

CASE STUDY

Sleep apnoea and Turner's syndrome

O. Orliaguet^{*,#}, J.L. Pépin^{*,#,¶}, G. Bettega^{+,#}, G. Ferretti[§], H.N. Mignotte^{*}, P. Lévy^{*,#,¶}

Sleep apnoea and Turner's syndrome. O. Orliaguet, J.L. Pépin, G. Bettega, G. Ferretti, H.N. Mignotte, P. Lévy. ©ERS Journals Ltd 2001.

ABSTRACT: A 32-yr-old female with Turner's syndrome and anatomical craniofacial abnormalities, presented with obstructive sleep apnoea syndrome. This was initially treated by nasal continuous positive airway pressure and secondarily cured by maxillomandibular advancement osteotomy. Anatomical upper airway abnormalities and hormonal factors, which predispose Turner patients to develop obstructive sleep apnoea syndrome, are discussed. A systematic assessment and treatment of sleep-disordered breathing is probably of interest in these patients.

Eur Respir J 2001; 17: 153–155.

*Dept of Respiratory Medicine, #Sleep Laboratory, [¶]Physiologie Respiratoire Experimentale Théorique et Appliquée (PRETA) Laboratory, ⁺Dept of Maxillofacial and Plastic Surgery and [§]Dept of Radiology, Centre Hospitalier Universitaire de Grenoble, France.

Correspondence: J.L. Pépin, Sleep Laboratory and Respiratory Unit, University Hospital, BP 217 X, 38043 Grenoble, France.
Fax: 33 476765617

Keywords: Cephalometry, obstructive sleep apnoea syndrome, Turner's syndrome, upper airway imaging

Received: December 31 1999
Accepted after revision July 14 2000

Turner's syndrome (gonadal dysgenesis) is a common X-linked chromosomal aneuploidy, affecting approximately 1 in 3,500 female births. It is characterized by a female phenotype, retarded growth, infertility and congenital heart disease [1]. Among various skeletal abnormalities, craniofacial modifications have been reported in Turner's syndrome. In this context, we report the case of an association between Turner's syndrome and obstructive sleep apnoea syndrome (OSAS), initially treated by continuous positive airway pressure (CPAP). Owing to the narrow upper airway associated with the usual harmonious brachycephaly that is found in Turner's syndrome, maxillomandibular advancement osteotomy (MMO) was secondarily performed, resulting in the disappearance of OSAS.

Case report

A 32-yr-old female was referred to the sleep laboratory (Chu de Grenoble, France) for excessive daytime sleepiness (Epworth sleepiness scale 14/24) and a history of snoring. She was diagnosed at fifteen with Turner's syndrome (45,X0) and was subsequently placed on hormonal replacement therapy. She was a nonsmoking, small and nonobese patient (height 150 cm, body mass index 19.5 kg·m⁻²). She had been treated for high blood pressure for many years but had no congenital heart disease. On oral examination jaw occlusion was normal, the tongue was enlarged and there was a high arched palate. Forced expiratory volume in one second (FEV₁ was 2.90 L and vital

capacity (VC) was 3.74 L (115% and 127% of predicted, respectively), FEV₁/VC ratio being 84%. Flow-volume loop and blood gases were normal.

Diagnostic polysomnography revealed an apnoea hypopnoea index (AHI) of 27·h⁻¹ (86% obstructive apnoeas, 6% central apnoeas, 8% hypopnoeas, respiratory arousal index: 16.5·h⁻¹ sleep), and no upper airway resistance episodes. Mean nocturnal Sa_{o2} was 96% with a minimal nocturnal Sa_{o2} of 90%. Rapid eye movement (REM) sleep was reduced (10% of total sleep time) and 14% of total sleep time was spent in slow wave sleep.

Upper airway imaging (cephalometric radiograph and pharyngeal computer tomography (CT) found no abnormalities regarding soft tissues (soft palate length 30 mm, normal values (Nal) 34±6 mm). Craniofacial size was reduced with a tendency towards harmonious brachycephaly (fig. 1). The pharyngeal size was significantly reduced as demonstrated by posterior airway space (PAS) measurement (3 mm; Nal 11±2 mm) and a reduction in cross sectional area determined by CT at oropharyngeal and hypopharyngeal level: 86 and 83 mm², respectively (normals: 260±8 and 320±17 mm², respectively). The shape of the upper airway demonstrated a predominant lateral long axis.

