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Neuroborreliosis as a cause of respiratory failure

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Abstract We report three cases of neuroborreliosis presenting with acute respiratory impairment. All the patients had encephalopathy and focal neurological signs with brain stem abnormalities in two. All three patients had respiratory arrest associated with progressive nocturnal hypoventilation or prolonged central apnoea. Tracheostomy and prolonged periods of ventilatory support were necessary in all cases and weaning was complicated by residual central respiratory disturbances. These cases emphasise that *Borrelia* infection should be considered in the differential diagnosis of unexplained respiratory failure.

Key words Neuroborreliosis · Respiratory failure

Introduction

Lyme disease is a multisystem tick-borne infectious disease caused by the spirochaete *Borrelia burgdorferi*. Human infection occurs from a bite of an infected tick of the genus *Ixodes*. Diagnosis can be difficult and many infections are subclinical, so the exact incidence of Lyme disease is not known [1]. The organism is neurotropic and may present as an acute or chronic disorder affecting both the central and peripheral nervous system. Well-recognised neurological syndromes include peripheral neuropathies, particularly Bell's palsy, acute or chronic meningitis, acute or chronic encephalopathy, leucoencephalitis, plexopathies and entrapment syndromes [2–6]. Demyelinating lesions and a Guillain-Barré like syndrome have also been attributed to *Borrelia* [1].

We report three cases in which acute respiratory failure occurred and required ventilatory support. In each case there was clinical and or laboratory evidence of borrelial infection.

Case reports

Case 1

A 70-year-old man presented with a 48-h history of lethargy, episodic confusion and somnolence with marked dyspnoea for 30 min prior to admission. He had been staying in a rural area, taking regular walks in the woods. There was no history of tick bites or rash. He was a non-smoker in good health with no history of cardiopulmonary disease. On arrival he was pyrexial, cyanosed, irritable and confused. He was tachycardic and tachyopnoeic with shallow respiratory pattern. His chest was clear to auscultation and a chest radiograph was normal. Arterial blood gases (pH 7.08, PCO_2 11 kPa, PO_2 5.2 kPa, venous bicarbonate 30 mmol), showed acute hypercapnic respiratory failure. Shortly after admission he had a respiratory arrest requiring intubation and transfer to the intensive care unit. Empirical treatment with broad-spectrum antibiotics and antifungals was commenced.

For the 1st week, consciousness level was severely impaired. Following this he gradually improved but remained intermittently confused for a further 3 weeks. Brain stem reflexes were intact throughout. Variable upper motor neuron signs were elicitable in the lower limbs during his admission. Cardiorespiratory examination was normal with no evidence of respiratory muscle weakness. Abdominal examination was normal; there was no rash and no evidence of arthritis or myopathy.

A tracheostomy was performed and he remained ventilator dependent for 17 days. Attempts at weaning led to progressive hypercapnoea associated with confusion and agitation. He continued to receive nocturnal ventilatory support because of apnoeic episodes lasting up to 30 s associated with severe desaturations. Normal ventilation was established after 5 weeks and the tracheostomy closed.

Serology for *Borrelia* was checked on four occasions and showed a pattern highly suggestive of acute infection with a persistently positive ELISA and a Western blot which showed multiple bands on the first three samples, followed by the emergence of a clear band for *Borrelia*-specific antibody. The cerebrospinal fluid (CSF) on one occasion early in the illness was negative. His liver function tests showed transiently elevated hepatocellular changes. An EEG showed low voltages attributable to sedative drugs. All other investigations, including viral and bacterial cultures and serology, CT and MRI, were normal. Two years later he remains well with mild residual pyramidal signs in the legs.

Case 2

A 22-year-old woman presented with a 5-day history of headache, dizziness, photophobia and vomiting. On admission she had a fluctuating pyrexia and impaired consciousness with meningism. She continued to deteriorate and was transferred to our care on day 22 of the illness; by this time she had developed a flaccid right-sided weakness with a right extensor plantar and intermittent rhythmical movements of the arms. She developed increasingly frequent apnoeic episodes requiring admission to the intensive care unit, where continuous ventilation via a tracheostomy was commenced. She had a fluctuating hypertension that required treatment with atenolol and epileptic activity requiring treatment with anticonvulsants. Empirical treatment with broad-spectrum antibiotics, acyclovir and antituberculous therapy was given. Ventilation was continued for 5 weeks and the tracheostomy closed after 9 weeks.

