

Primary alveolar hypoventilation and XXXXY chromosopathy

D. Samolski¹, A. Antón¹, M. Mayos¹, M. Subirana², R. Güell¹

ABSTRACT: *Primary alveolar hypoventilation and XXXXY chromosopathy. D. Samolski, A. Antón, M. Mayos, M. Subirana, R. Güell.*

The association of primary alveolar hypoventilation (PAH) and chromosomal diseases has not been described previously. A 19 year-old man with Fraccaro's syndrome (XXXXY karyotype) was admitted to evaluate chronic hy-

percapnic respiratory failure, pulmonary arterial hypertension and cor pulmonale. PAH was diagnosed. As effective treatment, such as non-invasive positive pressure ventilation (NIPPV), is available for this disorder we should intensify the search for PAH in patients with chromosome disease.

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Keywords: *Primary alveolar hypoventilation, chromosome diseases, noninvasive ventilation.*

¹ *Pneumology Dept. Hospital de la Santa Creu i Sant Pau, Barcelona Spain.*

² *Cardiology Dept. Hospital de la Santa Creu i Sant Pau, Barcelona Spain.*

Correspondence: Daniel Samolski M.D., Pneumology Dept., Hospital de la Santa Creu i Sant Pau, Sant Antoni M^a Claret 167, 08025 Barcelona Spain; e-mail: dsamolski@hsp.santpau.es

Introduction

Primary alveolar hypoventilation (PAH) is a rare clinical entity characterised by respiratory failure in the absence of pulmonary parenchyma or respiratory pump abnormalities. Diagnosis of PAH requires the presence of hypoventilation (hypercapnia) and the demonstration of normal respiratory function tests, especially during voluntary ventilation maneuvers. Functional disorders of the respiratory centre [1-3] are also a constant feature. Known diseases of the central nervous system must be ruled out to support this diagnosis [1-4]. The main objectives of the present study are to report a case of PAH associated to a chromosome disease (Fraccaro's syndrome), to describe clinical manifestations of this unusual syndrome, and to discuss the clinical implications of PAH in genetic diseases.

Clinical Case

We describe a 19 year-old man diagnosed with Fraccaro's syndrome in childhood (chromosome disease with XXXXY karyotype). He presented the typical phenotype characteristics of this entity: mental retardation, radioulnar synostosis, hypogonadotropic hypogonadism and congenital heart disease (persistent ductus arteriosus and interventricular communication, surgically resolved at the age of 3 months and 4 years, respectively). The patient remained cardiologically stable in spite of moderate pulmonary arterial hypertension manifested by mean pulmonary arterial pressure (mPAP) up to 50 mmHg. Over the last few years, the patient had suffered from progressive dyspnea,

evolving from functional class II (NYHA) to III-IV, and also diurnal sleepiness. Physical examination showed cor pulmonale syndrome. Blood tests were normal. Chest X ray revealed only an increased cardio-thoracic index. A thoracic Computed Tomography (CT) scan also demonstrated the presence of pulmonary hypertension signs without pulmonary thromboembolic disease or intravascular clots. Arterial blood gases demonstrated hypercapnic respiratory failure (PaO₂ 48 mmHg PaCO₂ 49 mmHg pH 7.37). A transthoracic echocardiographic test showed severe dilation and dysfunction of right ventricle and mPAP of 70 mmHg. A polysomnographic recording performed immediately after these findings evidenced the presence of non-obstructive episodes of hypopnea and a constant decrease in arterial oxygen saturation (SpO₂) suggestive of hypoventilation (fig. 1). The patient's mental disorder ruled out the possibility of performing respiratory functional tests. However, he was able to complete a eucapnic hypoxia stimulus test. This test was evaluated using Rebeck and Campbell's method to assess the ventilatory response to hypoxia [5]. It demonstrated poor ventilatory response: $\Delta MV/\nabla PaO_2$ 0.13 L/min/mmHg, $\Delta MV/\nabla SpO_2$ 0.13 L/min/%, $\Delta pO_1/\nabla SpO_2$ 0.02 cmH₂O/%. With the diagnosis of central hypoventilation syndrome associated with a chromosomal disease, which presents as respiratory failure and cor pulmonale, we decided to begin anti-coagulation treatment and non-invasive positive pressure ventilation (NIPPV). We used a bi-level positive pressure ventilator (VPAP III, ResMed, Australia) with its own single limb circuit and a nasal mask (UltraMirage, ResMed, Australia). Using the common techniques for NIPPV adaptation, we reached an IPAP

