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CASE STUDY

Multiple system atrophy presenting as central sleep apnoea

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Multiple system atrophy presenting as central sleep apnoea. L.J. Cormican, S. Higgins, A.C. Davidson, R. Howard, A.J. Williams. ©ERS Journals Ltd 2004.

ABSTRACT: A 61-yr-old male presented with apparent idiopathic central sleep apnoea but after 4 yrs developed features of autonomic, cerebellar and extrapyramidal dysfunction consistent with a diagnosis of multiple system atrophy (MSA).

Though central sleep apnoea can occur in multiple sleep apnoea, it is less frequent than obstructive sleep apnoea and occurs in the later stages of the disease.

The pathogenesis of MSA involves gliosis and neuronal cell loss in specific areas of the central nervous system. Central sleep apnoea in MSA may be due to the depletion of cholinergic neurons in the arcuate nucleus of the medulla by apoptosis.

This is the first description of multiple system atrophy presenting as central sleep apnoea. The current authors believe that multiple system atrophy should be considered in the differential diagnosis of late onset central sleep apnoea and progressive hypoventilation.

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Case history

A 61-yr-old White male presented with a 2-yr history of depression, weight loss of 12.5 kg to a body mass index 25.5 $kg \cdot m^{-2}$, a 3-month history of confusion and a 1-week history of slurred speech and ataxia. Over a period of 16 days, he developed progressive hypersomnolence due to respiratory failure. He was admitted to hospital, intubated and ventilated. Attempts to wean were unsuccessful on three occasions because of progressive hypoventilation. Following each extubation, he developed respiratory failure usually on the second or third night. He had a past history of hypertension and epilepsy, but had been seizure-free for 30 yrs.

On examination, he had myoclonic episodes and was ataxic. Cranial nerves, pupillary reactions and ocular movements were normal. Fundoscopy was unremarkable. Magnetic resonance imaging of his brain and brainstem revealed mild cerebellar atrophy and nonspecific white matter lesions, and was otherwise normal. Electroencephalogram revealed nonspecific abnormalities of both hemispheres, but no epileptiform discharges. Cerebrospinal fluid (CSF) examination revealed a protein of 0.51 $g \cdot L^{-1}$ and glucose of <2.9 $mMol \cdot L^{-1}$, with red and white cell counts both $<1 \cdot cm^{-3}$. He had matched oligoclonal bands on CSF and serum.

There were no obvious neuropsychiatric abnormalities upon bedside testing. All of his neurological symptoms were attributed to hypoxia and hypercapnia, as they eventually resolved.

He was weaned on to positive pressure ventilation (PPV) with a NIPPY 1 ventilator (B&D Electromedical, Stratford-upon-Avon, UK) administered *via* a tracheostomy tube. Despite several attempts at weaning from PPV, he repeatedly developed episodes of hypercapnia and hypoxia, often not on the first night of self-ventilation. Spirometry demonstrated a forced expiratory volume in one second of 2.9 L and a forced vital capacity of 3.9 L (predicted values were 3.2 $L \cdot s^{-1}$ and 4.2 L respectively). Carbon monoxide transfer studies were within normal limits (transfer factor of the lung for carbon monoxide 9.72 $mmol \cdot min^{-1} \cdot kPa^{-1}$, carbon monoxide transfer coefficient 1.35 $mmol \cdot min^{-1} \cdot kPa^{-1} \cdot L^{-1}$, predicted values were 9.78 and 1.35, respectively). There was no evidence of left-ventricular dysfunction. Arterial blood gas while self-ventilating on room air demonstrated an arterial oxygen tension of 61.5 kPa, carbon dioxide arterial tension (P_{a,CO_2}) of 36.3 kPa, pH of 7.48, standard bicarbonate of 26.6 mMol·L and a base excess of 3.1. A thoracic and abdominal strain-gauge impedance plethysmogram (Respitrace®; NIMS, Miami Beach, FL, USA) demonstrated the periodic absence of thoracic and abdominal-wall movement (apnoea/hypopnoea index of $55 \cdot h^{-1}$, normal <5), associated with oxyhaemoglobin desaturation to a nadir of 60% (4% oxygen-desaturation index of $57 \cdot h^{-1}$) in the absence of airflow during self-ventilation while asleep (fig. 1). This confirmed the presence of central sleep apnoea.

He was eventually discharged home, with PPV at night administered *via* a permanent tracheostomy tube and self-ventilation during the daytime.

