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# Anti-Hu-associated brainstem encephalitis

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## Abstract

**Objective:** We review a series of patients with anti-Hu-associated brainstem encephalitis to better define the clinical presentation and to improve its recognition.

**Methods:** We collected data from 14 patients diagnosed by members of the Paraneoplastic Neurological Syndromes Euronetwork, and eight patients from the literature who presented with isolated brainstem encephalitis and had anti-Hu antibodies.

**Results:** The median age of the 22 patients was 64 years (range 42-83) and 50% were men. All patients developed a subacute neurological syndrome, in days or weeks. Brain MRI was always normal. Mild CSF pleocytosis was reported in only two patients. The following syndromes were identified on admission: A *medullary syndrome* was seen in 11 (50%) patients. Seven of them presented with dysphagia, dysarthria and central hypoventilation. The other four in addition of bulbar symptoms, without central hypoventilation, presented pontine manifestations. Six (27%) patients developed a *pontine syndrome* with paresis of the VI or VII cranial nerves, nystagmus, usually vertical, and gait ataxia. There was a rapid downward progression to the medulla in all patients. Five (23%) patients presented a *ponto-mesencephalic syndrome* with uni or bilateral palsy of the III and VI cranial nerves and gait ataxia, but rapidly progressed to complete gaze paresis and medullary dysfunction.

**Conclusions:** The study confirms the predominant medullary involvement but also shows that half of the patients present with clinical features that indicate an upper, mainly pontine, dysfunction before downward progression.

## Introduction

Anti-Hu antibodies are well known markers of paraneoplastic encephalomyelitis (PEM), one of the most frequent remote effects of cancer. PEM usually antedates the diagnosis of the underlying tumor, almost always small cell lung cancer (SCLC).[1] The clinical symptoms of PEM may be confined to one particular part of the nervous system or, more frequently, involve overtime multiple areas. Classical clinical syndromes at presentation of PEM include sensory neuronopathy, and limbic encephalitis.[2] The clinical syndrome of brainstem encephalitis was well recognized in the initial descriptions of PEM[3] and represents the predominant syndrome in 11% of patients with anti-Hu antibodies.[4] However, a detailed analysis of the clinical symptoms of patients who present with isolated brainstem encephalitis was not done in previous series of paraneoplastic neurological syndromes (PNS) associated with anti-Hu antibodies.[1,4-6]

The aim of this study was to review a series of patients with anti-Hu antibodies who presented with isolated involvement of the brainstem to better define the clinical syndrome with the goal of improving the recognition of this disorder.

## Methods

We collected data from 14 patients with anti-Hu-associated brainstem encephalitis diagnosed by members of the Paraneoplastic Neurological Syndromes Euronetwork, an international panel of neurologists interested in the field of PNS founded in November, 2002.[7] Three patients were previously reported.[8] Inclusion criteria included positive anti-Hu antibodies according to recommended criteria,[7] diagnostic criteria of definite PNS,[7] clinical presentation compatible with brainstem involvement, and adequate information on the neurological symptoms, severity of neurological dysfunction, delay in the neurological diagnosis, tumor diagnosis, treatments received and outcome. Patients who presented with predominant pancerebellar ataxia or involvement of other areas of the nervous system were excluded even if they had symptoms suggestive of brainstem dysfunction because they were considered to have PEM or paraneoplastic cerebellar degeneration.

The information was obtained from forms filled out by the referring neurologists and review of the clinical records. The forms received for the final analysis did not contain any data that could identify the patient or the hospital of origin.

Literature review about paraneoplastic brainstem encephalitis was also done and the findings of eight reported patients were added to our analysis.[4,8-15] Articles published in English on brainstem encephalitis and anti-Hu antibodies were identified by search of PubMed and from relevant articles and personal files of the authors. Abstracts and reports from meetings were not included. Eight reported patients were excluded from the analysis because they presented predominant involvement of the nervous system in addition to the brainstem symptoms.[16-23] One patient was excluded due to an encephalitis caused by herpes virus at the same time of the brainstem dysfunction.[24]

## Results

The 22 patients (eight from the literature review) had a median age of 64 years (range: 42-83). Eleven patients (50%) were men. A histological diagnosis of cancer was obtained in 15 patients (SCLC: 11; hypernephroma: 1; prostate adenocarcinoma: 1; breast carcinoma: 1; myxoid liposarcoma: 1). Two patients showed radiological evidence of lung cancer but histological diagnosis was not obtained. No tumor was diagnosed in five patients. One of them is alive nine years after the diagnosis of the brainstem encephalitis.

