UNIVERSITAT DE BARCELONA

El sueño en las prionopatías insomnio letal y enfermedad de Gerstmann-Sträussler-Scheinker

Laura Pérez Carbonell

EL SUEÑO EN LAS PRIONOPATÍAS INSOMNIO LETAL Y ENFERMEDAD DE GERSTMANN-STRÄUSSLER-SCHEINKER

Memoria de tesis doctoral presentada por

Laura Pérez Carbonell

para optar al título de doctora por la Universitat de Barcelona

Dirigida y tutorizada por

Alejandro Iranzo de Riquer

Sección de pruebas funcionales, Servicio de Neurología, Hospital Clínic de Barcelona,
Universitat de Barcelona

Programa de Doctorado en Medicina e Investigación Traslacional
Facultad de Medicina y Ciencias de la Salud
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ABREVIATURAS Y ACRÓNIMOS

AASM: del inglés *American Academy of Sleep Medicine* (Academia Americana de Medicina del Sueño)

AOS: apnea obstructiva del sueño

EEG: electroencefalograma

EMG: electromiografía

FLAIR: del inglés *fluid-attenuated inversion recovery* (recuperación de la inversión atenuada de fluido)

GSS: Gerstmann-Sträussler-Scheinker

IL: insomnio letal

ILe: insomnio letal esporádico

ILf: insomnio letal familiar

LCR: líquido cefalorraquídeo

MPPS: movimientos periódicos de las piernas durante el sueño

NREM: no REM

PrP^{C}: proteína priónica de conformación normal

PrP^{Sc}: proteína priónica anómala

PSG: polisomnografía

REM: del inglés *rapid eye movement* (movimientos oculares rápidos)

RM: resonancia magnética

RT-QuIC: del inglés *real-time quaking-induced conversion* (conversión inducida por temblor en tiempo real)

SINBAR: *Sleep Innsbruck Barcelona*

SPI: síndrome de piernas inquietas

SpO_2: saturación de oxihemoglobina

TCSR: trastorno de conducta del sueño REM

V-PSG: vídeo-polisomnografía

PRESENTACIÓN

Esta Tesis Doctoral se presenta en formato de compendio de publicaciones que corresponden a una línea de trabajo: el estudio de las alteraciones durante el sueño en las prionopatías.

La tesis consta de cuatro objetivos principales que se desarrollan en dos artículos científicos originales.

El primer objetivo de esta tesis es la descripción detallada de la arquitectura del sueño y hallazgos respiratorios durante el sueño en pacientes con insomnio letal. El segundo objetivo es estudiar la relación entre las alteraciones durante el sueño y las características clínicas y neuropatológicas en los pacientes con insomnio letal. El tercer objetivo de esta tesis es investigar la presencia de hallazgos neuropatológicos relacionados con el control del sueño y la respiración en pacientes con insomnio letal.

Estos tres objetivos se abordan en el primer trabajo:

Pérez-Carbonell L, Muñoz-Lopetegi A, Sánchez-Valle R, Gelpi E, Farré R, Gaig C, Iranzo A, Santamaria J. Sleep architecture and sleep-disordered breathing in fatal insomnia. Sleep Medicine. 2022 Dec;100:311-346.
Factor de impacto (JCR 2021): 4.842. Cuartil (JCI 2021): Q1. Cuartil (JCR 2021): Q2.

El cuarto objetivo es el estudio y la descripción detallada del sueño en pacientes con la enfermedad de Gerstmann-Sträussler-Scheinker.

Este último objetivo se aborda en el segundo trabajo:

Pérez-Carbonell L, Sarto J, Gaig C, Muñoz-Lopetegi A, Ruiz-García R, Naranjo L, Augé JM, Perissinotti A, Santamaria J, Iranzo A, Sánchez-Valle R. Sleep in Gerstmann-Straüssler-Scheinker disease. Sleep Medicine. 2023 May 22;108:11-15.
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1. INTRODUCCIÓN

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1.1. ¿Qué es el sueño, por qué es importante y cómo se estudia?

1.1.1. El sueño y sus funciones

El sueño es un estado fisiológico con características distintivas con respecto a la vigilia en cuanto a conducta, parámetros electrofisiológicos (como el electroencefalograma - EEG), autonómicos (como la respiración), y estado de conciencia o nivel de alerta. El concepto de arquitectura del sueño hace referencia a la organización estructural del sueño en fases no REM (NREM) y REM. En condiciones normales, a lo largo de una noche, los seres humanos tenemos 4-5 ciclos de sueño de una duración de 90-110 minutos, en los que hay una transición por las fases N1 (o adormecimiento), N2 (o sueño ligero) y N3 (o sueño profundo) del sueño NREM, a las que sigue el sueño REM. La fase N1 del sueño NREM constituye el 2-5% del periodo total de sueño; la fase N2 forma el 45-55%, es decir, la mayor parte de nuestro sueño; el sueño profundo o N3 ocupa el 20-25%; y el sueño REM constituye otro 20-25%. Al inicio de la noche, hay más cantidad de sueño profundo o N3, y en la segunda mitad de la noche hay una mayor proporción de sueño REM. Durante el sueño NREM las diversas funciones fisiológicas se mantienen estables a través del control de los quimio, baro y termorreceptores, predominantemente por acción del sistema nervioso parasimpático. En el sueño REM hay una mayor inestabilidad (variabilidad en el sistema nervioso simpático y actividad fásica a nivel parasimpático), que resulta en variaciones en la frecuencia cardiaca, presión arterial, frecuencia respiratoria, y ausencia de adaptación a cambios ambientales de temperatura. Asimismo, es característica de la fase del sueño REM la presencia de atonía de la musculatura esquelética, con excepción de la musculatura ocular y del diafragma.(1)

Se postula que las funciones del sueño son diversas y complejas. Éstas incluyen la conservación de energía y esfuerzo, la secreción de hormonas como la GH y la PRL, el refuerzo del sistema inmune, la consolidación de la memoria, y efectos reguladores del ánimo.(2) Asimismo, se ha demostrado la eliminación de proteína amiloide y otros productos metabólicos durante el sueño profundo,(3) reforzando la idea del papel crucial que tiene el sueño en mantener un adecuado estado de salud.

1.1.2. Codificación e interpretación de la vídeo-polisomnografía

La polisomnografía (PSG) es el estudio más utilizado para evaluar de forma objetiva el sueño. El montaje estándar de una PSG se realiza de acuerdo a la normativa propuesta por la Academia Americana de Medicina del Sueño (AASM por sus siglas en inglés), e incluye EEG con canales F3, F4, C3, C4, O1 y O2, electrooculograma, electromiografía (EMG) de músculos mentoniano y tibiales anteriores, electrocardiograma, sensor de saturación de oxihemoglobina (SpO_2), sensores de temperatura y presión del flujo de aire, detector de ronquido, bandas torácica y abdominal para caracterización de eventos respiratorios, banda de postura e, idealmente, monitorización audiovisual sincronizada, constituyendo así una vídeo-polisomnografía (V-PSG).(4)

La identificación de las fases del sueño y la detección de eventos motores y respiratorios durante el sueño también se realiza siguiendo la normativa de la AASM. Para la revisión y codificación de una PSG, normalmente la duración total del estudio se divide en segmentos (denominados épocas) de 30 segundos.(4)

En una PSG, una época se codifica como vigilia si más del 50% contiene ritmo posterior dominante (ritmo alfa: 8-13 Hz) con cierre ocular, y/o movimientos oculares de pestañeo (movimientos conjugados verticales a 0,5-2 Hz), movimientos oculares rápidos (movimientos conjugados, irregulares, con inicio de duración menor de 500 milisegundos) con EMG mentoniano mantenido, o movimientos oculares de lectura (movimientos conjugados con una fase lenta seguida de fase rápida y dirección opuesta).

La codificación de la fase N1 del sueño NREM comienza cuando más del 50% de una época tiene un cambio en el EEG, con atenuación del ritmo alfa y sustitución por un ritmo de baja amplitud y frecuencias mixtas. Si el sujeto no generaba ritmo alfa, se considera sueño N1 cuando el EEG pasa a tener frecuencias de 4-7 Hz con enlentecimiento de la frecuencia de fondo de al menos 1 Hz con respecto a la vigilia, cuando aparecen las ondas de vértex (máximas en regiones centrales y de duración menor de 0,5 segundos), o cuando aparecen movimientos oculares lentos (movimientos conjugados, sinusoidales, con inicio de duración mayor de 500 milisegundos). La fase N2 del sueño NREM se codifica cuando hay uno o más complejos K no asociados con *arousal* (separado por al menos un segundo), y/o cuando hay uno o más husos de sueño. Los complejos K están formados por una onda aguda negativa a la que le sigue un componente positivo, con una duración de al menos 0,5 segundos, y máxima amplitud en derivaciones frontales. Los husos de sueño son ondas sinusoidales de 11-16 Hz y duración

de al menos 0,5 segundos, de máxima amplitud en derivaciones centrales. Se identifica la fase N3 del sueño NREM cuando al menos el 20% de la época contiene actividad de ondas deltas, definida como ondas de frecuencia 0,5-2 Hz con amplitud mayor de 75 μV medido en derivaciones frontales (F4-M1, F3-M2). La fase REM se codifica cuando la época contiene EEG de baja amplitud y mezcla de frecuencias (sin complejos K ni husos de sueño), EMG mentoniano con actividad mínima o ausente (la menor de todo el estudio), y movimientos oculares rápidos. Si bien estas normas son aplicables en condiciones normales, su aplicabilidad en determinadas enfermedades neurológicas no es posible. Con frecuencia, es necesaria una aproximación más descriptiva y flexible en la codificación e interpretación de estudios con V-PSG en el contexto de ciertas patologías.(5)

Se identifica un *arousal* (o microdespertar) cuando hay un cambio abrupto de las frecuencias del EEG, de al menos 3 segundos de duración, con al menos 10 segundos de sueño estable previamente. Para identificar un microdespertar durante la fase REM, debe haber además un incremento de la actividad EMG mentoniana de al menos 1 segundo de duración.(4)

Se codifica una apnea obstructiva durante el sueño cuando hay una caída de la excursión del pico de la señal de flujo aéreo (medido con sensor térmico oronasal) de al menos el 90% con respecto a la línea de base, de una duración de al menos 10 segundos, y con esfuerzo inspiratorio asociado. Las apneas centrales se codifican en las mismas condiciones pero cuando hay ausencia del esfuerzo inspiratorio, y las apneas mixtas cuando hay esfuerzo inspiratorio sólo en la segunda parte del evento respiratorio. Las hipopneas se diagnostican cuando la excursión del pico de la señal de flujo aéreo (medido con cánula de presión nasal) cae al menos un 30% con respecto a la línea de base, durante al menos 10 segundos, y se asocia a una desaturación de al menos el 3% con respecto a la saturación pre-evento y/o con un *arousal*. El punto de corte normalmente utilizado para indicar si hay un número elevado de apneas o hipopneas por hora de sueño (índice de apnea-hipopnea) es por encima de 5 eventos por hora.(6)

La identificación de una serie de movimientos periódicos de las piernas durante el sueño (MPPS) medidos en los músculos tibiales anteriores se da cuando se observan al menos cuatro movimientos consecutivos, con una duración de entre 0,5 y 10 segundos

cada uno, una amplitud mínima de al menos 8 μV superior a la amplitud del EMG de base, y una separación entre dos movimientos consecutivos de 5-90 segundos. Si dos movimientos están separados por menos de 5 segundos se consideran como un solo movimiento (aunque afecten a piernas distintas). Los movimientos que se encuentran a menos de 0,5 segundos anterior o posteriormente a un evento respiratorio no se contabilizan. Se considera que el índice de MPPS está elevado en adultos cuando éste es mayor de 15 por hora.(6)

Según la AASM, cuando se evalúa la pérdida de atonía fisiológica durante el sueño REM se puede identificar la presencia de 1) actividad muscular excesiva mantenida (tónica), si hay un aumento de la amplitud de EMG mentoniano de al menos el doble de la actividad de base en REM, durante al menos el 50% de una época; 2) actividad muscular excesiva transitoria (fásica), si al menos el 50% de las mini-épocas de 3 segundos en una época (por lo tanto, al menos 5 mini-épocas) contienen actividad muscular en EMG mentoniano o EMG tibiales de amplitud al menos el doble de la actividad de base en REM, y de duración 0,1-5 segundos; y 3) cualquier actividad a nivel de EMG mentoniano (tónica o fásica), cuando al menos un 50% de las mini-épocas de 3 segundos de una época contienen actividad muscular con una amplitud de al menos el doble de la actividad de base en REM, incluyendo actividad de duración de 5-15 segundos. Se considera una época de sueño REM con pérdida de atonía cuando uno de los tres supuestos anteriores se cumple. Aunque no se realiza de forma rutinaria en todos los centros, se ha demostrado que la incorporación de EMG en miembros superiores (músculo flexor digital superficial), permite una mejor identificación de casos de pérdida de atonía durante el sueño REM. El grupo SINBAR (*Sleep Innsbruck Barcelona*) propuso un punto de corte del 32% de las mini-épocas de 3 segundos con cualquier actividad en el EMG mentoniano o la actividad fásica en el EMG de los músculos flexores digitales superficiales en los antebrazos, para el diagnóstico de trastorno de conducta del sueño REM (TCSR). No se recomienda evaluar la actividad EMG fásica en los músculos tibiales anteriores de las piernas debido a su pobre especificidad.(7)

1.2. ¿Cómo se controla el sueño?

Para entender cómo y por qué la presencia de un sueño alterado es una característica clínica presente en ciertas enfermedades, es necesario conocer el control fisiológico del mantenimiento del sueño y la vigilia, y de la transición entre las distintas fases del sueño, así como el control de la respiración a nivel central.

1.2.1. Control fisiológico del sueño y la vigilia

El ciclo sueño-vigilia está controlado por el proceso homeostático y el proceso circadiano, y se ve además influido por factores individuales (como la edad o la etnia) y ambientales (como el ruido, la temperatura y la intensidad de la luz).(8) El proceso homeostático consiste en el incremento de la presión de sueño a medida que aumenta el tiempo en vigilia, y está mediado por la acumulación de adenosina.(9) Por otro lado, a medida que transcurre tiempo en el que estamos dormidos, los niveles de adenosina y la actividad de ondas lentas en el EEG disminuyen, siendo mínimas al final del periodo de sueño.(10) El núcleo supraquiasmático del hipotálamo anterior es el marcapasos u oscilador central del ritmo circadiano, y la melatonina es la principal hormona reguladora del sistema circadiano. El proceso circadiano controla tanto los ciclos sueño-vigilia como los ritmos biológicos de otros órganos y células de nuestro cuerpo (osciladores periféricos). Asimismo, el sistema circadiano se sincroniza con factores exógenos denominados *zeitgebers*, de los cuales el más importante es la luz. En la oscuridad, la ausencia de activación del núcleo supraquiasmático va a dar lugar a la desinhibición de neuronas del núcleo paraventricular del hipotálamo, y activación de neuronas en la columna intermediolateral y del ganglio cervical superior, que envían proyecciones noradrenérgicas a la glándula pineal, secretando melatonina. Sin embargo, en presencia de luz, la activación del haz retino-hipotalámico da lugar a una inhibición GABAérgica del núcleo paraventricular, inhibiéndose la síntesis de melatonina. La secreción de melatonina ocurre también a nivel extra-pineal y, además de su efecto regulador circadiano, se considera que tiene propiedades anti-oxidantes y anti-inflamatorias.(11)

La transición entre el estado de vigilia y el sueño, y entre las distintas fases del sueño (fases N1, N2, y N3 del sueño NREM, y sueño REM), es compleja e implica cambios importantes en numerosas variables fisiológicas, incluyendo la respiración, la actividad electroencefalográfica cortical, la apertura ocular, y el tono muscular. El control

para mantener el sueño y la vigilia va a depender de la interacción entre grupos de neuronas y vías en el sistema nervioso central, a través de diversos neurotransmisores. Actualmente, se considera que hay núcleos y proyecciones que promueven la vigilia o el sueño, que se inhiben mutuamente, en un modelo denominado *flip-flop*.(12)

Se van a encargar de mantener la vigilia neuronas colinérgicas (desde núcleos tegmental pedunculopontino y tegmental laterodorsal en la protuberancia) con proyección al tálamo, y neuronas monoaminérgicas (desde el *locus coeruleus* en la protuberancia, sustancia negra y área tegmental ventral del mesencéfalo, núcleos dorsal y medial del rafe, y núcleos túberomamilares del hipotálamo) y glutamatérgicas (desde tegmento pontino y mesencefálico) que proyectan al hipotálamo, a la corteza frontobasal y a áreas más extensas de la corteza cerebral, constituyendo el sistema reticular ascendente. Asimismo, las neuronas orexinérgicas del hipotálamo lateral, refuerzan la activación de la corteza cerebral para inducir el despertar.

El sueño está fundamentalmente promovido por el núcleo preóptico ventrolateral y medial del hipotálamo, que inhiben a su vez las vías de mantenimiento de la vigilia a través de neurotransmisores GABA y galanina. El núcleo preóptico ventrolateral se relaciona también con el núcleo supraquiasmático para mantener un control circadiano de los ciclos de sueño-vigilia. El tálamo es el responsable de la generación de husos de sueño, característicos de la fase N2. La actividad sincronizada oscilatoria de las neuronas reticulares del tálamo da lugar a una hiperpolarización del circuito tálamo-cortical, interrumpiéndose el flujo de información desde y hacia la corteza cerebral que existe normalmente en vigilia,(13) y facilitando la aparición de husos de sueño, complejos K y actividad de ondas lentas.(14)

La transición entre el sueño NREM y el sueño REM se consigue por la relación de inhibición recíproca entre dos grupos de neuronas (REM-*on* y REM-*off*). El núcleo subcerúleo de la protuberancia permite la transición al sueño REM inhibiendo las neuronas REM-*off* de la sustancia gris periacueductal ventral y del tegmento lateral pontino. Asimismo, habrá también desde el núcleo subcerúleo proyecciones al núcleo reticular gigantocelular en el bulbo, y de ahí a interneuronas inhibitorias de motoneuronas espinales, dando lugar a la atonía fisiológica durante el sueño REM. Los núcleos colinérgicos tegmental pedunculopontino y tegmental laterodorsal también promueven el sueño REM. Las neuronas noradrenérgicas del *locus coeruleus* y las neuronas serotoninérgicas del rafe dorsal inhiben el sueño REM mediante activación de neuronas

REM-*off* e inhibición de neuronas REM-*on*.(15) Las neuronas que contienen hormona concentradora de melanina en el hipotálamo lateral se encuentran también activas durante el sueño REM. Sin embargo, las proyecciones orexinérgicas desde el hipotálamo lateral se encargan de activar las neuronas REM-*off*, impidiendo una transición de la vigilia al sueño REM en condiciones fisiológicas.(12,16)

1.2.2. Control central de la respiración y cómo cambia durante el sueño

El control central de la respiración depende de grupos neuronales situados a nivel de la parte baja del tronco del encéfalo que actúan en respuesta a estímulos provenientes de quimiorreceptores centrales y periféricos. Las principales áreas implicadas en generar la respiración automática incluyen el núcleo del tracto solitario, el núcleo arcuato, y las neuronas serotoninérgicas del rafe (Figura 1).(17) El núcleo del tracto solitario recibe aferencias de los cuerpos carotideos, y envía proyecciones al núcleo dorsal del vago, al núcleo ambiguo, al bulbo caudal y rostral, y al grupo respiratorio ventral del bulbo. El núcleo parabraquial recibe proyecciones del núcleo solitario, y se ha relacionado con el control de la generación de *arousals* desde el sueño como respuesta a cambios en niveles de CO_2. Las neuronas serotoninérgicas del rafe, que envía proyecciones al núcleo arcuato, están implicadas también en la quimiosensibilidad. Por otro lado, el grupo respiratorio ventral, ubicado dorsalmente a las olivas inferiores en el bulbo, parece tener un papel importante en generar el ritmo de la respiración, permitiendo la transición entre la inspiración y la espiración.(18) Desde el grupo respiratorio ventral y el núcleo ambiguo, emergen motoneuronas vagales que inervan músculos de la laringe, y por lo tanto parecen estar implicados en la fisiopatología del estridor.(19,20)

Durante la vigilia, el control de la respiración puede modularse de forma consciente para así adaptarla a acciones tales como estar en movimiento, o detener la respiración al tragar o nadar. Sin embargo, con el inicio del sueño, la ventilación pasa a estar gobernada exclusivamente por cambios metabólicos generando respuestas reflejas de los quimiorreceptores centrales y periféricos, si bien la respuesta está en general reducida tanto en el sueño NREM como en el sueño REM respecto a la vigilia.

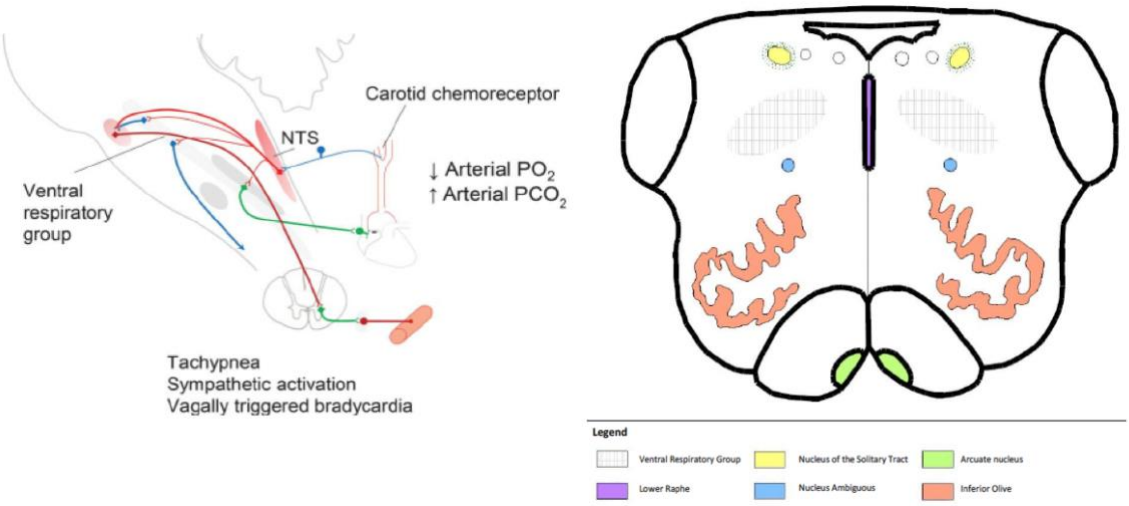

Figura 1. **Control central de la respiración**. A la izquierda, figura tomada de Cutsforth-Gregory y colaboradores:(17) quimiorreceptores en el cuerpo carotideo estimulados por hipoxia o hipercapnia activan neuronas del núcleo del tracto solitario, que proyectan hacia el grupo respiratorio ventral dando lugar a taquipnea. A la derecha (figura propia): representación esquemática de un corte axial a nivel del bulbo, incluyendo los grupos neuronales involucrados en el control central de la respiración y su relación anatómica con las olivas inferiores.

En la transición de la vigilia al sueño, pequeñas reducciones en la presión arterial de CO_2, harán que los quimiorreceptores den la señal de detener la respiración, dando lugar a una apnea central que elevará los niveles de CO_2 a un nivel suficiente como para reanudar la respiración.(21) Esta situación es especialmente importante en presencia de un sueño fragmentado, en el que hay una consecución de transiciones entre vigilia y sueño, que modifican de forma cíclica los niveles de CO_2, pudiendo dar lugar a apneas centrales de transición al sueño. A medida que nos adentramos en las distintas fases del sueño NREM, cambios fisiológicos de la respiración incluyen la presencia de una quimiosensibilidad respiratoria reducida y una reducción de la activación de la musculatura de la vía aérea superior. A pesar de estos cambios con respecto a la vigilia, el sueño profundo se considera un estado en el que la respiración se mantiene relativamente estable, con mínimas variaciones del volumen corriente.(22) Sin embargo, durante el sueño REM, se observan patrones de respiración irregular con aumento de la frecuencia respiratoria y reducción del volumen corriente durante movimientos fásicos oculares, así como una reducción de la respuesta ventilatoria a la hipoxia (todavía más marcada que en el sueño NREM), y un claro efecto de la atonía muscular que caracteriza a esta fase.(23)

Teniendo en cuenta la elevada complejidad del control fisiológico para un adecuado mantenimiento del sueño y de la vigilia, así como para la transición normal entre fases, no es inesperado que la afectación patológica de algunas de las estructuras del sistema nervioso central implicadas, pueda dar lugar a alteraciones importantes de la arquitectura del sueño. De la misma manera, debido a los cambios fisiológicos de la respiración en función del estado en el que nos encontremos (dependiendo incluso de la fase del sueño), y a la delicadeza del control de dicha función vital, alteraciones neuropatológicas que afecten los centros respiratorios o áreas centrales encargadas del mantenimiento del sueño y la vigilia, pueden resultar en patrones respiratorios prominentemente alterados y patología respiratoria durante el sueño.

1.3. El sueño en enfermedades neurológicas

1.3.1. El sueño en enfermedades neurodegenerativas no priónicas

Las alteraciones del sueño pueden darse como causa y como consecuencia de procesos neurodegenerativos.(24) Duraciones extremas del tiempo total de sueño (por debajo de 4h o por encima de 10h) se han establecido como factores de riesgo de deterioro cognitivo.(25) Asimismo, se ha demostrado recientemente que, en situaciones de privación de sueño, la eliminación de productos cerebrales como la proteína amiloide se encuentra alterada.(26) No sólo la duración del sueño, también la disrupción de su arquitectura, se ha relacionado con procesos neurodegenerativos. Tanto una menor cantidad como la fragmentación del sueño profundo, se asocia a mayores concentraciones de beta-amiloide en líquido cefalorraquídeo (LCR) en sujetos sanos, y a alteraciones en la consolidación de la memoria.(27,28) Alteraciones de los ritmos circadianos también han sido identificadas en fases preclínicas de la enfermedad de Alzheimer, y se proponen como un factor de riesgo de la misma.(29,30) La hipoxia intermitente, el sueño fragmentado, y los incrementos cíclicos de la presión intratorácica en el contexto de la apnea obstructiva del sueño (AOS) se relacionan con un mayor riesgo de deterioro cognitivo.(31) Es especialmente relevante la evidencia que asocia la presencia del TCSR con el desarrollo posterior de enfermedades neurodegenerativas (sinucleinopatías) tales como la enfermedad de Parkinson, la demencia por cuerpos de Lewy o la atrofia multisistémica.(32) La forma aislada o idiopática del TCSR se considera la fase

prodrómica de una sinucleinopatía, con un mayor riesgo de desarrollar una demencia por cuerpos de Lewy en la presencia de deterioro cognitivo y de éste cuando hay enlentecimiento en el EEG.(33,34)

Numerosas alteraciones del sueño han sido descritas también en pacientes con un diagnóstico ya establecido de una enfermedad neurodegenerativa. Las alteraciones del sueño en pacientes con enfermedad de Alzheimer son diversas. Se ha descrito una mayor prevalencia de AOS que en la población general, así como una tendencia al sueño durante el día, con fragmentación del sueño nocturno y despertar precoz, debido en parte a la degeneración del núcleo supraquiasmático. Los estudios con PSG de estos sujetos con enfermedad avanzada muestran una eficiencia de sueño reducida, con mayor proporción de sueño superficial y menor cantidad de sueño profundo y sueño REM, a menudo con desaparición del ritmo alfa en vigilia y de los husos de sueño y complejos K en el sueño.(35)

En la enfermedad de Parkinson, hay una elevada prevalencia de somnolencia diurna excesiva persistente que se ha relacionado con la neurodegeneración de estructuras que controlan el sueño y la vigilia, y con efectos sedativos de fármacos dopaminérgicos. El TCSR se da en un 40-50% de los casos, y se relaciona predominantemente con sexo masculino, mayor edad, parkinsonismo de larga duración, síndrome rígido-acinético, caídas, y deterioro cognitivo.(36) Se ha demostrado un mayor enlentecimiento del ritmo alfa, alteración de la arquitectura del sueño NREM, y somnolencia diurna excesiva en pacientes con enfermedad de Parkinson con demencia que en aquellos sin demencia, sin haberse hallado una reducción de los niveles de orexina en LCR.(37) En la demencia por cuerpos de Lewy, son frecuentes la somnolencia diurna excesiva, con siestas durante el día, e insomnio durante la noche, así como episodios de confusión nocturna. En torno al 50-80% de estos pacientes sufre además un TCSR.(36) El análisis detallado de estudios con V-PSG de pacientes con demencia por cuerpos de Lewy, indica la presencia de una arquitectura del sueño alterada, que dificulta la identificación de vigilia y fases de sueño con el uso de la metodología habitual, siendo necesario el desarrollo de nueva terminología y reglas para determinar el estado del paciente.(38) Un trabajo que incluyó 35 pacientes con demencia por cuerpos de Lewy, describió la presencia de un enlentecimiento occipital en vigilia en el EEG, definió un sueño NREM indiferenciado (con actividad EEG theta-delta y ausencia de características típicas del sueño NREM como ondas de vértex, complejos K y husos de sueño), describió la presencia de actividad

delta, pérdida de atonía y alteraciones de la conducta en el sueño REM, y la presencia de alucinaciones nocturnas o despertares confusos con conductas elaboradas.(38) El TCSR es especialmente frecuente en sujetos con atrofia multisistémica, ya que este trastorno del sueño está presente en prácticamente todos los casos. Asimismo, estos pacientes presentan a menudo alteraciones respiratorias durante el sueño como apneas obstructivas, centrales y estridor debido a la disfunción de la abducción de las cuerdas vocales durante la inspiración.(36)

En la parálisis supranuclear progresiva, la queja de sueño fundamental es el insomnio. Hasta un 20% de estos pacientes tienen TCSR, si bien habrá ocasiones en las que las alteraciones de la conducta por la noche se deban a despertares confusos, como ocurre en otros casos en el contexto de deterioro cognitivo. El estudio con PSG muestra una reducción de la eficiencia de sueño y del sueño REM, y posible reducción de husos de sueño, complejos K y ausencia de ritmo alfa. Los pacientes con enfermedad de Huntington sufren somnolencia diurna excesiva, insomnio y un adelanto de fase. El estridor nocturno se ha descrito en las ataxias espinocerebelosas 1 y 3, y el TCSR se da hasta en el 50% de los casos de esta última. Sujetos con esclerosis lateral amiotrófica refieren con frecuencia nocturia, insomnio, calambres musculares nocturnos y somnolencia diurna excesiva, a menudo con evidencia de alteraciones respiratorias durante el sueño. El estudio con PSG de pacientes con demencia frontotemporal ha demostrado la presencia de un tiempo total de sueño reducido, con aumento del sueño superficial y reducción de la proporción del sueño REM.(36,39)

1.3.2. Neuroinmunología y sueño

La evidencia de alteraciones del sueño en enfermedades autoinmunes que afectan al sistema nervioso central es amplia. Sin embargo, éstas se ven frecuentemente eclipsadas por la presencia de otros síntomas neurológicos prominentes. Más allá de los trastornos del sueño con fisiopatología que se sospecha de origen autoinmune, tales como la narcolepsia tipo 1 o el síndrome de Kleine-Levin, hay numerosas enfermedades neuroinmunes que pueden asociar alteraciones del sueño.

Los pacientes con esclerosis múltiple refieren con frecuencia problemas de insomnio, así como síndrome de piernas inquietas (SPI), si bien no está claro que haya una mayor prevalencia que en la población general. Se han descrito también casos de TCSR en pacientes con placas desmielinizantes afectando a las estructuras del sistema nervioso central que controlan la atonía del sueño REM, así como casos de narcolepsia

secundaria debido a la presencia de placas desmielinizantes a nivel hipotalámico.(40) En el trastorno del espectro de neuromielitis óptica, se ha demostrado la presencia de somnolencia diurna excesiva y reducción de niveles de orexina en LCR, sin evidencia de cataplejia.(41) Estudios de sueño realizados en la fase aguda del síndrome de Guillain-Barré han demostrado una reducción de la eficiencia de sueño y la proporción de sueño REM, así como un incremento del índice de MPPS, y un aumento de apneas-hipopneas durante el sueño en pacientes con afectación de musculatura bulbar.(42) En pacientes con Guillain-Barré que sufren alucinaciones y que requieren ingreso en la unidad de cuidados intensivos, alteraciones prominentes de la arquitectura del sueño incluyendo una reducción de la latencia al sueño REM, pérdida de la atonía en REM y posible reducción de los niveles de orexina en LCR han sido descritos.(43) Síntomas de somnolencia diurna excesiva, reducción de la duración del tiempo de sueño, y SPI han sido referidos por pacientes con polineuropatía desmielinizante inflamatoria crónica.(44,45)

Los síntomas relacionados con un sueño alterado son comunes en las encefalitis autoinmunes. Los pacientes con encefalitis por anticuerpos anti-NMDA presentan típicamente insomnio al inicio de la enfermedad, y posteriormente desarrollan hipersomnia, y despertares confusos demostrados en V-PSG. En la encefalitis anti-LGI1, insomnio y somnolencia diurna excesiva pueden ser referidas, así como la demostración de TCSR en V-PSG en la fase aguda de la enfermedad. En pacientes con síndrome de Morvan y anticuerpos anti-CASPR2 es típica la presencia de insomnio grave y disautonomía, llegando a darse un estado extremo de disociación sueño-vigilia denominado *agrypnia excitata* (término inicialmente acuñado en el insomnio letal familiar).[1] En la encefalitis con anticuerpos frente a DPPX puede aparecer insomnio, MPPS y parasomnias. Tanto insomnio como hipersomnia se pueden dar en la encefalitis anti-AMPA. Los pacientes con encefalitis anti-Ma2 con afectación hipotalámica pueden desarrollar una narcolepsia secundaria incluyendo niveles reducidos de orexina en LCR. La afectación a nivel del tronco del encéfalo en la encefalitis anti-Hu da lugar a hipoventilación central.(46)

Las alteraciones del sueño son prominentes y a menudo el motivo de consulta inicial de la enfermedad anti-IgLON5. La presencia de apneas durante el sueño, parasomnias, insomnio, somnolencia diurna y estridor durante el sueño ha sido descrita en estos pacientes.(47) La noción de un sueño NREM indiferenciado (EEG theta irregular

[1] Ver secciones 1.4.3.2 y 1.5.2.2 de esta introducción para mayor detalle.

de moderada amplitud, sin ondas de vértex, complejos K, husos de sueño, ni características del sueño REM), y fase N2 pobremente estructurada (con complejos K y husos de sueño ocasionales, y frecuentes vocalizaciones o movimientos) fueron introducidos para representar las alteraciones substanciales de la arquitectura del sueño observadas en las V-PSGs de estos pacientes.(48)

1.3.3. Sueño e ictus

Existe una relación bidireccional entre el ictus y el sueño, siendo esta evidencia especialmente sólida para la asociación entre AOS y el ictus. La AOS es un factor de riesgo independiente de ictus, con un incremento del riesgo a medida que aumenta la gravedad de la AOS.(49) Además de la frecuente comorbilidad de otros factores de riesgo cardiovascular en estos pacientes, se postula que factores fisiopatológicos asociados a las apneas obstructivas tales como el aumento de la presión intracraneal y reducción de perfusión cerebral, anomalías en la respuesta vascular cerebral a la hipercapnia, una actividad simpática aumentada, una agregación plaquetaria y niveles de fibrinógeno elevados, contribuyen también a un riesgo aumentado de ictus.(50) Por otro lado, es frecuente el diagnóstico de AOS en pacientes que previamente han sufrido un ictus o accidente isquémico transitorio.(51) Esta asociación que puede deberse a la afectación de áreas centrales encargadas del control de la respiración, alteraciones del tono de la musculatura de la vía aérea superior como consecuencia del ictus o, más probablemente, a la pre-existencia de un trastorno respiratorio del sueño no diagnosticado.

Tanto una duración aumentada como disminuida del tiempo total de sueño, han sido propuestos como factores de riesgo de ictus.(52) Se ha planteado asimismo un riesgo aumentado de sufrir ictus en pacientes con MPPS,(53) si bien estudios longitudinales son necesarios para establecer esta posible asociación.

Por otro lado, pacientes que han sufrido un ictus presentan con frecuencia otras alteraciones del sueño tales como insomnio, somnolencia diurna excesiva o SPI, pudiendo tener éstos un impacto en la recuperación funcional tras el evento cerebrovascular.(54)

1.3.4. El sueño en otras enfermedades neurológicas

La relación entre epilepsia y sueño es compleja. Tanto la actividad epiléptica, como el uso de fármacos antiepilépticos, pueden afectar al sueño. Ciertos tipos de epilepsias se dan sólo durante el sueño, y hay un efecto claro de los ritmos circadianos en la actividad epiléptica en muchos casos. Asimismo, la privación de sueño y la

fragmentación del mismo como consecuencia de ciertos trastornos del sueño, pueden empeorar el control de la epilepsia. De hecho, los pacientes con epilepsia refieren síntomas de SPI e insomnio, y tienen AOS, con mayor frecuencia que controles sanos o que la población general. Por último, hay episodios durante el sueño que son difíciles de caracterizar y para los que tanto epilepsia durante el sueño como ciertos tipos de parasomnias se incluirían en el diagnóstico diferencial.(55)

Las cefaleas se dan con frecuencia en trastornos del sueño tales como la AOS y el insomnio, si bien en este último caso, la relación esté probablemente mediada por otras comorbilidades como alteraciones del ánimo, dolor crónico o fibromialgia. Por otro lado, hay cefaleas primarias que se ven significativamente influidas por el sueño. Las migrañas pueden verse desencadenadas por la falta o el exceso de sueño, y alteraciones en la calidad del sueño son a menudo referidas como síntoma premonitor de las migrañas. Sujetos con cefaleas tensionales frecuentemente refieren síntomas relacionados con el sueño tales como el insomnio, hipersomnia o alteraciones circadianas. Tanto las migrañas como la cefalea en racimos tienen características circadianas, y las cefaleas hípnicas se dan exclusivamente durante el sueño (se postula que ocurren durante el sueño profundo, la fase REM o como consecuencia de desaturaciones).(56,57)

1.4. Enfermedades priónicas en el ser humano

1.4.1. Definición y epidemiología

Las enfermedades priónicas, prionopatías o encefalopatías espongiformes transmisibles, son patologías neurodegenerativas producidas por una conformación alterada de la proteína priónica celular (PrP^{C}), glicoproteína de superficie, dando lugar a la proteína priónica patogénica (PrP^{Sc}).(58) Estas partículas proteicas fueron descritas por el premio Nobel de Medicina y Fisiología en 1997, Stanley Prusiner, quien acuñó el término prion.(59) La proteína priónica está codificada por el gen *PRNP*, localizado en humanos en el cromosoma 20. La PrP^{C} se expresa ampliamente en neuronas y otras células del sistema nervioso central.(60) El modelo de enfermedad priónica sugiere que la forma anómala de la proteína, o PrP^{Sc}, actúa como plantilla de modo que, al entrar en contacto con PrP^{C}, la convierte en PrP^{Sc}.(61) La formación de PrP^{Sc}, y la agregación y acumulación de la misma, da lugar a muerte neuronal y a los cambios espongiformes patognomónicos de este grupo de enfermedades.(62) Además de afectar al ser humano,

las enfermedades priónicas pueden darse en otros mamíferos, y transmitirse de forma accidental o experimental entre especies.(63)

1.4.2. Clasificación y características de las enfermedades priónicas

Las enfermedades priónicas se clasifican según su etiología en: 1) **esporádicas** (85% de los casos) – la conversión de PrP^{C} a PrP^{Sc} ocurre de forma espontánea, o por una mutación somática del gen *PRNP*; 2) **genéticas** (10-15%) – hay una susceptibilidad aumentada al plegamiento anómalo de PrP^{C} debido a mutaciones en el gen *PRNP* de herencia autosómica dominante; 3) **adquiridas** – la proteína PrP^{Sc} es transmitida de forma accidental a una persona, ya sea de forma iatrogénica o por consumo de productos contaminados.

Además de las etiologías que pueden dar lugar a las distintas prionopatías, la heterogeneidad fenotípica de estas patologías está influida por el polimorfismo del gen *PRNP* en el codón 129 (el cual puede codificar metionina o valina), y la isoforma de la proteína priónica predominantemente involucrada en cada caso. Aproximadamente la mitad de la población general es heterocigota metionina-valina en el codón 129. Se postula que la homocigosis en el codón 129 es un factor predisponente tanto para la enfermedad de Creutzfeldt-Jakob esporádica, como para la forma iatrogénica cuando es valina-valina.(64,65) Las PrP^{Sc} tipo 1 y tipo 2, tienen un centro resistente a la proteína kinasa de 21 y 19 kDa respectivamente; y hay también un fragmento molecular de PrP^{Sc} con masa intermedia ("i") de 20 kDa.(61,66) Asimismo, ciertos polimorfismos del gen *PRNP* están relacionados con la amplia variedad en los hallazgos neuropatológicos y la presentación clínica de estas enfermedades.

