4·2[51]	*KCND2* (coding for Kv4) mutations in *Drosophila melanogaster*: delayed sleep onset rescued by restoring Kv4 expression, supporting its role in sleep–wake transition[52]
IgLON5 (Ig-like domain 2)	Insomnia, NREM parasomnia, REM sleep behaviour disorder, obstructive sleep apnoea; stridor, excessive daytime sleepiness	Unknown	In cultures of neurons: irreversible internalisation of IgLON5; neuronal loss, deposits of tau (unclear mechanism)[7]	Autopsy studies in humans show neuronal loss in brainstem medulla most likely affecting: (1) parafacial zone* (centre for NREM sleep initiation); (2) nucleus ambiguous (respiratory centres and vocal cord control); (3) ventral medulla (generator of REM sleep atonia)[53]
Ma2	Symptomatic narcolepsy	Unknown	Passive transfer experiments negative; pathogenic effects related to cytotoxic T-cell mechanisms[28,54]	Autopsy studies in humans show loss of hypothalamic neurons, including hypocretin neurons, in patients with secondary narcolepsy and Ma2 antibodies[55]
AQP4	Symptomatic narcolepsy	Water channel protein that conducts water through the cell membrane; expressed in astrocytes	In animal models: antibody-mediated complement cytotoxicity in areas of expression of AQP4, particularly areas in contact with CSF[56]	MRI studies show hypothalamic lesions in patients with secondary narcolepsy and AQP4 antibodies[57]
Hu	Central alveolar hypoventilation	RNA-binding protein	Passive transfer experiments negative; pathogenic effects related to cytotoxic T-cell mechanisms[25,54]	Autopsy studies in humans show loss of brainstem neurons, most likely affecting respiratory centres[58]

REM=rapid eye movement. NREM=non-rapid eye movement. *Parafacial zone is a GABAergic NREM sleep inducing centre in rats and an analogous centre is probably present in humans and damaged in patients with anti-IgLON5 disease. However, there is no information about this nucleus in autopsy studies of this disease.

Table 1: **Summary of protein targets of autoimmune encephalitis, antibody effects, and potential involvement of the antigens in sleep disorders**

cell-mediated mechanisms cause neuronal loss at specific brain regions that vary according to the syndrome, and often allow tracing the pathophysiological mechanisms of sleep dysfunction, like hypothalamic lesions causing narcolepsy in patients with anti-Ma2 encephalitis, or brainstem damage causing central hypoventilation in patients with anti-Hu encephalitis. The exact mechanisms of how cell surface antibodies cause sleep dysfunction are unknown. The pathogenicity of these antibodies has been shown in experimental studies using cultured neurons

	Approximate number of reported cases; sleep symptoms (%)*	Sleep symptom			V-PSG findings					
		Insomnia	Abnormal sleep behaviour	Excessive daytime sleepiness (hypersomnia)	NREM sleep: spindles and K-complexes and N3 sleep stage	REM sleep	Quasi-purposeful behaviours	Periodic limb movements during sleep or other NREM movements	Obstructive sleep apnoea†	Stridor
NMDAR	>2000; 21–100%[6,23]	Almost universal at onset;[6] can be severe	Reported in 30% in one series (confusional arousals)[6]	Frequent in the recovery phase[6]	Normal[6]	Normal	Absent	Absent	Absent	Absent
LGI1‡	>500; 65%[59]	Frequent; can be severe[59]	Reported (REM sleep behaviour disorder)[8,22]	Reported[8]	Normal[60]	REM sleep behaviour disorder reported (acute phase)[8,22]	Absent	Unknown	Absent	Absent
Caspr2‡	200; 55% In series of Morvan syndrome: 60; 93%[21,61]	Almost universal[21]	Very frequent (quasi-purposeful behaviours, hallucinations)[30,31]	Reported[21]	Decreased or absent[3,8]	Decreased; brief periods of REM with and without atonia[3,8]	Very frequent, eyes open or closed; dream recall[3]	Frequent (jerks, motor hyperactivation)[3,8,30]	Absent	Absent
DPPX	50; 45%[17]	Frequent[17,51,62]	Reported (REM sleep behaviour disorder, jerks)[17,51]	Reported[17,51]	Ambiguous sleep reported[17,51,62]	REM sleep behaviour disorder reported[51]	Reported[17,51]	Frequent (periodic limb movements during sleep)[17]	Reported (rare)[17]	Absent
AMPA	80; 22%[63-66]	Reported[63,64]	Unknown	Reported[63,64]	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Ma2‡	120; 30–45%[2,8,67]	Absent	Reported (REM sleep behaviour disorder)[22]	Frequent, can be severe (with cataplexy)[28]	Normal[22]	REM sleep behaviour disorder reported (within secondary narcolepsy)[22]	Absent	Absent	Absent	Absent
IgLON5	>100; ≥80%[18,68]	Frequent, rarely severe[13,68]	Very frequent (quasi-purposeful behaviours, jerks)[13,19,69-72]	Frequent, can be severe, improves with continuous positive airway pressure therapy[16,68]	Absent in some parts of the night, normal in others[16,19]	REM sleep behaviour disorder frequent[16,68,71]	Very frequent, eyes always closed (highest intensity during undifferentiated NREM sleep); no dream recall[16,19,70-72]	Very frequent (rapid periodic limb movements during sleep, jerks)[16]	Very frequent[18,68]	Frequent[18]

Reported=described in single case reports or in small case series where the symptom has not been systematically assessed, so the frequency is unknown. Frequent=reported in >50% of the patients. Very frequent=reported in >75%. Almost universal=reported in >90% of the patients. Ambiguous sleep=sleep stages cannot be differentiated. REM=rapid eye movement. NREM=non-rapid eye movement. V-PSG=video-polysomnography. *The global percentage of sleep symptoms in each autoimmune encephalitis and frequencies displayed for particular symptoms are estimates based on published data. †Absent obstructive sleep apnoea as frequency not different from general population. ‡Symptoms refer to anti-LGI1 associated limbic encephalitis, anti-Caspr2 associated Morvan syndrome, and anti-Ma2 with hypothalamic involvement.

Table 2: Sleep symptoms and V-PSG findings in specific autoimmune encephalitis

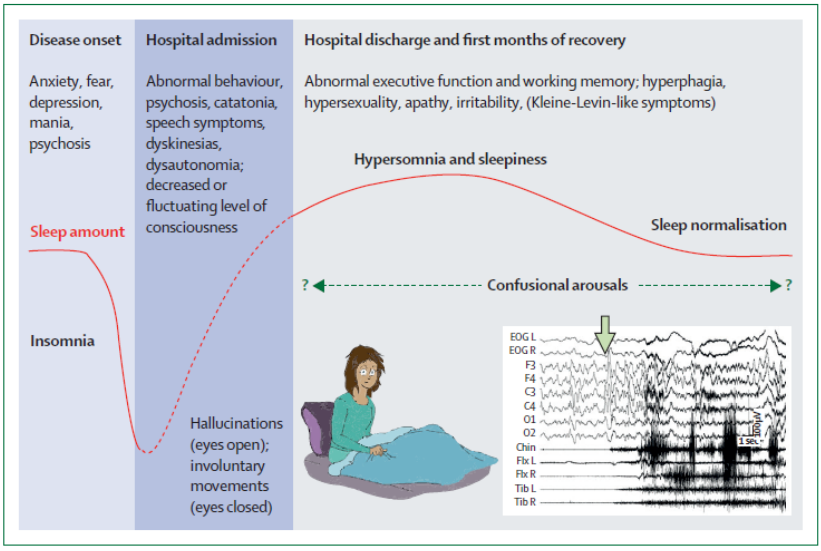

Figure 3: **Two-stage evolution of sleep disorders in patients with anti-NMDA receptor encephalitis**
Acute and severe insomnia form part of the initial presentation of the disease, and often precede other symptoms. Insomnia persists during the first days of admission, at disease peak, without response to hypnotic drugs. After the acute phase of the disease that might last several weeks, there is a progressive shift in the sleep pattern and most patients develop hypersomnia, with more than 10 h of daily sleep and long daytime naps in association with behavioural symptoms (eg, hyperphagia and hypersexual behaviour) sometimes resembling a Kleine-Levin syndrome (although without relapsing-remitting features). Overall, hypersomnia can persist for many months (rarely years) despite tapering or removing sedative medications and overlaps with the recovery phase of the disease. During this phase, patients can have confusional arousals during sleep: they suddenly open the eyes, staring or looking around disoriented or frightened; they often sit up or talk, resuming normal sleep thereafter. The polysomnography segment shows normal NREM N3 sleep (left) abruptly interrupted by an arousal (green arrow), with persistent frontal high-voltage delta EEG activity and increased electromyogram activity (indicating movement). Chin=mentalis muscle. EOG=electrooculogram. Flx L=flexor digitorium superficialis muscle left. Flx R=flexor digitorium superficialis muscle right. NREM=non-rapid eye movement. Tib L=anterior tibialis muscle left. Tib R=anterior tibialis muscle right.

See online for video 3

and animal models (table 1).[7,21,25,28,34–58] Although these antibodies cause multiple symptoms (eg, memory deficit, anhedonia, depressive-like behaviour, psychotic features), their effects on sleep function have not been assessed, and that should be an aim of future studies. In the next section, we focus on the main sleep disorders described in distinct autoimmune encephalitis (table 2).[3,6,8,13,16–19,21–23,28,30,31,51,59–72]

Encephalitis with antibodies against neuronal surface antigens

Anti-NMDA receptor encephalitis

Anti-NMDA receptor encephalitis usually affects children and young adults, predominantly female, and is characterised by acute-onset neurological and psychiatric symptoms including psychosis, agitation, seizures, abnormal movements, decreased level of consciousness, and dysautonomia.[73] Patients usually recover after immunotherapy and tumour removal (if applicable), although the recovery is slow, often taking months or even years.[73]

Clinical experience with patients who have anti-NMDA receptor encephalitis suggests that sleep disorders are frequent,[23,74,75] but are poorly characterised.[73,75,76] A study specifically addressed sleep function in a cohort of 18 patients with anti-NMDA receptor encephalitis and found that all patients had important alterations.[6] At disease onset, up to 90% of patients had insomnia, sometimes preceding (even by weeks) any other symptom. At the peak of the disease, sleep time and sleep need were severely reduced for several days or weeks, but without daytime sleepiness.[6,15,75,77] During recovery, a shift in the sleep pattern occurred and patients transitioned into a period of hypersomnia, with increased night-time and daytime sleep. Associated behavioural abnormalities such as hyperphagia (sometimes with episodes of nocturnal eating), hypersexual behaviours (ranging from flirting on social media to troublesome behaviours prompting readmission at psychiatric wards), apathy, or irritability were common, similar to that of the Kleine-Levin syndrome, although no periodic recurrences were observed.[6,78–80] Despite normal sleep architecture, V-PSG recordings during the recovery phase showed confusional arousals in a third of patients, without previous history of NREM sleep parasomnias, suggesting a direct relationship with the encephalitis (figure 3; video 3).[6] It is unclear whether confusional arousals are limited to the recovery phase or are residual from a process already occurring in the acute phase.

The shift from insomnia to hypersomnia during the course of the disease is in line with the concept that during the active phase of the disease (when inflammatory changes are most prominent) the clinical features (predominantly positive symptoms of psychosis, dyskinesias, and autonomic dysfunction) are different from features observed during the recovery phase (predominantly negative symptoms and executive dysfunction). Importantly, hypersomnia persists beyond withdrawal of medications, such as antipsychotics, antiepileptics, or benzodiazepines, suggesting that hypersomnia forms part of the disease. A task for this feature is to evaluate the consequences of long-term sleep dysfunction or the effects of sleep-modifying therapies on cognitive or global recovery of NMDA receptor encephalitis.

Anti-LGI1 limbic encephalitis

Most patients with LGI1 antibodies are rarely associated with tumours and show limbic encephalitis at a median age of 60 years.[59] Symptoms follow a temporal sequence, presenting with faciobrachial dystonic seizures (30–50% of patients), focal non-motor seizures, and inability to form memories, followed by cognitive impairment, behavioural symptoms, and tonic-clonic seizures. Less frequently, patients might develop Morvan syndrome with or without concurrent Caspr2 antibodies, or isolated seizures.[59]

Information about sleep in patients with anti-LGI1 limbic encephalitis is succinct, but insomnia seems prevalent (45–65% of patients), sometimes severe, appearing relatively early in the course of the disease, and often with excessive daytime sleepiness.[59,81,82] Small case series or case reports with V-PSG recordings show low sleep efficiency, with absence of sleep in some cases.[8,60,83] REM sleep behaviour disorder is common in the acute phase of the disease; the initial description of patients with limbic

encephalitis and voltage-gated potassium channel antibodies (subsequently proven to be anti-LGI1)[84] described nightmares and dream-enacting behaviours typical of REM sleep behaviour disorder in five of six patients, with V-PSG confirmation in two of the five assessed patients. Similar findings have been reported since then.[8,60,85]

Immunotherapy usually resolves REM sleep behaviour disorder and improves sleep patterns,[8,22,60,82,83] although, at least 20% of patients remain with milder insomnia and poor perceived sleep quality for several months thereafter.[59] Further studies are needed to assess the full spectrum of sleep problems in patients with anti-LGI1 encephalitis.

Caspr2 antibodies and Morvan syndrome

Caspr2 antibodies react with the juxtaparanodal region of myelinated peripheral nerves and with neurons of many brain regions, resulting in different clinical phenotypes including neuromyotonia, limbic encephalitis, Morvan syndrome, and cerebellar symptoms. Around 20% of patients with Caspr2 antibodies (50% of those with Morvan syndrome) have an underlying thymoma.[61] Response to immunotherapy is usually good, although relapses might occur.[5,86]

Morvan syndrome has been described since 1890. The disorder is characterised by the combination of peripheral nerve hyperexcitability (neuromyotonia and neuropathic pain), severe insomnia, autonomic dysfunction (hyperhidrosis, hyperthermia, cardiovascular instability, urinary incontinence, and erectile dysfunction), encephalopathy with confusion, and frequent visual hallucinations throughout the day and night.[21] Although initially considered associated with voltage-gated potassium channel antibodies,[87] later evidence showed that about 80% of patients with Morvan syndrome have Caspr2 antibodies, sometimes with concurrent LGI1 antibodies.[21]

Insomnia affects up to 90% of patients with Morvan syndrome and is an early symptom.[21] Some patients develop a complex disorder, in which partial insomnia evolves (in weeks or a few months) to a complete inability to initiate and sustain sleep, with severe autonomic and motor hyperactivation throughout the 24 h (referred to as agrypnia excitata). Patients have frequent episodes of quasi-purposeful behaviours, in which they seem to represent daily life activities (eg, eating, dressing, combing their hair, doing job-related tasks, and talking), with eyes closed or open, interpreted as sleep with dream enactment, called oneiric stupor in this clinical context, because once aroused some patients recall the content of an oneiric scene (video 1).[30,31]

The term agrypnia excitata was coined to describe the sleep disorder of patients with fatal familial insomnia. These patients spend long periods of time in a state between wakefulness and sleep (subwakefulness),with slowing of the normal awake alpha rhythm, absence of NREM sleep markers (ie, spindles, K-complexes, and high voltage delta slowing), and presence of interspersed short REM sleep periods (without electromyogram atonia) accompanied by episodes of quasi-purposeful behaviours.[88] The concept of agrypnia excitata was later extended to Morvan syndrome,[31] in which some similarities were observed, although reports with information about sleep symptoms and V-PSG findings are scarce,[3,5,30,32,86,89–92] and the possibility that some patients were awake and hallucinating cannot be completely excluded.

Regardless of the term used, Morvan syndrome should be considered in patients who develop severe acute-onset insomnia, profuse perspiration, and 24 h motor hyperactivation with dreaming or hallucinatory-like episodes simulating daily-life activities, especially if combined with neuromyotonia. These patients should be examined for the presence of Caspr2 antibodies and undergo tumour screening, particularly for thymoma.

DPPX encephalitis

For DPPX encephalitis, antibodies against DPPX associate with CNS hyperexcitability, manifesting as hyperekplexia, myoclonus, tremor, cognitive dysfunction, and seizures, also frequently with prodromal diarrhoea and prominent weight loss. The protracted symptom progression often results in diagnostic delay. Most patients respond to immunotherapy, with complete or partial resolution of symptoms.[17,62]

In the largest case series,[17] about 50% of 20 patients had sleep symptoms, and 30% suffered insomnia. Five patients underwent V-PSG, showing periodic limb movements during sleep. Parasomnias seem to occur frequently but the scarce data available precludes their characterisation. For example, REM sleep behaviour disorder, parasomnia, ambiguous sleep, jerks, and spasms are mentioned but without further details.[17,51,62] Overall, sleep dysfunction is probably important in this disease, but systematic assessments in larger number of patients are needed.

Anti-AMPA receptor encephalitis

AMPA receptor antibodies cause limbic encephalitis, with additional extralimbic symptoms in about 40% of patients. A few patients present with rapidly progressive dementia or psychosis.[33] Underlying tumours are found in 70% of patients, mainly small-cell lung carcinoma, thymoma, or gynaecological cancers, often with concurrent onconeuronal antibodies, and have poorer treatment responses than other autoimmune encephalitis.[64]

Among approximately 70 reported patients with anti-AMPA receptor encephalitis, 20% had assessable information on sleep symptoms.[63–66] At disease onset, insomnia was the most frequently reported sleep symptom; two patients had hypersomnia, one of them with an inflammatory hypothalamic lesion. Both insomnia and hypersomnia occurred during recovery too. In general, clinical descriptions of sleep are poor, V-PSG studies are absent, and potentially confounding treatment-related effects are not considered, which substantially limit the interpretation.

Encephalitis with antibodies against intraneuronal antigens

Anti-Ma2 encephalitis

Anti-Ma2 encephalitis is characterised by limbic, diencephalic, and upper brainstem dysfunction, occurring in any combination. Single cases of cerebellar ataxia, myelopathy, radiculoplexopathy, chorea, and hearing loss have been reported.[28,93–96] Men younger than 45 years usually have an underlying testicular germ cell tumour (associated with Ma2 antibodies), whereas women of all ages and older men have lung or gastrointestinal cancers (with Ma2 and Ma1 antibodies).[28,93]

Patients with hypothalamic involvement could develop secondary narcolepsy. A comprehensive description of 38 patients with anti-Ma2 encephalitis showed that 12 (32%) patients, all with diencephalic involvement, developed excessive daytime sleepiness, of which two patients had additional cataplexy or hypnagogic hallucinations.[28] Acute-subacute hypersomnolence is usually the presenting symptom of secondary narcolepsy, frequently with unintended lapses into sleep.[22,55,96,97] These patients might have REM sleep behaviour disorder, which tends to be mild and has always been described as part of the narcolepsy syndrome. In patients with anti-Ma2 encephalitis and narcolepsy, CSF hypocretin concentrations (a biomarker of primary narcolepsy) are low.[22,28,55,97] Autopsy studies in patients with anti-Ma2 encephalitis and narcolepsy have shown neuronal loss in the lateral hypothalamus, including, but not restricted to, hypocretinergic neurons; this finding is different from those of patients with idiopathic narcolepsy in which neuronal loss is restricted to these neurons.[55] Improvement of narcolepsy symptoms after treatment of encephalitis was reported in one patient with low hypocretin concentrations, suggesting potential clinical reversibility.[28]

Anti-Hu brainstem encephalitis

Anti-Hu antibodies are typically associated with paraneoplastic encephalomyelitis, affecting limbic structures, brainstem, cerebellum, spinal cord, or dorsal root ganglia. The disorder usually associates with small-cell lung cancer, and the response to treatment is poor.[98] Patients with anti-Hu brainstem encephalitis often develop central alveolar hypoventilation along with other brainstem symptoms. The involvement of the dorsal medulla and pontine tegmentum[58] results in the inability to automatically control respiration during drowsiness or sleep. Central alveolar hypoventilation has also been described in a patient with anti-Ri antibodies and breast cancer.[99]

In other classical paraneoplastic syndromes with antibodies against Yo, CV2, SOX1, or MAP1B, no specific sleep disorders have been described. In patients with glutamic acid decarboxylase antibodies, there are no studies specifically addressing sleep disorders, although patients with limbic encephalitis might have insomnia at disease onset and patients developing drug-resistant epilepsy often have nocturnal seizures.[100]

Other antibody-mediated disorders of the CNS

Anti-IgLON5 disease

Anti-IgLON5 disease is characterised by a complex sleep disorder associated with brainstem dysfunction and gait instability, starting around age 50–60 years, without association to cancer. These core manifestations are present in about 70% of patients,[18] although different phenotypes have been described: (1) sleep disorder with insomnia, parasomnia, and sleep-disordered breathing; (2) bulbar syndrome with dysphagia, dysarthria, and episodes of respiratory failure (either related to laryngeal obstruction or central hypoventilation); (3) progressive supranuclear palsy-like syndrome with gait instability and gaze palsy; (4) cognitive decline, often with chorea; (5) peripheral nervous system manifestations reminiscent of motor neuron disease or peripheral nerve hyperexcitability; and (6) cerebellar syndrome with tremor.[18,72,101–103] The pathophysiology of anti-IgLON5 disease is intriguing because it associates with features suggesting autoimmunity (eg, autoantibodies causing irreversible decrease of cell surface IgLON5, and a tight HLA link with the alleles *DRB1*1001* and *DQB1*0501*),[104,105] but the pathological findings often suggest neurodegeneration. These findings include neuronal loss and deposits of phosphorylated tau predominantly involving the hypothalamus, dorsal brainstem, and medulla, where centres and nuclei are present that are involved in NREM sleep initiation (parafacial zone), REM sleep atonia (ventral medulla), or control of breathing and vocal cord motility (nucleus ambiguous), thus offering a plausible explanation for most of the sleep manifestations.[53]

The fact that this disease is rare, relatively unknown, and frequently progresses slowly (over months or years), probably results in diagnostic delays, which might explain why immunotherapy is less effective than in antibody-mediated encephalitis.[16,18,68,106]

The sleep disorder in anti-IgLON5 disease is so unique that it led to the discovery of the disease,[7] and is also distinctive enough to be conspicuous when combined with the aforementioned presenting phentoypes.[7,13,18,68,69] 70% of patients might complain of insomnia with non-restorative, fragmented sleep and excessive daytime sleepiness. Partners who share a bed additionally report witnessed sleep apnoeas, laryngeal stridor, and abnormal behaviours during sleep, including frequent vocalisations and various motor activities, from simple jerky movements to complex quasi-purposeful behaviours (figure 1D–F; video 2).[16]

V-PSG recordings show that sleep is broken and the sleep time moderately reduced, but severe reduction of sleep efficiency is rare.[20,69] The most characteristic finding is abnormal NREM sleep at sleep onset, with an absence of vertex waves, sleep spindles, K-complexes, and delta slowing, that prevents any further differentiation of NREM (undifferentiated NREM); vocalisations and abnormal behaviours are of the highest intensity in this period. Characteristically, a progressive normalisation of NREM sleep (with the emergence of K-complexes and sleep

spindles) and behaviour occurs during the night, unless sleep is interrupted by an awakening, which seems to reset the process.[16,19,70–72] Additionally, most patients have REM sleep behaviour disorder with relatively discrete behavioural symptoms, mostly body jerks of the trunk and proximal limbs, and occasionally other more elaborated movements, but these are rarely violent.[16,68,71]

If patients are systematically assessed, obstructive sleep apnoea occurs in most patients, with associated nocturnal laryngeal stridor in many patients.[18,68] Both symptoms respond to CPAP therapy, and daytime sleepiness also improves. However, as the disease progresses, patients might need more intensive therapies, eventually requiring tracheostomy and mechanical ventilation.[16,101] Half of the patients can suddenly die, often during sleep,[18,69,71] suggesting that respiratory or cardiac causes are involved.[18]

Patients who show clinical (generally subjective) improvement of sleep symptoms have been reported, but substantial improvement of V-PSG attributable to immunotherapy is rare.[16,19] NREM sleep improved in one patient after high-dose intravenous steroids (with persistence of apnoeas and REM sleep behaviour disorder), but while still on immunotherapy, the NREM sleep abnormalities reappeared 3 months later.[16] Longer and prospective series are needed to better understand this intriguing disease.

Neuromyelitis optica spectrum disorder and aquaporin 4 antibodies

Secondary narcolepsy is one of the core clinical features of neuromyelitis optica spectrum disorder,[107] accompanied by typical MRI lesions involving the hypothalamus or periependymal surface of the third ventricle, and additional manifestations of an acute hypothalamic syndrome (eg, hypotension, arrhythmias, deregulated body temperature, syndrome of inappropriate antidiuretic hormone secretion, or endocrine imbalance).[108] Almost all reported cases of narcolepsy in this disorder are in Japanese women with severe acute-onset hypersomnia (up to 16 h of daily sleep) often associated with sleep attacks, but without cataplexy, hypnagogic hallucinations, or sleep paralysis.[108–110] Despite the absence of cataplexy, CSF hypocretin concentrations are low,[108–110] and multiple sleep latency tests show short mean sleep latency and sleep onset REM periods,[109] fulfilling the criteria of narcolepsy.[14] Immunotherapy usually resolves the hypersomnolence and normalises hypocretin concentrations.[108,110,111]

Management of sleep disorders in autoimmune encephalitis

Treatment of sleep disorders in patients with autoimmune encephalitis is symptomatic and should be given along with immunotherapy. Future studies should find out if optimising sleep quality might improve the recovery of other clinical features, such as cognitive performance or seizures. There are no specific drugs for the sleep symptoms of autoimmune encephalitis; medications used in conventional sleep disorders might be less effective in patients with autoimmune encephalitis.[6,8] Stimulants, hypnotic-sedative drugs, or anticataplectics have been used for sleepiness, insomnia, or cataplexy with variable results.[77,96,101,112]

It is important to be aware that drugs used to treat autoimmune encephalitis might alter sleep. For example, steroids produce insomnia, neuroleptics hypersomnolence, and some benzodiazepines (eg, zolpidem) can cause abnormal behaviours during sleep.[113–115] These side-effects are common in general clinical practice and are probably under-reported in patients with autoimmune encephalitis due to the difficulty in distinguishing them from the symptoms of the disease. Disease activity can be detected by closely monitoring sleep symptoms, appearing early at disease onset or at relapses (eg, insomnia with anti-NMDA receptor, anti-LGI1, or anti-Caspr2)[6,59,61] or indicating progression of the disease (eg, parasomnias and sleep-disordered breathing in anti-IgLON5 disease).[16]

Search strategy and selection criteria

We searched PubMed for articles published in English from Nov 1, 1991, to Aug 11, 2020, using the search terms "encephalitis", "autoimmune", "antibodies", "NMDA receptor", "AMPA receptor", "LGI1", "Caspr2", "DPPX", "IgLON5", "Ma2", "Hu", "GAD65 antibodies", "sleep", "REM", "NREM", "insomnia", "hypersomnia", "somnolence", "parasomnia", "REM sleep behavior disorder", "narcolepsy", and "Morvan syndrome". The final reference list was generated on the basis of relevance to the topics covered in this Review.

Conclusions and future directions

Sleep disorders are an essential part of autoimmune encephalitis and have relevant clinical implications; therefore, an effort should be made to recognise them. The neural mechanisms behind sleep symptoms might be diverse, spanning local lesions and more global dysfunction of sleep centres. Systematic and unified clinical assessments of sleep disorders in patients with autoimmune encephalitis are needed to gather multicentre data and to identify the real prevalence and distinctive features in each type of autoimmune encephalitis. Comprehensive and accurate clinical and V-PSG descriptions, and the development of animal models, are crucial to better understand the pathophysiological mechanisms involved. These studies will advance our knowledge in sleep physiology and might help to develop mechanism-specific treatments (eg, allosteric modulation of receptors)[116] in addition to immunotherapy, which might accelerate general symptom improvement, including, among others, sleep dysfunction of most patients.

Contributors

AM-L wrote the initial draft of the manuscript. FG, JD, and JS provided additional information, reviews, and editing changes.

Declaration of interests
JD receives royalties from Athena Diagnostics for the use of Ma-2 as an autoantibody test, and from Euroimmun for the use of NMDA, GABAb receptor, GABAa receptor, DPPX, and IgLON5 as autoantibody tests; and has received research support from SAGE Therapeutics. FG receives royalties from Euroimmun for the use of IgLON5 as an autoantibody test. AM-L and JS declare no competing interests.

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HYPOTHESES

1. Sleep disorders in anti-NMDAR encephalitis are rarely reported in the literature, but a systematic assessment of sleep symptoms will show a higher-than-expected prevalence.