Initial CSF analysis showed an elevated white cell count of 60 cells/mm^3, predominantly lymphocytes, protein 1.0 g/l, glucose 3.2 mmol/l, blood glucose 6.1 mmol/l). Stains and culture for fungi and acid-fast bacilli were negative and chest radiograph ECG, CT and MRI were normal. EEG showed generalised slow waves initially, with later recordings returning to normal.

The only other positive finding was of positive serum serology for *B. burgdorferi* with IgG 1/512, IgM 1/16, ELISA 46, indicating recent *Borrelia* infection. However, the CSF was negative for Borrelia, although it did show an oligoclonal distribution of IgG. The abnormality of respiratory function and focal neurological deficits resolved; however, recovery was complicated by marked cognitive deficits and behavioural abnormalities. There were deficits in memory, perception and visuo-spatial tasks with profound problems with reasoning and insight. Her affect was childlike and she was disinhibited with hypersexuality and violent behaviour, which required her to be placed on section 2 of the Mental Health Act. She was eventually discharged from hospital 7 months later with some residual deficits in concentration and attention; she was still disinhibited.

Case 3

A 43-year-old man was admitted with a 10-day history of unsteadiness, oscillopsia, severe occipital headache and episodic hypertension. Two days later he had a respiratory arrest and was intubated and ventilated with intermittent positive pressure support for 24 h. Over the following week he remained alert, orientated and apyrexial but developed mild meningism and dysphasia. There was vertical nystagmus in the neutral position, gaze-evoked horizontal nystagmus and a reduced pharyngeal reflex. He became increasingly drowsy before a further respiratory arrest occurred. Following resuscitation he was alert but made no significant respiratory effort except to direct command. On examination new features were moderate gait ataxia without limb ataxia and a positive Romberg sign. Apart from intermittent tachycardia and hypertension, systemic examination was unremarkable with no skin rashes.

Investigations showed a mild leucocytosis (18.9×10^9 /l) and a raised sedimentation rate (45 mm in the 1st h). There were mild hepatocellular abnormalities with a liver biopsy showing mild reactive changes. CSF examination showed a normal pressure, normal protein and glucose with a lymphocytic pleocytosis (29×10^6/l). Oligoclonal bands were present in both CSF and serum. Viral and *Borrelia* titres were negative and all other investigations, including CT and MRI, were normal. He gradually improved and could breathe independently but did have nocturnal periods of apnoea lasting up to 60 s. with desaturations to 80% associated with hypoxia and hypercapnia. There were also prolonged periods of chronic alveolar hypoventilation during rapid eye movement sleep. A tracheostomy was performed and he was commenced on domiciliary respiratory support with intermittent positive pressure ventilation.

Three months later he developed bilateral sixth nerve and vocal cord palsies. CSF cytology and biochemistry was normal, but the serum and CSF Borrelia titres were elevated. Over the sext 6 months he developed a right lower motor facial palsy and severe personality changes characterised by aggressive behaviour and euphoria. His respiratory deficits remained unaltered. A further MRI showed multiple discrete periventricular lesions in the cerebral hemispheres but no brain stem abnormalities. Repeat CSF cytology and biochemistry were normal but *Borrelia* titres (ELISA) were again elevated on three separate occasions to a titre of 53 units in serum and 90 units in the CSF. He was treated with a course of cefotaxime. Over the following year the cranial nerve abnormalities resolved and the personality changes improved. Repeat studies showed that the central alveolar hypoventilation had resolved and the tracheostomy was closed. Six months later he was found dead at home after complaining of malaise and dyspnoea for a week.

Post-mortem examination revealed chronic leptomeningitis with perivascular inflammatory cuffs in the cerebral hemispheres, right thalamus, caudate, putamen and brain stem, particularly the medulla. At the level of the tenth and twelfth cranial nerves there were multiple lymphocytic cuffs in the area of the nucleus ambiguus, reticular formation and inferior olivary nucleus. The pons and midbrain showed discrete foci of inflammation and astrocytic gliosis. Staining with Warthin-Starry did not reveal the presence of spirochaetes.

The myocardium showed perivascular inflammatory cells, mainly lymphocytes and plasma cells in the myocardium. The cause of death was myocarditis.