Las prionopatías esporádicas son la enfermedad de Creutzfeldt-Jakob (ECJ) esporádica (ECJe), el insomnio letal esporádico (ILe), y la prionopatía con sensibilidad variable a proteasa. Las formas genéticas incluyen la ECJ hereditaria (ECJh), el insomnio letal familiar (ILf), y la enfermedad de Gerstmann-Sträussler-Scheinker (GSS). Las enfermedades priónicas adquiridas son las formas iatrogénica y enfermedad de Creutzfeldt-Jakob variante (ECJv – popularmente conocida como “enfermedad de las vacas locas”), y el Kuru (considerada extinta en la actualidad).(62) La Tabla 1 contiene un resumen de las principales características de estas enfermedades, a excepción del

insomnio letal (IL) y la enfermedad de GSS.[2] Las enfermedades priónicas tienen un curso progresivo y desenlace fatal, sin haber disponible en la actualidad un tratamiento curativo para las mismas.

En torno al 90% de los casos de enfermedades priónicas diagnosticadas son ECJe, con una incidencia de 0,5-2 por millón de personas-año.(63,67) Hay principalmente seis subtipos de ECJe dependiendo del polimorfismo en el codón 129 (metionina o valina) y de la isoforma de PrP^{Sc} presentes (Tabla 1). Hasta en un 35% de los casos las PrP^{Sc} tipo 1 y tipo 2 coexisten, y la denominación utilizada hace referencia a la que es más predominante.(66,68)

Las formas de ECJe más frecuentes son la MM1/MV1 (normalmente agrupadas ya que son clínicamente indistinguibles) y la VV2. La presentación clínica típica de las formas MM1/MV1 consiste en una demencia rápidamente progresiva, mioclonías, ataxia, síntomas visuales, y signos piramidales y extrapiramidales.[3]

A nivel neuropatológico, se caracteriza por la presencia de degeneración espongiforme, astrogliosis y pérdida neuronal a nivel cortical (especialmente del lóbulo occipital), en el estriado, tálamo, y en la sustancia blanca cerebelosa. Se puede encontrar también la formación de placas amiloides de PrP^{Sc}.(69)

La resonancia magnética (RM) cerebral en sujetos con ECJe típicamente muestra restricción a la difusión en al menos dos áreas corticales y/o en el caudado, seguido de putamen y tálamo. El EEG puede evidenciar complejos periódicos de ondas agudas bifásicas o trifásicas en fases avanzadas de la enfermedad. Biomarcadores en LCR que han demostrado una buena sensibilidad y especificidad para el diagnóstico de ECJe son la proteína 14-3-3 y tau total. El método RT-QuIC (del inglés *real-time quaking-induced conversion* - conversión inducida por temblor en tiempo real) para la amplificación de PrP^{Sc} en LCR es un biomarcador de prionopatías altamente específico. Los criterios diagnósticos de la ECJe fueron actualizados en 2018 con la incorporación del uso de RT-QuIC,(70) y fueron ligeramente modificados en 2021 haciendo especial énfasis en los hallazgos de la RM cerebral y en la necesidad de realizar un estudio completo que permita excluir otras posibles causas (Figura 2).(71)

[2] El IL y la enfermedad de GSS serán tratados en mayor detalle en las secciones 1.4.3. y 1.4.4.
[3] Las alteraciones durante el sueño descritas en la ECJ se revisan en la sección 1.5.2.1 de esta introducción.

Enfermedad	Etiología	Síntomas principales (polimorfismo codón 129)	Pruebas complementarias			
			Histopatología e inmunohistoquímica	RM cerebral	EEG	LCR
Creutzfeldt-Jakob esporádica	Esporádica	Demencia rápidamente progresiva. Ataxia. Mioclonías. Posibles alteraciones visuales y disfasia (MM1/MV1)	Cambios espongiformes con pérdida neuronal, gliosis y vacuolación Acumulación de PrP^{Sc} Identificación de PrP^{Sc} resistente a proteasa	Restricción a la difusión en corteza, caudado y/o putamen Hiperintensidad cortical en FLAIR	Complejos periódicos generalizados de ondas agudas bifásicas o trifásicas (avanzada)	Prot total elevadas 14-3-3, NSE, tau, y S100β elevadas PrP^{Sc} con RT-QuIC
		Insomnio. Ataxia. Deterioro cognitivo (MM2T - talámico)*				
		Demencia progresiva (MM2C - cortical)				
		Deterioro cognitivo. Ataxia (MV2)				
		Demencia progresiva, alteraciones conductuales (VV1)				
		Ataxia rápidamente progresiva y posterior deterioro cognitivo (VV2)				
Prionopatía con sensibilidad variable a proteasa	Esporádica	Síntomas neuropsiquiátricos, deterioro cognitivo, alteración motora (VV/MV)	Cambios espongiformes y gliosis Escasa PrP^{Sc} resistente a proteasa	Atrofia generalizada	No ayuda a diagnóstico	No ayuda a diagnóstico
		Parkinsonismo, mioclonías, síntomas psiquiátricos y cognitivos (MM)				
Creutzfeldt-Jakob hereditario	Genética (AD, mutaciones en *PRNP*, E200K es la más prevalente)	Demencia, ataxia, mioclonías, parkinsonismo, síntomas neuropsiquiátricos. Inicio a edad más joven que esporádica	Similar a forma esporádica	Restricción a la difusión en corteza, caudado y/o putamen	Complejos periódicos de ondas agudas (avanzada)	14-3-3, NSE, tau, y S100β elevadas. PrP^{Sc} con RT-QuIC
Creutzfeldt-Jakob iatrogénico	Adquirida (por uso accidental de material biológico o instrumentos contaminados)	Ataxia y posterior deterioro cognitivo. Polimorfismos en codón 129 afecta susceptibilidad y tiempo de incubación	Degeneración microvacuolar.(72) Forma MMiK tiene placas kuru unicéntricas amiloideas(66)	Anomalías en FLAIR o secuencias de difusión en giro cingulado, corteza frontal, tálamos, ganglios basales, vermis cerebeloso.(72)	Actividad lenta difusa(72)	Prot total y 14-3-3 elevadas (72)
Creutzfeldt-Jakob variante	Adquirida (por consumo de productos contaminados con encefalopatía espongiforme bovina)	Síntomas neuropsiquiátricos, ataxia, alteraciones movimiento, deterioro cognitivo	Placas y acúmulo de PrP^{Sc} en cerebro y cerebelo, cambios espongiformes en caudado y putamen, gliosis en tálamo.(66) PrP^{Sc} detectable en biopsia de amígdalas	Signo del palo de hockey (hiperintensidad de núcleo pulvinar y región dorsomedial del tálamo)	No alteraciones específicas.(73) Posibles complejos periódicos(74)	14-3-3 y tau elevadas (75)
Kuru	Adquirida (por rituales caníbales en Papúa Nueva Guinea)	Ataxia, disfagia, disartria, temblor y alteraciones motoras progresivas	Cambios espongiformes en cerebelo, corteza cerebral, ganglios basales y tálamo	-	-	-

Tabla 1. Características de las principales enfermedades priónicas. Adaptado de Baldwin y Correll,(62) excluyendo el insomnio letal y la enfermedad de Gerstmann-Sträussler-Scheinker comentadas en detalle en secciones 1.4.3. y 1.4.4 de esta introducción.

RM: resonancia magnética; EEG: electroencefalograma; LCR: líquido cefalorraquídeo; MM1: metionina-metionina y PrP^{Sc} tipo 1; MV1: metionina-valina y PrP^{Sc} tipo 1; MM2: metionina-metionina y PrP^{Sc} tipo 2; MV2: metionina-valina y PrP^{Sc} tipo 2; VV1: valina-valina y PrP^{Sc} tipo 1; VV2: valina-valina y PrP^{Sc} tipo 2; MMiK: metionina-metionina y forma intermedia de PrP^{Sc}; FLAIR: *fluid-attenuated inversion recovery* (recuperación de la inversión atenuada de fluido); Prot: proteínas; NSE: *neuron-specific enolase* (enolasa neuronal específica); RT-QuIC: *real-time quaking-induced conversion* (conversión inducida por temblor en tiempo real); AD: autosómico dominante. *La forma MM2T se denomina también insomnio letal esporádico.

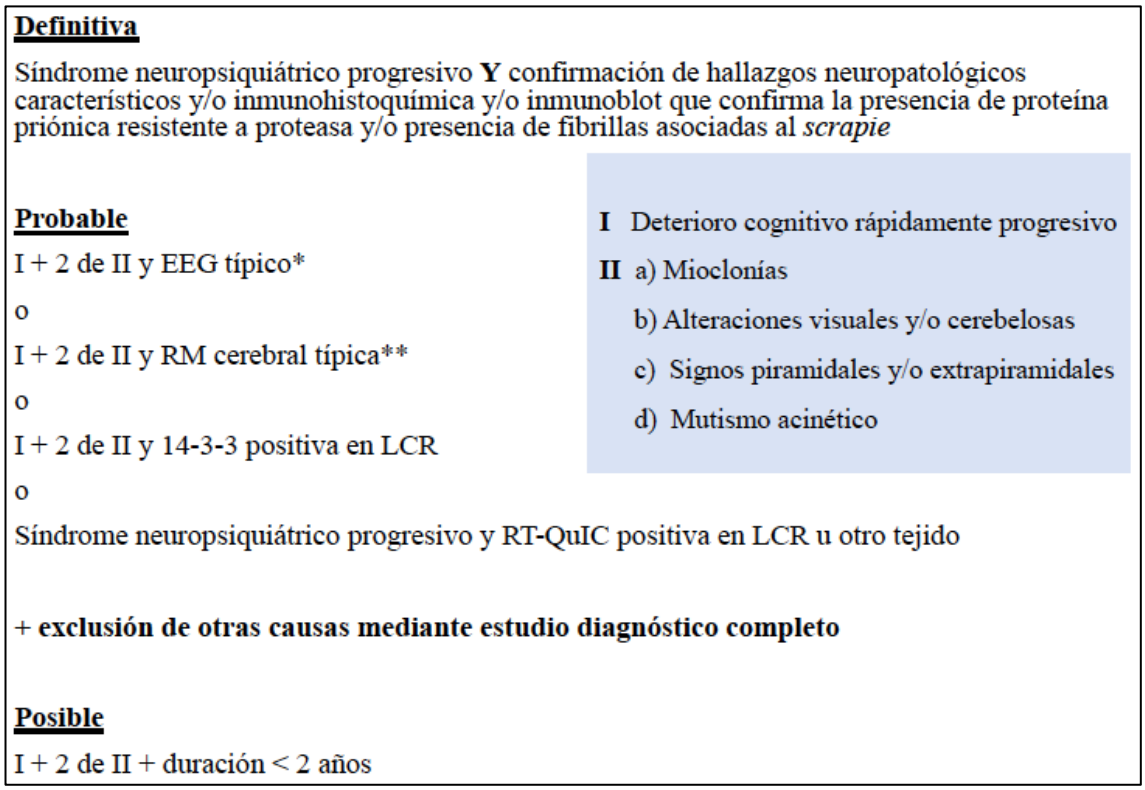

Figura 2. Criterios diagnósticos de la enfermedad de Creutzfeld-Jakob esporádica. Adaptada de Hermann y colaboradores.(70,71) EEG: electroencefalograma; RM: resonancia magnética; LCR: líquido cefalorraquídeo; RT-QuIC: *real-time quaking-induced conversión* (conversión inducida por temblor en tiempo real). *Complejos periódicos generalizados de ondas agudas. **Restricción a la difusión en caudado o caudado/putamen o caudado/putamen/tálamo, o al menos dos regiones corticales (temporal, parietal, occipital) en RM cerebral, sin afectación de sustancia blanca subcortical o restricción a la difusión en el tálamo de forma aislada. Las

hiperintensidades características pueden verse en secuencias FLAIR (del inglés *fluid-attenuated inversion recovery* - recuperación de la inversión atenuada de fluido), pero las secuencias de difusión son necesarias para confirmar los hallazgos típicos de la ECJe.

1.4.3. Insomnio letal

1.4.3.1. Etiopatogenia

El insomnio letal (IL) es una enfermedad priónica comúnmente de etiología genética y transmisión hereditaria en familias (insomnio letal familiar, ILf), pero hay casos descritos en la literatura científica sin agregación familiar en los que no se identifica mutación (insomnio letal esporádico, ILe). El ILf fue formalmente descrito por primera vez en un caso publicado en 1986 por el equipo de Elio Lugaresi en la Universidad de Bolonia, Italia.(76) Similares hallazgos fueron referidos ese mismo año por otro grupo.(76,77) En la actualidad, el ILf ha sido descrito en la literatura científica en unas 70 familias en todo el mundo.

El ILf es de herencia autosómica dominante, y se produce por la mutación con cambio de sentido en el codón 178 del gen *PRNP*.(78) La mutación en el codón 178 resulta en el cambio del aminoácido aspartato por asparagina (mutación D178N característica de la enfermedad), dando lugar a la forma patogénica de la proteína priónica. En el ILf, además de la mutación D178N, habrá un polimorfismo del codón 129 del gen *PRNP*, de forma que codifica para metionina en el alelo mutado (D178N-129M). Dependiendo de la codificación a metionina o valina del codón 129 del alelo no mutado (resultando en homocigosis metionina-metionina, o heterocigosis metionina-valina), se darán expresiones fenotípicas y cursos de la enfermedad diferentes.(79–81) Un modelo *in vitro* de la enfermedad (mediante el uso de organoides cerebrales con la mutación D178N), ha demostrado la presencia de una alteración del balance energético a nivel celular, consecuente estrés oxidativo, astrogliosis y compromiso de la actividad neuronal, que se propone como mecanismo fisiopatológico del ILf.(82)

En el ILe no hay presencia de mutación, pero los casos en los que se encontraba homocigosis para metionina en el codón 129 y afectación talámica prominente, se clasificaban previamente como una forma de ECJe (denominada MM2T).(66) Por otro lado, en presencia de la mutación D178N, con valina en codón 129 del alelo mutado (D178N-129V), se establece el diagnóstico de un subtipo de ECJh.(83)

1.4.3.2. Presentación clínica

La edad de inicio de la enfermedad es típicamente entre los 35 y los 60 años, con casos reportados también a otras edades.(80) Ambos sexos son afectados por igual. El curso de la enfermedad es progresivo, e invariablemente da lugar a la muerte en 18 meses de media desde el inicio de los síntomas.(79) En sujetos homocigotos para el codón 129 se ha descrito un curso más corto de la enfermedad, posiblemente por una conversión más pronunciada de PrP^{C} en PrP^{Sc} (debido a una interacción de ambas formas priónicas más eficiente cuando la estructura primaria de las proteínas es idéntica), resultando en una afectación neuropatológica y síntomas más prominentes que en heterocigotos.(84,85)

El ILf suele iniciar con la presencia de síntomas no específicos, a menudo pasados por alto, tales como astenia, depresión, ansiedad, y dificultades para iniciar o mantener el sueño. Otras manifestaciones pueden incluir síntomas disautonómicos como diaforesis, hipertensión, hiperventilación y pirexia vespertina.(79) La pérdida de peso, dando lugar a caquexia, es común. Síntomas motores y cerebelosos, con alteraciones de la marcha, dismetría, disartria y mioclonías, pueden aparecer en el curso de la enfermedad. En el paciente con ILf, hay característicamente un deterioro cognitivo progresivo con alteración de la atención, la memoria, y posteriormente el lenguaje, llegando a estar en una situación de dependencia.(80) La afectación del mantenimiento de la vigilia y el sueño con síntomas de insomnio y somnolencia diurna excesiva son prominentes en el ILf.(84) Se han descrito asimismo la presencia de vocalizaciones, e inquietud motora que se acompaña de movimientos o conductas propositivas durante el sueño.(79–81) La combinación clínica de insomnio, pérdida de los ritmos circadianos, e hiperactividad motora y autonómica constituye la denominada *agrypnia excitata*.(79,86–88)[4]

La heterogeneidad fenotípica de la enfermedad se ha relacionado con diferentes polimorfismos genéticos.(78) En pacientes homocigotos para metionina en el codón 129, se ha descrito recientemente una mayor frecuencia de movimientos anormales durante el sueño, disnea durante el sueño, demencia rápidamente progresiva, hipertensión, sudoración y taquicardia; así como significativamente mayor presencia de ataxia e hipertermia en sujetos heterocigotos.(85)

La sintomatología en ILe es similar a la observada en ILf, si bien una elevada presencia de síntomas neuropsiquiátricos y un tiempo de supervivencia mayor en casos de ILe, han sido recientemente descritos.(89)

[4] Los hallazgos relacionados con alteraciones del sueño y la vigilia en el ILf se revisan en mayor detalle en la sección 1.5.2.2. de esta introducción.

1.4.3.3. Neuropatología

El estudio neuropatológico de sujetos con ILf muestra típicamente una prominente pérdida neuronal y astrogliosis reactiva en núcleos anteroventral y mediodorsal del tálamo, y en olivas inferiores. Esta afectación neuropatológica tiene especial importancia cuando consideramos las alteraciones del sueño y la vigilia observadas en estos pacientes.[5]

Los cambios espongiformes son de intensidad leve-moderada y afectan a la corteza cerebral de forma parcheada.(66) Una astrogliosis y espongiosis moderadas pueden observarse en la corteza entorrinal, y una pérdida de células de Purkinje y astrogliosis a nivel cerebeloso.(90,91) Se ha descrito asimismo una astrogliosis moderada sin pérdida neuronal en la sustancia gris periacueductal del mesencéfalo e hipotálamo.(92) El análisis inmunohistoquímico es negativo en la mayoría de las áreas afectadas, pero se puede identificar PrP^{Sc} en localizaciones tales como la capa molecular del cerebelo o en pequeños depósitos granulares en la corteza cerebral.(66) La PrP^{Sc} en esta enfermedad es la tipo 2, mientras que la tipo 1 se encuentra típicamente en ECJh asociada a la mutación D178N-129V.(93) Tanto la cantidad de depósitos de PrP^{Sc} como la espongiosis se han relacionado con la duración de la enfermedad. La afectación neuropatológica en el ILe es superponible a las descrita en ILf.(79)

1.4.3.4. Diagnóstico

El diagnóstico del ILf requiere un cuadro clínico sugestivo y la identificación de la mutación D178N en sangre. Las pruebas complementarias como la RM cerebral, el EEG, y la punción lumbar, son útiles fundamentalmente para descartar otras enfermedades con presentación clínica similar.

La RM cerebral puede mostrar alteraciones no específicas, especialmente en fases avanzadas de la enfermedad, tales como la atrofia cerebral y cerebelosa.(79) Un aumento de la difusión en el tálamo y cerebelo ha sido observado en secuencias de difusión en RM, y está en probable relación con pérdida neuronal.(94) La pérdida de volumen específicamente de los núcleos mediodorsal, anterior y pulvinar del tálamo ha sido recientemente descrita, y se relaciona con los hallazgos neuropatológicos típicos de la enfermedad.(95) En estudios con tomografía por emisión de positrones con ^{18}F-

[5] Ver la sección 1.5.2.2. de esta introducción para mayor detalle.

fluorodesoxiglucosa en ILf, se ha demostrado hipometabolismo fundamentalmente a nivel talámico y del giro cingulado, pero también en áreas más extensas de la corteza cerebral, en ganglios basales, y cerebelo.(96,97) Se postula una correlación entre zonas con hipometabolismo y mayor depósito de PrP^{Sc}.(96)

Los complejos periódicos que se objetivan en registros EEG de sujetos con ECJ no se encuentran en el ILf. Las alteraciones descritas en PSG realizada a pacientes con ILf se detallan más adelante.

La determinación de la proteína 14-3-3 y el uso de RT-QuIC, para detección de PrP^{Sc} en LCR, tienen una sensibilidad mucho menor que en la ECJ y, por lo tanto, no suelen ser de utilidad.(80,98) La cantidad de tau total en LCR puede estar elevada en ILf en comparación con controles.(99)

Un algoritmo, basado en la presencia de alteraciones orgánicas del sueño, disautonomía, y síntomas y signos focales neurológicos, fue previamente propuesto para la sospecha e identificación tempranas de estos casos de difícil diagnóstico.(100) En 2022 se propusieron nuevos criterios diagnósticos de ILf, con tres niveles de certeza (Tabla 2).(101)

Criterios clínicos principales, generalmente con duración <2 años a. Alteraciones del sueño de probable origen orgánico: insomnio resistente al tratamiento, *agrypnia excitata*, asociados o no a estridor laríngeo, síndrome de apnea-hipopnea del sueño y/o movimientos involuntarios. b. Síntomas neuropsiquiátricos: demencia rápidamente progresiva, síntomas psiquiátricos incluyendo alucinaciones, delirios, alteración de la personalidad o de la conducta. c. Síntomas simpáticos progresivos: hipertensión, taquicardia, respiración irregular, hipertermia, sudoración y/o pérdida de peso.
Criterios de apoyo a. Historia familiar de insomnio de probable origen orgánico. b. Insomnio de probable origen orgánico, asociado o no a estridor laríngeo, síndrome de apnea-hipopnea del sueño y/o movimientos involuntarios, demostrados en vídeo-polisomnografía. c. Hipometabolismo o hipoperfusión en tálamo evidenciado con PET o SPECT.
Criterios de exclusión a. Complejos periódicos de ondas agudas en EEG. b. Señal hiperintensa en caudado y putamen o al menos dos áreas corticales (temporo-parieto-occipital) en secuencias de difusión o FLAIR. c. La sintomatología puede ser explicada por otra patología.
Criterio diagnóstico Mutación D178N-129M del gen *PRNP*
Niveles de certeza para el diagnóstico • ILf posible: al menos dos criterios clínicos principales y ningún criterio de exclusión. • ILf probable: cumplir criterios de ILf posible + uno o más criterios de apoyo. • ILf definitivo: al menos dos criterios clínicos principales + criterio diagnóstico.

Tabla 2. Nuevos criterios propuestos para el diagnóstico de insomnio letal familiar. Adaptado de Chu y colaboradores.(101) PET: *positron emission tomography* (tomografía por emisión de positrones); SPECT: *single-photon emission computerized tomography* (tomografía computarizada por emisión de fotón único); EEG: electroencefalograma; FLAIR: *fluid-attenuated inversion recovery* (recuperación de la inversión atenuada de fluido).

1.4.4. Enfermedad de Gerstmann-Sträussler-Scheinker

1.4.4.1. Etiopatogenia

En 1936 se publicaron los primeros casos de la enfermedad de Gerstmann-Sträussler-Scheinker (GSS), la cual fue formalmente clasificada como prionopatía décadas más tarde.(102–104) Su incidencia o prevalencia exacta es desconocida, pero ésta se estima en 1-10 casos por 100.000.000 en la población general.

La enfermedad de GSS es de herencia autosómica dominante. La mutación inicialmente descrita y más frecuentemente asociada se halla en el codón 102 del gen *PRNP*, dando lugar a una sustitución de prolina por leucina en la proteína priónica, asociada al codón 129 codificando para metionina (P102L-129M).(105) Otras

mutaciones asociadas a la enfermedad de GSS han sido descritas, incluyendo la segunda más frecuente, en codón 117 con sustitución de alanina por valina, y con el polimorfismo de codón 129 codificando para valina (A117V-129V).(106,107) La transmisibilidad del prion en la enfermedad de GSS, previamente puesta en duda, ha sido demostrada en los últimos años en diversos modelos animales.(108–110)

1.4.4.2. Presentación clínica

El inicio de la enfermedad se da típicamente en la quinta década de la vida, con una supervivencia media de cuatro años.(111) Se ha descrito una asociación de homocigosis para metionina en el codón 129 y un inicio más temprano de la enfermedad, sin haberse encontrado diferencias en la supervivencia relacionadas con este polimorfismo. Asimismo, se ha hallado un efecto del genotipo de *APOE* en el inicio de los síntomas de la enfermedad de GSS, siendo éste más tardío en los portadores del alelo *E4*.(112) Sin embargo, otros estudios han reportado una menor edad de inicio de la enfermedad en sujetos heterocigotos, y ausencia de asociación con *APOE*.(113,114)

Su presentación clínica consiste principalmente en ataxia cerebelosa y deterioro cognitivo progresivo. Una amplia variedad de síntomas, indicando afectación piramidal, extrapiramidal, sensitiva, cognitiva y psiquiátrica, se ha asociado también con esta enfermedad.(115) Inestabilidad de la marcha, dismetría, rigidez, temblor, nistagmo, disartria, disfagia, paresia, hiperreflexia, espasticidad, disestesias, disfasia, enlentecimiento de la velocidad de procesamiento, reducción de la atención, labilidad emocional, irritabilidad, apatía, y alteraciones conductuales han sido descritas en la enfermedad de GSS.(115) Dentro de los casos de enfermedad de GSS con mutación P102L-129M, hay principalmente dos fenotipos. El primero está caracterizado por la presencia de un síndrome cerebeloso progresivo (con ataxia, disartria, alteración de movimientos sacádicos oculares), frecuentemente acompañado de signos piramidales y pseudobulbares, y alteración cognitiva y conductual. Dentro de este grupo se han propuesto tres subgrupos: a) enfermedad de GSS típica: con ataxia temprana y posterior desarrollo de deterioro cognitivo; b) enfermedad de GSS con arreflexia y parestesias: con inicio más tardío de ataxia y de demencia; y c) enfermedad de GSS con demencia pura: con inicio temprano de deterioro cognitivo y ataxia tardía.(116) El segundo fenotipo, es indistinguible clínicamente de la ECJ, y es de curso rápidamente progresivo.(106) Asimismo, existen formas de la enfermedad de GSS con mutaciones menos frecuentes y una presentación clínica atípica.(115) Como síntomas o signos precoces de la

enfermedad, se han identificado: marcha inestable, ataxia de tronco, ausencia de reflejos tendinosos en miembros inferiores, disestesias en miembros inferiores, debilidad proximal en miembros inferiores, y disartria.(117) La amplia variabilidad fenotípica de esta enfermedad se ha descrito incluso entre individuos de la misma familia y gemelos monocigotos.(112,118,119)

1.4.4.3. Neuropatología

Los hallazgos neuropatológicos en la enfermedad de GSS son variados y están influidos por la forma genética asociada, pero es típica en esta enfermedad la presencia de placas multicéntricas de PrP-amiloide en corteza cerebral y cerebelosa. Puede haber asimismo patología tau con ovillos neurofibrilares. Los cambios espongiformes no son constantes, sino que se observan especialmente cuando la presentación fenotípica es similar a la ECJ. Otros hallazgos que pueden encontrarse son la degeneración de sustancia blanca (afectando a hemisferios cerebrales y cerebelosos, columnas posteriores de la médula espinal, tractos espinocerebeloso y corticoespinal), gliosis reactiva y pérdida neuronal (especialmente en córtex cerebral y cerebeloso).(66,106,115) En la PrP^{Sc}, el centro resistente a la proteína kinasa es frecuentemente de 7 u 8 kDa aunque, en casos con la mutación P102L, puede observarse también la de mayor masa molecular (típica de la ECJe) y se correlaciona con la degeneración espongiforme.(106,115)

1.4.4.4. Diagnóstico

El diagnóstico de la enfermedad de GSS se basa en un cuadro clínico sugestivo y la detección de la mutación responsable de la enfermedad. Si bien la Organización Mundial de la Salud propuso unos criterios diagnósticos englobando todas las encefalopatías espongiformes transmisibles hereditarias,(120) en la actualidad no hay unos criterios específicos para la enfermedad de GSS. Hasta en un 30% de los casos no se conocen antecedentes familiares lo cual, asociado a la heterogeneidad en su presentación clínica, dificulta enormemente el diagnóstico.(113,121) La RM cerebral suele ser normal al inicio de la enfermedad, y puede mostrar atrofia cerebral o cerebelosa con la progresión de la misma.(117) No se han descrito alteraciones específicas en secuencias de difusión.(122,123) De forma esporádica, se ha reportado la presencia de hiperintensidad de la señal en secuencias FLAIR afectando a diferentes regiones cerebrales, así como hipoperfusión a nivel talámico.(124,125) Los registros EEG son con frecuencia normales al inicio, y pueden mostrar un enlentecimiento generalizado en el

curso de la enfermedad.(62) Aunque con menor frecuencia que en la ECJ, complejos periódicos de ondas agudas, así como descargas periódicas bitemporales en fases avanzadas, se han descrito en estos pacientes.(113,126) La proteína 14-3-3 puede estar elevada en LCR, si bien con menor frecuencia que en la ECJ.(113,123) La sensibilidad de RT-QuIC para detectar la proteína priónica en LCR de pacientes con la enfermedad de GSS es mucho menor que en la ECJ.(127,128)

1.5. Fisiopatología del sueño en enfermedades priónicas

1.5.1. La proteína priónica, sus funciones, y el sueño

La PrP^C se expresa fundamentalmente en el sistema nervioso central, si bien se han hallado también niveles inferiores de PrP^C en otros órganos (corazón, páncreas, intestino, hígado, riñones, bazo, y en células inmunes) en el ser humano y en otros mamíferos. A nivel del sistema nervioso, la PrP^C se expresa en neuronas, oligodendrocitos, astrocitos, microglía, y en el sistema nervioso periférico.(129)

Debido a los resultados descritos en numerosos estudios, mayoritariamente con modelos animales, se postula que la PrP^C puede estar implicada en diversos procesos fisiológicos. Han sido descritas funciones de la PrP^C relacionadas con la protección frente al estrés celular, incluyendo en la protección frente a la apoptosis y al estrés oxidativo y, posiblemente también, su implicación en la respuesta frente al estrés del retículo endotelial causado por la acumulación de proteínas con plegamiento anómalo. Asimismo, la PrP^C se ha relacionado con procesos de diferenciación celular, gracias a su efecto promotor del crecimiento de neuritas y su actividad en procesos de diferenciación celular desde la embriogénesis. Por otro lado, se cree que la PrP^C influye en la excitabilidad neuronal debido a sus interacciones con receptores tales como colinérgicos nicotínicos, de kainato, y NMDA. Se postulan también los posibles efectos de la PrP^C en el mantenimiento de la mielina, la modulación de la respuesta inmune, la homeostasis del hierro y la homeostasis mitocondrial. Dada su relación con procesos neurodegenerativos cuando la proteína priónica se encuentra alterada, es relevante tener en cuenta sus efectos en la regulación de proteína amiloide y tau. La PrP^C se ha asociado con el procesamiento del precursor de la proteína amiloide, así como con la regulación de la transcripción de proteína tau, ambos mecanismos relacionados con el sustrato patológico de la enfermedad de Alzheimer si se ven alterados.(129)

Con respecto a las funciones de la PrP^C en el control del sueño, sus efectos en mantener un ritmo circadiano y un sueño normal fueron inicialmente demostrados en estudios con modelos animales.(130) Estos autores postularon la implicación de la PrP^C en el control del sueño dada la presencia de un sueño fragmentado y alteración de la actividad de ondas deltas, así como ciclos circadianos de mayor longitud y un retraso de fase, en modelos murinos PrP^C-*knockout*. Su implicación en el mantenimiento de los ritmos circadianos se propuso asimismo debido a la evidencia de alteraciones en la secreción de melatonina (secretada durante el día y no durante la noche) en modelos animales PrP^C-*knockout*,(131) y a las oscilaciones circadianas de los niveles de ARN mensajero de la proteína priónica.(132) Se contempla también la posibilidad de que las funciones circadianas de la PrP^C se deban a efectos en sistemas monoaminérgicos relacionados con la síntesis de melatonina en el haz retino-hipotalámico.(133,134)

1.5.2. Alteraciones del sueño descritas en enfermedades priónicas

Las alteraciones durante el sueño han sido previamente estudiadas en algunas enfermedades priónicas tales como la ECJ y el ILf. Sin embargo, tanto la descripción detallada de los hallazgos en PSG en el ILf, como los estudios relacionados con el sueño en pacientes con enfermedad de GSS son muy escasos.(135,136)

1.5.2.1. El sueño en la enfermedad de Creutzfeldt-Jakob

Los pacientes con ECJ a menudo refieren síntomas relacionados con un sueño alterado.(137,138) Insomnio, somnolencia diurna excesiva, sueño no reparador, confusión nocturna, alucinaciones, SPI, movimientos involuntarios de las piernas, y parasomnias pueden estar presentes durante el sueño en la ECJ.(138–141)

La caracterización del sueño en sujetos con ECJe indica la presencia de numerosas alteraciones de la arquitectura del sueño, que pueden aparecer incluso en fases iniciales de la enfermedad. Trabajos incorporando PSG o EEG nocturno han demostrado un sueño desestructurado, con eficiencia de sueño disminuida, reducción o ausencia del sueño REM, pérdida de husos de sueño, complejos K y ondas de vértex, un aumento de frecuencias theta-delta en el EEG, complejos pseudoperiódicos, alteraciones respiratorias (incluyendo apneas centrales), y pérdida de atonía durante el sueño REM.(138,140,142–145) Estas alteraciones observadas en ECJe parecen relacionarse con un depósito importante de PrP^{Sc} en el tálamo, y con la posible afectación neuropatológica de otras

áreas implicadas en el control del sueño y la vigilia tales como los ganglios basales, el tronco del encéfalo, y el hipotálamo.(138)

La mutación más frecuente en ECJh en Europa es la E200K, pudiendo asociar metionina o valina en el codón 129. Esta mutación se asocia con una presentación clínica y unos hallazgos neuropatológicos típicos de la ECJ. Sin embargo, la presencia de insomnio es importante, probablemente debido a la importante afectación talámica (hallazgo a tener en cuenta en el diagnóstico diferencial con el ILf). Además de insomnio, los pacientes con la mutación E200K también pueden presentar otras alteraciones del sueño tales como parasomnias, ronquido, apneas, alucinaciones, somnolencia diurna excesiva, y conductas durante la vigilia que parecen relacionadas con contenido onírico.(139,146–148) Estudios incluyendo el uso de PSG, han demostrado una eficiencia de sueño marcadamente disminuida, con reducción o ausencia de fases N3 y REM, así como escasez o falta de husos de sueño y complejos K.(139,146–149) La reducción o ausencia de fase N3 se ha relacionado con la gravedad de la enfermedad.(139) Por otro lado, también se han reportado en el sueño de estos pacientes la presencia de una respiración irregular, apneas obstructivas, centrales y mixtas, pérdida de atonía durante el sueño REM con movimientos frecuentes, y mioclonías.(139,149) En el registro de EEG nocturno se han identificado ondas periódicas trifásicas, y complejos de ondas agudas generalizadas.(147,148)

El insomnio se ha mencionado también como síntoma en la ECJv, si bien no es tan grave ni persistente como en la ECJh asociada a E200K o en el ILf.(150)

1.5.2.2. El sueño en el insomnio letal familiar

Los trabajos en los que se describieron los primeros casos de ILf ya mencionaban la presencia de alteraciones prominentes del sueño, incluyendo insomnio, sueños vívidos, episodios de conductas propositivas, respiración irregular, y somnolencia diurna.(76,77,151,152) Las conductas observadas en estos pacientes parecen ocurrir en el denominado estupor onírico, parte de la presentación clínica de la *agrypnia excitata*. En el estupor onírico, se dan episodios que interrumpen la vigilia en los que los sujetos parecen representar sus sueños, incluyendo frecuentemente actividades cotidianas. Si se les despierta, recuerdan una escena onírica que se relaciona con las conductas observadas. Con la progresión de la enfermedad, los pacientes se encuentran cada vez más confusos y con mayor deterioro cognitivo, alternando de forma frecuente entre vigilia y estas conductas oníricas, y no recordando el contenido de los sueños como tal.(88) Para

establecer el diagnóstico de estupor onírico en el contexto de la *agrypnia excitata*, se deben dar dos hallazgos típicos a nivel clínico y neurofisiológico: alteración del ritmo sueño-vigilia con pérdida del sueño profundo, e hiperactividad motora, simpática y monoaminérgica.(153) Se ha propuesto previamente que el sustrato neurofisiológico de las alteraciones del sueño-vigilia y conductas observadas en episodios de estupor onírico, tanto diurnas como nocturnas, es el estado denominado "subvigilia".(154) Ésta se caracterizaría por un estado relativamente continuo de sueño N1, intercalado por periodos, de segundos o minutos de duración, que contienen movimientos oculares rápidos, con o sin atonía muscular conservada.

De forma general, las alteraciones en PSG, V-PSG o EEG nocturno descritas en ILf incluyen la desorganización de la arquitectura del sueño, reducción marcada del tiempo total de sueño, reducción o ausencia de husos de sueño y complejos K, y del sueño profundo, periodos de sueño REM intercalados con vigilia, y presencia de conductas propositivas casi continuas.(76,151,152) La reducción progresiva del tiempo total de sueño, enlentecimiento del EEG y del ritmo alfa occipital, haciéndose éste difuso, con reducción del sueño REM, se ha reportado en el estudio longitudinal de estos pacientes.(152) Se ha descrito asimismo la aparición de onda aguda cuasi-periódica a 1-2Hz correlacionando con mioclonías en vigilia,(152) sin estar presentes los típicos complejos periódicos de ECJ. Se propone un rol del polimorfismo genético del codón 129 en los cambios a nivel del EEG durante el sueño. En un estudio incluyendo un grupo de sujetos sanos portadores de la mutación D178N y un grupo sin dicha mutación, aquellos homocigotos para metionina mostraban una mayor cantidad de actividad lenta y menos husos en comparación con heterocigotos (metionina-valina en codón 129), sin observarse diferencias en función de la presencia o ausencia de mutación.(155)

Sintomatología respiratoria durante el sueño, tales como la presencia de una respiración irregular, apneas observadas, o estridor, ha sido previamente mencionada en sujetos con ILf. Sin embargo, a pesar de haberse propuesto incluso la implicación de las apneas centrales en la muerte de estos pacientes,(80) la descripción de alteraciones respiratorias en estudios PSG es escasa y no detallada.(76,81,152,156–162)

Las alteraciones circadianas y la hiperactividad simpática, características de la *agrypnia excitata* en el ILf, se han demostrado con el hallazgo de una ausencia de reducción de la presión arterial por la noche, niveles elevados de catecolaminas durante 24h, y la pérdida del pico normal de secreción nocturna de melatonina y GH.(86,154,163) En un caso de ILf, se reportó el mantenimiento de la función normal del núcleo

supraquiasmático (con temperatura central normal), pero disociación de los ritmos circadianos de la melatonina y el cortisol.(164) Asimismo, se ha propuesto recientemente la alteración del sistema nervioso parasimpático, con evidencia de una alteración de la variabilidad en la frecuencia cardiaca durante el sueño en ILf con respecto a sujetos con ECJ y a controles.(165)

1.5.2.3. El sueño en la enfermedad de Gerstmann-Sträussler-Scheinker

El estudio del sueño en enfermedad de GSS es extremadamente escaso en la literatura científica, con un total de tres casos publicados.(135,136)

El primer caso publicado de enfermedad de GSS en el que se realizó PSG, se trataba de un individuo de 31 años con forma atáxica de la enfermedad, antecedentes familiares de demencia (en el padre, fallecido a los 55 años), con la mutación P102L del gen *PRNP* y heterocigoto metionina-valina en el codón 129. La PSG mostró una arquitectura normal del sueño, si bien con un incremento de la proporción de sueño superficial (fases N1 y N2 del sueño NREM) y una reducción del sueño profundo. La eficiencia de sueño fue normal. Asimismo, se realizó en este sujeto un estudio de la temperatura corporal central, niveles plasmáticos de melatonina, y determinaciones repetidas de la presión arterial a lo largo de 24h. Éstos mostraron perfiles normales, con la excepción de una temperatura media ajustada al ritmo de 24h mayor que en los controles.(135)

En los otros dos casos publicados de enfermedad de GSS con estudio de sueño, se realizó registro PSG durante 48h y determinaciones de la temperatura corporal central cada dos minutos. Este trabajo incluía dos hermanas con la mutación P102L, con síntomas cerebelosos, hiperreflexia, y alteraciones en el estudio neuropsicológico. No referían insomnio. En una de estas pacientes, de 36 años, el registro PSG de la segunda noche mostró una eficiencia de sueño reducida (en la primera noche el estudio se detuvo por problemas técnicos), con un índice de *arousals* de 19 por hora. Su hermana, de 32 años, mostró en ambas noches una eficiencia de sueño reducida, con un incremento del sueño superficial, y una reducción de la proporción del sueño profundo (la primera noche) o del sueño REM (la segunda noche). En ambos casos, el ritmo circadiano de la temperatura corporal central fue normal.(136)

En estos tres casos, no se indicó la presencia de síntomas relacionados con el sueño, se reportó la presencia de figuras normales del sueño y la conservación de la atonía

fisiológica del sueño REM, sin evidencia de TCSR. No se dispuso de estudio neuropatológico en ninguno de los casos.(135,136)

La presencia de insomnio se reportó en dos casos con enfermedad de GSS de una cohorte de pacientes de origen chino en Taiwan, y en un caso de una familia italiana, siendo un síntoma temprano en uno de ellos y asociándose con demencia en otros dos.(124,166) RM cerebrales seriadas en uno de estos casos mostraron un aumento de la señal en FLAIR a nivel talámico y atrofia talámica, a los nueve y 23 meses del inicio de la enfermedad respectivamente.(124) Se mencionó asimismo de forma general la presencia de alteraciones del sueño a los cinco años del inicio de la enfermedad en una paciente de origen chino.(167) No se incluyó una evaluación más específica del sueño ni se dispuso de estudio neuropatológico en ninguno de estos casos.(124,166,167) En otro estudio, se incluyó una serie de 11 pacientes con enfermedad de GSS originarios de Japón para identificar signos y síntomas precoces de esta patología. La presencia de síntomas relacionados con el sueño no se mencionó como parte de la presentación clínica en la enfermedad de GSS, y no se llevó a cabo un estudio específico del sueño en estos sujetos.(117)

2. HIPÓTESIS

2. HIPÓTESIS

1) El sueño de los pacientes con insomnio letal, incluyendo su arquitectura y su control respiratorio, está alterado.
2) Las alteraciones del sueño en pacientes con insomnio letal se relacionan con determinadas características clínicas y neuropatológicas.
3) El estudio neuropatológico de áreas que controlan el sueño y la respiración está alterado en pacientes con insomnio letal.
4) El sueño de los pacientes con la enfermedad de Gerstmann-Sträussler-Scheinker puede mostrar alteraciones del sueño como las descritas en otras prionopatías.