2. Sleep disorders persist in the post-acute stage of anti-NMDAR encephalitis.

3. A systematic V-PSG assessment during the post-acute stage of anti-NMDAR encephalitis may reveal previously unreported sleep disorders.

4. Sleep disorders have not been well characterized in anti-LGI1 encephalitis and a systematic assessment may reveal a higher prevalence and variety than previously reported.

5. Sleep disorders persist in the post-acute stage of anti-LGI1 encephalitis.

6. A systematic and longitudinal V-PSG assessment during the post-acute stage of anti-LGI1 encephalitis may uncover sleep disorders previously unreported in this stage of the disease.

7. Seizures may persist in the long term after anti-LGI1 encephalitis and a systematic and longitudinal assessment with nocturnal and daytime EEG may help in the recognition of subclinical seizures or in determining the risk to develop chronic epilepsy.

OBJECTIVES

Objective 1) To determine the frequency and type of sleep disorders in the acute and post-acute stages of anti-N-methyl-D-aspartate receptor encephalitis.

Objective 2) To provide the video-polysomnography characterization of the sleep in the post-acute stage of anti-N-methyl-D-aspartate receptor encephalitis.

Objective 3) To describe the profile of neurologic and sleep alterations in the acute and post-acute stages of anti-leucine-rich glioma-inactivated protein 1 encephalitis.

Objective 4) To provide the video-polysomnography and electroencephalography characterization of the sleep in the post-acute stage of anti-leucine-rich glioma-inactivated protein 1 encephalitis.

MATERIAL, METHODS, AND RESULTS

Publication 1:

Sleep disorders in anti-NMDAR encephalitis

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ARTICLE

Sleep disorders in anti-NMDAR encephalitis

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Abstract

Objective

To describe the sleep disorders in anti–NMDA receptor encephalitis (anti-NMDARe).

Methods

Patients recovering from anti-NMDARe were invited to participate in a prospective observational single-center study including comprehensive clinical, video-polysomnography (V-PSG) sleep assessment, and neuropsychological evaluation. Age- and sex-matched healthy participants served as controls.

Results

Eighteen patients (89% female, median age 26 years, interquartile range [IQR] 21–29 years) and 21 controls (81% female, median age 23 years, IQR 18–26 years) were included. In the acute stage, 16 (89%) patients reported insomnia and 2 hypersomnia; nightmares occurred in 7. After the acute stage, 14 (78%) had hypersomnia. At study admission (median 183 days after disease onset, IQR 110–242 days), 8 patients still had hypersomnia, 1 had insomnia, and 9 had normal sleep duration. Patients had more daytime sleepiness than controls (higher Barcelona Sleepiness Index, $p = 0.02$, and Epworth Sleepiness Score, $p = 0.04$). On V-PSG, sleep efficiency was similar in both groups, but patients more frequently had multiple and longer confusional arousals in non-REM (NREM) sleep (videos provided). In addition, 13 (72%) patients had cognitive deficits; 12 (67%) had psychological, social, or occupational disability; and 33% had depression or mania. Compared with controls, patients had a higher body mass index (median 23.5 [IQR 22.3–30.2] vs 20.5 [19.1–21.1] kg/m^2; $p = 0.007$). Between disease onset and last follow-up, 14 (78%) patients developed hyperphagia, and 6 (33%) developed hypersexuality (2 requiring hospitalization), all associated with sleep dysfunction.

Conclusions

Sleep disturbances are frequent in anti-NMDARe. They show a temporal pattern (predominantly insomnia at onset; hypersomnia during recovery), are associated with behavioral and cognitive changes, and can occur with confusional arousals during NREM sleep.

From Clinical and Experimental Neuroimmunology (H.A., A.M.-L., E.M.-H., T.A., M.R.-J., D.E., F.G., G.S., J.C.-F., A.C., J.D., J.S.), Institut d'Investigació Biomèdica August Pi i Sunyer; Departments of Neurology (A.M.-L., E.M.-H., D.E., N.M., J.D., J.S.) and Child and Adolescent Psychiatry and Psychology (T.A., G.S., J.C.-F.), Hospital Clinic, and Pediatric Neuroimmunology Unit (T.A.), Sant Joan de Déu Children's Hospital, University of Barcelona, Spain; Department of Neurology (J.D.), University of Pennsylvania, Philadelphia; and Institució Catalana de Recerca i Estudis Avançats (J.D.), Barcelona, Spain.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

BMI = body mass index; **DSM** = *Diagnostic and Statistical Manual for Mental Disorders*; **EDS** = excessive daytime sleepiness; **HAM-D** = Hamilton Rating Scale for Depression; **IQR** = interquartile range; **KLS** = Kleine-Levin syndrome; **NMDAR** = NMDA receptor; **NREM** = non-REM; **PANSS** = Positive and Negative Syndrome Scale; **PSG** = polysomnography; **V-PSG** = video-polysomnography; **YMRS** = Young Mania Rating Scale.

Anti–NMDA receptor (NMDAR) encephalitis is an antibody-mediated disease associated with neurologic and psychiatric symptoms that often respond to immunotherapy and tumor removal (when it applies), with a process of recovery that may take up to several months or years. Sleep disorders appear to be frequent, but the severity and complexity of the disease often drive physicians' attention to psychosis, agitation, seizures, abnormal movements, or decreased level of consciousness, which can mask the presence of sleep disorders and complicate their assessment. During the recovery phase, the clinical picture is dominated by cognitive, behavioral, and executive dysfunction, and although the presence of sleep disorders is sometimes suggested, they have not been systematically studied. In large series of patients with anti-NMDAR encephalitis, the occurrence of sleep dysfunction is not mentioned,[1,2] succinctly described as "patients having sleep dysfunction,"[3] or documented as insomnia or hypersomnia predominating either at onset or during recovery, sometimes with conflicting results.[3–6] Systematic reviews and meta-analyses reflecting the extant literature suggest a prevalence of sleep dysfunction ranging from 21% to 39.5%.[7,8] However, the frequency of sleep dysfunction may be more accurately reflected in reports by clinicians taking care of the patients. A study of 32 pediatric patients with anti-NMDAR encephalitis whose clinical information was retrospectively obtained by chart review or phone interviews described the sleep dysfunction as frequent. However, when only the patients who had been visited personally by the authors were considered (n = 8), all had sleep disorders (insomnia more frequent than hypersomnia).[3]

Assessing sleep dysfunction in anti-NMDAR encephalitis is important because it appears to be frequent and can potentially affect neuropsychiatric recovery and quality of life. Here, we report the results in a cohort of patients prospectively recruited during the recovery phase of the disease, along with age-/sex-matched controls, all comprehensively assessed in a single institution. We describe the frequency and type of sleep disorders, along with other features (psychological, psychiatric symptoms, eating disorder, weight gain) that frequently accompany sleep dysfunction.

Methods

Participants and study design

From January 2017 until February 2019, patients who were recovering from anti-NMDAR encephalitis (median interval from symptom onset 6 months, range 3–14 months) and their families were contacted after hospital discharge to participate in a prospective observational study assessing the recovery phase of the disease with no specific mention of sleep disorders. All patients except 1 patient from Munich were initially diagnosed in hospitals in Spain (9 were identified on antibody testing in our laboratory, which is a referral center for autoimmune neurologic diseases, and the rest were referred by their treating neurologists after a national call to all the members of the Spanish Society of Neurology and a network of frequent collaborators). The patient from Munich contacted the investigators to be included in the study. There were no exclusion criteria for patients, and only 3 of 21 identified patients refused to participate because they did not want to travel. The study design includes 5 visits (the initial visit at the time of recruitment and subsequent visits ≈3, 6, 12, and 24 months after recruitment) during which patients undergo neurologic, cognitive, neuroimaging, and EEG studies, as well as comprehensive clinical and video (V)-polysomnography (PSG) assessment of sleep. The current study focuses on the sleep, cognitive, and behavioral investigations performed during the initial visit (which includes 2 days of assessment and 1 night admission) at Hospital Clinic, University of Barcelona. To assess changes in the body mass index (BMI) during the first months of the study, we used information from the second study visit (available from 16 patients). Information about other clinical features at or beyond the second study visit is not yet available for all patients and will be reported as part of a prospective longitudinal study in the future. Healthy volunteers matched by sex and age served as controls after an assessment for psychiatric disorders based on the Structured Clinical Interview for Axis Disorders of the DSM was negative.

Neurologic and sleep assessment

Demographic and clinical data, current medications, and information for rating the Anti-NMDAR Encephalitis One-Year Functional Status[9] score were collected by neurologists with experience in autoimmune diseases and sleep disorders. A neuropsychologist administered the Hamilton Rating Scale for Depression (HAM-D),[10] the Young Mania Rating Scale (YMRS),[11] the Positive and Negative Syndrome Scale (PANSS) for psychotic symptoms,[12] the Global Assessment of Functioning (GAF),[13] and a battery of standardized tests to assess 6 domains of cognitive function (general intellectual abilities, working memory, processing speed, learning and memory, executive function, and attention) (supplementary material, doi.org/10.5061/dryad.0zpc866tt).

A structured interview with the patient and ≥1 family members living with them assessed history of sleep disorders in the

patient and family; patient's current sleep habits and complaints such as sleep-onset insomnia (difficulty falling asleep within 30 minutes); sleep fragmentation (>2 awakenings of >15 minutes); early awakening (waking up >2 hours earlier than desired); daytime naps; excessive daytime sleepiness (EDS; difficulty staying awake during the day, resulting in unintended episodes of sleep); nightmares; dream-enacting behaviors, and other abnormal behaviors during sleep such as confusional arousals, sleepwalking, or sleep terrors.

A semiquantitative analysis of the total amount of daily sleep during the course of the disease was obtained from patients and families at the first study admission visit using a graphic representation (y-axis = score; x-axis = time) of the total daily sleep time (supplemental material, doi.org/10.5061/dryad.0zpc866tt). In addition to the current assessment, patients and relatives were asked to provide the same information retrospectively from disease onset. In 1 case (patient 11), no close relative was available to confirm the patient's self-report. A similar assessment was repeated at the 3- and 6-month follow-up visits.

Current sleep disturbances and nocturnal disability were assessed with the Pittsburgh Sleep Quality Index[14]; EDS with the Barcelona Sleepiness Index[15] and the Epworth Sleepiness Scale[16]; REM sleep behavior disorders with the International Classification of Sleep Disorders-3 criteria[17]; restless legs syndrome (RLS) with the International Restless Legs Syndrome Study Group criteria[18]; and the circadian rhythm type with a self-assessment questionnaire version of the Morningness-Eveningness Questionnaire.[19]

All patients underwent V-PSG, which was performed as reported[20] (supplemental material, doi.org/10.5061/dryad.0zpc866tt). Sleep stages and associated events were scored according to standard criteria[21] with the allowance for REM sleep without atonia. Arousals and motor and vocal manifestations detected in the audiovisual recording during wakefulness were evaluated as previously described (supplemental material).

All the above questionnaires and investigations (except for the longitudinal change of the total amount of daily sleep) were similarly applied to controls.

Statistical analysis

The Fisher exact test or Mann-Whitney *U* test, when appropriate, was used to analyze the clinical and paraclinical features of patients with anti-NMDAR encephalitis compared with age- and sex-matched controls. Missing data were not imputed. Statistical analyses were performed with STATA 13.1 (StataCorp, College Station, TX).

Standard protocol approvals, registration, and patient consents

Written informed consent was obtained from all patients participating in the study. A signed Patient Consent-to-Disclose Form has been obtained for videos of any recognizable patient. The study protocol was approved by the Hospital Clinic Institutional Review Board.

Data availability

Supplemental material is available from Dryad (doi.org/10.5061/dryad.0zpc866tt). Any data not published will be shared anonymized by request from any qualified investigator.

Results

General clinical features

Eighteen patients with anti-NMDAR encephalitis (2 Asian, 1 black, and 15 white; 16 [89%] female) with a median age at disease onset of 26 (range 10–56) years and 21 controls (17 female, median age 23 [range 14–42] years) were included in the study. The first study visit took place a median of 85 (interquartile range [IQR] 48–139) days after hospital discharge and 183 (IQR 110–242) days after disease onset.

At symptom onset, 9 (50%) patients were misdiagnosed with psychiatric disorders (4 anxiety, 2 dissociative or somatoform disorder, 2 bipolar, and 1 acute psychosis), 4 (22%) with encephalitis of unclear etiology (1 suspected viral), 2 (11%) with new-onset seizures, and 3 (17%) without diagnosis of any specific disorder. Eleven patients (61%) recognized an important vital stressor during the 3 months preceding the disease, in 4 cases in association with a reduction of the amount of sleep. Seven patients (39%) were initially admitted to psychiatry wards and transferred days later to neurology on diagnosis of anti-NMDAR encephalitis.

Initial behavioral and sleep symptoms are shown in table 1, and other initial symptoms are shown in table e-1 (doi.org/10.5061/dryad.0zpc866tt). The median Anti-NMDAR Encephalitis One-Year Functional Status score was 1 (IQR 1–2); 2 patients (patients 11 and 18) had a score of 3. All patients had been treated with first-line immunotherapy (14 with steroids and IV immunoglobulin; 2 with steroids, IV immunoglobulin, and plasma exchange; 1 with IV immunoglobulin, and 1 with steroids), 14 with rituximab (4 accompanied by cyclophosphamide), and 3 with long-term oral steroids. The median time between disease onset and first immunotherapy was 28 (range 5–117) days. Four patients (patients 6, 12, 13, and 17) had an ovarian teratoma that was removed after a median time of 36 (range 10–43) days. The median duration of hospital stay was 28 (range 11–195) days, with 8 patients (44%) requiring intensive care support and 4 of them needing tracheal intubation or vasoactive drugs (figure 1).

Premorbid sleep disorders

Six patients reported premorbid sleep problems. Patient 1 had history of sleepwalking and talking, currently inactive. Patients 9 and 12 reported sleep-talking during childhood (which in patient 12 was accompanied by hypnagogic hallucinations). Patient 15 had a history of sleepwalking, currently inactive. Patient 16 had chronic sleep onset and sleep fragmentation insomnia

Table 1 Behavioral and sleep disorders in anti-NMDAR patients

Patient (sex/age, y)	Behavioral and sleep symptoms at disease onset (n days)[a]	Symptoms from hospital discharge to visit 1 (n days)	Visit 1 (study admission)				
			Treatment	Hypersomnia[c] (ESS, BSI scores)	Behavioral symptoms	HAM-D; YMRS; PANSS scores	BMI at V2 (increase since V1), kg/m^2
P1 (M/25)	Childish, irritable, apathy, hypersomnia (27[b])	Hypersexual, compulsive shopping, smoking, hyperphagia, insomnia (86)	ST, LV	No (6, 2)	Hyperphagia, hypersexual, compulsive shopping	7; 10; 45	33.8 (2.4)
P2 (F/12)	Irritable, disorganized, compulsive hyperphagia, bradypsychia, insomnia (56)	Hypersomnia (372)	None	No (2, 1)	None	1; 7; 36	22 (0.7)
P3 (F/22)	Anxiety, psychosis, insomnia, nightmares, IMA (55)	Depressed, hyperphagia, polydipsia, irritability, hypersomnia (35)	None	Yes (10, 0)	Hyperphagia, polydipsia, irritability	15; 5; 54	24.9 (2.6)
P4 (F/14)	Manic, pressured speech, hypersexual, hyperphagia, hallucinations, insomnia, nightmares, IMA (40)	Irritability, intolerant of noise (86)	LV, VP	No (9, 2)	Irritability, intolerant of noise	5; 2; 44	26.7 (3.1)
P5 (F/28)	Apathy; months later manic, psychosis, catatonia, insomnia, nightmares (164[b])	Apathy, hyperphagia, bradypsychia, hypersomnia (51)	ST, RS QT, LV	Yes (13, 2)	Hyperphagia, apathy, bradypsychia	17; 2; 77	35.5 (6.2)
P6 (F/23)	Psychosis, insomnia (53)	Apathy, bradypshychia, hypersomnia (244)	None	No (7, 0)	None	0; 1; 33	20.3 (1.2)
P7 (F/16)	Anxiety, psychosis (catatonia), insomnia, IMA (73)	Emotional lability, impulsivity, hyperphagia, hypersomnia (139)	VP	Yes (12, 2)	Hyperphagia, irritability	0; 2; 35	27.2 (4.9)
P8 (F/29)	Psychosis, hypersomnia, nightmares (44)	Irritability, anxiety, hyperphagia (35)	ST, HL, CZ, LC CB	No (7, NA)	Irritability	7; 2; 55	23.9 (−1.8)
P9 (M/35)	Panic attacks, insomnia (87)	Flat affect, hyperphagia, hypersomnia (78)	LV	No (6, 0)	Hyperphagia	NA; NA; NA	32.9 (2.7)
P10 (F/20)	Euphoric, anxiety, psychosis, insomnia, nightmares (208)	Impulsivity, hypersexual, irritability, childish, hyperphagia, hypersomnia, nightmares (85)	CZ, LC, ZS, PX	Yes (9, 0)	Hyperphagia, irritability, compulsivity, childish behavior	5; 19; 54	22.8 (0.4)
P11 (F/38)	Manic, psychosis, insomnia (59)	Apathy, abulic, irritability, hypersomnia (162)	None	No (12, 1)	No	5; 9; 33	33.1 (2.4)
P12 (F/27)	"Depressed-like," psychosis, insomnia (69)	Lability, apathy, intolerant of noise, hypersomnia (30)	ST	No (4, 0)	Apathy, emotional lability	10; 0; 59	NA in V2 (34.7 in V1)
P13 (F/29)	Anxiety, hyperphagia, flat affect, perplexity, psychosis, insomnia, nightmares (54)	Emotional lability, intolerant of noise, hypersomnia (33 days)	LC	Yes (10, 2)	Emotional lability, intolerant of noise	11; 2; 57	29.1 (5.6)
P14 (F/26)	Anxiety, compulsive shopping, hyperphagia, panic attacks, hypersexual, psychosis (catatonia), insomnia (158)	Apathy, flat affect, hypersomnia (84)	ST, VP, LC, CT	Yes (16, 2)	Flat affect	7; 4; 55	49.6 (3.4)
P15 (F/27)	Psychosis (catatonia), hyperphagia, hypersexual, impulsivity, insomnia, nightmares, IMA (152)	Childish, emotional lability, intolerant of noise, hypersomnia (48)	ST, CL, BS	Yes (11, 2)	Impulsivity, childish, intolerant of noise, emotional lability	10; 3; 68	23.1 (0.3)

Continued

Table 1 Behavioral and sleep disorders in anti-NMDAR patients *(continued)*

Patient (sex/age, y)	Behavioral and sleep symptoms at disease onset (n days)[a]	Symptoms from hospital discharge to visit 1 (n days)	Visit 1 (study admission)				
			Treatment	Hypersomnia[c] (ESS, BSI scores)	Behavioral symptoms	HAM-D; YMRS; PANSS scores	BMI at V2 (increase since V1), kg/m^2
P16 (F/56)	Impatient, anxiety, obsessive, delusions, insomnia (112)	Apathy, hyperphagia, hypersociable (49)	CT, QT	No (5, 2)	Increased sociability	5; 6; 45	22.9 (2.2)
P17 (F/10)	Psychosis, insomnia, IMA (~26–56)	Hypersomnia (~100–124)	ST	No (NA, 0)	NA	0; 0; 30	NA in V2 (22.4 in V1)
P18 (F/25)	Psychosis, hyperphagia, hypersexual, impulsivity, insomnia (168)	Bradypsychia, irritability, hypersomnia (105)	QT	Yes (10, 0)	Irritability, bradypsychia	5; 6; 55	27.3 (−0.3)

Abbreviations: BMI = body mass index; BS = bisoprolol; BSI = Barcelona Sleepiness Index (excessive daytime sleepiness >1); CB = carbamazepine; CL = clozapine; CT = escitalopram; CZ = clonazepam; ESS = Epworth Sleepiness Scale (excessive daytime sleepiness >10); HAM-D = Hamilton Depression Rating Scale (normal 0–7, mild depression 7–19, moderate-severe depression ≥20); HL = haloperidol; IMA = increased motor activity at night; LC = lacosamide; LV = levetiracetam; NA = not available; NMDAR = NMDA receptor; PANSS = Positive and Negative Syndrome Scale (normal total score 30–57, mild 57–74, moderate 75–94, severe ≥95); PX = paroxetine; QT = quetiapine; RS = risperidone; ST = steroids; V1 = first visit of the study; V2 = second visit; VP = valproic acid; YMRS = Young Mania Rating Scale (normal 0–11, hypomania ≥12, mania ≥20); ZS = zonisamide.
[a] Other symptoms at onset listed in supplemental table e-1 (doi.org/10.5061/dryad.0zpc866tt).
[b] Patients who needed a second admission due to clinical progression (the date of discharge refers to the second admission).
[c] Hypersomnia refers to excessive number of hours slept per day.

irregularly treated with lormetazepam and also had history of undiagnosed RLS. Patient 17 (a 10-year-old child) had sleep-talking that was active.

Among the 21 healthy controls, 4 had a history of sleep-walking and sleep-talking, 2 of sleepwalking, 2 of sleep-talking, and 1 of sleep terrors. Six of these participants reported occasional episodes of sleep-talking. Another participant described occasional episodes of sexsomnia.

Sleep disorders between disease onset and assessment during the first study admission

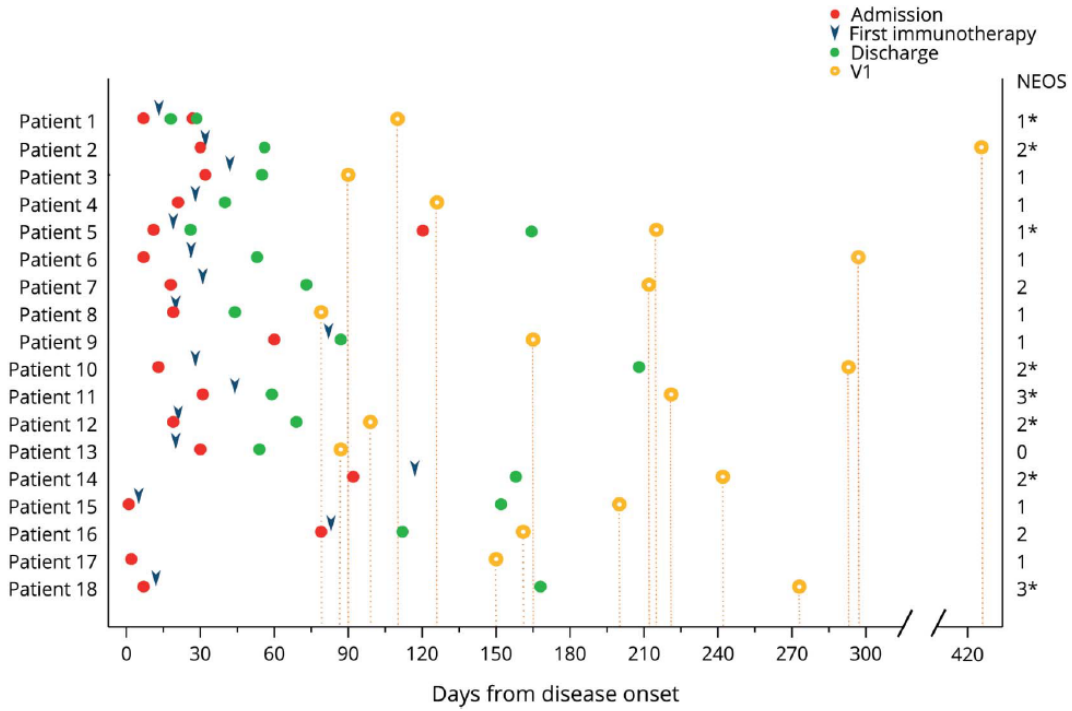
All 18 patients reported sleep disturbances throughout the course of the disease, although the sleep disorder was not the main reason for initial consultation in any of the cases. In the acute stage of the disease, 16 of 18 (89%) patients described a reduction of the total sleep time, which in 13 patients (72%, 95% confidence interval 46%–90%) occurred before hospital admission (figure 2). In 4 cases, the sleep reduction started several weeks before other symptoms of encephalitis. In 2 patients (patients 1 and 5), the sleep time reduction was noted during the second hospitalization after they failed to respond to first-line immunotherapy (0.5–3 months after disease onset). Patient 1 (see below) developed insomnia preceded by hypersomnia (figure 2).

All patients with a reduction in the amount of sleep reported multiple awakenings, which in 9 cases were associated with sleep onset insomnia and in 1 case with a "decreased need for sleep" along with symptoms of mania. Patients or relatives often used the expression "not sleeping at all" to describe the severity of the sleep disorder at the peak of the disease, with a total sleep time of ≈2 to 3 hours in 10 cases. Despite this dramatic reduction in the amount of sleep, none of the patients reported EDS. The severe reduction of total sleep time lasted a maximum of 7 days, except in 2 patients who reported having this symptom for 1 month. Five patients (patients 3, 7, 10, 13, and 16) had received benzodiazepines for insomnia and anxiety, without any effect.

Two (11%) of 18 patients had had hypersomnia in the acute stage of the disease. In one of these patients (1), the hypersomnia was replaced after a few days by insomnia along with new-onset seizures; the other patient (patient 8) did not develop insomnia.

Six of the aforementioned patients with insomnia and 1 with hypersomnia developed increased nightmares (table 1, supplemental material, doi.org/10.5061/dryad.0zpc866tt). Patient 10 had dream-enacting behaviors (talking, shouting, and kicking), but this patient also had seizures and was later shown to have hypermotor seizures and normal REM sleep during V-PSG. Five patients had increased motor activity during the night, 2 of them (patients 7 and 17) requiring physical restraints to prevent self-injury. A more precise description of sleep or dreaming during the acute stage of the disease was limited due to alterations of consciousness in 14 (78%)

Figure 1 Timeline of major events until the first visit of the study



Times of hospitalization (red circle), first immunotherapy (arrow), hospital discharge (green circle), and visit 1 (V1; yellow circle) are represented. Note that 2 patients had a second hospital admission (patients 1 and 5) and that the exact dates of first immunotherapy and hospital discharge were unknown in patient 17 (first immunotherapy was given at some point during the first 2 weeks of admission). Clinical severity during the acute phase (Anti-NMDAR Encephalitis One-Year Functional Status [NEOS] score from 0 [minimal severity]–4 [maximal]) is marked at the right side of the figure for each patient. Asterisk indicates that the patient needed to be admitted to the intensive care unit.

patients (4 in catatonic state, 3 with disease-related or induced coma, 7 with fluctuations of the level of consciousness) and lack of V-PSG (before the first study visit in our center).

After the acute stage of the disease (median time 3 months, range 1–9 months), 14 (78%) of the 18 patients developed hypersomnia (figure 2). Hypersomnia was generally mild and in 10 patients did not substantially affect the activities of daily living. One of the other 4 patients (patient 1) required naps that disrupted his work time, and the other 3 patients (patients 5, 8, and 14) developed a total amount of daily sleep of 12 to 16 hours.

