Eur Respir J 1998; 12: 1482–1485
DOI: 10.1183/09031936.98.12061482
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European Respiratory Journal
ISSN 0903 - 1936

CASE STUDY

Central sleep apnoea in Arnold–Chiari malformation: evidence of pathophysiological heterogeneity

C. Rabec, G. Laurent, N. Baudouin, M. Merati, F. Massin, P. Foucher, L. Brondel, O. Reybet-Degat

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ABSTRACT: We report on the case of two young patients with type I Arnold–Chiari malformation (ACM), as revealed by a central sleep apnoea (CSA) syndrome without any other neurological defect.

Case 1 was a 14-yr-old male patient, who developed severe alveolar hypoventilation and needed long-term mechanical ventilation *via* a tracheostomy.

Case 2 was a 39-yr-old male patient, who developed features suggestive of sleep apnoea and responded to nasal continuous positive airway pressure ventilation despite the central type of apnoeas.

These two cases illustrate the different pathophysiological mechanisms involved in CSA, namely a blunted chemical drive (in hypercapnic patients) and an increased chemical drive, which destabilizes the breathing pattern during sleep (in normo/hypocapnic patients).

Central sleep apnoea can be the initial manifestation of Arnold–Chiari malformation and can lead to a life-threatening condition.

Eur Respir J 1998; 12: 1482–1485.

Service de Pneumologie et Réanimation Respiratoire, Centre Hospitalier Universitaire de Dijon, France.

Correspondence: O Reybet-Degat
Service de Pneumologie et Réanimation Respiratoire
Centre Hospitalier Universitaire de Dijon
2 Bvd Maréchal de Lattre de Tassigny
21034 Dijon
France
Fax: 33 380293625

Keywords: Arnold–Chiari malformation
central sleep apnoea

Received: December 30 1996
Accepted after revision September 3 1998

The pathophysiology of central sleep apnoea (CSA) is complex and multifactorial. CSA has been reported in association with Arnold–Chiari malformation (ACM) [1–3]. Because of the proximity of respiratory structures of the brain with the structures involved in ACM, one might expect that CSA in ACM is related to local anatomical derangements. However, different pathophysiological mechanisms may be encountered in different ACM patients with CSA. We present two cases highlighting these consid-erations.

Case 1

A 14-yr-old patient was admitted to our intensive care unit, in June 1995, with respiratory failure. The patient had felt well until 2 months earlier, when morning headaches, abnormal diurnal sleepiness and progressive dyspnoea developed. On admission to another hospital 17 days earlier, arterial blood gas (ABG) levels breathing room air were pH 7.10, arterial carbon dioxide tension (P_{a,CO_2}) 13 kPa, arterial oxygen tension (P_{a,O_2}) 5.3 kPa, and bicarbonate 30 mmol·L^{-1}. He was intubated and mechanically ventilated. Weaning trials were followed by a rapid deterioration in ABG levels. He was then referred to our respiratory intensive care unit.

Clinical examination revealed obesity (weight 80 kg, height 173 cm), gynaecomastia, and hypogonadism, strongly suggestive of Klinefelter syndrome. This was later confirmed by karyotyping, which showed an XXY chromosome complement. Auscultation of the chest was normal. Neurological examination was also normal after normalization of ABG levels. Several episodes of sinus bradycardia, second degree atrioventricular heart block, and severe symptomatic hypotension suggested autonomic dysfunction. Laboratory tests and the chest radiograph were normal. Pulmonary function tests performed during a weaning trial showed a forced expiratory volume in one second (FEV_1) of 4.0 L (94% of the predicted value), forced vital capacity (FVC) of 5.5 L (96% pred), and a FEV_1/FVC ratio of 72%. All weaning trials failed and the patient had to be tracheotomized. Brain computed tomography (CT) was normal. Cervicomedullary magnetic resonance imaging (MRI) disclosed a type I ACM, with a basilar imprint, syringomyelia, and bulbar compression by the odontoid apophysis, as suggested by a high signal in T2 (fig. 1). The odontoid apophysis was surgically resected 10 days later.