3.OBJETIVOS

3. OBJETIVOS

1) Describir de forma detallada la arquitectura del sueño y los hallazgos respiratorios durante el sueño en pacientes con insomnio letal.
2) Estudiar la relación entre las alteraciones durante el sueño y las características clínicas y neuropatológicas en el insomnio letal.
3) Investigar la presencia de hallazgos neuropatológicos relacionados con el control del sueño y la respiración en pacientes con insomnio letal.
4) Describir el sueño y sus alteraciones en pacientes con la enfermedad de Gerstmann-Sträussler-Scheinker.

4. MATERIAL, MÉTODOS Y RESULTADOS

4. MATERIAL, MÉTODOS Y RESULTADOS

Trabajo 1

Sleep architecture and sleep-disordered breathing in fatal insomnia

Pérez-Carbonell L, Muñoz-Lopetegi A, Sánchez-Valle R, Gelpi E, Farré R, Gaig C, Iranzo A, Santamaria J.

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RESUMEN

Introducción: el insomnio letal es una enfermedad priónica rara que afecta de forma importante la arquitectura del sueño. La respiración durante el sueño no ha sido estudiada de forma sistemática en esta enfermedad. Nuestro objetivo era caracterizar la arquitectura del sueño, patrones respiratorios, y hallazgos neuropatológicos del insomnio letal.

Métodos: se realizó una vídeo-polisomnografía entre los años 2002 y 2017 a once pacientes consecutivos con insomnio letal (diez con forma familiar y uno esporádico). Las fases del sueño, la vigilia y la respiración fueron evaluadas usando un sistema de codificación modificado. Se obtuvo estudio neuropatológico *post-mortem* en siete pacientes.

Resultados: la mediana de edad de comienzo de los síntomas fue 48 años y la mediana de supervivencia tras la realización de vídeo-polisomnografía fue de un año. Todos los pacientes tenían diferentes combinaciones de alteraciones de la respiración durante el sueño incluyendo una variabilidad de la frecuencia respiratoria elevada (n = 7), estridor (n = 9), apnea central del sueño (n = 5), hipo (n = 6), catatrenia (n = 7), y otros ruidos respiratorios (n = 10). La variabilidad de la frecuencia respiratoria en sueño NREM se correlacionó con la degeneración de los núcleos ambiguo y solitario (r = 0,9; p = 0,008) y con una menor supervivencia (r = -0,7; p = 0,037). Se han caracterizado dos nuevas fases, subvigilia1 y subvigilia2, presentes en todos los pacientes. El sueño NREM (convencional o indiferenciado) era identificable en diez pacientes, y tenía una duración reducida en ocho. El sueño REM ocurría en periodos cortos en nueve pacientes, y su duración mostraba una correlación inversa con la degeneración de los núcleos del rafe bulbar (r = -0,9; p = 0,005). Siete pacientes mostraban una pérdida de atonía del sueño REM. Se han identificado tres patrones vídeo-polisomnográficos: agitado, con movimientos aperiódicos, manipulativos y finalísticos (n = 4); tranquilo-apneico, con apneas centrales del sueño (n = 4); y tranquilo-no apneico (n = 3).

Conclusiones: los pacientes con insomnio letal tienen frecuentes alteraciones de la respiración durante el sueño, asociadas a la afectación de los núcleos que controlan la respiración. Además de alteraciones del sueño NREM, el sueño REM se encuentra gravemente alterado y está relacionado con la degeneración de los núcleos del rafe. La afectación del tronco del encéfalo es una característica crucial en el insomnio letal.

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Sleep architecture and sleep-disordered breathing in fatal insomnia

Laura Pérez-Carbonell [a, 1, 2], Amaia Muñoz-Lopetegi [a, b, c, 1], Raquel Sánchez-Valle [d, e], Ellen Gelpi [e, f], Ramon Farré [g, h], Carles Gaig [a, b, c], Alex Iranzo [a, b, c, **], Joan Santamaria [a, b, c, *]

[a] Sleep Center, Neurology Service, Hospital Clínic de Barcelona, Barcelona, Spain
[b] Clinical Neurophysiology Group, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS)
[c] CIBER de Enfermedades Neurodegenerativas, Barcelona, Spain
[d] Alzheimer Disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain
[e] Neurological Tissue Bank of the IDIBAPS, Barcelona, Spain
[f] Division of Neuropathology and Neurochemistry, Department of Neurology, Medical University of Vienna, Austria
[g] Unitat de Biofísica i Bioenginyeria, Facultat de Medicina, Universitat de Barcelona-IDIBAPS, Barcelona, Spain
[h] CIBER de Enfermedades Respiratorias, Bunyola, Spain

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ABSTRACT

Study objectives: Fatal insomnia (FI) is a rare prion disease severely affecting sleep architecture. Breathing during sleep has not been systematically assessed. Our aim was to characterize the sleep architecture, respiratory patterns, and neuropathologic findings in FI.

Methods: Eleven consecutive FI patients (ten familial, one sporadic) were examined with video-polysomnography (vPSG) between 2002 and 2017. Wake/sleep stages and respiration were evaluated using a modified scoring system. Postmortem neuropathology was assessed in seven patients.

Results: Median age at onset was 48 years and survival after vPSG was 1 year. All patients had different combinations of breathing disturbances including increased respiratory rate variability (RRV; n = 7), stridor (n = 9), central sleep apnea (CSA) (n = 5), hiccup (n = 6), catathrenia (n = 7), and other expiratory sounds (n = 10). RRV in NREM sleep correlated with ambiguous and solitary nuclei degeneration ($r = 0.9$, $p = 0.008$) and reduced survival ($r = -0.7$, $p = 0.037$). Two new stages, Subwake1 and Subwake2, present in all patients, were characterized. NREM sleep (conventional or undifferentiated) was identifiable in ten patients but reduced in duration in eight. REM sleep occurred in short segments in nine patients, and their reduced duration correlated with medullary raphe nuclei degeneration ($r = -0.9$, $p = 0.005$). Seven patients had REM without atonia. Three vPSG patterns were identified: agitated, with aperiodic, manipulative, and finalistic movements (n = 4); quiet-apneic, with CSA (n = 4); and quiet-non-apneic (n = 3).

Conclusions: FI patients show frequent breathing alterations, associated with respiratory nuclei damage, and, in addition to NREM sleep distortion, have severe impairment of REM sleep, related with raphe nuclei degeneration. Brainstem impairment is crucial in FI.

1. Introduction

Fatal familial insomnia (FFI) is a rare hereditary, autosomal dominant, invariably lethal prion disease [1–3]. The age of onset ranges between 19 and 76 years and the average time from symptoms onset to death is about 18 months [4–6]. The disease is caused by a missense mutation of the prion protein gene (D178 N), in conjunction with a methionine at the codon 129 polymorphic site on the mutated allele (D178 N (*cis*-129 M). This mutation induces a progressive neurodegenerative disorder associated with

* Corresponding author. Biomedical Research Institute (IDIBAPS), Barcelona, 08036, Spain.
** Corresponding author. Neurology Service, Hospital Clínic de Barcelona, Barcelona, 08036, Spain.
E-mail addresses: airanzo@clinic.cat (A. Iranzo), jsantama@clinic.cat (J. Santamaria).
[1] These authors contributed equally.
[2] Current address: Sleep Disorders Centre, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom.

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deposits of the pathogenic prion protein (PrP^{Sc}) in restricted brain areas [5,7]. Patients with the sporadic form of fatal insomnia (sFI) show similar clinical and neuropathological findings, but have no family history of the disease and the mutation is absent [8]. Neuropathology shows marked neuronal loss and astrocytic gliosis of the mediodorsal and ventral anterior thalamus, and the inferior olives, with only mild or even absent spongiform changes and only discrete pathological PrP^{Sc} deposits. Involvement of the cerebellum, hypothalamus, periaqueductal region, and raphe nuclei in the medulla have been described as well [9–11]. [18F]-FDG PET shows decreased metabolism in thalamic, cortical and cerebellar areas where neurodegenerative changes (neuronal loss and gliosis) are more prominent [12,13], and significant volume loss in the anteromedial thalamus, cerebellum and medulla oblongata, and increased thalamic and cerebellar diffusivity in quantitative MRI studies [14].

The disease often begins with disturbances of vigilance and inability to initiate and maintain sleep, symptoms usually overlooked or trivialized into manifestations of stress or fatigue. Personality changes, depression, anxiety, hypertension, diaphoresis, evening pyrexia, gait disturbances, dysmetria, dysarthria, myoclonus, and cognitive impairment develop later [7]. Insomnia of severe intensity combines with loss of circadian rhythms, and motor and autonomic hyperactivity, an association known as *agrypnia excitata* (AE) [2]. Longitudinal polysomnographic studies show sleep fragmentation and total sleep time reduction together with a progressive disappearance of NREM sleep waveforms (spindles, K complexes and slow wave activity), and appearance of short, recurrent periods of N1 NREM sleep, often with interspersed rapid eye movements (also known as N1/REM sleep), or brief episodes of REM sleep with or without normal muscle atonia [15]. In addition, patients develop peculiar pseudopurposeful behaviors (known as *oneiric stupor*) during sleep, during wakefulness, or during the transition between both states [15–17]. The rarity of Fatal Insomnia (FI) and the complexity of its polysomnographic patterns suggest that a detailed video-polysomnografic (vPSG) characterization of the wake/sleep changes would still enhance the knowledge of the disease.

An aspect that needs further evaluation is the presence of respiratory disturbances. Central apneas, irregular breathing, respiratory distress or stridor have been described in isolated case reports of FI and sometimes pointed out as the cause of death in these patients [1,2,17–27], but the actual frequency and detailed characterization of these alterations is unknown. The central control of breathing depends on several lower brainstem centers [28–30] which are anatomically close to affected regions in FI (e.g., inferior olives in the medulla) and occasional reports suggest that they might be impaired by the disease process [25,27]. Pathological findings in these structures, however, are not routinely reported in patients with FI [28,29]. The aim of our study was to characterize the wake/sleep patterns and respiratory findings during sleep in a sizable group of patients diagnosed with FI, evaluate their relationship with clinical and paraclinical features, and investigate the underlying neuropathological findings in brainstem areas related to the central control of sleep and breathing.

2. Methods

2.1. Patients

Eleven consecutive FI patients (10 with FFI and 1 with sFI), evaluated at our center between 2002 and 2017 who had a vPSG recording were included in the study. Six patients were homozygous for methionine at codon 129, including the case with sFI, while the remaining five were methionine-valine (Met/Val) heterozygotes. Evaluation included clinical assessment, brain MRI, genetic study, one-night vPSG and clinical follow-up. Postmortem neuropathologic assessment was performed in seven of the 11 patients. Demographic and clinical data were obtained from the clinical charts. The study was approved by the institutional board of our center.

2.2. Video-polysomnography

A polysomnogram with synchronized audiovisual recording was performed with Coherence 7 (Deltamed, Paris, France) and consisted in electroencephalography (EEG) recorded from F3, F4, C3, C4, O1, and O2 (in two patients studied before 2007, F3 and F4 were not included), in the remaining nine, electrooculography (EOG), electromyography (EMG) from the mentalis muscle, upper limbs (right and left flexor digitorum superficialis in nine patients, or right and left biceps in two) and lower limbs (right and left anterior tibialis), and electrocardiography. Nasal cannula, nasal and oral thermistors, thoracic and abdominal strain gauges, and finger pulse oximeter were used to assess respiration. Nine age- and sex-matched sleep-laboratory controls with normal vPSG, were used for comparison of the respiratory findings.

2.2.1. Scoring of wake/sleep patterns

Sleep and associated events were scored, whenever possible, according to the American Academy of Sleep Medicine manual [31]. However, as pointed out previously [17] this sleep scoring system is difficult to be applied in FI because the following reasons:

1. The awake EEG may be abnormal, with slow/sharp EEG activity that complicates the identification of additional sleep-related slowing.
2. The wake/sleep transition shows unconventional patterns, including the presence of posterior dominant or diffuse alpha/subalpha frequencies simultaneous with diffuse or anterior dominant theta/delta slowing, with the patient behaviorally relaxed, eyes closed, with slow eye movements or even displaying breathing signs typically associated with sleep, such as apneas or snoring.
3. The distinctive vPSG patterns that identify conventional sleep stages (vertex waves, sleep spindles, K complexes, high voltage delta slowing and muscle atonia in REM sleep), change or even disappear during the course of the disease.
4. There are short-lasting vPSG changes that cannot be well captured using conventional 30-s epochs.

To overcome these problems, we have implemented the following modifications in the scoring rules, which refer to a) epoch duration, b) unconventional wake/sleep stages, c) identification of REM sleep and Wake, d) arousals, and e) stage stability:

A Epoch duration

We used 15 s as the duration of the scoring epochs. This allows a more accurate description of the changes occurring in the wake/sleep studies without compromising the feasibility of the task. Although shorter-duration epochs would probably have given more detailed information, we chose 15 s to reach an equilibrium between the increase in detail and the perspective offered by a 30-s epoch. To obtain 15-s epochs, the monitor screen showed 30 s, but the focus was placed alternatively on each 15-s half by blurring the other half of the screen. Each 15-s epoch was designated with the stage that occupied at least 8 s (>50%) of the epoch (see Fig. 1).

B Unconventional wake/sleep stages

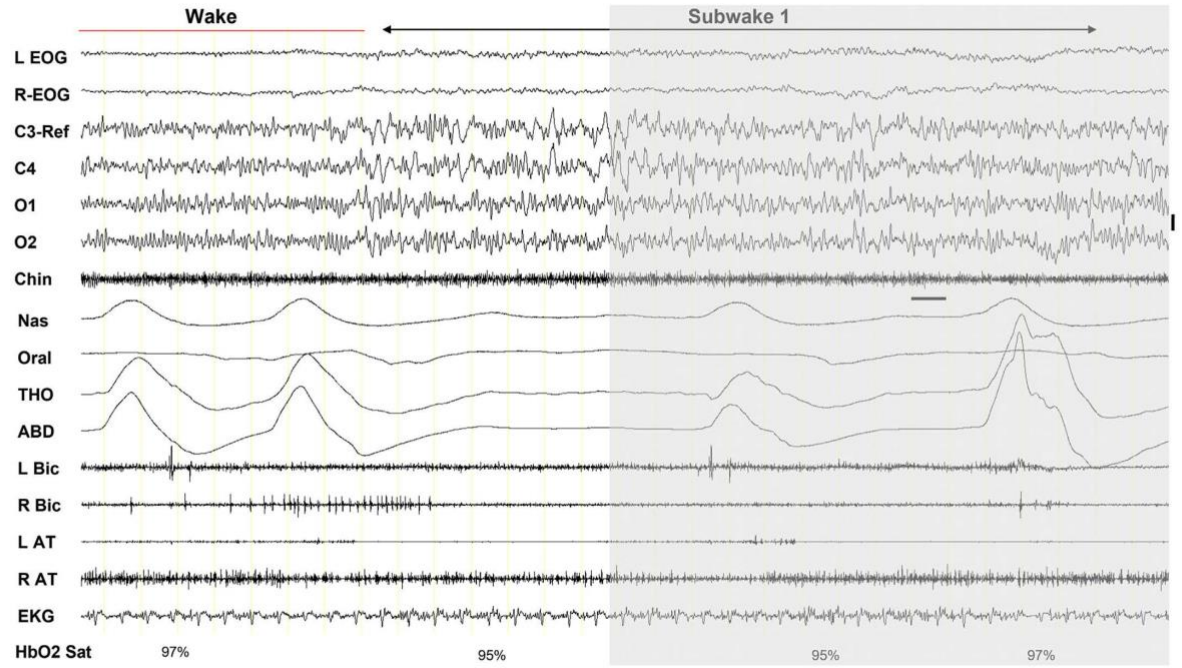


Fig. 1. Example of scoring using 15-s epochs in Pat#1. A 30-s screen is split in two 15-s halves (epoch A and epoch B) by blurring the right half to identify its limits. Epoch A is scored as Wake because it contains 8 s of Wake (top horizontal red line), characterized by moderate amplitude 8–9 Hz posterior alpha activity, small rapid eye movements and chin muscle tone and 7 s of Subwake1 (left-right horizontal arrow), which continues throughout epoch B (therefore scored as Subwake1) characterized by a mixture of moderate amplitude 2–6 Hz diffuse, anterior predominant, theta delta activity, beginning of slow eye movements and a decrease in breathing frequency, with a hypopnea shorter than 10 s. Note the slowing of the posterior alpha rhythm to 7 Hz as compared with wake. L EOG, R-EOG: Electro-oculogram, left eye and right-eye, respectively, referred to combined ears; C3-Ref, C4, O1, O2: Electroencephalogram recorded from these electrode positions, referred to combined ears; Chin: EMG from mentalis muscle; Nas: nasal thermistor; Oral: Oral thermistor; THO: thoracic respiratory effort band; ABD: Abdominal respiratory effort band; L Bic, R Bic: Upper limb EMG recording from left and right biceps; L AT, R AT: Lower limb EMG from left and right anterior tibialis: EKG: electrocardiogram. HbO2 Sat: Oxyhemoglobin saturation values. Calibration bars: Vertical bar on the right: 50 μV; horizontal bar: 1 s. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Subwake1 (Fig. 1): This consists of diffuse moderate-amplitude alpha/subalpha frequencies (typically 6–8 Hz) with superimposed moderate-amplitude, anterior predominant, irregular theta/delta slowing (typically 3–6 Hz, different from the awake patterns recorded during the calibration part of the recording) and lasting a few seconds or appearing in more prolonged periods, with the eyes closed or half-open with slow or absent eye movements or with changes in breathing. We considered that a portion of the recording contained subalpha frequencies when they had the same distribution and reactivity of regular alpha rhythm, usually intermingled with it, but with a slower dominant frequency, typically 6–8 Hz. This term was preferred to theta activity, to emphasize its similarities with alpha rhythm. Isolated or recurrent bursts of sharp/slow wave activity, sometimes with high voltage K-complex-like delta activity (Fig. 2, Figure S1) associated with diffuse, centrofrontal predominant alpha of higher amplitude and 2–3 Hz slower than occipital dominant alpha could also appear. Subwake1 occurred mostly associated with a relaxed behavior or less often with aperiodic limb movements (see below).

Subwake2 (Fig. 3): This pattern appeared often when Subwake1 lost the intermixed theta/delta slowing, and the EEG attenuated its amplitude or, paradoxically, showed relatively higher posterior dominant frequencies, in the range of subalpha or alpha awake frequencies with absent or slow eye movements. These periods often occurred after one or several 15 s-epochs of Subwake1. Subwake2 typically appeared in the final part of apneas and usually corresponded to the "deepest" part of the transition from wake to sleep, with more relaxed behavior than in Subwake1 (Fig. 4). Subwake2 occurred only in the direction from Wake to sleep (if not interrupted) and did not appear immediately after an alerting stimulus. Subwake1 and Subwake2 could be differentiated from stage N1 NREM or UNREM sleep (see below) by the presence of alpha/subalpha activity and from REM sleep, in addition to the above characteristics, by the absence of rapid eye movements.

Undifferentiated non-rapid eye movement (UNREM) sleep (Fig. 5): These were epochs with diffuse irregular delta-theta EEG activity at 0.5–4 Hz and 40–50 μV, that was clearly different from the dominant occipital background activity seen during wakefulness and the alpha/subalpha frequencies from Subwake1 or Subwake2. UNREM lacked vertex sharp waves, K complexes, sleep spindles and rapid eye movements. In some patients with UNREM sleep, periods of delta-theta activity of 0.5–4 Hz with low-to-moderate amplitude (20–40 μV) were clearly discernible from other periods of delta activity at 0.5–1 Hz with higher amplitude (60–90 μV). We have termed these two types of periods **light** (amplitude 20–40 μV) and **deep** (amplitude 60–90 μV) UNREM sleep, respectively [32,33]. Although the EEG pattern of N1 NREM sleep, taken isolated, has similarities with that of light UNREM sleep, we scored N1 NREM when it lasted no more than a few epochs and was followed by epochs of clear N2, with its characteristic waveforms (sleep spindles and K complexes).

C Identification of REM sleep and wakefulness

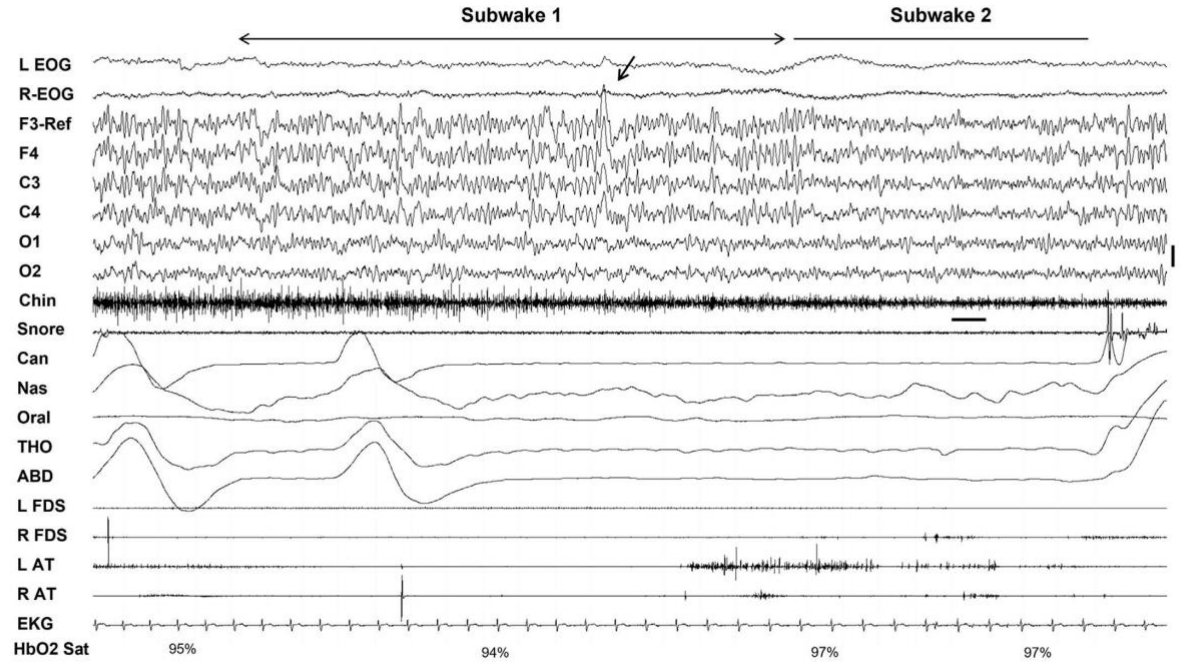


Fig. 2. Subwake1 and Subwake2. This 30-s epoch in Pat#3 shows in the first 15 s a Subwake1 pattern (left right horizontal arrow), with low amplitude posterior alfa at 7.5–8 Hz, with simultaneous moderate amplitude centrofrontal theta at 7 Hz and a single burst of high voltage delta activity, K-complex like (arrow) and associated to a central apnea. The second 12 s (top horizontal line) shows the Subwake2 pattern, with persistent posterior alpha/subalpha frequencies (7.5–8 Hz) but of lower amplitude than in Subwake1, disappearance of anterior theta frequencies, slow eye movements and slight decrease in chin EMG amplitude. This pattern ends with resumption of respiration in the last part of the figure. L EOG, R-EOG: Electro-oculogram, left eye and right-eye, respectively, referred to combined ears; F3-Ref, F4, C3, C4, O1, O2: Electroencephalogram recorded from these electrode positions, referred to combined ears; Chin: EMG from mentalis muscle; Snore: snoring vibration from nasal pressure cannula, Can: nasal pressure cannula; Nas: nasal thermistor; Oral: Oral thermistor; THO: thoracic respiratory effort band; ABD: Abdominal respiratory effort band; L FDS, R FDS: Upper limb EMG recording from left and right flexor digitorum superficialis; L AT, R AT: Lower limb EMG from left and right anterior tibialis: EKG: electrocardiogram. HbO2 Sat: Oxyhemoglobin saturation values. Calibration bars: Vertical bar on the right: 50 μV; horizontal bar: 1 second

REM sleep (Figs. 6–8)**.** Episodes of REM sleep with normal atonia and a duration of >4 consecutive minutes only occurred in a few patients. In these cases, the AASM rules were applied. For the rest, we developed specific modifications taking into consideration that chin EMG atonia was often incomplete or absent in many REM sleep epochs (Fig. 6) and that the duration of many episodes was shorter than 1 min (Fig. 7). In these cases, REM sleep was scored if there was a combination of rapid eye movements (excluding those occurring within 1 s of the reappearance of alpha/subalpha frequencies) and at least two of the following:

a) A decrease in the amplitude or an irregularity of the chin EMG in comparison with preceding epochs, often with a relative decrease in the muscle artifact in the EEG channels (Fig. 8A).
b) The presence of discontinuous, jerky movements with the patient having the eyes closed, reminding of those occurring in REM sleep behavior disorder (RBD). These movements were clearly different from the unfragmented, steady movements of wakefulness (Fig. 8B).
c) Relative slowing of EEG compared to fully awake periods.

Quantification of EMG activity in REM sleep. Given the short duration, the increased background EMG amplitude, and the atypical characteristics of the REM episodes, we scored each 15-s REM epoch as having or not excessive EMG activity in chin and limbs when at least 50% of the epoch contained bursts of any EMG activity of more than 100 msec duration and an amplitude of at least 10 μV [34]. We then calculated the REM without atonia (RWA) index as the percentage of stage REM 15-s epochs meeting the above criteria.

Wakefulness. On occasions it was difficult to differentiate wakefulness from subwakefulness or from REM sleep without atonia. In these cases, we looked back to all signals (including video) during the calibration performed awake at the beginning of the test or other periods showing a proper interaction of the patient with the caregiver or the technician. During these periods of clear wakefulness, we particularly focused on the EEG activity with eyes open and closed, which could contain some theta/delta activity intermixed with the alpha rhythm. During the recording, periods showing similar patterns were considered awake.

D Arousals

Scoring of arousals was not performed in most patients with abnormal sleep stages given the unusual EEG patterns and the frequent and short-lasting changes that were recorded. Only in 2 patients (Pat#8 and 10) with long enough periods of normal sleep structure, we could score arousals following AASM rules [31].

E Stage stability

Consolidated NREM sleep: Periods longer than 10 min of NREM sleep (either conventional N2 and N3 stage, or undifferentiated light and deep) running uninterruptedly or with occasional stage

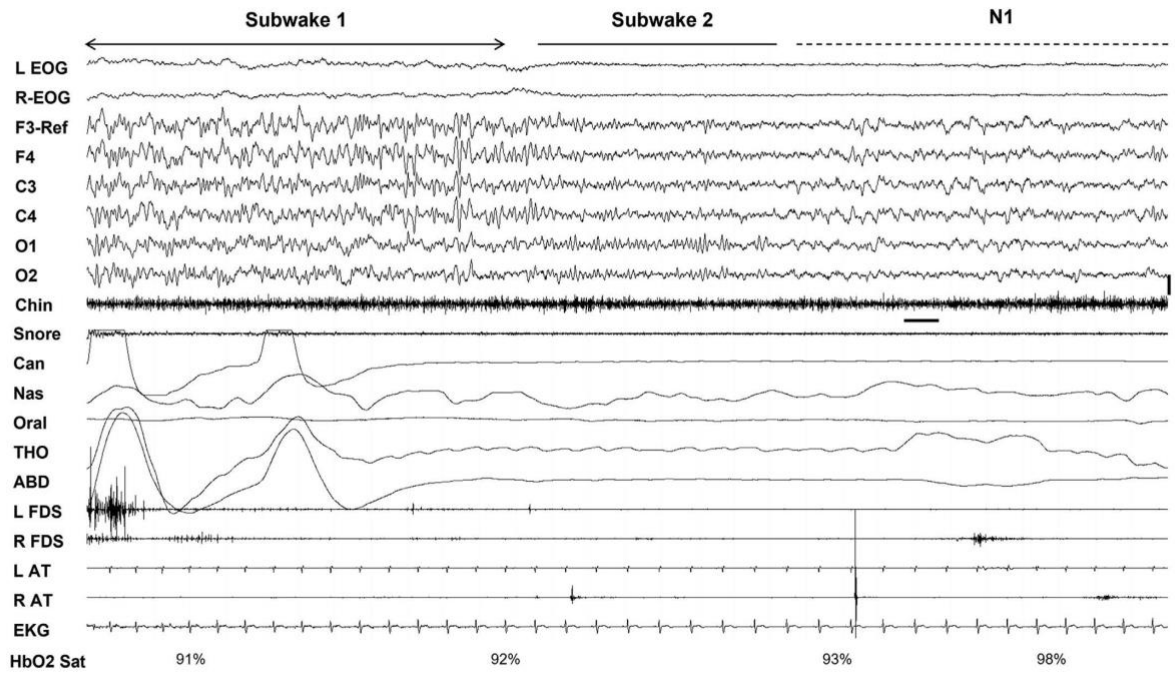


Fig. 3. Subwake1 leading into Subwake2 and then into N1 NREM. The figure shows the relatively rapid changes of stage taking place within a 30-s epoch (Pat#3), better captured using 15-s epochs. The left half shows a 15-s epoch of Subwake1 (left right horizontal arrow) characterized by a mixture of anterior predominant, irregular, moderate amplitude theta/delta activity at 3–6 Hz mixed with irregular 7–8 Hz posterior alpha activity and chin EMG tone. This is followed by a short segment of Subwake2 (top horizontal continuous line), characterized by EEG amplitude attenuation with disappearance of the theta/delta activity and with lower amplitude posterior predominant alpha/subalpha activity at 7–8Hz simultaneous with the onset of a central apnea with moderate oxyhemoglobin desaturations. Finally, stage N1 NREM sleep appears (*top dashed line*), where alpha/subalpha frequencies disappear and are substituted by low amplitude diffuse delta/theta activity, and continuation of the central apnea episode (N2 follows; not shown). Eye movements are slow or absent. Montage as in previous figure. **Calibration bars**: Vertical bar on the right: 50 μV; horizontal bar: 1 second

shifts no more than one-epoch long, were defined as consolidated NREM sleep. Consecutive periods of consolidated NREM sleep separated by less than 30 epochs were considered one single bout of consolidated NREM sleep.

Stable wake, NREM and REM sleep: Wake or sleep periods occurring at least for four consecutive minutes without stage shifting were considered stable. This length was chosen to better capture the periods of non-shifting stage occurring in many parts of the recording.

Fluctuating Wake-Subwake and wake-REM: Periods in which wakefulness was interrupted before 4 consecutive minutes by interspersed epochs of Subwake, were classified as fluctuating Wake-Subwake and when interrupted by interspersed epochs of REM, as fluctuating wake-REM.

2.2.2. Interrater agreement

Scoring of sleep stages in random samples of two different recordings was performed by two different scorers (JS, AM-L) to measure interrater agreement. The kappa ratio was 0.81.

2.2.2.1. Scoring of movements and vocalizations. Synchronized audiovisual recordings were reviewed to evaluate the presence of movements and vocalizations in each 15-s epoch. We identified the following types:

Aperiodic limb movements (Fig. 9, Video 1) were typically leg or leg-trunk movements and less often arm movements, having neither apparent purpose nor giving the impression of a comfort movement, including flexion, extension of the proximal parts of the lower limbs, occurring either suddenly or relatively fast, producing large displacements of the limbs and recurring incessantly without any discernible periodic cadency.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.sleep.2022.08.027

Manipulative movements (Video 2) were movements where the patient appeared to take voluntarily or by chance any of the objects around, in particular EEG electrodes or other cables and sensors, the sheet or the blanket, touching them repeatedly as if trying to use or remove them off the head or limbs, or chewing them and using them in either a seemingly appropriate or inappropriate way. This activity could occur with the eyes open or closed, but typically with the patient awake.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.sleep.2022.08.027

Finalistic/Quasi-purposeful movements (Video 3) were those where the patients gestured or acted out executing seemingly elaborated movements that resembled activities of daily life, such as eating, drinking, or gesturing with imaginary objects, without actually touching any of the objects around. These movements typically happened with eyes closed during apparent sleep but could also occur with eyes open during hallucinations, or less often awake with eyes closed.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.sleep.2022.08.027

Jerks (Video 4) were isolated, short-duration sudden contractions of any body part, usually limbs but also trunk or head (sudden contractions of a single or several muscle groups).

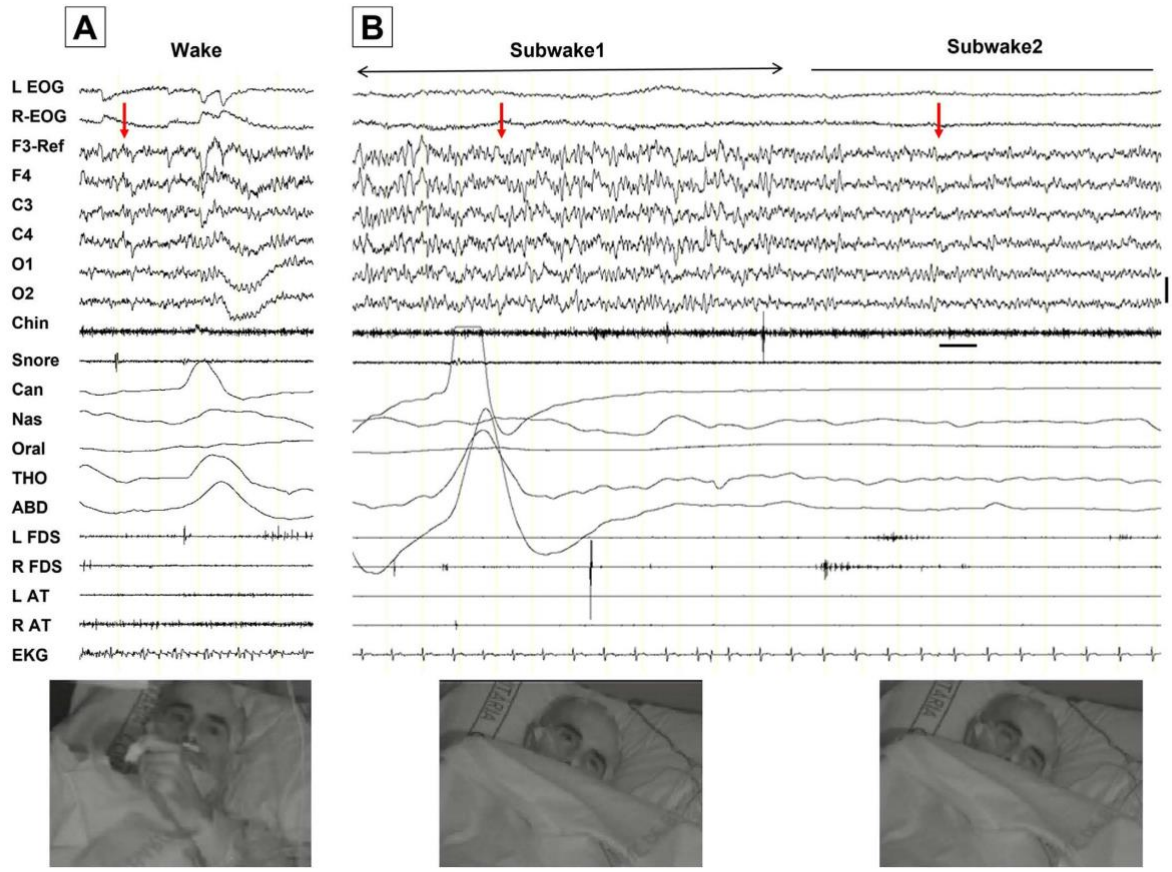


Fig. 4. The vPSG pattern in Wake, Subwake1 and Subwake2 with associated eye-opening level. The left part of the figure (A) shows (Pat#3) a 7-s segment of wake, with eyes opened, rapid eye movements, low amplitude alpha activity and EMG tone, The right part (B) of the figure show a 15-sec epoch of Subwake1 (left right horizontal arrow) characterized by a mixture of anterior predominant, irregular, moderate amplitude theta/delta activity at 3–6 Hz mixed with irregular 7–8 Hz posterior alpha activity and chin EMG tone followed by an epoch of Subwake2 (top horizontal continuous line), characterized by an EEG amplitude attenuation with disappearance of the theta/delta activity and with lower amplitude posterior predominant alpha/subalpha activity at 7–8 Hz simultaneous with the onset of a central apnea. Eye movements are slow or absent. The video caption shows the different degrees of eye-opening and eye-contact: Full in wakefulness, limited during Subwake1 (the eyes are half open and without contact, whereas during Subwake2 they are closed. The red arrows signal the exact moment of the recording when de video caption was taken. Montage as in previous figure. **Calibration bars**: Vertical bar on the right: 50 μV; horizontal bar: 1 s. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Supplementary video related to this article can be found at https://doi.org/10.1016/j.sleep.2022.08.027

Simple movements (Video 4) were typically isolated limb movements of longer duration and greater body involvement than jerks (e.g., raising the arms, kicking, punching), but without a complex pattern or apparent purpose.

Vocalizations: *Simple vocalizations* were short (1 s or less) vocal sounds, other than stridor, groaning or respiratory related sounds (see below). Complex vocalizations were more elaborated, sometimes understandable words or sentences.

When more than one type of movement was present within the same epoch, we applied the following rule: aperiodic movements were scored whenever present, independently of its association to other type of movements because typically affected the lower limbs or trunk. For the rest of movements, that were often centered in the upper limbs, the more complex event was selected to categorize the epoch, with manipulatory prevailing over quasi-purposeful and these over simple and jerks. Vocalizations were scored separately, and if more than one type appeared in the same epoch complex vocalizations prevailed over simple.

Hallucinations/Hallucinatory behavior. We also identified epochs where the patient seemed to be hallucinating when she/he had the eyes opened most of the time or had easy change from eyes closed to eyes opened while looking around without a reasonable purpose, often with inappropriate vocalizations or limb movements (finalistic or manipulatory) of variable intensity. The patient had preserved muscle tone, rapid eye movements, and often an irregular low amplitude theta or theta/alpha activity (Fig. 10). Epochs with hallucinations were scored as Wake.

Finally, we also identified behaviors occurring with the patient having rhythmic movements with identifiable sexual characteristics and were designated as sexsomnia (Video 5).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.sleep.2022.08.027

Periodic leg movements of sleep (PLMS) and periodic leg movements during wakefulness (PLMW) were scored independently of the other movements following the AASM recommendations [31].

