The prevalence of obstructive sleep apnea and its association with cardiovascular diseases in Marfan’s syndrome children: The state of the art and the early orthodontic treatment

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Obstructive sleep apnea (OSA) is a sleep disorder that involves a cessation or a significant decrease in airflow in the presence of breathing effort. It is the most common type of sleep-disordered breathing and it is characterized by recurrent episodes of upper airway collapse during sleep. Several studies have documented a higher prevalence of OSA among patients with Marfan’s syndrome (MFS), which has been associated with abnormalities in maxillary morphology and craniofacial structures, and abnormally high collapsibility of the connective tissue. There is an association between OSA and vascular disease. From the complex physiological changes that actually occur during OSA and the results obtained from animal models and laboratory-based studies in recent years, plausible hypotheses have been given to link OSA with vascular disease. Intermittent hypoxia, the intermittent arousal from sleep and increased intrathoracic pressure swings are these plausible hypotheses, however, the only mechanism supported by randomized controlled trials (RCTs) able to explain the associations observed between OSA and vascular disease is the increased sympathetic nervous system activity. The aortic dilation, the associated aortic dissection, and the subsequent rupture are still the main cause of morbidity and mortality in MFS patients. The identification of any treatable risk factor for aortic complications in MFS subjects is thus of major scientific and clinical interest. There is some preliminary evidence that OSA may be a risk factor for the development and progression of aortic aneurysms in patients with and without Marfan’s syndrome. In literature, it was recently reported that the severity of OSA in MFS subjects is associated with an increased aortic root diameter and that MFS patients with OSA, have a significantly shorter aortic event-free survival than MFS patients without OSA. Furthermore, the skeletal class II malocclusion with mandibular retrognathia and correlated increased overjet has long been recognized to be not only the most typical malocclusion of MFS children but also a significant risk factor for OSA development in all patients. From this overview followed the research of an early orthodontic treatment aimed at the reduction of risk factors for the development of OSA in this particular population. The rapid maxillary expansion and mandibular advancement significantly improved the airway patency and reduced the frequency of apneas in MFS children.

Keywords: Marfan’s syndrome; Obstructive sleep apnea; Aortic Dilatation; Rapid maxillary expansion; Mandibular advancement device; Sleep studies and questionnaire; Cephalometric analysis

Marfan’s syndrome

Marfan’s syndrome (MFS) is an autosomal dominant disorder of connective tissue. It is caused by mutations in the FBN1 gene localized on chromosome 15q21, which encodes a glycoprotein known as fibrillin-1. Fibrillin-1 is the main component of the microfibrils in the extracellular matrix of the connective tissue [1]. The prevalence of Marfan’s syndrome is estimated to be between 1 and 3 per 10,000 individuals [2,3]. The diagnosis primarily depends on a combination of major and minor clinical findings defined in the Ghent criteria. Major criteria are diseases rarely observed in the general population and with a high diagnostic specificity; minor criteria are relatively common diseases within the general population [4]. Ghent major criteria are mostly found in the cardiovascular, ocular and skeletal systems but the disease also causes pulmonary, skin, and nervous dysfunctions [5]. Recently the diagnosis was based on the revised Ghent nosology for MFS, which can be summarized in five major proposals [6]. The first proposal was to give more weight to the two cardinal features of MFS: aortic root aneurysm/dissection and ectopia lentis. The combination of ectopia lentis and aortic root enlargement/dissection is sufficient to make the diagnosis. All other cardiovascular and ocular manifestations of MFS and findings in other organ systems contribute to develop a scoring, defined as a “systemic” score, that guides diagnosis when aortic disease is present but ectopia lentis is not. The second proposal was to assign a more prominent role to molecular genetic testing of the FBN1 and other relevant genes (eg, TGFBR1 and 2). This does not make the FBN1 testing a formal requirement for diagnosis, since it does not yet have 100% sensitivity and specificity, but allows its appropriate use when available. The third proposal was characterized by the reduction of the less specific manifestations of the MFS, but these clinical findings have been removed or made less influential in the diagnostic evaluation of MFS patients. The fourth proposal was for the patients with sufficient manifestations to satisfy the criteria for MFS but also with unexpected findings: further diagnostic considerations and testing are required. Regarding the differential diagnosis, a particular emphasis has been placed on the Sphrintzen-Goldberg syndrome (SGS), the Loeyse-Dietz syndrome (LDS), and the vascular form of the Ehlerse-Danlos syndrome (vEDS). Finally, with the fifth proposal, the revised nosology helps to allay concerns regarding delayed or ambiguous diagnoses by providing context specific recommendations for patient counselling and follow-up [6]. Aortic root dilation and subsequent dissection is the main cause of premature death in MFS patients. Dilation of the aortic root can begin in childhood or early adulthood and increases at an unpredictable rate [7,8]. It is a matter of debate which factors contribute to a rapid progression of aortic root dilatation. Given its impact on survival, monitoring of patients with Marfan’s syndrome is emphasized to control aortic disease.