After 4 yrs from the time of his original presentation, he was re-admitted to the current authors' unit because of his increasing dependency on his carers. This was a consequence of unsteadiness of gait and inability to care for himself. He had also developed urinary incontinence and reported the loss of early morning erections over the previous 4 months.

On examination, he was alert and orientated. There was no cognitive defect. There was bilateral impairment of vertical ocular movement, but his cranial nerve examination was otherwise normal. There was bilateral-cogwheel rigidity in both upper limbs and a resting tremor, but no evidence of myoclonus. There was a mild ataxic tremor and bradykinesia bilaterally in the upper and lower limbs. Power and

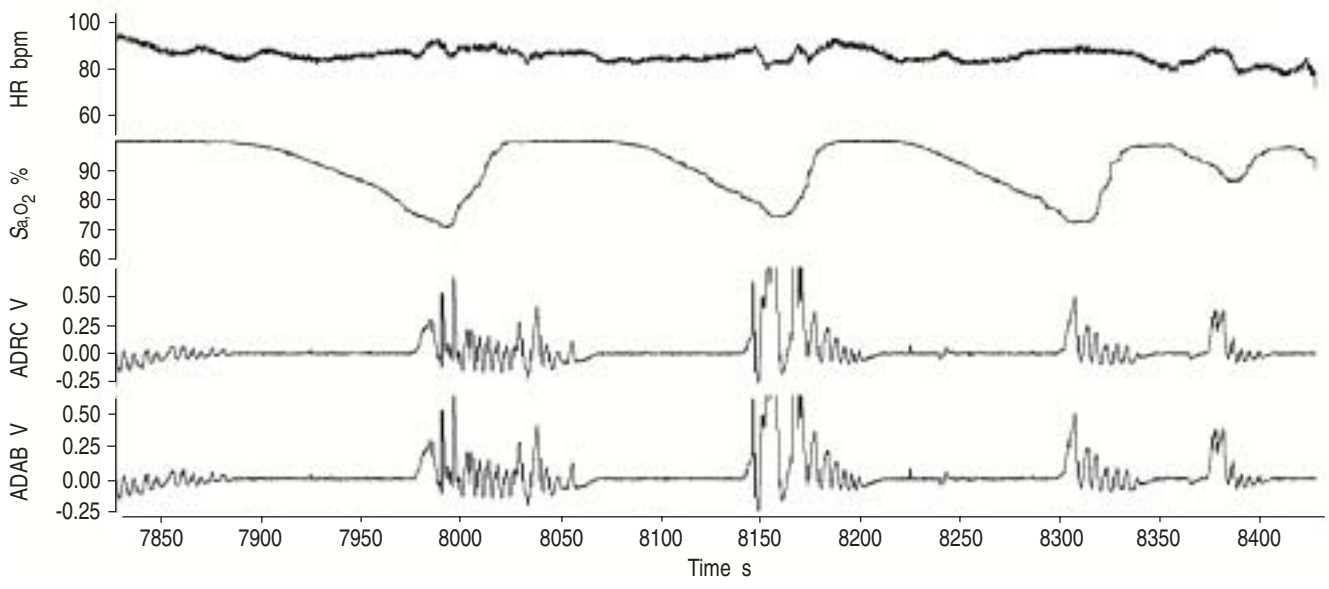

Fig. 1. – Graphic representation of the nocturnal respiratory strain gauge impedance plethysmogram, which demonstrates the periodic cessation of abdominal and chest wall movement associated with oxyhaemoglobin desaturation. HR: heart rate; S_{a,O_2}: oxyhaemoglobin saturation; ADRC: chest wall impedance; ADAB: abdominal wall impedance; bpm: beats per minute.

coordination were normal throughout. Reflexes were brisk and the plantar responses were flexor.

He developed faecal incontinence. He was noted to have postural hypotension.

Autonomic dysfunction was confirmed as systolic-only hypotension upon head up-tilt, absent blood pressure responses to isometric exercise and mental arithmetic, and absent sinus arrhythmia during deep breathing. An external anal sphincter electromyogram [1] was performed. This was abnormal, demonstrating a severely depleted interference pattern and changes of chronic re-innervation. The mean duration of motor units was prolonged at 14.5 ms.

The eventual presentation with these symptoms and signs, and the results of the subsequent investigations confirmed a diagnosis of probable multiple system atrophy (MSA) in this patient, who initially presented 4 yrs previously with acquired central sleep apnoea.