Nasal CPAP therapy was initiated to treat sleep apnoea syndrome and pursued for three months. The patient then refused to continue the treatment owing to her young age, although there were no significant side effects with nCPAP. Taking into account the obviously narrowed upper airway and the nCPAP refusal, a staged maxillofacial surgical procedure [2] was decided.

First step surgery (phase 1) associating uvulopalatopharyngoplasty (UPPP), genioglossal advancement, hyoid myotomy and hyothyroidopexy was unsatisfactory as the AHI increased six months after surgery (AHI 50 h⁻¹). MMO was then performed (phase 2), leading to a dramatic improvement (AHI 9 h⁻¹). This procedure was technically difficult in relation to poor bone quality. After phase 1 the patient complained of local oropharyngeal pain related to UPPP in the first 3–5 days after surgery, and experienced transient chin and lower lip anesthesia and paraesthesia, resolving after several months. After MMO, there was an enlargement of the nose base and nostrils associated with a convex aspect of the superior lip. The patient and her husband did not complain about these aesthetic modifications.

Six months after surgery, slow wave sleep increased from 14% to 20.3% of the total sleep time. Similarly, REM sleep increased from 10–30% of total sleep time, whilst snoring and sleepiness dramatically improved. In accordance, concurrent pharyngeal CT showed a significant increase in cross sectional area at the oropharyngeal and hypopharyngeal level (125 and 130 mm², respectively) and cephalometric PAS was then measured at 7 mm, compared to 3 mm before surgery (table 1). Clinically after one year, the patient is still without any excessive daytime sleepiness.

Discussion

To our knowledge, this is the first case reported in the literature of an association between sleep apnoea and Turner's syndrome. OSAS is a common condition in the general population, affecting an estimated 4% of females between 30 and 60 yrs [3]. Thus it is not surprising that the two syndromes could coexist. However, the well known reduction in upper airway size and the gonadal dysgenesis occurring in Turner patients are a convincing rationale for a nonfortuitous association.

In OSAS, the reduction in upper airway size, owing to craniofacial skeletal abnormalities or redundant soft tissues, is the major explaining factor of the upper airway collapse during sleep, which occurs mainly in young and lean subjects [4, 5]. In Turner patients, several anatomical factors can contribute to the reduction in upper airway size and thus predispose to OSAS. As in our patient, JENSEN *et al.* [6], in a cephalometric study of Turner patients, found a tendency towards harmonious brachycephaly and a shorter pharyngeal depth, in comparison to normal females. The maxilla and the mandible were significantly smaller, retrognathic and posteriorly inclined. These abnormalities seem to be specifically related to the lack of an X chromosome. Accordingly, an additional X chromosome (Klinefelter's syndrome) produced a mirror effect with mandibular and maxillary prognathism [7]. Moreover, an enlarged tongue, short neck and high arched palate are frequent in Turner patients [1] and can also favour the occurrence of OSAS. In summary, genetically determined anatomical abnormalities of the upper airway exist in Turner's syndrome, and might predispose these patients to OSAS.

Turner's syndrome is characterized by gonadal dysgenesis with total or partial absence of female sex hormones and, in most cases, infertility. In the general population, sleep disordered breathing is less common in females than in males until after the menopause [8]. It has been postulated that female sex hormones may protect against the development of sleep disordered breathing and that the decline in oestrogen and progesterone levels after menopause may explain this phenomenon. However, short-term hormone replacement with oestrogen and progesterone is unlikely to improve sleep apnoea in peri- and postmenopausal females. Other factors, including oestrogen related change in body fat distribution, and the influence of female sex hormones (possibly progesterone) on upper airway dilator muscle activity and ventilatory control, may also increase the risk of OSAS [9]. Thus, hormonal deficit must be considered as a potential mechanism leading to OSAS in Turner's syndrome.