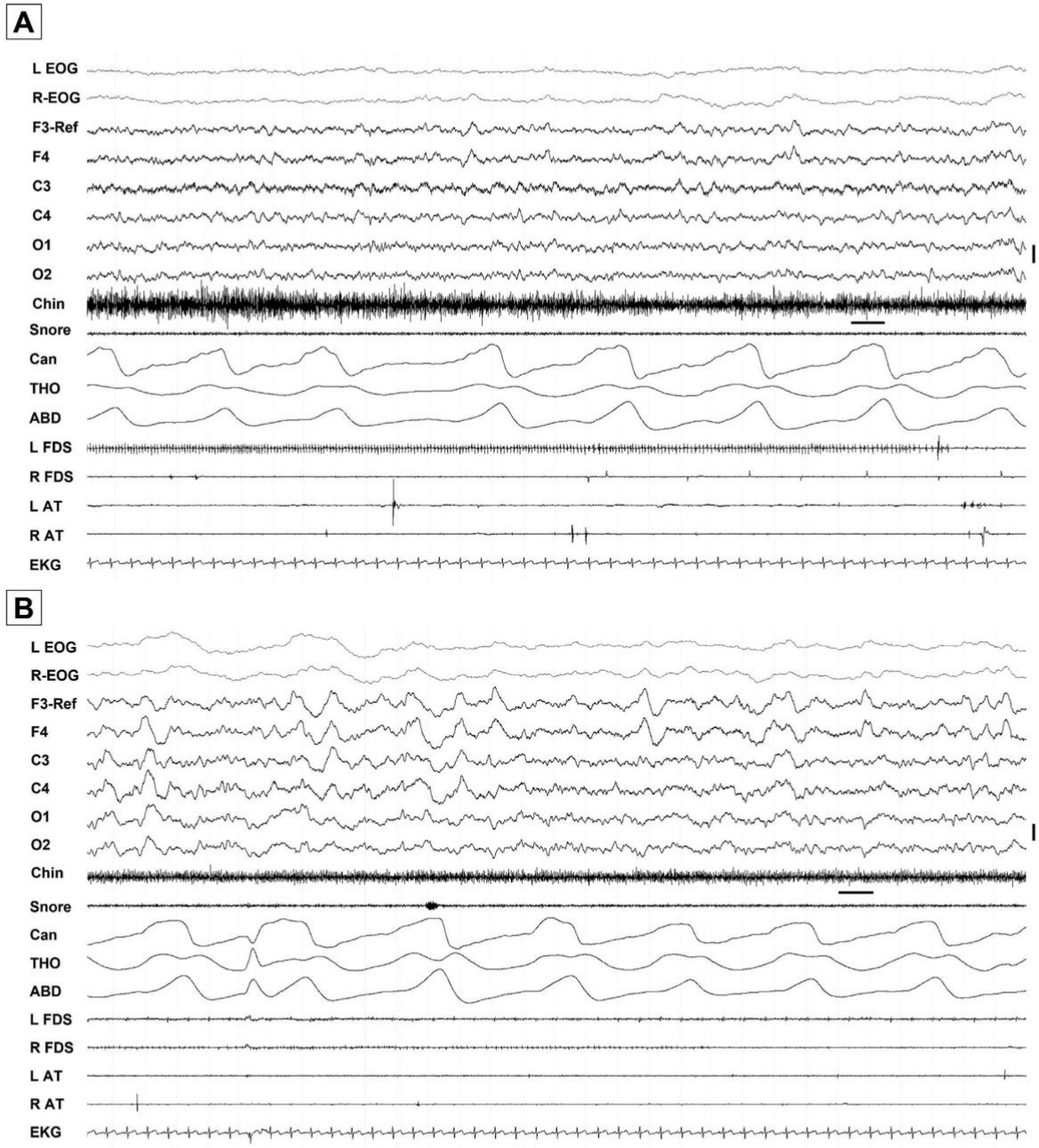
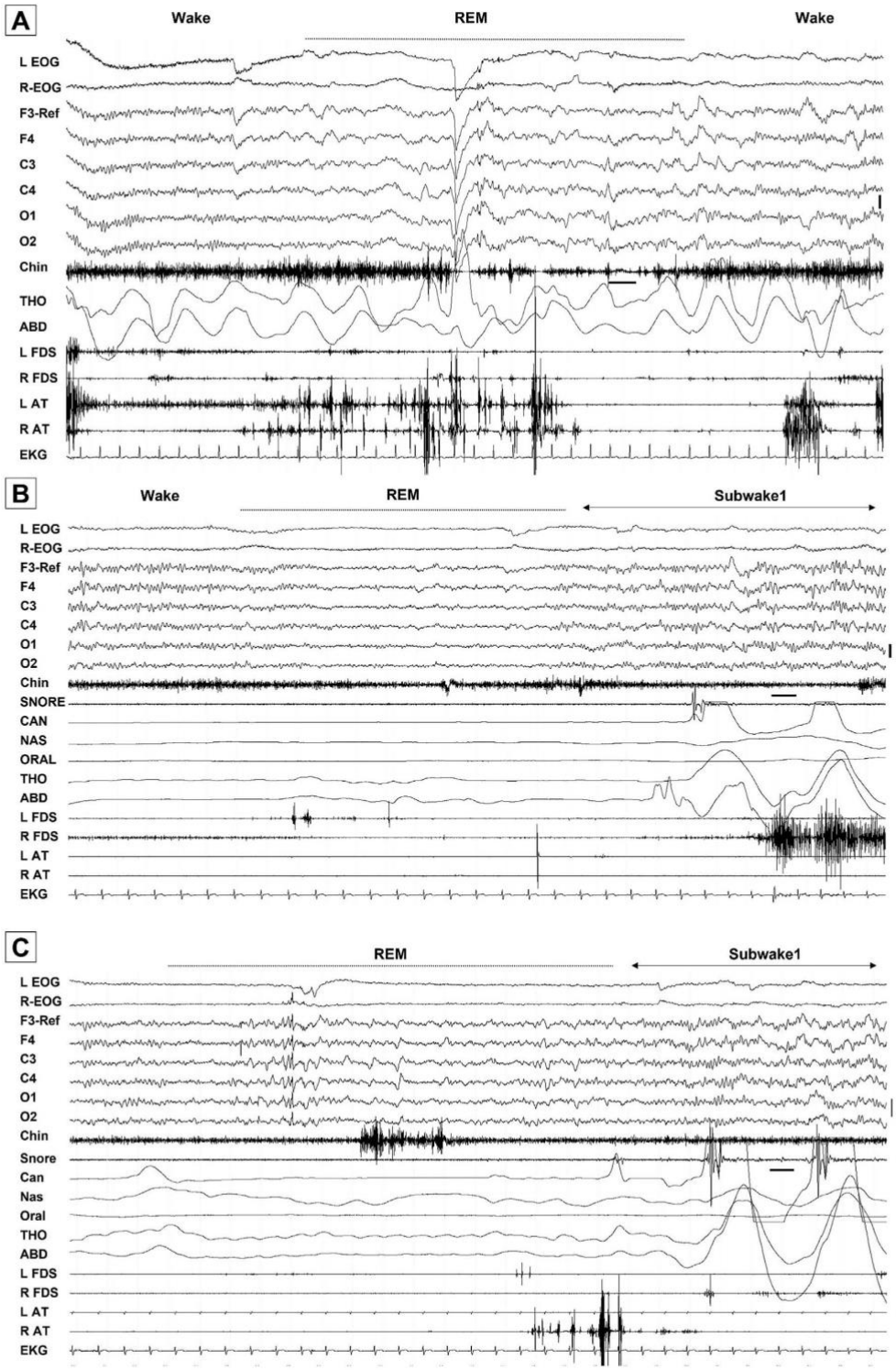


Fig. 5. Undifferentiated light and deep NREM sleep. In A, light UNREM (Pat#7) with a diffuse irregular 40–50 μV delta–theta activity at 0.5–4 Hz. In B (same patient), deep UNREM, with a greater amplitude (60–80 μV) and slower 0.5–1 Hz) diffuse irregular delta activity. In both cases there is a lack of vertex sharp waves, K complexes, sleep spindles and rapid eye movements. Montage as in previous figures. Calibration bars: Vertical bar on the right: 70 μV; horizontal bar: 1 s. Note: During this part of the recording the patient did not tolerate the thermistors.

2.3. Analysis of respiration

Respiratory events were scored following the AASM recommendations, whenever possible [31]. A central sleep apnea was scored when there was a drop in the peak thermal sensor excursion by at least 90% of the pre-event baseline, that lasted for 10 s or more, with absent inspiratory effort. Hypopneas were scored when airflow dropped by at least 30% from baseline. Hypopneas were


A
Wake
REM
Wake
L EOG
R-EOG
F3-Ref
F4
C3
C4
O1
O2
Chin
THO
ABD
L FDS
R FDS
L AT
R AT
EKG
B
Wake
REM
Subwake1
L EOG
R-EOG
F3-Ref
F4
C3
C4
O1
O2
Chin
SNORE
CAN
NAS
ORAL
THO
ABD
L FDS
R FDS
L AT
R AT
EKG
C
REM
Subwake1
L EOG
R-EOG
F3-Ref
F4
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O1
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R FDS
L AT
R AT
EKG

considered central if inspiratory effort signals dropped accordingly, in the absence of snoring, nasal pressure signal flattening and paradoxical thoracoabdominal movements during the event and were scored as obstructive, if otherwise. Cheyne-Stokes breathing was scored according to standard criteria [31]. Cluster-breath referred to bursts of a few breaths interspersed with central apneas of variable duration [35]. Catathrenic events (see below) were not considered as apneas.

Given the complexity of breathing patterns encountered in FI patients, we used the following additional criteria for scoring respiratory events.

First, respiratory events (especially central apneas or hypopneas) in patients with FI occurred not only during conventional sleep, but also during relaxed wakefulness and subwakefulness. To avoid underestimation, apneas occurring during non-sleep epochs were also scored.

Second, patients with central apneas and hypopneas frequently had similar events that lasted less than 10 s, therefore not fulfilling AASM apnea criteria. We scored these episodes as separate events and we term them as "short central apneas" when they had at least the duration of two breaths during the pre-event baseline, using the same rationale as for apnea detection in children [31]. Baseline breathing was calculated as the mean breath-to-breath interval during the 2 min preceding the event, excluding apneas.

Third, separate central apnea-hypopnea indexes (CAHI) were calculated for stable Wake time, fluctuating Wake-Subwake time and consolidated NREM (see above) time. In addition, we calculated CAHI for all non-wake time, excluding periods of stable Wake only (but not Wake epochs of fluctuating Wake-Subwake periods). REM sleep of sufficient length to provide a reliable CAHI was absent in most patients and was not calculated. CAHI was expressed as the number of central apneas and hypopneas per hour of each corresponding stage.

Fourth, as wake/sleep stages shifted quickly and apneas often lasted longer than one epoch, beginning and ending in different stages, the stage attributed to the apnea was the one where the apnea predominated.

In addition, other events breaking respiratory rhythmicity like isolated large inspirations, or breaths irrupting out of place were identified and recorded as well.

Respiratory rate variability. We assessed the regularity of the breathing pattern by measuring the respiratory rate variability (RRV) independently of apneas (standard or short). To calculate RRV, we manually identified inspiratory peaks and measured peak-to-peak intervals (i.e., the length of respiratory cycles). Peak-to-peak intervals encompassing an apnea or hypopnea (including short apneas) and catathrenia events were excluded from analysis (Figure S2). We explored two alternatives to measure RRV: by comparing each interval 1) to the previous one, and 2) to the average duration of the preceding 2-min intervals. Results are provided for both measures in the text, but only the second one was used for figures, tables, and correlations with other study variables. Since RRV in normal subjects depends on the wake/sleep stage (from highest to lowest: wake, REM, NREM) [36], we analyzed it for the total recording time and separately for specific sleep stages (stable wake, subwake, stable NREM sleep, and stable REM sleep, when possible) and compared it with nine age- and sex-matched normal sleep-laboratory controls. Reasons to have a vPSG study in controls were insomnia (n = 4), sleepiness (n = 2), suspected obstructive sleep apnea (n = 2), and fatigue (n = 1). As a cut-off for abnormal RRV we chose 3 standard deviations (SD) above the controls' mean.

In each vPSG, measurements were performed on the respiratory channel that had the highest signal quality in that recording, as peak-to-peak intervals were comparable among all the channels used. Respiratory signal changes associated with artifacts (e.g., major body movements, touching the sensors, or talking) were excluded from the analysis (Figure S2).

Respiration-related sounds were analyzed with synchronized audiovisual recordings. The inspiratory and expiratory part of the respiratory cycle was scrutinized during apneic events, more specifically after alerting changes, and at any visually identifiable irregularity of respiratory signals throughout the recording. Additionally, during periods without identifiable irregularities of respiratory signals, the audio was also screened every few epochs to detect any respiratory sounds. Respiratory sounds were scaled semi-quantitatively according to frequency of appearance as: frequent, if there was at least some period of the night where the sound was recorded continuously across consecutive breaths during 2 min or more in a row, accepting brief interruptions after alerting changes or movements, if resumed afterwards; discontinuous, if appeared recurrently in association with particular events, such as end of apneas, or more intermittently, but typically more than 15–20 times per recording; occasional/isolated, when occurring in a less predictable way in association with intermittent events (typically less than 10 events per recording), and absent.

Inspiratory sounds included ***stridor and hiccup.*** Stridor was a high-pitched inspiratory sound that could appear continuously throughout consecutive breaths during a period of the recording, or in isolated inspirations. Hiccup referred to a sudden, short, and abruptly interrupted inspiration with an accompanying hic sound, that could appear at any stage of the respiratory cycle, producing a well-identifiable, short-sharp peak on the nasal pressure canula signal, and a hump on the respiratory effort bands' signal (Fig. 11).

Expiratory sounds were classified according to their nature (groaning, moaning, vocalizations) and to their relationship with the respiratory signal and pattern. ***Expiratory Groaning*** was defined as a groaning or moaning sound occurring during exhalation, in one isolated or several concatenated breaths, that did not meaningfully alter the duration of the expiratory excursion. We used the term ***Rhythmic Expiratory Vocalizations*** to refer to vocalizations only appearing synchronously with rhythmic exhalations, without modifying the respiratory cycle, and occurred repeatedly across consecutive exhalations. These were different from events scored as vocalizations alone, because in this case breathing modulated or adapted to speaking cadency. ***Catathrenia*** consisted of a post-inspiratory breath-hold and a protracted expiration (identifiable as a flattening of all respiratory signals) with groaning, typically ending with a final exhalation (with a downward deflection on respiratory channels) (Fig. 12). Catathrenic events were not counted as apneas.

Fig. 6. REM sleep epochs with different characteristics. In A (Pat#11), Wake leading into a short period of REM sleep and then Wake again. The left half shows 4 s of Wake with rapid eye movements, alpha at 7- Hz, and preserved muscle tone (horizontal bar, between arrows) which are followed by a short REM period of 13 s duration, characterized by rapid eye movements, alfa disappearance, increase in slow activity, intermittent chin EMG atonia, irregular breathing, and phasic upper and lower limb EMG activity, associated with limb jerks. This short period of REM leads again into wakefulness, with posterior alpha reappearance. Note that the flow and thermal sensor channels are not shown, because the patient did not tolerate them during long periods of the recording. Calibration: vertical line: 100 μV, horizontal line: 1 s. In B (Pat#3) a 10-s REM episode (top horizontal bar) showing disappearance of alpha activity and a rapid eye movement ending with resumption of Subwake1 (left-right top horizontal arrow), with a mixture of anterior theta and delta with posterior alpha/subalpha frequencies. There is also a central apnea during the REM period, and a persistent but irregular chin EMG activity with left FDS and TA EMG bursts. Calibration: vertical bar: 70 μV, horizontal bar 1 s. In C (Pat#3) a 14-s REM episode without atonia, with a rapid eye movement, a short, transient, discontinuous increase in chin EMG activity, and phasic EMG activity in the right TA and left FDS, while there is a central apnea of similar duration and leading into Subwake1 (between arrows left-right horizontal bar in the right half). Calibration marks: Vertical 50 μ V, horizontal 1 s. Montages as in previous figures but with the airflow channels in place.

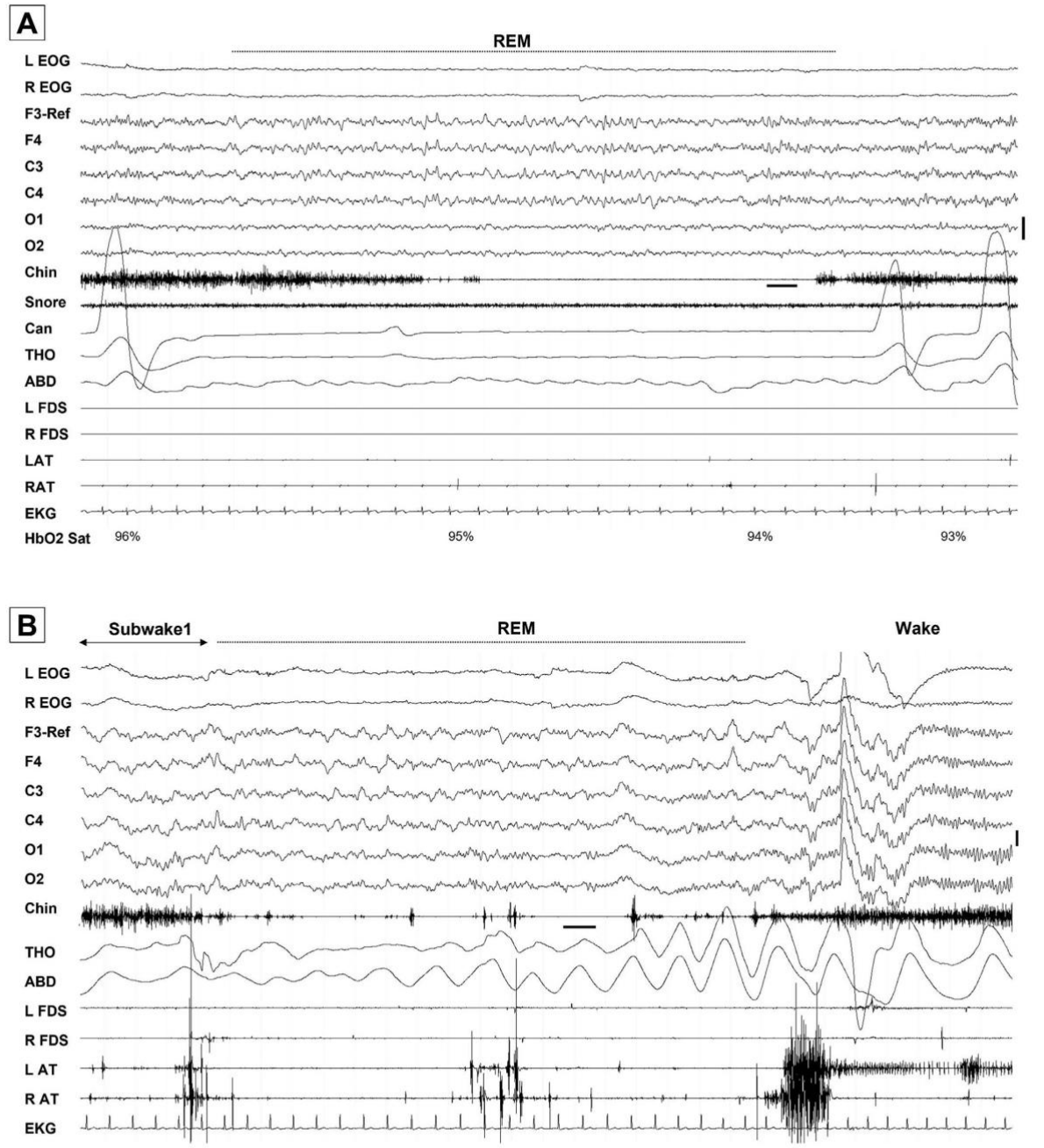


Fig. 7. REM sleep epochs containing complete and incomplete atonia. In A (Pat#2) the figure shows a 20-s episode of REM sleep characterized by relative slowing of the EEG as compared to the short Wake period in the left, a single rapid eye movement in the center and a change in chin EMG continuity, with progressive decrease followed by full atonia. There is a central apnea with minimal oxyhemoglobin desaturation. The end of the apnea is simultaneous with the end of this period of REM sleep. Calibration bars: Vertical bar on the right: 50 μV; horizontal bar: 1 s. In B (Pat#11) a 20-s REM episode (top horizontal bar) is shown, appearing after a brief period of Subwake1 with intermixed alpha with anterior 2 Hz delta (left side of the figure), and characterized by rapid eye movements, disappearance of alpha rhythm with moderate amplitude theta-delta slowing, a short hypopnea and by EMG atonia only interrupted by a few phasic bursts in the chin and legs, leading into wakefulness in the right part of the figure. In both figures, note that the flow and thermal sensor channels are not shown, because the patient did not tolerate them during long periods of the recording. Calibration: vertical line: 100 μV, horizontal line: 1 s. Montages as in previous figures.

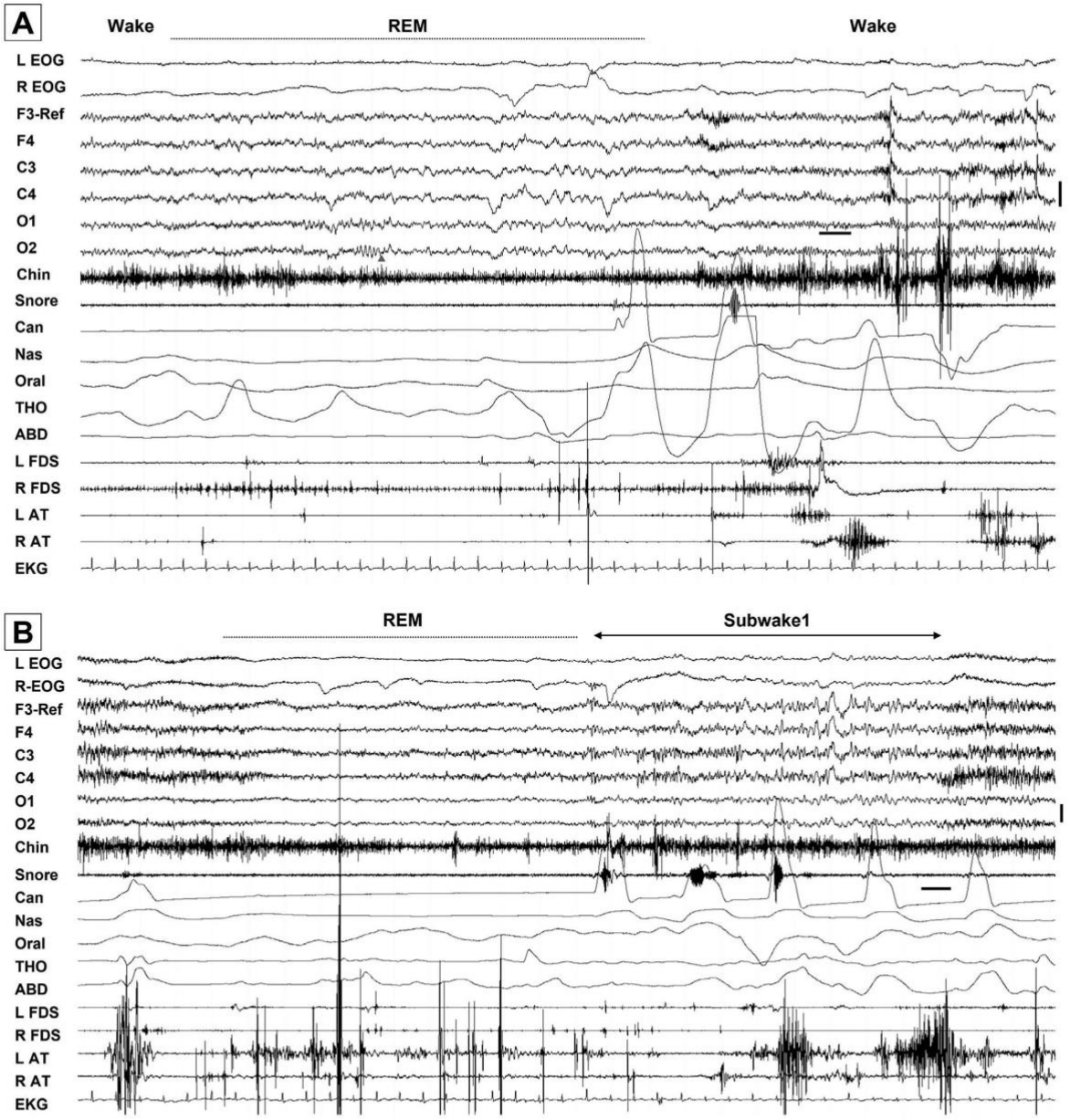


Fig. 8. Difficulties in scoring REM sleep in FI. Panel A (Pat#9) shows a short segment of REM sleep without atonia, after a brief Wake segment on the left side of the figure, and characterized by low amplitude mixed EEG activity, rapid eye movements, a brief burst of theta activity (arrowhead) and irregular chin EMG activity followed by a relative decrease in EMG amplitude without reaching atonia, multifocal limb jerks and a hypopnea ending with a return to a period of Wake with 9–10 Hz posterior alpha activity. Panel B (Pat#6) shows an 8-s REM period (top horizontal bar) that appears after wakefulness (left hand side) and characterized by a decrease in chin EMG and short phasic EMG bursts in the legs, associated with jerks, rapid eye movements and a disappearance of alpha activity, which leads into Subwake1 in the second half of the figure. There is also a central apnea episode associated with the event (note that respiratory effort bands move with the jerks). Montages as in previous figures. Calibration bars: vertical 100 μV, horizontal 1 s.

2.4. Neuropathological study

The neuropathological assessment was performed on formalin-fixed and paraffin-embedded tissue sections available at the Neurological Tissue Bank of the Biobank-Hospital Clinic-IDIBAPS. Brain tissue had been processed according to standardized procedures for diagnostic and research purposes after obtaining written informed consent from the next of kin [37].

For the present analysis, we performed a semiquantitative assessment of neuronal loss and gliosis on 5 μm thick paraffin section in selected brain regions. These included the caudate nucleus, putamen, globus pallidus, the anterior, middle, and posterior

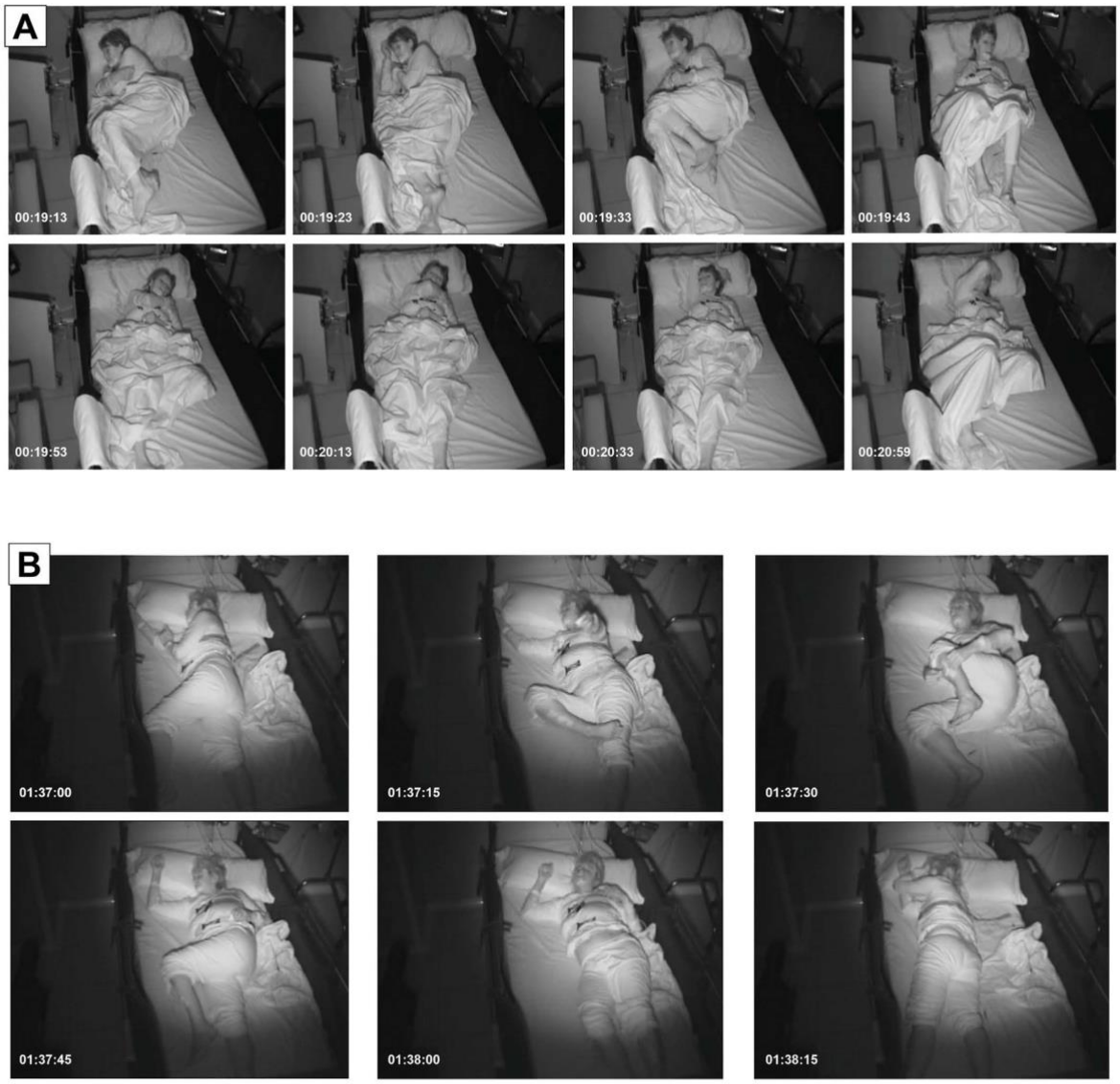


Fig. 9. Aperiodic movements in two FI patients: Consecutive captions of the video recording taken every 10–20 s to show the important body movements that Pat#5 (A) and Pat#6 (B) had throughout many Wake periods of the recording.

thalamic subnuclei, hypothalamus, midbrain, pons, medulla oblongata and cerebellar vermis. Microglial reaction was assessed separately in nuclei of the medulla oblongata. The scoring was performed as follows: absent; + mild; ++ moderate, +++ severe, and was blinded to sleep and breathing parameters. Moreover, we evaluated the presence and distribution of concomitant pathologies such as microvascular brain lesions and abnormal ßA4-amyloid, alpha-synuclein, phospho-TDP43 and prion protein accumulation, that could potentially influence phenotypic expression. For details on the antibodies used see Table S1. Results were interpreted in relation to control brain tissue.

2.5. Statistical analysis

SPSS Statistics 24 was used for statistical analysis and additionally GraphPad Prism 8 and Microsoft Excel for plotting. Means, SD, medians, and ranges are provided for descriptive statistics. P values from Mann-Whitney U or two-way ANOVA are provided for group comparisons, and Spearman Rho and r square correlation coefficients for correlation and regression analyses. Factor analysis was used to explore correlations among multiple variables. For survival analysis, Kaplan-Meier curves and Breslow-Wilcoxon tests were used.

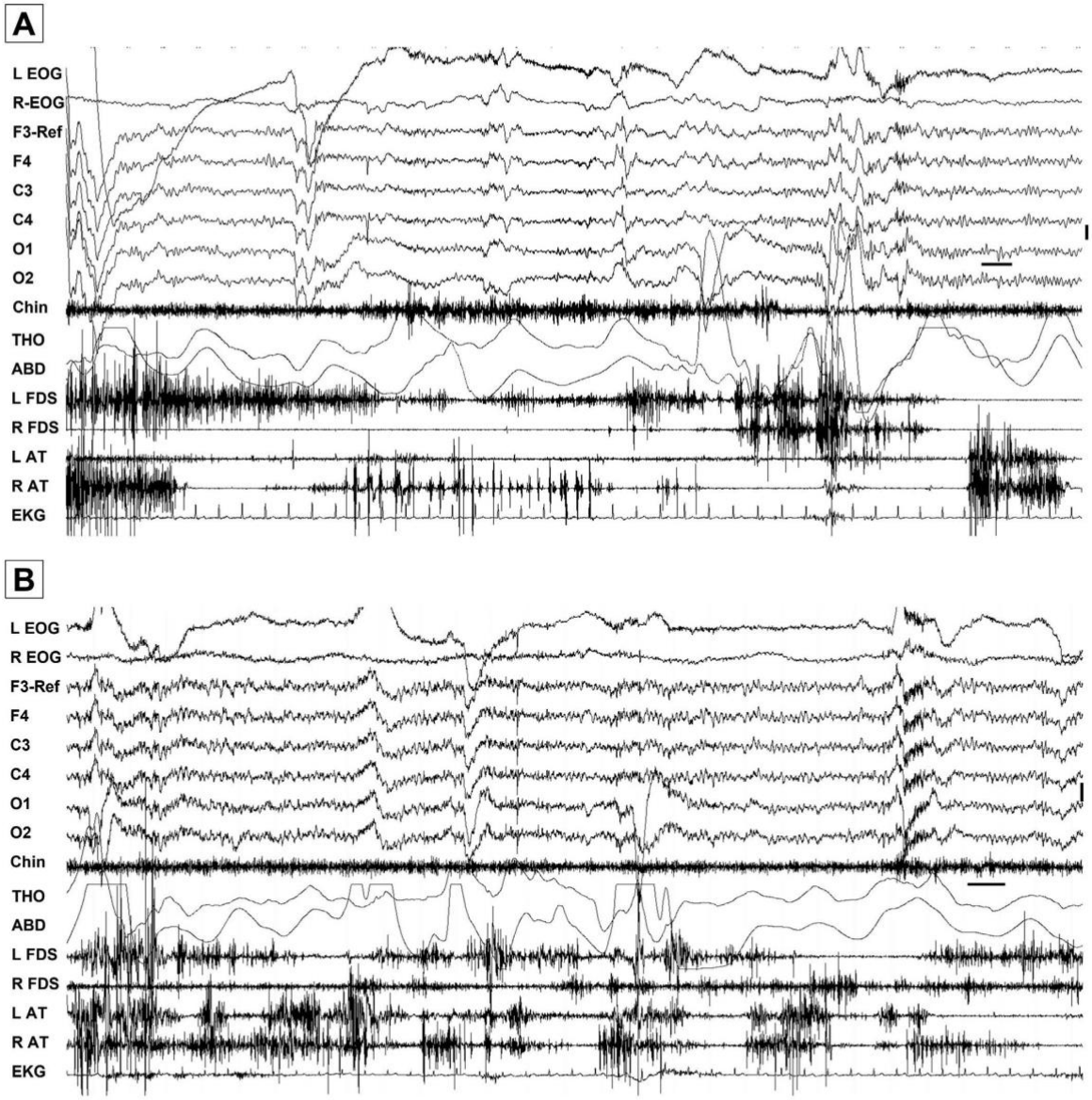


Fig. 10. Hallucinations. In A (Pat#11) there is a moderate amplitude posterior dominant or diffuse 7–8 Hz alpha activity in the first and last 5–8 s, while the patient had the eyes mostly closed, whereas in the center a low amplitude irregular theta, with rapid eye movements, continuous chin EMG activity and periods of sustained EMG activity in the limbs, with superimposed phasic bursts and irregularities in breathing. The patient this time had the eyes open and looked to points of the room with pseudopurposeful or manipulatory movements. In B the figure shows another period of hallucinations (Pat#11). The EEG shows at 8 Hz alpha activity of moderate amplitude with superimposed movement and EMG artifact. The movement artifact affects the respiratory effort bands as well. There is almost continuous EMG activity in arms and legs, while the patient manipulated cables, looked around without apparent purpose. Montages as in previous figures. Calibration: Vertical bar 100 μV; horizontal 1 s.

3. Results

3.1. Demographic and clinical features (Table 1)

Eleven patients (8 women) were included in the study, one with sporadic FI (Pat#6). Median age at disease onset was 48 years (range 20–66), vPSG was performed a median of 7 months (range 2–24) after disease onset and the median disease duration (onset to death) was 12 months (range 7.5–51.9 months), with one patient (Pat#2) alive at the time of this writing (80 months since onset). Median survival time form vPSG to death was 5.3 months (range 2.0–33.3 months). Post-mortem studies were performed in 7 of the 10 deceased patients (Pat#1, 3, 5–8, 11).

The first symptoms of the disease were mood changes (n = 4), insomnia (n = 3), diplopia (n = 3), gait instability (n = 2), dysphagia (n = 1), and excessive perspiration (n = 1), alone or in combination.

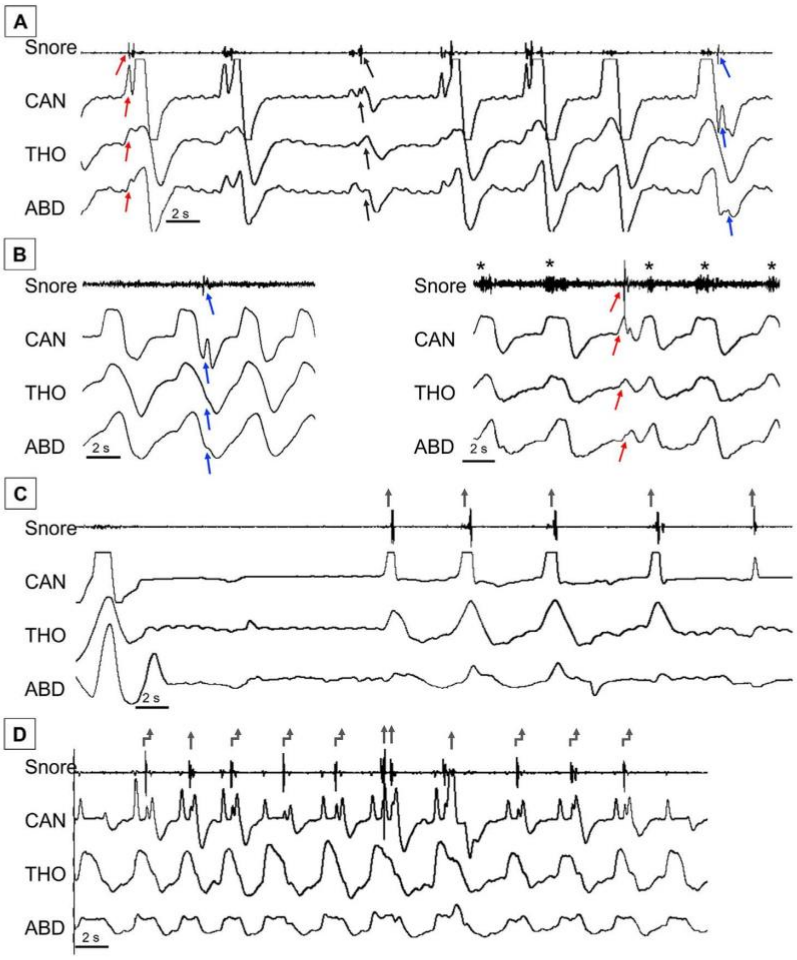


Fig. 11. Hiccups. The figure shows episodes of hiccup in different patients, identifiable as a brief deflection irrupting abruptly over a flat background on the snoring channel simultaneous with a sharp peak mounted over the breathing signal on nasal pressure canula (CAN), and as a little hump on thoracic (THO) and abdominal (ABD) effort channels. Panel A (Pat#3) shows 6 hiccup episodes (present in all breaths but the penultimate one) during a period of NREM sleep, that occur at different moments of the respiratory cycle: proto-inspiratory (red arrows), mid-inspiratory (black arrows) and expiratory (blue arrows). Panel B shows two captions with one isolated hiccup preceded and followed by normal breath; the one in the left (Pat#7) is expiratory (blue arrows) and the one in the right (Pat#10) is proto-inspiratory (red arrows), both occurring in NREM sleep. Note that the hiccup signal is clearly differentiable from snoring (*). Panel C (Pat#3) shows a series of respirations where normal breaths have been replaced by consecutive hiccups (gray arrows) after an apnea (see Video 8). Hiccup is best appreciated on the snoring channel but note how the inspiratory deflection in CAN is shorter and sharper than the normal one preceding the apnea. Panel D (Pat#10) shows a segment with hiccup across consecutive breaths, which is two-stepped in most of them (elbowed arrows) doubled in some of them (double arrows) (see Video 8). See that there is also flattening of the signal in the canula, suggesting the presence of increased upper airway resistance. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Most patients (n = 8) developed gait difficulties with instability and cognitive complaints in the course of the disease. Dysautonomia occurred in 6 patients and presented as profuse sweating (n = 5), high blood pressure (n = 2), or urinary retention (n = 1). Nine patients complained of insomnia of variable severity, six of abnormal nocturnal behaviors (dream enactment, wandering, hallucinations, nocturnal confusion, falling out of bed), two reported the recent appearance of snoring (progressing in intensity in one), two patients complained of a loud respiratory noise and two reported episodes of breathing cessation. Despite the restless nights described by their relatives, four patients referred to have a nocturnal sleep of good quality.

Seven patients were treated with benzodiazepines (Table 1), as an anxiolytic therapy in two cases, and as a hypnotic treatment in five, and received either one (5 cases) or two benzodiazepine drugs (two other cases). None of these therapies appeared to produce a clinical improvement of sleep. Three patients were treated with antidepressants (sertraline, venlafaxine, and trazodone + mirtazapine) and two received antipsychotics (clozapine and chlorpromazine).