All patients developed the neurological syndrome, in days or weeks. Two patients had a relapsing course (patient 10 and 11, table). The initial symptoms spontaneously improved but after a few days or weeks they relapsed and made a relentless progression. At the time of the initial evaluation, five (36%) of the 14 patients identified in the database had a Rankin score higher than 3 (symptoms clearly prevent independent existence). Brain MRI was normal in the 22 patients. CSF analysis was available from 19 patients. CSF pleocytosis was detected in only two patients. Elevated protein concentration was a more common finding observed in 14 patients (median 81 mg/dl; range 46-146 mg/dl).

Three neurological syndromes that pointed to a dysfunction of specific brainstem levels were identified at the time the patients were first evaluated:

*Ponto-mesencephalic syndrome*

Five (23%) patients (patients1-5, table) presented clinical features of involvement of mesencephalon and pons. Main initial complains were diplopia, ptosis, and gait ataxia. On the neurological examination, there was oculomotor impairment due to supranuclear gaze palsy, motor ocular cranial nerves palsies or both. Unilateral or bilateral involvement of the sixth and third cranial nerves was observed in four patients. The pupillary responses were always present. The neurological findings worsened, in days or a few weeks, to complete gaze paralysis and progression to medullary involvement in four of the five patients.

*Pontine syndrome*

Six (27%) patients (patients 6-11, table) developed for several weeks progressive dizziness, gait ataxia or diplopia. Two patients (10 and 11 from the table) presented a spontaneous improvement of the symptoms and were misdiagnosed of vertebrobasilar ischemia or Miller-Fisher syndrome. The neurological examination disclosed paresis of the VI or VII cranial nerves, gait ataxia, and nystagmus usually vertical. Over the ensuing days or weeks, five patients developed clinical features suggestive of downward progression to the medulla.

*Medullary syndrome*

Eleven (50%) patients (patients 12-22, table) were admitted with symptoms of bulbar impairment. Two groups of patients were distinguished. Patients 12 to 18 developed in a few days, dysphagia, dysarthria, and central hypoventilation that required intubation at the emergency room or a few days after admission. The clinical description of some of these patients was consistent with an Ondine's curse or failure of automatic respiration that causes nocturnal alveolar hypoventilation. The other four patients (patients 19 to 22), in addition to the bulbar impairment, presented with dizziness, diplopia, and paresis of the VI or VII cranial nerves compatible with a pontine dysfunction that had progressed to involve the medulla at the time of admission. None of them developed central hypoventilation.

*Treatment and outcome*

Sixteen patients (73%) were treated: eight with immunotherapy (steroids, immunoglobulins or both), five with oncological therapy (surgery, chemotherapy or radiotherapy), and three with oncological and immunomodulatory therapy. Six patients did not receive any treatment. Patients with the ponto-mesencephalic syndrome at presentation died from the brainstem encephalitis with the exception of the two treated with immunoglobulins or tumor resection (Patients 3 and 5). All patients with the pontine syndrome were treated with immunotherapy and three with oncological therapy and none improved. Four patients died from the brainstem syndrome and one due to the SCLC. Only two patients with the medullary syndrome improved and none of them had central hypoventilation. In summary, 15 patients died with a median survival of 3 months (range: 1 to 30 months). Three of the six patients who are alive improved but none of them had central hypoventilation. One patient was lost to follow-up.

## Discussion

Brainstem encephalitis is not a classical paraneoplastic syndrome and the clinical clues that may raise the correct diagnosis are not well established. The present study confirms the predominant involvement of the medulla but also shows that at least half of the patients present with clinical features that indicate an upper involvement in the pons and more rarely the mesencephalon before the downward progression. As in other Hu-associated neurological syndromes, patients rarely improved despite treatment of the tumor and immunotherapy.[1] The involvement of the medulla during the evolution of the syndrome probably contributed to the short overall survival of patients with this syndrome.

We identified several clues that may help in the diagnosis of Hu-associated brainstem encephalitis. The clinical course was subacute. With one exception, that was previously seen in another hospital,[12] patients with bulbar presentation developed the full-blown syndrome after a median time of two weeks. Median time from onset of the syndrome to the first neurological evaluation was eight weeks for patients who presented with pontine or ponto-mesencephalic and all but the patient whose tumor was removed,[15] rapidly progressed to involve the medulla. Brain MRI was always normal. However, some patients were diagnosed in the early nineties and evaluated with older generation MRIs that could have missed subtle brainstem changes. CSF analysis was almost always normal in contrast with other Hu-associated CNS syndromes that show CSF pleocytosis in around 50% of the patients.[25]