The normal respiratory physiology during sleep and obstructive sleep apnea

Sleep is a major physiological drive. The average child spends almost one-half of his or her life asleep. A newborn will sleep, as reported by Marcus, for as much as sixteen hours a day [9]. Thus, respiratory disorders during sleep are of particular importance during childhood. Although some respiratory disorders- such as sleep apnea- occur only during sleep, virtually all the respiratory disorders, (including upper airway obstruction, central hypoventilation, and chronic lung disease), are worse during sleep than during wakefulness [9]. Recently, interest within the medical community for the scientific evaluation of sleep has been growing, however, there are still large gaps in our knowledge. We all breathe better awake than asleep. During sleep, there is a decrease in ventilation per minute [9]. In adults, the ventilation per minute decreases by approximately 13-15% compared with the value during wakefulness; the respiratory rate tends to remain constant and the decrease is due primarily to a decrease in tidal volume [9,10]. In contrast, studies of infants, children, and adolescents have shown that the respiratory rate decreases during sleep [9,11,12]. Only one study, mentioned by Marcus and performed on adolescents during sleep, showed a decrease in tidal volume [9,13]. The functional residual capacity (FRC) decreases with sleep [9,14], and upper airway resistance doubles [9,15]. The ventilatory drive decreases, particularly during rapid eye movement (REM) sleep [9,16,17]. During REM sleep, breathing is erratic, with variable respiratory rate and tidal volume and frequent central apneas. REM sleep is also associated with a decrease in intercostal and upper airway muscle tone [9,17]. Thus, breathing is impaired during sleep and is further impaired during REM sleep [9]. This is particularly dangerous for children, as they sleep more than adults, and have relatively more REM sleep. In newborns, active sleep, (an REM-like state), can occur for up to two-thirds of total sleep time [9,18], as compared to 20–25% of sleep time in adults [9,19]. The explanation of this statement is to be found in the development, from childhood to adulthood, of the anatomical structures involved in breathing [9]. The chest wall and upper airway change during infancy and childhood in order to respond to the physiological needs of the developing organism. The compliant chest wall of the newborn allows for compression during the birth process. In addition, this compression aids in expelling pulmonary fluid. After birth, however, the compliant chest wall places the infant at a mechanical disadvantage during respiration [9]. In infants, chest wall...
compliance is three times the lung compliance $^{[9,20]}$. This causes a paradoxical inward rib cage motion during inhalation, with a resulting increase in breathing effort, particularly during REM sleep when intercostal muscle activity is decreased. Ossification of the sternum and vertebral begins in utero and continues until 25 years of age, resulting in a stiffer chest wall $^{[9]}$. Although chest wall compliance equals lung compliance by the age of 2 $^{[9,20]}$, the paradoxical inward rib cage motion during inhalation is seen in normal children during REM sleep until at least 31 months of age $^{[9,21]}$. Children with upper airway obstruction have relatively more paradoxical breathing during sleep than adults $^{[9]}$. By adolescence, the paradoxical inward rib cage motion during inhalation is not seen in normal subjects $^{[9,13]}$. The shape of the rib cage also changes during early childhood. In infants, the ribs are orientated horizontally, resulting in a circular thorax with little potential for further expansion. The zone of apposition of the diaphragm is smaller $^{[9]}$. Thus, the rib cage contribution to tidal breathing during the quiet/non-REM sleep is only one-third at 1 month of age $^{[9,22]}$, as compared with two-thirds in older subjects $^{[9,13]}$. As the child begins to assume a more upright posture over the first 2 years of life, the muscles force the ribs to produce the adult configuration $^{[9,23]}$. In addition, muscle mass develops progressively from childhood to adulthood. Although infants can produce high inhalation pressure, they tend to function close to the diaphragmatic fatigue threshold $^{[9,24]}$. They are therefore more likely to decompensate if they develop cardiopulmonary disease, including the upper airway obstruction. Obstructive sleep apnea (OSA) is a prevalent disorder characterized by repetitive events of collapse and reopening of the upper airway during sleep $^{[9]}$. The higher collapsibility observed in OSA is usually attributed to obesity and other alterations in structural or functional properties of the upper airways $^{[9,25]}$. It is important to make a clear distinction between OSA and the central apneas $^{[9]}$. The central apneas are common in infants and children, particularly during REM sleep $^{[9,12,26]}$. Traditionally, central apneas in children have been considered significant if they are greater than 20 seconds in length, or if they are associated with desaturation, bradycardia, or arousal $^{[9]}$; however, central apneas greater than 20 seconds are commonly seen in normal children, particularly after body movement or sighs of the patients during sleep, and are frequently associated with desaturation $^{[8,12,27,28]}$. Data on normal infants has shown central apneas of up to 25 seconds in duration, associated with an oxygen desaturation of less than 81% $^{[9,29]}$. Thus, the clinical significance of these central apneas is dubious $^{[9,30]}$, unless they occur very frequently or are associated with prolonged gas exchange abnormalities.