3.2. Video-PSG evaluation

Sleep recordings were started between 23:00 and 24:00 and continued until 7:00 in all but Pat#9 who only tolerated the sensors for 3 h and was recorded with only video for two additional hours, until 4:30 a.m. (with a combined total of 5 h and 26 min). Pat#1 had two vPSG evaluations separated by six months. We used values

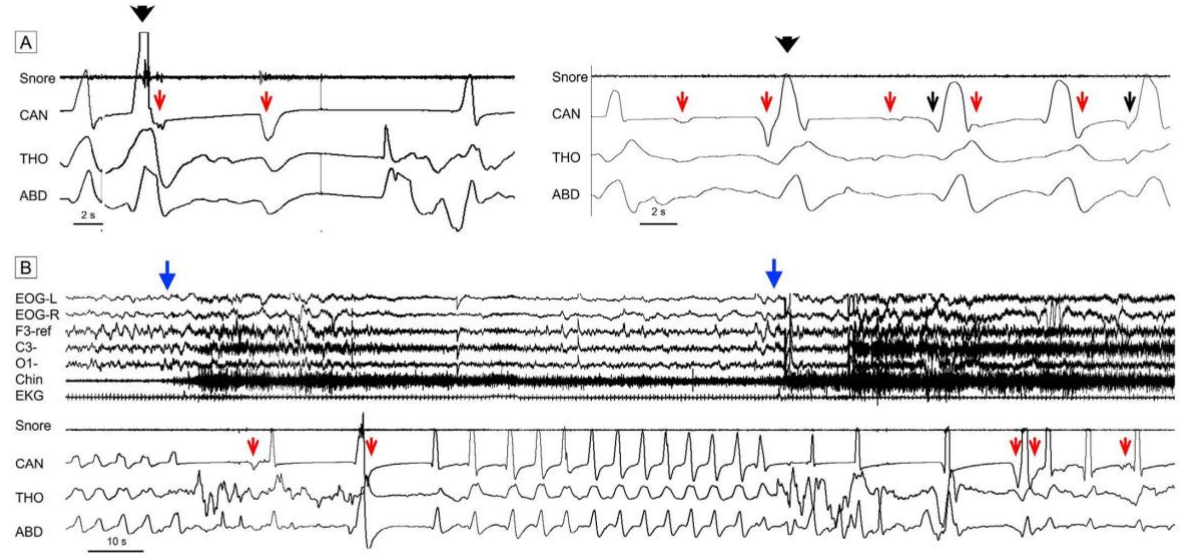


Fig. 12. Catathrenia. Panel A (left half side): An episode of catathrenia (Pat#9) beginning with a large inspiration (arrowhead) followed by a protracted expiration with groaning sounds at the beginning and at midpoint of the episode, identified by downwards deflections in the respiratory signals (red arrows). In the right half side of the panel four concatenated events of catathrenia (Pat#7) are shown. Only the second one has an initial relatively large inspiration (arrowhead) and a typical final downward deflection in the first two. Red arrows point to groaning sounds while black arrows indicate silent final exhalations. Panel B shows a 4-min period (Pat#7) with several catathrenic breaths triggered by an arousal (left blue arrow); note increased amplitude in Chin EMG, EMG artifact on EEG channels and movement artifact on respiratory effort bands). Three breaths with a protracted expiration follow the arousal, with groaning sounds at the end of the first one and the beginning of the third one (red arrows), whereas no sounds nor downward signal deflections can be identified in the second one. In the middle part of the figure (horizontal bar), with the patient falling asleep again, there is a period of deep breathing bradypnea (compared to the pattern before the arousal) and then the cycle repeats after a new arousal (right blue arrow) which triggers another episode of concatenated catathrenia events, with groaning sounds at the points indicated by the red arrows. EOG-L and R: left and right electrooculogram; electroencephalogram from F3, C3, O1 referred to combined ears; Chin EMG; Snore: snoring vibration from nasal pressure cannula, CAN: nasal pressure cannula, THO: thoracic respiratory effort band; ABD: Abdominal respiratory effort band. Note than time calibration is different in Panel A and B. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

from the second study to describe the patient' sleep characteristics, and perform clinicopathologic correlations, whereas those from the first recording were employed only to illustrate the changes occurring with progression of the disease.

3.3. Wake/sleep patterns

3.3.1. General overview of wake and sleep activity throughout the night

All patients but one (Pat#9) had periods of NREM sleep of variable duration, whether conventional or undifferentiated, and all had at least a few epochs of REM sleep. Wakefulness was very unrestful in four patients (Pats#5,6,9, and 11) and less intensely in Pat#7 with abundant movements and EMG artifacts, and frequent changes in body position (median of 40 per night, range 22–125) only terminating during consolidated NREM sleep. In contrast, patients Pats#1–4 and 8 spent long parts of the recordings quiet and changes in body position were minimal (median of 15 per night, range 13–25; $p = 0.025$ compared with the group with abundant movements), fluctuating between Wake and Subwake and associated typically with CSA. Pat#10 spent most of the night quiet and asleep. Hypnograms of four patients with distinctive wake/sleep patterns are shown in Fig. 13. The remaining hypnograms are shown in Figure S3.

3.3.2. Wakefulness

Wakefulness represented more than a quarter of the TRT in ten of the eleven patients (Table 2) with three patients (Pats#5, 9, and 11) spending 80% or more of TRT awake. In these three, stable Wake occupied 64.6–68.9% of TRT, along with fluctuations between wake and REM sleep (4.2–10.7% of TRT), whereas stable Wake represented less than 10% of TRT in Pats# 1, 3, 4, 8, and 10, who typically had high percentages of Subwake and frequent fluctuations between Wake and Subwake (14.3–73.6% of TRT). Pat#6, with sFI, had both Wake-to-REM (4.2% of TRT) and Wake-to-Subwake oscillations (56.4% of TRT).

3.3.3. Subwake1 and 2

All the patients had periods of Subwake1 and ten had Suwake2. Subwake 1 occupied twice as much time as Subwake2 (median 16% vs 6% of TRT, respectively) (Table 2). Subwake1 appeared after several epochs of Wake or typically after one or two Wake epochs following an alerting change from sleep or previous subwake (defined by a movement after a quiet period, resumption of breathing at the end of an apnea and increase in EMG artifact). Subwake1 lasted a median of 1 epoch (with maximum consecutive epochs in Subwake1 ranging from 3 to 19), ending typically –if not interrupted– in a short period of Subwake2, with a median duration of 1 epoch (maximums ranging from 3 to 6 Subwake2 epochs). Whereas in 10 patients Subwake1 appeared scattered throughout the recording in Pat#10 it appeared almost limited to the final part of the vPSG and was associated with a period of increased respiratory rate variability and central sleep apnea (Fig. 13). Subwake1 and 2 appeared both in patients with conventional and undifferentiated NREM sleep. Subwake1 in Pat#1 was absent in the first sleep study and appeared clearly in the follow-up recording performed 6 months later, associated with a reduction in Wake and in sleep time, with a dramatic increase in central sleep apnea index (Table 3, Fig. 14).

Table 1
Demographic, clinical and paraclinical data of individual patients.

	Gender	Onset (years)	Onset-PSG (mo)	PSG-death (mo)	Disease duration (mo)	First symptom	Sleep symptoms	Treatment at PSG	Nocturnal respiratory symptoms	Other symptoms during disease	Brain MRI/PET	Genetics
Pat#1	F	65	24	5.6	29.6	Mood changes	Insomnia	LZP, CLZ	–	Perspiration, parkinsonism, CI	–	D178 N (129 MM)
Pat#2	M	30	19	na	na	Mood changes	Witnessed apneas	CZP	Apneas	Gait disturbance, anxiety, paranoid thoughts, dysphagia, dysarthria, CI, perspiration.	Bithalamic hypometabolism	D178 N (129 MV)
Pat#3	M	47	6	3.2	9.2	Diplopia	Witnessed apneas, sleep-onset jerks	CLZ	Apneas	Gait disturbance, diplopia, dysphagia, dysphonia, dysmetria, CI, pyramidalism, visual hallucinations	Normal	D178 N (129 MV)
Pat#4	F	45	5	2.0	7.0	Mood changes, insomnia	Insomnia, EDS		–	CI, confabulation, urinary retention, anorexia, gait disturbance, parkinsonism	Diffuse atrophy	D178 N (129 MM)
Pat#5	F	64	6	2.2	8.2	Mood changes, insomnia	Insomnia, abnormal behaviors, vocalizations, falling from bed, EDS	LZP	Stridor	Dysphonia, gait disturbance, parkinsonism, diplopia, CI, daytime confusion	Normal	D178 N (129 MM)
Pat#6	F	48	14	6.5	20.5	Diplopia	Insomnia, dreaming-like state (night and day)	VLF, ALP	–	Gait disturbance, tremor, dysmetria, dysarthria, dysphagia, pyramidalism, CI, confabulation	Normal	D178 (129 MM)
Pat#7	F	39	15	14.1	29.1	Dysphagia	Insomnia, nightmares, EDS with daytime hallucinatory-like state	LMZ, CLZ, SER	–	Hypertension, diplopia, CI, gait impairment, perspiration, hyperthermia	Normal	D178 N (129 MV)
Pat#8	F	53	6	6.0	12.0	Gait	Insomnia, progressively increasing snoring, jerks, EDS		Snoring new, progressive	Hypertension, diplopia, dysarthria, dysmetria, dysphonia, nystagmus, hypotonia, CI, visual hallucinations	Normal	D178 N (129 MV)
Pat#9	M	62	7	3.0	10.0	Perspiration	Insomnia, nocturnal confusion, hallucinations, wandering, unsteadiness, perspiration, stridor, EDS	CLZ	Stridor	Diplopia, CI, daytime myoclonus	Frontal atrophy	D178 N (129 MM)
Pat#10	F	20	18	33.3	51.3	Diplopia and gait	Insomnia, snoring and other breathing sounds	TZD, MRT, CPZ	Acute snoring	Gait disturbance, oculomotor disturbance, dysmetria, CI	Bithalamic hypometabolism	D178 N (129 MV)
Pat#11	F	66	2	4.9	6.9	Insomnia, sleep behaviors	Insomnia, dreaming-like behaviors, EDS			Dysphonia, dysphagia, perspiration, tremor, CI	Bifrontopolar bilateral caudate hypometabolism	D178 N (129 MM)

Medications: LZP: lorazepam; CLZ: clonazepam; CZP: clozapine; VLF: venlafaxine; ALP: alprazolam; LMZ: lormetazepam; SER: sertraline; TZD: trazodone; MRT: mirtazapine; CPZ: chlorpromazine; PSG: polysomnography; mo: months; EDS excessive daytime sleepiness; CI: cognitive impairment.

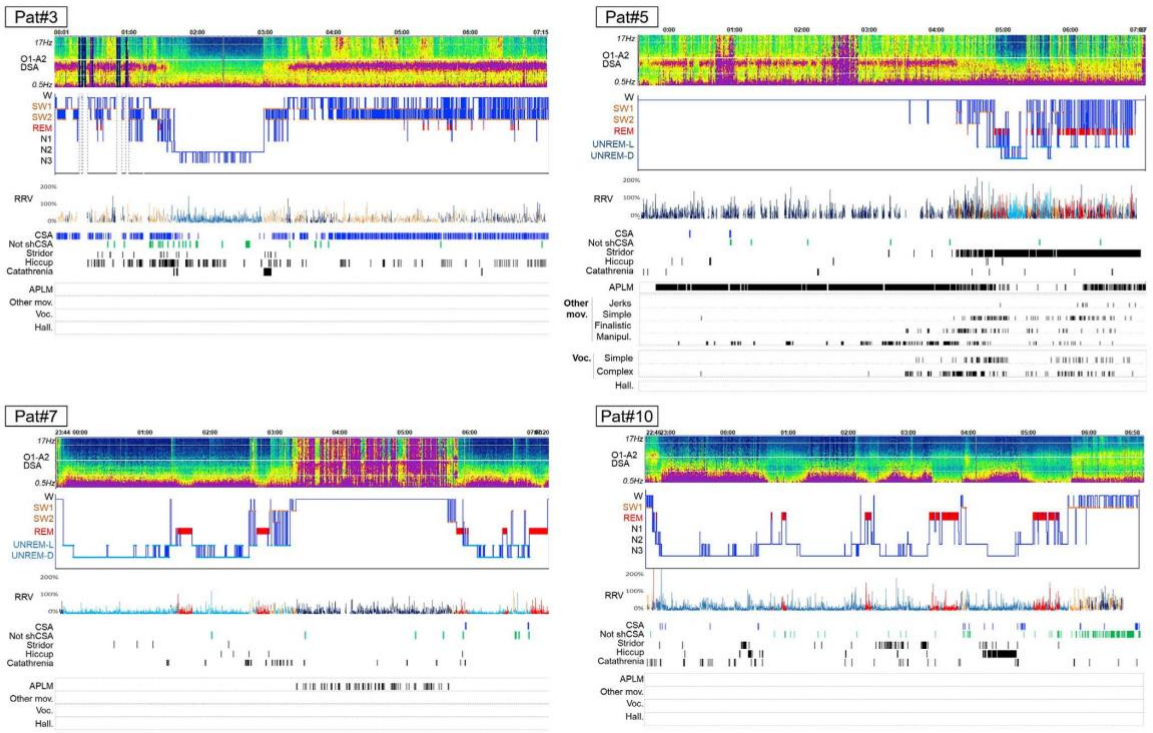


Fig. 13. Different wake/sleep patterns in FFI. Each chart contains in the upper part a spectrogram of the O1-A2 EEG channel, below appears the hypnogram (with the different stages in a descending order from Wake (W), Subwake1 (SW1), Subwake2 (SW2), REM, and finally NREM sleep (from N1 to N3 or from light UNREM (UNREM-L) to deep UNREM (UNREM-D), then follow the respiratory measures, including respiratory rate variability (RRV) in the center (with the vertical axis showing the percentual change of each consecutive breath with respect to the previous one and depicted with the colors of the sleep stage used in the hypnograms, see methods), apneas, events scored as potential short CSA (<10 s) eventually not fulfilling apnea criteria (No CA; see methods), stridor, and cathatrenia; and in the bottom part, the different types of movements. Pat#3 has a consolidated NREM sleep portion in the middle of the night with large portions of SW1 and frequent central apneas without associated movements and recurrent stridor and isolated catathrenia. Pat#5 has a long period of initial wakefulness with very frequent aperiodic and manipulatory movements followed by a final part with undifferentiated NREM and fragmented REM sleep, frequent stridor, finalistic movements, and vocalizations. Pat#10 has an almost normal hypnogram, except for frequent hiccups and stridor and a final part with fluctuating Wake-Subwake associated with increased respiratory rate variability and numerous short central apneas (Figure S4), without abnormal movements. Pat#7 has long portions of undifferentiated NREM sleep, a central long Wake period with aperiodic movements and five REM episodes, only one of them without atonia. She also had catathrenia and occasional stridor and increased respiratory rate variability awake. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.3.4. NREM sleep

All the patients but Pat#9 had NREM sleep periods of variable duration. Conventional NREM sleep stages appeared in only 4 patients (Pats#1, 3, 8 and 10) whereas six patients (Pats#2, 4, 5, 6, 7, and 11) had undifferentiated light and deep NREM sleep (Table 2). In the four patients with conventional NREM sleep, the characteristic waveforms (e.g., sleep spindles or K complexes) were infrequent but could still be recognized. In the patient re-evaluated with vPSG six months later (Pat#1) there was an almost complete disappearance of these waveforms in the second study (Fig. 14) with reduction in NREM sleep time from 158.3 min (35.2% of TRT) to 55.3 min (19.3% of TRT), along with a large increase in Subwake1 (Table 3, Fig. 12). NREM sleep was absent in Pat#9, who was most of the time awake with brief periods of Subwake and REM, and appeared in a few, isolated epochs in Pat#11, whereas all the remaining patients generated periods of consolidated NREM sleep. In two patients (Pats#7 and 10) these periods occupied most of the night. In the rest, consolidated NREM sleep occurred in a single (Pats#1 to 6) or in two (Pat#8) bouts with a median duration of 45.4 (range 10.5–78.0) minutes. The single bout of consolidated NREM sleep occurred in the first half of the night in Pats#1 and 3; in the second half of the night in Pats# 4–6; in the middle of the night in Pat#2 and one bout in each half of the night in Pat#8. NREM sleep, particularly in its consolidated periods, was the quietest period of the night, only disturbed by PLMS in one patient (Pat#3) (see hypnograms in Fig. 13 and Figure S3). There were no differences in benzodiazepine treatment in patients with conventional (Pats#1, 3) and undifferentiated NREM sleep (Pats#5, 6, 7).

Patients tended to spend more time in NREM sleep (though not significantly) when it was conventional than when it was undifferentiated (mean 183.6 min, 38.8% of TRT vs 101.4 min, 26.6% of TRT respectively; $p = 0.18$). Patients with undifferentiated NREM sleep had more Wake time than those with conventional NREM (UNREM 42.0%, range 33–93%; vs 24.9%, range 9–33%; $p = 0.01$).

3.3.5. REM sleep

REM sleep periods of variable length could be identified in all the patients, but in only two had a relatively normal duration (Pats#10 and 7; with 59.5 and 55.3 min respectively and 12.1% of TRT in both, maximal duration of REM episodes of 12.5 and 17 min) (Table 2). In both cases, REM sleep was fragmented with frequent shifts to wake and UNREM (median duration of the REM episodes without change of stage was 2.5 and 1.2 min). In the remaining 9 patients, the episodes of REM sleep were very short (median

Table 2
Wake/sleep stages.

	Pat#10	Pat#8	Pat#3	Pat#1	Pat#7	Pat#5	Pat#6	Pat#4	Pat#11	Pat#2	Pat#9
TRT, *min*	492	478	434	441	456	453	421	447	450	453	178.75
W, *% of TRT*	8.9%	33.2%	27.0%	28.5%	34.6%	79.4%	42.0%	32.7%	93.0%	38.9%	92.3%
SW, *% of TRT*	7.8%	21.5%	47.0%	50.5%	5.2%	5.2%	37.7%	49.1%	2.4%	32.5%	6.5%
SW1	7.8%	15.5%	21.3%	37.9%	4.0%	3.7%	23.6%	36.9%	1.3%	16.1%	3.8%
SW2	0.0%	6.0%	25.7%	12.6%	1.2%	1.5%	14.1%	12.2%	1.1%	16.4%	2.7%
Stable W, *% of TRT*	0.9%	7.0%	7.4%	2.3%	32.3%	64.6%	17.3%	0.0%	68.9%	23.9%	69.0%
Fluctuating W-SW, *% of TRT*	14.3%	42.1%	63.8%	73.6%	6.0%	14.1%	56.4%	68.3%	8.7%	39.5%	24.9%
Fluctuating W-REM, *% of TRT*	–	0.1%	1.1%	1.1%	–	10.7%	4.2%	–	10.7%	–	4.2%
NREM, *% of TRT*	71.2%	42.9%	21.6%	19.3%	48.2%	8.2%	14.8%	15.2%	7.1%	26.6%	0.0%
N1	2.1%	4.3%	3.1%	3.3%	–	–	–	–	–	–	–
N2	26.2%	21.5%	15.2%	6.8%	–	–	–	–	–	–	–
N3	42.9%	17.1%	3.3%	9.2%	–	–	–	–	–	–	–
UNREM-L	–	–	–	–	17.3%	4.7%	6.1%	7.8%	7.0%	17.0%	–
UNREM-D	–	–	–	–	30.9%	3.5%	8.7%	7.4%	0.1%	9.6%	–
Consolidated NREM bouts, *% of TRT*	14.7%	9.5%	18.0%	13.9%	9.2%	2.3%	13.5%	6.9%	0.0%	11.9%	0.0%
Number of NREM bouts	4	2	1	1	4	1	1	1	0	1	0
REM, *% of TRT*	12.1%	2.4%	1.3%	0.9%	12.1%	7.2%	5.5%	3.1%	3.9%	2.0%	0.7%
Consecutive REM epochs, *median (max)*	10 (50)	5 (11)	1 (3)	2 (5)	5.5 (68)	2 (6)	1 (5)	1.5 (5)	1 (3)	2 (4)	3 (3)
RWA, *% of REM epochs*	4.6%	2.2%	94.4%	81.3%	16.7%*	98.5%	78.5%	85.7%	98.6%	16.7%	100%
Sleep efficiencies, *% of TRT*											
Sleep time without SW	83.3%	45.3%	26.1%	21.0%	60.3%	15.4%	20.2%	18.3%	4.7%	28.6%	1.3%
Sleep time + SW2	83.3%	51.3%	51.8%	33.6%	61.4%	16.9%	34.2%	30.5%	5.7%	45.0%	3.9%
Sleep time + SW1+SW2	91.1%	66.8%	73.0%	71.5%	65.4%	20.6%	58.0%	67.3%	7.0%	61.1%	7.7%
Movement index, *n/h of recording*	0.5	0	2.6	0	14.5	184.2	123.0	0.3	177.3	1.2	106.7

Results are percentages per total recording time of the different wake/sleep stages. Patients are ordered in two groups: on the left those with conventional NREM sleep stages present (Pats# 10,8,3,1) and on the right those without conventional NREM sleep (Pats# 7, 8, 6, 4, 11, 2, 9). Within groups, patients are ordered by the percentage of REM sleep in decreasing order. Sleep efficiencies are presented in three different forms, first considering sleep time only (conventional or undifferentiated NREM + REM, excluding all Subwake time), then considering Subwake time also as sleep time and finally, considering all Subwake time as sleep time. *For Pat#7 RWA was 0% in 4/5 REM episodes and 100% in the remaining one. TRT: total recording time; W: Wake; SW: Subwake; UNREM-L: undifferentiated NREM-Light; UNREM-D: undifferentiated NREM-Deep; RWA: REM without atonia.

duration of two 15-sec epochs and a maximum of 2.5 min). In seven patients the percentage of RWA was highly abnormal with values over 80%. Normal EMG atonia in all REM periods occurred only in Pat#10, in pat#8 and in 4 of the 5 REM periods in Pat#7, who had an 18-min REM episode (the third) with high percentage of EMG activity (the percentage of RWA in that episode was 100% vs 0% in the other REM episodes) (Fig. 15). Pat#2 had an intermediate but still normal value (16.7%). (Table 2). All patients with RWA presented limb jerks, sometimes with vocalizations and rarely finalistic behaviors (Video 6, Figs. 6 and 15). The amount of RWA and maximal duration of REM bouts were inversely related ($r = -0.7$; $p = 0.014$). Pat#1 had a decrease in REM sleep with disease progression, from 5.1% of TRT at baseline to 0.9% six months later, along with an increase in RWA, from 5.4% at baseline to 81.3% at follow-up (Table 3, Figs. 14 and 16).

There was a positive correlation of the amount of REM sleep with the amount of NREM sleep (whether conventional or undifferentiated; $r = 0.7$, $p = 0.021$), the amount of deep NREM sleep (N3 or UN Deep $-r = 0.81$, $p = 0.002-$), and the number of bouts of consolidated NREM sleep ($r = 0.81$, $p = 0.002$ respectively).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.sleep.2022.08.027

3.4. Sleep efficiency (Table 2)

We calculated sleep efficiencies in three different forms. First counting as sleep time only conventional and undifferentiated NREM sleep and REM sleep time. Second, considering also Subwake2 –but not Subwake1– as sleep time and finally including all Subwake time (Subwake1 + Subwake2) as sleep time. Using the first form, only three patients (Pat#8, 7 and 10) had values close or over 50% (45, 60 and 83% respectively), whereas 8 had sleep efficiencies severely decreased, ranging from 1.4 to 26%. Including Subwake2 as sleep time increased sleep efficiency to values around 50% in two additional patients (Pat#3 and 2) and in 3 more (Pats#1, 4, and 6) if Subwake1 was also considered as sleep time (a total of 8). Follow-up studies in Pat#1, showed that Subwake time increased from 10.1 to 50.5% with disease progression, mostly explained by the increase in Subwake1 time with no change in Subwake2, whereas both Wake time and sleep time (NREM and REM) decreased (Table 3).

3.5. Movements and vocalizations

3.5.1. Movements

The pattern of movements was not uniform among the 11 patients. Four patients (Pats#5, 6, 9 11) had a large number of movements with a median of 51.2% (range 44.5–76.8%) of the epochs containing abnormal movements with 106–184 movements per hour of recording. One patient (Pat#7) had a moderate number of movements (present in 6% of the epochs, 14/h of recording) and the remaining six patients (Pats# 1–4, 8, and 10) had very few or absent movements (median 1% of the epochs, 0.2/h of recording) (Table 4).

Aperiodic limb movements: The most common type of movement in the 5 patients with increased movements was the aperiodic limb movement type (APL), which represented a median of 90.0% (range 64.8–91.0%) of all the movements present in these patients and occupied between 5.5 and 69.1% of the 15-s epochs. APL occurred mostly during Wake (50.8%–96.6% of 15-s epochs) but could persist in a minority in Subwake (0–4.8%), except for Pat#6 (with sFI) who had 47% of this type of movements in Subwake1. Considering only the epochs with any movement, APL movements were the only abnormal movement in 59.5–91.8% (median 69.7%) of the epochs and occurred combined with other types of movements in 0–31.4% (median 11%) of the epochs, whereas the other type of movements occurred alone in 8–11.2% of the epochs.

Table 3
Evolution of vPSG findings in Pat#1, with two recordings performed 6 months apart.

Pat#1	Wake/sleep stages	Sleep efficiency	REM sleep		NREM sleep	Central apneas				Mean RRV, %	
	W-SW1&2-NREM-REM, % of TRT	SW in-SW out, %	Longest REM bout, min	RWA, % of REM	NREM bouts, n	Total number	Time in CSA, min (% of TRT)	Breaths between apneas, median n	CAHI inNonW-WSW-NREM-R, n/h	CT90	Global	W-WSW-NREM
Baseline	50-10-35-5	51–40	31	5%	3	65	14.1 (3.1%)	19	11-17-0-16	2.3%	17.00%	12-23-12
+6 months	29-**51**-**19**-1	72–21	5	81%	1	572	147.6 (33.5%)	3	80-97-2-NA	32.4%	23.20%	31-29-13

There was a notable change in wake/sleep stages, with a large increase in Subwake time (from 10 to 51% of the TRT), resulting mainly from stable Wake (21% reduction) and NREM sleep (occupying 16% less time of the TRT and occurring in one single bout −3 in the first study−). REM sleep, which was already reduced in the first study (5% of recording time), was almost absent in the second study (1% of the time), more fragmented (longest bout of only 5 min), and with a remarkable increase of the percentage of RWA. There was a nine-fold increase of the number of CSA and a eleven-fold decrease of the CT90, with a 5-point increase in the mean RRV, which remained stable only in NREM sleep; W: Wake; SW1&2: Subwake1 + Subwake2; TRT: total recording time; RWA: REM without atonia; CSA: central sleep apnea; CAHI: central apnea hypopnea index; WSW: fluctuating Wake-Subwake, CT90: percentage of the recording time below 90% of oxyhemoglobin saturation; RRV: respiratory rate variability; NA: not applicable.

We identified another four types of movements (see description in methods) that occurred either isolated or in combination with APL movements: manipulative, which were the most frequent, followed by quasi-purposeful/finalistic, jerks, and simple movements (Table 4).

Manipulative movements: These movements appeared in more than 200 epochs in 4 patients (Pats#5, 6, 9, and 11), representing 16.8–38.3% of the movement-containing epochs. Manipulative movements occurred mostly awake, and less often persisted in Subwake1. There were almost no APL or manipulative movements during REM sleep. When the patient had manipulative movements, they had the eyes open most of the time, touched, picked, moved, sucked, or bit the electrodes, sensors, sheets or other elements, in isolated or more often series of consecutive movements lasting sometimes several epochs. The movements looked like those performed by an awake subject normally touching these objects, but with no apparent purpose.

Finalistic/pseudopurposeful movements: Finalistic movements appeared mainly in three patients (Pats#5, 6 and 11) in 75, 41 and 26 epochs respectively, and represented a minority (2–5%) of the movement-containing epochs in these patients. Pat#3 had 11 epochs with these types of movements out of a total of 19 (1%) movement-containing epochs. The remaining seven patients had no finalistic movements. The movements occurred with the patient lying in bed and were distributed throughout three stages: in wake, during REM sleep and less often in Subwake (Table 4). When occurring during Wake, we considered that the patients were probably experiencing hallucinations since they had the eyes open, looking around with apparent interest or pointing or trying to grab an imaginary object. Finalistic movements also appeared during REM sleep, with the eyes closed, although jerks and simple movements, either isolated or repeated, were recorded more often in this stage (Table 4). The duration of the episodes of finalistic movements was not long and rarely consisted of more than 3 uninterrupted epochs (45 s).

Jerks and simple movements: These less elaborated movements occurred frequently in three patients (Pats#5, 6, 11) where they appeared in 2.6–5.9% of the epochs, and less often in the other eight patients. Jerks occurred mainly in REM sleep (39.5–91.2% of the times) whereas simple movements were more evenly distributed.

Finally, PLMS were recorded only in Pat#3 during consolidated NREM sleep (PLM index 67.2), and Pat#7 had PLMW (index 109.6), intermixed with aperiodic limb movements during a long bout of wakefulness in the middle of the night.

3.5.1.1. ***Vocalizations*** *(Table 5).* Frequent vocalizations occurred only in 4 patients (Pats#5, 6, 9, and 11) whereas the other 7 patients had none (Pat#1–4, and 8) or only occasional vocalizations (Pats#7 and 10, with only 3 and 5 episodes during the recording, respectively, less than 0.3% of the epochs), so this description refers only to the former four. These patients also had the largest number of aperiodic movements during the recording.

Vocalizations were recorded 33 to 221 times, in 2.5–12.2% of the epochs, 6 to 29 times per hour of recording. In Pats#5, 6, and 11 most of vocalizations were complex, whereas patient 9 had a larger proportion of simple vocalizations. There were almost no vocalizations (either complex or simple) occurring in NREM sleep. Complex vocalizations appeared more often in Wake than in REM sleep, whereas simple vocalizations predominated in REM sleep. However, the stage with the highest percentage of epochs containing vocalizations was REM sleep (11–33% of the REM epochs).

3.6. Hallucinations/Hallucinatory behavior

Five (of the 11) patients had hallucinations/hallucinatory

behaviors, that appeared in more than 20 epochs in Pats#2, 5 and 11 (21–62; 1–3.5% of the epochs) and in only 6 epochs in Pats#6 and 9. Hallucinations were absent in the remaining six patients. By definition, hallucinations occurred during Wake epochs and mostly associated with movements (65–100% of the times), especially pseudopurposeful/finalistic movements, and rarely without limb movements and never with jerks (Table 4).

3.7. Sexsomnia

The patient (Pat#6) with sFI presented during fluctuating Wake-Subwake a behavior resembling sexual activity, with rhythmic pelvic contractions when lying in the prone position (Video 5) in short episodes, lasting 1–3 epochs in a row, that were repeated several times within variable intervals and were associated with rhythmic movement artifact in the vPSG recording.

3.8. Analysis of respiration

All patients presented impairment of breathing during vPSG consisting of different combinations of central sleep apnea, increased RRV and a series of inspiratory or expiratory breathing-related noises.

3.8.1. Central sleep apnea

Four patients (Pats#1–4) had frequent central sleep apneas (CSA) that occurred especially in subwakefulness and fluctuating Wake-Subwake and typically decreased in frequency in NREM sleep. These patients had a median of 512.5 apneas (range 276–596), with a median CAHI of 82.6 for non-Wake time, 80.2 for fluctuating Wake-Subwake time, and 8.3 for stable NREM time (either N2, N3, or undifferentiated NREM). Total time in apnea represented a median of 32.2% (range 16.2–43.2%) of TRT (median 141.0 min, range 73.5–193.2 min) (Table 6). CSA significantly decreased in frequency during stable NREM sleep in Pats#1–3 (Fig. 13, Figure S3) but persisted unmodified in Pat#4 even in this stage. Stable REM sleep was not recorded in any patient with frequent CSA. Pats#1, 3, and 4 had a cluster-breath respiratory pattern, with clusters of median 3 breaths in between apneas, while Pat#2 had a Cheyne-Stokes breathing pattern (without any known cardiopathy) (Fig. 17).

Pat#10 had a CAHI (for total non-Wake time) below 5, but the breathing irregularities and central apneas took place in a fluctuating Wake-Subwake period occurring in the last hour of recording. At the beginning of this period, longer breath-to-breath intervals (like short CSAs) appeared first every few regular breaths, and progressively increased in number and duration until CSA of standard-duration appeared in the very end of the recording. All in all, a total of 90 short CSAs were scored in this 60-min period (77% of the recording), with a cluster of 10 standard-duration CSA in the last 4 min of the study (Figure S4). These breathing alterations appeared also in a shorter period of fluctuating Wake-Subwake at the beginning of the night. In Pat#9 almost no sleep was recorded, but similar to Pat#10, the few CSA (n = 13) and shorter potential CSA (n = 20) events recorded appeared during fluctuating Wake-Subwake periods (Figure S3). The remaining patients had a few

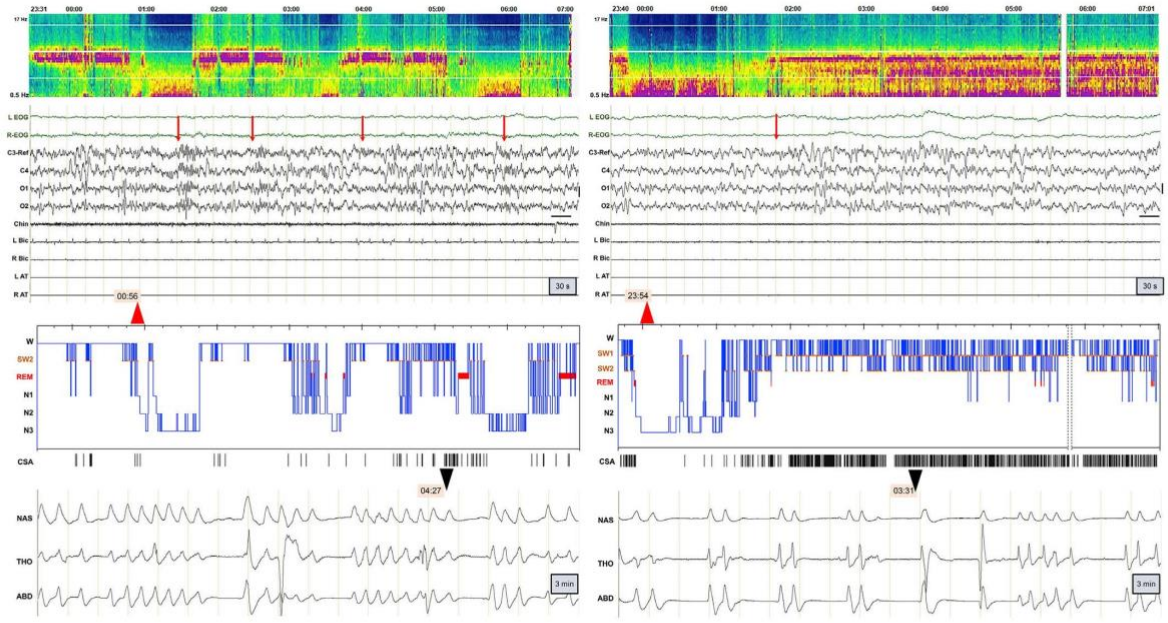


Fig. 14. Evolution of PSG changes with disease progression in Pat#1. PSG findings corresponding to the sleep studies performed in February (left half-side) and August 2006 (right half-side) respectively. The spectrogram of the C3-A2 channel and the corresponding hypnogram (with CSA events marked below) of the first PSG study are shown in the upper and center part of the left half-side, respectively. In between them a 30-s caption during stage N2 in the first part of the night (the time signaled by the red arrowhead) shows several bursts of clearly identifiable sleep spindles of standard amplitude (red arrows). In the lower part a 3-min caption of respiratory channels (taken at the time marked by the black arrowhead) shows irregular breathing with occasional CSA and short CSA. In the follow-up study (right half-side), recorded 6 months later with similar EEG montage and amplitude display, there is a meaningful decrease in the number and amplitude of sleep spindles (red arrow), with reduction in NREM and REM sleep time, and appearance in the spectrogram of a theta band in parallel with the alpha band during most of the night corresponding to Subwake1 and 2. The respiratory channels show almost continuous and longer duration CSA. See the increase in CSA events as well. Montages as in previous figures, respiratory signals shown separated in the bottom part. **Calibration bars**: Vertical bar on the right: 70 μV; horizontal bar: 1 s. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

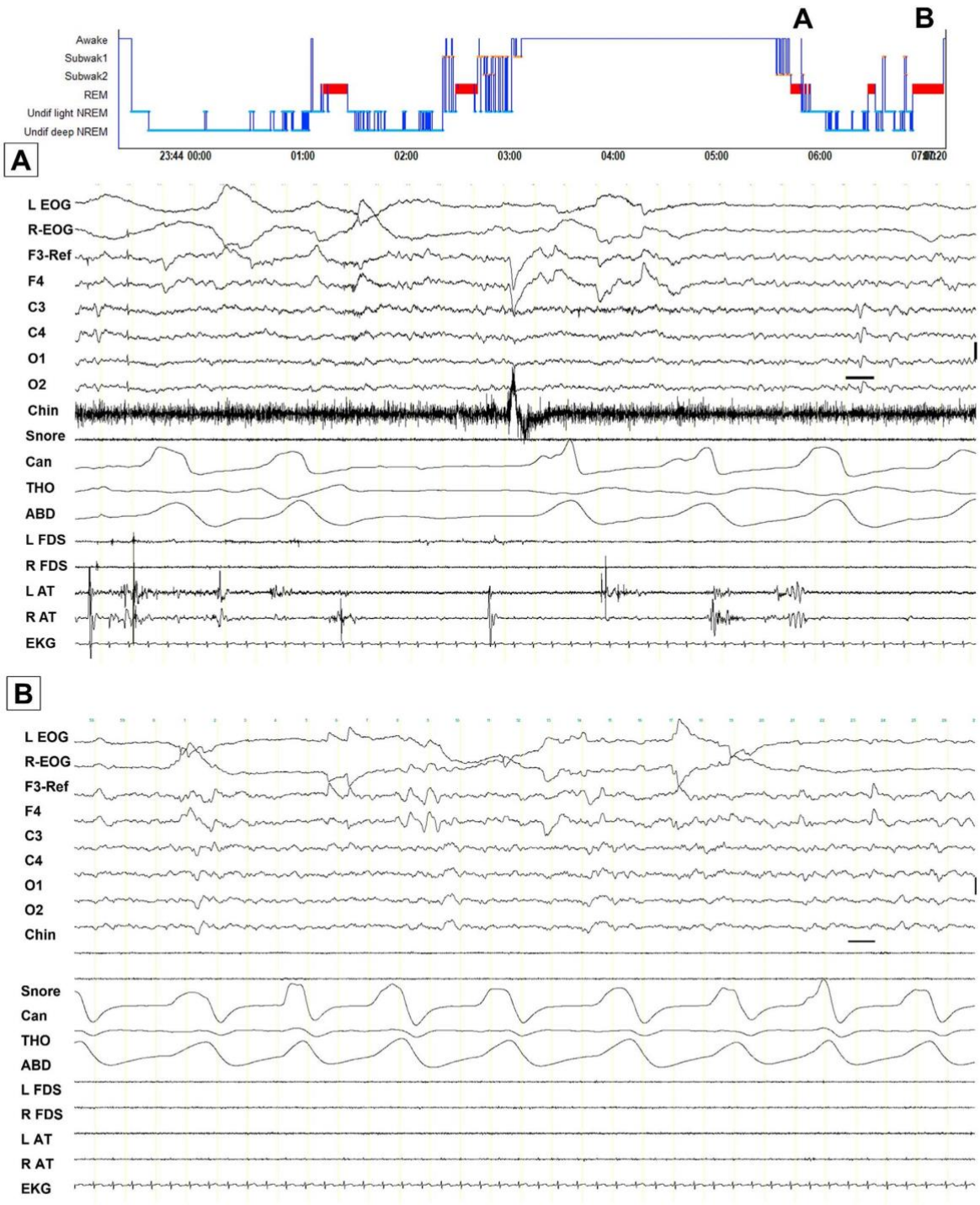


Fig. 15. Selective impairment of EMG atonia in a single REM sleep period in Pat#7. In A, a sample of the third REM episode of the night (see the hypnogram signaling with A the time of the figure caption) characterized by low amplitude mixed frequency EEG and rapid eye movements but with a persistent tonic EMG activity in the chin and intermittent phasic bursts in the tibialis anterior muscles associated with jerks of mild intensity. A 6-sec episode of central apnea is seen in the center of the screen. In B, a sample of the 5th REM episode (see the hypnogram marking with B the corresponding time of the night), shows a completely normal EMG atonia, like in the 1st, 2nd, and 4th REM episodes (not shown). There is a low amplitude mixed frequency EEG with rapid eye movements. Montages as in previous figures, except that the patient did not tolerate a thermistor. Calibration bars: vertical: 70 μV; horizontal: 1 second

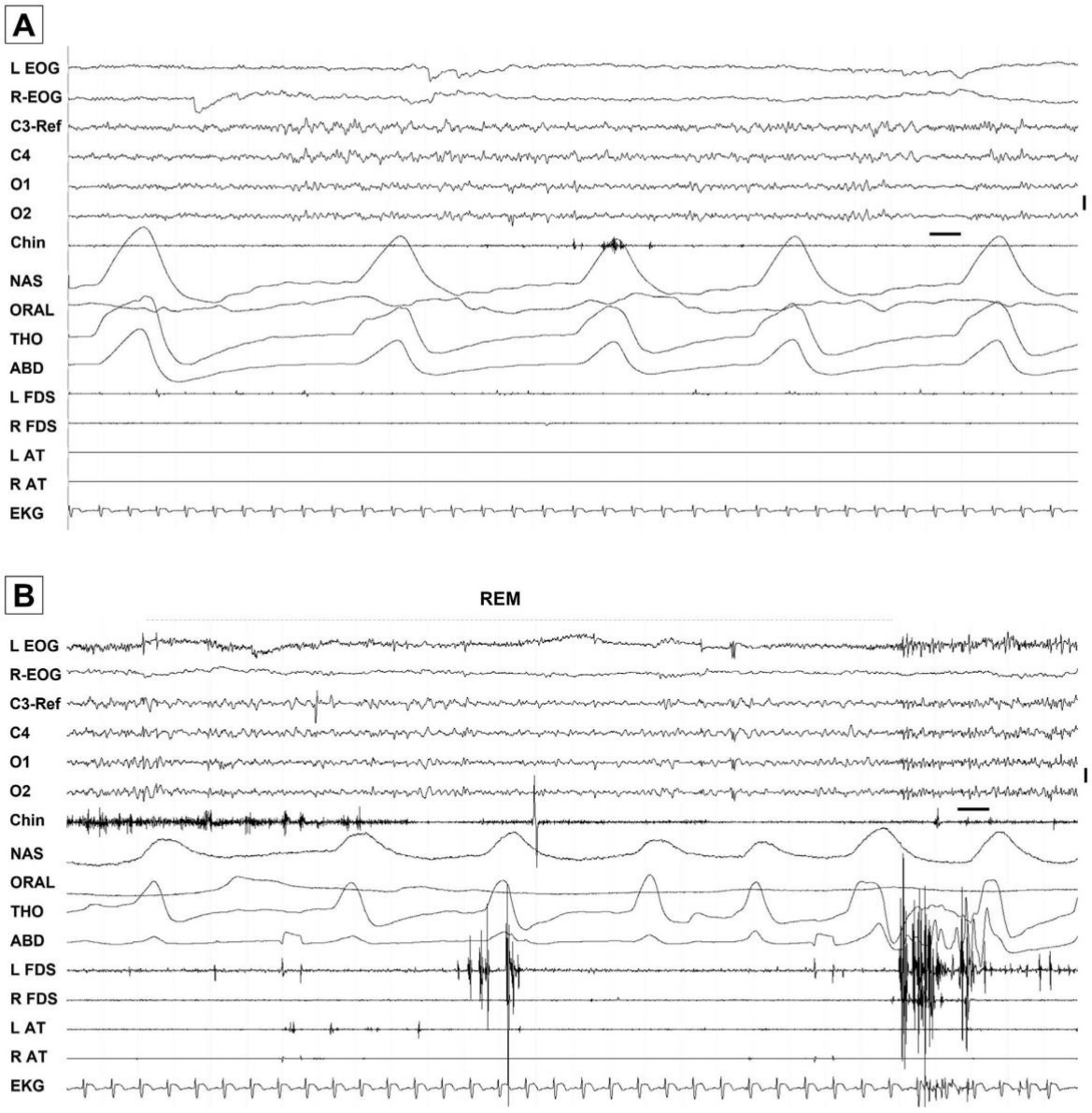


Fig. 16. Evolution of REM sleep atonia with disease progression in Pat#1. PSG findings corresponding to the sleep studies performed in February (panel A) and August 2006 (panel B) respectively. In A the patient had normal REM sleep periods, with normal EMG atonia as is shown here. Six months later (B) with progression of the disease, REM sleep occurred in short bouts without complete chin and limb EMG atonia. Montages as in previous figures except that the F3–F4 electrodes were not used. Calibration: vertical line: 100 μV, horizontal line: 1 second

isolated CSA events (typically following an arousal) or no CSA at all (Table 6, Fig. 13, Figure S3).