The study confirmed the frequent clinical presentation suggestive of medullary involvement described in PEM patients before the discovery of Hu antibodies[2,3] with dizziness, nausea and vomiting, dysarthria, dysphagia, that usually required nasogastric feeding, and central hypoventilation. However, our series emphasizes that patients may present with a medullary syndrome in absence of involvement of other areas of the nervous system that would favor the diagnosis of a paraneoplastic etiology.[2]

The medullary syndrome of these patients can usually be distinguished from other causes of bulbar palsy due to motoneuron disease, myasthenia, or other neuromuscular syndromes, by the frequent presence of dizziness or nystagmus and sparing of the tongue and neck muscles. Similarly, the progression in days or weeks, the frequent absence of sensory symptoms, corticospinal dysfunction,

and the presence of clinical features that indicate involvement of more that one vascular territory should rule out the possibility of vascular disease.

Although almost all the patients developed during the evolution of the syndrome clinical involvement of the medulla, 50% presented at the first evaluation with clinical features that suggest a pontine or ponto-mesencephalic dysfunction. Patients presented with diplopia sometimes associated with dizziness and the clinical examination disclosed unilateral or bilateral palsy of the abducens nerve alone or with other oculomotor nerves. Pupillary reflexes were always spared. The patients showed additional features of brainstem involvement mainly nystagmus and gait ataxia. This type of presentation may lead to an initial misdiagnosis of Miller Fisher syndrome,[26] as occurred in Patient 11 of this series, or Bickerstaff encephalitis.[27] Patients with Bickerstaff encephalitis usually present with variable degrees of drowsiness and stupor, a feature not reported in the Hu-positive patients unless they had central hypoventilation. In addition, other common features in Bickerstaff encephalitis or Miller Fisher syndrome such as internal ophthalmoplegia, limb or bilateral facial motor weakness, are not found in Hu-associated brainstem encephalitis and they should help in the diagnosis.[28] Lastly, up to 30% of patients with Bickerstaff encephalitis show in the brain MRI high-intensity abnormalities on T2-weighted images of the brainstem.[27]

None of the patients in this series had a pure mesencephalic syndrome. This feature differentiates the Hu-associated brainstem syndrome from that observed in patients with Ma2 antibodies.[29] Patients with Ma2-associated brainstem encephalitis usually present vertical gaze palsies suggesting that the disorder predominantly targets the upper brainstem structures involved in the supranuclear control of vertical gaze, followed during the course of the disease by involvement of the oculomotor nuclei. Unlike patients with Hu-associated brainstem encephalitis, the brain MRI of Ma2-positive patients may show hyperintense lesion of T2-weighted sequences in the superior colliculi and periaqueductal region.[29]

Patient 15 of this series developed during the evolution of his encephalitis weakness of the neck, shoulders, and arms compatible with extension of the inflammatory process to the spinal cord. Previous to the description of Hu antibodies, a patient was reported, in two separated publications, [30,31] with a particular medullary and spinal cord involvement that antedated the diagnosis of a SCLC. Although none of the patients in this series had this presentation, we think this particular form should be added to those defined in this study. The patient presented with unilateral deafness of sudden onset followed by progressive motor weakness of the shoulders, arms, and neck over the ensuing weeks. On admission, the neurological examination did not show any paresis of the lower cranial nerves. There was atrophy and paresis of the muscles of the neck, shoulders and arms and diminished pain and temperature sensation in the cervical dermatomes. Patient had a rapid downhill course with respiratory insufficiency and dysphagia. At autopsy, there was neuronal loss and inflammatory infiltrates in the medulla and cervical spinal cord and severe loss of cochlear neurons of the affected auditory nerve.[31]

In conclusion, Hu-associated brainstem encephalitis is a rare disorder with devastating effects. The current study provides clinical features that should be useful to consider this diagnosis in patients with rapidly evolving brainstem syndromes to make a prompt diagnosis, direct the search of the tumor, and

start the appropriate therapy. Despite the poor outcome, treatment should be considered in all patients because a clinical improvement occurred in three of the 16 patients who received either immunotherapy or oncological treatment.