In contrast to central apneas, obstructive apneas are rare in normal children $^{[9]}$. Marcus considered three studies. A study performed on more than 1,000 infants found a mean obstructive apnea index of zero (range: 0–4/h) $^{[9,26]}$. Another study performed on 50 normal children, aged between 1 and 18 years, found that only 18% had even a single obstructive apnea during the night, and all obstructions were less than or equal to 10 seconds in duration. The mean obstructive apnea index was 0.1±0.5/h $^{[9,27]}$. These data apply to the complete apneas only; there is no normative data for the hypopneas in children. One study, evaluating the hypopneas in children, did not publish the hypopnea data separately but found a total respiratory disturbance index (i.e., central apneas, obstructive apneas, and hypopneas) of 1.1/h $^{[9,31]}$.

The prevalence and the possible etiological factors of the OSA in Marfan’s syndrome children

Several studies have documented a higher prevalence of OSA among patients with Marfan’s syndrome. Cistulli and Sullivan reported that sixteen of the twenty five patients (64%), with Marfan’s syndrome had OSA (defined as an AHI greater than 5) $^{[32]}$. The possible explanations for the very high prevalence of OSA found in this study may be the selection bias due to the relatively small number of randomly recruited patients and the percentage of females included in the study, as the prevalence of OSA is known to be lower in women than in men $^{[33]}$. Verbraecken and colleagues found that four of the fifteen patients (27%) had features and symptoms of sleep apnea, although this study was based on questionnaires only $^{[34]}$. The first large case control study on the prevalence of OSA in patients with Marfan’s syndrome was the study of Kohler and colleagues. In this study, a considerably higher frequency of OSA in the MFS patients was shown, compared with matched control subjects using either a threshold for AHI of greater than 5 or greater than 15. Furthermore, the authors found that approximately 30% of all MFS patients had an AHI and ODI of greater than 5, which is a considerably higher prevalence of OSA than in the matched controls (only 3.9% had an ODI greater than 5) $^{[35]}$. With regard to the possible etiological factors of OSA in MFS children, Cistulli and colleagues correlated the sleep-disordered breathing (SDB) with abnormalities in maxillary morphology and craniofacial structures $^{[36]}$. This cephalometric study, performed on MFS patients, provides the evidence that such subjects have a high prevalence of craniofacial abnormalities. The finding of a relationship between indexes of apnea severity and various cephalometric measurements suggests that these structural abnormalities are likely to play a role in predisposing these individuals to OSA. Various craniofacial abnormalities have been described in MFS patients, although literature on this topic has been limited primarily to case studies. The reported abnormalities include dolichocephaly, maxillary constriction with a high arched palate, maxillary and mandibular retrognathia,
prognathia, and macrocephaly [37-42]. The study of Cistulli and colleagues was the first to examine airway measurements in addition to conventional orthodontic measurements from cephalometric radiographs in MFS patients and has confirmed the high prevalence of abnormalities in these subjects. The authors found that all of the patients with Marfan’s syndrome had at least four of the assessed variables outside the limits of normality; the significant abnormalities were: maxillary and mandibular retrusus with mandibular growth predominantly vertical, a reduced maxillary length, an increased total anterior face height, a long lower anterior face height (LAFH), an obtuse gonial angle, a steep mandibular plane, a reduced posterior nasal