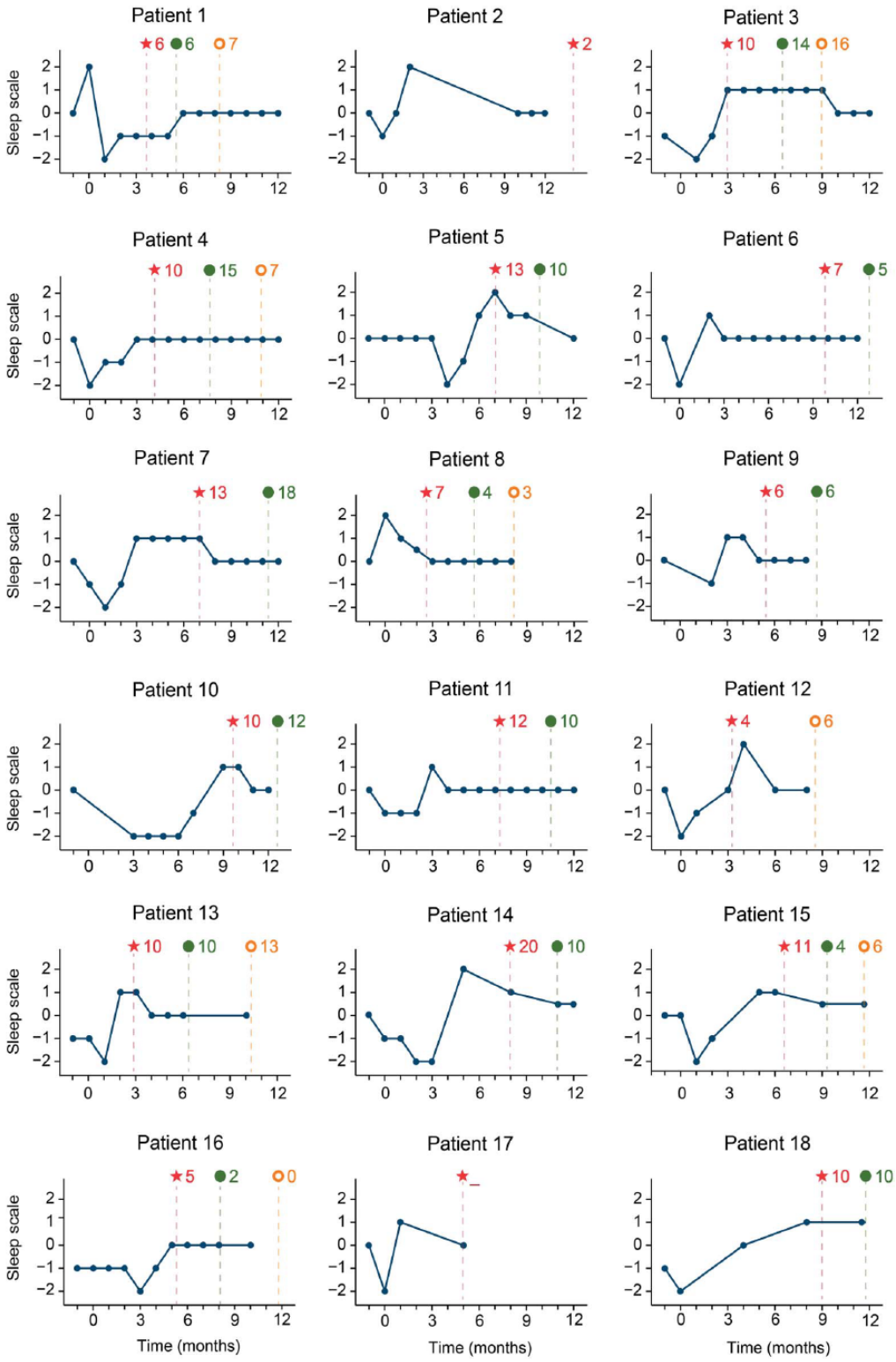
These sleep disorders were frequently accompanied by behavioral changes (table 1). Hyperphagia occurred in 14 (78%) patients: in 6 of them before hospital discharge and associated with disinhibited behavior and in the other 8 after hospital discharge (3 with impulsivity, 3 with apathy, and 2 with flat affect and irritability). One patient (patient 5) developed episodes of nocturnal eating during night awakenings of which she was unaware. Hypersexuality (increased libido or sexual behaviors) occurred in 6 (33%) patients, in 4 at disease onset or during hospitalization (disinhibition, exhibitionism, or attempted sexual assault) and in the other 2 during recovery (inappropriate flirting activity in social media and text messaging). Two of these patients (patients 15 and 18) required prolonged admission (2–4 months) to psychiatric wards due to severe organic personality change that emerged after a period of clinical improvement.

Sleep investigations during the first study visit

At the first study visit, 8 (44%) patients reported increased 24-hour sleep duration (hypersomnia), 1 reported reduced sleep time (insomnia), and 9 had a normal sleep duration compared to premorbid sleep habits (table 1 and figure 2). Patients slept a median of 84.5 min/d more than controls ($p = 0.05$) with an increased duration of daytime naps ($p = 0.02$) and had more daytime sleepiness, showing higher Barcelona Sleepiness Index ($p = 0.02$) and Epworth Sleepiness Scale ($p = 0.04$) scores (table e-2, doi.org/10.5061/dryad.0zpc866tt). The interval between hospital discharge and first study visit was similar in patients with or without hypersomnia (median 84.5 [IQR 41.5–122] vs 86 [49–162] days; $p = 0.67$). Among the 8 patients with hypersomnia, 7 still had 1 or more of the following: irritability, childish behavior, apathy, or hyperphagia (table 1). Compared with patients without hypersomnia, those with hypersomnia were more often receiving treatment with antiepileptics, antipsychotics or antidepressants (7 of 8 vs 5 of 10; $p = 0.12$), or sedative drugs such as clonazepam, clozapine, risperidone, or quetiapine (4 of 8 vs 1 of 10; $p = 0.09$).

Compared with the premorbid state, 13 (72%) patients had gained weight (mean 8.6 kg, range 1–19), so by the time of the

Figure 2 Temporal evolution of the daily sleep amount during the first 12 months of disease



Each panel represents (blue line) the evolution of the 24-hour sleep amount of an individual patient during the first 12 months of disease (horizontal axis; 0 = month of encephalitis onset; vertical axis; amount of sleep compared to the premorbid state, from severe insomnia [−2] to severe hypersomnia [2]). Note that the month before the onset of encephalitis is also indicated. In 4 patients, sleep problems were present weeks before any other symptom suggestive of encephalitis. Each dot along the blue line indicates the average value for that month (note that information was not always available for each of the 12 months in all patients). Visits of the study during the 12-month period are marked in the upper part of each box (red star = first visit, green dot = second visit, yellow circle = third visit). Seven patients had a later visit, beyond the 12 months represented in the graph, at which the information about the preceding months was gathered. Patient 12 skipped the second visit. The numbers by the symbols correspond to the Epworth Sleepiness Scale scores of each visit (_ indicates missing information in the youngest patient due to poor collaboration in some of the tests).

Table 2 PSG characteristics in patients and controls at first study-visit

	Encephalitis (n = 18)	Control (n = 21)	*p* Value
Sleep duration, median (range), min	470.5 (269.5–527.5)	473.5 (291.0–548.0)	0.67
Sleep efficiency, median (range), %	91.9 (55.2–97.9)	93,4 (55.2–98.8)	0.75
Percent of N1 sleep, median (range)	5.5 (0.6–34.1)	5.3 (1.3–18.3)	0.86
Percent of N2 sleep, median (range)	52.2 (39.7–75.8)	58.1 (43.5–75.8)	0.15
Percent of N3 sleep, median (range)	20.8 (0.0–42.8)	17.3 (5.5–28.7)	0.31
Percent of REM sleep, median (range)	19.3 (9.5–30.3)	18.0 (5.8–27.6)	0.92
No. of REM stages, median (range)	4 (2–6)	4 (1–6)	0.62
REM sleep latency,[a] median (range)	96.3 (41–239)	124.5 (41.5–316)	0.52
N3 sleep latency,[a] median (range)	21.5 (1.5–112)	17.5 (8–91.5)	0.71
AI, median (range)	9.3 (2.4–51.6)	10.1 (4.3–30.5)	0.55
AI_REM, median (range)	9.3 (3.6–23.1)	12.6 (3.9–22.7)	0.92
AI_NREM, median (range)	10.0 (2.0–56.1)	11.0 (4.6–32.8)	0.92
Participants with confusional arousals, n	6	4	0.46
Participants with ≥2 confusional arousals, n	4	0	0.037
Duration of confusional arousals, median (range), s	26 (9–87)	12 (7–24)	0.033
AHI, median (range)	2.0 (0–44.4)	0.9 (0–13.3)	0.49
PLMI, median (range)	2.2 (0.4–13)	2.2 (0–18.6)	0.67

Abbreviations: AI = arousal index (n/hour); AHI = apnea-hypopnea index (n/hour); NREM = non-REM; PLMS = periodic leg movement index (n/hour); PSG = polysomnography.
[a] Latency = minutes from first N1 epoch.

first study visit, the median BMI of all patients was higher than that of controls (median 23.5 [IQR 22.3–30.2] vs 20.5 [19.1–21.1] kg/m^2; $p = 0.007$), and 8 patients were overweight (BMI ≥25 kg/m^2). Despite decreasing the number of drugs and doses (steroids, valproate, or antipsychotics), 14 (87.5%) of 16 patients gained weight between the first and second study visits (mean 7.5 kg, range 1–16 kg) (table 1).

By the time of the first study visit, none of the patients reported dream-enacting behaviors, RLS, or cataplexy. The Pittsburgh Sleep Quality Index scores were similar in patients and controls, and circadian rhythm types were also comparable between patients and controls (10 of 17 patients and 13 of 20 controls in the intermediate range [scores 42–58]) (table e-2, doi.org/10.5061/dryad.0zpc866tt).

Patients had higher scores on all psychiatric scales (HAM-D, YMRS, PANSS) compared with controls ($p < 0.001$; table 1 and table e-3, doi.org/10.5061/dryad.0zpc866tt). Five patients (4 with hypersomnia) had scores in the range of mild depression (HAM-D score 10–17, normal 0–7), and 1 with insomnia had scores in the range of hypomania (YMRS score 19, normal 0–11). Three patients with depression also had mild symptoms of psychosis, but only 1 had delusions or hallucinations (total PANSS score 59–77, mild abnormal 58–74). The other 12 patients had normal scores (11) or missing information (1) (table 1).

Cognitive function evaluation at the first study visit showed impairment in 13 (72%) patients, involving 1 domain in 4 patients (22%), 2 to 3 domains in 6 (33%), and 4 to 6 domains in 3 (17%). Five patients (28%) had normal cognitive function. Global functionality assessment with the Global Assessment of Functioning scale showed the presence of severe psychological, social, and occupational disability in 12 (67%) patients (all <50 points) (table e-4, doi.org/10.5061/dryad.0zpc866tt).[13] The extent of cognitive dysfunction (number of domains affected) and sleep dysfunction were not related (table e-4).

Video-polysomnography

The median duration of patients' sleep was 470.5 minutes, with a sleep efficiency of 92%, similar to controls (table 2). Low sleep efficiency (≤75%) due to prolonged sleep latency occurred in 3 patients and 2 controls. The sleep architecture was preserved in patients with encephalitis, except for N3 non-REM (NREM) sleep, which was almost absent (<2.5 SD of the control's mean: 3.2%) in 2 patients and increased (>2.5 SD of the controls' mean: 30.2%) in another 3 patients. NREM sleep confusional arousals were more frequent in patients than in controls (described separately below). REM sleep was

unremarkable, without abnormal movements or behaviors suggestive of REM sleep behavior disorder. One control had a brief episode of sleep-talking in REM sleep. Three patients and 2 controls had mild to moderate position-dependent obstructive sleep apnea.

Epileptic seizures were recorded in only 1 patient (patient 10), who had 4 seizures during the V-PSG. One occurred while the patient was awake and showed a 12-minute-long right frontal rhythmic theta activity associated with staring and unresponsiveness for a few seconds. The other 3 seizures occurred during NREM N2 sleep, manifesting as hypermotor seizures with tonic leg extension, kicking, body rolling, vocalizations, and mumbling that lasted 25 to 40 seconds, without clear epileptiform activity in the EEG (obscured by EMG artifact).

NREM arousals

Six (33%) patients had confusional arousals during N3 or N2 sleep, with a total of 22 (range 1–7) episodes (table 3). In the control group, 4 (19%) participants had confusional arousals but only 1 episode each. None of these patients or controls had epileptic seizures during PSG recording. Multiple confusional arousals occurred only in patients (4 of 18 vs 0 of 21 controls; $p = 0.037$). Moreover, individual confusional behaviors had a longer duration in patients (median 26 [range 9–75] vs 12 [range 7–24] seconds in controls; $p = 0.046$). Episodes with agitation occurred in 3 patients, including screaming and kicking (1) and looking frightened (2) (figure 3 and videos). None of the 6 patients had history of parasomnias before disease onset. In 2 patients, episodes of sleep-talking after disease onset were recognized by their relatives, but in the other 4 patients, no episodes were reported. In contrast, 3 of the 4 controls with confusional arousals reported a history suggestive of NREM parasomnia (sleepwalking or somniloquy) since childhood or adolescence ($p = 0.03$). Compared with patients without confusional arousals, those with confusional arousals had similar age at disease onset, severity of symptoms, duration of hospitalization, delay in immunotherapy, type of immunotherapy, and type and number of additional drugs (data not shown). Behavior patterns in patients with multiple confusional arousals were similar throughout the night, although different from one patient to another.

Discussion

In this study, we show that all patients with anti-NMDAR encephalitis developed sleep disorders that usually followed a temporal pattern of presentation characterized by severe reduction in sleep duration at disease onset (89% of patients), followed by hypersomnia during recovery (78%). In the recovery phase, 33% of patients had confusional arousals (an NREM parasomnia) that, compared with those of controls (19%), were significantly more often multiple and longer-lasting. In addition, 72% of patients showed impairment in 1 or more cognitive domains (memory, attention, or executive function); 67% had psychological, social, or occupational disability; and 33% had ratings in depression or mania scales meeting clinical threshold. These symptoms were accompanied by hyperphagia (78%) and hypersexuality (33%), which in some patients led to prolonged hospital readmission.

Although the number of publications on anti-NMDAR encephalitis has rapidly increased in recent years,[22] this study suggests that the disease is still frequently missed at presentation. Indeed, 78% of the patients were not suspected of having encephalitis at disease onset; 50% were considered to have a primary psychiatric disorder; and 39% were admitted to psychiatric wards. Because the clinical anamnesis related to symptom onset is difficult to obtain from patients, we used structured questionnaires that were administered to families and patients (after the acute phase of the disease), which in all cases described remarkable alterations of sleep at disease onset. Most of them used the expression "not sleeping at all" to describe the severity of the sleep disorder, with a total sleep time of <3 hours in 10 (56%) of patients. Moreover, in 4 (22%) patients, insomnia preceded all symptoms of encephalitis by several weeks. These findings are in line with the authors' experience with other patients preceding this study[3] and multiple case reports or series (predominantly pediatric) in which insomnia is usually mentioned at disease onset.[23–28]

It has been suggested that the 2 main phases of anti-NMDAR encephalitis (e.g., acute phase: psychosis, agitation, seizures, dyskinesias, dysautonomia; and recovery phase: behavioral, cognitive and executive dysfunctions) result from the acute inflammatory process accompanied by a rapid decrease of NMDAR clusters and impairment of synaptic plasticity, followed by a gradual restoration of NMDAR function during recovery.[29] The current findings indicate that insomnia also has a phase preference, usually presenting early in the acute stage, and subsequently being replaced by hypersomnia. Studies with rodents showing that selective noncompetitive NMDAR blockers increase the time spent awake and change the sleep architecture[30] suggest that, in patients with anti-NMDAR encephalitis, the decreased levels of NMDAR[31] play a pathogenic role in insomnia. Thus, insomnia is part of the disease, but the pathogenic link with hypersomnia is more difficult to establish because many patients are taking medications (antiepileptics, antipsychotics, or antidepressants) by the time hypersomnia is noted. Some studies have suggested hypersomnia as part of the disease, but the timing and association with medications were not clearly specified.[4,32]

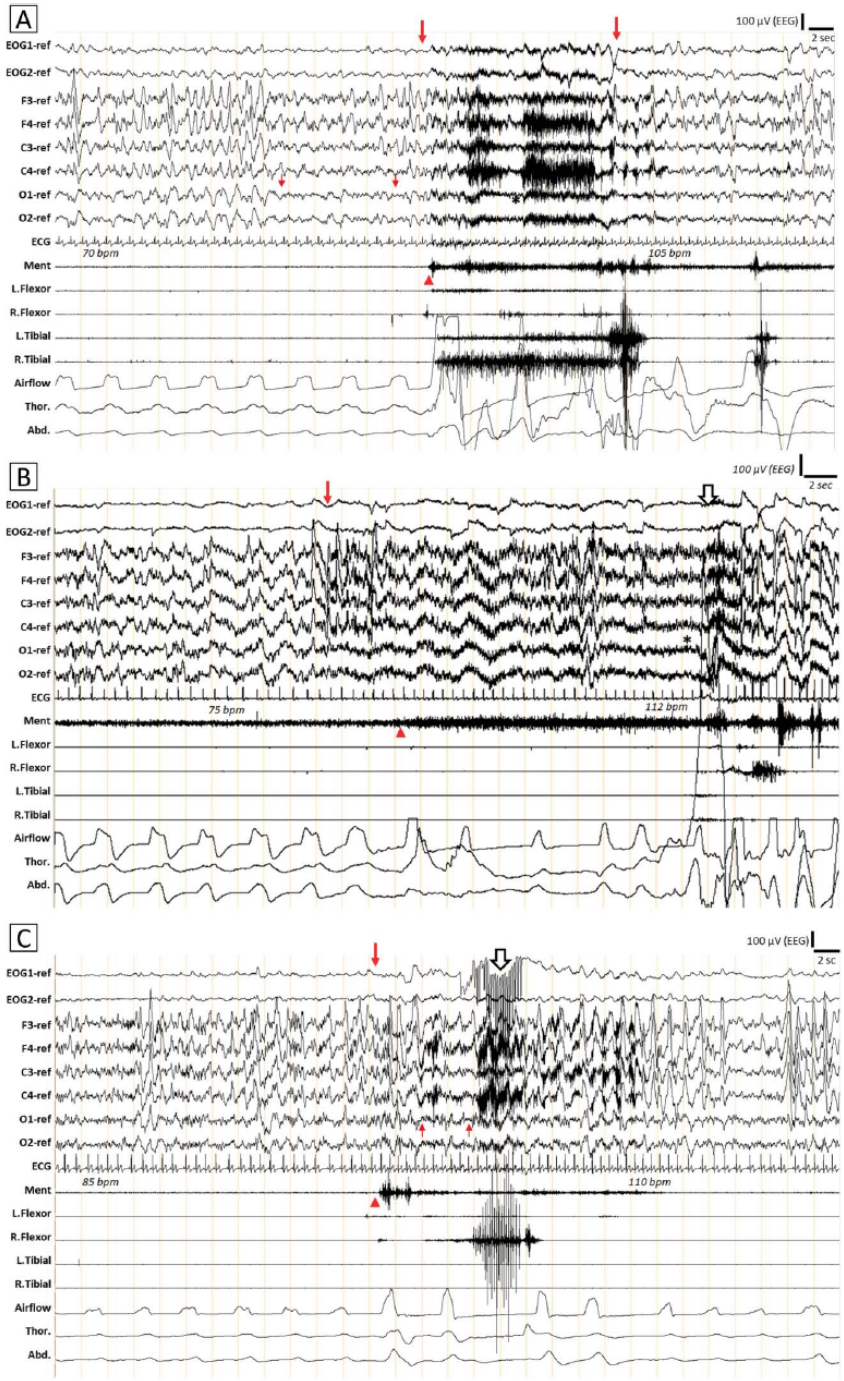
In the current study, we identified a group of patients who during V-PSG recording developed multiple confusional arousals from NREM sleep (typically from N3), which, in contrast to controls, lasted longer and were not associated with a history of NREM sleep parasomnias. This suggests that they may be either caused or facilitated by the encephalitis. Confusional arousals typically occur in NREM parasomnias (as well as sleepwalking and sleep terrors), have a genetic predisposition, and may be promoted by sleep deprivation, which increases the amount of N3 sleep in the recovery night.[33] The severe sleep reduction of the acute phase might be compensated for by a transient increase in

Table 3 Confusional arousals from stages N3 and N2 NREM sleep

Participant (sex/age, y)	CAs, n	Preceding sleep stage (n)	Part of the night	Percent of N3	Trigger (n)	Behavior	Emotional state (n)/eyes (n)	Duration of behaviors, s
P2 (F/12)	5	N2 (1), N3 (4)	First and second halves	18.6	Caregiver noise (5)	Terror scream, kicking, limb and body movements (struggling with sheets), vocalizations, sigh	Agitated (3), quiet (2)/open (4), closed (1)	26–35
P3 (F/22)	5	N2 (1), N3 (4)	First half	31.3	Spontaneous (4), noise (1)	Staring, frightened, disoriented, raising hands, sitting up, touching cables with perplexity	Quiet (4), agitated (1)/open (5)	9–35
P5 (F/28)[a]	3	N2 (1), N3 (2)	Second half	24.9	Spontaneous (3)	Sitting up, inappropriately talking to roommate, staring	Quiet (3)/open (3)	34–87
P6 (F/23)	1	N2	First half	24.2	Spontaneous	Gesticulating with arms	Quiet/closed	26
P7 (F/16)[b]	7	N2 (1), N3 (6)	First and second halves	42.8	Spontaneous (5), caregiver noise (1), cough (1)	Groaning, sighs, vocalizations, frightened, disoriented, staring, perplexed, chewing, raising arms, tapping her face, irregular breathing	Quiet (6), agitated (1)/open (7)	15–53
P16 (F/56)[c]	1	N3	First half	6.6	Postapnea	Raising hand, gesticulating	Quiet/open	20
C11 (F/16)[d]	1	N3	First half	15.9	Snoring	Touching and moving bed cables perplexed and with difficulty	Quiet/closed	24
C12 (F/16)	1	N3	First half	18.3	Spontaneous	Touching and scratching her face, perplexed, confused, sigh	Quiet/open	8
C14 (F/18)[d]	1	N3	First half	24.4	Spontaneous	Talking, looking around	Quiet/open	7
C18 (F/15)[d]	1	N3	First half	21.3	Spontaneous	Talking	Quiet/closed	16

Abbreviations: C = control; CA = confusional arousal; NREM = non-REM; P = patient.
[a] Patient treated with quetiapine, risperidone, and levetiracetam.
[b] Patient treated with valproic acid.
[c] Patient treated with citalopram.
[d] History of NREM parasomnias.

Figure 3 Examples traces of polysomnography in 3 patients with confusional arousals



Each recording shows a 1-minute epoch. The first red arrow at the top indicates the beginning of the clinical episode, typically with eye opening; the second red arrow (if applicable) indicates the end. Arrowhead on the mentalis channel marks an increase in EMG activity starting at that point. Note heart rate acceleration (ECG channel) and change in the breathing pattern (lower 3 channels). (A) Patient 3 (video 1, episode1 in supplemental material, doi.org/10.5061/dryad.0zpc866tt). Preceding the clinical episode, there is a 5-second moderate decrease in slow activity (between small arrows); there is then (red arrow) a generalized EEG amplitude attenuation with superimposed EMG artifact (*) lasting 14 seconds, while the patient looks around and raises the arms, apparently disoriented. After the second arrow, patient closes eyes and slow-wave sleep is resumed. (B) Patient 5 (video 2, in supplemental material). After eye opening (red arrow), EEG shows amplitude attenuation, EMG, and movement artifact. At the empty arrow, the patient sits up and starts talking incoherently. Note change in EMG activity in the chin and limbs. These features continue until the end of the episode in the following epoch (not shown). (C) Patient 7 (video 3, episode 1 in supplemental material). EEG shows (between small arrows) a 5-second amplitude attenuation and frequency acceleration, followed by high-amplitude anterior predominant rhythmic delta activity (10 more seconds). There is superimposed electrode tapping artifact (empty arrow), when the patient rhythmically touches her left temple with her right hand (see EMG activity at R. Flexor channel). Slow-wave activity resumes at the end of the epoch. Abd = abdominal respiratory movement; Airflow = nasal pressure cannula; bpm = beats per minute; EOG1 and EOG2 = left and right electrooculograms; F3, F4, C3, C4, O1, and O2 = left and right frontal, central and occipital EEG channels; L.Flexor, R.Flexor = EMG of left and right flexor digitorum superficialis muscles of the upper limbs; L.Tibial, R.Tibial = EMG of left and right anterior tibialis muscles; Ment = EMG of mentalis muscle; ref. = reference (combined ears); Thor: thoracic respiratory movement.

the amount of N3 sleep during recovery, facilitating the appearance of these episodes. A clear increase in N3, however, occurred in only 2 of the 6 patients. The observed confusional arousal episodes could also be the residual events of a process occurring more intensely during the acute phase of the disease. Different from the duration of sleep, which can be affected by medications, there is no clear evidence that confusional arousals are affected by any of the drugs that our patients were receiving.

In contrast to other autoimmune encephalitis such as anti-LG1, anti-CASPR2, or anti-IgLON5,[34–36] REM sleep was normal in anti-NMDAR encephalitis, suggesting that the disease process, at least in the recovery phase, does not impair the brainstem areas generating REM sleep. Although dream-enacting behaviors were described in 1 patient, we cannot exclude that these were secondary to hypermotor seizures. Unfortunately, there is no way to learn more about these questions without recording sleep during the acute

phase of the disease, something that has proved to be very difficult.

Accompanying the sleep disorders, patients developed multiple behavioral abnormalities. Whereas insomnia frequently occurred together with psychosis, mania, or disorganized behavior in the acute phase, hypersomnia was more often associated with hyperphagia, apathy, or impulsive behaviors in the recovery phase. The temporal evolution of these sleep and behavioral patterns supports the concept that both insomnia and hypersomnia are part of the natural history of the disease and that hypersomnia is not simply a side effect of the treatment. The frequent association of hypersomnia and weight gain (77% of the patients), usually accompanied by hyperphagia, apathy, and hypersexual behaviors, may remind clinicians of Kleine-Levin syndrome (KLS),[37] as previously suggested in a single case report[38] and our own experience.[39] However, an association of genuine KLS with antibodies to NMDAR has never been reported, and none of our patients presented the typical recurrences of KLS during follow-up.

The current study has limitations related to the type of disease and symptoms studied. Sleep studies are challenging in the acute phase of anti-NMDAR encephalitis due to the frequent medical problems that these patients develop (admissions to the intensive care unit, extreme agitation, deep sedation, antiepileptics, or respiratory support). Moreover, the spectrum of symptoms dynamically change during the disease so that, after the acute stage, the clinical picture, including sleep disorders, is different. This offers an advantage for some studies because patients are more able to participate and sleep studies including V-PSG are easier to perform, but there are also limitations such as the fact that virtually all patients are taking medications, which should be considered in the interpretation of some of the findings. A task for the future is to characterize hypersomnia with more objective data (actigraphy, long-term monitoring, multiple sleep latency test).

Overall, this study reveals that patients with anti-NMDAR encephalitis develop multiple sleep and behavioral problems that have not been fully appreciated previously, emphasizing the need of a comprehensive clinical evaluation with patients and families and V-PSG recording. The findings have implications at multiple levels: (1) the high frequency and severity of insomnia should be considered a diagnostic clue (along with the better-known psychiatric, behavioral, and neurologic symptoms) in the initial assessment of patients with anti-NMDAR encephalitis; (2) during the diagnostic evaluation, these symptoms should be considered part of a dynamic process that change along the course of the disease; (3) V-PSG recordings during the recovery phase suggest the presence of an underlying complex sleep dysfunction (confusional arousals), exclusively affecting NREM sleep, which should be further studied in the future; (4) several underrecognized symptoms after the acute phase of the disease (e.g., hypersomnia, hyperphagia, apathy, overweight, and hypersexuality) have important implications for patients, families, and social interactions, emphasizing the need for prolonged multidisciplinary care during the recovery phase of these patients; and (5) there are currently no symptom-specific treatments addressing these complications in anti-NMDAR encephalitis. The current study forms part of an ongoing longitudinal assessment of patients, including regular clinical and V-PSG sleep investigations, and cognitive and neuropsychological studies for 2 years, which we hope that, when completed, will help to answer some of these questions.

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Disclosure

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Appendix *(continued)*

Name	Location	Contribution
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Josep Dalmau, MD, PhD	Hospital Clínic, IDIBAPS, Institució Catalana de Recerca i Estudis Avançats, Barcelona, Spain; University of Pennsylvania, Philadelphia	Designed and conceptualized study; analysis and interpretation of the data, revised the manuscript for intellectual content; obtained funding; wrote the final version
Joan Santamaria, MD, PhD	Hospital Clínic and IDIBAPS, Barcelona, Spain	Designed and conceptualized study; acquisition of clinical data; analysis and interpretation of the data; revised the manuscript for intellectual content; wrote the final version

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SUPPLEMENTAL MATERIAL

Methods

a. Batteries of tests for assessment of psychosis, depression and mania

1. Hamilton Depression Rating Scale (HAM-D): normal, 0–7; mild depression, 7-19; moderate-severe depression, ≥20.
2. Young Mania Rating Scale (YMRS): normal, 0-11; hypomania, ≥12; mania, ≥20.
3. Positive and Negative Syndrome Scale (PANSS): it includes 3 subscales: General Psychopathology, Negative and Positive. Normal total score, 30-57; mild, 57-74; moderate, 75-94; severe, ≥95.

b. Batteries of tests for assessment of cognitive function

A battery of tests exploring 6 domains: general intellectual abilities, working memory, processing speed, learning and memory, executive function and attention

1. General intellectual ability: Wechsler Adult Intelligence Scale (WAIS-IV), consisting in 4 indices: Four indices: Verbal Comprehension Index, Perceptual Reasoning Index,

Working Memory Index, Processing Speed Index. In patients under 16 years, the Wechsler Intelligence Scale for Children (WISC-V) was used instead.