Discussion

The development of nocturnal stridor and/or obstructive sleep apnoea (OSA) is a common occurrence in MSA. The development of central sleep apnoea is unusual. However, the presentation of central sleep apnoea for a prolonged period, prior to the development of MSA, is exceptional.

MSA is a progressive neurodegenerative disease of unknown aetiology; it occurs sporadically and causes Parkinsonism, cerebellar, autonomic, urinary and pyramidal dysfunction in many combinations [2]. On the basis of the recent consensus statement on the diagnosis of MSA [2], the patient described previously, who initially presented with central sleep apnoea, eventually developed probable MSA; definite MSA being a pathological/post-mortem diagnosis. He exhibited both of the criteria for autonomic failure (orthostatic hypotension and urinary incontinence accompanied by erectile dysfunction), in addition to the criteria for cerebellar dysfunction (gait ataxia and sustained gaze-evoked nystagmus). He also exhibited some features of Parkinsonism (rigidity and a resting tremor).

However, the symptoms and signs indicating MSA did not arise until 4 yrs after his initial presentation with central sleep apnoea. This is an unusual sequence of events that has not previously been described.

Respiratory dysfunction in MSA usually occurs in the form of sleep-disordered breathing, but is more commonly obstructive rather than central in aetiology. Laryngeal stridor can occur, presenting as OSA. It is due to selective denervation and atrophy of the posterior cricoarytenoid muscles, resulting in unopposed laryngeal adduction by the thyroarytenoid [3] and consequent inwards and downward pulling of the vocal cords by negative inspiratory pressure [4]. OSA may also be a manifestation of impaired coordinated activity of the respiratory retroambigual premotor or ambigual motor neurons [5]. Nocturnal obstructive events of the upper respiratory tract are believed to be responsible for the occurrence of sudden death in this patient population and to be preventable by the institution of either tracheostomy or continuous positive pressure ventilation [6].

Central sleep apnoea, when it occurs, may reflect impaired automatic control of ventilation.

There is a lack of understanding of the pathogenesis of central sleep apnoea in MSA. The central pathological process in MSA involves neuronal-cell loss and gliosis throughout the central nervous system (CNS), especially in the putamen, caudate, *substantia nigra*, *locus coerulus*, pontine nucleus, inferior olivary nucleus purkinje cells and the intermediolateral cell columns of the thoracic spinal cord, and Onuf's nucleus of the sacral spinal cord [7]. The pathological hallmarks of MSA are argyrophyllic cellular inclusions in oligodendrocytes throughout the involved regions of the CNS [8]. In MSA, oligodendrocyte apoptosis occurs in a distribution similar to the finding of these cellular inclusions [9].

NODA *et al.* [10] have demonstrated the depletion of neurons in the arcuate nucleus in subjects who died from MSA. Functional magnetic resonance studies have demonstrated the activation of the arcuate nucleus of the ventral surface of the medulla in response to hypercarbia [11]. More recently, BENARROCH *et al.* [12] have demonstrated that these depleted neurons of the arcuate nucleus are cholinergic. The presence of alpha-synuclein positive glial cytoplasmic

inclusions in this area was also demonstrated. However, in that study, only two-thirds of the MSA subjects suffered from sleep-related breathing disorders (OSA or rapid eye movement sleep-behaviour disorder). The diagnosis of a sleep-related breathing disorder was made on the basis of reported symptoms, rather than nocturnal polysomnography. It is, therefore, unclear if any of the subjects actually suffered from central sleep apnoea. Abnormalities of the arcuate nucleus have, however, also been described in other disorders of central respiratory control, including primary alveolar hypoventilation [13] and sudden infant death syndrome [14]. These reports indirectly support the possible role of arcuate nucleus neuronal depletion in the pathogenesis of central sleep apnoea in MSA.

The diagnosis of central sleep apnoea requires the demonstration of intermittent absence of respiratory effort and airflow during sleep, either by nocturnal polysomnography or an attended sleep study. Normal resting daytime P_{a,CO_2}, spirometry and tests of respiratory-muscle strength help to exclude a neuromuscular association with central sleep apnoea. Additionally, the exclusion of cardiac failure, and degenerative, infectious, inflammatory, vascular and structural brain disease, supports an idiopathic cause.