airway height, a reduced posterior airway space (PAS), and an increased distance from the mandibular plane to the hyoid bone (MP-H) [36]. The observed cephalometric abnormalities are similar to those reported in the general OSA population [43]. Another study showed that all investigated patients with Marfan’s syndrome exhibited increased collapsibility of the upper airways respect to weight-matched controls. The authors suggested that this abnormally high collapsibility could be caused by the MFS-induced changes in the connective tissue. Therefore, it is possible that the laxity of the upper airways is an important pathophysiologic mechanism for the high prevalence of OSA in these patients [44]. Recently, an interesting study was performed on animal model. The authors, used a murine MFS model to investigate the potential changes of collapsibility of the upper airways in this disease. This work shows new evidence that Marfan’s syndrome can increase the collapsibility of the upper airways, suggesting that this disease could produce, in the connective tissue, structural abnormalities which could then in turn, make these individuals more susceptible to obstructive apneas. Therefore, Marfan’s syndrome could increase the risk of OSA, explaining the higher prevalence of obstructive sleep apneas observed in MFS patients [45].

The mechanism of vascular damage in OSA and the impact of obstructive sleep apnea on aortic disease in Marfan’s Syndrome

There is clearly an association between obstructive sleep apnea and vascular disease [46-48]. Most vascular diseases remain unexplained even after allowing for well-known risk factors, such as hypertension and the dyslipidaemia [49] and, because obstructive sleep apneas are common, they certainly could provide a significant extra contribution. In recent years, several potential hypotheses have been made to link OSA with vascular disease, derived from the complex physiological changes that actually occur during OSA [50], and supported by animal models and laboratory-based studies [51-53], including intermittent hypoxia, intermittent arousal from sleep, and increased intrathoracic pressure swings. Correlation between OSA and vascular disease is probably due to many factors, including augmented sympathetic activity, with less evidence for oxidative stress, systemic inflammation, and vibration damage to the carotid arteries [46]. However, because of the close association between central obesity and both obstructive sleep apneas [54] and vascular disease [55], it has been very difficult to disentangle the inter-relations and demonstrate that OSA is truly an independent risk factor for vascular disease. Although laboratory studies may support plausible hypotheses, this does not prove their relevance to clinical medicine; indeed these plausible hypotheses, based on laboratory experiments and cross-sectional studies, failed to be supported by randomized controlled trials (RCTs). Therefore, well-organized studies that will help to identify the true cause are essential. Each of the fore-mentioned mechanisms that possibly underpin the association between OSA and vascular disease needs to be proven and to be clinically relevant in the RCTs. At present, such data is most supportive of increased sympathetic nervous system activity, which appears more than adequate as a mechanism to explain the associations observed between OSA and vascular disease [46]. Thus, despite several plausible hypotheses to explain an increased vascular risk in OSA, only the increased sympathetic activity has convincing supporting evidence from relevant clinical trials [56-60]. Although there may be additional contributory factors (e.g. systemic inflammation) there is little concrete evidence for these hypotheses and they are not able to explain the adverse vascular outcomes associated with OSA [46].