2. Working memory: Verbal Working Memory (Digit span, Letter-Number Sequencing) from WAIS-IV, Corsi's blocks - Spatial Span (visual working memory) contained in the Wechsler Memory Scale (WMS-III) for adults and the Wechsler Non-Verbal Scale (WNVS) for children under 16 years old.;

3. Processing Speed: Processing Speed Index (PSI) from WAIS-IV/WISC-V, Trail Making Test A (TMT), Phonemic Fluency score (FAS);

4. Learning and Memory: Spain-Complutense verbal learning test (TAVEC) with several indices analogous to those in California Verbal Learning Test, Brief Visuospatial Memory Test - Revised (BVMT-R);

5. Planning and Executive Functions (Tower of London—TOL) and STROOP test (interference);

6. Selective and sustained attention: Conners' Continuous Performance Test 2nd and 3rd Edition (CPT).

Scores for the neuropsychological instruments were age-corrected and converted into z scores, standard T-scores, or percentiles, as appropriate, using normative data.

Results

Medications taken at the time of V-PSG:
At the time of VPSG 15/18 patients were taking medications that could affect sleep including antiepileptics (9 patients), oral steroids (7 patients, dose range 2.5-35 mg/day prednisone), neuroleptics (4 patients), selective serotonin reuptake inhibitors (3 patients) and/or benzodiazepines (2 patients).

Examples of the nightmares:
"…I was hiding behind a column and saw shadows of men, who instead of hands had knives and were approaching to her…" or "…My friends were sitting unaware of a giant sea wave moving towards them, meanwhile I saw it coming and waited and smiled, without warning them"; "…In the hospital she described very frequent dreams related to the burning of a building, or that she was pregnant, of that she was burglarized, or sometimes multiple mixed topics in the same dream."

Supplemental Table e-1. Symptoms other than behavioral and sleep disorders at disease onset

Subject code (Sex/Age at onset)	Onset to hospital discharge Symptoms (number of days)
P1 (M/25)	Seizures, myoclonus, dysautonomia, fluctuating level of consciousness, severe short-term memory loss, brainstem/cerebellar symptoms, disorganized speech (27*)
P2 (F/12)	Status epilepticus, dyskinesia, dysautonomia, coma, cognitive dysfunction, focal deficit, speech disorganization (56)
P3 (F/22)	Dyskinesia, dysautonomia, fluctuating level of consciousness, cognitive dysfunction, brainstem/cerebellar signs, disorganized speech (55)
P4 (F/14)	Focal seizures, dyskinesia, cognitive dysfunction (40)
P5 (F/28)	Generalized seizures, dystonia, cognitive dysfunction, focal deficit, brainstem/cerebellar symptoms, decreased verbal output (164*)
P6 (F/23)	Cognitive dysfunction, speech disorganization (53)
P7 (F/16)	Dystonia, dysautonomia, cognitive dysfunction decreased verbal output (73)
P8 (F/29)	Focal seizures, cognitive dysfunction (44)
P9 (M/35)	Seizures (generalized), fluctuating level of consciousness, dysautonomia, cognitive dysfunction (87 d)
P10 (F/20)	Status epilepticus, coma, dysautonomia, hypoventilation, severe short-term memory loss, focal deficit, decreased verbal output (208)
P11 (F/38)	Generalized seizures, fluctuating level of consciousness, cognitive dysfunction, brainstem/cerebellar symptoms (59)
P12 (F/27)	Generalized seizures, coma, myoclonus, dysautonomia, hypoventilation, cognitive dysfunction, decreased verbal output (69)
P13 (F/29)	Focal seizures, fluctuating level of consciousness, severe short-term memory loss, focal deficit (54)
P14 (F/26)	Myoclonus, dysautonomia, severe short-term memory loss, decreased verbal output (158)
P15 (F/27)	Dystonia, dysautonomia, cognitive dysfunction, decreased verbal output (152)
P16 (F/56)	Generalized seizures, fluctuating the level of consciousness, short-term memory loss, speech disorganization (112)
P17 (F/10)	Dyskinesia, fluctuating level of consciousness, severe short-term memory loss, decreased verbal output (~ 26-56)
P18 (F/25)	Dysautonomia, cognitive dysfunction, decreased verbal output (168)

Supplemental Table e-2. Sleep characteristics in patients and controls

	ENCEPHALITIS (n:17)	CONTROLS (n:20)	*p value*
Epworth, median (range)	9 (2-16)	6 (0-13)	0.04
Barcelona Sleepiness Index (BSI), median (range)*	1 (0-2)	0 (0-2)	0.02
Morningness–eveningness questionnaire (total score), median (range)	45 (26-59)	45 (34-61)	0.68
Pittsburgh Sleep Quality Index (PSQI) (total score), median (range)	5 (2-12)	4 (2-11)	0.56
Time in bed at night (minutes), median (range)	555 (300-840)	472.5 (405-630)	0.09
24-h sleep duration (minutes), median (range)	510 (300-765)	425.5 (330-570)	0.05
Sleep duration at night (minutes), median (range)	420 (300-720)	420 (330-540)	0.50
Daytime naps (minutes), median (range)	8.5 (0-180)	0 (0-30)	0.02

For patient #17 only BSI available, for control #14 only ESS available.

*BSI missing in patient #8.

Epworth Sleepiness Scale (ESS) ≥11 is suggestive of excessive daytime sleepiness (EDS). Barcelona Sleepiness Index (BSI) ≥ 2 is suggestive of EDS. Pittsburgh Sleep Quality Index (PSQI) total score: >5 is indicative of reduced sleep quality. *Time in bed at night* was calculated from PSQI items 1 and 3 (time to go to bed at night, and time to get up in the morning, respectively) and *Sleep duration at night* with PSQI item 4 (hours of actual sleep at night); duration of *Daytime naps* was calculated averaging the duration of weekday and weekend naps as detailed in a sleep schedule filled by patients/caregivers.

Supplemental Table e-3. Main features in 21 control subjects.

Control	Age	Sex	History of sleep disorders	Confusional arousal during V-PSG	HAM-D	YMRS	PANSS	ESS, BSI	BMI at first study-visit
C2	23	F	Sleep-talking	No	0	0	30	8, 0	24.1
C3	28	F	Night terrors	No	0	0	30	11, 2	23.4
C4	30	F	Sleep-talking	No	0	2	30	7, 0	29.4
C5	24	F	Sleepwalking and sleep-talking	No	2	0	33	10, 0	19.2
C6	14	F	None	No	0	0	30	6, 0	21.4
C7	23	F	None	No	7	3	36	6, 0	18.7
C8	23	M	Sleepwalking	No	0	0	30	5, 0	18.8
C9	22	M	None	No	0	0	30	3, 0	20.0
C10	18	F	None	No	0	0	30	9, 1	19.0
C11	16	F	None	Yes	0	0	30	9, 1	24.7
C12	16	F	Sleepwalking	Yes	0	0	30	6, 0	21.3
C13	31	M	None	No	0	0	30	3, 0	20.8
C14	18	F	Sleep-talking	Yes	0	0	30	n/a	n/a
C15	18	F	None	No	0	0	30	8, 1	20.1
C16	25	F	Sleepwalking	No	4	4	32	3, 0	18.1
C17	26	M	Sexsomnia	No	0	0	30	6, 0	20.2
C18	15	F	Sleepwalking and sleep-talking	Yes	0	0	30	0, 0	18.3
C19	27	F	None	No	0	0	30	6, 1	21.1
C20	18	F	None	No	1	1	32	4, 0	22.6
C21	42	F	None	No	0	0	30	4, 0	19.3
C22	22	F	None	No	n/a	n/a	n/a	13, 1	21.1

V-PSG: video-polysomnography; HAM-D: Hamilton Depression Rating Scale (normal, 0–7; mild depression, 7-19; moderate-severe depression, ≥20); YMRS: Young Mania Rating Scale (normal, 0-11; hypomania, ≥12; mania, ≥20); PANSS: Positive and Negative Syndrome Scale (normal total score, 30-57; mild, 57-74; moderate, 75-94; severe, ≥95); ESS: Epworth Sleepiness Scale score (excessive daytime sleepiness: >10); BSI: Barcelona Sleepiness Index (excessive daytime sleepiness: > 1); BMI: body mass index

Supplemental Table e-4. Cognitive and functional evaluation of patients* and associated sleep disturbances

Patient #	10	5	8	16	7	15	4	12	18	2	9	13	17	1	3	14	6	11
General Intellectual Ability:																		
General intellectual abilities (100, 15)**	**61**	**67**	**68**	99	86	91	81	80	86	99	109	109	97	109	99	110	100	116
Verbal Comprehension (100, 15)	88	**73**	88	104	100	100	95	86	82	101	103	112	**73**	116	100	106	112	110
Perceptual Reasoning (100, 15)	**50**	**68**	**66**	93	**75**	85	**76**	79	90	100	115	104	106	100	97	112	87	115
Working Memory:																		
Verbal Working Memory (100, 15)	**69**	**76**	**73**	106	111	**69**	78	94	91	100	86	97	103	85	103	88	97	142
Corsi's Block (50, 10)	**23**	37	40	50	n/a	43	41	43	37	41	n/a	60	60	37	47	57	60	60
Processing Speed:																		
Processing Speed Index (100, 15)	**56**	**73**	**73**	92	114	100	103	103	100	89	n/a	100	138	114	100	114	111	127
Trail Making Test A (50, 10)	**26**	n/a	43	46	51	56	56	59	57	n/a	58	58	n/a	60	58	58	64	n/a
Phonemic Fluency score (50, 10)	43	n/a	48	53	**31**	58	n/a	46	54	n/a	37	52	n/a	56	69	50	48	n/a
Learning and Memory:																		
TAVEC Immediate Recall (50, 10)	46	36	37	38	50	44	50	59	44	60	39	40	65	53	50	46	42	72
TAVEC Long Delay Free Recall (50, 10)	**25**	**21**	**33**	**28**	50	50	50	58	50	45	53	**21**	40	58	39	54	53	n/a
BVMT Immediate Recall (50, 10)	**20**	**33**	**20**	**28**	51	38	50	**29**	44	62	**20**	45	75	50	56	53	61	46
BVMT Delay Recall (50, 10)	**20**	41	**29**	**31**	54	61	45	41	54	63	**20**	**20**	72	60	45	48	60	51
Planning and Executive Functions:																		
STROOP interference[a] (50, 10)	57	n/a	37	61	38	51	51	58	42	54	n/a	51	40	58	52	55	59	n/a
TOL Total Moves (50, 10)	**27**	**23**	36	49	38	**19**	**34**	35	46	**34**	49	51	48	41	51	47	45	n/a
TOL Rule Violations (50, 10)	**34**	54	53	**20**	53	54	53	54	**34**	**20**	53	54	39	**34[c]**	**14[c]**	54	54	n/a
TOL Execution Time (50, 10)	**25**	40	48	48	48	40	37	**14**	35	46	53	42	58	47	56	53	62	n/a
TOL Initiation Time (50, 10)	57	43	42	51	47	44	53	52	50	45	57	51	39	43	43	43	46	n/a
Selective and sustained attention:																		
CPT Global Index[b] (%)	**100**	n/a	50	**72**	**76**	n/a	50	11	50	n/a	n/a	50	50	40	37	25	17	n/a
CPT[a] Omission Errors (50, 10)	**104**	n/a	52	55	62	46	48	47	50	40	45	45	50	44	45	47	50	45
CPT[a] Commission Errors (50, 10)	**71**	n/a	43	63	44	**66**	52	58	50	34	47	44	59	55	55	**68[c]**	64	56
CPT[a] Reaction Time (50, 10)	61	n/a	**75**	48	65	42	55	43	58	42	46	65	48	42	45	47	38	49
CPT[a] Reaction Time Variability (50, 10)	**94**	n/a	**67**	48	49	47	48	32	**67**	39	42	44	61	61	57	42	47	48
Psychological, social, occupational:																		
GAF	35	35	60	45	71	44	55	45	45	65	45	45	81	45	45	45	80	45
Sleep disturbances:																		
Hypersomnia	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	No	Yes	No	No	Yes	Yes	No	No
ESS;BSI	9;0	13;2	7;na	5;2	12;2	11;2	9;2	4;0	10;0	2;1	6;0	10;2	na;na	6;2	10;0	16;2	7;0	12;1
PSQI total score	11	8	2	11	3	5	4	2	9	3	7	11	na	4	9	12	3	2
Confusional arousals	No	Yes	No	Yes	Yes	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes	No

*Additional information in supplemental material (Batteries of tests for assessment of cognitive function).
**Assessed with Wechsler Adult Intelligence Scale IV, or with the Wechsler Intelligence Scale for Children V for patients younger than 16 years.
Scores below average normal values (< 1.5 standard deviations) are highlighted in bold. [a]Different from the other tests, higher scores (>1.5 SD) correspond to pathological values. [b]Probability of inattention (over 50% is considered pathological). n/a: not assessable or not obtained. [c]In absence of other deficits, these tests indicate impulsivity (no cognitive impairment).TAVEC: Spain-Complutense Verbal Learning Test (a test of learning and memory); TOL: Tower of London (a test of planning and executive functions); CPT: Conner's Continuous Performance (a test of selective and sustained attention); GAF : Global Assessment of Functioning (normal: >90, mild-moderate impairment: 51-70, severe deficits: 0-50); ESS: Epworth Sleepiness Scale score (excessive daytime sleepiness: >10); BSI: Barcelona Sleepiness Index (excessive daytime sleepiness: > 1); PSQI: Pittsburgh Sleep Quality Index (reduced sleep quality: >5)

Video legends:

Video 1. Two episodes of confusional arousal from N3 NREM sleep in patient #3. Episode 1 (see also Figure 3A): the patient suddenly opens her eyes, looking confused, and raises her hands. After 14 seconds she closes the eyes and continues sleeping. Episode 2 (PSG recording not shown): the patient opens her eyes, sits up and touches and looks around with confusion in her face.

Video 2. A long confusional arousal from N3 sleep in patient #5 (see also Figure3B): immediately after several noises made by the roommate, the patient opens her eyes and initially stays still, looking around, apparently confused. After 10 seconds she sits ups and whispers three times to the roommate ("open the door"), showing perplexity in her face. She finally lies down and continues sleeping.

Video 3. Two episodes of confusional arousal from N3 NREM sleep in patient #7. Episode 1 (see also Figure 3C): the patient suddenly opens her eyes and groans briefly, staring and tapping rhythmically with the right hand the left temple for 4 seconds. Then she closes the eyes and continues sleeping. Episode 2 (PSG recording not shown): the patient opens her eyes mumbling and touches briefly her left temple with the right hand. Next she raises her head, looks around apparently frightened and says "take me out of here now" with agitated breathing and moaning during a few seconds, until she gets comfortable and continues sleeping again.

Publication 2:

Neurological, psychiatric, and sleep investigations after treatment of anti-leucine-rich glioma-inactivated protein 1 (LGI1) encephalitis in Spain: a prospective cohort study

Amaia Muñoz-Lopetegi**,** Mar Guasp, Laia Prades, Eugenia Martínez-Hernández, Mireia Rosa-Justícia, Víctor Patricio, Thaís Armangué, Lorena Rami, Roger Borràs, Josefina Castro-Fornieles, Albert Compte, Carles Gaig, Joan Santamaria, Josep Dalmau.

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Neurological, psychiatric, and sleep investigations after treatment of anti-leucine-rich glioma-inactivated protein 1 (LGI1) encephalitis in Spain: a prospective cohort study

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See Comment page 221

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Summary

Background Anti-leucine-rich glioma-inactivated protein 1 (LGI1) encephalitis is an autoimmune disorder that can be treated with immunotherapy, but the symptoms that remain after treatment have not been well described. We aimed to characterise the clinical features of patients with anti-LGI1 encephalitis for 1 year starting within the first year after initial immunotherapy.

Methods For this prospective cohort study, we recruited patients with anti-LGI1 encephalitis as soon as possible after they had received conventional immunotherapy for initial symptoms; patients were recruited from 21 hospitals in Spain. Patients were excluded if they had an interval of more than 1 year since initial immunotherapy, had pre-existing neurodegenerative or psychiatric disorders, or were unable to travel to Hospital Clínic de Barcelona (Barcelona, Spain). Patients visited Hospital Clínic de Barcelona on three occasions—the first at study entry (visit 1), the second 6 months later (visit 2), and the third 12 months after the initial visit (visit 3). They underwent neuropsychiatric and videopolysomnography assessments at each visit. Healthy participants who were matched for age and sex and recruited from Hospital Clínic de Barcelona underwent the same investigations at study entry and at 12 months. Cross-sectional comparisons of clinical features between groups were done with conditional logistic regression, and binary logistic regression was used to assess associations between cognitive outcomes at 12 months and clinical features before initial immunotherapy and at study entry.

Findings Between May 1, 2019, and Sept 30, 2022, 42 participants agreed to be included in this study. 24 (57%) participants had anti-LGI1 encephalitis (mean age 63 years [SD 12]; 13 [54%] were female and 11 [46%] were male) and 18 (43%) were healthy individuals (mean age 62 years [10]; 11 [61%] were female and seven [39%] were male). At visit 1 (median 88 days [IQR 67–155] from initiation of immunotherapy), all 24 patients had one or more symptoms; 20 (83%) patients had cognitive deficits, 20 (83%) had psychiatric symptoms, 14 (58%) had insomnia, 12 (50%) had rapid eye movement (REM)-sleep behaviour disorder, nine (38%) had faciobrachial dystonic seizures, and seven (29%) had focal onset seizures. Faciobrachial dystonic seizures were unnoticed in four (17%) of 24 patients and focal onset seizures were unnoticed in five (21%) patients. At visit 1, videopolysomnography showed that 19 (79%) patients, but no healthy participants, had disrupted sleep structure (p=0·013); 15 (63%) patients and four (22%) healthy participants had excessive fragmentary myoclonus (p=0·039), and nine (38%) patients, but no healthy participants, had myokymic discharges (p=0·0051). These clinical and videopolysomnographic features led to additional immunotherapy in 15 (63%) of 24 patients, which resulted in improvement of these features in all 15 individuals. However, at visit 3, 13 (65%) of 20 patients continued to have cognitive deficits. Persistent cognitive deficits at visit 3 were associated with no use of rituximab before visit 1 (odds ratio [OR] 4·0, 95% CI 1·5–10·7; p=0·0015), REM sleep without atonia at visit 1 (2·2, 1·2–4·2; p=0·043), and presence of LGI1 antibodies in serum at visit 1 (11·0, 1·1–106·4; p=0·038).

Interpretation Unsuspected but ongoing clinical and videopolysomnography alterations are common in patients with anti-LGI1 encephalitis during the first year or more after initial immunotherapy. Recognising these alterations is important as they are treatable, can be used as outcome measures in clinical trials, and might influence cognitive outcome.

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Introduction

Encephalitis associated with antibodies against leucine-rich glioma-inactivated protein 1 (LGI1) is the second most common neuronal-antibody-associated encephalitis, with an estimated annual incidence of almost 1 per 1 million people.[1] Anti-LGI1 encephalitis usually

See Online for appendix

Research in context

Evidence before this study

We searched MEDLINE and Embase for articles published in English from database inception to July 1, 2023, using the MeSH terms "anti-LGI1 encephalitis", "post-acute phase", "recovery phase", "sleep disorder", "seizures", "cognitive", "psychiatric", and "dysfunction". This search showed that anti-leucine-rich glioma-inactivated protein 1 (LGI1)-encephalitis is characterised by an acute phase that often presents with faciobrachial dystonic seizures or other seizures, as well as memory and cognitive alterations that are accompanied by hyponatremia, in approximately two-thirds of patients. After initial immunotherapy and symptomatic therapies, patients have residual, albeit improved, memory or cognitive deficits and absent or reduced frequency of seizures. Seven case series or single-case reports of 28 patients total from Spain, the USA, China, Türkiye, and Japan showed the presence of rapid eye movement (REM)-sleep behaviour disorder (RBD) in some patients, mainly in the acute phase, but subsequent comprehensive sleep investigations were not systematically done. Ten case series (one from France, three from the USA, two from the UK, one from the Netherlands, two from Spain, and one from Germany) focused on long-term (eg, >1 year) residual cognitive deficits or epilepsy; however, except for a few reports based on retrospective information that was extracted from clinical charts or questionnaires, no previous prospective studies have systematically examined patients during the post-acute stage (approximately 1 year after immunotherapy).

Added value of this study

Our prospective cohort study provides a deep characterisation of the post-acute stage of anti-LGI1 encephalitis. Our findings show frequent persistence of faciobrachial dystonic seizures, focal onset seizures, and alterations of sleep structure that might contribute to cognitive deficits and depression. Furthermore, up to two-thirds of patients had signs of central or peripheral nervous system hyperexcitability that improved during clinical follow-up. This knowledge is important as all these symptoms responded to additional treatment.

Implications of all the available evidence

Patients with anti-LGI1 encephalitis often have ongoing, albeit less noticeable, symptoms after initial immunotherapy. Many of these symptoms can be missed or considered resolved (eg, faciobrachial dystonic seizures or other seizures) or not investigated (eg, disruption of sleep structure) and, therefore, are undertreated or not treated at all. Moreover, these symptoms affect sleep function, which could contribute to cognitive deficits and depressive behaviour. Therefore, after immunotherapy and apparent clinical improvement (eg, in faciobrachial dystonic seizures, focal onset seizures, or short-term memory loss), patients should be followed up to assess the presence of ongoing symptoms or electrographic findings that are indicative of disease activity. Many of these symptoms are uncovered by videopolysomnography. If videopolysomnography is not available, extensive video-EEG might reveal some, but not all, of these alterations. Wrist actimetry can be useful to follow up the frequency of motor seizures at home. Persisting symptoms, such as seizures or sleep dysfunction, usually respond to additional immunotherapy and might lead to better outcomes. Early use of second-line immunotherapies, such as rituximab, might be associated with improved cognitive outcomes and should be assessed in future studies. Our findings show important differences in the clinical features and type of monitoring needed for patients with anti-LGI1 encephalitis compared with patients with anti-NMDA receptor encephalitis, which has implications for clinical trials.

manifests as limbic encephalitis and, less frequently, as new onset seizures or rapidly progressive cognitive decline.[2,3] In 40–70% of patients presenting with limbic encephalitis, symptoms are preceded by or associated with faciobrachial dystonic seizures or hyponatremia.[4,5] Patients might also have insomnia, rapid eye movement (REM)-sleep behaviour disorder (RBD), or other sleep alterations, but the frequency, duration, and outcome of these disorders are unknown.[6–8] Studies suggest that prompt immunotherapy, starting with steroids and escalating to other treatments if needed, prevents the progression of symptoms in patients presenting with faciobrachial dystonic seizures and is also effective in patients with limbic encephalitis or cognitive decline.[9,10] However, despite symptom improvement, about 70% of patients are left with residual deficits that reduce the prospect of returning to their usual activities.[2,3] The stereotyped and distinctive manifestations of faciobrachial dystonic seizures, as well as the severity of other symptoms at onset (eg, short-term memory loss or focal onset seizures) and their apparent response to immunotherapy, probably contribute to the underestimation of less noticeable, but persisting, symptoms that might lead to protracted deficits, such as cognitive impairment.

Previous reports on anti-LGI1 encephalitis focused on two stages: the acute stage, which spans from symptom onset until improvement or stabilisation after initial immunotherapy,[5,9,10] and a later stage usually considered more than 1 year after symptom onset, in which residual cognitive deficits or seizures are investigated.[2,11–14] However, there is an important gap in knowledge of the period in between, spanning the 12 months after the acute stage. Except for a few reports based on retrospective extraction of information from clinical charts or questionnaires,[2,9,10] the post-acute stage has not been investigated with prospective systematic examinations. We aimed to characterise the post-acute stage to reveal symptoms or alterations that are potentially treatable, can assist in clinical follow-up, or can influence disease outcome. We therefore designed a prospective longitudinal cohort study of patients with anti-LGI1 encephalitis who had been

	Before initial immunotherapy (n=24)	Visit 1 (n=24)	Visit 3 (n=20)
Age, years	63 (12)	63 (12)	65 (11)
Sex			
Female	13 (54%)	..	10 (50%)
Male	11 (46%)	..	10 (50%)
Ethnicity			
White	21 (88%)	..	18 (90%)
Latino	2 (8%)	..	2 (10%)
Moroccan	1 (4%)	..	0 (0%)
*HLA-DRB1*07:01* and *HLA-DQA1*02:01*	24 (100%)	..	20 (100%)
CSF cell count per mm³	1 (0–2)	..	NA
LGI1 antibodies in CSF*	22/23 (96%)	..	NA
LGI1 antibodies in serum*	21/21 (100%)	18 (75%)	8 (40%)
Hyponatremia	16 (67%)	0 (0%)	0 (0%)
Cognitive complaints	24 (100%)	19 (79%)	13 (65%)
Cognitive tests altered†	NA	20 (83%)	13 (65%)
Memory deficits predominantly	NA	15/20 (75%)	10 (50%)
Executive deficits predominantly	NA	4/20 (20%)	2 (10%)
Generalised dysfunction	NA	1/20 (5%)	1 (5%)
Behavioural or psychiatric complaints‡	21 (88%)	22 (92%)	12 (60%)
Psychiatric tests altered	NA	20 (83%)	9 (45%)
Global psychosocial functioning altered	24 (100%)	22 (92%)	8 (40%)
Faciobrachial dystonic seizures reported	13 (54%)	5 (21%)	0 (0%)
Faciobrachial dystonic seizures recorded	4 (17%)	9 (38%)	0 (0%)
Focal onset seizures reported	21 (88%)	4 (17%)	2 (10%)
Focal onset seizures recorded	9/23 (39%)	7 (29%)	1 (5%)
Sleep symptoms reported	17 (71%)	14 (58%)	2 (10%)
Insomnia	11 (46%)	14 (58%)	2 (10%)
Excessive daytime sleepiness	4 (17%)	6 (25%)	1 (5%)
Hypersomnia	3 (13%)	0 (0%)	0 (0%)
RBD episodes reported	12 (50%)	2 (8%)	0 (0%)
RBD episodes recorded	NA	12 (50%)§	0 (0%)
Other nocturnal behaviours reported¶	10 (42%)	1 (4%)	0 (0%)
Other nocturnal behaviours recorded¶	NA	4 (17%)	0 (0%)

(Table continues on next page)

recently treated with conventional immunotherapy to characterise the symptoms and other alterations of the post-acute stage using comprehensive neurological, sleep, psychiatric, and cognitive investigations.

Methods

Study design and participants

In this prospective cohort study, patients with anti-LGI1 encephalitis who had been treated with conventional immunotherapy were invited to participate. Anti-LGI1 encephalitis was diagnosed in patients who had difficulty forming new memories (ie, short-term memory deficit), had seizures, or had cognitive or psychiatric alterations with or without CSF inflammatory changes and with or without brain MRI showing T2-fluid-attenuated inversion recovery increased signal in medial temporal lobes, accompanied by the demonstration of LGI1 antibodies in serum or CSF. Immunotherapy was in line with that used in previous studies.[2,3,10,15,16] Treatment before entry into this study could have included initial steroids plus intravenous immunoglobulins or plasma exchange depending on the severity and persistence of symptoms at the discretion of the physician and, if no recovery, escalation to second-line immunotherapy, usually including rituximab or cyclophosphamide.

Patients were identified by advertising the study through a network of hospitals in Spain and to physicians who contacted Hospital Clínic de Barcelona (Barcelona, Spain) for neuronal antibody testing. Patients were excluded if they had an interval of more than 1 year since initial immunotherapy, pre-existing neurodegenerative or psychiatric disorders, or were unable to travel to Hospital Clínic de Barcelona; patients were recruited from 21 hospitals.

This study consisted of three visits at Hospital Clínic de Barcelona: the first at study entry (visit 1), the second 6 months later (visit 2), and the third 12 months after the initial visit (visit 3). At each visit, patients underwent neurological examination, cognitive assessment, psychiatric and functional evaluation, sleep studies, daytime EEG, and brain MRI. Similar assessments, without sleep investigations at 6 months, were done in a group of healthy individuals without current evidence or history of encephalitis or neuropsychiatric disorders, matched by sex and age (within a range of 5 years) and recruited in Hospital Clínic de Barcelona.

The study was approved by the Ethical Board Committee of Hospital Clínic de Barcelona. Written informed consent was obtained from all participants at study entry.

Procedures

We obtained demographic information through interviews with participants and their families and obtained clinical information about symptom onset and initial immunotherapy though review of medical records and data provided by initial treating physicians. At study visits, patients were accompanied by a caregiver who provided additional information on neurological symptoms and sleep problems through structured questionnaires (appendix p 2). Sex data were self-reported by participants; the options were male or female.