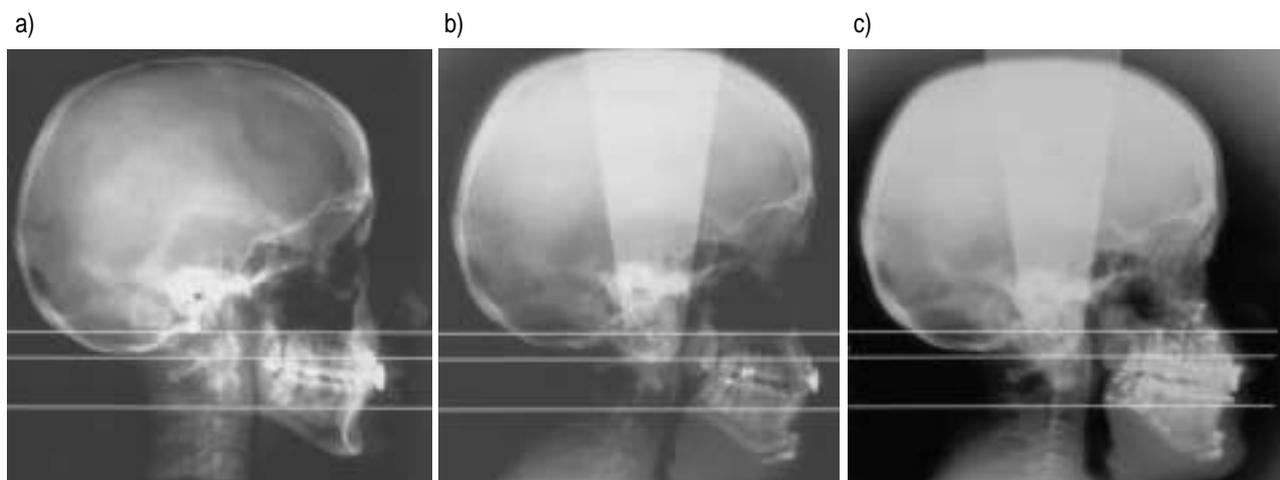


Fig. 1. – Cephalometric radiography. a) Before; b) after phase 1 surgery; and c) after phase 2 surgery (MMO). Phase 1 surgery lead to a limited increase in upper airway size. Phase 2 surgery enlarged the upper airway size, both at the retropalatal and at the posterior airway space level. White lines indicate the level of cross-sectional area of upper airway determined by computed tomography.

Table 1. – Cross sectional area of upper airway determined by computer tomography. PAS: posterior airway space

	Initial	After phase 1 surgery	After phase 2 surgery
Nasopharyngeal level cm ²	0.74	0.79	1.38
Retropalatal level cm ²	0.86	0.90	1.25
Retrobasilingual level cm ²	0.83	0.74	1.3
PAS mm	3	5	7

The surgical treatment of OSAS includes several procedures, each designed to increase the patency of the upper airway at a specific level. In cases with suspected oro and hypopharyngeal narrowing in relation to correctable anatomical abnormalities, maxillofacial surgery can be proposed [10]. Our patient, owing to young age, low BMI, predominant lateral long axis upper airway shape [11] and correctable anatomical abnormalities was considered as a good surgical candidate. Phase 1 surgery was unable to increase upper airway size and as a consequence was ineffective, as it is in the general population of OSAS [10]. Conversely as previously reported in OSAS, MMO was highly effective in our patient. However, in Turner patients, this surgical procedure must be evaluated with care on account of the poor quality of bone and frequently associated osteoporosis [1]. Among the other classical therapies addressed to OSAS, oral appliances could be proposed, but frequent periodontal disease in Turner patients might restrict this procedure [12] and finally, nCPAP should remain the reference treatment.

Recent epidemiological studies have shown that cardiovascular morbidity is increased and life expectancy is markedly reduced in Turner's syndrome. A significantly increased relative risk (RR) was found with regards to heart disease and atherosclerosis (RR 2.11), hypertension (RR 2.91) and stroke (RR 2.71) [13]. Turner's syndrome patients are extraordinarily prone to abnormalities constituting the metabolic syndrome "syndrome X" (e.g., hypertension, dyslipidaemia, diabetes mellitus, obesity, hyperinsulinaemia and hyperuricemia) [13]. Chronic oestrogen deficiency, frequent hypothyroidism, obesity and congenital heart malformation cannot explain such a high level of cardiovascular morbidity. Thus, the coexistence of OSAS and Turner's syndrome may have potential implications. Indeed, the association between "syndrome X" and OSAS is extremely frequent and has recently been called "syndrome Z" [14]. Thus, there is increasing need for further studies examining the role of OSAS as an independent factor for cardiovascular consequences in Turner patients. Finally, aortic dilatation and dissection are well known complications of Turner's syndrome [15]. Markedly negative intrathoracic pressure generated during obstructive apnoeas might increase the risk of aortic dilatation and rupture.

Conclusion

This is the first report of an association between Turner's syndrome and OSAS. With this single case, the authors cannot make any firm comments about the causal relationship of the two syndromes. However they can speculate about the potential contribution of pharyngeal size reduction and gonadal dysfunction in the development of sleep apnoea in adult patients with Turner syndrome. Further studies should be addressed to the prevalence of obstructive sleep apnoea syndrome in unselected populations of Turner patients.

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