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Apneusis responding to buspirone in multiple sclerosis

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Apneusis is a disturbance of respiratory rhythm characterized by severely prolonged inspiratory effort, and is caused by bilateral lesions in the dorsal pons. In humans it is most commonly caused by pontine infarction and has rarely been reported in multiple sclerosis (MS). Here we report on a patient with MS who developed episodic apneusis which responded to treatment with buspirone, a serotonin type 1A receptor agonist. *Multiple Sclerosis* 2008; **14:** 705–707. http://msj.sagepub.com

Key words: apneusis; buspirone; hypoxia; multiple sclerosis; pons; respiratory; serotonin agonist

Introduction

Apneustic breathing is defined as the arrest of respiration in tonic inspiration [1] and reflects a disturbed inspiratory off-switch mechanism leading to a delayed transition from the inspiratory phase to the expiratory phase of respiration [2]. In experimental animals as well as in humans, apneusis is associated with lesions involving both sides of the dorsal pons, especially the lateral pontine tegmentum [1]. Clinically, apneustic breathing is a sign of great localizing value and usually denotes pontine infarction due to basilar artery occlusion, although it may also occur with other pathology involving the dorsal pons [3]. Apneusis has rarely been reported in patients with multiple sclerosis (MS) [4]. Here we report on a patient with MS who developed episodic apneusis which responded to treatment with buspirone, a 5-hydroxytryptamine (serotonin) type 1A (5-HT_{1A}) receptor agonist.

Case report

A 44-year-old woman with relapsing–remitting MS with onset in 1985 presented, in December 2006, with episodes of breathing difficulty requiring admission to hospital. Her most recent relapse had been in August 2005 when she developed increased unsteadiness of gait, increased upper limb tremor and swallowing difficulty requiring the insertion of a percutaneous endoscopic gastrostomy tube. In retrospect she thought that her episodes of breathing difficulty had been occurring for approximately 4 years, with the onset having no clear relationship to a relapse, and with progressive worsening over the 18 months prior to presentation. By the time of presentation her episodes of breathing difficulty had become sufficiently severe as to result in cyanosis and collapse, requiring transient positive pressure ventilation with a bag and mask apparatus to terminate the episodes and restore spontaneous ventilation.

The episodes of breathing difficulty were noted by the patient to be sometimes triggered by singing, laughing, prolonged talking, physical exercise and hot showers. She described a sensation of being unable to breathe in or out; direct observation of these episodes in hospital revealed cessation of the respiratory cycle in full inspiration, with no airways noise or stridor and no chest wall or abdominal excursion to suggest ongoing respiratory effort against an upper airway obstruction. On a number of occasions oxygen saturation as measured by pulse oximetry was significantly reduced, sometimes below 80% (normal ≥94%), and cyanosis was observed, with or without loss of consciousness. Episodes resolving spontaneously ended with a forceful expiration. Her breathing difficulties were consistent with episodic apneusis.

At the time of admission to hospital her medication comprised interferon β-1b 8×10^6 IU by subcutaneous injection on alternate days, gabapentin 300 mg three times daily, baclofen 15 mg four

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times daily, omeprazole 20 mg daily, fluoxetine 40 mg daily, oxybutynin 5 mg twice daily, docusate sodium with sennosides 100 mg/16 mg daily and a cranberry tablet once daily.

Neurological examination revealed titubation of the head and a pathologically brisk jaw jerk. Cranial nerve examination was otherwise normal, and laryngoscopy demonstrated normal anatomy and movement of the vocal cords. On examination of the upper limbs there was a bilateral mild proximal coarse postural (wing-beating) tremor. Power was mildly reduced proximally and bilaterally. The deep tendon reflexes in the upper limbs were pathologically brisk and there was marked ataxia and intention tremor bilaterally. Vibration sense and proprioception were normal. In the lower limbs there was bilateral mild weakness affecting flexors more than extensors, the deep tendon reflexes were pathologically brisk and the plantar responses were extensor. Coordination was impaired bilaterally, worse on the left. Vibration sense was reduced in the left toes, and proprioception was impaired in the toes bilaterally. She had a spastic ataxic gait. Her Kurtzke Expanded Disability Status Scale score was 6.5.

A plain chest radiograph was normal and arterial blood gases between events showed no abnormality. On pulmonary function testing, spirometry was normal, as were the maximal inspiratory and expiratory pressures. A magnetic resonance imaging (MRI) brain scan at this time showed multiple cerebral white matter lesions, including periventricular lesions, which were hyperintense on fluid-attenuated inversion recovery imaging. There were bilateral lesions in the dorsal pons, particularly involving the lateral pontine tegmentum (Figure 1), but there were no lesions in the medulla.