All participants underwent structured cognitive and psychiatric evaluations at each visit. Cognitive assessment comprised eight domains (ie, general intellectual abilities, verbal learning and memory, visual learning and memory, language, working memory, attention, processing speed, and executive functions) that measured 22 variables (appendix p 6).

Psychiatric and functional evaluation comprised socioeconomic status, psychiatric diagnosis interview, psychotic symptom severity, depression symptom severity, mania symptom severity, global psychosocial performance (assessed with the Global assessment of

functioning scale [GAF]), and clinical state (based on the modified Rankin scale [mRS]; appendix p 7).

Sleep studies included a structured interview with patients and their families, four sleep questionnaires, and nocturnal videopolysomnography with extended EEG (appendix p 2). Furthermore, all participants had a 30-min daytime EEG that was recorded the morning after videopolysomnography. Healthy individuals did not undergo videopolysomnography at visit 2.

Actimetry recordings were obtained 2 weeks after each visit (appendix 2).

Patients who received additional treatment at study entry on the basis of clinical and videopolysomnography findings (eg, short-term memory loss, faciobrachial dystonic seizures, or focal onset seizures) underwent another videopolysomnography in the next 3 months to assess clinical response.

Statistical analyses

Sample size was based on the duration of the project; the total number of patients identified during this period; and our experience with a previous study examining the post-acute stage of anti-NMDA receptor encephalitis, in which a similar number of patients was recruited.[17] The unequal number of patients with anti-LGI1 encephalitis and healthy participants was due to the restricted period of recruitment and unexpected logistics issues caused by the COVID-19 pandemic, which restricted hospital admissions for healthy participants.

Descriptive statistics are shown as mean (SD), if a normal distribution was confirmed by the Kolmogorov-Smirnov test, or median and IQR for quantitative variables, and as absolute frequency for qualitative variables.

Cross-sectional comparisons of clinical features between groups at each visit were done via conditional logistic regression to account for matching. Comparisons within patients with anti-LGI1 encephalitis were done with χ^2, Fisher's exact, Mann-Whitney U, Wilcoxon signed-rank, and McNemar's tests. Results for cognition included comparisons of patients' performance with healthy participants (raw data) and to normative data of the general population based on each test guidelines (appendix p 3). Binary logistic regression was used to assess associations between cognitive outcomes at 12 months (categorised as having or not having deficits in each cognitive domain) and clinical features before initial immunotherapy and at study entry to predict a binary outcome at 12 months on the basis of baseline clinical variables; the linearity assumption underlying the logistic regression model for quantitative predictors was tested by cubic regression splines with three knots.

To address missing data, we used an all available data strategy. We analysed longitudinal follow-up data with a multilevel mixed-effects models, adjusting for age, sex, and socioeconomic status as potential confounders. Loss to follow-up was considered to be missing at random and post-hoc analyses were done with the Tukey method for correction for multiple testing.

In all analyses, p values were two-tailed and statistical significance was established at $p<0·05$. Statistical analyses were conducted with SPSS version 24 and R version 4.2.1.

	Before initial immunotherapy (n=24)	Visit 1 (n=24)	Visit 3 (n=20)
(Continued from previous page)			
Dizzy spells reported	8 (33%)	0 (0%)	0 (0%)
Autonomic dysfunction‖	10 (42%)	2 (8%)	0
Leg pain and cramps reported	4 (17%)	0 (0%)	0 (0%)
Atypical MRI	17 (71%)	13 (54%)	10 (50%)
Limbic inflammatory signs (unilateral)	7 (29%)	2 (8%)	0 (0%)
Limbic inflammatory signs (bilateral)	8 (33%)	1 (4%)	0 (0%)
Extralimbic inflammatory	1 (4%)	0 (0%)	0 (0%)
Temporal atrophy	0 (0%)	10 (42%)	10 (50%)
Temporal hippocampal sclerosis	0 (0%)	5 (21%)	10 (50%)
Treatments other than immunotherapy			
Hypnotics	10 (42%)	12 (50%)	6 (30%)
Antidepressants	7 (29%)	5 (21%)	4 (20%)
Anti-seizure drugs	16 (67%)	20 (83%)	12 (60%)

Data are n (%), mean (SD), or median (IQR). Sex and ethnicity data were self-reported. CSF was not obtained at any of the study visits. CASPR2=contactin-associated protein-like 2. LGI1=leucine-rich glioma-inactivated protein 1. NA=not available. RBD=REM-sleep behaviour disorder. REM=rapid eye movement. *None of the patients had CASPR2 antibodies in serum or CSF. †Patterns of cognitive impairment showing moderate to severe deficits. ‡Behavioural or psychiatric complaints included anxiety, irritability, aggressiveness, bizarre or uninhibited behaviour, psychotic symptoms, depressive mood, obsessions, and compulsive eating. §These 12 patients included nine who described RBD-like episodes before initial immunotherapy and three patients without information regarding RBD-like episodes (eg, patients unaware of them or without testimonies). The proportion is calculated using a denominator of 21 patients, the other three could not be assessed due to absent REM sleep. ¶One or more other nocturnal behaviours including finalistic or manipulatory behaviours asleep (three [13%] of 24 before initial immunotherapy and 0 [0%] of 24 at visit 1), confusional episodes (three [13%] before initial immunotherapy and two [8%] of 24 at visit 1), nocturnal eating (three [13%] before initial immunotherapy and one [4%] at visit 1), and nocturnal enuresis (four [17%] before initial immunotherapy and two [8%] at visit 1). ‖Autonomic dysfunction included new onset urinary incontinence, hypertensive crises, episodes of intense cold, increased sweating, bradycardia or cardiac pauses, erectile dysfunction, hyperphagia with weight gain, early satiety, and weight loss.

Table: **Clinical features of patients with anti-LGI1 encephalitis**

Role of the funding source

The funder of the study had no role in study design, data collection, data analyses, data interpretation, or writing of the report.

Results

Between May 1, 2019, and Sept 30, 2022, 42 participants agreed to be included in this study. 24 (57%) of 42 participants had anti-LGI1 encephalitis (mean age 63 years [SD 12]; 13 [54%] were female and 11 [46%] were male; table) and 18 (43%) were healthy individuals (mean age 62 years [10]; 11 [61%] were female and seven [39%] were male). Ten additional patients declined to participate (appendix p 4). 20 (83%) of 24 patients completed the study (four [17%] did not have a 12-month visit due to COVID-19 pandemic logistics). The first hospital visit was a median of 88 days (IQR 67–155) after initial immunotherapy, the second visit was a median of

9 months (8–11) after initial immunotherapy, and the third visit was a median of 15 months (14–20) after initial immunotherapy. Overall, including both patients and healthy participants, this study comprised 206 days and 103 nights in hospital and 911 h of videopolysomnography and EEG recordings.

General clinical features, HLA genotypic, and antibody studies are shown in the table. Before disease onset, all patients had a GAF score greater than 70 (median 86 [80–94]); individuals were judged to have functional impairment if their score was below 71. In 21 (88%) of 24 patients, the diagnosis of anti-LGI1 encephalitis was initially missed (appendix p 4).

The chronology of symptom presentation until initial immunotherapy and visit 1 is shown in figure 1. Median time from symptom onset until initiation of immunotherapy was 84 days (IQR 52–229). Before initial immunotherapy, patients had a median of five symptoms (3–7). All 24 (100%) patients had cognitive impairment, 21 (88%) had psychiatric or behavioural symptoms, 21 (88%) had focal onset seizures, 17 (71%) had sleep disturbances, 13 (54%) had faciobrachial dystonic seizures, ten (42%) had autonomic dysfunction, eight (33%) had dizzy spells, and four (17%) had leg pain and cramps (table).

All patients were initially treated with steroids (ie, intravenous methylprednisolone pulses then steroid taper); 14 (58%) received intravenous immunoglobulins and 11 (46%) received rituximab (appendix p 8). After these treatments, patients, their families, and treating physicians estimated a >75% reduction of faciobrachial dystonic seizures and focal onset seizures per day, and a general substantial improvement of symptoms. Nevertheless, at visit 1, 23 (96%) patients described persisting symptoms and 11 (46%) continued taking prednisone.

At visit 1, cognitive complaints were reported by 19 (79%) patients or their caregivers, compared with 24 (100%) before initial immunotherapy. Psychiatric or behavioural symptoms were reported by 22 (92%) patients or their caregivers, compared with 21 (88%) before initial immunotherapy. During examination at visit 1, 20 (83%) patients had moderate to severe cognitive deficits, which were predominantly amnestic in 15 (63%) of 24 patients, predominantly executive in four (17%), and occurred across all domains in one (4%; table). Only four (17%) of 24 patients had a psychiatric evaluation indicating no alterations. At visit 1, median GAF score was 58 (46–69) and 22 (92%) patients had a score of less than 71. Comparisons between patients and healthy participants assessing cognitive and psychiatric features are shown in the appendix (pp 9–10).

At visit 1, five (21%) patients described faciobrachial dystonic seizures, compared with 13 (54%) before

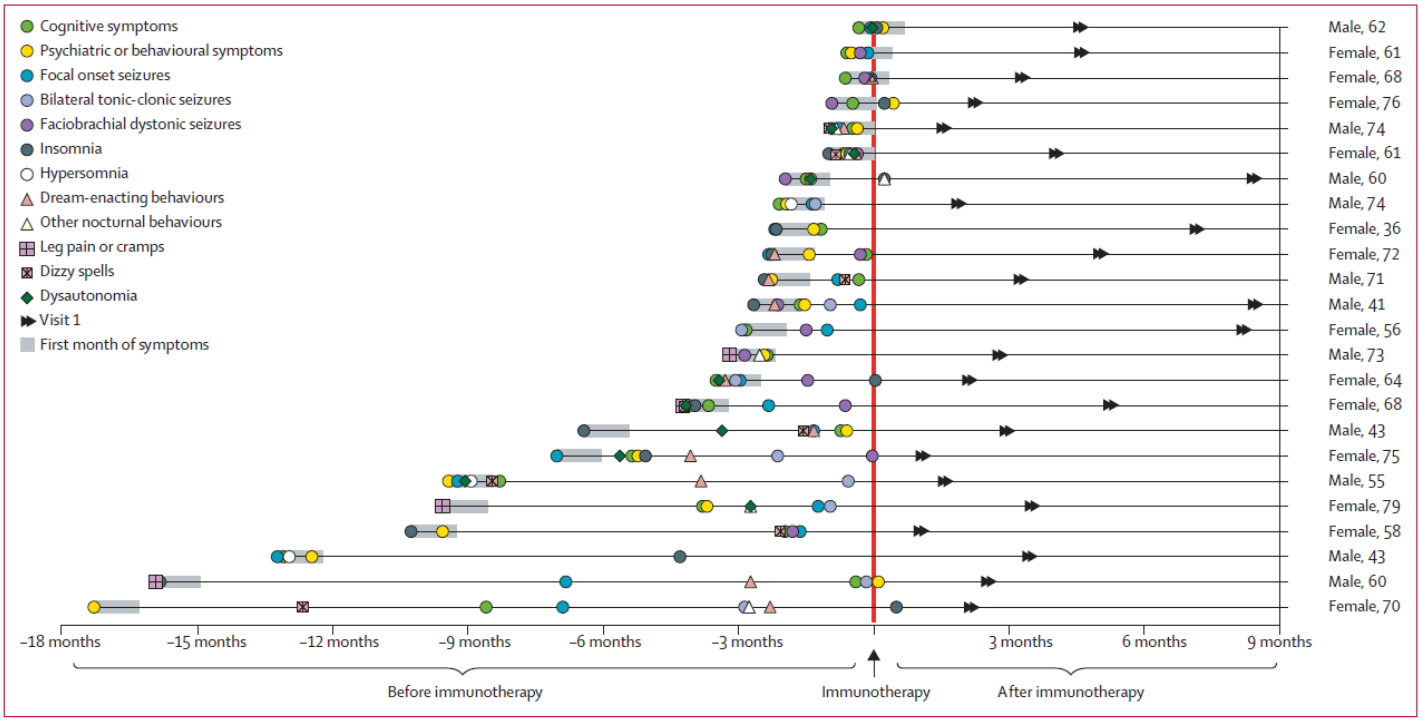

Figure 1: **Chronology of symptom presentation, initial immunotherapy, and first study visit for patients with anti-LGI1 encephalitis**
Each horizontal line corresponds to one of the 24 patients, who were sorted according to their interval from symptom onset to immunotherapy. Initiation of immunotherapy was set as timepoint zero (vertical red line), left of the red line shows symptom development before initial immunotherapy (negative months), and right of the red line shows symptom development after initial immunotherapy and until the first study visit. Symptom presentation was categorised as acute (ie, all symptoms before initial immunotherapy developed within 1 month; from top to bottom, lines 1–9 and 14), subacute (ie, all symptoms developed within 3 months before initial immunotherapy; lines 10–13 and 15), or chronic (ie, all symptoms developed during a period of more than 3 months before initial immunotherapy; lines 16–24). Numbers next to sex data are patient age (in years) at symptom presentation.

immunotherapy. Three (60%) of the five patients described daily episodes and the other two (40%) described fewer than three episodes per week. By contrast, we recorded faciobrachial dystonic seizures in these five patients and four additional patients (total nine [38%] patients with confirmed faciobrachial dystonic seizures *vs* only five [21%] being aware of them; p=0·0033) overall, comprising 72 nocturnal episodes (median 10 [IQR 7–11] per night) and 13 diurnal episodes (10 episodes in one patient and one episode each in three patients). Among the 72 nocturnal faciobrachial dystonic seizures, 55 (76%) occurred during non-REM sleep, six (8%) occurred during REM sleep, and 11 (15%) occurred when the patient was awake. Regardless of the sleep stage, 71 (99%) of 72 nocturnal faciobrachial dystonic seizures were preceded (median 5 s [3–10]) by an EEG arousal. In 32 (44%) nocturnal faciobrachial dystonic seizures, an identifiable stimulus was recorded, including 25 (78%) intentional or comfort movements, four (13%) episodes of obstructive apnoea, two (6%) coughing episodes, and one (3%) noise disturbance (video 1). Only two (22%) of these nine patients recalled the nocturnal faciobrachial dystonic seizures.

Focal onset seizures were reported at visit 1 by four (17%) of 24 patients, compared with 21 (88%) patients before initial immunotherapy. One (25%) of the four patients reported daily episodes of behavioural arrest and automatisms, one (25%) had episodes of mental block and piloerection, and two (50%) described episodes of ascending epigastric sensation. By contrast, we recorded focal onset seizures in seven (29%) of 24 patients: two of the four patients who self-reported focal onset seizures and five (21%) additional patients whose seizures had been unnoticed. Among 78 recorded focal onset seizures, 72 (92%) were nocturnal (median 14 [IQR 8–16] per night) and six (8%) were diurnal. All focal onset seizures had a frontotemporal onset (appendix pp 4–5).

Among the 72 nocturnal focal onset seizures, 63 (88%) arose from non-REM sleep, three (4%) arose from REM sleep, and six (8%) arose when awake. Most nocturnal seizures were asymptomatic or mildly symptomatic (video 2). Only one patient had conspicuous nocturnal seizures, during which she sat up, talked, and had motor automatisms (video 3). In 37 (51%) of the 72 nocturnal focal onset seizures, ictal EEG changes were immediately preceded or accompanied by a central apnoea, which was the only clinical manifestation in 21 (29%) of 72 nocturnal focal onset seizures (video 2); the other 16 (22%) seizures associated with mild symptoms. In two patients, focal onset seizures were preceded or followed by faciobrachial dystonic seizures (video 3).

Interictal epileptiform activity was identified in nine (38%) of 24 patients, two (8%) patients had intermittent bursts of diffuse delta slowing, and the remaining 13 (54%) patients and all healthy participants had an unremarkable EEG, without asymmetry, pathological slowing, or epileptiform activity.

A structured sleep anamnesis identified premorbid complaints in nine (38%) of 24 patients and four (22%) of 18 healthy participants (appendix p 4). Insomnia presented with several patterns and was prominent before initial immunotherapy (11 [46%] of 24 patients) and at visit 1 (14 [58%] of 24 patients), with some patients complaining of associated daytime sleepiness (four [17%] before immunotherapy and six [25%] at visit 1). Hypersomnia occurred only before initial immunotherapy in three (13%) patients who reported spending 2–7 h more than usual in bed (figure 2). Other sleep parameters are described in the appendix (p 4).

At visit 1, videopolysomnography showed that 19 (79%) patients, but no healthy participants, had atypical sleep structure (p=0·013). Compared with healthy participants, patients were more likely to have a higher percentage of wake after sleep onset (WASO), long WASO periods (ie, >30 min), and lower percentages of non-REM N3 and REM sleep (appendix p 11). These alterations resulted in low sleep quality (ie, <1·5 SD of the mean of healthy participants; appendix p 2) in 14 (58%) patients versus in one (6%) healthy participant (p=0·019). Sleep quality was particularly influenced by seizures. In patients with focal onset seizures during sleep, 44 (67%) of 66 seizures awakened the patient for a median of 4·0 min (IQR 1·5–12·0); in patients with faciobrachial dystonic seizures during sleep, 59 (97%) of 61 episodes awakened the patient for a median of 1·0 min (0·5–2·0). All these alterations resulted in three atypical patterns of hypnograms (figure 2B).

See Online for video 1

At visit 1, dream-enacting behaviours suggestive of RBD (eg, jerks, punches, kicks, and vocalisations) were reported by the families of two (8%) of the 24 patients whereas similar, but more intense, behaviours were reported in 12 (50%) patients before initial immunotherapy (table). Three patients had finalistic behaviours, similar to Morvan syndrome, including manipulation of inexistent objects before initial immunotherapy (video 4). By contrast with the low number of patients with reported dream-enacting behaviours (two [8%]), we identified, via videopolysomnography, ten additional patients (total 12 [57%] of 21 patients who were assessable) with behaviours and motor events that were typical of RBD (appendix p 11; video 5). Three (13%) of 24 patients could not be assessed due to insufficient REM sleep.

See Online for video 4

See Online for video 2

See Online for videos 3 and 5

Electromyography during videopolysomnography identified two patterns suggesting neuronal or peripheral nerve hyperexcitability (figure 2C). The first pattern was random, multifocal, polymorphic, short-lasting discharges affecting limbs and rarely the chin (or excessive fragmentary myoclonus),[18] seen in 15 (63%) patients compared with four (22%) healthy participants (p=0·039). The second pattern was rhythmic single unit discharges or bursts of high-frequency discharges involving the chin and rarely the limbs (ie, myokymic discharges), which were more evident during deep non-REM or REM sleep (due to lower background muscle tone) an, were seen in

nine (38%) patients and no healthy participants (p=0·0051; appendix p 11). Although none of the patients complained of cramps or pain at visit 1, three (75%) of four patients who had these symptoms before initial immunotherapy showed electromyography hyperexcitability at visit 1.

The unexpected number of alterations (eg, faciobrachial dystonic seizures, focal onset seizures, and sleep

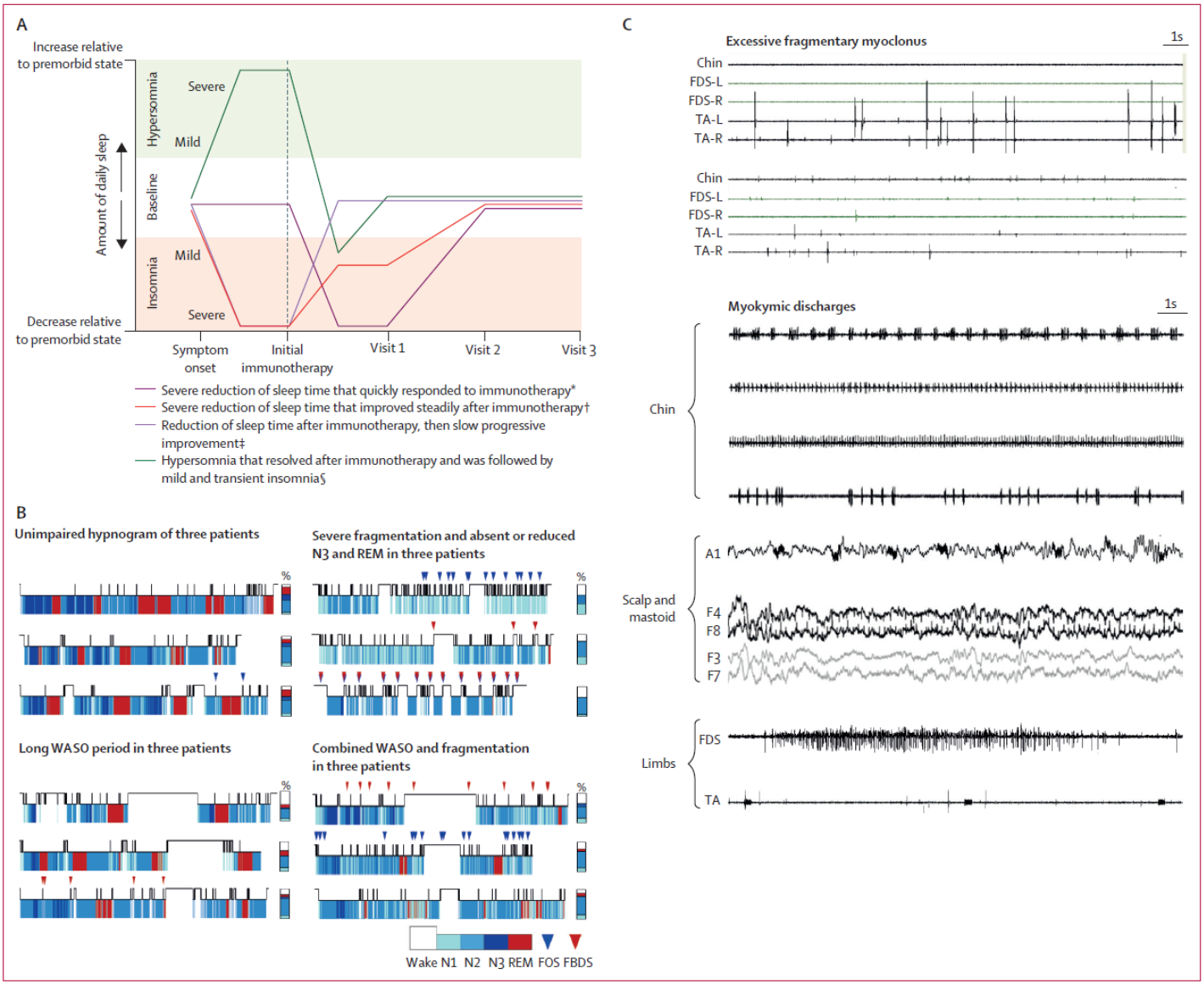

Figure 2: **Clinical sleep study and videopolysomnography findings**
(A) Different patterns of insomnia and hypersomnia in patients with anti-LGI1 encephalitis, represented as the amount of daily sleep (vertical axis) at indicated timepoints, scored by patients in a semiquantitative scale that ranges from severe insomnia to severe hypersomnia and compared with their premorbid state (baseline). Dotted line indicates initiation of immunotherapy. (B) Representative hypnograms (based on one nighttime in-bed period) of the four main patterns of sleep structure in patients with anti-LGI1 encephalitis. Unimpaired hypnograms of three patients show low percentages of wake and normal distribution and percentages of non-REM N3 and REM sleep. The middle hypnogram here terminates earlier than the other two, but is otherwise unremarkable. In hypnograms showing a long WASO period, all other sleep stages are present but mildly reduced as a consequence of the increased wake time. In the hypnograms indicating severe sleep fragmentation and absent or reduced non-REM N3 and REM sleep, all three patients had focal onset seizures (blue arrows), faciobrachial dystonic seizures (red arrows), or both. Hypnograms representing combined WASO and fragmentation indicate a combination of a long WASO period and severe sleep fragmentation and absent or reduced non-REM N3 and REM sleep. Vertical columns next to each hypnogram show the distribution of wake-sleep epochs by proportions of time in bed (ie, whole size represents 100% of time in bed). (C) Excessive fragmentary myoclonus is shown in two examples. Random, irregular, short-lasting discharges were recorded over lower limb channels (top example) and lower limb and chin channels (bottom example). Myokymic discharges show regular patterns that varied in frequency, periodicity, and duration. For each location, each channel corresponds to a different patient, except for the lowest four channels in scalp and mastoid (ie, one patient). Here, the myokymic discharges were present on the right side (black channels) and absent on the left (grey channels). A1, F4, F8, F3, and F7 represent scalp electroencephalogram electrodes placed at these positions of the 10–20 International System. 1s=1 s of recording. FBDS=faciobrachial dystonic seizures. FDS=flexor digitorum superficialis. FOS=focal onset seizures. L=left. LGI1=leucine-rich glioma-inactivated protein 1. R=right. REM=rapid eye movement. TA=tibialis anterior. WASO=wake after sleep onset. *Three (100%) male patients. †Six (100%) female patients. ‡Two (40%) male patients and three (60%) female patients. §Three (100%) male patients.

fragmentation) at visit 1 led to additional immunotherapy in 15 (63%) of 24 patients (appendix p 8), which resulted in improvement of these features in all patients. A new videopolysomnography obtained in these 15 patients 9–12 weeks after additional immunotherapy showed remission or a greater than 75% decrease of seizure frequency in all patients, as well as normalisation or improvement of RBD in six (60%) of ten patients and of sleep quality in seven (78%) of nine patients. No differences regarding initial immunotherapy (ie, steroid dose, taper, or immunotherapy escalation) were noted between patients who showed high morbidity, requiring additional treatment, at visit 1 and those who did not. However, among patients who had received rituximab before the initial study visit, those who were treated earlier were less likely to have high morbidity (appendix p 8).

One (4%) patient had a relapsing episode of anti-LGI1 encephalitis 5 months after the initial study visit that resolved with immunotherapy (panel; appendix p 13). Here and with other patients, actimetry was useful to track disease activity in outpatient settings (appendix p 4).

Regarding follow-up of symptoms (table), all patients had a progressive decrease in the number of symptoms, although 14 (70%) of 20 still had 1–4 symptoms at visit 3 (figure 3A). Faciobrachial dystonic seizures was the only feature that resolved in all patients (figure 3B).

The most substantial cognitive improvement occurred between visits 1 and 2; however, some domains plateaued during visits 2 and 3 (appendix p 14). Overall, at visit 3, 13 (65%) of 20 patients had cognitive deficits. They were predominantly amnestic in ten (50%) of 20, executive in two (10%), and generalised in one (5%; table). Visual learning and memory was the most affected domain, remaining impaired in 11 (55%) of 20 patients (appendix p 14). At visit 3, the only remaining psychiatric symptoms were mild depression in nine (45%) of 20 patients—one of them also had psychotic features. These nine patients had concurrent cognitive deficits, compared with four (36%) of 11 without psychiatric alterations (p=0·0053).

None of the patients had seizures at visit 2, but three (15%) of 20 patients had seizure recurrence at visit 3 (figure 3B). Two of these three patients had temporal lobe sclerosis and the other had an MRI without evidence of temporal lobe sclerosis. Ten (50%) of 20 patients had hippocampal sclerosis or atrophy by visit 3. Despite the reduction of seizures, 12 (60%) patients remained on anti-seizure medication.

At visit 3, eight (40%) patients still had long WASO periods, which was the only videopolysomnography parameter that was different from healthy participants (appendix p 11). Only two (10%) of 20 patients, compared with 14 (58%) of 24 at visit 1, continued to have low quality of sleep (appendix p 11). Excessive fragmentary myoclonus persisted in four (20%) of 20 patients at visit 3, compared with 15 (63%) of 24 patients at visit 1, and remained unchanged in four (22%) of 18 healthy participants. Two (10%) of 20 patients continued to have myokymic discharges at visit 3, compared with nine (38%) of 24 patients at visit 1 (appendix p 11).

Median GAF score at visit 3 was 75 (IQR 55–80); 12 (60%) of 20 patients had returned to their premorbid score, four (20%) had moderate deficits, and four (20%) had severe disabilities. Only 13 (65%) of 20 patients had returned to their previous activities or jobs. Median GAF score for healthy participants was 89 (85–91) and each participant remained with a GAF score of more than 70 (appendix p 10).

