Central hypoventilation with PHOX2B expansion mutation presenting in adulthood
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Congenital central hypoventilation syndrome (CCHS, "Ondine's Curse") classically presents in neonates with sleep-dependent hypoventilation. Affected infants have an impaired ventilatory response to hypercapnia and hypoxaemia which is not caused by other identifiable disease. CCHS has associations with Hirschsprung disease, neural crest tumours and abnormalities of autonomic nervous system (ANS) control. Amiel et al identified PHOX2B mutations in 18 of 29 infants with CCHS, most commonly an expansion of a 20-residue polyalanine encoding sequence by an additional 5–9 alanine encoding triplets. A subset of children with CCHS and PHOX2B mutations present after the neonatal period, with new diagnoses reported up to the age of 10 years described as late onset central hypoventilation syndrome (LOCHS). There has been one reported case of adult onset where the father of two girls with LOCHS developed respiratory failure acutely following surgery for sleep apnoea and was found to have a PHOX2B mutation identical to his daughters.

CASE REPORT
A 41-year-old man was admitted in 2005 complaining of ankle swelling, morning headaches, low mood and hypersomnolence for 2 months. In 1996 he had required mechanical ventilation for community acquired pneumonia and had been slow to wean from ventilation with poor respiratory effort. Oxygen desaturation at sleep onset was noted during the acute illness. No abnormality was found at respiratory and neurological outpatient reviews in 1997. In 2003 he was seen in the cardiology clinic with ankle oedema which was ascribed to gout following a normal cardiorespiratory assessment.

He had never smoked but had a history of alcohol consumption estimated at 80 units per week in 1996 and 70 units per week in 2005. Furosemide 80 mg daily had been prescribed 1 month before admission. He worked as a civil servant, was single with no children, and had no family history of respiratory disease, hypoventilation or ANS disease. His body mass index was 35 kg/m². He was drowsy, confused and had oedema to the mid thigh. Physical examination was otherwise unremarkable. An anteroposterior chest radiograph suggested cardiac enlargement and an ECG showed right heart strain. Oxygen saturation by pulse oximetry (SpO₂) on air was 80% and arterial blood gas analysis on 24% fractional inspired oxygen showed hypercapnic respiratory failure (pH 7.21, oxygen tension 8.6 kPa, carbon dioxide tension 10.3 kPa). He was polythaemic with haemacotocrit 64%. He was treated with antibiotics, diuretics, controlled oxygen therapy and face mask non-invasive positive pressure ventilation (NIV).

From day 2 his daytime oxygenation was satisfactory on low flow oxygen without ventilatory support; he remained on nocturnal NIV. Two attempts to record overnight oximetry without ventilatory support failed: his SpO₂ fell below 50% due to apnoea within 30 min of sleep onset and the nursing staff recommended NIV on each occasion. Overnight oximetry on air with auto-adjusting continuous positive airway pressure (Auto-CPAP; REMSTAR-Auto, Respironics, Murrysville, Penn, USA) showed episodes of profound desaturation with a mean SpO₂ of 84% and a nadir of 45%. On air with NIV the mean SpO₂ was 94% with a nadir of 89% (fig 1). From this response to NIV compared with the response to auto-CPAP, we concluded that his apnoeic episodes were primarily central rather than obstructive.

He was investigated for neuromuscular causes of hypoventilation. Maximal respiratory mouth pressure measurement was within normal limits, showing +77 cm H₂O in expiration and −63 cm H₂O in inspiration. Cranial MRI, nerve conduction, electromyogram and edrophonium testing were normal. A borderline increase in acetylcholine receptor antibodies was found on one occasion but a repeat assay was negative. An echocardiogram was normal.

He was discharged after 23 days with domiciliary nocturnal pressure controlled NIV with assured minimum tidal volume of 500 ml (Synchrony AVAPS, Respironics). His oedema had resolved and awake SpO₂ on air was 97%. On review at 6 months he was asymptomatic and physical examination was normal. Spirometric tests showed a mildly restrictive pattern in keeping with his body habitus, with forced expiratory volume in 1 s of 2.8 litres (72% predicted) and a ratio of forced expiratory volume in 1 s to forced vital capacity of 84%. The data recorded by his NIV device, averaged over 6 months, showed that 31% of the breaths delivered had been triggered by his respiratory effort. This compares with >90% seen in our patients on domiciliary NIV without central hypoventilation.

Physiological assessment of his responses to hypercapnia when clinically stable showed a ventilatory increment of 0.07 l/min/kPa carbon dioxide tension using Read’s carbon dioxide rebreathing method (normal 0.15–0.83) and a mouth occlusion pressure at 100 ms (a marker of respiratory drive) increment of 0.061 cm H₂O/mm Hg carbon dioxide tension (normal 0.52 (SD 0.19)). Genetic analysis by the Bristol...
Clinical Genetics Department using GC-rich PCR and expansion sizing on a Beckman Coulter analyser showed a heterozygous five alanine expansion mutation of the 20-residue polyanaline tract in exon 3 of the PHOX2B gene.

DISCUSSION
We report a case of CCHS associated with PHOX2B mutation presenting with chronic respiratory failure in adulthood, with quantified impairment of the response to hypercapnia.

In retrospect, our patient showed evidence of reduced respiratory drive and sleep related hypoventilation during his pneumonia in 1996 at the age of 32 years. He was then asymptomatic until he developed oedema at the age of 39. When admitted at 41 years of age he had chronic respiratory failure and profound nocturnal hypoventilation. His moderate obesity and alcohol consumption did not seem sufficient explanation for this degree of hypoventilation, and no other cause was identified until we found the genetic abnormality characteristic of childhood CCHS.

The size of the PHOX2B polyanaline expansion mutation in children with CCHS varies from 5 to 13 nucleotide triplets; larger numbers of copies are associated with more severe hypoventilation and other features of neural crest maldevelopment. Both our subject and the other reported adult onset case had five expansion copies, supporting the hypothesis that smaller copy numbers are associated with later presentation of hypoventilation. The spectrum of CCHS associated with PHOX2B mutation can now be extended to include sleep related hypoventilation causing respiratory failure presenting in adulthood.

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