The patient described in this case report initially presented with an acquired "idiopathic" central sleep apnoea. The central nature of the respiratory disturbance was confirmed by abdominal and thoracic strain-gauge plethysmography (Respitrace® study) which demonstrated the periodic simultaneous absence of chest wall and abdominal movement, in association with subsequent oxyhaemoglobin desaturation and the absence of airflow during periods of sleep (fig. 1). The institution of nocturnal PPV, with the associated normalisation of daytime arterial blood gases, confirmed the limitation of the respiratory disturbance to periods of sleep. However, the presentation of central sleep apnoea, 4 yrs prior to the development of MSA, is an unusual sequence of events and has not previously been reported.

Late-onset neurogenic respiratory failure is usually neuromuscular in origin and due to motor neuron disease, myasthenia gravis, paraneoplastic syndrome or myositis. Central causes are rarer and encompass vascular, degenerative, paraneoplastic syndromes and the direct effect of tumour.

This case should increase the awareness of clinicians to search for neurodegenerative disease if apparent idiopathic central sleep apnoea is present. Furthermore, this case illustrates the importance of considering multiple system atrophy in the differential diagnosis of the neurogenic causes of late-onset central sleep apnoea and progressive alveolar hypoventilation. It underscores the broad anatomical distribution of the neuropathological changes within the central nervous system in multiple system atrophy. There is an obvious necessity for longitudinal studies to determine the frequency and spectrum of neurodegenerative disease in the idiopathic central sleep apnoea patient population. The lack of clarity regarding this association raises the question as to whether the term central sleep apnoea should be reserved for truly idiopathic central sleep apnoea.

References

1. Palace J, Chandiramani V, Fowler C. Value of sphincter electromyography in the diagnosis of multiple system atrophy. *Muscle Nerve* 1997; 20: 1396–1403.
2. Gilman S, Low P, Quinn N, *et al.* Consensus statement on the diagnosis of multiple system atrophy. *J Neurol Sci* 1999; 163: 94–98.
3. Bannister R, Gibson W, Michaels L, Oppenheimer DR. Laryngeal abductor paralysis in multiple system atrophy. A report on three necropsied cases, with observations on the laryngeal muscles and the nuclei ambigui. *Brain* 1981; 104: 351–368.
4. Isozaki E, Naito A, Horiguchi S, Kawamura R, Hayashida T, Tanabe H. Early diagnosis and stage classification of vocal cord abductor paralysis in patients with multiple system atrophy. *J Neurol Neurosurg Psychiatry* 1996; 60: 339–402.
5. Benarroch E. New findings on the neuropathology of multiple stem atrophy. *Auton Neurosci* 2002; 96: 59–62.
6. Isozaki E, Miyamoto K, Osanai R, Hayashida T, Tanabe H. Clinical studies of 23 patients with multiple system atrophy presenting with vocal cord paralysis. *Rinsho Shinkeigaku* 1991; 31: 249–254.
7. Wenning G, Tison F, Ben Schlomo Y, Daniel S, Quinn N. Multiple system atrophy: a review of 203 pathologically proven cases. *Mov Disord* 1997; 12: 133–147.
8. Lantos P. The definition of multiple system atrophy: a review of recent developments. *J Neuropathol Exp Neurol* 1998; 57: 1099–1111.
9. Probst-Cousin S, Rickert C, Schmid K, Gullotta F. Cell death mechanisms in multiple system atrophy. *J Neuropathol Exp Neurol* 1998; 57: 814–821.
10. Noda K, Katayama S, Watanabe C, Yamamura Y, Nakamura S. Decrease of neurons of the medullary arcuate nucleus of multiple system atrophy: quantitative comparison with Parkinson′s disease and amyotrophic lateral sclerosis. *J Neurol Sci* 1997; 151: 189–191.
11. Gozal D, Hathout G, Kirlew K, *et al.* Localization of putative neuronal respiratory regions in the human by functional magnetic resonance imaging. *J Appl Physiol* 1994; 76: 2076–2083.
12. Benarroch E, Schmeichel A, Parisi J. Depletion of cholinergic neurons of the medullary arcuate nucleus in multiple system atrophy. *Auton Neurosci* 2001; 87: 293–299.
13. Folgering H, Kuyper F, Kille J. Primary alveolar hypoventilation (Ondine′s curse syndrome) in an infant without external arcuate nucleus. Case Report. *Bull Eur Physiopathol Respir* 1979; 15: 659–665.
14. Kinney H, Filiano J, Sleeper L, Mandell F, Valdes-Dapena M, White W. Decreased muscarinic receptor binding in the arcuate nucleus in sudden infant death syndrome. *Science* 1995; 269: 1446–1550.