Panel: **A patient with relapsing symptoms of anti-LGI1 encephalitis**

A woman aged 61 years with unremarkable medical history, other than well controlled high blood pressure, developed insomnia due to recurring unexplained nocturnal awakenings and dizzy spells. Treatment with lorazepam 1 mg at bedtime for 3 days was unsuccessful and her symptoms worsened, with frequent nightmares, movements, and vocalisations during sleep. 10 days after symptom onset, she became forgetful for recent events, repeated herself, was disoriented, had obsessive behaviours, and complained of short-lasting episodes (ie, only seconds) of feeling "freezing cold", which was initially attributed to anxiety by her physician. 2 weeks later, she developed short-lasting involuntary movements that were compatible with faciobrachial dystonic seizures and recurrent hypertensive crises (highest blood pressure 205/110 mm Hg), for which she was brought to the emergency room. After detecting hyponatremia (125 mEq/L) and asymmetric increase in signal in the medial temporal lobes on MRI fluid-attenuated inversion recovery, the woman was admitted to hospital for suspected autoimmune encephalitis and started on intravenous methylprednisolone (1 g per day for 5 days). The frequency of faciobrachial dystonic seizures decreased rapidly (from approximately 100 per day to <10 per day) and resolved within 2 weeks. Memory and behaviour progressively improved during the next 7 days and leucine-rich glioma-inactivated protein 1 (LGI1) antibody testing returned positive, supporting the diagnosis of anti-LGI1 encephalitis. The woman was then discharged with progressive tapering of oral prednisone and lacosamide 100 mg per day, which resulted in stable cognitive deficits and absent faciobrachial dystonic seizures. However, when the dose of prednisone was reduced to 30 mg per day, her sleep symptoms and faciobrachial dystonic seizures returned, prompting an increase of the doses of prednisone (45 mg per day) and lacosamide (200 mg per day), which led to substantial improvement.

At visit 1, 4 weeks after the indicated readjustments of treatment, the patient reported about five daily episodes that were compatible with faciobrachial dystonic seizures and frequent nocturnal awakenings with a feeling of startle. However, videopolysomnography showed 11 episodes of faciobrachial dystonic seizures that awakened her repeatedly (appendix p 13). Overall, the findings at visit 1 led to additional treatment with intravenous methylprednisolone (1 g per day for 5 days) combined with intravenous immunoglobulins (0·4 g/kg per day for 5 days), resulting in progressive improvement. Repeat videopolysomnography 2 months later showed only two faciobrachial dystonic seizures and clear improvement of the sleep structure (eg, reduced sleep fragmentation and increased non-rapid eye movement [REM] N3 and REM time; appendix p 13). Treatment was then planned to be maintained with prednisone 30 mg per day and lacosamide 200 mg per day until visit 2. However, 2 weeks before visit 2 (approximately 10 months after disease onset), the patient's family reported relapsing symptoms, supported by worsening actimetry recordings (appendix p 13). 2 weeks later, during the visit 2 admission, 8-h videopolysomnography showed 25 faciobrachial dystonic seizures and severe sleep fragmentation that responded to intravenous immunoglobulins and rituximab (appendix p 13). At visit 3, the videopolysomnography and actimetry showed no sleep disruption and only mild cognitive-executive deficits and minor depressive symptoms were identified (appendix p 13).

Eight (62%) of 13 patients with residual cognitive deficits had other residual symptoms, compared with one (14%) of seven who had full cognitive recovery (p=0·073). Cognitive performance did not normalise in any of the 5 (25%) of 20 patients who still had RBD at visit 3. Through binary logistic regression, we found that persistent cognitive deficits at visit 3 were associated with no use of rituximab before visit 1 (odds ratio [OR] 4·0, 95% CI 1·5–10·7; p=0·0015), REM sleep without atonia at visit 1 (2·2, 1·2–4·2; p=0·043), and presence of LGI1 antibodies in serum at visit 1 (11·0, 1·1–106·4; p=0·038; appendix p 12).

Discussion

More than 90% of patients with anti-LGI1 encephalitis who were treated with conventional immunotherapy had one or more persisting symptoms 3 months later (ie, by the time of visit 1). Most patients had cognitive and psychiatric deficits that were somewhat expected on the basis of findings from previous studies on long-term residual deficits.[2,3,11,12] However, about two-thirds of patients had one or more alterations (eg, faciobrachial dystonic seizures or focal onset seizures) that were unnoticed after immunotherapy, clinically undetectable (eg, RBD and other sleep alterations), or for which severity was incorrectly estimated unless they were examined with videopolysomnography. Characterisation of these unanticipated features is important because all patients improved after additional immunotherapy.

Oligosymptomatic or subclinical focal onset seizures occur in people with anti-LGI1 encephalitis,[19,20] but our results suggest that their frequency and duration, as well as the frequency and duration of faciobrachial dystonic seizures and RBD, beyond the acute phase have been underestimated previously.[3,21,22] The design of our study, with extensive videopolysomnography, revealed these alterations and the interweaving effects of some symptoms. For example, in addition to primary sleep disturbances such as insomnia, RBD, long WASO periods, or Morvan-syndrome-like manipulatory behaviours, we quantitatively showed how faciobrachial dystonic seizures and focal onset seizures disrupted sleep, leading to its fragmentation and poor quality. These alterations might have contributed to the suboptimal recovery of cognitive functions (eg, none of the five patients with residual RBD had full recovery of cognitive functions), but further studies with larger cohorts and longer follow-up are needed to substantiate this association.

We found a complex group of sleep disturbances and signs of neuronal or peripheral nerve hyperexcitability (eg, excessive fragmentary myoclonus and myokymic discharges) that had not been previously reported. Fasciculations, myokymia, and neuromyotonia have been described in the context of neuropathic pain or

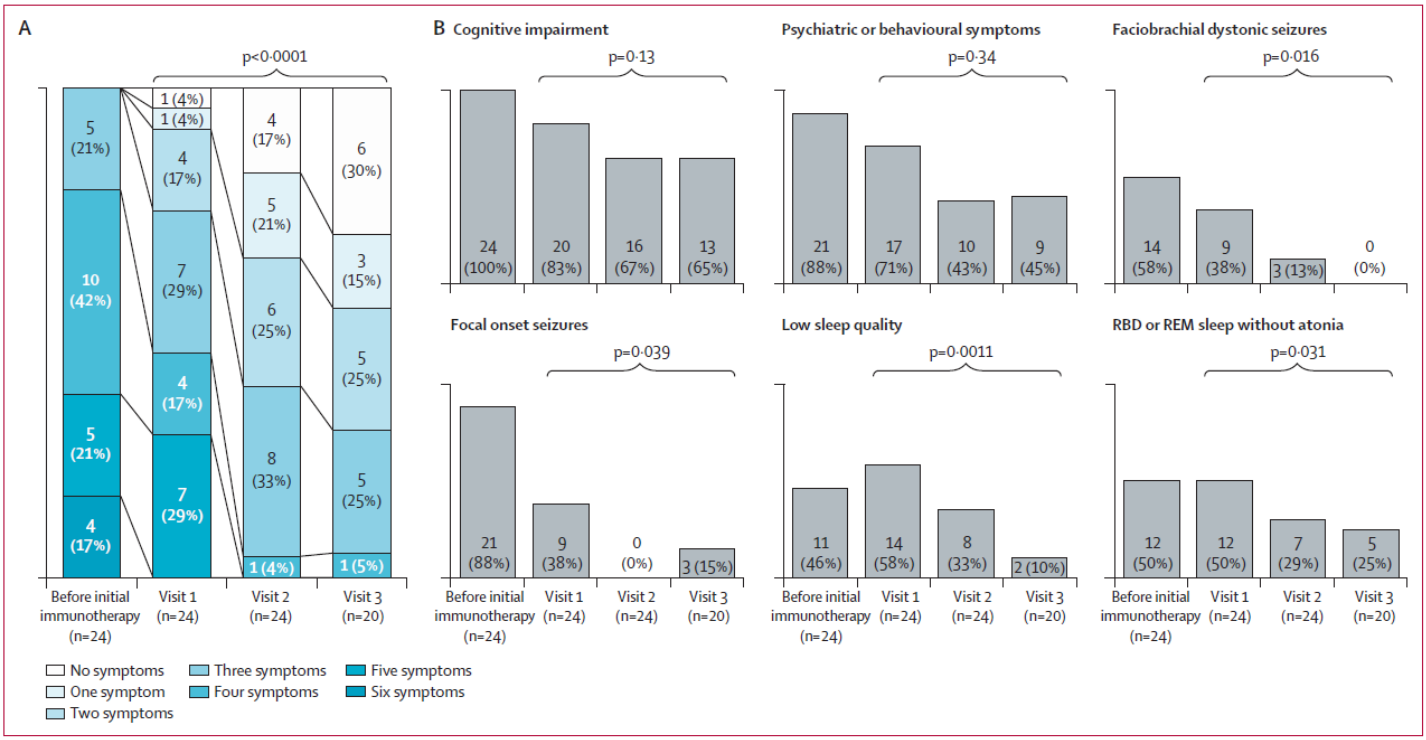

Figure 3: **Time course of symptoms and specific symptom evolution in patients with anti-LGI1 encephalitis**
(A) Proportions of patients with one to six major sets of symptoms (ie, cognitive impairment, psychiatric or behavioural symptoms, faciobrachial dystonic seizures, focal onset seizures, low quality of sleep, and RBD or REM sleep without atonia) before initial immunotherapy and during the three follow-up visits. (B) Proportions of patients with the indicated symptoms at the indicated timepoints. p values were obtained by comparing the number of symptoms per patient at visit 1 and visit 3 via the Wilcoxon signed-rank test. Sleep quality before initial immunotherapy was estimated on the basis of patient complaints. LGI1=leucine-rich glioma-inactivated protein 1. RBD=REM-sleep behaviour disorder.

cramps in patients with anti-LGI encephalitis, but not in patients without these symptoms or in the post-acute stage.[21] Although LGI1 antibodies affect neuronal hyperexcitability,[23] the exact mechanisms underlying these electromyography findings are unclear.

Compared with a report on the post-acute stage of anti-NMDA receptor encephalitis that used a similar study design,[17] symptoms in patients with anti-LGI1 encephalitis are different. Patients with anti-NMDA receptor encephalitis usually present with severe insomnia, followed by a protracted symptom inversion (ie, hypersomnia) during the post-acute stage.[24,25] By contrast, patients with anti-LGI1 encephalitis present with transient insomnia or hypersomnia without a clear inversion of symptoms during follow-up. The only videopolysomnography finding in patients during the post-acute stage of anti-NMDA receptor encephalitis was an increase of confusional arousals, without faciobrachial dystonic seizures, absent or rare focal onset seizures, absence of the indicated sleep alterations, and undisturbed sleep structure.[17,24] By contrast, in patients with anti-LGI1 encephalitis, most of these alterations are present, except confusional arousals, and only one-fifth of patients have an unimpaired sleep structure. Furthermore, in patients with anti-NMDA receptor encephalitis, post-acute psychiatric and cognitive symptoms (eg, executive profile and steady working memory deficits) transiently resemble those of schizophrenia,[17] whereas in patients with anti-LGI encephalitis, post-acute cognitive symptoms show a predominant amnestic profile and the psychiatric component is mainly represented by depressive symptoms.

Systematic 8-h diurnal video EEG, similar to that included in our videopolysomnography studies, might have identified a similar frequency of faciobrachial dystonic seizures or focal onset seizures. However, videopolysomnography provided several advantages beyond the study of sleep.[26] For example, synchronised EEG with breathing function facilitated the identification of seizures heralded by ictal apnoeas. Moreover, the reduction of muscle tone during sleep uncovered myokymic discharges, which can be difficult to detect in daytime recordings due to an increased awake electromyography background.

Our study has several considerations and limitations. Patients with anti-LGI1 encephalitis were unselected, had the expected symptom repertoire, and were treated with an immunotherapy approach similar to that recommended in previous studies,[2,3,10,15,16] which allows for generalisation of our findings. However, comparison with previous studies is difficult because in most of them the exact dose of steroids, duration of taper, or pace of immunotherapy escalation are not well defined. Many alterations (eg, focal onset seizures, faciobrachial dystonic seizures, and sleep symptom complex) do not occur in healthy people, minimising the need for a larger control group. Nonetheless, 18 healthy participants were recruited despite the challenges posed by the COVID-19 pandemic. The small sample size of our study restricts confounding adjustment and, together with the low prevalence of some events and the large amount of data obtained, might lead to imprecise associations.[27] We therefore emphasise the exploratory nature of our study and have focused on the findings that are potentially relevant as suggested by their coherence and plausibility. Although some treatments (eg, steroids, hypnotics, antidepressants, or anti-seizure medications) can potentially affect sleep structure, we did not find differences related to their use (data not shown).

Our findings have several important implications. Patients with anti-LGI1 encephalitis usually have ongoing, albeit less noticeable, symptoms after initial immunotherapy; these symptoms are prematurely considered to be resolved or not investigated and, therefore, are undertreated or not treated. These symptoms unequivocally affect sleep function, which, in turn, can contribute to cognitive deficits and depressive behaviour. Our findings should be considered in the design of any clinical trial that aims to assess the effects of interventions on different aspects of the disease. We also suggest the need for close clinical and EEG follow-up, ideally with videopolysomnography. If videopolysomnography is not available, periodic EEG monitoring should be considered—for example an 8-h EEG (including sleep) obtained about 3 months after initial immunotherapy and, if that EEG shows an altered pattern, every 4 months according to the clinical course after additional treatment. Wrist-actimetry can assist in monitoring some of the symptoms (eg, faciobrachial dystonic seizures or focal onset seizures) at home,[28,29] but is less sensitive and specific and should complement videopolysomnography, which is the gold-standard sleep investigation. Finally, persisting symptoms, such as seizures or sleep dysfunction, usually respond to additional immunotherapy.

Tasks for the future include the assessment of the potential role of some investigations (eg, REM sleep without atonia or electromyography hyperexcitability) as quantitative markers of early outcomes or long-term cognitive impairment in clinical trials. Another task will be to establish whether early or extended second-line immunotherapies (eg, rituximab), combined with cognitive training and symptomatic management of sleep dysfunction, improve cognitive outcomes.

Contributors

AM-L designed and conceptualised the study; collected, interpreted, and verified the data; conducted the sleep and EEG investigations, statistical analyses, and the literature search; created the figures, videos, and tables; and wrote the final manuscript. MG designed and conceptualised the study; collected, interpreted, and verified the data; conducted the antibody investigations, statistical analyses, and literature search; created the figures and tables; and wrote the final manuscript. JS designed and conceptualised the study, conducted the sleep and EEG investigations and the literature search, interpreted data, created the figures and tables, and wrote the manuscript. JD designed and conceptualised the study, interpreted and verified the

data, conducted the literature search, wrote the manuscript, and obtained funding. LP, EM-H, and MR-J designed the study and collected and interpreted data. VP, TA, and LR interpreted data. RB conducted statistical analyses. JC-F and AC designed and conceptualised the study. CG interpreted the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JD has patents for the use of Ma2, N-methyl-D-aspartate receptors, $GABA_B$ receptors, $GABA_A$ receptors, dipeptidyl-peptidase-like protein-6, and IgLON5 as autoantibody tests. All other authors declare no competing interests.

Data sharing

Anonymised participant data can be shared with qualified investigators on request to the corresponding author, from the date of publication onwards.

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SUPPLEMENTARY MATERIAL

Neurologic, psychiatric, and sleep investigations after initial treatment of anti-LGI1 encephalitis: a prospective cohort study

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e-METHODS

Sleep studies

1) A structured interview was carried out with the patient and family members assessing history of sleep disorders, current sleep habits, and complaints such as sleep-onset insomnia (difficulty falling asleep within 30 minutes); sleep fragmentation (more than two awakenings of >15 minutes); early awakening (waking up > 2 h earlier than desired); hypersomnolence including excessive daytime sleepiness (difficulty to stay awake during the day resulting in unintended episodes of sleep) or hypersomnia (excessive need for sleep with increased number of hours of sleep per day); nightmares; dream-enacting behaviours; episodes of nocturnal confusion; presence of pseudopurposeful/finalistic behaviours (goal-directed movements that seem purposeful and resemble an identifiable activity of daily life), and restless legs syndrome (following the International Restless Legs Syndrome Study Group criteria).

2) Sleep questionnaires assessing current sleep disturbances and nocturnal disability included the Pittsburgh Sleep Quality Index (PSQI),[1] the Barcelona Sleepiness Index (BSI),[2] the Epworth Sleepiness Scale (ESS);[3] and the circadian rhythm type (the degree to which respondents are active and alert at certain times of day) with a self-assessment questionnaire version of the morningness-eveningness questionnaire (MEQ-SA).[4]

3) Nocturnal video-polysomnography (VPSG) with extended EEG was performed using a digital polygraph (BrainRT™, software version 2019, Waarloos, Belgium) to record a 21-channel electroencephalogram using a sampling rate of 512 Hz, with electrodes placed according to the 10/20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, A1, T7, C3, Cz, C4, T8, A2, P7, P3, Pz, P4, P8, O1, O2). Additionally, we recorded right and left electro-oculograms (EOG), submental electromyogram (EMG), bilateral surface EMG of the flexor digitorum superficialis (FDS) in upper-limbs and the tibialis anterior (TA) in lower-limbs, electrocardiogram (ECG), nasal airflow by a pressure cannula, thoracic and abdominal movements, and oxyhemoglobin saturation.

   Sleep stages and associated events were scored according to standard criteria.[5] Sleep efficiency was defined as the percentage of sleep regarding the time in bed (from lights off to lights on). Sleep period time (SPT) was the time from the first to the last epoch scored as sleep, and wake-after-sleep-onset (WASO) was the wake time within the SPT. Sleep quality percentage was calculated as the sum of non-REM N3 and REM sleep divided by the SPT and was considered abnormal below normal subjects' mean minus 1.5 times the standard deviation. The percentage of REM sleep without atonia was calculated on the EMG channels of the chin and left and right FDS, using 3-second-miniepoch rule.[6] Briefly, epochs of REM sleep were divided into 3-second miniepochs and each miniepoch was scored as either having or not having any EMG activity. The percentage of REM without atonia corresponded to the percentage of the miniepochs with EMG activity of the total of miniepochs of REM sleep. At least 5 minutes of REM sleep were required to calculate the percentage of REM without atonia. Patients were considered to have definite REM sleep behaviour disorder if the VPSG showed motor events or behaviours typical of REM sleep behaviour disorder ("RBD episodes") during REM sleep *and* a percentage of REM without atonia of >30% (abnormal threshold).[7,8] When only one of these features (RBD episodes or REM without atonia >30%) was detected, patients were considered to have REM sleep behaviour disorder if they had either a history compatible with dream enacting behaviors in earlier stages of the disease or REM sleep behaviour disorder demonstrated by VPSG in previous study visits.

   Audiovisual recordings were scrutinized during wakefulness, all sleep stages, and arousals, for the identification of motor and vocal manifestations. For all motor events, we analyzed the anatomical distribution (face, arm, or leg, unilateral or bilateral), duration, sleep-wake state when they occurred, potential triggers (apneas, noises, etc.), and EEG changes preceding or accompanying the motor events.

   A 30-minute daytime EEG was recorded the morning after VPSG using 27 scalp electrodes (the former 21 and F9, F10, T9, T10, P9, and P10 to cover better the basal frontotemporal area),[9] EOG, ECG, and thoracic respiratory effort, with hyperventilation and photic stimulation maneuvers.

4) At each visit, sleep questionnaires were completed by patients or family members providing for the previous 15 days the following information: bedtime; perceived sleep latency; nocturnal awakenings (if any); wake-up and get-up times in the morning, and daytime sleep periods (when applicable).

Actimetry

A two-week actimetry (Actiwatch AW7, CamTech Ltd., UK) was performed at each study visit, as reported.[10] The device was placed in the nondominant wrist and the software was set to record motor activity as counts per epoch of 60 seconds, starting the night of the VPSG (visit 1, visit 2, visit 3) and continuing for the following 15 days at home. Recordings were downloaded and analyzed with the MotionWare software (CamTech Ltd., UK). The sleep analysis function provided a number of objective measures from overnight data for the whole recorded period. During the same period patients fulfilled sleep logs where they annotated the period of time in bed. The actimetry recordings were visually scrutinized, particularly the recording of the VPSG, to determine if any clinical event that was evidenced in the VPSG (e.g, focal seizures, faciobrachial dystonic seizures, REM sleep behaviour disorder, or long awake periods) could also be identified by the actimeter to monitor similar events while the patient was at home.[11]

Analysis of additional electromyographic activity

We looked for the presence of any type of EMG discharges outstanding from the background, other than that associated to changes in body position, periodic limb movements of sleep, hypnagogic foot movements, REM without atonia-related activity, or seizures, using electrodes placed on the chin (mentalis), arms (flexor digitorum superficialis), and legs (tibialis anterior muscles) and the scalp electrodes in the perimastoid and temporal areas. For such EMG discharges we analyzed ad hoc the localization, frequency, pattern of repetition (rhythmicity, periodicity), and persistence throughout the different sleep stages. Periods of immobile wakefulness that could potentially contain mixed rhythmic and irregular EMG discharges, and waned a few epochs after the beginning of sleep, were excluded.

HLA genotyping

HLA Class I and Class II genotyping was performed by techniques previously described.[12]

Cognitive and psychiatric assessments

Cognitive evaluation included 8 domains (general intellectual abilities/intelligence quotient, verbal learning and memory, visual learning and memory, language, working memory, attention, processing speed, and executive functions), which encompassed 22 variables explored with the instruments shown in eTable 1. Verbal and visual learning and memory functions were considered as two different domains given the limbic nature of anti-LGI1 encephalitis, previous knowledge on cognitive profiles,[13,14] and the concern to capture in detail the evolution of the full spectrum of cognitive deficits. To avoid confounding factors related to the learning effect of some tests, the general intellectual abilities (IQ) were not assessed at visit 2. Premorbid intelligence was estimated with the vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS-IV)[15] and the cognitive reserve with a standardized questionnaire.[16] Additionally, the Montreal Cognitive Assessment (MoCA)[17] was used as a global cognition-screening test. Results of the aforementioned 22 cognitive variables were standardized using the corresponding normative data (of the general population based on each test's guidelines) matched by age and education level. Raw scores were transformed into standard T-scores (mean 50 ± standard deviation [SD] 10) and a score below 35 (≤ 1.5 SD below normative mean) was considered significantly decreased. Moreover, in order to stratify the severity of the deficits, T-scores between 32 and 34 were considered mildly altered, T-scores 29-31 moderately impaired, and T-scores ≤ 28 severely impaired. A cognitive domain was defined as impaired if at least one of the corresponding variables had a score that was significantly decreased.

Psychiatric and functional evaluations included socioeconomic status, structured psychiatric interviews based on the SCID guidelines for DSM-5 criteria,[18] and scales quantifying 7 variables: symptoms of psychosis, depression, mania, and global level of psychosocial functioning.

Study assessments on cognition encompassed comparisons of anti-LGI1 encephalitis patients' performance with normative data of the general population, and with our cohort of age- and sex-matched healthy participants. When comparing to normative data, impairment was defined as at least 1.5 standard deviations below the mean ($z \leq -1.5$), and when comparing to healthy participants, the threshold for significance was $p<0.05$.

The cognitive and psychiatric alterations of anti-LGI1 encephalitis patients were cross-sectionally and longitudinally compared with our group of healthy participants using multilevel linear mixed-effect models, with group, time, age, sex and socio-economic status (which includes the level of education) as fixed variables, and the time x group as longitudinal interaction effect, using R package (v4.2.1; Vienna). The normal distribution for the random intercept terms was assumed. Lme4 R package (v1.1.30) was used to fit linear mixed-effectt models, and residual plots were used to validate the normality assumptions of the residuals. The Mauchly's test of sphericity and the visual examination of the residuals were used to assess whether or not the assumptions of sphericity and heteroscedasticity were met, respectively. Comparisons were performed with emmeans library (v1.8.1-1) and Tukey method for correction for multiple testing.

e-RESULTS

General features of patients who declined to participate in the study

10 patients declined to participate in the study because of the unwillingness to travel or to attend extra medical visits or be admitted for the indicated study investigations during or immediately after the COVID-19 pandemic. Otherwise, compared with the patients that participated (Table 1), no differences were identified regarding patients' sex (50% female, 50% male; as reported in medical charts), age (median 72, IQR 66-77), hospital of origin (50% from our region; 50% from other hospitals in Spain), time from symptom onset to diagnosis (median 70 days, IQR 33-109 days), type of presentation (3 acute, 6 subacute, 3 chronic), and use of first-line (100%) or second line (50%) immunotherapy. Two additional patients (86 and 72 years-old) died before the study could be offered, both due to respiratory complications unrelated to the encephalitis.

Diagnostic delays and treatments used before the diagnosis of anti-LGI1 encephalitis

Before the diagnosis of anti-LGI encephalitis was considered, 21 (88%) patients sought medical attention 1 to 9 times, 15 (63%) of them during the first month, including emergency department visits (14 [58%] patients); hospital admissions with alternative diagnoses (5 [21%] patients); and consultations with neurologists (12 [50%] patients), general practitioners (10 [42%] patients), or psychiatrists (2 [9%] patients). Sixteen (67%) patients received anti-seizure medications, 7 (29%) anxiolytics or antidepressants, and 6 (25%) hypnotics, for a median of 46, 58 and 63 days respectively, before the diagnosis of encephalitis was considered.

Premorbid sleep complaints in patients and healthy participants

Premorbid sleep complaints were reported by 9 (38%) patients and 4 (22%) healthy participants, including one or more of the following: sleep onset insomnia (2 [9%] patients), sleep-maintenance insomnia (3 [13%] patients, and 2 [11%] healthy participants), obstructive sleep apnea treated with CPAP (4 [18%] patients, and 1 [5%] healthy participant), restless legs syndrome (1 [4%] patient), occasional somniloquy (1 [5%] healthy participant), and nocturnal eating (1 [4%] patient).

Actimetry

Patients (#7-24) and healthy participants (#4-18) underwent actimetry assessments at each study visit and continuously during the 15 days that followed each visit. The reason for not examining the first six patients and 3 healthy participants was that actimetry was not included in the initial study design. Compared to VPSG, actimetry recordings showed high specificity (92%) but low sensitivity (34%) for the identification of wake periods during the night (data not shown); the low sensitivity was due the inability to detect VPSG-confirmed wake periods without movements. However, compared to healthy participants, patients with anti-LGI1 encephalitis were more likely to have higher activity scores (median 5005 [IQR 3906-6519] vs 1775 [IQR 1130-3738] counts per night, p=0.021) and more mobility bouts (median 44 [IQR 41-54] vs 23 [IQR 20-29] bouts per night; p=0.027) with higher fragmentation indexes (median 36 [IQR 22-47] vs 20 [IQR 15-26] p=0.010). By visual examination of actimetry recordings, seizures were distinguishable from other nocturnal movements (such as comfort movements) because they produced short-lasting, high-score bars of activity; this activity was found to be synchronous to VPSG-confirmed focal onset seizures or faciobrachial dystonic seizures. Thus, in patients with frequent faciobrachial dystonic seizures or with focal onset seizures accompanied by movements, the actigraphy served to monitor seizure frequency, response to immunotherapy, and relapses outside the hospital (Panel 1, eFigure 1).

Other sleep parameters obtained from questionnaires to patients and healthy participants

At visit 1 the PSQI showed that 20 (83%) patients had poor sleep quality (PSQI >5; median 9, IQR 5-13) as compared to 4 (22%) healthy participants (median 4, IQR 3-5) (p=0.033). At visit 3, 11 (55%) patients remained with poor perceived sleep quality (median 7, IQR 4-9). Questionnaires for excessive daytime sleepiness (ESS, BSI) did not show significant differences between patients and healthy participants (p=0.54). The circadian type was also similar between groups (intermediate type in 15 [63%] patients and 9 [50%] healthy participants, morningness type in 8 [33%] patients and 9 [50%] healthy participants, eveningness type in 1 [4%] patient only) (p=0.53), without significant changes during follow-up.

EEG characteristics of focal onset seizures

Focal seizures had frontotemporal or temporal onset in all patients: 49 (63%) episodes involved the left side, 13 (17%) the right side, and 16 (20%) were bilateral. We identified two patterns of seizures that developed recurrently: 1) a focal rhythmic 4-5 Hz theta activity evolving into slower delta frequencies and ending either abruptly or after a period of <1 Hz focal periodic discharges; and 2) a 1.5 Hz rhythmic or periodic delta barely or not evolving in frequency but evolving in amplitude, morphology, and less often in localization.

Ictal central apneas, recorded in 37 (51%) nocturnal and 2 (33%) daytime seizures, facilitated the identification of seizures that were initially unnoticed when examining EEG signals alone, particularly for focal onset seizures with barely-evolving EEG pattern. The apnea started first and the ictal EEG activity occurred simultaneously or immediately before the expected time for the first missed breath (Video 2).

