SHORT REPORT

Central hypoventilation as the presenting symptom in Hu associated paraneoplastic encephalomyelitis

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Central hypoventilation is usually caused by ischaemic or neoplastic lesions of the medulla and upper cervical spinal cord. An autoimmune disorder is not usually considered in the differential diagnosis of this syndrome. We retrospectively identified 14 patients from our database of 202 patients with Hu antibodies who presented with brainstem symptoms. Three were admitted to hospital because of central hypoventilation. All underwent intubation and mechanical ventilation. They could breathe properly while they were awake but suffered deep apnoeas during sleep. Two died, but one is still alive requiring ventilatory assistance during sleep. Autopsy was performed in one of the patients which showed severe inflammatory infiltrates and neuronal loss in the medulla. All patients had normal brain imaging studies and the cause of central hypoventilation was an unsolved problem until Hu antibodies were determined.

Acquired central hypoventilation, leading to loss of automatic respiration with preserved voluntary breathing (Ondine's curse), occurs with medullary lesions, usually ischaemic infarctions,¹ Chiari malformation,² brainstem glioma³ or cervical spinal damage.⁴ Although central hypoventilation related to anti-Hu associated paraneoplastic encephalomyelitis has been reported,^{5–6} the frequency of this complication among these patients is not known. We reviewed our database of patients with anti-Hu antibodies to describe those who presented with central hypoventilation.

METHODS

We retrospectively selected from our database of 202 patients with Hu antibodies (Hu-ab), 14 who presented with symptoms of brainstem encephalitis. The characteristics of the database have been reported previously.⁷ We identified three patients (1.5%) whose cause of admission to hospital was central hypoventilation. Two of the three patients included in this report were personally seen by at least one of the authors. The clinical features of these patients are summarised in table 1.

Hu-ab and other onconeural antibodies (Yo, Ri, Tr, CV2, amphiphysin, Ma2) were screened by immunohistochemistry on frozen sections of rat brain. Hu-ab were confirmed by immunoblot of isolated neuronal nuclei, as described previously.⁷ No additional onconeural antibodies, other than Hu-ab, were detected.

CASE REPORTS

Patient No 1

A 77-year-old woman, non-smoker, was admitted with cyanosis and progressive obtundation. She had been complaining of progressive dizziness, gait unsteadiness and dysarthria for 12 days. In the emergency room, she was intubated and ventilated with rapid recovery of her normal mental status. Arterial bicarbonate level was normal, suggesting subacute

onset of respiratory failure. Neurological examination showed an alert patient who was able to answer questions correctly by moving the arms or the eyelids. There was a right facial paresis, horizontal gaze evoked nystagmus, mild right arm paresis and bilateral extensor plantar reflex responses. Routine blood analysis, including thyroid hormones, CSF examination, EEG, whole body CT scan, bronchoscopy and brain MRI were negative or normal. Hu-ab were positive in serum (titre 1:10 000). Repeated attempts at weaning the patient from the respirator were limited by prolonged apnoeas, particularly when the patient was asleep. The respiratory symptoms did not improve despite treatment with a 5 day course of intravenous immunoglobulins. The clinical course was complicated by the onset of dysautonomic symptoms (severe hypertension and bradycardia) and bronchopneumonia that was the cause of death 1 month later. The autopsy disclosed a localised small cell lung carcinoma. Brain examination disclosed widespread perivenous and parenchymal inflammatory infiltrates and severe neuronal loss in the medulla involving the 12th neuronal nuclei, inferior olives, nucleus ambiguus and reticular system. Less intense inflammatory changes were identified in the cerebral cortex and anterior horns of the spinal cord.

Patient No 2

A 70-year-old man was admitted with severe dyspnoea and respiratory failure. In the emergency room, he underwent orotracheal intubation and mechanical ventilation and was admitted to the ICU. Arterial bicarbonate level was normal, suggesting subacute onset of respiratory failure. He had complained of progressive dysphonia and dysphagia in the previous 3 weeks. A local prostatic adenocarcinoma had been diagnosed 6 months earlier. He had been receiving hormonal treatment with return of prostate specific antigen levels to normal values.

Neurological examination disclosed an intubated patient who was alert and able to follow commands. There was paralysis of the right 9th and 10th cranial nerves. The patient could breathe without any problem while awake. However, the presence of severe apnoeas when he was asleep prevented any attempt to wean him from the respirator.

Routine blood analysis, including prostate specific antigen levels, brain and cervical spine MRI, bronchoscopy with alveolar lavage and body positron emission tomography scan were normal or negative. Hu-ab were found in the serum with a titre of 1:20 000. The patient was treated with three courses of high dose methylprednisolone and intravenous immunoglobulins without improvement. He underwent a percutaneous gastrostomy. A tracheostomy was performed and a volumetric ventilator (BREAS) was adapted to help the patient's breathing during sleep.