Partial diurnal weaning from the ventilator was possible within the next 2 weeks. However, trials of spontaneous ventilation were followed by progressive hypercapnia. Exploration of the sensitivity of the respiratory centre by getting the patient to breathe a hypercapnic mixture (inspiratory oxygen fraction (F_{I,O_2}) = 21%, inspiratory carbon dioxide fraction (F_{I,CO_2}) = 3%) showed a lack of ventilatory response (minute ventilation = 3.8 L·min^{-1} breathing the hypercapnic mixture *versus* 4.3 L·min^{-1} breathing room air). Overnight polysomnography (Respisomnographe; SEFAM, Nancy, France) (with recording of airflow by a

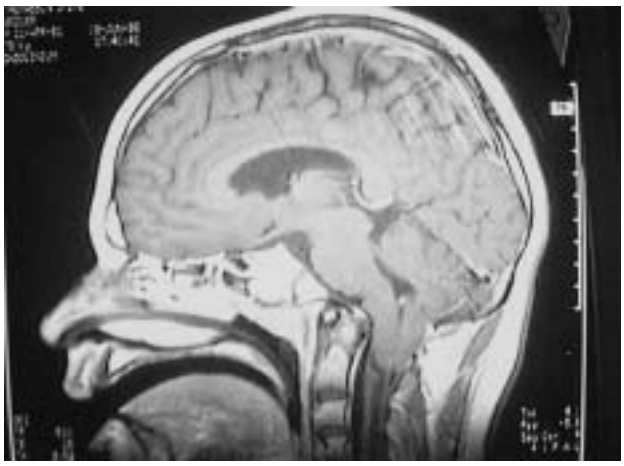

Fig. 1. – Cervicomedullary magnetic resonance imaging of patient 1 showing a type I Arnold-Chiari malformation, syringomyelia, and bulbar compression by an odontoid apophysis.

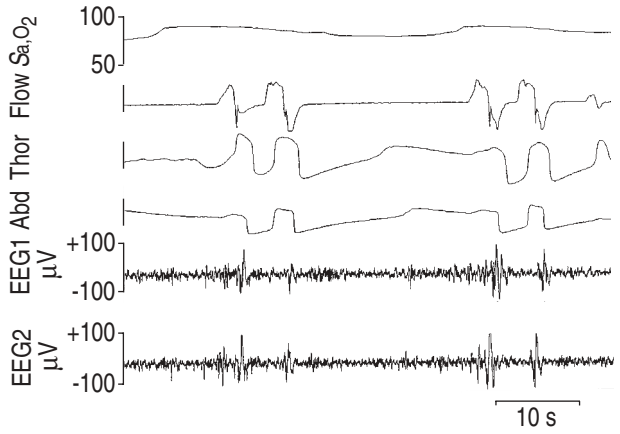

Fig. 2. – Typical central apnoeas in patient 2. Sa,O_2: oxygen saturation; Flow: airflow (pneumotachography); Thor: thoracic movements; Abd: abdominal movements; EEG1: C4 A2 electroencephalogram (EEG) derivation; EEG2: C3 A1 EEG derivation.

pneumotachograph, thoracic and abdominal movements by strain gauges, pulse oximetry, two-channels electroencephalogram, electro-oculogram, and chin electromyogram) revealed prolonged central apnoeas as soon as the patient fell asleep. The apnoea/hypopnoea index (AHI) was 118 events·h^{-1}. Peaks of oxygen desaturation reached a nadir of 50%. The patient was discharged at day 60 on nocturnal mechanical ventilation *via* tracheostomy.

During the following months, successive weaning trials for nocturnal mechanical ventilation remained unsuccessful. A second polysomnography performed in September 1995 showed a decrease in the duration of the apnoeic episodes and in the depth of oxygen desaturation peaks, without alteration of the AHI.