Treatment with oral buspirone was commenced 3 weeks after admission to hospital at a dose of 5 mg twice daily and gradually increased to 20 mg three times daily. Dose increases were made cautiously because of the potential risk of serotonin syndrome as the patient was also taking fluoxetine 40 mg daily. The occurrence of apneustic episodes decreased after commencement of buspirone, and major apneustic episodes ceased completely 2 weeks after reaching the 60 mg daily dose (Figure 2). After 13 weeks in hospital, she was discharged to a nursing home. There she continued to experience minor transient respiratory rhythm disturbances which sometimes required positive pressure ventilation with a bag and mask for several breaths. On two occasions she experienced a recurrence of major apneustic episodes triggered by fever associated with urinary tract infections.

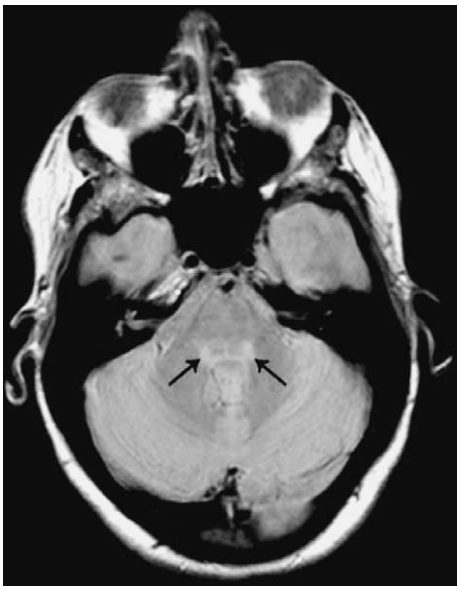

Figure 1 MRI brain scan axial proton density image showing bilateral lesions involving the dorsal pons, particularly the lateral pontine tegmentum (arrows).

Discussion

Our patient with established relapsing–remitting MS presented with episodes of apneusis which are explained by the bilateral lesions in her dorsal pons. To our knowledge there are only two other reported cases of apneusis in patients with MS [4]. Experimentation in rats has shown that excitation of the Kölliker–Fuse nuclei in the dorsolateral pons results in activation of postinspiratory neurons which

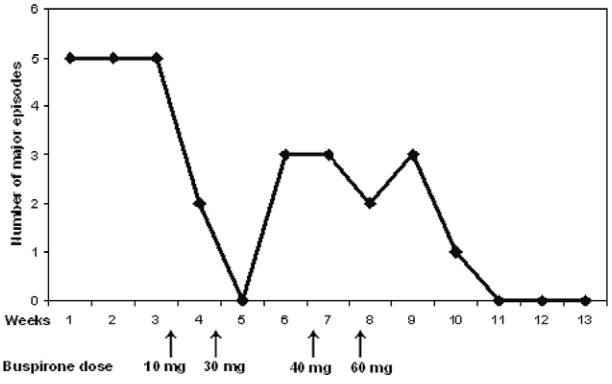

Figure 2 Frequency of major episodes of respiratory difficulty before and after treatment with buspirone, from the time of admission to hospital until the time of discharge. Major episodes of respiratory difficulty were defined by the occurrence of one or more of the following: loss of consciousness; cyanosis; arterial oxygen saturation under 94%; and intervention with manual ventilation. The times of initiation and escalation of the daily dose of buspirone are indicated by arrows.

switch off inspiration; conversely, inhibition of the Kölliker–Fuse nuclei triggers apneusis [2]. Thus, the apneustic breathing in our patient could be explained either by involvement of the Kölliker–Fuse nuclei or of efferent pathways from these nuclei in the dorsolateral pons.

As apneustic respiratory patterns in experimental animals can be abolished by administration of 5-HT_{1A} receptor agonists [5], this treatment was successfully trialed in a child with severe apneusis following neurosurgery for an astrocytoma in the pons and medulla oblongata [6]. Subsequently it has also been used successfully in a patient with apneusis due to brainstem infarction [7], but to our knowledge has not been used to treat apneusis due to MS.

In conclusion, our case emphasizes the importance of distinguishing between apneusis and other respiratory complications of MS, because apneusis may be amenable to treatment with 5-HT_{1A} receptor agonists such as buspirone.

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