Follow-up of cognitive and psychiatric features

At visit 1, anti-LGI1 encephalitis patients showed worse cognitive performance compared to healthy participants in all 8 domains explored, involving 3 of 3 variables of general intellectual abilities (IQ), 2 of 4 variables of verbal learning and memory domain, 3 of 4 variables of visual learning and memory, 1 of 1 variable of language, 1 of 2 variables of working memory, 1 of 2 variables of attention, 1 of 2 variables of processing speed, and 1 of 4 variables of executive functions (eTable 4). At the longitudinal follow-up, we analyzed trajectories of cognitive variables between and within groups using generalized multilevel mixed effect for repeated measures with time per group as longitudinal interaction fixed effects. While in general the cognitive performance was clearly influenced by the group (eTable 4, effect of group), patients with anti-LGI1 encephalitis had a significantly different (worse) trajectory of scores compared to that of healthy participants (eTable 4, time x group interaction) only in one variable of visual learning and memory (i.e., visual discrimination index). On the other hand, only the mean scores of verbal learning and memory, and working memory domains showed substantial improvement in time (eTable 4, effect of time), in parallel with the reduction of the proportion of patients showing clinically meaningful deficits throughout the study (eFigure 2).

Regarding the psychiatric assessment, at visit 1 patients scored a median of 54 (IQR 47-61) in the total Positive and Negative Syndrome Scale (PANSS; abnormal if score >57), a median of 11 (6-15) in the Hamilton Depression Rating Scale (HDRS; abnormal if score >7), and a median of 7 (3-9) in the Young Mania Rating Scale (YMRS; abnormal if score >12) (eTable 5). Individual scores were consistent with mild psychotic symptoms in 8 (33%) patients, moderate psychotic symptoms in 1 (4%) and severe psychotic symptoms in 1 (4%); mild depression levels in 13 (54%) and moderate in 4 (17%); and hypomanic symptoms in 5 (21%). At the longitudinal follow-up, patients with anti-LGI1 encephalitis significantly improved their psychiatric symptoms scores compared to healthy participants in all variables involving psychotic symptoms and mania; only depression scores remained higher than those of healthy participants (eTable 5), with individual scores consistent with mild depressive symptoms in 9 patients (1 with psychotic features).

The psycho-social and occupational disability was measured with the Global Assessment Functioning scale (GAF, abnormal if score ≤70). At visit 1, the anti-LGI1 group median GAF score was 58 (IQR 46-69) (eTable 5), which was significantly lower than that of healthy participants and with individual scores consistent with severe disability in 9 (38%) patients, mild-moderate disability in 13 (54%), and normal functioning in only 2 (8%). At the longitudinal follow-up, patients with anti-LGI1 encephalitis underwent a significant improvement in their global level of functioning, although at visit 3 still showed lower performance compared to healthy participants.

eTable 1: Cognitive assessment and variables for each domain studied

Cognitive domains	Instruments used	Variables included
General Intellectual Abilities / Intelligence Quotient	General Ability Index (GAI) of the Wechsler Adult Intelligence Scale (WAIS-IV)[15]	– **General ability index**: composite score of intellectual functioning based on the verbal Comprehension Index and the Perceptual Reasoning/Fluid Reasoning indexes without the influence of the Working Memory and the Processing Speed indexes. – **Verbal comprehension index**: includes the Vocabulary and Similarities subtests. It assesses word knowledge and concept formation. – **Perceptual reasoning index**: includes Matrix reasoning and Block design subtests. It assesses visuospatial relationships and visual concept formation.
Verbal Learning and Memory	Test de Aprendizaje Verbal España-Complutense (TAVEC)[19]	– **Verbal immediate memory**: total of words recalled in five learning trials of a list of 16 nouns. – **Verbal long-term memory**: total of words recalled of the list 20 minutes later. – **Verbal retention index**: percentage of the difference in information recalled between long-term and short-term recall. – **Verbal discrimination index**: percentage of the number of words erroneously recognized as belonging to and omitted from the aforementioned list, divided by the total number of words, minus one.
Visual Learning and Memory	Brief Visuospatial Memory Test Revised (BVMT-R)[20]	– **Visual immediate memory**: amount of information recalled in 3 learning trials of 6 different pictures. – **Visual long-term memory**: total information recalled 20 minutes later. – **Visual retention index**: percentage of information retained in the long term (delayed recall / the highest score in trial 2 or 3 of learning phase) x 100. – **Visual discrimination index**: capacity of discriminating coded information from other information (well-recognized items minus false positives).
Language	Word Semantic Fluency[21]	– **Semantic verbal fluency**: number of words given in the category of animals in 1 minute.
Working Memory	Indirect order task of Digit subtest (WAIS-IV)[15] Indirect order task of Spatial Location subtest (WMS-III)[22]	– **Verbal working memory**: sequences of numbers to repeat backward. – **Visuospatial working memory**: ability to repeat sequences backward of block tapping task spatially distributed on a board.
Attention	Phonological loop [Direct order task of Digit subtest (WAIS-IV)][15] Visuospatial sketch [Direct order task of Spatial Location subtest (WMS-III)][22]	– **Phonological loop:** the task consists of repeating longer and longer series of numbers. – **Visuospatial sketch:** the task consists of repeating sequences forward of block tapping task spatially distributed on a board.
Processing Speed	Symbol Search subtest (WAIS-IV)[15] Trail Making Test part A (TMT-A)[23,24]	– **Processing speed**: task of visual search in a limited time. – **Graphomotor speed and visuomotor sequencing**: total execution time.
Executive Functions	Tower of London test[25]	– **Planning errors**: total moves, namely total of errors in completing the trials. – **Planning impulsivity**: initiation time, being the time that is considered the patient thinks about the strategy needed to solve the problem. – **Planning time**: execution time, being the time needed in completing the trials. – **Inhibitory control**: violation of rules variable, meaning the total of errors for not following the task rules.

eTable 2: Psychiatric assessment and instruments used

Outcome measures	Instrument used	Content
Socioeconomic status	Hollingshead-Redlich index[26]	Years of education and current occupational level of the participant. Ranged between 1 (low status) to 63 (high status).
Psychiatric diagnoses interview	Structured Clinical Interview for DSM-5 (SCID)[18]	Semi-structured psychiatric interviews for all DSM-5 diagnostic disorders.
Psychotic symptom severity	Positive and Negative Syndrome Scale (PANSS)[27]	Includes 3 subscales that compose a total score: - Positive symptoms: 7 items - Negative symptoms: 7 items - General psychopathology: 16 items Items are scored from 1 to 7: absent, 1; minimal, 2; mild, 3; moderate, 4; severe, 5; markedly severe, 6; extreme, 7. Normal total score, ≤57; mild, 58-74; moderate, 75-94; markedly, 95-115; severe, ≥116.
Depression symptom severity	Hamilton Depression Rating Scale (HDRS)[28]	21 items scored on a 3 or 5-point scale. Normal score, 0-7; mild depression, 8-16; moderate, 17-23; severe, ≥24.
Mania symptom severity	Young Mania Rating Scale (YMRS)[29]	7 items scored 1-4 and 4 items scored 1-8. Normal score, 0-12; hypomania, 13-19; moderate mania, 20-24; severe ≥25.
Global psychosocial performance and clinical state	Global Assessment of Functioning Scale (GAF)[30]	Numeric scale used to rate the social, occupational, and psychological functioning of an individual (Axis V of DSM-IV-TR). Scores range from 100 (extremely high functioning) to 1 (severely impaired). Normal score, ≥71; mild-moderate impairment, 51-70; severe dysfunction, ≤ 50.

eTable 3: Immunotherapies before and after study inclusion

	All patients n=24	Patients who needed retreatment at visit 1 n=15	Patients who did not need retreatment at visit 1 n=9	p value
Immunotherapy at disease onset and before visit 1				
Patient's age (years)	63 (±12)	64 (±13)	60 (±9)	0.16
Weeks from symptom onset to steroids	12 (5-38)	10 (4-41)	13 (9-28)	0.88
Any immunotherapy	24 (100%)	15 (100%)	9 (100%)	1.00
• IV methylprednisolone*	24 (100%)	15 (100%)	9 (100%)	1.00
• Prednisone >0.5 mg/Kg/day** for > 6 weeks	15 (63%)	10 (67%)	6 (67%)	1.00
• Number of weeks with prednisone >0.5 mg/Kg/day**	9 (1-15)	8 (1-15)	9 (1-16)	0.74
• IV immunoglobulins	14 (58%)	8 (53%)	6 (67%)	0.68
• Rituximab	11 (46%)	5 (33%)	6 (67%)	0.21
• Weeks between initial steroids and rituximab	12 (4-22)	16 (58-27)	5 (2-12)	0.052
• Weeks from rituximab to visit 1	9 (7-13)	7 (6-7)	11 (9-24)	0.045
Patients still receiving immunotherapy by the time of visit 1				
Weeks from symptom onset to visit 1	38 (22-48)	35 (17-48)	45 (24-48)	0.46
Any immunotherapy	22 (92%)	15 (100%)	7 (78%)	0.13
• Prednisone (any dose)	11 (46%)	6 (40%)	5 (56%)	0.58
• Prednisone (> 0.5 mg/Kg/day)	5 (21%)	4 (27%)	1 (11%)	0.62
• IV immunoglobulins previous month	3 (13%)	3 (20%)	0 (0%)	0.27
Immunotherapy added at visit 1				
Immunotherapy added due to visit 1 findings	15 (63%)	15 (100%)	0	-
• IV methylprednisolone	10 (42%)	10 (67%)	-	-
• Prednisone	4 (17%)	4 (27%)	-	-
• Patients treated with prednisone >0.5 mg/Kg/day for >6 weeks	3 (13%)	3 (20%)	-	-
• IV immunoglobulins	7 (29%)	7 (47%)	-	-
• Rituximab	9 (38%)	9 (60%)	-	-
• Other*	3 (13%)	3 (20%)	-	-
Immunotherapy added or maintained through the study				
Any immunotherapy added or maintained after visit 1 for >3 months	21 (88%)	14 (93%)	7 (78%)	0.53
Any immunotherapy added or maintained after visit 1 for >6 months	18 (75%)	14 (93%)	4 (44%)	0.015
Any immunotherapy added or maintained after visit 1 for >1 year	7 (29%)	5 (33%)	2 (22%)	0.68

Values provided as number (percentage), mean (± SD), or median (IQR).
visit 1: visit 1 (study inclusion); iIT: initial immunotherapy; IV: intravenous; Steroids: IV methylprednisolone or oral prednisone.
*1g intravenous methylprednisolone per day for 5 days.
**4 patients (3 in the group who needed retreatment, and 1 in the group who did not) were treated with regular courses of 1-gram methylprednisolone boluses every 4-6 weeks for 8-12 weeks, all receiving total doses of methylprednisolone equivalent to >0.5 mg/Kg/day prednisone

eTable 4. Cross-sectional and longitudinal comparisons of the cognitive performance between patients and healthy participants at first study visit (visit 1) and during the follow-up (visit 1 to visit 3)

	Cross-sectional evaluation at visit 1			Cross-sectional evaluation at visit 3			Longitudinal study[a]				
	Patients	HP	p-value	Patients	HP	p-value	Patients	HP	Effect of Group	Effect of Time	Time x Group interaction
							p-value	p-value	p-value	p-value	p-value
General Intellectual Abilities (IQ) domain											
General ability index	55 ± 12	66 ± 10	0·014	56 ± 14	70 ± 9	0·046	0·66	0·87	0·040	0·19	0·77
Verbal comprehension	57 ± 12	66 ± 9	0·032	57 ± 12	69 ± 9	0·0071	0·66	0·99	0·012	0·33	0·38
Perceptual reasoning	51 ± 13	61 ± 10	0·010	54 ± 14	65 ± 10	0·010	0·53	0·78	0·011	0·11	0·86
Verbal Learning and Memory domain											
Verbal immediate memory	44 ± 12	55 ± 9	0·013	47 ± 12	63 ± 9	0·0034	0·046	0·64	0·001	0·0011	0·89
Verbal long-term memory	40 ± 12	56 ± 10	0·00044	48 ± 14	61 ± 9	0·035	0·0030	0·59	<0·0001	<0·0001	0·24
Verbal retention index	51 ± 19	52 ± 8	0·85	53 ± 12	54 ± 5	0·91	0·99	1·00	0·45	0·70	0·95
Verbal discrimination index	41 ± 16	51 ± 12	0·25	49 ± 16	59 ± 5	0·65	0·029	0·41	0·0029	0·0024	0·18
Visual Learning and Memory domain											
Visual immediate memory	40 ± 12	59 ± 10	<0·0001	42 ± 15	60 ± 9	0·0048	0·95	0·071	<0·0001	0.80	0.14
Visual long-term memory	41 ± 13	56 ± 8	0·0013	41 ± 15	56 ± 8	0·0042	0·98	1·00	<0·0001	0·67	0·41
Visual retention index	46 ± 15	53 ± 7	0·19	42 ± 20	55 ± 5	0·12	0·97	1·00	0·022	0·91	0·68
Visual discrimination index	38 ± 18	53·3 ± 6	0·00098	36 ± 20	55 ± 2	<0·0001	1·00	1·00	0·0013	0·32	0·019
Language											
Semantic verbal fluency	50 ± 12	64 ± 11	0·0011	55 ± 14	66 ± 11	0.012	0·64	0·75	<0·0001	0·060	0·91
Working Memory domain											
Verbal working memory	47 ± 10	55 ± 10	0·017	50 ± 9	59 ± 8	0·040	0·75	0·97	0·0060	0·029	0·38
Visuospatial working memory	52 ± 8	58 ± 13	0·17	55 ± 14	60 ± 14	0.72	0·95	1·00	0·064	0·039	0·95
Attention domain											
Phonological loop	45 ± 12	51 ± 8	0·091	46 ± 12	50 ± 6	0·92	0·93	0·99	0·076	0·89	0·33
Visuospatial sketch	49 ± 9	59 ± 9	0·0022	53 ± 11	59 ± 11	0·85	0·64	1·00	0·0020	0·015	0·16
Processing Speed domain											
Processing speed	49 ± 11	61 ± 9	0·0050	53 ± 10	67 ± 5	0·0069	0·024	0·077	<0·0001	<0·0001	0·93
Graphomotor speed & visuomotor sequencing	49 ± 12	58 ± 7	0·13	50 ± 16	61 ± 4	0.048	0·81	0·92	0·0060	0·27	0·95
Executive Functions domain											
Planning errors	48 ± 13	49 ± 9	0·92	51 ± 15	54 ± 12	0·99	1.00	1.00	0·62	0·36	0·57
Planning impulsivity	50 ± 8	51 ± 6	0·69	50 ± 6	53 ± 8	0·94	0.95	0.40	0·16	0·070	0·29
Planning time	47 ± 11	53 ± 67	0·049	50 ± 13	53 ± 8	0·77	0.38	0.87	0·048	0·71	0·53
Inhibitory control	44 ± 17	51 ± 11	0·088	46 ± 16	53 ± 3	0·082	0.64	0.75	0·046	0·75	0·96
MoCA	21 (17-26)	--	--	24 (20-26)	--	--	0.11	--	--	--	--

(a) Intragroup comparisons among each study visit for anti-LGI1 encephalitis patients and healthy participants (HP), and the effect of group, time and time x group interaction between them during visit 1-visit 3. Data expressed as standard T-scores (mean 50 ± SD 10) for all cognitive variables, except median (interquartile range) for MoCA; higher values indicate better performance; MoCA: Montreal Cognitive Assessment test.

eTable 5: Cross-sectional and longitudinal comparison of the main psychiatric features between patients and healthy participants at first (visit 1) and last (visit 3) study visits, and during the follow-up (visit 1 to visit 3)

	Cross-sectional evaluation at visit 1			Cross-sectional evaluation at visit 3			Longitudinal study[a]				
							Patients	HP	Effect of Group	Effect of Time	Time x Group interaction
	Patients	HP	p value	Patients	HP	p value	p value	p value	p value	p value	p value
PANSS positive score	11 (9-14)	7 (7-9)	<0.0001	9 (7-11)	7 (7-8)	0·71	<0.0001	1.00	0·0020	0·0001	0·0023
PANSS negative score	13 (10-17)	7 (7-7)	0.00024	8 (7-13)	7 (7-7)	0·13	0.0002	1.00	<0·0001	0·0016	<0·00010·00039
PANSS general score	30 (25-36)	18 (16-20)	0.00011	22 (18-27)	18·5 (17-20)	0·15	0.0001	1.00	<0·0001	0·0047	<0·00010·0013
PANSS total score	54 (47-61)	33 (30-35)	<0.0001	38 (32-51)	33 (31-35)	0·11	<0.0001	1.00	<0·0001	0·00022	<0·0001
HDRS score	11 (6-15)	2 (0-4)	0.51	7 (2-13)	2 (1-4)	0·028	0.51	1.00	<0·0001	0·54	0·1328
YMRS score	6·5 (3-9)	2 (0-4)	0.067	4 (2-7)	0·5 (0-3)	0·52	0.071	1.00	0·00043	0·020	0·14
GAF	58 (46-69)	88 (85-90)	0.0001	75 (55-80)*	89 (85-91)**	<0·0001	0.0001	1.00	<0·0001	<0·001	0·0040

(a) Intragroup comparisons among each study visit for anti-LGI1 encephalitis patients and healthy participants (HP), and the effect of group, time and time x group interaction between them during visit 1-visit 3. The data is shown as median (interquartile range); GAF: Global Assessment Functioning scale; HDRS: Hamilton Depression Rating Scale; PANSS: Positive And Negative Syndrome Scale; YMRS: Young Mania Rating Scale.

*12 (60%) patients had returned to their premorbid GAF score, 4 (20%) had moderate deficits, and the remaining 4 (20%) had severe disabilities.

**Each healthy participant remained with a GAF score >70 (considered normal; see appendix p 7)

eTable 6: Video-polysomnography findings in patients and healthy participants

	Patients, visit 1	HP	Patients, visit 3	*p value Pvisit 1/HP*	*p value Pvisit 1/Pvisit 3*	*p value Pvisit 3/HP*
Sleep stages and general sleep architecture						
Sleep efficiency %	77 (63-88)	85 (70-92)	85 (74-88)	0·13	0·00063	0·35
Sleep latency (min)	7 (3-20)	11 (5-19)	8 (4-12)	0·46	0·011	0·43
Number of awakenings	39 (27-45)	34 (23-35)	27 (23-50)	0·43	0·16	0·36
Participants with WASO periods of > 30 min	16 (67%)	1 (6%)	8 (40%)	0·049	0·091	0·028
Longest WASO period (min)	33 (22-53)	18 (3-27)	20 (12-52)	0·037	0·20	0·071
% of Wake	20 (12-33)	15 (5-22)	12 (9-25)	0·051	0·0062	0·38
% of NREM N1	14 (10-16)	10 (8-15)	12 (7-17)	0·53	0·96	0·51
% of NREM N2	44 (34-55)	42 (36-48)	42 (38-47)	0·39	0·70	0·81
% of NREM N3	7 (2-11)	14 (10-21)	13 (6-19)	0·031	0·00022	0·19
% of REM	10 (6-17)	15 (13-19)	16 (11-19)	0·049	0·0011	0·97
% of sleep quality	17 (13-24)	29 (25-37)	30 (21-36)	0·018	0·00036	0·90
Participants with low sleep quality	14 (58%)	1 (6%)	2 (10%)	0·019	0·0011	0·49
Participants with RBD episodes	12/21* (57%)	0 (0%)	4/20 (20%)^	0·0077	0·0084	0·22
Participants with REM without atonia >30%	7/21* (33%)	0 (0%)	4/20 (20%)^	0·024	1·00	0·66
% of REM without atonia	19 (13-35)	5 (4-7)	9 (5-25)	0·0032	0·013	0·11
Participants with EMG hyperexcitability	16 (67%)	4 (22%)	6 (30%)	0·038	0·13	0·59
Excessive fragmentary myoclonus	15 (63%)	4 (22%)	4 (20%)	0·039	0·016	0·87
Myokymic discharges	9 (38%)	0 (0%)	2 (10%)	0·0051	0·13	0·70

The data is shown as median (interquartile range) or absolute numbers (%).

*Three patients were not assessable due to insufficient REM sleep; ^3 of 20 patients had both RBD episodes and >30% REM sleep without atonia; 1 had RBD episodes with <30% REM sleep without atonia, and 1 had >30% REM sleep without atonia, without RBD episodes.

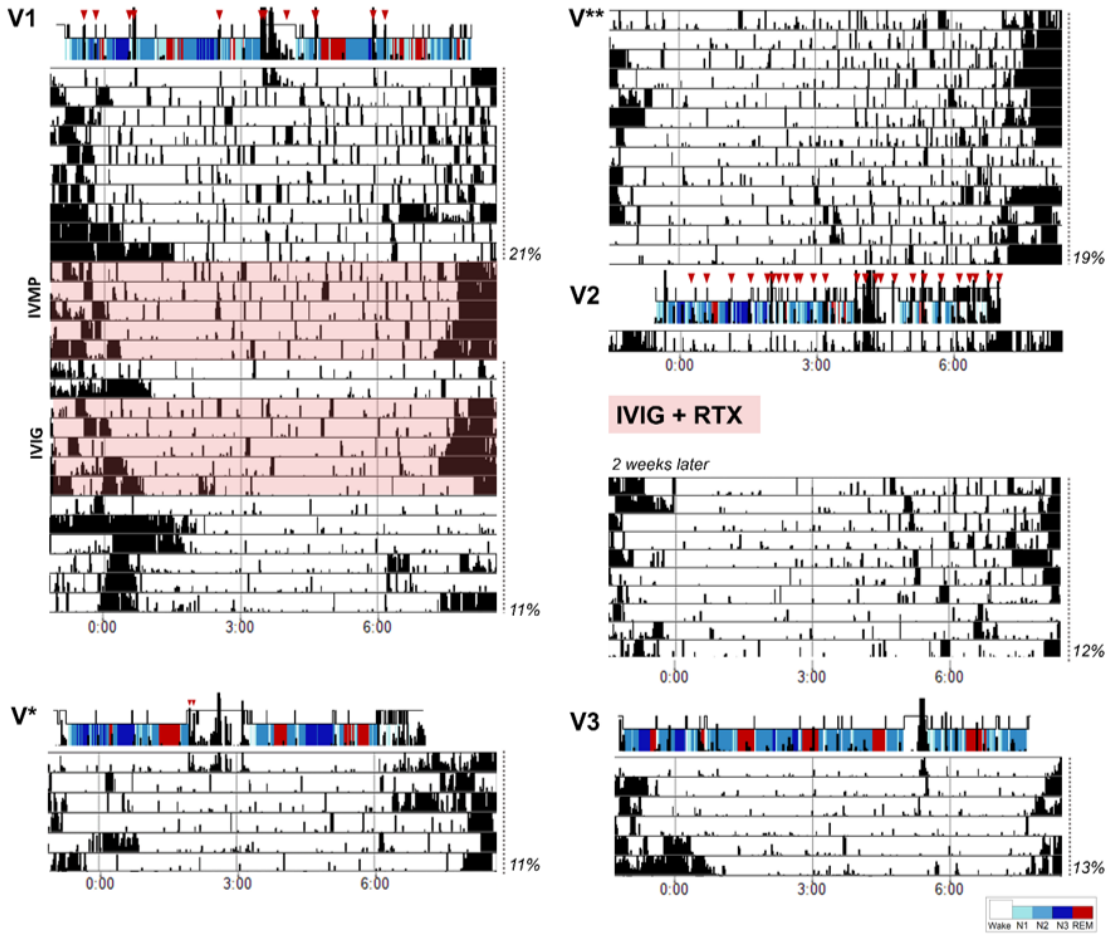
visit 1: initial study visit; HP: healthy participants; visit 3: one-year follow-up; Pvisit 1: patients at visit 1; Pvisit 3: patients at visit 3; REM sleep: rapid eye movement sleep; NREM: non-rapid eye movement; WASO: wake-after-sleep-onset; RBD: REM sleep behaviour disorder; EMG: electromyogram

eTable 7: Predictors of cognitive outcome

	Cognitive deficits at visit 3
Rituximab before visit 1	OR 4 (95% CI 1·5-10·7), p=0·0015
Interval (days) from iIT to rituximab	OR 1·2 (95% CI 1·0-1·3), p=0·051
REM without atonia > 30% at visit 1	OR 2·2 (95% CI 1·2-4·2), p=0·043
LGI1 antibodies at visit 1	OR 11 (95% CI 1·1-106·4), p=0·038

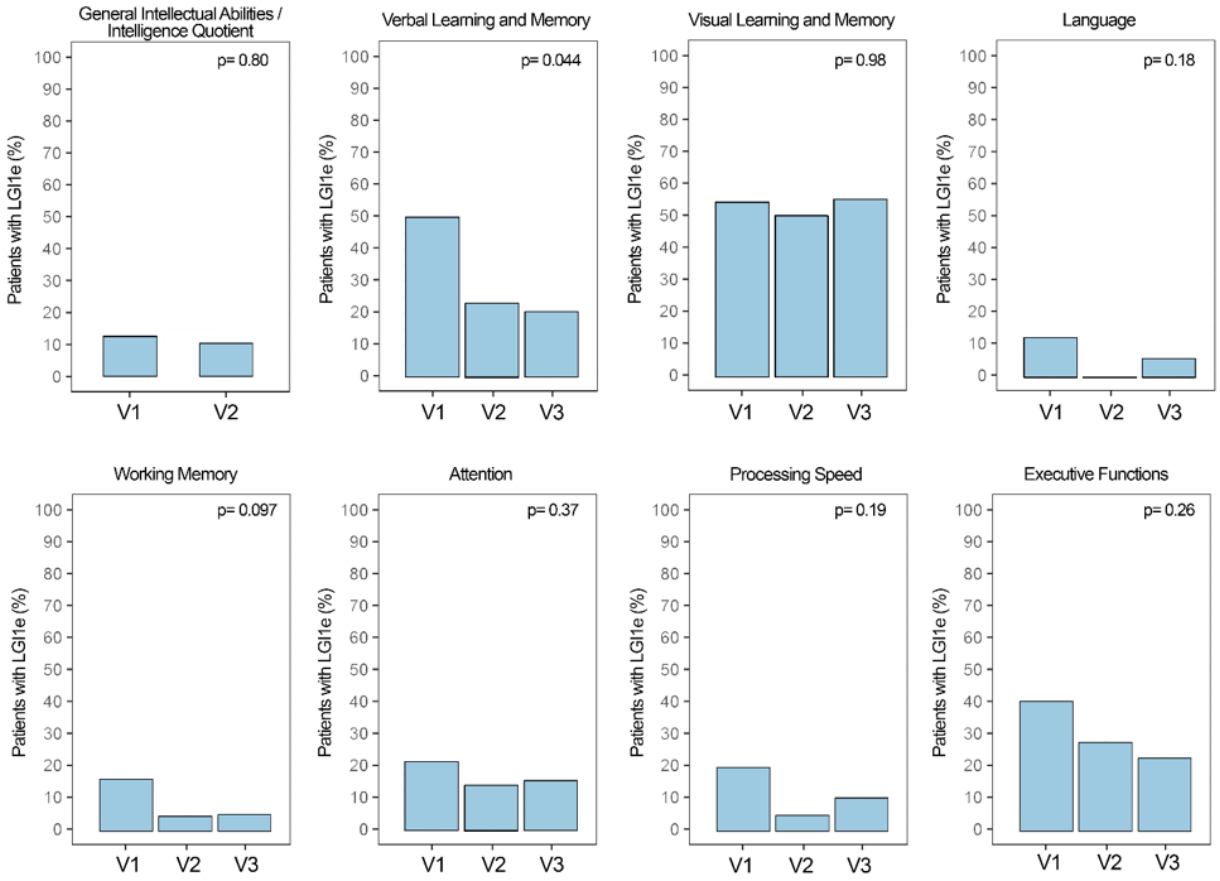
visit 1: study inclusion; visit 3: 1-year follow up; iIT: initial immunotherapy, OR: odds ratio; CI: confidence interval

eFigure 1: Video-polysomnography and actimetry assessment of faciobrachial dystonic seizures in a patient with anti-LGI1 encephalitis



V1 (visit 1) shows the hypnogram provided by the video-polysomnography (VPSG) obtained during this visit (1st row) indicating with red arrowheads several faciobrachial dystonic seizures. Black vertical bars superposed to the hypnogram show wrist-actimetry recorded during that night (also shown separately in the 2nd row). The higher the bar, the greater the amount of movement recorded by the actimeter. Note that in the superposed hyponogram/actimetry (1st row) many of the black bars correspond with VPSG-confirmed faciobrachial dystonic seizures. Smaller bars correspond to other, non-specific movements during the night. Longer-lasting black periods associate with large body movements (eg, turning in bed, going to restroom, etc.). Below the hypnogram and first night actimetry, the next 27 rows show the actimetry recording for the following 27 nights. Time is displayed in the horizontal axis, as indicated at the bottom of each graph. Daytime activity (which would follow at the right part of each row) was also recorded by the actimeter but is not displayed here for the sake of clarity. The 10 pink colored rows indicate the periods during which the patient received intravenous methylprednisolone and intravenous immunoglobulins (with a 2-day gap between courses). After these treatments, the number of short-lasting high vertical bars (most likely representing faciobrachial dystonic seizures) progressively decreased. **V*** corresponds to the hypnogram obtained 2 months later in a follow-up (out of study protocol). Only 2 faciobrachial dystonic seizures were recorded; moreover, compared with V1, there was a clear improvement in the sleep structure (lower fragmentation and increased non-REM N3 and REM times). There is also a reduction of events noted in the actimetry. **V**** shows actimetry recordings (each row corresponds to one night) obtained ~2 weeks before the planned V2 visit. There is a substantial increase in the number of vertical black bars suggesting faciobrachial dystonic seizures, described by the family as recurrence of night symptoms and frequent awakenings. **V2** Hypnogram and actimetry obtained a few days after the indicated recurrence of symptoms (V**). 25 faciobrachial dystonic seizures suggested by the actimetry were confirmed with VPSG (red arrows). Treatment with intravenous immunoglobulins and rituximab resulted in progressive decrease of faciobrachial dystonic seizures along with improvement of the actimetry recordings (recording period started 2 weeks after treatments administration). **V3** Hypnogram and actimetry show normalization of the sleep structure and absence of faciobrachial dystonic seizures. For all panels the dashed vertical line on the right side indicates the mean nocturnal awake time for all nights (defined as time in bed according to the sleep-logs provided by patients), calculated by wrist actimetry.

eFigure 2. Follow-up of distinct cognitive domains in the post-acute stage of anti-LGI1 encephalitis



Tendency of recovery of cognitive deficits in anti-LGI1 encephalitis patients represented as the proportion of patients with deficits in each cognitive domain compared to normative data of the general population, assessed with the Cochran-Armitage test for trend.