Pat#1 had two vPSG recordings 6 months apart. In this time lapse, the CAHI increased from 11.3 to 80.1 and the total number of CSA from 64 to 569, while the median number of breaths between apneas decreased from 19 to 3 (Table 3, Fig. 14).

Five patients (Pats#2, 7–9, 11) had occasional large inspiratory excursions followed by a longer-than-normal expiration. Four patients (Pats#3, 7–9) had occasional dysrhythmic breaths coming earlier than expected or arising out of place in between two otherwise normal breaths, that then continued at their normal pace, with or without associated hiccup (see below) (Figure S5).

Median oxyhemoglobin saturation (SaHbO2) was 94% (range 89.0–97.0), with a median CT90 of 3.7% (range 0.1–46.5%). The number of desaturation events with a drop of 3% or more (ODI3%), was significantly higher in patients with frequent CSA than those without CSA (median 52.0 vs 21.1, $p = 0.006$), but neither the mean

Table 4
Types and frequency of abnormal movements during vPSG.

	Pat#5	Pat#11	Pat#6	Pat#9	Pat#7	Pat#3	Pat#2	Pat#10	Pat#4	Pat#1	Pat#8
Epochs with any type of movements, *n (%)*	1391 (77%)	1330 (74%)	863 (51%)	580 (45%)	110 (6%)	19 (1%)	9 (0.5%)	4 (0.2%)	2 (0.1%)	0	0
Movement index, *n/h of recording**	184.2	177.3	123.0	106.7	14.5	2.6	1.2	0.5	0.3	0.0	0.0
% of epochs in W-SW-NREM-REM with any mov.	86-50-15-68	75-76-31-65	58-63-2-43	40-46-na-11	16-2-0-3	2-1-0-17	1-0-0-0	0	0	–	–
Epochs with ApLM, *n (% of total epochs)*	1252 (69%)	1181 (66%)	779 (46%)	376 (29%)/ 168(24%)	101 (6%)	0	0	0	0	0	0
ApLM in: W-SW-NREM-REM , *n*	1182-35-17-18	1141-26-2-12	396-366-6-11	159-8-0-1	101-0-0-0	–	–	–	–	–	–
% per stage	95-3-1-1	96-2-1-1	51-47-1-1	95-5-0-0	100-0-0-0	–	–	–	–	–	–
Epochs with only ApLM, *n (% of any mov.)*	968 (67%)	1035 (78%)	524 (61%)	345 (60%)	101 (92%)	–	–	–	–	–	–
Epochs with both ApLM and other, *n (% of any mov)*	284 (21%)	146 (11%)	255 (30%)	32 (6%)	0 (0%)	–	–	–	–	–	–
Epochs with only other mov*, *n (% of any mov)*	138 (10%)	149 (11%)	179 (19%)	203 (35%)	9 (8%)	–	–	–	–	–	–
Epochs with other mov*, *n (% of all epochs)*	422 (23%)	295 (16%)	434 (26%)	235 (18%)	9 (0.5%)	19 (1%)	9 (0.5%)	4 (0.2%)	2 (0.1%)	0	0
Type: J -S-F-M , *n*	11-96-75-240	34-12-26-223	39-54-33-308	2-1-10-222	7-1-0-1	7-1-11-0	1-0-0-8	1-2-1-0	0-0-0-2	–	–
*, % of epochs with other mov**	2-23-18-57	11-4-9-76	9-12-8-71	1-1-4-94	78-11-0-11	37-5-58-0	11-0-0-89	25-50-25-0	0-0-0-100	–	–
Jerks in: W-SW-NREM-REM , *n*	1-0-1-9	1-0-2-31	6-18-3-16	0	0-2-0-5	0-4-0-3	0-1-0-0	0-0-0-1	0	0	0
, % per stage	9-0-9-82	3-0-6-91	14-42-7-37	–	0-29-0-71	0-57-0-43	0-100-0-0	0-0-0-100	–	–	–
Simple in: W-SW-NREM-REM , *n*	28-10-6-52	8-1-0-3	12-38-0-11	0	0-0-0-1	0-1-0-0	0	0-0-1-1	0	0	0
, % per stage	29-10-6-54	67-8-0-25	20-62-0-18	–	0-0-0-100	0-100-0-0	–	0-0-50-50	–	–	–
Finalistic in: W-SW-NREM-REM , *n*	35-15-1-24	17-1-0-8	3-27-3-8	0	0	11-0-0-0	0	0-0-1-0	0	0	0
, % per stage	47-20-1-32	65-4-0-31	7-66-7-20	–	–	100-0-0-0	–	0-0-100-0	–	–	–
Manipulative in: W-SW-NREM-REM , *n*	229-7-1-3	216-5-1-1	183-116-4-5	126-13-0-0-	1-0-0-0	0	8-0-0-0	0	1-1-0-0	0	0
, % per stage	95-3-1-1	97-2-1-1	59-38-1-1	91-9-0-0	100-0-0-0-	–	100-0-0-0	–	50-50-0-0	–	–
Epochs with hallucinations, *n (%)*	63 (3.5%)	52 (2.9%)	6 (0.4%)	6 (0.5%)	0	0	21 (1.2%)	0	0	0	0
& Any movement, *n (% of hallucinations)*	60 (95.2%)	49 (94.2%)	6 (100%)	4 (66.7%)	–	–	–	–	–	–	–
& ApLM-J-S-F-M, *n*	45-0-13-30-13	29-0-3-16-25	2-0-1-3-1	0-0-0-0-4	0	0	0	0	0	0	0
& None-OnlyApLM-onlyOther-Both, *n*	3-4-15-41	3-5-20-24	0-1-1-4	2-0-4-0	0	0	21-0-0-0	0	0	0	0

Patients are divided in two groups (on the left those with frequent movements, on the right those with scarce movement), and ordered from highest to lowest total movements. Hallucinations and movements associated with them are also presented. Note that Pat#9 had only 179 min of vPSG signal, but 120.5 more minutes of video, so that movements scored with only video could not be attributed to any stage (undetermined), thus the total number of movements exceeds the sum of movements in each stage. W: Wake; SW: Subwake; mov: movements; ApLM: aperiodic limb movements; J: jerks; S: simple movements; F: finalistic movements; M: manipulative movements. *Other movements are jerks, simple, finalistic, and manipulatory; *Note: periodic leg movements not included here.*

Table 5
Number and type of vocalizations per patient.

	Pat#5	Pat#6	Pat#11	Pat#9	Pat#10	Pat#7	Pat#8	Pat#1	Pat#2	Pat#3	Pat#4
Epochs containing vocalizations, *n (%)*	221 (12.2%)	108 (6.4%)	46 (2.6%)	33 (2.5%)	5 (0.3%)	3 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Simple vocalizations, *n (% of voc)*	74 (33.5%)	50 (46.3%)	18 (39.1%)	25 (75.8%)	4 (80%)	1 (33.3%)	–	–	–	–	–
Complex vocalizations, *n (% of voc)*	147 (66.5%)	58 (53.7%)	28 (60.9%)	8 (24.2%)	1 (20%)	2 (66.7%)	–	–	–	–	–
Vocalization index, *n/h of TRT*	29.3	15.4	6.1	6.1	0.6	0.4	0.0	0.0	0.0	0	0
Simple voc in: W-SW-NREM-REM , *n*	29-8-3-34	11-27-1-11	7-1-0-10	15-2-0-0	0-0-2-2	1-0-0-0	–	–	–	–	–
, % per stage	39-11-4-46	22-54-2-22	39-6-0-55	88-12-0-0	0-0-50-50	100-0-0-0	–	–	–	–	–
Complex voc in: W-SW-NREM-REM , *n*	84-16-3-44	17-18-2-11	17-2-1-8	2-1-0-1	0-1-0-0	0-0-1-1	–	–	–	–	–
, % per stage	57-11-2-30	29-49-3-19	60-7-4-29	50-25-0-25	0-100-0-0	0-0-50-50	–	–	–	–	–
% of W-SW-NREM-REM epochs with simple voc	2-8-2-26	2-4-0.3-12	0.4-2-0-14	2-4-na-11	0-0-0.1-1	0.2-0-0-0.5	–	–	–	–	–
% of W-SW-NREM-REM epochs with complex voc	6-17-2-33	2-4-0.5-12	1-5-8-11	0.3-2-na-11	0-0.7-0-0	0-0-0.1-0.5	–	–	–	–	–

Patients are divided in two groups (on the left those with frequent vocalizations, on the right those with scarce vocalizations). Most occurred in four patients during both wakefulness and REM sleep and in Pat#6 (sFI) also happened in subwake. Two patients had only rare vocalizations and five patients did not have any. Considering the duration of each stage, epochs with vocalizations occupied a higher percentage of REM sleep than of wakefulness. TRT: total recording time; voc: vocalizations; W: wake; SW: subwake.

Table 6
Respiratory findings in vPSG for individual patients.

	Pat#2	Pat#4	Pat#1	Pat#3	Pat#10	Pat#5	Pat#9	Pat#11	Pat#6	Pat#8	Pat#7
CSA Total number	276	596	572	453	27	3	13	0	3	9	2
CSA duration, Me s. (range)	14 (8–38)	18 (8–46)	15 (8–32)	18 (9–36)	11 (9–20)	7 (7–7)	13 (10–18)	–	12 (10–14)	10 (8–13)	10 (9–11)
CAHI (n/h) Non-W	42.8	79.5	80.0	68.1	3.3	0.4	9.4	0.0	0.5	1.2	0.4
Fluctuating W-SW	44.6	68.3	98.2	75.4	6.8	0.0	9.4	0.0	0.8	2.2	2.2
NREM consolidated	8.9	98.8	1.9	9.1	2.7	0.0	–	0.0	0.0	0.0	0.0
Non-central apneas, n (n/h of non-wake)	0 (0)	0 (0)	0 (0)	9 (2)	23 (3)	–	0 (0)	–	1 (0.2)	15 (3)	3 (0.6)
SatHbO2, Nadir, %	89	70	59	87	89	91.0	66	90.0	91	85	92
CT90, %	0.2%	15.7%	32.4%	3.7%	0.1%	0.4%	4.9%	0.0%	6.7%	46.8%	6.7%
ODI 3, %	28.0	66.4	51.0	66.4	5.3	21.2	21.7	21.1	23.0	10.2	4.3
RRV, Mean Global	**27.4%**	**29.6%**	**23.2%**	**20.7%**	**15.4%**	**28.0%**	**20.4%**	**18.0%**	**11.6%**	**11.1%**	**10.6%**
Stable W	26.0%	–	30.6%	17.8%	30.6%	26.0%	20.0%	16.2%	11.4%	10.0%	14.2%
Fluctuating W-SW	28.5%	29.5%	24.4%	21.5%	29.5%	29.7%	20.5%	17.9%	12.5%	12.6%	18.7%
Stable NREM	22.5%	42.4%	12.5%	18.7%	12.9%	28.8%	–	–	7.4%	8.1%	7.8%
Stable REM	–	–	–	–	14.8%	–	–	–	–	–	11.4%
Respiratory Rate, Mean rpm	13.0	14.3	13.0	12.0	14.8	27.2	12.7	24.8	23.8	16.8	14.5
Stridor	–	++	+++	++	++	+++	+	+	–	+	+
Hiccup	–	–	–	+++	+++	+	++	+	–	+	+
Expiratory groaning	–	+++	++	+	++	++	+++	+	++	+	++
Catathrenia (n of episodes*)	–	–	+(3)	++(4^)	+++(>30)	+(9)	+++(>30)	+(4)	+(6)	–	+++(21)
Movement index, n/hour	1.2	0.3	0.0	2.6	0.5	184.2	106.7	177.3	123	0	14.5

Patients are grouped first by the presence (left side) or absence (right side) of CSA and then ordered within each group from highest to lowest mean RRV. Empty cells (–) mean values were not applicable, while 0.0 means the variable was absent (e.g.: CAHI in NREM could not be calculated in Pat#9 as consolidated NREM was not recorded). CAHI in REM not provided due to lack of stable REM in most patients. Severity of respiratory sounds is indicated according to the frequency of appearance as –: absent, +: occasional (<10 episodes), ++: discontinuous (>15 episodes), and +++: frequent (continuous during at least some period of the recording). *For catathrenia, number of episodes is provided, and one episode may include one single event or breath or a few concatenated ones; ^ in Pat#3 is to indicate that it was given category ++ despite only 4 episodes, due to one of the episodes of concatenated catathrenia (intermingled with CSA) lasting up to 5 min. Note that three of the 4 patients with a high movement index had a respiratory rate higher than 20 rpm. CSA: central sleep apnea, Me: Median; CAHI: central apnea-hypopnea index; W: Wake; SW: Subwake; SatHbO2: oxyhemoglobin saturation; CT90: percentage of time below 90% of SatHbO2; RRV: respiratory rate variability; rpm: respirations per minute.

SaHbO2 nor the CT90 were significantly different between the two groups. Of note, in six patients (Pats#4–7, 9 and 11) had non-valid SaHbO2 signal for 41.6–90.1% of the recording time mostly due to the instability of the finger sensor caused by the frequent movements.

3.9. Respiratory rate variability

The respiratory rate in FI patients was median 14.4 breaths per minute (range 12.0–27.2), similar to healthy controls (median 16.0, range 12.2–19.2 breaths per minute; $p = 0.28$). However, RRV was significantly greater in FI patients, with a mean variation of each peak-to-peak interval with respect to the mean interval of the preceding 2 min of median 20.4% (range 10.6–29.6%), and of 27.8% (range 12.1–37.8%) with respect to the immediately preceding interval. Controls showed a variability of 9.6% (mean of the preceding 2 min, $p = 0.001$) and 10.8% (preceding interval; $p = 0.0003$). Using the mean of the preceding 2 min as reference, RRV in FI patients was highest in Subwake (22.9%) followed by Wake (18.9% vs 9.4% in controls; $p = 0.003$), and lowest in NREM sleep (12.9%), although still higher than in controls (7.3%, $p = 0.009$). RRV was similar in patients and controls in REM sleep (13.1% vs 13.7% respectively $p = 0.64$), the sleep stage where healthy controls had highest RRV values (Fig. 18), as expected [36].

Within FI patients, there were no significant differences in RRV between patients with CSA (that remained quiet) and patients without CSA (who had excessive motor activity) ($p = 0.36$), but the group with CSA had a tendency towards higher RRV in all stages (Fig. 18). The three patients with the highest index of movements (Pats#5, 6 and 11) had also the highest RR (mean RR > 20 breaths per minute; Table 6).

Patients with increased RRV (higher than mean + 3SD of RRV in healthy controls) had significantly shorter survival times ($p = 0.01$; Fig. 18). Pat#2 was considered an outlier due to the extremely and atypically long survival time and was therefore excluded from this survival analysis.

3.10. Respiration-related sounds

Ten out of the 11 patients had breathing-related sounds, occurring either during inspiration, expiration or in both phases.

3.10.1. Stridor

Nine patients had inspiratory stridor appearing variably throughout the night. In two, stridor was frequent during at least some period of the recording, in Pat#1 during N3 NREM sleep (the only period of her recording without CSA) and in Pat#5 (Video 7) gradually increasing its frequency from isolated stridulous breaths awake, becoming much more frequent with the first Subwake epochs, and clearly intensifying frequency and loudness during UNREM sleep (especially deep UNREM) and REM sleep). In Pat#4, who had continuous CSA events across the night, stridor was discontinuous, appearing recurrently during the first breath or couple of breaths following the end of a CSA episode (Video 7). In the remaining nine patients, stridor was seen typically at the peak of a larger inspiratory excursion, usually following the end of a central apnea or an arousal or activation. In Pats#3, 9 and 10 it appeared intermittently during parts of the recording (Fig. 13, Figure S3) and had more than 15 episodes of stridor during the night, often combined (in the same inspiration) or intermingled (in preceding or subsequent breaths) with hiccup. The remaining 3 patients with stridor (Pat#7, 8, and 11) had only very occasional, isolated events.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.sleep.2022.08.027

3.10.2. Hiccup

Six patients (Pats#3, 5, 7, 9–11) had hiccup, arising in different moments of the respiratory cycle (Fig. 11, Video 8). Hiccup was well-identifiable by the characteristic short-sharp peak drawn in the nasal pressure cannula with an accompanying hump in the respiratory effort bands, that on some occasions showed a thoracic-abdominal phase inversion as well. Although most frequently

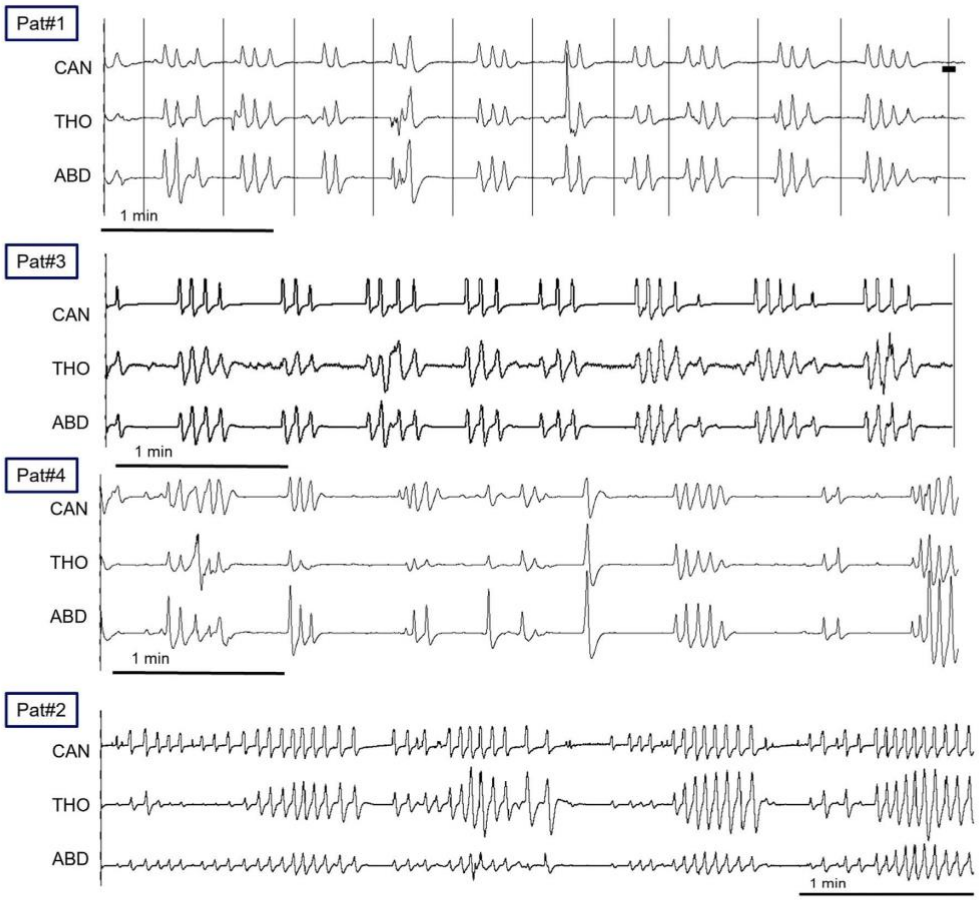


Fig. 17. Central sleep apnea characteristics. The figure shows 5-min segments of respiratory recordings from Pats#1, 3, 4 and 2, showing the aspect of the events in the four patients with CSA, Pats#1, 3, and 4 had a cluster-breath pattern, with bursts of just a few breaths in between consecutive apneas and typically with large, compensatory inspiratory excursions that progressively decreased in amplitude after the first post-apneic breath. Pat#2 had a Cheyne-Stokes breathing, with a periodic pattern of waxing and waning of respiratory effort and airflow interspersed with a central apnea. Can: nasal cannula; Tho and Abd: thoracic and abdominal effort bands. Calibration: horizontal bar: 1 min..

single, hiccup could be double-peaked (especially for those occurring at the proto- or tele-inspiratory part), resulting in a multi-step, multi-noise inspiratory excursion (Fig. 11, Video 8). Hiccup was frequent in Pats#3 and 10, who had periods where it appeared almost in every breath, while it was occasional or absent during the rest of the recording (Table 6, Video 8). In the remaining four patients hiccup appeared as an isolated event: recurrently every few minutes in Pat#9 (without any identifiable pattern; 21 in the whole night) and occasionally in Pats#5, 7, and 11.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.sleep.2022.08.027

3.11. Respiratory-related groaning, moaning and vocalizations

Expiratory groaning (EG) was recorded in 10 patients (absent in Pat#2). Alerting or activation, either spontaneous or stimulus-induced, typically triggered expiratory groaning in one to a few concatenated breaths (Video 9). Some activating stimuli were jerks, external or internal noises (snoring, gasp, stridor), resuming breathing at the end of an apnea, or breaths following or interspersed with cathatrenic events. For example, in Pats#1 and 4, the first 1–3 breaths after a central apnea typically consisted of a stridulous inspiration followed by a groaned expiration of progressively decreasing intensity (Video 7 and 9). In Pats#1, 4, and 10, there were periods (lasting 2–10 min) where expiratory groaning became frequent and independent of activating stimuli, in all three cases within periods of fluctuating Wake-Subwake. Pats#5, 6, 7, and 9 had long Wake periods with motor hyperactivity where expiratory groaning mixed up with almost incessant movements, moaning, prattling, speaking or hallucinations. Expiratory groaning was not recorded during stable periods of NREM or REM sleep in any of the patients (Table 6).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.sleep.2022.08.027

Repetitive expiratory vocalizations were recorded in 5 patients (Pat#4, 5, 6, 9, and 11). These were brief episodes involving 2–4 breaths, where patients emitted unintelligible words or prattled regularly on a few exhalations in a row, fitting it with in the respiratory rhythm. Patients had between 1 and 11 episodes throughout the night, which always appeared in periods of Wake or fluctuating Wake-Subwake, but not stable sleep (often with groaning and non-respiration-related vocalizations) (Video 9).

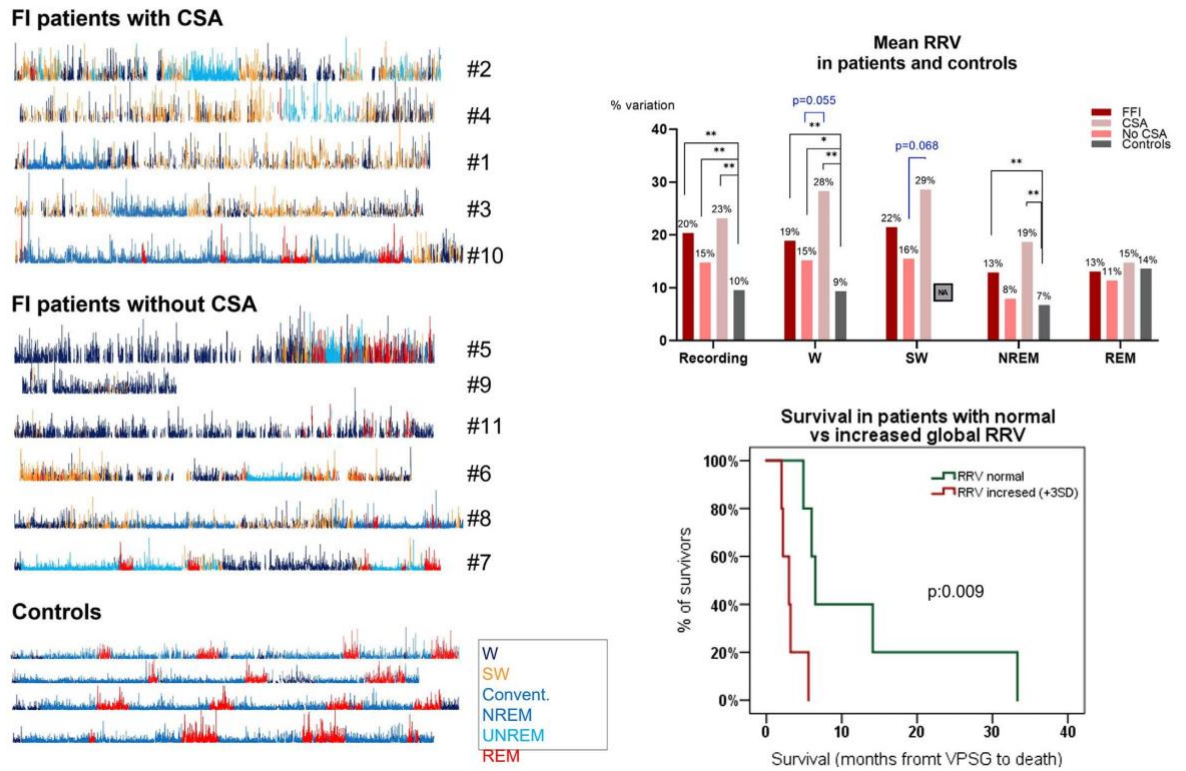


Fig. 18. Respiratory Rate Variability (RRV) in FI patients and control subjects and relation with survival. The left half of the figure shows RRV in each patient measured throughout the whole night, in the upper part for patients with central sleep apnea (CSA), in the middle part for patients without CSA (each group ordered from higher to lower RRV) and in the bottom for normal controls. Since RRV in controls was stable in each of the different sleep stages, only four controls were measured throughout the whole night. In the other five we measured separate segments of wakefulness, NREM and REM sleep, which are not represented graphically here. RRV is depicted with the colors of the sleep stage used in the hypnograms (Fig. 13, Figure S3) and shown here in the middle-bottom square box. Each vertical bar corresponds to a breathing interval throughout the night and its height represents the relative difference (in absolute percentage values) with respect to the mean interval duration of the previous 2 min; higher bars mean higher variability. Note that apneas and periods with artifacts were excluded as valid intervals for RRV analysis (blank spaces across the time bar/horizontal axis). On the upper right, a comparison between RRV in the different stages between patients and controls also grouped by the presence of CSA. There is a significantly higher RRV in patients than in controls in all the different stages except in REM sleep, which is already higher in controls. Below, a Kaplan-Meyer representation of survival according to the degree of RRV, where patients with increased RRV had shorter survival time. Pat#2 was considered an outlier and excluded from survival analysis due to the extremely long survival. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.12. Catathrenia

Catathrenia was found in 8 patients (Pats#1, 3, 5–7, 9–11) and similarly to expiratory groaning, tended to occur following an alerting change (Fig. 12C, Video 10). Pats#7, 9 and 10 had more than 20 episodes of catathrenia. Three patients had catathrenia during stable Wake (Pat#5, 8, and 9), and only one event was scored in REM (in Pat#10) (Fig. 13, Figure S3). The groaning could appear at the beginning of the expiration, during the signal flattening part, or at the final air-release, producing an identifiable irregularity or a downward peak of the respiratory signals whenever it appeared (Fig. 12, Video 10), and could be continuous or fragmented. Occasionally catathrenic events had the typical flattening of all respiratory signals with the final downgoing deflection but had no associated groaning sound (Fig. 12, Video 10). Catathrenic episodes could involve one single respiratory cycle or be a sequence of concatenated catathrenic breaths (Fig. 12B and C), lasting up to 5 min in one patient (Pat#3; after arousal from stable NREM). In two patients (Pat#7 and 10) arousal-induced catathrenia characteristically associated with marked bradypnea afterwards, lasting up to 2 min, with progressive return to baseline respiratory rate (Fig. 12C).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.sleep.2022.08.027

Combinations of respiratory findings (Table 7). One patient (Pat#3) had all six types of breathing impairments described above (increased RRV, CSA, stridor, hiccup, expiratory groaning/rhythmic expiratory vocalizations, and catathrenia), four patients had five (Pats#5, 9, and 11 all but CSA; Pat#9 all but increased RRV), and another three had four types of impairments (Pats#1 and 4 lacked hiccup and catathrenia, and Pat#7 did not have CSA nor increased RRV). The remaining three patients (Pat#2, 6 and 8) had two types of impairments each, in different combinations.

Two patients (Pat#2 and 10) with long survival time used a nasal CPAP device at 9 and 8 cm of H2O, respectively, starting several months after vPSG evaluation at our center, and prescribed by their local physicians. No titration or follow-up PSG studies were performed. In Pat#2, still alive, with severe CSA, intermittent CPAP was used in combination with oxygen to treat episodes of suspected nocturnal desaturations. In Pat#10, with loud inspiratory noises, the CPAP seemed to effectively reduce them, but the treatment was withdrawn apparently because of morning bradypsychia.

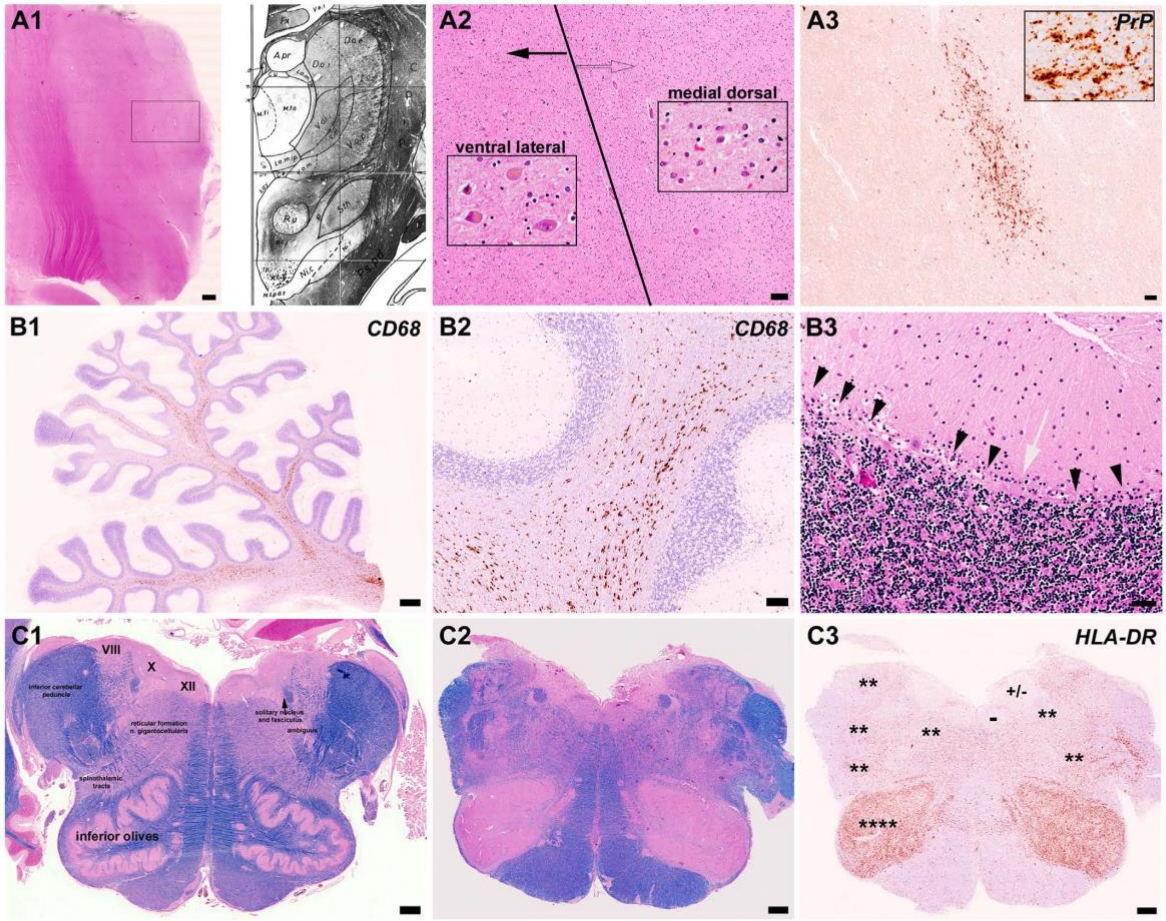


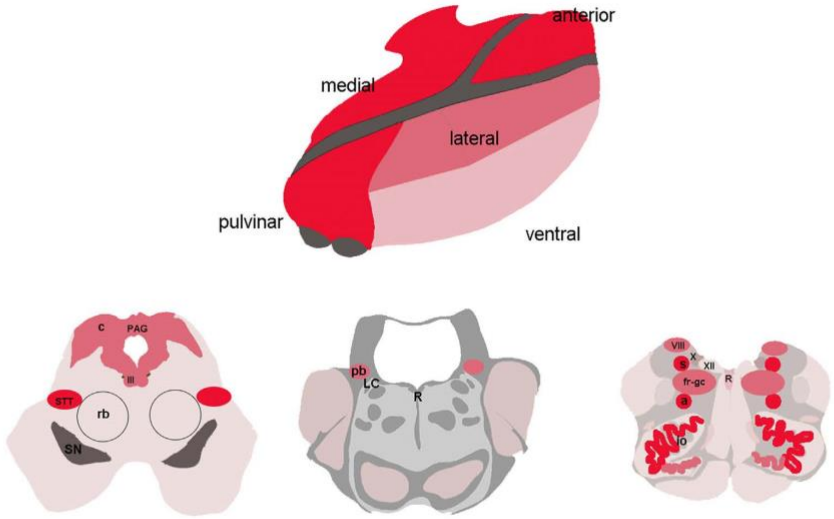
Fig. 19. Classical neuropathological features of FFI. **A1-A2**: Hematoxilin-Eosin (HE) stained coronal sections of the thalamus show prominent neuronal loss and gliosis in different thalamic subnuclei, particularly of the medial regions (A2). **A3**: Immunohistochemistry for PrP reveals usually only focal or even absent pathological PrP^{sc} deposits (inset higher magnification). **B1–B3**: In the cerebellum there is frequently a diffuse loss of Purkinje cells with secondary axonal degeneration in the white matter with increased macrophagic activity (B1, B2; immunohistochemistry for the macrophagic marker anti-CD68). In B3 an HE stained section shows axonal swellings of the degenerating Purkinje cells (torpedoes) visible in the Purkinje cell layer or within the molecular layer (white arrow). Arrowheads point to missing Purkinje cells. **C1–C3**: The medulla oblongata is prominently affected in FFI. C1 is a luxol-fast-blue/nuclear red stained section of a normal brain for comparison. C2 (LFB/NR) stained section) and C3 (immunohistochemistry for the microglial marker HLA-DR) reveals prominent neuronal loss and microglial activation of the respiratory nuclei, the formatio reticularis and particularly of the inferior olives. Scale bars: A1, B1, C1, C2, C3: 1 mm; A2, B2: 100 um; A3, B3: 50 um. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.13. ***Neuropathological assessment*** *(Figs. 19 and 20)*

All cases showed neuropathological features consistent with those described in FFI and sFI (MM2T). There was severe neuronal loss and gliosis in several thalamic subnuclei, particularly affecting the dorsal/posterior segments. The hypothalamic nuclei were comparatively less affected, particularly the supraoptic, paraventricular, and mamillary bodies. Moreover, a prominent degeneration of the inferior olives with a gradient of pathology from dorsal (more involved) to ventral aspects (involved in later disease stages) was observed as well as a variable affection of the cerebellar cortex with segmental Purkinje cell loss, frequent torpedoes within the granule cell layer and gliosis of the molecular layer. The dentate nucleus showed variable gliosis, mainly in its medial parts.

In the brainstem, there was relatively marked neuronal loss and gliosis in the nucleus ambiguus, the solitary nucleus and frequently also at the level of the spinal trigeminal nuclei. Medullary raphe neurons were variably reduced. The vestibular nuclei were invariably affected. The parabrachial nuclei, medial and lateral, could be examined in 5 patients and showed moderate changes. The periaqueductal gray/midbrain raphe neurons were also affected. Gliosis of the central tegmental tract was relatively prominent in all cases. The subcoeruleus/coeruleus region was only mildly affected in two patients while cell loss in the gigantocellularis nucleus was more marked. Results of the semiquantitative evaluation are presented in Fig. 20.

Spongiform change was only focally present in some patients in frontobasal areas and subiculum and was practically absent in thalamus, brainstem and cerebellum. Only few patients showed mild to moderate small vacuoles in the basal ganglia, involving mainly the putamen and cortical regions. Large confluent vacuoles were identified in one patient in the parieto-occipital cortex. In parallel to spongiform change, PrP^{Sc} deposits were also mild and were detected only focally in areas with vacuoles, in the internal



Pat.	Thalamus	PAG/ Midbrain raphe	LC/SC	ParaBch Lat/Med	Solit./ Ambig.	GC	Lower raphe	Inf. Olives	Cereb. Vermis
#11	+++	+++	+	++/+++	+++	++	++	+++	++
#3	+++	++	–	+++/+++	+++	++	++	+++	+++
#8	+++	+++	–	++/++	++	++	+	+++	+++
#5	+++	++	–	+++/++	+++	++	+	+++	+
#1	+++	+	+	na	++	+	+	+++	++
#6	+++	+	–	na	+	++	++	+++	+
#7	+++	+	–	++/+	++	+	+	+++	++

Fig. 20. Distribution of neurodegenerative pathology of the thalamus and of several brainstem nuclei. In the upper part, average impairment in the different subregions for the seven patients examined neuropathologically. Color gradient indicates the severity of neurodegeneration within each anatomical level, being deep red the most affected area and pale rosa the less affected areas. Midbrain: C = colliculi, PAG = periaqueaductal gray, rb = n. ruber, SN = substantia nigra, STT = spino and trigemino-thalamic tract; Pons: pb = parabrachial nuclei, LC = locus coeruleus, R = upper raphe; Medulla: io = inferior olives, XII hypoglossus, X dorsal motor nucleus of the vagal nerve, VIII n. vestibularis, GC = nn. gigantocellularis, a = n. ambiguus, s = n. solitarius, R = lower raphe. In the lower part, the table shows the degree of neuronal loss, astrogliosis, and microglial activation in each individual patient, +++ meaning severe; ++ moderate and + mild. PAG: periaqueductal gray matter; LC: locus coeruleus; SC: subcoeruleus; ParaBch: parabrachialis; Lat/Med: lateral/medial; Solit.: solitary; Ambig.: ambiguous; GC: gigantocellularis; Inf.Olives: inferior olives; Cereb.Vermis: cerebellar vermis. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 7
Types and number of respiratory impairments in each patient.

