

CASE REPORTS

Clinical and pathological correlation in an uncommon motor neurone disease presenting with Type II respiratory failure

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ABSTRACT

A 57-year-old female with asthma presented recurrently to hospital with autonomic instability and type II respiratory failure requiring invasive ventilation in intensive care unit (ICU). She was able to be discharged home with non-invasive ventilation but subsequently died from another episode of acute respiratory failure. Post-mortem examination revealed an uncommon variant of a degenerative neurological disease and highlights issues related to limitations in current diagnostic criteria.

Key Words: Motor neuron disease, Respiratory failure

1. INTRODUCTION

We report an atypical presentation of motor neuron disease (MND) with a paucity of supportive clinical and electrophysiological findings. Posthumous neuro-pathological analysis of diseased tissue revealed findings infrequently reported in the literature.

2. CASE REPRESENTATION

A 57-year-old, non-smoking female of Sudanese background presented to the emergency department with acute dyspnoea, palpitations and severe central chest pain, radiating to her back.

Past medical history included type 2 diabetes mellitus, asthma and hypertension. Current medications were met-

formin, fluticasone-salmeterol and salbutamol inhalers. On presentation, she was afebrile, tachypnoeic (RR 48 per minute), tachycardic (HR 112 bpm) and hypertensive (SBP > 200 mmHg). Chest auscultation revealed poor air entry bilaterally. Chest X-ray showed hyper-inflated lung fields with peri-bronchial thickening, consistent with asthma. Chest CT angiography excluded aortic dissection.

Emergent medication consisted of inhaled bronchodilators and intravenous hydralazine for the treatment of malignant hypertension. After receiving intravenous morphine for chest pain, she developed respiratory depression and decreased conscious state, requiring naloxone rescue. Arterial blood gas (ABG) on 36% fraction of inspired oxygen (FiO₂) revealed Type II respiratory failure (pH of 7.24, PaCO₂ of 80

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mmHg, PaO₂ of 64 mmHg and A-a gradient of 61 mmHg). Laboratory testing revealed an elevated white cell count of $11.8 \times 10^9/L$. C-reactive protein, renal and liver function tests were within the normal range. Continued hypercapnia-associated respiratory failure persisted despite non-invasive ventilation (NIV). She required intubation and ventilation in ICU. The patient recovered after 12 days and she could be discharged home.

She re-presented two days later with cough, tachypnoea (RR 40 – 60 per minute), hypoxia (O₂ saturation 89% on room air) and hypertension (SBP > 200 mmHg) with blood gases again revealing Type II respiratory failure. Rapidly deteriorating conscious state led to intubation and ventilation.

She was successfully extubated and sent to the ward. During this admission, transient (< 24 hours) weakness in both upper limbs and the left lower limb (Grade 4+/5) with incoordination was noted, not associated with muscle wasting or changes to reflexes. During the latter part of this admission, tongue fasciculation was also noted. Clinical findings were verified by a neurologist.

An echocardiogram demonstrated normal ventricular and valvular function with no evidence of pulmonary hypertension. High resolution pulmonary CT did not show evidence of interstitial lung disease. Lung function tests confirmed a restrictive ventilatory pattern (FEV₁: FVC ratio:1.04). A sleep study identified mild obstructive sleep apnoea with no central apnoeic events.

Cerebral imaging (including MRI), electro-encephalogram, CSF analysis (microscopy, culture, cryptococcal antigen level, protein and glucose levels), nerve conduction studies and electromyography were unremarkable. An extensive myopathy and connective tissue diagnostic panel that included creatinine kinase, thyroid function tests, urinary porphyrin, viral hepatitis serology, rheumatoid factor, anti-citrullinated peptide antibody, antinuclear antibodies, extractable nuclear antigen antibodies, double-stranded DNA antibodies and anti-neutrophil cytoplasmic antibodies was also unrevealing. A connective tissue disease antibody screen which included rheumatoid factor, anti-citrullinated peptide antibody, antinuclear antibodies, extractable nuclear antigen antibodies, double-stranded deoxyribonucleotide antibodies and anti-neutrophil cytoplasmic antibodies was also negative. A sniff nasal inspiratory test to identify diaphragmatic weakness was unable to be successfully performed. There was no accessible affected peripheral muscle to biopsy and diaphragmatic biopsies are not performed at our institution. The response to NIV and mechanical ventilation supported the diagnosis of central respiratory hypoventilation. She was discharged home and compliant with variable positive air-

way pressure (VPAP) NIV as assessed at early medical and neurology clinic appointments.