Case 2

A non-obese, nonsmoking 39-yr-old engineer was admitted to our Department in January 1996, because of snoring and nocturnal respiratory pauses which had been noticed by his wife. His medical history disclosed only dyslipidaemia for which he received fenofibrate. He reported no daytime sleepiness, morning headaches or involuntary naps. Sleep was not disrupted. He did not take any drug known to alter the sleep pattern.

At physical examination he was nondyspnoeic, and pulmonary and cardiac auscultation were normal. The neurological examination, including cognitive function, was also normal. Pulmonary function tests revealed an FEV1 of 4.3 L (94% pred), FVC of 4.9 L (92% pred), and an FEV1/FVC ratio of 88%. The haemoglobin concentration was 16 g·L^{-1}, ABG analysis showed a pH 7.43, P_{a,CO_2} 4.6 kPa, P_{a,O_2} 11.8 kPa, and bicarbonate levels of 23 mmol·L^{-1}. The chest radiograph was normal. A polysomnography (as in case 1) revealed a severe CSA, whose type was characterized by strain gauges (fig. 2). The AHI was 57 events·h^{-1}, the duration of the apnoeas averaged 20 s, and the minimal oxygen saturation reached was 75%. This type of sleep apnoea was so atypical in a young patient that MRI of the cervical region was performed, which showed type I ACM. Neither syringomyelia nor bulbar compression were noted in this patient. Exploration of the respiratory drive by a hypercapnic challenge (rebreathing method) showed values of 29 L·min^{-1}·kPa $P_{a,CO_2^{-1}}$ (normal: 16 L·min^{-1}·kPa $P_{a,CO_2^{-1}}$).

Despite the central type of the apnoeas, nasal continuous positive airway pressure (CPAP) was attempted, allowing a mild improvement in the AHI and a reduction in apnoea duration. Surgical anterior decompression is currently under consideration in this case.

Discussion

There are two main types of ACM; type I is characterized by the caudal prolapse of the cerebellar tonsils, extending to the upper cervical spinal canal and lying in close contact with the medulla. Type II ACM is a more extensive malformation, which also includes downward displacement of the medulla [4].

Type I ACM is a common congenital abnormality. The most common findings include motor deficiency, sensory loss, lower cranial palsy, and cerebellar syndrome [5, 6]. Respiratory insufficiency seems to be particularly uncommon [6], and is frequently unmasked in situations characterized by increased ventilatory demand [4]. It is of note, that central and obstructive apnoeas often associate with ACM [1, 4].

Due to the unusual mode of presentation of ACM, the authors consider these observations original. To the authors' knowledge, respiratory failure as the first manifestation of ACM (as seen in case I), has only been reported once [7]. The cases presented here are the first to be reported in the literature, which presented initially as CSA. Recently, however, SHIIHARA *et al.* [8] reported a case of a mixed-type sleep apnoea without other neurological abnormalities in an 11-yr-old female.

Respiratory manifestations during sleep in ACM are generally ascribed to two types of abnormality: upper airway dysfunction, and abnormalities of respiratory control [9, 10]. Understandably, upper airway dysfunction is mainly associated with obstructive apnoeas, whereas abnormalities of respiratory control presumably play a central role in the pathophysiology of CSA in ACM patients.

CSA is characterized by transient cessation of central respiratory output during sleep. Three distinct pathophysiological mechanisms can be proposed to account for the transient cessation of respiratory drive: firstly, an outright defect in respiratory drive or respiratory muscle function; secondly, a transient instability in an otherwise intact respiratory control system; and thirdly, a transient active inhibition of respiratory motor drive [11]. In view of these considerations, CSA reflects a heterogeneous group of disorders.

