International Journal of Pediatric Otorhinolaryngology 112 (2018) 6–9

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Obstructive sleep apnea in children with Marfan syndrome: Relationships between three-dimensional palatal morphology and apnea-hypopnea index☆

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ARTICLE INFO

Keywords:
OSA
Marfan children
Palatal shape
AHI index

ABSTRACT

Objective: To evaluate the relationship between the severity degree of OSA (apnea/hypopnea index AHI > 1) and palatal area and volume, measured by 3D analysis of digital casts in Marfan children.
Methods: Twenty children with a clinical diagnosis of MS were recruited from a tertiary medical center. All the subjects underwent standard nocturnal polygraphy testing. Sixteen Marfan patients (7F,9 M; mean age 8.8yy ± 1.5yy) with AHI > 1 were enrolled. Marfan Group (MG) was compared with a control group (CG) of 17 children without Marfan syndrome (9F,8 M; mean age 8.5yy ± 1.7yy) presenting with nose-breathing pattern. For each subject maxillary digital casts were taken and palatal area and volume were measured. Unpaired *t*-test was used to test significant differences between MG and CG for area and volume measurements. Pearson correlation coefficient (PCC) was used to measure the linear correlation between the degree of OSA (AHI index) and palatal volume and palatal area.
Results: 80% of Marfan children presented an AHI > 1 and a diagnosis of OSA. MG presented statistically significant lower values of palatal surface area (662.68 mm^2; $P < 0.0001$) and palatal volume (2578.1 mm^3; $P < 0.0001$) with respect to CG (923.0 mm^2 and 3756.6 mm^3, respectively). Correlation analysis showed that AHI index had no linear correlation with palatal area (r = - 0,07) and with palatal volume (r = − 0,11).
Conclusion: OSA is highly prevalent in children with Marfan's syndrome (80%). Marfan children present a reduction of palatal area and volume when compared to healthy subjects. OSA in Marfan children is not linear correlated to the palatal morphology and it shows a multifactorial aetiology.

1. Introduction

Marfan's syndrome (MS) is an autosomal dominant inherited multisystem disorder that occurs worldwide and affects both sexes equally. The incidence of MS is estimated to be 2–3 per 10,000 individuals without any racial predilection [1]. MS occurs due to mutations in the FBN1 gene localized on chromosome 15q21, which encodes the matrix protein fibrillin 1 [2,3].

Marfan's syndrome is characterized by changes in three major connective tissue systems: the musculoskeletal, the eyes, and the cardiovascular system [4]: aortic root dilatation and subsequent dissection are the commonest life threatening manifestations [5–7]. MS is associated with various craniofacial abnormalities mainly comprising maxillary/mandibular retrognathia, long face and high and narrowly arched palate [8–11].

Moreover in MS patients, the prevalence of obstructive sleep apnea syndrome (OSA) is considerably higher than in matched control subjects (64%) [4,7,12,13]. OSA may be a risk factor for aortic root dilatation in MS. Possible underlying pathophysiological mechanisms are post-apnoea reflex sympathetic activation and consequent marked increases in blood pressure. Furthermore, largely negative intrathoracic pressure swings increase transaortic pressures and may therefore accelerate aortic dilatation [7,14,15].

The precise mechanisms accounting for the high prevalence of OSA in patients with Marfan's syndrome are not certain. Increased upper airway collapsibility during sleep and high nasal airway resistance, due to maxillary constriction and high arched palate, has been reported as possible causes [16,17]. Several studies have suggested that structural abnormalities may play a role in its pathophysiology [11]. However these studies analysed only adult subjects with MS by using linear measurements and without a three-dimensional evaluation of the palatal morphology. None of them focused on children, in which

☆ All authors have seen and approved the manuscript.

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https://doi.org/10.1016/j.ijporl.2018.06.014
Received 23 May 2018; Received in revised form 7 June 2018; Accepted 9 June 2018
Available online 12 June 2018
0165-5876/

obstructive sleep apnea is diagnosed with an apnea hypopnea index (AHI) greater than 1 (AHI > 1) [17,18]. Recently Laganà et al. [3], in a preliminary study, evaluated the variability of the total palatal shape in a group of Marfan children compared with a control group by means of geometric morphometric three-dimensional analysis, but they did not correlate these data to the presence of respiratory diseases.

Since the strong correlation between OSA and craniofacial structures and OSA and cardiovascular disease in MS children subjects, further researches are necessary.

The primary objective of this study was to evaluate if there is a relationship between the degree of severity of OSA (AHI > 1) and the anatomical characteristics of the maxillary arch, identified as palatal surface area and volume, using three-dimensional (3D) analysis of digital dental casts, in young patients with Marfan's syndrome.

The null hypothesis was: the more the OSA is severe, the more the palate is reduced.

2. Materials and methods

This project was approved by the Ethical Committee of the University of Rome Tor Vergata (Protocol number: 4544/2017) and informed consent was obtained from the patients' parents.

Twenty subjects (11 males, 9 females) with a clinical diagnosis of MS were consecutively recruited from September 2015 to September 2017 from the Centre for Rare Diseases for Marfan Syndrome and Related Disorders of Tor Vergata University Hospital and evaluated in the Departments of Orthodontics of the same University.