Four months later, she presented to a district hospital with nausea and abdominal pain. Intravenous morphine for the pain likely precipitated another episode of Type II respiratory failure. Despite initial response to NIV, worsening respiratory function developed and she subsequently died in ICU. Post-mortem examination revealed significant denervation of the diaphragm, neuronal loss and gliosis of brainstem motor nuclei leading to a posthumous diagnosis of motor neuron disease (MND) (see Figures 1-3). Genetic testing for familial variants of MND was not performed.

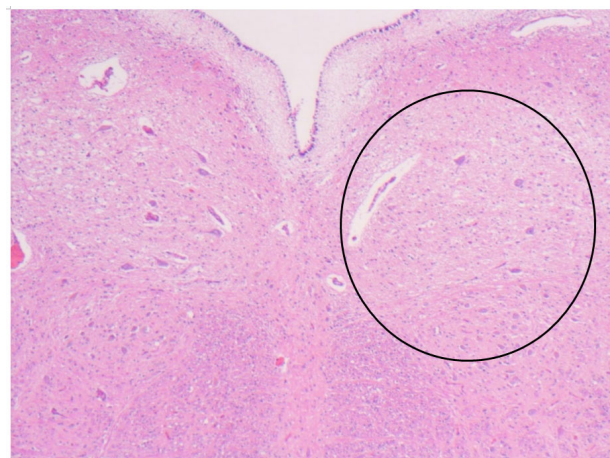


Figure 1. Midline floor of the fourth ventricle (at top) showing hypoglossal nuclei (circled) largely depleted of motor neurons with only a few motor neurons remaining in a pale rarefied neuropil background. (H&E stain at 40× magnification)

3. DISCUSSION

MND is a progressively fatal neurological disease characterised by degeneration and loss of upper and lower motor neurons leading to weakness of bulbar, thoracic and abdominal muscles with sparing of oculomotor muscles and sphincter function.^[1] MND occurs both sporadically, in about 95% of cases, and in a familial manner.^[2] Whilst the aetiology of sporadic MND remains unknown, familial MND has enabled the identification of several causal genes.^[2]

Although the diagnostic criterion (i.e. revised El Escorial criteria) for amyotrophic lateral sclerosis (ALS)/MND has high sensitivity and specificity, ALS/MND are challenging to diagnose with one review citing a median time of 14 months from onset to diagnosis.^[3]

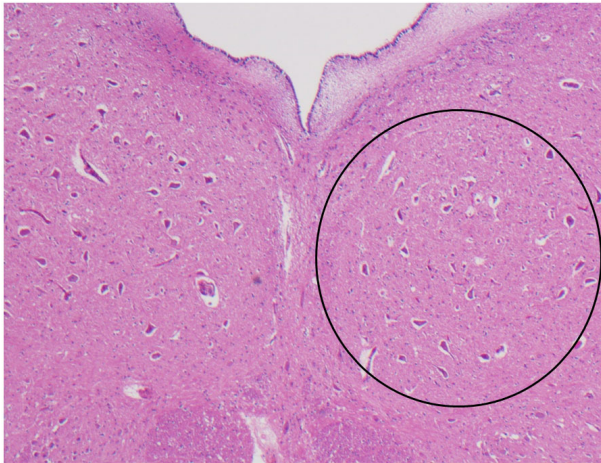


Figure 2. Midline floor of the fourth ventricle (at top) showing age matched normal hypoglossal nuclei (circled) with more numerous and more avidly staining motor neurons than in Figure 1. (H&E stain at 40× magnification)