	RRV high	CSA	Stridor	Hiccup	EG/REV	Catathrenia	*Total*	Ambiguous/solitary n. degeneration
Pat#3	+	+	+	+	+	+	***6***	+++
Pat#10		+	+	+	+	+	***5***	
Pat#5	+		+	+	+	+	***5***	+++
Pat#9	+		+	+	+	+	***5***	
Pat#11	+		+	+	+	+	***5***	+++
Pat#1	+	+	+		+	+	***5***	++
Pat#4	+	+	+		+		***4***	
Pat#7			+	+	+	+	***4***	++
Pat#2	+	+					***2***	
Pat#6*					+	+	***2***	+
Pat#8			+		+		***2***	++
Total	***7***	***5***	***9***	***6***	***10***	***7***		

+: present; empty: absent, with magnitude of pathological damage in ambiguous and solitary nuclei (+++: severe; ++: moderate; +: mild). RRV high: greater than mean+3SD of the mean RRV in healthy controls; CSA: central sleep apnea; EG: expiratory groaning; REV: Rhythmic expiratory vocalizations. *: sporadic FI.

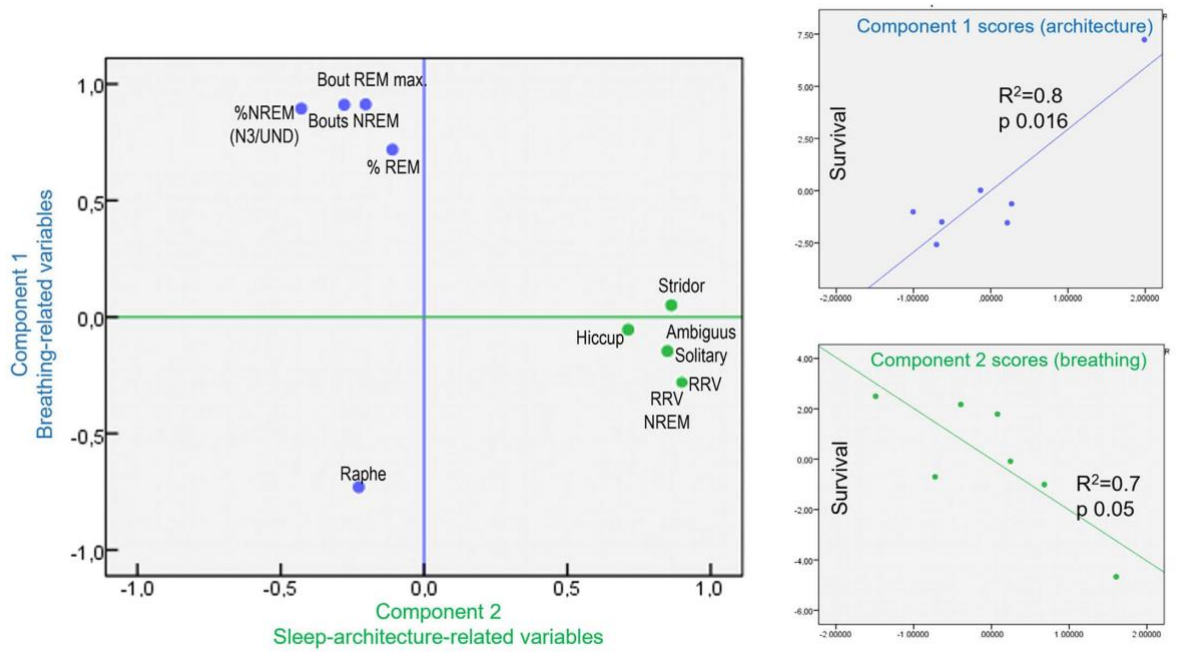


Fig. 21. Panel A represents, for patients who underwent neuropathological analysis, the correlations (with standardized/z-scored correlation coefficients) among the different clinical/PSG and neuropathological variables. The Principal Component Analysis shows in axes Y and X the two major components (vectors) that explain most of the variance in the observed data. Note the high correlation among REM and NREM percentages and bout durations, which are all negatively correlated with raphe nuclei degeneration, and are best explained by the Component 1 (Y axis; blue); as well as the high correlation of respiratory variables among them and with the degree of degeneration of the brainstem respiratory nuclei (ambiguous and solitary), which are explained best by the second component (X axis; green). The two plots in the right show regression lines for survival time and impairment of sleep architecture (above; scores obtained from component 1) and breathing (below; scores obtained from component 2). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

medullary lamina of the thalamus and in single cases in the molecular layer of the cerebellum with a peculiar stripe-like pattern perpendicular to the cerebellar surface. Mild punctate cytoplasmic PrP^{Sc} granules were identified in some thalamic and olivary neurons.

No obvious structural alterations of the substantia nigra pars compacta or pars reticulata, nucleus ruber, nucleus subthalamicus (STN) or globus pallidus were identified, only Pat#8 and 11 showed a mild gliosis of the lateral aspects of the STN. Except for Pat#11, who had very mild alpha-synuclein aggregates in single brainstem neurons and more prominently in the olfactory system, no other cases of Lewy body pathology, TDP43-proteinopathy, prominent AD-neuropathologic changes or vascular pathology were identified. One patient (Pat#3) had a moderate amount of intranuclear, p62/ubiquitin positive, polyglutamine negative, hyaline inclusions in neurons of the frontal cortex, basal ganglia and hippocampus suggestive of intranuclear hyaline inclusions. This patient had, however, no atypical clinical findings regarding FI.

3.13.1. Relation between vPSG findings, neuropathology and survival

We found a positive correlation between the number of breathing symptoms (Table 7) and the degree of neurodegeneration in the ambiguous/solitary nuclei ($r = 0.91$, $p = 0.004$). RRV in NREM sleep correlated with ambiguous/solitary nuclei degeneration ($r = 0.9$, $p = 0.008$ for both). In addition, the number of REM bouts and maximal duration of REM episodes was inversely related to the damage to the raphe nuclei (Figs. 21 and 22). Impairment of the parabrachial nucleus was linked to NREM bout number in the five patients where it could be examined. Since impairment in the thalamus was so extensive in all patients, we could not relate it to any of the different changes in sleep encountered. The same was true for the inferior olives and spinothalamic and trigeminothalamic tracts.

The interval from disease onset to vPSG and from vPSG to death was not different between patients with conventional NREM sleep and those with UNREM (11.8 months vs 8, $p = 0.9$; and 5.5 vs 5.5, $p = 0.8$, respectively). Survival time from PSG however correlated with NREM sleep amount (percentage) ($r = 0.71$, $p = 0.023$) and number of NREM bouts ($r = 0.67$, $p = 0.035$). RWA percentage was related to disease duration and survival time ($r = -0.65$ and -0.75, $p = 0.043$ and 0.013, respectively) as well as with the number ($r = -0.9$, $p < 0.001$) and maximal duration ($r = -0.75$, $p < 0.012$) of NREM sleep bouts and with the maximal duration of REM sleep bouts ($r = -0.79$, $p = 0.007$). Patients with increased RRV (Pats#1–5, 9, and 11) had significantly shorter survival times than patients without (median survival 3.1 months, range 2–5.6 vs 10.3 months, range 6–33; $p = 0.009$; Figs. 18 and 21); and RRV in NREM negatively correlated with survival ($r = -0.7$, $p = 0.037$). In contrast, patients with or without CSA had similar survival.

3.13.2. Relation with codon 129 polymorphism

Six patients were homozygous (Met/Met) and five were heterozygous (Met/Val) for the codon 129 polymorphism in *PRNP*. Compared with patients with Met/Val polymorphism (Table 8), those with Met/Met had a later disease onset (median 63 vs 39 years; $p = 0.03$) and a tendency for a shorter disease duration (9.8 vs 29.1 months; $p = 0.1$), The only patient still alive after 80 months

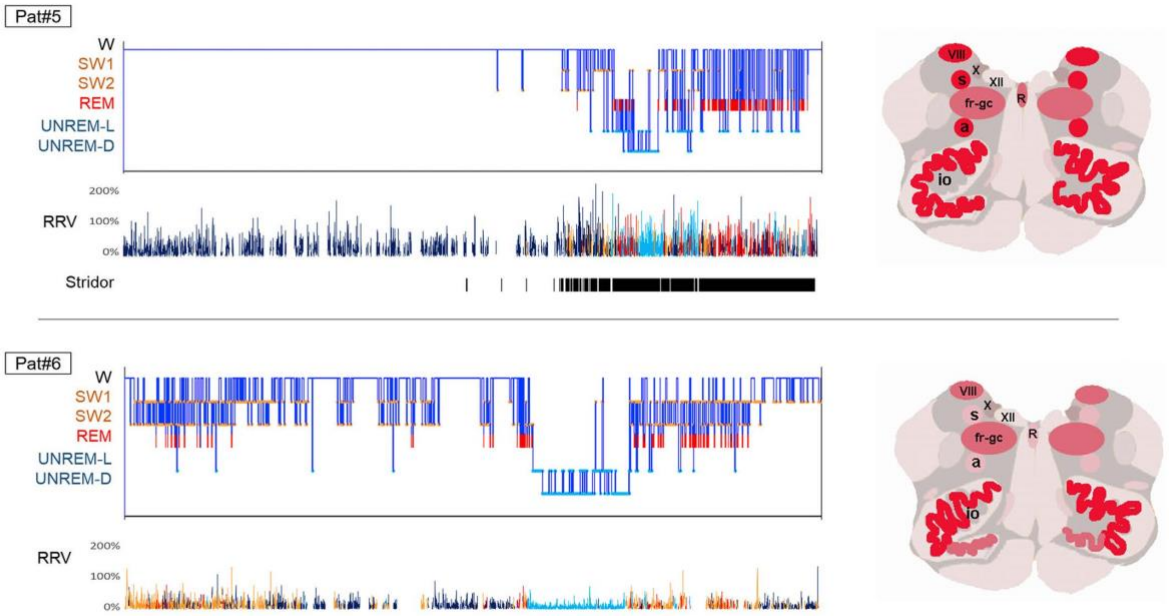


Fig. 22. Examples of two FI patients with differential degrees of respiratory impairment and sleep disruption. In the left half of the figure the hypnogram with the RRV measured throughout the whole night is represented in Pat#5 (upper panel) and Pat#6 (lower panel). On the right half, the overall distribution of neurodegenerative pathology among the different subregions of the medulla. Color gradient indicates the severity of neurodegeneration within each region, being deep red the most affected area and pale rosa the less affected areas. Damage is more severe in Pat#5, with higher RRV and frequent stridor. io = inferior olives, XII hypoglossus, X dorsal motor nucleus of the vagal nerve, VIII n. vestibularis, fr-gc = formatio reticularis and nn. gigantocellularis, a = n. ambiguus, s = n. solitarius, R = lower raphe. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

				Sleep architecture								Respiration				Movements				
	Pat.	PRNP codon129	PSG to death (month)	SE (%, SW out	Wake (%TRT)	Fluct. W-SW (%TRT)	Fluct. W-REM (%TRT)	NREM (%TRT)	NREM bouts (n)	REM (%TRT)	Consec. REM epochs (max)	RWA (% of REM)	CSA (n)	RRV global mean%	Inspir. noises	Expir. noises	Any mov. (n)	ApLM (n)	Manip. mov. (n)	Final. mov (n)	Vocaliz (n)
Agitated	#9	MM	3	1	92	25	4	0	0	1	3	100	13	20	++	+++	580	376	222	10	33
	#11	MM	5	5	93	9	11	7	0	4	3	99	0	18	+	+	1330	1141	223	26	46
	#5	MM	3	15	79	14	11	8	1	7	6	99	3	28	+++	++	1391	1252	240	75	108
	#6	MM	6	20	42	56	4	15	1	6	5	79	3	12	-	++	863	779	308	33	231
Quiet-Apneic	#4	MM	2	18	33	68	0	15	1	3	5	86	596	30	++	++	2	0	2	0	0
	#1	MM	6	21	29	74	1	19	1	1	5	81	572	23	+++	+	0	0	0	0	0
	#3	MV	3	26	27	64	1	22	1	1	3	94	453	21	+++	+++	19	0	0	11	0
	#2	MV	60*	29	39	40	0	27	1	2	4	17	276	27	-	-	9	0	0	1	0
Quiet-Non apneic	#8	MV	8	45	33	42	0	43	2	2	11	2	9	11	+	+	0	0	0	0	0
	#7	MV	14	60	35	6	0	48	4	12	68	17 (1)	2	11	+	+++	110	101	1	0	3
	#10	MV	33	83	9	14	0	71	4	12	50	5	27	15	+++	+++	1	0	0	0	5

Fig. 23. Summary of vPSG findings in the 11 FI patients. Darkest colors represent worst results (brown for sleep architecture, green for respiratory findings and blue for movements). Patients are ordered mainly by sleep efficiency (SE). Three groups can be distinguished: 1) Agitated, with very low sleep efficiencies, a very high number of movements (mainly aperiodic and manipulative, less often finalistic) and vocalizations, the lowest percentage of NREM time and bouts (all undifferentiated - in italics, underlined), the highest percentage of fluctuating W-REM time, a high percentage of RWA, and a low number of consecutive REM epochs. These patients had low CSA index, but high RRV values and variable inspiratory and expiratory noises; 2) Quiet-apneic, with intermediate/low SE, a very low number of movements and no vocalizations, very high CSA indexes, intermediate/low percentage and bouts of NREM sleep (two undifferentiated, two conventional), along with the highest fluctuating Wake-Subwake percentage, a low but variable percentage of REM and of consecutive REM epochs, and a high RWA percentage. RRV was high with frequent inspiratory and expiratory noises; 3) "Quiet non-apneic", with the highest SE (>45%), percentage of NREM sleep (conventional or undifferentiated) and number of NREM bouts (two conventional, one undifferentiated), and number of consecutive REM epochs, and lowest percentage of RWA. These 3 patients were quiet, had a low CSA index, lower RRV values with variable inspiratory and expiratory noises. All patients in the Agitated group had the MM polymorphysm, those in the Quiet-Nonapneic group were all MV, while patients in the Quiet Apneic group had both types. Survival from PSG was highest in the Quiet Non-apneic group. *Patient still alive. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 8
Main differing characteristics among patients with Met/Met and Met/Val polymorphism at codon 129 of the PrP gene. P values obtained from comparison of medians by the Mann-Whitney *U* test, except for the categorical variable Type of NREM sleep (*), where a Chi Square was used. (–) indicates that a median could not be provided for this variable. RRV: respiratory rate variability; TRT: total recording time; C: conventional NREM; UN undifferentiated NREM; RWA: REM without atonia.

Codon 129 polymorphism	*Met/Met*							*Met/Val*						*p value*
	Pat#1	**Pat#4**	**Pat#5**	**Pat#6**	**Pat#9**	**Pat#11**	*Median*	**Pat#2**	**Pat#3**	**Pat#7**	**Pat#8**	**Pat#10**	*Median*	
Age at onset	65	45	64	48	62	66	**63.0**	30	47	39	53	20	**39.0**	**0.030**
Disease duration, months	29.5	7.5	8.6	20.9	10.9	7.7	**9.8**	73.2	9.9	29.1	12	75	**29.1**	0.1
RRV global, %	23%	30%	28%	12%	20%	18%	**22%**	27%	21%	11%	11%	15%	**15%**	0.201
CAHI, n/h	77.6	80	0.4	0.4	2.4	0	**1.4**	36.6	62.5	0.3	1.1	3.3	**3.3**	0.855
Sleep efficiency %	21%	18%	15%	20%	1%	5%	17%	29%	26%	60%	45%	83%	45%	0.004
NREM, % of TRT	19%	15%	8%	15%	0%	1%	**12%**	27%	22%	48%	43%	71%	**43%**	**0.004**
Longest bout, min	61.5	31.8	10.5	41.5	0	0	**21.1**	53.8	78	98.8	45.6	110.3	**78.000**	**0.017**
Type*	C	UN	UN	UN	Absent	UN	-	UN	C	UN	C	C	-	0.242
REM, % of TRT	1%	3%	7%	6%	1%	4%	**4%**	2%	1%	12%	2%	12%	**2%**	0.711
RWA	81%	86%	98%	78%	100%	99%	**92%**	17%	94%	17%	2%	5%	**17%**	**0.030**
Aperiodic limb mov. index	0.0	0.0	165.8	111.0	69.2	157.5	**90.1**	0.0	0.0	13.3	0.0	0.0	**0.0**	**0.073**
Vocalization index	0.0	0.0	29.3	15.4	6.1	6.1	**6.1**	0.0	0.0	0.4	0.0	0.6	**0.0**	0.126

of disease is Met/Val, and the second with the longest duration (also Met/Val) died 51 months after disease onset, both being the youngest at disease onset as well (30 and 20 years, respectively). Patients with Met/Met polymorphism had, in addition, lower sleep efficiencies (median 17% vs 45%, $p = 0.004$), with less NREM sleep (median 12% vs 43%; $p = 0.006$), whether conventional or undifferentiated, fewer (median 1 vs 2; $p = 0.05$) and shorter (median 21.1 vs 78.0 min; $p = 0.017$) NREM sleep bouts, increased percentages of RWA (median 92% vs 17%, $p = 0.03$) and a tendency towards a higher vocalization index (6.1 vs 0; $p = 0.1$). There were no differences in the degree of neuropathological alteration.

3.14. ***Summary of vPSG patterns*** *(Fig. 23)*

Combining sleep architecture data, movements, and respiration we were able to define three groups. Patients in the **Agitated group** had a very large number of movements (mainly aperiodic and manipulative and less often finalistic) and vocalizations, a very low sleep efficiency (SE; 15% or less in Pats# 5, 11 and 9, and 20% in Pat#6), the lowest percentages of NREM sleep (all undifferentiated), lowest number of NREM bouts, with the highest percentage of fluctuating Wake-REM time, and very abnormal REM sleep (low number of consecutive REM epochs and a high RWA percentage). These patients had high RRV values, frequent inspiratory/expiratory noises but a very low number of CSA, and all of them had the MM codon 129 polymorphism. Patients in the **Quiet-Apneic group** (Pats# 2, 3, 1, and 4) had practically absent movements and vocalizations, a very high CSA index, and intermediate/low SE (18–30%), less altered NREM sleep measures (two UNREM, two conventional NREM sleep), a high percentage of Subwake time and Wake-Subwake fluctuations and a low but variable percentage of REM sleep, with a high RWA percentage. In these patients RRV was high but variable, with frequent inspiratory/expiratory noises. Two patients in this group had the MM and another two the MV polymorphism. Patient#1 remained quiet-apneic throughout the follow-up. Survival time from PSG to death was similar in the Agitated and Quiet-apneic-group. Finally, patients in the **Quiet-non-apneic group** had the highest SE (>45%; Pats#10, 7 and 8), the highest percentage of NREM sleep (two conventional, one undifferentiated), and number of NREM bouts and a relatively normal REM sleep architecture (highest median number of consecutive REM epochs and the lowest RWA percentage). These patients had three of the four lowest RRV values, with variable amount of inspiratory and expiratory noises a low CSA index and a low number of movements and had all the MV codon 129 polymorphism and survival time from PSG was longer than in the other two groups.

4. Discussion

We report here detailed clinical, polysomnographic, respiratory and neuropathologic findings in a group of 11 patients with fatal insomnia, 10 familial and one sporadic. Using an innovative scoring system, we have expanded significantly previous observations and showed that impairment of respiration is common and distinctive in FI, and often associated with shorter survival time. Neuropathological evaluation of seven patients confirms that, in addition to the extensive thalamic impairment, the brainstem respiratory control centers are also affected, likely explaining the changes observed in breathing, while the degeneration of brainstem centers involved in REM sleep regulation might explain the changes observed in this sleep stage, an aspect that has received less attention than the NREM sleep alterations of the disease.

Previous reports in FI [2,16,17,38,39] described a vPSG wake/sleep patterns characterized by: 1) a severe reduction in sleep time with important sleep fragmentation, 2) a progressive loss of NREM sleep, with disappearance of its characteristic waveforms (sleep spindles, K complexes, and high voltage delta slowing), 3) frequent oscillations between relaxed wakefulness (with periods of diffuse alpha activity) and short episodes of sleep with EEG desynchronization, often with interspersed rapid eye movements, or of REM sleep, with or without EMG atonia; **4**) episodes of peculiar, quasi-purposeful behaviors and gesticulations with decreased reactivity (oneiric stupor) that appear during sleep or wakefulness.

This description leaves several areas of uncertainty. One such area is the nature of the PSG activity that is left after the disappearance of NREM sleep. Montagna et al. [40], in a very comprehensive study, described that patients spent the majority of the time in a "non-wake-non-sleep" state, a stage characterized by "the presence of diffuse alpha activity mixed with theta activity, similar to "stage1 NREM sleep", and used for the first time the term **subwakefulness** to designate it. Tinuper [16] described that diffuse alpha activity could also be recorded during periods of behavioral sleep. In later reviews, however, subwakefulness has been depicted as an EEG pattern with a desynchronized theta activity with superimposed rapid eye movements, rather than a diffuse alpha activity with superimposed theta (Fig. 1 from Baldelli et al., 2019) [2]. It has been also described as a condition with mixtures of stage N1 and REM or stage 1/REM [15] with brief, continuous oscillations between relaxed Wake and stage 1/REM or with REM sleep –with or without atonia– [2,17,39]. The use of different names to describe apparently similar patterns in different studies (e.g., Stage 1 NREM,

Stage 1-REM, or Subwakefulnes) [15,39,41] has increased the difficulty to understand them. In addition, there are not many detailed figures illustrating the characteristics of these stages with sufficient time resolution. Our study, by taking advantage of the use of 15-s epochs, adds meaningful information to the previously reported literature by describing in more detail the patterns occurring in these patients.

4.1. Wakefulness

Wakefulness represented an important percentage of the recording time, but in most patients, Wake time was not stable, and showed frequent oscillations between Wake and Subwake, particularly in patients with CSA. Less often, patients had high percentages of stable Wake time, typically associated with frequent aperiodic limb movements. In this group, there were also periods with frequent Wake instability, but between Wake and REM sleep rather than between Wake and Subwake, with direct transitions between Wake and REM sleep. These findings have been previously reported in part, but we have observed that patients had typically one or the other type of transitions and more rarely both, something that was unclear from previous studies on FI [17].

4.2. Subwakefulness

We have identified a vPSG state of subwakefulness –Subwake1–, characterized by frequencies in the alpha/subalpha range, slower than those recorded during periods of active wakefulness, and often combined with anterior theta delta activity and slow or absent eye movements. This stage is most often associated with eyes closed and the beginning of relaxation, and likely represents the early part of the wake to sleep transition. It is frequently associated with episodes of central apnea, which are usually absent in wakefulness, suggesting that the EEG changes follow the direction from wake to sleep. We have also identified a second state of subwakefulness –Subwake2– which usually follows Subwake1. This state is associated with increased relaxation, slow eye movements, attenuation of EEG amplitude compared to Subwake1, but with persistent alpha/subalpha frequencies, which differentiates it from sleep. In some patients, this is the state with lowest alertness that can be reached during long periods and occurs often at the end of a central apnea episode. In line with previous observations, we consider subwakefulness a state in between wake and sleep, with Subawake1 perhaps being closer to wakefulness than subwake2, but reflecting the disorganization of the sleep onset mechanisms that take place in the disease.

4.3. NREM sleep

The majority of our patients had at least one period of >30 min of NREM sleep, either conventional or undifferentiated, appearing in a single or several bouts throughout the night. Although NREM sleep was reduced in duration it still could occur even in advanced cases, that is, in those patients with a short survival time after vPSG. Its characteristic organization –as consistently reported in the literature– was severely impaired with disappearance of sleep spindles and K complexes in 60% of the patients, although with remaining periods of deep and light undifferentiated NREM sleep in most patients, suggesting that some form of basic NREM sleep could still be generated. The fact that some FI patients could generate "rudimentary" NREM sleep periods was also mentioned by Sforza [17], who described an intermediate, transient period as light NREM sleep that appeared during direct transitions from Wake to REM sleep, in between both stages (Fig. 6 of their paper). This was also reported by Montagna et al. [40], although occurring preferentially in patients with long disease duration or with the Met/Val polymorphism. We have found, however, these NREM periods also in some patients with short survival or with the Met/Met polymorphism. We have been able to confirm the progressive decrease of sleep spindles and K complexes along two consecutive vPSG studies performed 6 months apart but with persistence of undifferentiated NREM, suggesting that before its complete disappearance there are still mechanisms able to generate NREM sleep slow EEG activity. The type of NREM sleep –conventional o undifferentiated– was not correlated with a different severity of REM sleep alterations. However, patients with UNREM sleep had longer periods of wakefulness than those with conventional NREM sleep. We found that involvement of the parabrachial nuclei related with the number of NREM bouts ($p = 0.04$), indicating that this area may have a role in NREM sleep modulation. Experimental evidence suggests that the medial and lateral parabrachial nuclei have specific functions controlling arousal from sleep induced by changes in CO2 and in maintaining wakefulness [42], and that inhibition of this area by afferents from the GABAergic parafacial nucleus induces NREM sleep in mice [43,44]. It cannot be excluded that impairment of the parabrachial nuclei may be implicated in the NREM sleep alterations of FI in addition to the thalamic degeneration.

4.4. REM sleep

There was a variety of impairments in REM sleep in our patients, a finding previously reported in other series [16,17,40]. Values ranged from normal quantity and structure –in two patients–, to the presence of intense and selective REM without atonia in only one of the five REM episodes (a pattern not previously described in FI nor in isolated or secondary RBD), and the development of short 30–60 s episodes, mostly without atonia, associated with body or limb jerks interrupted by a repeated reactivation of alertness. These REM episodes, despite their short duration, might be suggestive of RBD, and this possibility was already considered by several authors [16,17,40]. The use of 15-s epochs to score sleep has allowed us to better characterize these episodes, revealing an inverse relationship between the amount of RWA and the duration of the REM episodes. In contrast to most patients with isolated or secondary RBD, the behaviors and movements observed in FI during REM sleep were less vigorous and much shorter, which might explain why patients do not show the distinctive dream-enacting and longer duration movements of RBD.

Previous authors have attributed the REM sleep fragmentation to the severe alteration in NREM sleep mechanisms [16,17] caused by the thalamic damage, which would increase the homeostatic sleep pressure and favor the emergence of recurrent episodes of REM sleep. This does not explain, however, why REM episodes should be of such a short duration and with abnormal atonia [17]. In other conditions selectively involving the thalamus, there is no significant impairment of REM sleep. [45–47] We found that the pathologic involvement of the medullary raphe nucleus correlated with the severity of REM sleep fragmentation and shortening, whereas the pontine raphe, which was less impaired, did not. The dorsal raphe nucleus, which overlapped with the periaqueductal gray in the available brain sections of our patients has been implicated in the mechanisms modulating REM sleep. Microinjection of $5HT_{1B}$ receptor agonists into the raphe nucleus significantly decreases the mean duration of REM periods, while its antagonist reduces its number [48]. The role of the medullary raphe on REM sleep characteristics, other than atonia, is less known. It cannot be excluded that its damage may alter the REM generating mechanisms, alone or in association with other REM modulating areas such as the periaqueductal gray in the midbrain, which is also

affected by the disease. Wanschitz et al. reported in a neuropathological study of 8 FFI patients an enhanced serotonergic function [49] based on the presence of increased tryptophan hydroxylase neurons in the raphe nuclei of the medulla and pons. Since the appearance of REM sleep is linked with inactivity of the brainstem serotonergic neurons [50], an enhanced serotonergic function could explain the reduction in REM sleep encountered in FI. Also, it might suggest that drugs augmenting serotonergic transmission, such as SSRI, could worsen sleep in these patients.

The presence of RWA in FI is likely not linked to lesions in the subcoeruleus/coeruleus area, which was not seen in our patients. In contrast, medullary nuclei such as the gigantocellularis/ventromedial medulla and the medullary raphe nuclei, which have all been implicated experimentally in the generation of RBD [51–53] are involved, although we could not find a direct correlation between their damage and the presence of RWA. It cannot be excluded that RBD in FI has different mechanisms than in isolated or secondary RBD to neurodegenerative diseases because it shows five distinctive characteristics: 1) the duration of the RWA episodes in FI is very short, 2) there is a negative correlation between the duration of REM episodes and the intensity of RWA, 3) when RWA occurs in patients with still normal REM duration it may involve selectively and intensely only one of the REM episodes, 4) the abnormal behaviors are not vigorous or intense; and 5) the episodes often arise directly from wakefulness. These differential characteristics suggest that RWA in FI may have a distinctive pathophysiology different from other neurodegenerative disorders.

4.5. Movements

Patients with FI had an increased number and wide variety of abnormal movements, but they occurred with substantial differences in frequency and variability in the patterns of movement among patients. The typical "oneiric stupor" with finalistic/pseudopurposeful movements represented only a minority of the movements recorded in our patients.

Abnormal movements were particularly frequent in five patients, four of them with the Met/Met polymorphism and comprised a combination of aperiodic limb/body movements, and manipulatory movements. Finalistic/quasipurposeful movements, jerks, and simple movements, although present, occurred less frequently. Aperiodic limb movements are not usually scored in sleep studies, probably because they occur less frequently than periodic limb movements in the typical situation of a patient with restless legs syndrome or PLM disorder. However, in FI they were the most frequent type of movement, occurring during wakefulness and incessantly during many parts of the night. They are different from PLMS or PLMW because they do not have a stereotyped pattern and involve larger portions of the body in a non-periodic pattern. The other frequent type of movements, mainly occurring in wakefulness, were manipulative movements where the patient touched and appeared to use objects that were close or in contact with her/him, without apparent purpose. These movements were different from finalistic/pseudopurposeful ones, because in the latter the patient does not use real objects around him/her but looks like if he/she was eating, working using imaginary objects or gesticulating with apparent purpose. Manipulative movements occur probably in other conditions, but its real prevalence is unknown. Finalistic movements occurring in different wake/sleep stages typical of FI (and labelled in previous studies as oneiric stupor), did not appear in all patients in our series, perhaps because we could not follow longitudinally all the patients with serial VPSG studies. Another possibility is that finalistic movements/oneiric stupor occur only in a subgroup of FI patients (Fig. 23).

4.6. Hallucinations/Hallucinatory behavior

We considered that finalistic behaviors performed with the eyes open were more likely explained as hallucinations with the patient awake. The vPSG pattern of hallucinations is not well known but the combination of eyes open, an awake EEG pattern with intermittent alpha activity and pseudopurposeful behaviors could suggest that the patient is acting as if he/she is seeing something. In other conditions, like anti-IgLON5 disease finalistic movements occur always with the eyes closed, whereas in Morvan's syndrome they occur both with eyes open and closed [54], similarly to FI suggesting that they may have a similar mechanism [2]. This clinical differentiation may help diagnose and better understand each condition.

4.7. Sexsomnia

The presence of sexsomnia in FI has been previously reported in a female [55], showing restlessness and sexual disinhibition with hand masturbatory stereotypes in the supine position, reminiscent of frontal behavioral disinhibition. In our case, the patient had rhythmic pelvic movements while in the prone position.

4.8. Respiration

Previous studies have reported the presence of breathing alterations in isolation, including central sleep apnea, stridor and respiratory failure as a cause of death in FI patients [1,17–21,23–27,40,56], but the actual prevalence of these findings in FI is not well known. Using a detailed analysis, we have identified frequent alterations in breathing function, including RRV, central apneas, stridor, hiccups, and a series of expiratory sounds indicating a relevant dysfunction of the respiratory centers, not well described previously. This impairment in breathing in FI correlates with neuropathological alterations in the brainstem respiratory centers and is associated with short survival time.

RRV changes with state level, being higher in REM sleep and Wake and lowest in deep NREM sleep [36]. Although there are several reports of irregularities in breathing rhythmicity, for instance in up to 16.8% of patients [17,57] there are no systematic evaluations of RRV in FI. Our findings of an increase in RRV in FI compared to controls, the correlation between RRV in NREM sleep (conventional or undifferentiated) and neuropathological damage in the ambiguous/solitary nuclei as well as with survival time, suggests that RRV is a clinically relevant finding in FI. This relationship was not explained by the presence of central apneas. We also found that 40% of the patients had very frequent central apneas that produced mild to moderate HbO2 desaturations and were highly associated with the presence of frequent oscillations between wakefulness and subwakefulness in a self-perpetuated loop of sleep initiation, central apnea, sleep interruption, overbreathing, and central apnea again, that makes one wonder whether correcting apnea episodes would have improved sleep continuity. Central apnea episodes tended to disappear during stable sleep of any type and were less frequent during REM sleep and absent in patients with excessive movements (aperiodic, finalistic, or manipulatory). Involvement of the parabrachial nuclei may modify the sensitivity to arousal from CO2 changes [42] leading to an instability of sleep and breathing in FI patients.

We have also found that FI patients have frequent respiratory sounds and noises during the night, both inspiratory (such as stridor or hiccup) and expiratory (such as catathrenia, expiratory groaning, or REV). Stridor occurs usually when there are lesions of the respiratory centers (like in multiple system atrophy) or of the vagal nerve [58] It has been previously reported in isolated cases of

FFI [25,27,59,60], although a recent analysis of its prevalence in a world-wide series review of 131 FFI patients showed that stridor occurs in up to 32%, with a tenfold prevalence in Asian patients [57]. Fukuoka et al. suggested a possible dystonic mechanism for stridor awake [60] but this is unlikely to occur during sleep. We found that stridor in FI has different intensities, is probably more common than reported and relates most likely to the degeneration of the medullary breathing centers.

Hiccups is a normal breathing response under certain conditions but may turn abnormal in patients with brainstem, spinal or phrenic nerve lesions [61] and has, to our knowledge, not been previously described in FI. Hiccups may be produced by medial medullary lesions [61,62] impairing the medullary raphe function. Experimental stimulation of the raphe obscurus and pallidus produces sudden changes in breathing movements that could explain, if occurring in humans, the irregularities we have reported, including hiccups [63]. Catathrenia is an uncommon phenomenon that occurs usually in young healthy individuals and has not been associated to neurological lesions [64], although its occurrence in FI might suggest that it could also relate with impairment of the brainstem respiratory centers. Expiratory noises are rare phenomena of unknown pathological correlations. While stridor can occur during stable sleep, and catathrenia occurs both during stable and unstable sleep, there is not much information about the state where the other breathing noises occur, although in our cases they tended to appear during the periods with unstable sleep (typically subwakefulness).

It is interesting that inspiratory noises such as stridor and hiccups are produced by constriction in the upper airway size during inhalation, typically at the level of the vocal cords, whereas expiratory sounds are produced by constriction at the level of the vocal cords during exhalation. This limitation in airway size in patients with FI is not associated with obstructive sleep apnea but with central apnea. It is likely that a motor discontrol of the vocal cords is responsible of all these changes and that their severity relates with survival time. However, this does not prevent considering that positive airway therapy could improve breathing in FI patients with stridor and merits consideration in the case of the other noises. Treatment of stridor with CPAP was also tried temporally in another FI patient [60]. This is therefore a therapeutic aspect to be considered in the future management of these patients.

One puzzling question is why all these frequent breathing alterations have not been reported before in FI patients. Our patients had the typical clinical, genetic, and neuropathological characteristics of the disease. It is possible that breathing impairment has received less attention because it is perceived as a less relevant problem than the rest of neurological symptoms occurring during the disease. Alternatively, the more systematic analysis in our study has allowed better identifying these phenomena. The clinical relevance of some of these findings is presently unknown, but their combined presentation in a patient should alert the possibility of FI.

4.9. Identification of three vPSG patterns in FI

Our results allow to classify the vPSG patterns in FI patients in three groups. First, an **Agitated group**, with a large number of movements and vocalizations during wakefulness and very low sleep efficiency (similar to the "agrypnia excitata" pattern) with severely decreased NREM sleep (all UNREM type) and REM duration and high RWA percentage, absent CSA but abnormal RRV, and frequent inspiratory/expiratory noises. This pattern appeared only in patients with the MM polymorphism, associated with a relatively short survival from vPSG and was probably comparable to the first pattern of Montagna et al. [40] Second, a **Quiet-Apneic group**, previously not identified, which had a less intense but still severe decrease in SE, but had instead a large CSA index, practically absent movements and vocalizations, and a large proportion of wake-subwake fluctuations, with also RRV and respiratory noise abnormalities. This pattern appeared both in MM and MV polymorphisms and had a similar survival than the agitated group. Finally, the **Quiet-non-apneic group** had the less severe SE reduction as well as of NREM and REM alterations, a very low number of movements and absent CSA. These patients had all the MV polymorphism and had the longest survival time from vPSG, suggesting that it could be in a more initial stage of the disease and has also similarities with the second pattern described by Montagna et al. [40] The classification proposed here allows, in our view, to better capture all the findings encountered in the disease.

4.10. Strengths and limitations

Strengths of our study are the inclusion of a relatively large number of FI patients, the systematic and detailed evaluation of sleep and breathing, plus the neuropathological examination in seven patients that provided a unique opportunity for a clinico-pathological correlation in this rare disease. Our study has also limitations. First, most patients were treated with benzodiazepines or antidepressants, what may have altered sleep architecture, although we could not associate the patterns observed with any particular treatment. In addition, we could perform a follow-up study in one patient only, what may have prevented us from capturing all the changes occurring with disease progression and closer to the neuropathological study. We also did not evaluate sleep/wake patterns during daytime what may made us underappreciate the full spectrum of the disease since sleep/wake changes in FI affect the entire 24-h sleep/wake cycle. Finally, we did not evaluate autonomic function, which is commonly altered in association to the sleep and respiratory problems of FI and could have allowed a better understanding of the changes encountered. These limitations, however, do not invalidate the relevance of our observations, which, instead, open a path to be corroborated in future investigations.

4.11. Implications for sleep scoring and respiratory analysis in neurological diseases

We believe that the scoring system used in this study may be applied in other neurological diseases. Using the term subwakefulness for transitional patterns with persistence of alpha or sub-alpha activity and of undifferentiated NREM sleep for non-REM patterns without the characteristic waveforms helps to better define the changes occurring in this and also in other neurological diseases [32,33] and does not force the scorer to choose among the standard NREM sleep stages which were designed for patients without neurological disorders. In addition, segmenting the study in epochs shorter than the standard 30 s may be necessary to better capture the wake/sleep characteristics in some conditions such as FI. Further studies are needed to validate this scoring system. Finally, a systematic analysis of breathing, including analysis of RRV may offer a new insight into the study of central disorders of breathing occurring in neurological diseases, although visual RRV analysis is too time-consuming and should be automatized.

In conclusion, we have quantified the sleep alterations in FI using an innovative scoring system that allows to better describe the complex sleep disorder of these patients in detail and identified three different vPSG patterns. In addition to NREM sleep impairment, REM sleep is also severely and distinctively altered in FI, and we have found that it is associated with degeneration of the raphe nuclei and other brainstem nuclei involved in REM sleep generation such as the parabrachialis and periaqueductal gray/midbrain raphe.

Breathing alterations are frequent in FI and relate with neuropathological changes in the respiratory centers in the medulla and likely determine survival. The potential role of CPAP or other ventilatory support devices needs to be evaluated in the future. Our results support that sleep scoring rules need to be amended in neurological diseases.

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CRediT authorship contribution statement

Laura Pérez-Carbonell: Data curation, Formal analysis, Investigation, Writing – original draft. **Amaia Muñoz-Lopetegi:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Raquel Sánchez-Valle:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Writing – review & editing. **Ellen Gelpi:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. **Ramon Farré:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. **Carles Gaig:** Formal analysis, Investigation, Validation, Visualization, Writing – review & editing. **Alex Iranzo:** Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Joan Santamaria:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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Trabajo 2

Sleep in Gerstmann-Straüssler-Scheinker disease

Laura Pérez-Carbonell, Jordi Sarto, Carles Gaig, Amaia Muñoz-Lopetegi, Raquel Ruiz-García, Laura Naranjo, Josep María Augé, Andrés Perissinotti, Joan Santamaria, Alex Iranzo, Raquel Sánchez-Valle

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RESUMEN

Introducción: la enfermedad de Gerstmann-Sträussler-Scheinker es una enfermedad priónica rara con presentación clínica heterogénea. Las alteraciones del sueño son prominentes en otras enfermedades priónicas tales como el insomnio letal familiar o la enfermedad de Creutzfeldt-Jakob. Sin embargo, la información relacionada con el sueño en la enfermedad de Gerstmann-Sträussler-Scheinker es limitada.

Métodos: se ha evaluado el sueño en tres casos de enfermedad de Gerstmann-Sträussler-Scheinker genéticamente confirmada, mediante historia clínica, escalas de sueño y vídeo-polisomnografía. Asimismo, se realizó exploración neurológica, se hizo uso de escalas neurológicas, estudio neuropsicológico, punción lumbar, resonancia magnética cerebral y ^{18}F-FDG-PET cerebral en todos los pacientes.