The prevalence of OSA in MFS patients has, therefore, important clinical implications since OSA can worsen the cardiovascular problems inherent to Marfan’s syndrome. Kohler and colleagues showed an association between the apnea–hypopnea index (AHI), namely the severity of OSA, and the diameter of the aortic root, which suggests that OSA may be a risk factor for the aortic root dilatation in MFS patients. This is the first study in which the potential relationship between OSA and aortic root dilatation in patients with Marfan’s syndrome has been investigated. The data shows that the severity of OSA is associated with an increased aortic root diameter and that the patients with OSA had a larger aortic root than patients without OSA. This suggests that OSA promotes the aortic dilatation in patients with Marfan’s syndrome [35]. Bearing in mind that aortic dilatation is the main cause of death in MFS patients [7,8,61], the treatment of OSA could determine the life expectancy of these subjects. A recent study of Kohler and colleagues is the first prospective cohort study providing data on the relationship between OSA and the aortic events in patients with Marfan’s syndrome. The authors found that MFS patients with OSA had a significantly shorter event-free
survival compared to MFS patients without OSA, which suggests that OSA may be an important risk factor for the aortic events \cite{62}. If this finding is confirmed in larger cohorts, then patients with Marfan’s syndrome should be evaluated and possibly treated for OSA in order to reduce the risk of aortic complications. The aortic dilation, the associated aortic dissection and the subsequent rupture are, as previously mentioned, still the main cause of morbidity and mortality in patients with Marfan’s syndrome \cite{7,8,61}. Thus, the prevention of aortic complications is of major concern for physicians caring for MFS patients. As it is largely unknown which factors contribute to a rapid progression of aortic root dilation in these patients, the prevention of the aortic dissection and the subsequent rupture currently rest on lifestyle habits, pharmacological treatments (e.g. β-blockers), prophylactic aortic surgery and the probable prevention of OSA \cite{61,64}. The identification of any treatable risk factor for aortic complications in MFS patients is thus of major scientific and clinical interest.

The early orthodontic treatment as prevention of OSA

In MFS adult patients, the gold standard treatment of OSA is the Continuous Positive Airway Pressure (CPAP); in medical literature, there are two case reports in which treatment of OSA with CPAP was associated with an attenuation of the aortic root dilatation in three patients with Marfan’s syndrome \cite{65,66}.

From this overview followed the research of an early orthodontic treatment for MFS children with the aim of reducing the risk factors, such as skeletal class II malocclusion with mandibular retrognathia and reduced sizes of the airways, for OSA development in this particular population \cite{67}. Skeletal Class II malocclusions caused by mandibular retrognathia and correlated increased overjet (defined as the anterior-posterior distance between the upper and lower incisors during normal occlusion), frequently found in Marfan’s syndrome \cite{6}, were in fact reported in the literature to be one of the risk factors for OSA development in all patients \cite{68}. The purpose of the study was the evaluation of the effects of rapid maxillary expansion and mandibular advancement on the upper airways in Marfan’s syndrome children through home sleep studies, the Epworth Sleepiness Scale questionnaire and cephalometric analysis of the upper airways on lateral radiographs. The study sample consisted of 30 children with Marfan’s syndrome. The control group consisted of 30 untreated and matched children. For MFS subjects, data was taken at different time points compared to treatment: at T0 (before treatment), T1 (after rapid maxillary expansion) and T2 (after mandibular advancement). For control subjects, data was taken at similar intervals, at three follow-up visits: at T0 (as a starting screening tool), T1 (after approximately 2 years) and T2 (in proximity of the peak skeletal growth). Apnea-hypopnea and oxygen desaturations were significantly higher in the study group at T0 and T1 compared with control children. At T2 the values were not significant (p value: 0.442 for both AHI and ODI). Horizontal airway dimensions were significantly reduced and vertical airway values were significantly increased in Marfan’s syndrome at T0 and T1 but not at T2 (p values at T2: 0.071 for Phw1-Psp, 0.106 for Phw1-Psp’, 0.101 for Phw2-Tb, 0.559 for UAL male and 0.560 for UAL female) \cite{67}. The rapid maxillary expansion and the mandibular advancement significantly improved the airway patency of Marfan’s syndrome children. Therefore this therapy is strongly encouraged as a routine treatment for both correction of Class II malocclusions and prevention of obstructive sleep apnea in MFS subjects.

Conflict of interest

The author declares that he has no conflict of interest.

References