Abbreviation: Hu-ab, Hu antibodies

Table 1 Clinical features of Hu positive patients who presented with central hypoventilation

Patient No	Age (y) /sex	Cancer	Associated symptoms	Dysautonomia	Time to intubation	MRI	Treatment	Outcome
1	77/F	SCLC	Dizziness, gait ataxia	Yes	12 days	Normal	Immunoglobulins	Dead
2	70/M	Prostate	Dysphonia	No	3 weeks	Normal	Immunoglobulins, methylprednisolone	Alive with ventilatory support during sleep
3	61/M	Enlarged mediastinal lymph node*	Dysphonia, neuropathy	Yes	3 months	Normal	Chemotherapy	Dead

SCLC, small cell lung carcinoma.

*Highly suspicious of lung cancer.

After 2.5 years, the patient's symptoms are unchanged. He requires ventilatory support at night. A follow-up polysomnographic napping study showed the persistence of severe central apnoeas during sleep. The tumour remains in remission.

Patient No 3

A 61-year-old man was admitted because he suffered prolonged apnoeas; "he had forgotten how to breath". In the previous 3 months, he had complained of lumbar pain that had spread to both legs, gait unsteadiness and dysphonia. Neurological examination performed elsewhere showed lower limb areflexia with mild leg weakness. The EMG was suggestive of axonal polyneuropathy.

At admission he underwent intubation and mechanical ventilation in the emergency room. The patient obeyed orders correctly, there was deep tendon areflexia in the legs with mild distal weakness. The rest of the neurological examination was normal. CSF showed raised protein level (146 mg/dl) with pleocytosis (37 lymphocytes). Brain MRI was normal. A body CT scan disclosed an enlarged mediastinal lymph node suggestive of lung cancer. Hu-ab were found in serum with a titre of 1:10 000.

Despite several attempts to wean, it was not possible because of recurrent apnoeas after ventilation withdrawal. Based on the positive anti-Hu antibodies, the patient was treated with chemotherapy although there was no pathological diagnosis of the mediastinal mass. There was no clinical improvement and the mediastinal mass remained stable. He developed progressive blood pressure instability, gastric paresis and intestinal ileus. The patient died from infectious complications 4 months after the onset of symptoms without improvement of the respiratory symptoms. An autopsy was not performed.

DISCUSSION

Our patients suffered central hypoventilation in the absence of airway obstruction or severe weakness that could justify respiratory failure. Severe apnoeas were present during sleep whereas they were able to breath spontaneously during the day (Ondine's curse). Although other symptoms suggesting brainstem involvement preceded the breathing failure for days or weeks, respiratory insufficiency was the problem that led to hospital admission in all cases. Two of our patients (patient Nos 1 and 3) developed severe dysautonomic symptoms, a well known complication of medullary involvement,⁸ and had a fatal outcome. The third patient (patient No 2) had restricted involvement of the right lateral medulla and could survive with a permanent tracheostomy and ventilatory support during sleep. Automatic respiration is controlled by neuronal nuclei located near the solitary tract and nucleus ambiguus in the medulla and dorsal pons.⁹ Although bilateral damage was thought necessary to induce central hypoventilation, autopsy proved unilateral ischaemic infarct of the dorsolateral medulla demonstrated that unilateral involvement of the nucleus

ambiguus and adjacent medullary reticular formation was sufficient to cause the syndrome.¹⁰

Central hypoventilation associated with Hu-ab is not usually included in reviews of neurological causes of impaired control of respiration or mentioned as a cause of central alveolar hypoventilation in standard neurology textbooks.⁹ However, anti-Hu associated paraneoplastic encephalomyelitis classically involves the medulla rather than other parts of the brainstem.¹¹ In our series, 14 patients with Hu-ab presented with symptoms of brainstem involvement, and central hypoventilation was the predominant feature in 1.5% of the series.

Our patients had a normal brain MRI and the cause of hypoventilation remained unclear until Hu-ab were determined. Our study shows that in patients with clinical criteria of central hypoventilation of subacute onset and normal brain MRI, the possibility of a paraneoplastic origin must be strongly considered. The associated features of dizziness, dysarthria, dysphagia or nystagmus suggest a medullary involvement and help in the diagnosis. Early diagnosis and treatment of the underlying tumour is the best guarantee to stabilise the syndrome.⁷ However, in one of our patients the paraneoplastic syndrome appeared while the tumour was in remission with hormonal treatment. Although the role of immunosuppressors in the anti-Hu associated syndrome is unclear, in this patient treatment with steroids was associated with stabilisation of the neurological symptoms, suggesting that a course of immunosuppression is warranted in these patients.

The development during the clinical course of vasomotor instability was related to a poor prognosis, as occurred in patient Nos 1 and 3. In contrast, patient No 2 is still being successfully treated with continuous airway positive pressure and has no disease progression. This suggests that the breathing disorder in itself should not necessarily mean a fatal evolution unless other medical complications are present.

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Competing interests: None.

Informed consent was obtained from one of the patients. The other two patients had died years before and it was not possible to contact their relatives.

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