Discussion

We have described three patients with probable neuroborreliosis who presented with respiratory impairment. A case of ventilatory failure with chronic *Borrelia* rhombencephalitis requiring intubation for 15 days has previously been described, although the nature of the underlying respiratory disorder was not clarified [7]. All our patients had evidence of meningo- or rhombencephalitis [8, 9]. They were pyrexial, encephalopathic and had focal neurological signs. There was also meningism (2 patients), episodic hypertension (2), brain stem/bulbar abnormalities (2) and epilepsy. All the patients had cognitive impairment or behavioural changes and one patient was left

with severe residual deficits. Two patients had transient hepatocellular abnormalities [1], but the pathognomic lesion of erythema chronicum migrans was not present. All three cases presented with respiratory impairment. In one patient respiratory arrest was precipitated by severe hypercapnic respiratory failure presumed to be due to progressive nocturnal hypoventilation. In two patients sudden apnoeic episodes developed, with one having a respiratory arrest on two occasions. All three patients were intubated and ventilated with intermittent positive pressure ventilation (one patient on two occasions) for periods varying from 1 day to 8 weeks; all underwent tracheostomy. In two patients weaning from ventilatory support was complicated by persisting nocturnal hypoventilation and apnoeic periods; one patient continued to require domiciliary nocturnal respiratory support for 1 year. There was no evidence of generalised, limb or respiratory muscle weakness and, in particular, no selective or predominant diaphragm weakness. It therefore seems likely this pattern of respiratory involvement was due to direct brain stem involvement. This is supported by the development of episodic hypotension and tachycardia in two cases, suggesting involvement in the region of the nucleus tractus solitarius [10]. Nocturnal alveolar hypoventilation is characterised by a reduced ventilatory response to CO_2 and consequent CO_2 retention in the absence of primary pulmonary disease. There is progressive reduction in the tidal volume and reduced hypoxic and hypercapnic arousal, which may culminate in central apnoea. These effects occur primarily in sleep, but hypercapnia may persist whilst the patient is awake and, as in at least one case in the present series, respiratory failure may supervene. Alveolar hypoventilation and apnoea may be caused by impaired automatic control of respiration due to central brain stem lesions or peripheral neuromuscular weakness [11]. The severity of the acute illness prevented any detailed study of respiratory function, but subsequent investigation confirmed the presence of episodic central sleep apnoea in case 3 and the absence of respiratory muscle weakness in any of the patients.

A variety of infective lesions may involve the brain stem and disrupt respiratory control. Acute respiratory failure in bulbar poliomyelitis has been correlated with focal necrosis and neuronal damage in the region of the nucleus ambiguus ventral to the descending trigeminal nucleus [12]. In brain stem encephalitis, particularly encephalitis lethargica, a variety of abnormal respiratory abnormalities occur, including alveolar hypoventilation, central sleep apnoea and respiratory dysrhthmias [13, 14]. Western equine encephalitis [15], *Listeria monocytogenes* [16], and postrubeolar and varicella encephalomyelitis [17] may also cause similar patterns of respiratory dysfunction.

The pathological changes in case 3 were typical of those previously described in *Borrelia* rhombencephalitis with fibrosis and perivascular infiltrates around the leptomeningeal vessels [18, 19]. Scanty spirochaetes may be seen in the leptomeninges but were not present in this case, presumably reflecting the effects of his previous antibiotics [1]. The pathological changes may bare a close resemblance to neurosyphilis [18]. The final cause of death in this case may have been due to cardiac involvement, Lyme carditis occurring in 8% of cases [20].

In the absence of erythema chronicum migrans or the isolation of spirochaetes, the diagnosis rests on the clinical picture and positive serology. The serological analysis may be unreliable with a high false-positive rate, up to 17% in nonendemic areas [21, 22]. Although the diagnostic value of the polymerase chain reaction (PCR) has yet to be confirmed [23], evidence of borrelial infection by this technique would have been desirable. However, two of the cases were treated prior to this test becoming generally available and PCR was not performed on the single sample of CSF that was obtained from the other patient (case 1). Thus, although the diagnosis is not proven by PCR, a positive ELISA test together with other associated findings such as CSF lymphocytosis and transient hepatocellular abnormalities make the diagnosis of *Borrelia* infection very likely.

These three cases represent probable neuroborreliosis in which respiratory failure requiring ventilatory support was the major presenting factor. Lyme disease should be considered in the differential diagnosis of someone presenting with idiopathic respiratory failure. If neuroborreliosis is confirmed or a high index of suspicion remains, then treatment with intravenous penicillin (stages II and III) or cephalosporins such as ceftriaxone or cefotaxime (stages I–III) is indicated [1, 24, 25].

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