LGI1e: anti-LGI1 encephalitis, V1: visit 1 (study inclusion), V2: visit 2 (6-months follow-up), V3: visit 3 (one-year follow-up)

Video legends

Video 1: Nocturnal faciobrachial dystonic seizures. Video captions of different faciobrachial dystonic seizures recorded during video-polysomnography in several patients. The faciobrachial dystonic seizures occur with the patients asleep or during wake periods, and are triggered by different stimuli.

Video 2: Focal onset seizures. Focal onset seizures were oligosymptomatic in most cases. The first two clips show one nocturnal and one daytime seizure in the same patient. Nighttime seizures had not been recognized, while daytime seizures had been interpreted as anxiety attacks and treated with sertraline. The following two clips show focal onset seizures with a central sleep apnea preceding the onset of ictal EEG activity. Based on clinical features alone, these nocturnal seizures could easily go unnoticed.

EOG1: left electrooculogram; EOG2: right electrooculogram; Fp1 to Pz: scalp EEG electrodes; ref: common average reference (electrodes directly involved or near the seizure focus as well as those producing large-potential artifacts -like blinking- removed from the average); ECG: electrocardiogram; Chin: chin EMG; Can: nasal pressure cannula; Tho: thoracic respiratory effort gauge; Abd: abdominal respiratory effort gauge. Scale: 20 seconds per screen. High frequency filter set to 30 Hz. Low frequency filter set to 0.53 Hz.

Video 3: Combined focal onset seizures and faciobrachial dystonic seizures. Two patients had focal onset seizures and faciobrachial dystonic seizures combined in the same episode. The first patient (first video clip) shows a nighttime episode with the patient sleeping in stage non-REM N2. After a brief arousal, there is a faciobrachial dystonic seizures and immediately afterwards the onset of a focal onset motor seizure with speech automatisms. All the ictal episodes in this patient were similar, with a faciobrachial dystonic seizures followed by a focal onset seizures (Figure 2B). The other patient (second clip) shows a right frontotemporal onset seizure occurring after the hyperventilation maneuver during daytime EEG; the seizure is clinically silent (increased blinking artifact, but no evident blinking on the video) and the faciobrachial dystonic seizures occurs just at the end of the focal onset seizures. A second faciobrachial dystonic seizures occurs a few seconds later. This patient had faciobrachial dystonic seizures recorded only during nighttime, and a single diurnal focal onset seizures.

EOG1: left electrooculogram; EOG2: right electrooculogram; Fp1 to Pz: scalp EEG electrodes; ref: common average reference (electrodes directly involved or near the seizure focus as well as those producing large-potential artifacts -like blinking- removed from the average); ECG: electrocardiogram; Chin: chin EMG; Can: nasal pressure cannula; Tho: thoracic respiratory effort gauge; Abd: abdominal respiratory effort gauge. Scale: 20 seconds per screen. High frequency filter set to 30 Hz. Low frequency filter set to 0.53 Hz.

Video 4: Manipulatory behaviours during the acute stage. During the acute stage of the disease, this patient performed manipulatory behaviours with both hands during non-REM sleep, recorded at different moments throughout the night. At the end of the video, a caption of awake EEG (left side) and of non-REM N2 sleep (right side) are shown to demonstrate that these behaviours occurred during non-REM N2 sleep. Note that the eyes remain closed during the episodes.

EOG1: left electrooculogram; EOG2: right electrooculogram; F3 to O2: scalp electrodes; ref: common reference to the averaged value of left and right auricular electrodes; ECG: electrocardiogram; Chin: chin EMG; FDS: flexor digitorium superficialis EMG (upper limbs); TA: tibialis anterior EMG (lower limbs); L: left; R: right; Can: nasal pressure cannula; Tho: thoracic respiratory effort gauge; Abd: abdominal respiratory effort gauge. Scale: 30 seconds per screen. High frequency filter set to 30 Hz. Low frequency filter set to 0.53 Hz.

Video 5: REM sleep behaviour disorder. The video shows different patients presenting jerks and vocalizations during REM sleep, typical of a REM sleep behaviour disorder, along with simultaneous increased phasic EMG activity recorded by chin and limb electrodes. The second part of the video shows abnormally increased EMG activity (REM without atonia) with more subtle accompanying jerky movements.

EOG1: left electrooculogram; EOG2: right electrooculogram; F3 to O2: scalp electrodes; ref: common reference to the averaged value of left and right auricular electrodes; ECG: electrocardiogram; Chin: chin EMG; FDS: flexor digitorium superficialis EMG (upper limbs); TA: tibialis anterior EMG (lower limbs); L: left; R: right; Can: nasal pressure cannula; Tho: thoracic respiratory effort gauge; Abd: abdominal respiratory effort gauge. Scale: 30 seconds per screen. High frequency filter set to 30 Hz. Low frequency filter set to 0.53 Hz.

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DISCUSSION

The two studies presented in this PhD thesis are aimed at describing and characterizing sleep and sleep-related disorders in the two most prevalent autoimmune encephalitis, namely anti-NMDAR and anti-LGI1 encephalitis. For both diseases, the number of cases reported grew quickly after the corresponding syndromes and associated antibodies were described, and large series including thorough clinical descriptions were published soon thereafter. Even though sleep was rarely or succinctly mentioned in those early series, the studies of this thesis show that sleep disorders are frequent, often severe, and tend to occur early in the disease course. Moreover, the indicated sleep alterations may persist or develop, often subclinically, after initial treatment of the encephalitis and despite the clinical improvement of other symptoms. In a meaningful number of patients, sleep studies in the post-acute stage of AIE, mainly anti-LGI1, uncovered ongoing, unsuspected disease activity. Overall, these findings together with those previously reported in other AIE, such as anti-IgLON5 disease, support that sleep is a relevant biological function that is frequently altered and should be assessed in neuroimmunological diseases.

Beyond these generalities, particular findings in anti-NMDAR encephalitis and anti-LGI1 encephalitis are substantially different, as are different the rest of neurological and psychiatric manifestations. This probably reflects the important differences in the physiopathological mechanisms of these two diseases involving distinct neurotransmitters and neuronal networks.

These studies were performed in the post-acute phase of the encephalitis, within broader projects designed to explore and characterize the many different aspects of this less-known stage of both diseases. By the time of study inclusion, patients had substantially improved their symptoms, had been discharged home, and were able to travel to our center and collaborate. It would have been extremely interesting to perform the same systematic, homogeneous, and thorough assessment of sleep disorders at disease onset or during the acute phase of the disease. However, carrying out sleep studies during the acute stage entails great technical and interpretative limitations, especially in anti-NMDAR encephalitis, due to the severity of the disease, the extreme behavioral alterations, or the use of anesthetics and diverse psychotropic drugs.

In the first publication (Objectives 1 and 2), we evaluated patients with anti-NMDAR encephalitis. Clinical and paraclinical data from the acute phase was retrospectively obtained at study inclusion, with a detailed and systematic anamnesis about sleep symptoms and their evolution over time. We found that sleep symptoms, especially insomnia, are almost universal and as frequent as cognitive symptoms in the initial states of anti-NMDAR encephalitis. Such a systematic assessment had not been done previously, what explains the difference with previous works reporting barely 20% prevalence of sleep symptoms in large series of patients with anti-NMDAR encephalitis [49].

Our study confirms that insomnia is a characteristic symptom of the acute phase of anti-NMDAR encephalitis, and it is typically severe and drug-resistant. However, following the initial stage of severe insomnia, during the first months after immunotherapy, the sleep pattern shifted to hypersomnia, where patients slept about 3 more hours than they did before developing the encephalitis. This shift to hypersomnia was indeed part of a more global phenomenon of symptom pattern change involving also psychiatric and behavioral aspects. That is, the acute-stage insomnia occurred together with psychotic or disorganized behavior, anxiety, or mania. By contrast, together with the shift of the sleep pattern to hypersomnia, the accompanying psychiatric-behavioral symptoms that predominated in the post-acute stage were apathy, hyperphagia, and sexual disinhibition, some of them underreported unless specifically assessed. This combination of symptoms in the post-acute stage remained that of the Kleine-Levine syndrome [155], which had already been suggested [130,156]. However, an association of genuine Kleine-Levine syndrome with antibodies to NMDAR has never been reported, and none of our patients presented the typical recurrences of Kleine-Levin syndrome during follow-up.

Regarding the potential mechanisms behind the indicated shift in the symptom pattern, it is believed that the acute-stage symptoms respond to an acute inflammatory process driven by the rapid antibody-mediated reduction of NMDAR clusters, altering synaptic plasticity. On the other hand, the post-acute stage symptoms, like the protracted executive cognitive and behavioral dysfunction, would result from a gradual restoration of synaptic function and NMDAR-related networks after autoimmune

inflammatory mechanisms decrease or resolve [157]. We saw that hypersomnia occurred independently of the use of drugs that may have a sedative effect, such as antiseizure, antipsychotic, or antidepressant medications, suggesting that it is part of the disease. V-PSG studies showed short sleep latencies and high sleep efficiency percentages in anti-NMDAR patients, which otherwise were not substantially different from those observed in healthy participants. One limitation of this study is that we did not quantify hypersomnia with objective measures, and we recorded only nocturnal sleep with V-PSG. One intriguing V-PSG finding in the post-acute stage of anti-NMDAR encephalitis was the presence of confusional arousals in patients without a prior history of NREM parasomnia. NREM parasomnias are classified within the disorders of arousal, taking place in deep NREM sleep, typically NREM N3 or slow-wave sleep.

The pathophysiology behind these sleep findings, comprising acute-stage insomnia, post-acute-stage hypersomnia, and confusional arousals, is unknown. Elucidating the molecular pathways or neuronal circuits that are involved is beyond the objectives of this PhD thesis, but works by other authors, show some feasible options.

After our study was published, Miracca and colleagues found that mice knocked out for the GluN1 subunit of the NMDAR in the preoptic area of the lateral hypothalamus developed fragmented sleep with difficulties to sustain NREM sleep and to generate REM sleep [158]. However, sleep drive was not affected by this selective deletion of hypothalamic NMDARs, so it would not explain the predominantly sleep-onset type of insomnia described by anti-NMDAR encephalitis patients, maybe because it is driven by NMDAR blockade in a different brain region involved in sleep regulation.

On the other hand, there are studies in rodents showing that NMDAR blockade during wakefulness (with noncompetitive antagonists like MK-801 or ketamine) increases the power of slow-wave activity during subsequent sleep [63] and that the effect of NMDAR blockade is similar to that of sleep deprivation [159]. Previous studies had proposed that an increase in the metabolism of neuronal plasticity systems during waking would increase the homeostatic need for delta sleep [160], and NMDA-dependent neurotransmission is known to be involved in neuron plasticity. Thus, it is possible that NMDAR blockade produces neuronal changes resulting in increased need

for sleep-dependent brain restoration, and thus increased homeostatic sleep pressure and increased intensity of slow-wave activity during sleep. Sleep deprivation increases slow-wave sleep homeostatic pressure and is one of the main triggers of NREM parasomnia episodes in predisposed persons [161]. Sleep homeostasis models indicate that sleep has a restorative function for the brain and that brain restoration takes place during NREM sleep in a way that is proportional to the intensity of the slow-wave activity. In studies using cultured neurons and models of anti-NMDAR encephalitis, NMDARs get internalized in neurons due to the effect of the antibodies and the levels of receptors are restored only after antibody removal. Given the biological effects produced by pharmacological NMDAR blockade, the hypersomnia in the post-acute stage of anti-NMDAR encephalitis could be explained by the increased homeostatic sleep pressure and the exacerbation of NREM parasomnia by the increased drive for slow-wave sleep. However, sleep deprivation by itself does not produce clinical episodes in patients not genetically predisposed to develop NREM parasomnia, so additional factors are likely involved in the development of these “de novo” confusional arousals. In particular, an increased arousability or NREM sleep instability has been described in patients with NREM parasomnias [162,163]. One hypothesis is that NREM fragmentation potentially produced by NMDAR blockade [158] in the acute stage, is still present at this disease stage due to residual NMDAR dysfunction.

In our study we did not find an increase in NREM N3 time or in the arousal index in patients with confusional arousals compared to those without confusional arousals. However, our analysis was based on visual scoring of sleep stages and we did not consider power spectra analyses to compare delta activity power or related features, which are tasks for future studies.

Importantly, in patients with anti-NMDAR encephalitis, different from anti-LGI1 encephalitis, we did not find remarkable REM sleep disturbances in V-PSG. As previously indicated, studies with hypothalamic NMDAR-knocked-out mice did show a significant reduction of REM sleep time, in addition to NREM sleep fragmentation [158]. One possibility is that REM sleep disturbances occur earlier in the disease course (acute phase of the disease), preceding the time of enrollment in our study and assessment with V-PSG (which by study design occurred during the post-acute stage of

the disease). Indeed, later during the course of this PhD thesis, we had the opportunity to study by V-PSG a patient during the acute stage of the disease (data not published), who had a severely disturbed sleep structure, with very poorly differentiated sleep stages, almost absent NREM N2, and an unremitting shift between NREM N1 and REM sleep, which was non-sustained and lacked its normal atonia, with several movements and behaviors typical of REM sleep behavior disorder. After immunotherapy intensification, the general sleep structure almost normalized in three months, including REM sleep.

In conclusion, this study revealed that sleep problems are frequent and often prominent in anti-NMDAR encephalitis, and that they differ in the acute and post-acute stages, accompanying and evolving together with multiple behavioral and cognitive problems, as part of a dynamic process intrinsic to the disease. The underlying physiopathological mechanisms, not part of this thesis, remain unknown and should be the goal of future investigations.

In the second publication (Objectives 3 and 4), we used a similar approach to evaluate patients with anti-LGI1 encephalitis, leading to various findings that were relevant and overall unexpected. The characterization of sleep and EEG in the post-acute stage uncovered symptoms that were unknown or clinically underestimated, especially the high frequency of oligosymptomatic seizures, but also primary sleep disorders, such as reduced sleep quality and RBD, and indirect signs of likely peripheral nerve hyperexcitability.

The most remarkable contribution of our study was the demonstration that seizures in anti-LGI1 encephalitis occur frequently but easily go unnoticed in the months following initial immunotherapy. We identified focal epileptic seizures and FBDS in more than one third of the patients, with high frequency of daily episodes. These were clinically unrecognized in approximately half of the patients and the number of episodes was underestimated in all cases. These findings have relevant clinical implications. First, although persistent focal seizures may reflect the development of chronic epilepsy, they can also indicate that the encephalitis is still active. Importantly, seizures improved or disappeared after additional immunotherapy, meaning that at this stage

of the disease, they are more likely a marker of active encephalitis than a residual symptom. The same stands for FBDS, which are expected to disappear soon after immunotherapy and have not been described in the long-term follow-up of these patients. When present, FBDS are prominent and clinically easy to identify in the acute stage of anti-LGI1 encephalitis, even by patients themselves, as they do not alter consciousness as focal onset seizures often do in this disease. Due to the high frequency of daily episodes, improvement after immunotherapy is readily identified as well. However, FBDS are as unrecognized as focal onset seizures in the post-acute stage of the disease. Two factors likely contributing to this fact are that FBDS are clinically more subtle than in the acute stage and their apparent nocturnal predominance or sleep-related facilitation. Indeed, both types of seizures occurred mainly during sleep, with most focal onset seizures arousing from NREM sleep and most FBDS occurring during arousals from any sleep stage. Both interfered with sleep continuity by producing recurrent awakenings, often followed by prolonged wake periods before sleep-resumption. While FBDS eventually disappeared in all patients following additional immunotherapy, focal epileptic seizures reappeared in 15% of the patients at 1 year follow-up, some with mesial temporal sclerosis, representing the development of chronic epilepsy.

An important clinical implication related to the high number of seizures detected in this study is that their oligosymptomatic nature indicates the necessity to closely monitor these patients with serial EEGs. These EEGs should be long enough to record sleep or should be recorded nocturnally and combined with V-PSG, which additionally provides data about sleep disorders, including sleep structure, sleep quality, and RBD. Moreover, seizure identification was challenging in some instances due to low-amplitude and barely-evolving EEG patterns, however simultaneously recording respiratory effort/signals facilitated the detection of seizures, which often manifested with an ictal central apnea. We also found that wrist-actimetry can assist in monitoring focal onset seizures or FBDS at home; however, it is less sensitive and specific than V-PSG or EEG and should be used as a complement, not replacement, of these tests.

Symptoms compatible with RBD were present in at least half of the patients in the acute stage of the encephalitis and we still detected it in half of the cohort at study

inclusion. At this stage, however, the sleep disorder was unnoticed by most of the patients and partners. V-PSG recordings showed a clinically mild form of RBD, despite high percentages of REM without atonia, the physiological marker of RBD. During follow-up, that often included additional immunotherapy, both clinical episodes and the percentage of REM without atonia resolved in most patients, but in one quarter of the patients RBD was still present in the follow-up at one year. One interesting observation was that none of these patients had complete cognitive recovery either. Indeed, higher percentages of REM without atonia at study inclusion were associated with greater probability to remain with cognitive deficits at the end of the study, suggesting that related neural circuits may play a role in the development of sleep and memory alterations. However, not all patients with residual cognitive symptoms had residual RBD. Overall, these findings support the idea that sleep studies have a role as a biological marker of early treatment-response and long-term prognosis that should be used in future clinical trials. Confirming this association between RBD and poorer cognitive prognosis as well as finding a physiopathological explanation for this link remain as tasks for the future.

The other most prevalent and consistent primary sleep disorder was insomnia, which was a main complaint in the acute stage of anti-LGI1 encephalitis (rarely presented with hypersomnia). Insomnia had several different patterns of presentation when compared with the more uniform manifestations in anti-NMDAR encephalitis (severe disease-onset insomnia and post-acute hypersomnia). In our cohort of anti-LGI1 encephalitis, insomnia presented differently in men (with sleep-onset insomnia leading to a severe reduction of total sleep hours) and women (with normal sleep-onset latencies, but severely fragmented sleep), and responded differently to immunotherapy as well (rapid improvement in the former, steadily over months in the latter). However, this observation needs to be confirmed in larger series before any explanatory hypothesis is considered.

Encephalitis-related insomnia and poor perceived sleep quality were active complaints, in contrast with other alterations described above, such as RBD or nocturnal seizures, that had been unnoticed by patients, families, and treating physicians. Low sleep quality was confirmed by V-PSG, with increased wake-after-sleep-onset times (with

characteristic hypnogram patterns) and reduced deep sleep stages (both NREM N3 and REM). The physiopathological mechanisms behind the sleep-pattern alterations in anti-LGI1 encephalitis are unclear, but they also improved during the follow-up, together with the other symptoms. LGI1 antibodies are known to increase neuronal excitability by reducing post-synaptic AMPA receptors (ionotropic glutamate receptors) in inhibitory neurons [66]. AMPA receptors are known to play a key role in synaptic potentiation and plasticity during sleep, in sleep-spindle production, and in the regulation of circadian rhythm [164,165], and their level and phosphorylation state change during wakefulness and sleep or after sleep deprivation [166]. Although an animal model of passive transfer of patients' antibodies to the cerebral system of mice has been reported, sleep studies were not included and should be the aim of future investigations.

Another V-PSG finding was excessive fragmentary myoclonus and myokymic discharges. These are signs of neuronal or peripheral nerve hyperexcitability that were previously unreported and unsuspected and were observed in the EMG channels of the mentalis am limb muscles during sleep recordings. Fasciculations, myokymia, and neuromyotonia have been described in the context of neuropathic pain or cramps in patients with LGI1 antibodies, but not in cases without these symptoms or in the post-acute stage [35]. Although LGI1 antibodies cause neuronal hyperexcitability [66] the exact mechanisms underlying these EMG findings are unclear and need to be further investigated in the future, with standard methods and techniques not included in our study (nerve conduction studies, electromyography, etc.).

Even though this PhD thesis is focused on characterizing sleep and EEG in the post-acute stage of anti-LGI1 encephalitis, in this work we thoroughly analyzed the evolution of cognitive and psychiatric symptoms as well. Cognition is the most limiting symptom in the long-term and is the actual factor determining the final prognosis in this disease. At study inclusion more than 80% of the patients had moderate to severe deficits in neurocognitive tests, predominantly amnestic and less often dysexecutive. There was an overall improvement in both the number of affected cognitive domains and the severity of the deficits during follow-up, however, two thirds of the patients remained with clinically meaningful cognitive deficits in at least one domain, especially in visual

learning and memory. Similarly, almost half of the patients had mild depressive symptoms at the end of the follow-up, all with associated cognitive deficits. The final determinants of the cognitive outcome in anti-LGI1 encephalitis are unclear and need to be further studied in the future. However, we observed that persistent cognitive deficits associated with no use of rituximab before study visit 1, REM sleep without atonia at visit 1, and sustained LGI1-antibody detection at visit 1. In our cohort, we were not able to establish statistically significant associations between final cognitive outcome and seizures or sleep quality, but it is feasible that persisting seizures, besides being a marker of active encephalitis, also interfere with cognitive recovery, either by themselves [167,168] or by the sleep disruption they cause [169,170]. The lack of robust associations may be in part due to a relatively low number of patients included in the study and need to be confirmed in larger series. However, the inclusion of unselected patients who were consecutively recruited, and the comprehensiveness of the investigations make the findings generalizable to other patients. Overall, including both patients and healthy participants, this study comprised 206 days and 103 nights in hospital and 911 hours of video-polysomnography recordings.

Lastly, besides the main objective of characterizing the post-acute stage of the encephalitis, another contribution of this work is that it provides new insights into the initial clinical presentation and natural history of anti-LGI1 encephalitis. Despite retrospective, the thorough and systematic assessment of all potentially disease-related symptoms revealed that subacute or even chronic presentations are not unusual. Up to half of the patients did not develop a full-blown encephalitis picture until several months after disease onset. Initial symptoms may be unspecific, like insomnia, anxious-depressive symptoms, or leg cramps, and not raise suspicion of encephalitis until seizures or cognitive impairment develop several weeks or months later. Similarly, seizures or cognitive impairment may be isolated symptoms or be accompanied by other less specific ones (e.g., mild behavioral-psychiatric symptoms or sleep symptoms) which can be misinterpreted as adverse drug reactions (e.g. antiseizure medications in patients with new-onset seizures). These findings emphasize that physicians must be aware of the heterogeneous, partial, or protracted disease

presentations, and of the variety of symptoms, including sleep, which conform the whole spectrum of anti-LGI1 encephalitis.

In summary, patients with anti-LGI1 encephalitis frequently have ongoing symptoms after initial immunotherapy, which are prematurely considered resolved or are not investigated, and therefore, are undertreated or not treated properly. These symptoms, especially seizures and sleep alterations, can contribute to the cognitive deficits and depressive behavior. Overall, these findings carry several important clinical and practical implications and provide a series of disease biomarkers that can assist in the selection of more optimal or targeted treatments in anti-LGI1 encephalitis. Based on these findings, future investigations and clinical trials should include comprehensive evaluations of sleep and EEG to assess the recovery of the patients and the effects of treatments.

Tasks for the future include the assessment in larger studies if variables like REM without atonia, EMG hyperexcitability, or seizures have a role as quantitative markers of early outcomes in clinical trials or of long-term cognitive impairment. Another task will be to determine whether earlier or prolonged second-line immunotherapies (e.g. rituximab) combined with cognitive training improve the final outcome.

As shown by the body of work of these studies, sleep and related disorders are frequent in the acute and the post-acute stage of anti-NMDAR and anti-LGI1 encephalitis, but these differ in many ways. In anti-NMDAR encephalitis, sleep symptoms are severe, intense, and uniform in the acute stage, while findings in the post-acute stage, despite still present and characteristic, are more discrete or have less clear clinical implications. On the other hand, the number and type of findings in anti-LGI1 encephalitis, many of them unexpected due to their oligosymptomatic nature or undetectable unless sleep studies are performed, represent a paradigm change in the understanding of the disease and in treatment and follow-up strategies. These findings reflect how different these diseases are and indicate that AIE, each with their specific clinical signatures and underlying mechanisms [1], should not be considered as a single entity, but study them individually. Finally, these works add to the previous evidence

[45] that in AIE the study of sleep can contribute to the diagnosis, prognosis, monitoring, and understanding of the individual diseases.

CONCLUSIONS

1. At onset of anti-N-methyl-D-aspartate receptor encephalitis insomnia is frequent and severe and should be considered a diagnostic clue in the initial work-up of patients with suspected autoimmune encephalitis.
2. Sleep alterations, such as insomnia in the acute stage and hypersomnia in the post-acute stage, are part of a dynamic process in anti-N-methyl-D-aspartate receptor encephalitis, and change together with psychiatric and behavioral symptoms during the course of the disease.
3. Video-polysomnography recordings during the recovery phase of anti-N-methyl-D-aspartate receptor encephalitis show normal sleep microstructure but reveal confusional arousals from non-rapid eye movement sleep, which need to be further studied in the future.
4. There are several underrecognized symptoms in the post-acute stage of anti-N-methyl-D-aspartate receptor encephalitis (g., hypersomnia, hyperphagia, apathy, overweight, and hypersexuality) that have important implications for patients, families, and social interactions, emphasizing the need for prolonged multidisciplinary care during the recovery phase of these patients
5. Patients with anti-leucine-rich glioma-inactivated protein 1 encephalitis still have ongoing symptoms after initial immunotherapy that are often underrecognized and are uncovered only by video-polysomnography and electroencephalography recordings, indicating that these investigations should be included in the clinical follow-up of these patients and in future clinical trials to monitor treatment response.
6. Focal onset epileptic seizures and faciobrachial dystonic seizures affect one-third of patients with anti-leucine-rich glioma-inactivated protein 1 encephalitis in the post-acute stage of the disease (most of them unnoticed), and respond to additional immunotherapy, indicating that the encephalitis remains active for longer time than previously considered.
7. Rapid eye movement sleep behavior disorder, affecting half of the patients with anti-leucine-rich glioma-inactivated protein 1 encephalitis after immunotherapy, persists for long time in some patients and associates with an increased risk of incomplete cognitive recovery.

8. Sleep structure and quality are disrupted in anti-leucine-rich glioma-inactivated protein 1 encephalitis as a result of both an intrinsic effect of the encephalitis and a direct effect of the seizures.
9. Up to two-thirds of patients with anti-leucine-rich glioma-inactivated protein 1 encephalitis had signs of hyperexcitability, including excessive fragmentary myoclonus and myokymic discharges, demonstrated by video-polysomnography, which need to be further studied with standard electromyography methods in the future.

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