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**Table. Hu-associated braintem encephalitis: neurological syndromes**

| Case (ref) | Time to admission | Main presenting symptoms | Neurological findings at admission | | | | | | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | | Supranuclear gaze palsies | Cranial nerve palsies | Nystagmus | Gait ataxia | Dysautonomia | Long tract dysfunction | |
| ***Ponto-mesencephalic syndrome*** | | | | | | | | | |
| 1 | 2 weeks | Diplopia, dizziness | Vertical | III, IV,VI unilateral | Bilateral, horitzontal | Yes | No | No | IX, X, death from pneumonia in 6 weeks. No tumor found at autopsy. |
| 2 | 4 weeks | Diplopia, ptosis | Horizontal | III, VI,VII unilateral | No | Yes | No | No | IX, X, CH, respiratory arrest. Death in 12 weeks. SCLC at autopsy. |
| 3 | 8 weeks | Diplopia, dizziness | No | III unilateral | Down-beating | Yes | No | Motor, Sensory | IX, X, patient stable and alive 9 years later. No tumor found. |
| 4 (10) | 8 weeks | Diplopia | No | III, IV,VI bilateral | No | Yes | No | Motor, bilateral | Dysphagia, dysarthria, death from pneurmonia. No tumor found |
| 5 (15) | 12 weeks | Ptosis | No | III,IV,VI bilateral | No | No | No | No | Gradual improvement in four months after sarcoma resection |
| ***Pontine syndrome*** | | | | | | | | | |
| 6 | 4 weeks | Diplopia | No | VI, unilateral | No | Yes | No | No | VII, IX, X, death in 9 weeks. Lung cancer by X-ray |
| 7 | 12 weeks | Dizziness, nausea/vomiting | No | VII, unilateral | Down-beating | Yes | OH | No | IX, X, CH, death in 5 months. No tumor found |
| 8 | 4 weeks | Diplopia, dizziness, nausea/vomiting | No | VI, unilateral | Down-beating | Yes | No | No | CH, death in 8 days. No tumor was found. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 9 | 16 weeks | Dizziness, diplopia, OH | No | VI, | Up-beating | Yes | OH | No | SCLC, patient lost |
| 10 | 8 weeks | Diplopia, dizziness | No | VII, unilateral | horizontal, bilateral | Yes | No | Motor | IX,X, sensory tract dysfunction, CH. SCLC. Death in 2.5 months |
| 11 | 4 weeks | Diplopia | No | VI, bilateral | No | Yes | No | Motor, bilateral | IX,X, sensory neuropathy, LEMS. Death in 2 years from SCLC |
| ***Medullary syndrome*** | | | | | | | | | |
| 12 | 2 weeks | CH, dysphagia, dysarthria | No | IX, X, unilateral | No | No | CH | No | Stabilization. Treated with steroids and hormones for prostate cancer |
| 13 | < 1 week | CH, dysphonia | No | NA* | No | No | CH | No | Blood pressure instability. Dead in four months. Lung cancer by X-ray |
| 14 | 2 weeks | Dizziness, dysarthria, CH | No | VII* | Horizontal | No | CH | Motor, unilateral | Blood pressure instability. Dead in four weeks. SCLC at autopsy |
| 15 | 2 weeks | Diplopia, dysarthria, Dysphagia, CH | No | VI, VII, IX, X | No | No | CH | No | XI, cervical motoneuron dysfunction. Death in 3 months. Kidney cancer |
| 16 (11) | 2 weeks | OH, CH | No | NA* | No | NA | OH, CH | No | Downbeat nystagmus, limb ataxia. SCLC. Ventilator dependent at six months. |
| 17 (9) | 6 weeks | Oscillopsia, dysphagia | Hypometric saccades | IX, X, bilateral | Vertical | Yes | No | No | CH, bilateral corticospinal signs. Death despite SCLC treatment. |
| 18 (14) | 4 weeks | Dizziness, diplopia, nausea/vomiting | NA | NA* | NA | Yes | No | NA | CH, Recurrent episodes of coma and death. SCLC not treated |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 19 | 1 week | Dizziness, diplopia, dysphagia | No | VI, IX, X | Up-beating | Yes | No | Sensory | Right hemiparesis. Dead from SCLC progression |
| 20 (4) | 4 weeks | Dizziness, OH | No | VII, IX, X | Right horizontal | Yes | OH | No | Not reported. SCLC at autopsy |
| 21 (12) | 20 weeks[&] | Dizziness, hoarseness, dysphagia | No | IX, X, bilateral | Vertical | No | No | No | Improved after SCLC treatment |
| 22 (13) | 2 weeks | Diplopia, hoarseness, dysphagia | No | VI, IX, X, bilateral | No | Yes | No | No | Improved with immunotherapy. Breast cancer discovered later |

* Intubation prevented evaluation of IX, X cranial nerves. &: Previously admitted to another hospital. Time not specified. CH: Central hypoventilation; NA: intubation prevented examination of lower cranial nerves; OH: Orthostatic hypotension. SCLC: small cell lung carcinoma.