Resultados: dos pacientes referían insomnio de mantenimiento, atribuido a espasticidad en la pierna y dolor de espalda, mientras que el paciente restante no refería problemas del sueño. La vídeo-polisomnografía demostró fases del sueño normales en todos los pacientes. Se encontraron hallazgos tales como una eficiencia de sueño reducida, un despertar confuso, apnea obstructiva del sueño, y movimientos periódicos de las piernas.

Conclusiones: al contrario de lo observado en el insomnio letal, en la enfermedad de Gerstmann-Sträussler-Scheinker las fases del sueño son normales, sugiriendo posibles diferencias en la afectación de estructuras del sistema nervioso central que regulan el sueño. Encontramos alteraciones no específicas del sueño en la enfermedad de Gerstmann-Sträussler-Scheinker, de relevancia clínica incierta en estos casos. Estudios incluyendo un mayor número de pacientes, evaluaciones del sueño seriadas, e incorporando estudios neuropatológicos, ayudarán a entender mejor el sueño en esta enfermedad.

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Sleep in Gerstmann-Straüssler-Scheinker disease☆

Laura Pérez-Carbonell [a, 1, 2], Jordi Sarto [b, 2], Carles Gaig [a], Amaia Muñoz-Lopetegi [a], Raquel Ruiz-García [c], Laura Naranjo [c], Josep María Augé [c], Andrés Perissinotti [d], Joan Santamaria [a], Alex Iranzo [a, 1, *], Raquel Sánchez-Valle [b, 3, **]

[a] Sleep Disorders Center, Neurology Service, Hospital Clínic Barcelona, Universitat de Barcelona, IDIBAPS, CIBERNED: CB06/05/0018-ISCIII, Barcelona, Spain
[b] Alzheimer's Disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic Barcelona, Universitat de Barcelona, IDIBAPS, Barcelona, Spain
[c] Immunology Department, Centre de Diagnòstic Biomèdic, Hospital Clínic Barcelona, Universitat de Barcelona, IDIBAPS, Barcelona, Spain
[d] Nuclear Medicine Service, Hospital Clínic Barcelona, Biomedical Research Networking Centre of Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), ISCIII, Barcelona, Spain

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ABSTRACT

Background: Gerstmann-Sträussler-Scheinker (GSS) is a rare prion disease with heterogeneous clinical presentation. Although sleep-related abnormalities are prominent and well-known in other prion diseases such as fatal familial insomnia and Creutzfeldt-Jakob disease, information on sleep is limited in GSS.

Methods: We evaluated sleep in three genetically confirmed GSS cases using clinical history, sleep scales and video-polysomnography. In addition, patients underwent neurological assessment, neurological scales, neuropsychological testing, lumbar puncture, brain MRI and brain ^{18}F-FDG-PET.

Results: Two patients reported sleep maintenance insomnia attributed to leg stiffness and back pain while the remaining patient did not report sleep problems. Video-polysomnography showed normal sleep staging in all of them. Findings such as reduced sleep efficiency in two patients, a confusional arousal in one patient, obstructive apneas in one patient, and periodic legs movements in sleep in two patients were observed.

Conclusions: In contrast to fatal familial insomnia, the normal sleep staging in GSS may suggest dissimilar involvement of the neuronal structures that regulate sleep. We found non-specific sleep alterations in GSS such as obstructive apneas and periodic leg movements in sleep which are of unknown origin and of uncertain clinical relevance. Studies including a larger number of patients, serial sleep evaluations and incorporating neuropathological assessment will further help to understand sleep in GSS.

1. Introduction

The prion diseases are neurodegenerative conditions caused by deposition of the scrapie prion protein (PrP) [1]. They are sporadic, inherited or acquired, and include fatal familial insomnia (FFI), Creutzfeldt-Jakob disease (CJD), and Gerstmann-Sträussler-Scheinker (GSS). They have a heterogeneous clinical presentation and devastating prognosis. Accurate diagnosis is important for proper management and counselling [1].

GSS is of autosomal dominant inheritance although often there is no family history. The most frequently associated mutation is the proline-to-leucine substitution at codon 102 (P102L) in the PrP gene [2]. The prevalence of GSS is estimated at 1–10/100,000 in the general population, with no sex differences. The key

Abbreviations: CJD, Creutzfeldt-Jakob disease; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; FFI, Fatal familial insomnia; GSS, Gerstmann-Sträussler-Scheinker; OSA, obstructive sleep apnea; PLMS, periodic leg movements in sleep; PrP, prion protein; PSQI, Pittsburgh Sleep Quality Index; RBD, REM sleep behavior disorder; RLS, restless legs syndrome; V-PSG, video-polysomnography.

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* Corresponding author. Neurology Service, Hospital Clínic de Barcelona, Villarroel 170, Barcelona, 08036, Spain.
** Corresponding author. Neurology Service, Hospital Clínic de Barcelona, Villarroel 170, Barcelona, 08036, Spain.
E-mail addresses: airanzo@clinic.cat (A. Iranzo), rsanchez@clinic.cat (R. Sánchez-Valle).
[1] Present address:Sleep Disorders Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK.
[2] Both authors contributed equally to this work.
[3] Both authors qualify as senior authors.

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neuropathological features of GSS are multicentric PrP-amyloid plaques in the cerebral and cerebellar cortices [1]. Diagnosis requires genetic mutation identification and clinical correlate. Symptoms commence in the fifth decade of life, with a mean duration of illness of four years [2]. Core neurological features include progressive cerebellar ataxia, spastic paraparesis and cognitive decline. A variety of additional symptoms and signs indicate extrapyramidal, sensory, and neurobehavioral involvement [3].

FFI and CJD patients consistently report sleep problems such as insomnia and excessive daytime sleepiness (EDS) while video-polysomnography (V-PSG) shows disorganized sleep architecture, obstructive sleep apnea (OSA), stridor and REM sleep behavior disorder (RBD) [4–8]. In contrast, available information on sleep in GSS is scarce [9,10]. The aim of this study is to comprehensively characterize sleep in GSS.

2. Methods

Three GSS patients were recruited at the Neurology Service at Hospital Clínic de Barcelona, Spain. Clinical and demographic information was obtained from interviews done by neurologists specialized in sleep disorders (LPC, AI), and prion diseases (JSarto, RSV). They all underwent a comprehensive sleep evaluation through clinical interview, sleep scales and V-PSG. All participants gave written informed consent for participation in the study. The study protocol was approved by our local Ethics Committee (HCB/2020/1410).

Sleep was assessed by a detailed semi-structured interview, with the patient and their bedpartner/caregiver. EDS was examined using the Epworth Sleepiness Scale (ESS) [11], and sleep quality with the Pittsburgh Sleep Quality Index (PSQI) [12]. Insomnia and restless legs syndrome (RLS) were defined according to current diagnostic criteria [13].

Sleep was objectively assessed by V-PSG, performed with BrainRT software, which included electroencephalography recorded from F3, F4, C3, C4, O1, and O2, electrooculography, electromyography from the mentalis muscle, right and left flexor digitorum superficialis and right and left anterior tibialis, and electrocardiography. Nasal pressure cannula, nasal and oral thermistors, thoracic and abdominal strain gauges, and pulse oximeter were used to assess respiration. Sleep stages, periodic leg movements and apneas were scored according to the American Academy of Sleep Medicine manual [14].

Additionally, all patients underwent 1) neurological examination, 2) neuropsychological testing using the Mini-Mental State Examination [15] and the Montreal Cognitive Assessment [16], 3) the Medical Research Council Prion Disease Rating Scale [17], 4) the Hospital Anxiety and Depression Scale [18], 5) lumbar puncture with amyloid β1-42, p-tau181, t-tau, and 14-3-3 CSF evaluation by standard methods, using local cut-offs, 6) brain MRI, and 7) brain ^{18}F-FDG-PET.

3. Results

Clinical characteristics, outcomes from neurological examination, scales, and investigations performed, are summarized in Table 1. All three cases had the P102L mutation. Patients were two women and one man. Disease course at the time of this study was 2–6 years. ^{18}F-FDG-PET did not disclose a common hypometabolic pattern, but mild hypoactivity compromising different brain areas were observed in all patients.

Clinical history regarding sleep and results from sleep questionnaires are included in Table 1. Findings from V-PSGs are presented in Table 2.

Patient 1 had a two-year history of spastic paraparesis. No sleep problems (including RLS) were reported. The patient mentioned sleepwalking episodes during childhood, not as an adult. The ESS and PSQI scores denoted absence of EDS, and good sleep quality. V-PSG demonstrated normal sleep efficiency and architecture. The index of periodic leg movement in sleep (PLMS) was 18 per hour. Three spontaneous arousals from slow wave sleep were observed, one being a typical confusional arousal, lasting for 40 s. V-PSG showed slow and diffuse theta activity at 7 Hz during wakefulness, reactive to eyes opening, and slow spindles at 10–11 Hz in N2.

Patient 2 reported five years of disease duration and was a wheelchair user due to paraparesis, cerebellar syndrome and parkinsonism. Depression and mild cognitive impairment were present. Sleep initiation and maintenance insomnia attributed to pain and stiffness were reported. There was no EDS or poor sleep according to ESS and PSQI scores. V-PSG showed sleep efficiency at 52%, with almost 4 h of wake after sleep onset and decreased REM sleep percentage. OSA with an overall apnea-hypopnea index of 21 was observed. Mean SpO_2 was 93.6% and time spent in SpO_2 below 90% was 1.6%. No stridor was present. Mentalis muscle EMG recorded at the end of the study brief (20–30 s) episodes of repetitive rhythmic discharges in the wake-N1 transition and in N2, suggesting myorhythmia.

Patient 3 presented with a disease duration of six years characterized by spastic tetraparesis, generalized stiffness, cerebellar syndrome, bulbar symptomatology, mild cognitive impairment, and depression. No symptoms of dysautonomia were reported. The patient described spasticity and pain, leading to sleep initiation and maintenance insomnia. No RLS or abnormal movements in sleep were reported. EDS was not present, but PSQI was 9, demonstrating mild poor sleep quality. V-PSG showed a sleep efficiency at 50%, and sleep onset latency at 27 min. PLMS index was 30 per hour, with a PLM arousal index at 6 per hour. There was no sleep-disordered breathing. Frequent episodes of tachycardia at 100–120 bpm in wake and all sleep stages were observed.

4. Discussion

Our study shows identifiable sleep features, allowing conventional sleep scoring of sleep stages and events in GSS. We also found non-specific sleep disturbances. One of our patients reported good sleep with previous history of non-REM sleep parasomnia. V-PSG showed a brief confusional arousal. In the other two patients, insomnia was the only sleep complaint in the context of stiffness and pain, affecting the patients' comfort in bed. In these two cases, V-PSG showed reduced sleep efficiency, to which comorbid mood disturbances, OSA and PLMS might have contributed. The reduced proportion of REM sleep in patient 2 was a probable consequence of reduced sleep efficiency and duloxetine treatment. Additionally, duloxetine and bupropion (the latter taken by patient 3), both antidepressants with alerting properties, might have altered the sleep architecture. We observed obstructive apneas, PLMS, slowing of alpha rhythm, mentalis muscle myorhythmia and tachycardia during sleep in our patients, all of uncertain clinical significance. There was no evidence of EDS, RLS, RBD, stridor, central sleep apneas, circadian wake-sleep disturbances, or other specific sleep alterations.

Two previous studies in other three GSS patients carrying the P102L mutation in whom sleep was evaluated by PSG reported normal sleep architecture with preserved REM sleep atonia and normal circadian profile [11,12]. Bitemporal independent periodic discharges in routine EEG have been reported in GSS [19].

The neuropathological findings in GSS with the P102L mutation are characterized by PrP-amyloid plaques affecting the cerebral and cerebellar cortices with no apparent involvement of the key

Table 1
Clinical characteristics, outcomes from neurological examination, completed scales, questionnaires, and results from investigations performed.

Participant	Case 1	Case 2	Case 3
Prion protein (*PRNP*) gene analysis	Heterozygous P102L (p.Pro102Leu) mutation	Heterozygous P102L (p.Pro102Leu) mutation	Heterozygous P102L (p.Pro102Leu) mutation
Codon 129 polymorphism	Val/Val	Met/Val	Val/Val
Family history	Negative	Negative	Negative
Past medical history	None relevant	None relevant	None relevant
Age at onset of neurological symptoms (years)	27	53	31
First symptoms	Bilateral lumbar and hip pain. Gait instability. Dysarthria. Leg weakness.	Bilateral lumbar and hip pain. Gait instability. Irritability, apathy, and attentional cognitive complaints.	Left lumbar and hip pain. Gait instability.
Additional symptoms at visit	Hands and feet paresthesia. Leg stiffness. Irritability. Urinary urgency.	Falls due to instability (wheelchair user). Dysarthria and dysphagia. Upper limb myoclonus and mild distal weakness. Urinary urgency	Weakness and spasticity of four limbs (wheelchair user). Dysarthria and dysphagia. Irritability, apathy, depression, attentional and executive cognitive complaints. Urinary urgency, increased sweating, changes in skin color in hands, xerostomia. A single episode of a tonic-clonic seizure.
Sleep symptoms	Sleepwalking during childhood (a)	Sleep initiation and maintenance insomnia	Sleep initiation and maintenance insomnia
Interval between onset of neurological and sleep symptoms (years)	Not applicable	3	2
Restless legs syndrome	No	No	No
Main neurological examination findings at visit	Spastic paraparesis. Dysarthria. Decreased vibratory and arthrokinetic sensation distally in lower limbs. Bilateral Babinski sign. Spastic gait.	Spastic paraparesis. Dysarthria. Decreased vibratory and arthrokinetic sensation distally in lower limbs. Parkinsonism. Dysmetria in upper limbs. Upper motor neuron signs in lower limbs. Occasional upper limb myoclonus. Hyperekplexia.	Spastic tetraparesis. Dysarthria. Decreased vibratory and arthrokinetic sensation distally in lower limbs. Cerebellar axial and limb ataxia. Upper motor neuron signs in upper and lower limbs.
Medication at visit	None	Duloxetine 60 mg/d, doxycycline 100 mg/d	Amantadine 100 mg/8h, baclofen 50 mg/8h, bupropion 150mg/12h, mirabegron 50 mg/d
Epworth Sleepiness Scale score (n)(b)	7	0	6
Pittsburgh Sleep Quality Index (n) (c)	1	4	9
Medical Research Council Prion Disease Rating Scale	20/20	16/20	15/20
Neuropsychological testing:	MMSE: 29/30. MoCA: 25/30. Mild attention and executive function impairment.	MMSE: 22/30. MoCA: 18/30. Moderate attention and executive function impairment.	MMSE: 24/30. MoCA: 19/30. Moderate attention and executive function impairment.
Mini-mental State Examination (MMSE)(d)			
Montreal Cognitive Assessment (MoCA)(e)			
Hospital Anxiety and Depression Scale (f)	A0 + D2 = 2 (No anxiety, no depression)	A7 + D10 = 17 (No anxiety, depression)	A5 + D10 = 15 (No anxiety, depression)
CSF amyloid beta 1−42 (N>600) [pg/mL]	739	391*	416*
CSF total-tau (N<385) [pg/mL]	667*	1272*	425*
CSF p-tau181 (N<65) [pg/mL]	35	149*	30
CSF quantitative 14-3-3 (N<3598)[AU/mL]**	8128*	8647*	4762*
PrP RT-QuIC Assay	Negative	Negative	Negative
Brain MRI	Normal	Mild subcortical small vessel disease.	Mild to moderate cerebellar atrophy and mild mesencephalic colliculi atrophy
Brain ^{18}F-FDG-PET	Mild bilateral superior parietal and precuneus hypometabolism	Mild left frontal hypometabolism	Mild bilateral cerebellar hemispheres hypometabolism

(*): abnormal CSF value. (**)Optimal 14-3-3 cut-off to discriminate between any neurodegenerative disease and healthy controls was 3598 AU/mL; (1) a 14-3-3 concentration above 20,000 AU/mL was suggestive of sporadic Creutzfeldt-Jakob disease.(2).

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[a] This patient had sleepwalking episodes during childhood that did not recur in adulthood.
[b] A score >10 points is indicative of excessive daytime sleepiness.
[c] A score >5 points is indicative of poor sleep quality.
[d] Normal MMSE score >24.
[e] Normal MoCA score >25.
[f] Normal HADS score 0–7.

Table 2
Summary of video-polysomnography findings.

Case	Video-polysomnography													
	EEG activity during wake (Hz)	SE (%)	TST (min)	Sleep latency (min)	WASO (min)	N1 (%)	N2 (%)	N3 (%)	REM sleep (%)	REM sleep with atonia	AHI(ev/h) / Mean SpO_2 (%) / CT90 (%)	PLMI (ev/h)	Arousal index (ev/h)	EEG, video analysis and other comments
1	7	84	404	4.4	71	15	39	19	27	YES	2 / 95.6 / 2.5	18	12	Slow and diffuse EEG activity, reactive to eyes opening; slow spindles.
2	8.5	52	258	3.7	232	25	41	28	6	YES	21 / 93.6 / 1.6	8	28	Chin EMG recorded bursts of repetitive rhythmic activity in wake-N1 and in N2 at the end of the recording
3	9	50	73	27	204	31	34	10	25	YES	3 / 96.6 / 0	30	17	Tachycardia at 100–120 bpm in wake and all stages of sleep

SE: sleep efficiency; TST: total sleep time; WASO: wake time after sleep onset; N1: stage N1 of NREM sleep; N2: stage N2 of NREM sleep; N3: stage N3 of NREM sleep; REM: rapid eye movement; AHI: apnea-hypopnea index; SpO2: saturation of oxyhemoglobin; CT90: proportion of time spent in saturations below 90%; PLMI: periodic leg movement index; EEG: electroencephalogram; Hz: hertz; min: minutes; h: hour; ev: events.

structures that regulate sleep [1].

In contrast to GSS, a variety of sleep symptoms and abnormal PSG findings are reported in other prion diseases. In FFI, insomnia, restless sleep, nocturnal confusion, nocturnal hallucinations, vocalizations and quasi-purposeful behaviors are often reported [6–8]. Sleep recordings in FFI show disrupted cyclical organization, reduction of total sleep time, progressive loss of sleep spindles, K complexes and slow wave sleep, and short periods of REM sleep interrupted by sub-wakefulness and loss of muscle atonia [6]. Importantly, in some FFI cases conventional sleep scoring rules are not applicable. Severe sleep architecture alterations, sleep-disordered breathing, and abnormal behaviors in sleep may be present [8]. Typical pathological findings in FFI, which may account for the prominent sleep alterations observed, are neuronal loss and gliosis within the mediodorsal and ventral anterior thalamus, and the brainstem nuclei that regulate sleep and respiration [6,20].

CJD patients often suffer from EDS, insomnia, OSA, RLS, hallucinations and complex behaviors in sleep [4,5]. PSG findings include sleep fragmentation, low sleep efficiency, reduction of slow wave sleep and REM sleep, loss of sleep spindles [4,5], loss of REM atonia and sleep-disordered breathing [4,5]. Whether the sleep disturbances in CJD correlate with neuronal loss in distinct brain regions or with disease progression remains unclear [4]. In CJD with the mutation E200K, where insomnia may be an early symptom, there is prominent thalamic damage [5].

Limitations of our study are a small sample size, lack of post-mortem neuropathology, single-night sleep recordings, no spectral power EEG analysis, lack of longitudinal sleep and V-PSG assessments, absent EEG recordings, and lack of autonomic or cardiovascular tests. Notably, GSS is a very rare condition, and neuropathology assessment was not possible since patients are alive. Strengths of our study include a comprehensive clinical assessment, and thorough sleep evaluation with subjective and objective measures.

5. Conclusions

Sleep staging in GSS is normal. However, several sleep disturbances were observed in our GSS cases, although findings seemed non-specific in contrast to FFI and CJD. Studies with larger sample size, longitudinal sleep data, and correlation with neuropathological assessments will help further elucidate sleep in GSS.

Declaration of competing interest

None.

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5. DISCUSIÓN

5. DISCUSIÓN

Los trabajos de esta tesis doctoral muestran que las alteraciones durante el sueño son prominentes en el IL, con la identificación de patrones distintivos en V-PSG que permiten agrupar las numerosas anomalías de la arquitectura del sueño, y las alteraciones de la respiración y de la conducta durante el sueño observadas en estos pacientes. Más allá de la afectación neuropatológica típicamente descrita en el IL, el primer trabajo pone de manifiesto la importante alteración de las áreas del tronco del encéfalo encargadas del control de la respiración y del sueño REM. Es más, hemos encontrado una asociación entre determinadas alteraciones durante el sueño y anomalías neuropatológicas en el ILf. A diferencia de lo observado en nuestros pacientes con IL, las alteraciones durante el sueño en la enfermedad de GSS son mucho menos frecuentes, menos características y no parecen específicas de esta patología. En la enfermedad de GSS, al contrario que en el IL, la arquitectura del sueño y los patrones respiratorios son normales.

Alteraciones del sueño como característica clínica distintiva entre las diferentes prionopatías

Los resultados de este trabajo ponen en evidencia la existencia de importantes diferencias en el sueño entre dos enfermedades priónicas. Las pruebas complementarias realizadas ante la sospecha de una prionopatía no muestran alteraciones específicas en el caso del IL y la enfermedad de GSS. El uso de biomarcadores en el LCR tales como los niveles de 14-3-3 y tau son de utilidad en el diagnóstico de la ECJ. Sin embargo, su sensibilidad está marcadamente disminuida en el IL y en la enfermedad de GSS.(168) Asimismo, el uso de RT-QuIC de segunda generación para la detección de la proteína priónica es altamente sensible en la ECJ, pero no en el IL y en la enfermedad de GSS.(127,169)

Si bien el sueño está típicamente alterado tanto en la ECJ como en el IL, las alteraciones del sueño no son una característica típica o específica de la enfermedad de GSS. De forma infrecuente, se ha reportado la presencia de insomnio o de alteraciones del sueño en pacientes con esta patología.(124,166,167) En un estudio identificando los signos precoces de enfermedad de GSS, no se mencionaban síntomas relacionados con el sueño.(117) En los tres casos previamente publicados de sujetos con enfermedad de GSS y estudio con PSG, la ausencia de síntomas relacionados con el sueño, y la presencia de un sueño con fases preservadas en PSG fueron reportados.(135,136) En dos de los tres

casos, se observó una reducción de la eficiencia de sueño, y en dos casos un aumento de la proporción de sueño superficial, con disminución del sueño profundo o del sueño REM. Uno de los sujetos estudiados tenía un índice ligeramente elevado de *arousals*.(136) En todos los casos, se identificaron las figuras normales del sueño y la atonía fisiológica del sueño REM. Asimismo, se distinguió un ritmo circadiano preservado con fluctuaciones en temperatura corporal central, presión arterial media y melatonina plasmática dentro de la normalidad.(135,136)

Estos hallazgos son similares a los encontrados en nuestros pacientes, en los que las figuras del sueño estaban preservadas, con fases normales claramente identificables. En dos de nuestros casos, había una reducción de la eficiencia de sueño. Estos pacientes referían insomnio, atribuido a incomodidad postural en la cama debido a sus síntomas neurológicos. Asimismo, observamos índices de MPPS ligeramente elevados en dos pacientes (índice de MPPS de 18 y 30 por hora) y AOS en un caso (índice de apnea-hipopnea de 21 eventos por hora). Uno de nuestros pacientes, sin síntomas del sueño referidos pero con historia de sonambulismo en la infancia, presentó un despertar confuso en la V-PSG. Debido a la alta prevalencia de MPPS en sujetos sanos sin quejas asociadas de impacto del sueño o durante el día,(170,171) así como la elevada frecuencia de AOS,(172), y de parasomnias NREM en la población general,(173) las alteraciones observadas son consideradas como probablemente inespecíficas. Estos hallazgos, así como posibles cambios con el curso de la enfermedad detectados con V-PSG seriadas, serán necesarios para corroborar nuestros resultados.

Las diferencias en el sueño entre prionopatías, pueden estar relacionadas con las distintas regiones del sistema nervioso central que se encuentran afectadas. En el IL, tanto el tálamo como áreas del tronco del encéfalo encargadas del control del sueño se encuentran típicamente alteradas.(90–92) Sin embargo, los resultados neuropatológicos descritos en la enfermedad de GSS se han centrado en hallazgos en corteza cerebral y cerebelosa.(66,106)

Además de su relevancia desde el punto de vista diagnóstico, las alteraciones durante el sueño pueden dar información pronóstica en el IL. La evidencia previa muestra el efecto del polimorfismo del codón 129 en el tiempo de supervivencia de estos pacientes, con un curso de la enfermedad más corto en el caso de sujetos homocigotos para metionina.(84,85) De acuerdo con nuestras observaciones en pacientes con IL, numerosas alteraciones del sueño se relacionan con una supervivencia más corta.

Encontramos una asociación entre una menor supervivencia y una menor presencia de sueño NREM, una mayor cantidad de pérdida de atonía durante el sueño REM, y una elevada variabilidad de la frecuencia respiratoria. En nuestra serie, además de haber encontrado una supervivencia menor en pacientes homocigotos para metionina, éstos tenían una eficiencia de sueño menor, menos y más cortos periodos de sueño NREM, y un mayor porcentaje con pérdida de atonía del sueño REM.

Dificultades en la codificación del sueño y la vigilia en el insomnio letal

Nuestros resultados en pacientes con IL ponen de manifiesto la necesidad de considerar adaptaciones en la interpretación de los hallazgos polisomnográficos en pacientes con determinadas patologías neurológicas que dañan las estructuras que modulan el sueño. Adaptaciones del sistema estándar de codificación propuesto por la AASM han sido previamente utilizadas para la descripción de los hallazgos durante el sueño en otras enfermedades neurológicas como la demencia por cuerpos de Lewy y la enfermedad anti-IgLON5. La presencia de un sueño NREM indiferenciado, una fase N2 pobremente diferenciada, las alteraciones del sueño REM, y las conductas anómalas durante el sueño observadas en estas patologías, han sido descritas sin seguir el sistema convencional de codificación del sueño, debido a la grave alteración de la arquitectura del mismo.(38,48)

En nuestra serie de pacientes con IL, fue necesaria la creación de un nuevo sistema de codificación que fuera descriptivo, ya que la representación detallada de los hallazgos en las V-PSGs de estos sujetos no era posible siguiendo la normativa estándar establecida por la AASM. En muchos casos, era difícil distinguir la vigilia del inicio del sueño, y los complejos K y los husos de sueño no estaban presentes. Debido a las rápidas transiciones entre diferentes estados y cambios conductuales a lo largo de los estudios, fue necesario describir nuevas fases del sueño, y analizar los registros en épocas de 15 segundos.

Trabajos previos ya mencionaron la evidencia de fases o estados en el IL que no eran típicamente de sueño o vigilia, entendidos de forma convencional. En un estudio con pacientes afectos de IL se describió la presencia de un ritmo alfa difuso en estados que conductualmente parecían corresponder a sueño.(151) En otro trabajo incluyendo pacientes con IL, se acuñó por primera vez el término subvigilia para denominar a un estado caracterizado por la presencia de actividad alfa difusa combinada con actividad theta, parecido al estado N1 del sueño NREM.(84) En estudios posteriores, se identificó

el estado de subvigilia como una actividad theta desincronizada y movimientos oculares rápidos superpuestos, o como rápidas oscilaciones entre fase N1 y sueño REM (con o sin atonía muscular).(87,154) En cuanto a los cambios en el sueño NREM, se describió previamente la evolución a un sueño NREM superficial, que parece rudimentario, observado entre la vigilia y el sueño REM, y especialmente evidente en fases avanzadas de la enfermedad.(84,152) En nuestros pacientes, utilizamos los términos subvigilia 1 y 2, así como sueño NREM indiferenciado superficial y profundo para una mejor caracterización de los cambios observados. El sueño NREM, aunque fuera indiferenciado, estaba presente incluso en sujetos con un tiempo de supervivencia reducido, así como en el paciente con V-PSG de seguimiento (el cual mostraba progresión de las alteraciones del sueño). Por otro lado, encontramos una proporción de vigilia más aumentada en aquellos pacientes con sueño NREM indiferenciado que en los que tenían un sueño NREM convencional, sugiriendo una mayor afectación general de la capacidad de generar un sueño normal. Alteraciones en el sueño REM han sido también descritas en el IL por otros autores.(84,151,152) En nuestro trabajo, hemos encontrado tanto la presencia de un sueño REM normal, como periodos de sueño REM de muy corta duración con pérdida de atonía y conductas y movimientos anormales sugestivos del TCSR, interrumpidos por vigilia. Hemos evidenciado también una correlación inversa entre la duración de los periodos REM y la cantidad de pérdida de atonía en esta fase del sueño. Asimismo, uno de los casos presentaba pérdida de atonía únicamente en uno de los cinco periodos REM en el registro.

La descripción detallada de los movimientos y conductas en nuestra serie de pacientes con IL ha sido fundamental para caracterizar los diversos hallazgos V-PSG observados más allá de las alteraciones en la arquitectura del sueño. Los movimientos de las extremidades aperiódicos, normalmente no estereotipados y a menudo involucrando también el tronco y la cabeza (como el famoso *cap i coll*), no son codificados en los estudios de sueño, y no aparecen en los criterios de codificación de la AASM. Sin embargo, éstos eran los movimientos más frecuentemente observados en nuestra cohorte de pacientes con IL, dándose en vigilia y persistiendo en algunos casos en subvigilia. Los movimientos manipulativos fueron también altamente prevalentes, especialmente en vigilia. Los movimientos finalísticos o pseudopropositivos, previamente descritos en el IL en el contexto del estupor onírico,(84) se evidenciaron en fases REM y subvigilia en

nuestros pacientes. Los movimientos finalísticos en vigilia y con ojos abiertos, fueron considerados como posibles alucinaciones.

Contrariamente a lo evidenciado en el IL, nuestros pacientes con enfermedad de GSS mostraban fases del sueño preservadas, con evidencia de complejos K y husos de sueño en sueño NREM, y atonía muscular durante el sueño REM, pudiendo hacer uso del sistema de codificación convencional propuesto por la AASM en estos estudios. La presencia de una eficiencia de sueño disminuida en dos de los casos parecía estar relacionada con el dolor y sintomatología neurológica resultando en incomodidad postural en la cama. Si bien observamos MPPS y AOS en dos pacientes, éstos eran de carácter leve-moderado. Asimismo, evidenciamos un despertar confuso en el paciente con historia de sonambulismo en la infancia. Debido a la alta prevalencia de estas patologías en la población general,(171–173) y a la preservación de un sueño esencialmente normal en nuestros pacientes, no se consideraron como hallazgos relacionados específicamente con la enfermedad de GSS.

La importancia de la respiración durante el sueño en el insomnio letal

Las alteraciones respiratorias durante el sueño han sido tangencialmente mencionadas como sintomatología o hallazgo en la PSG de pacientes con IL. El estudio sistemático de los hallazgos respiratorios en las V-PSGs de estos pacientes han recibido clásicamente escasa atención.

En nuestra serie, hemos encontrado un elevado número de alteraciones respiratorias, incluyendo la presencia de apneas, estridor, hipo y catatrenia, así como otros ruidos respiratorios. Hemos observado una mayor variabilidad de la frecuencia respiratoria en sujetos con IL que en controles, y una relación de ciertas alteraciones respiratorias con una menor supervivencia y una mayor afectación neuropatológica. Tanto el número de síntomas respiratorios, como la presencia de una variabilidad de la frecuencia respiratoria aumentada en el sueño NREM, se correlacionaron con la degeneración de los núcleos ambiguo y solitario. Por otro lado, dada la función del núcleo parabraquial en condiciones normales,(174) la afectación de dicho núcleo que encontramos podría explicar la presencia de inestabilidad respiratoria y una respuesta alterada a niveles de CO_2, dando lugar a las apneas centrales que observamos con frecuencia en cuatro de nuestros pacientes. Los pacientes que presentaron una elevada variabilidad de la frecuencia respiratoria, y una elevada variabilidad de la frecuencia

respiratoria especialmente en sueño NREM, tuvieron una menor supervivencia. Sin embargo, las apneas centrales no se asociaron con la supervivencia. El significado clínico de algunos de estos hallazgos es incierto. Dada la relación de algunas de las alteraciones respiratorias encontradas en el IL con un mayor daño en los centros de control respiratorio o con una supervivencia menor, se podría postular el papel pronóstico de las mismas en el curso de la enfermedad.

En nuestros pacientes con enfermedad de GSS, no se hallaron alteraciones específicas de la respiración. Se observó una forma moderada de AOS en uno de los casos, sin evidencia de apneas centrales, u otras alteraciones respiratorias.

Patrones vídeo-polisomnográficos en el insomnio letal

El nuevo sistema de codificación que hemos propuesto ha permitido la identificación y descripción de numerosos hallazgos relacionados con la alteración de la arquitectura y fases del sueño, los movimientos y conductas anómalas, y las alteraciones de la respiración en estos sujetos. De esta manera, propusimos tres patrones diferenciados de V-PSG que tienen en cuenta los hallazgos en la arquitectura del sueño, las conductas motoras, la respiración y las alteraciones en el codón 129.

- Grupo **agitado**. Estos pacientes tienen muy baja eficiencia de sueño, con proporciones y número de periodos de sueño NREM reducidos, elevado porcentaje de transiciones vigilia-REM, con periodos de sueño REM cortos y marcada pérdida de atonía. Estos individuos presentaban un gran número de movimientos, especialmente aperiódicos y manipulativos, pero también algunos finalísticos. Desde el punto de vista respiratorio, mostraban una variabilidad de la frecuencia respiratoria incrementada, numerosos ruidos respiratorios, pero no apneas centrales. Todos ellos eran homocigotos para metionina en el codón 129.

- Grupo **tranquilo-apneico**. Se observa una eficiencia de sueño intermedia-baja, con proporciones elevadas de subvigilia y de transiciones vigilia-subvigilia, pero menor alteración del sueño NREM, y marcada pérdida de atonía del sueño REM. En estos casos, no había prácticamente movimientos o conductas anormales, pero los pacientes presentaban un gran número de apneas centrales, con variabilidad de la frecuencia respiratoria elevada. Dos de los cuatro pacientes clasificados en

este grupo, eran homocigotos (metionina-metionina) y los otros dos heterocigotos (metionina-valina) para el codón 129. La supervivencia era similar a la del grupo agitado.

- Grupo **tranquilo-no apneico**. La eficiencia de sueño en estos casos está por encima del 45%, con sueño NREM y sueño REM relativamente preservados. Entre estos individuos, se encontraron las variabilidades de frecuencia respiratoria más bajas, el menor índice de apneas centrales, y la menor presencia de movimientos anormales durante el sueño. Todos estos sujetos eran heterocigotos metionina-valina para el codón 129. Los pacientes clasificados en este grupo presentaban una mayor supervivencia respecto a los otros dos grupos.

Debido a la presencia de una estructura del sueño, conductas y respiración durante el sueño normales en nuestros pacientes con enfermedad de GSS, no había evidencia de patrones de V-PSG específicos, al contrario de lo observado en el IL.

Hallazgos neuropatológicos y su relación con alteraciones del sueño en el insomnio letal

Los estudios *post-mortem* de sujetos con ILf muestran característicamente una pérdida neuronal y astrogliosis reactiva en los núcleos anteroventral y dorsomedial del tálamo, y una marcada pérdida neuronal en las olivas inferiores.(175) Las estructuras implicadas en el control central de la respiración no se han analizado de forma sistemática, o se han considerado normalmente preservadas, a pesar de su proximidad topográfica con respecto a las áreas típicamente afectadas en el IL.(91,152,176,177)

El estudio patológico de nuestros pacientes con IL demostró, además de los hallazgos típicos de la enfermedad, marcadas pérdida neuronal y gliosis en los núcleos solitario y ambiguo, posible pérdida neuronal en el rafe bulbar, y afectación de los núcleos vestibular, parabraquial y sustancia gris periacueductal/rafe mesencefálico.

En nuestra serie, un menor número de periodos de sueño NREM se asoció a una mayor alteración del núcleo parabraquial. Este hallazgo sugiere que este núcleo modula el sueño NREM, como evidencian modelos animales.(178,179) Por otro lado, se ha encontrado una relación inversa entre el número y la duración de los periodos de sueño REM, y la afectación del rafe a nivel bulbar en nuestros pacientes. La implicación de la actividad serotoninérgica de los núcleos del rafe en el sueño REM se ha demostrado

previamente en modelos animales.(180) Asimismo, se ha postulado en estudios previos una alteración de la actividad serotoninérgica en el ILf.(181,182)

La presencia de las diversas alteraciones respiratorias durante el sueño en nuestra serie de pacientes con IL, y su correlación con la afectación de distintas áreas troncoencefálicas encargadas del control de la respiración, se ha comentado anteriormente en esta discusión.

Si bien la afectación talámica y de ciertos núcleos del tronco del encéfalo ha sido descrita previamente en la enfermedad de GSS, no parece ser el caso en las formas asociadas a la mutación P102L (hallada en nuestros pacientes).(106) En la enfermedad de GSS, no ha sido descrita la afectación neuropatológica de áreas y núcleos relevantes en el control del sueño tales como el hipotálamo, núcleos del rafe, *locus coeruleus* y núcleo subcerúleo, núcleo gigantocelular, o sustancia gris periacueductal. En nuestro trabajo con pacientes con enfermedad de GSS, no disponemos de estudio neuropatológico, ya que los tres sujetos incluidos están vivos. Estudios incorporando el análisis neuropatológico y con V-PSG en la enfermedad de GSS serán de utilidad para aportar un mayor conocimiento sobre la relación clínico-neuropatológica del sueño en sujetos con esta prionopatía.

Fortalezas, limitaciones, y propuestas para el futuro

De forma conjunta, los dos trabajos contribuyen a incrementar el conocimiento de las enfermedades priónicas, centrándonos en las alteraciones del sueño.

Hemos estudiado el sueño de dos enfermedades priónicas que son muy poco frecuentes, el IL y la enfermedad de GSS. Nuestro estudio del sueño ha incluido la historia clínica, escalas específicas de sueño y la V-PSG. Nuestros resultados dan también a conocer los hallazgos neuropatológicos de una cohorte relativamente grande de sujetos con IL, y de otras características clínicas y de neuroimagen en pacientes con IL y enfermedad de GSS. Asimismo, en el IL hemos aportado datos desde un punto de vista pronóstico, debido a las relaciones encontradas entre alteraciones durante el sueño, ciertas características clínicas y neuropatológicas, y la supervivencia.

Limitaciones de este trabajo incluyen 1) un tamaño muestral pequeño en ambos trabajos debido a que evaluamos enfermedades con muy baja prevalencia, 2) la realización en algunos casos de V-PSG en sujetos que tomaban medicaciones

(benzodiacepinas, antidepresivos) con potencial efecto en la arquitectura del sueño y en el patrón respiratorio, 3) la ausencia de información longitudinal en la mayoría de los casos, 4) la falta de estudios con V-PSG durante el día o EEG de rutina, 5) la falta de estudios de función autonómica, y 6) la ausencia de estudio neuropatológico en algunos casos de IL y en todos los casos de GSS (si bien, esto se debe a que los pacientes no han fallecido).

Futuros trabajos con un mayor número de pacientes con estas patologías serán de ayuda para corroborar nuestros hallazgos. Se deberán idealmente explorar también los cambios en las alteraciones durante el sueño en el IL y en la enfermedad de GSS de forma seriada, a medida que avanza la enfermedad. Asimismo, será importante disponer de información neuropatológica en la enfermedad de GSS y ampliar el análisis de las estructuras que controlan el sueño y la respiración que están afectadas en otras prionopatías como el IL. Sería relevante dilucidar si las diferencias clínicas y de V-PSG observadas entre IL y la enfermedad de GSS se deben a afectaciones de áreas distintas a nivel del sistema nervioso central. Por otro lado, aunque el sistema de codificación creado para la descripción de los hallazgos en el IL ha resultado imprescindible para la caracterización de los resultados, su conversión a una forma automatizada sería de utilidad para poder implementar y extender su uso de forma rutinaria.

6. CONCLUSIONES

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1) En los pacientes con insomnio letal, la arquitectura del sueño y la respiración durante el sueño están gravemente afectadas.
2) En los pacientes con insomnio letal, a menudo es necesario el uso de formas adaptadas de codificación de los estudios vídeo-polisomnográficos para la identificación de la vigilia y las distintas fases del sueño, que son patológicas.
3) En el insomnio letal, algunas alteraciones del sueño se relacionan con la afectación neuropatológica de las áreas troncoencefálicas que controlan el sueño y la respiración.
4) En el insomnio letal, algunas alteraciones de la arquitectura del sueño y de la respiración se asocian a una menor supervivencia.
5) En la enfermedad de Gerstmann-Sträussler-Scheinker la arquitectura del sueño y la respiración durante el sueño son normales.
6) Las alteraciones durante el sueño encontradas en los pacientes con la enfermedad de Gerstmann-Sträussler-Scheinker (apneas obstructivas, movimientos periódicos de las piernas durante el sueño y parasomnia NREM) son inespecíficas y de significado incierto.
7) Las magnitud y gravedad de las alteraciones durante el sueño son muy diferentes entre dos prionopatías como el insomnio letal y la enfermedad de Gerstmann-Sträussler-Scheinker.

7. BIBLIOGRAFÍA

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