All the subjects underwent nocturnal polygraphic cardiorespiratory monitoring analysed in the Department of Neurophysiopathology.

The inclusion criteria for the Marfan group of this study were: genetic assessment of MS, Caucasian ancestry, eruption of the first permanent molars and second deciduous molars still present, prepubertal stage of cervical vertebral maturation as assessed on lateral cephalograms (CS1, CS2), good quality of records, AHI > 1. Exclusion criteria were: presence of oral habits (thumb and lip sucking), previous orthodontic treatment, cleft lip and/or palate, other genetic diseases.

16 of 20 Marfan patients (9 males, 7 females; mean age 8.8 years ± 1.5 years) presented an AHI > 1 and were enrolled in the study.

The Marfan Group (MG) was compared with a control group (CG) of 17 healthy prepubertal subjects (8 males and 9 females) without Marfan syndrome and OSA, with no transverse or vertical skeletal discrepancies presenting with nose-breathing pattern and mean age of 8.5 years (SD 1.7 years). The CG matched the MG in terms of dentition stage and skeletal maturation.

For each subject (MG and CG), dental casts were taken before any treatment. Maxillary study casts of all subjects were scanned using the extraoral scanner OrthoXscan (OrthoXscan; Dentaurum GmbH&co, Ispringen, Germany) with a manufacturer's reported accuracy < 20 μm. All models were exported in a Standard Tesselation Language format (.stl digital file).

As described in a previous study by Primozic et al. [19] each dental cast was preprocessed to remove unwanted data. In order to measure palatal surface area and calculate palatal volume, the gingival plane and a distal plane were used as boundaries for the palate. The gingival plane was obtained by connecting the centre of the dentogingival junction of all erupted permanent and deciduous teeth. The distal plane was created through two points at the distal of the second deciduous molars perpendicular to the gingival plane [20] (Fig. 1).

All measurements of study casts were performed by the same operator (V.P.).

Since CG has not OSA, apneic status was determined only in Marfan group through nocturnal polygraphy by the apnea/hypopnea index (AHI). Data were collected from the Sleep Medicine Center of Tor Vergata University Hospital.

The nocturnal polygraphy was performed in the child's home.

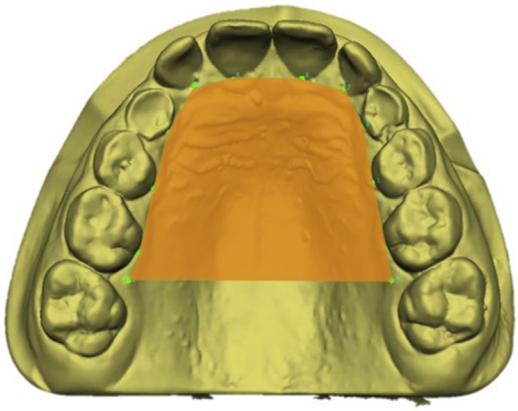

Fig. 1. Definition of the palatal volume (orange) and surface area of the maxilla. A gingival plane and a distal plane were used as the boundaries. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Oronasal flow was recorded by oronasal thermistor, and a nasal cannula was used to assess pressure, individual chest and abdomen movements and their sum by impedance plethysmography, body position by sensor position, snoring by microphone, and heart rate and blood oxygen saturation by means of pulse oximetry [17].

According to the criteria of the National Institutes of Health Consensus and American Academy of Sleep Medicine, obstructive apnea was defined as a decrease in oronasal flow equal to or greater than 90% for at least two respiratory cycles in the presence of respiratory effort, and obstructive hypopnea was defined as a drop in oronasal flow greater than 50% for at least two respiratory cycles accompanied by a 3% or greater decrease in SatO2 [21].

2.1. Statistics

To determine the reliability of the method, all the measurements on dental casts were performed by one trained examiner and repeated by the same examiner after an interval of approximately 2 weeks. A paired *t*-test was used to compare the two measurements (systematic error).

Unpaired *t*-test was used to test significant differences between MG and CG for area and volume measurements.

The Pearson correlation coefficient (*r* value) was used to measure the correlation between the degree of OSA in Marfan patients, as reflected by polygraphy measurement (AHI index), and their palatal volume and their palatal surface.

3. Results

No systematic error was found between the repeated digital measurements. The systematic error was reduced by precise definitions of points in the presence of a previously trained examiner.

The 80% of Marfan children, recruited from the Centre Of Rare Diseases For Marfan Syndrome and Related Disorders of Tor Vergata University Hospital, presented an AHI > 1 and a diagnosis of OSA.

The comparison between the two groups (MG vs CG) confirmed the presence of maxillary contraction in Marfan subjects. The MG presented statistically significant lower values of the palatal surface area ($662.68\,mm^2 \pm 96.73\,mm^2$; $P < 0.001$) and palatal volume ($2578.1\,mm^3 \pm 588.91\,mm^3$; $P < 0.001$) with respect to the CG ($923.0\,mm^2 \pm 88.14\,mm^2$ and $3756.6\,mm^3 \pm 559.70\,mm^3$, respectively) Table 1.

The results of the correlation analysis performed in MG showed that the apnoea–hypopnoea index had no correlation with the palatal area palatal area (r = - 0.07) (Fig. 2) and with the palatal volume (r = − 0.11) [7] (Fig. 3). Therefore no correlation was found between the