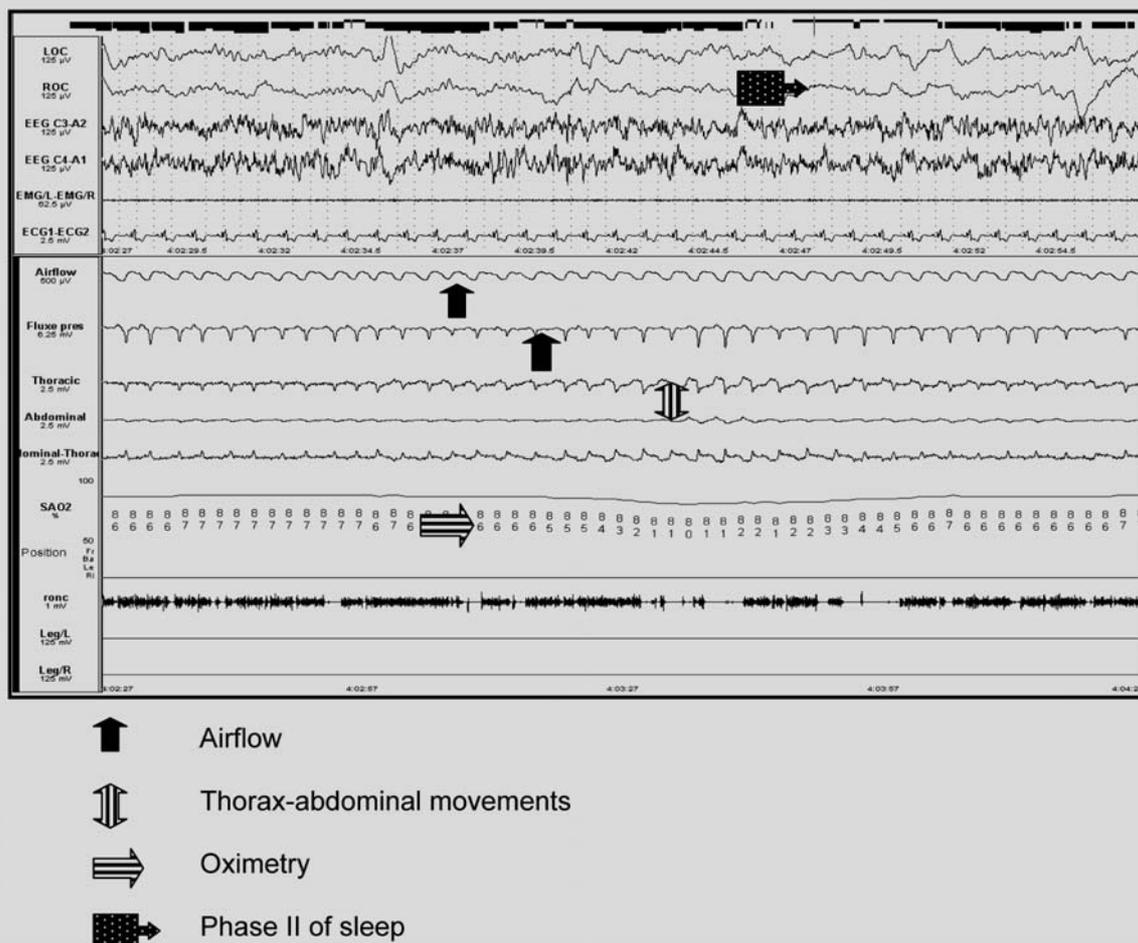


Figure 1. - Polysomnographic* recording showing constant decrease in SpO₂ without obstructive respiratory disorders.