Schematically, two types of patients can be identified, namely hypercapnic and nonhypercapnic [12, 13]. The hypercapnic group includes patients with central hypoventilation, neurological syndromes and/or impaired respiratory mechanics. Pathophysiologically, this group is consistent with the first mechanism. P_{a,CO_2} while awake is high, and patients have blunted hypercapnic ventilatory responses. These patients commonly complain of morning headaches due to carbon dioxide retention and have excessive daytime somnolence due to sleep disruption. The nonhypercapnic group includes patients with idiopathic hyperventilation and periodic breathing. Pathophysiologically, this group is consistent with the second or third mechanism. These patients typically have a low or normal awake P_{a,CO_2} and an increased hypercapnic ventilatory response. They complain of insomnia, and daytime somnolence is determined by the extent of sleep disruption.

In ACM, abnormalities in respiratory control seem to be multifactorial. The first patient has the "hypercapnic type" of CSA, with impairment or loss of the automatic control of ventilation. Causative mechanisms may include: 1) lack of functional chemoreceptor afferents, owing to carotid body denervation *via* injury to the 9th cranial nerve pair; 2) insensitivity of peripheral chemoreceptors, owing to lo-wer brain stem involvement [14]; 3) compression of the phrenic motoneurons in the anterior horn of the medulla by the associated syringomyelia, or compromised vascular supply to the brain stem [4]; and 4) direct bulbar compression of the respiratory centre by an odontoid apophysis or by downward displacement of the cerebellar tonsils [15].

The pathophysiology of CSA in our second patient seems more complex. In fact, this patient was never found to be hypercapnic and an exploration of the respiratory drive showed a supranormal response. He probably corresponds to the "normo-hypocapnic type". In this type of CSA, P_{a,CO_2} and ventilatory response may be critical factors. XIE *et al*. [16] emphasized that, in comparison with normal subjects, the slopes of the rebreathing and single-breath ventilatory response were elevated in normo-hypocapnic CSA patients. These findings suggest that normo-hypocapnic CSA patients chronically hyperventilate, probably in relation to increased ventilatory drive, which may be related to high chemoreceptor gain [16]. Chronic hyperventilation in these patients could maintain P_{a,CO_2} close to the apnoea threshold during sleep. Thus, the intrusion of a large tidal volume (as during brief arousals) could readily drive P_{a,CO_2} below the apnoeic threshold and trigger post-hyperventilatory central apnoeas. Desaturation related to apnoeas can amplify the postapnoeic hyperventilatory response and this ventilatory overshoot can lead to a new apnoea, thus perpetuating the phenomenon [12, 17, 18]. In brief, in these patients, the increased ventilatory responsiveness, often amplified by accompanying hypoxaemia, can destabilize the respiratory control system leading to rebound central apnoeas.

The mechanisms explaining the increased ventilatory responsiveness in this second patient are not clear. One hypothesis is that anatomical modifications may lead to mechanical stimulation of chemoreceptors and, therefore, to increased ventilatory responsiveness.

As mentioned above, nasal CPAP in this patient was effective in improving the AHI and apnoea duration. The mechanisms by which CPAP improved CSA may include increased oxygen and carbon dioxide stores, which could dampen oscillations in feedback control, and even stabilization of the upper airways [12, 18, 19].

Decompressive surgery in our first patient was able to shorten central apnoeas as described by others [1], but it did not allow weaning from the nocturnal mechanical ventilation.

Only three cases of ACM and CSA have been described [1–3], but in none of these was CSA the first manifestation. Moreover, the cases currently under consideration are noteworthy because of the severity of their CSA. The severity of apnoeas may explain the reported increased incidence of death during sleep in ACM patients [4].

In our first patient, the existence of autonomic dysfunction, without any neurological signs and its association with Klinefelter syndrome must be emphasized. The association of ACM and Klinefelter syndrome has, to the authors' knowledge, never been reported. It may simply be a chance association.

In summary, central sleep apnoea can be the initial manifestation of Arnold–Chiari malformation and may be a life-threatening condition.

Acknowledgements: The authors gratefully acknowledge L. Jeannin and Ph. Camus for their contribution to this manuscript.

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