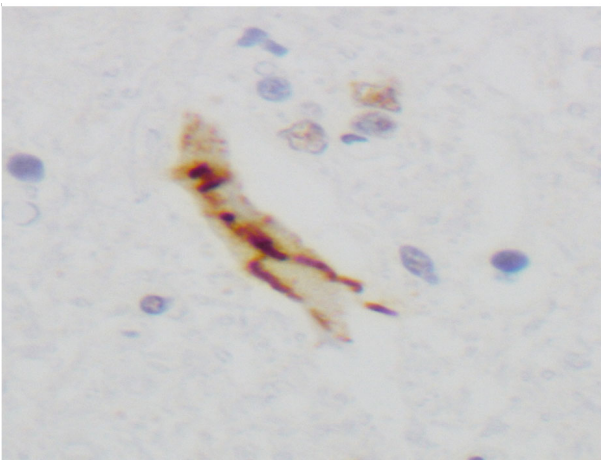


Figure 3. TDP-43 immunohistochemistry showing a hypoglossal nucleus motor neuron with a thread-like TDP-43 cytoplasmic inclusion. (400× magnification)

Our patient presented with recurrent Type II respiratory failure. She also exhibited autonomic instability, tongue fasciculation, occasional drooling and transient limb weakness. Autopsy examination showed significant denervation of the diaphragm, indicating anterior horn cell lesions of cervical nerves C3, C4 and C5. Recurrent Type II respiratory failure is likely due to diaphragmatic weakness. There was also moderate to severe neuronal loss and gliosis of brainstem cranial nuclei (CN) VII and XII. Less severe changes were seen in the nucleus ambiguus and CN V motor nucleus. Involvement of CN XII explains tongue fasciculation while involvement of nucleus ambiguus accounts for the pharyngeal dysmotility and autonomic dysfunction observed. Neuro-pathological staining for ubiquitin and TDP-43 (inclusions typically seen

in ALS) showed involvement of brainstem motor nuclei. There was also degeneration of the substantia nigra and subthalamic nucleus not associated with tau or alpha-synuclein inclusions. The pathological pattern of neuronal degeneration crosses several traditional clinical classifications of MND. Involvement of lower motor neurons innervating the diaphragm suggests progressive muscular atrophy (PMA) while involvement of CN V, VII and XII favours progressive bulbar palsy (PBP). The involvement of substantia nigra raises the possibility of an ALS-plus syndrome. A recent prospective observational study of clinical phenotypes of ALS/MND diagnosed between 2005 and 2015 identified five revised clinical classification; ALS bulbar onset, ALS cervical onset, ALS lumbar onset, flail arm and leg and primary lateral sclerosis (PLS).^[4] Our patient would have fit the clinical phenotype of ALS cervical onset based on the presentation of recurrent Type II respiratory failure. Riluzole is a pharmacological agent for definite and probable ALS (with symptoms less than five years, forced vital capacity greater than 60% and age < 75 years) with evidence of modestly increased median survival (up to 3 months).^[5] More recently, edaravone has shown to have slight efficacy in early stage definite and probable ALS (with symptoms less than 2 years duration, forced vital capacity greater than 80% and aged between 20 to 75 years).^[6]

As per revised El Escorial criteria, our patient would not have been eligible for riluzole or edaravone up to 11 months after symptom onset despite having pathological evidence of ALS at autopsy. At the time of her death, our patient had only lower motor neuron signs which would have classified as suspected ALS. Reports that 87% of patients with PBP progress to ALS^[7] and more than half of PMA patients had pathological and radiological changes consistent with ALS^[8] indicate that these sub-set of patients could benefit from earlier diagnosis and management.

The revised El Escorial criteria remain the gold standard for diagnosis of ALS. However, as early or variant cases may not fulfil these criteria, we highlight the importance of developing more sensitive and specific diagnostic tools.

4. CONCLUSION

This case suggests that the revised El Escorial is not sensitive for diagnosing early or variant forms of MND. As our case suggests, variant forms of MND do progress into an ALS clinical phenotype. Our knowledge of the pathophysiology of MND is enhanced by post-mortem examination by experienced neuropathologists.

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CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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