* Polysomnographic studies (Ultrason WS, Nicolet, Madison, Wisconsin) included the recording of electroencephalogram (2 unipolar leads), left and right electrooculogram and chin electromyogram for sleeping staging, electrocardiogram, oro-nasal airflow with thermistor and nasal cannula, rib cage and abdominal wall displacement measured by piezoelectric bands, oxyhemoglobin saturation and snoring by sternal notch. Sleep staging was manually interpreted in 30-second periods according to standard criteria. Apnea was defined as an airflow cessation lasting > 10 seconds. Hypopnea was defined as an airflow reduction lasting for > 10 seconds associated with a 3% decrease in saturation level and/or an arousal. Arousals were scored according to the American Sleep Disorders Association recommendation [20]. SpO₂: arterial oxygen saturation measured by pulse oxymetry

of 16 cmH₂O and an EPAP of 6 cmH₂O. Clinical and blood gas response to NIPPV was not as good as we expected. This was probably related to cognitive alterations, which affected treatment tolerance and compliance. A pulse-oxymetry evaluation and blood gas analysis performed prior to hospital discharge showed a small improvement in SpO₂ and PaO₂, associated with a slight decrease in PaCO₂. Blood gas analyses continued to show oscillations in later follow-ups.

Discussion

Fraccaro's syndrome, named after the physician who first described it in 1960 [6], is a very rare chromosomal aneuploidy (XXXXY karyotype) with an incidence of about 1/ 85,000 live births [7-10]. It is characterised by mental retardation, typical facies, radioulnar synostosis, hypogonadotropic hypogonadism and congenital heart disease (mainly, persistent ductus arteriosus) in 20% of cases. Only 100 cases have been described

to date and none so far have described the ventilatory disorders observed in our patient.

Morales *et al.* [11] described a potential relationship between chromosomal diseases and respiratory pathology, although they did not report the presence of a ventilatory control disorder. They demonstrated the existence of restrictive disease in patients with Klinefelter syndrome (XXY karyotype), expressed by reduced total lung capacity and normal FEV₁/FVC ratio. Maximal inspiratory pressure was also normal and there was a reduced pulmonary compliance. They suggested that the reduction in pulmonary matrix elasticity, together with the aforementioned reduced compliance, could be due to testosterone deficiency. Against this idea is the lack of improvement in respiratory dysfunction with testosterone replacement therapy treatment [11]. In the present case, the patient had been receiving this hormone since the age of 13.

To our knowledge, this is the first case describing PAH in a patient with a XXXXY chromosome disease. We have not found any reports in the

literature regarding the relationship between chromosome disease and respiratory centre dysfunction. However, the relationship between those disorders and other components of the nervous system such as autonomic dysfunction is better known. Alterations of the sympathetic-parasympathetic balance may cause cardiovascular and/or respiratory dysregulations [3, 12-14]. This imbalance explains the appearance of cardiac arrhythmias, and decreased beat-to-beat variability during sleep, as well as the association of this entity with others which reflect autonomic dysfunction such as Hirschsprung's disease [15], pupil abnormalities, profuse perspiration and decrease in body temperature [3].

A report on PAH in monozygotic twins suggests that the PAH syndrome may have a genetic component [16]. In another study, a series of adult women with central congenital hypoventilation syndrome (CCHS) had children with this disease [15] supporting a genetic basis in CCHS. Knowing the association between CCHS and Hirschsprung's disease (20% of the patients), the genes involved could be those which codify for tyrosin kinase receptor, glia-derived neurotrophic factor, and endothelin receptor. The PHOX2B gene which codifies for a transcription factor to promote neuronal differentiation, is also been implicated in CCHS [14]. No one gene potentially related to this syndrome has been linked to the sex chromosome. There is consequently a lack of knowledge regarding whether the supernumerary X chromosome (as present in our patient) could play a role in the etiopathogenesis of central hypoventilation syndrome.

Hypoventilation and impaired cor pulmonale could be under-estimated in these patients, since part of their symptomatology is generally attributed to their cognitive deterioration and cardiac disorders. Presently available treatments, such as NIPPV, have proven useful in patients with hypoventilation disorders [18, 19]. For this reason, diagnosis of central hypoventilation in patients with this type of chromosome disorder is of great importance, since early prescription of home mechanical ventilation may modify the natural course of these diseases.

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