Int. J. Oral Maxillofac. Surg. 2010; 39: 115–121
doi:10.1016/j.ijom.2009.11.021, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper

Congenital Craniofacial Anomalies

Obstructive sleep apnea in children with syndromic craniosynostosis: long-term respiratory outcome of midface advancement

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Abstract. Almost 50% of patients with Apert, Crouzon or Pfeiffer syndrome develop obstructive sleep apnea (OSA), mainly due to midface hypoplasia. Midface advancement is often the treatment of choice, but the few papers on long-term outcome report mixed results. This paper aimed to assess the long-term respiratory outcome of midface advancement in syndromic craniosynostosis with OSA and to determine factors contributing to its efficacy. A retrospective study was performed on 11 patients with moderate or severe OSA, requiring oxygen, continuous positive airway pressure (CPAP), or tracheostomy. Clinical symptoms, results of polysomnography, endoscopy and digital volume measurement of the upper airways on CT scan before and after midface advancement were reviewed. Midface advancement had a good respiratory outcome in the short term in 6 patients and was ineffective in 5. In all patients without respiratory effect or with relapse, endoscopy showed obstruction of the rhino- or hypopharynx. The volume measurements supported the clinical and endoscopic outcome. Despite midface advancement, long-term dependence on, or indication for, CPAP or tracheostomy was maintained in 5 of 11 patients. Pharyngeal collapse appeared to play a role in OSA. Endoscopy before midface advancement is recommended to identify airway obstruction that may interfere with respiratory improvement after midface advancement.

Keywords: obstructive sleep apnea; midface advancement; craniosynostosis; children.

Accepted for publication 27 November 2009
Available online 6 January 2010

Craniosynostosis is a congenital disorder affecting in 1 in 2500 births; it is characterized by the premature fusion of calvarial sutures. This fusion restricts normal growth of the skull, brain, and face, and necessitates surgical correction. In about 40% of cases it is part of a syndrome such as the Apert, Crouzon, Pfeiffer, Muenke or Saethre-Chotzen syndrome[11].

Almost 50% of children with Apert, Crouzon or Pfeiffer syndrome develop obstructive sleep apnea (OSA), mainly during the first 6 years of life[9,13,18]. These patients are at risk for OSA due to midface hypoplasia, but other factors such as adenotonsillar hypertrophy, and mandibular hypoplasia may be involved as well[8,13]. According to its severity and cause, OSA

0901-5027/020115 + 07 $36.00/0

can be treated pharmacologically, surgically (e.g. with adenotonsillectomy, midface advancement or tracheostomy), or non-surgically (e.g. with nocturnal oxygen or continuous positive airway pressure (CPAP))[1,8]. If OSA is not treated sufficiently, disturbed sleep patterns may result in major physical and functional impairment, for instance failure to thrive, recurrent infections, disturbed cognitive functions, delayed development, cor pulmonale or sudden death[16]. As midface hypoplasia is the main cause of OSA in syndromic craniosynostosis, midface advancement appears to be the treatment of choice[17].

In the long-term, mixed respiratory results were reported following midface advancement in patients with syndromic craniosynostosis[15]. It is unclear how long and to which level the improvement in breathing lasts, and which factors are predictors of respiratory outcome. To assess the respiratory outcome of midface advancement for moderate to severe OSA and to determine predictive factors, the authors carried out a retrospective study in patients suffering from Apert, Crouzon or Pfeiffer syndrome.

Material and methods

Study group

Over 100 patients with Apert, Crouzon and Pfeiffer syndrome have been treated at the Dutch Craniofacial Center since 1983. For this study, the authors were only interested in the 14 patients with moderate or severe OSA, requiring treatment with nocturnal oxygen, CPAP, nasopharyngeal tube (NPT), or tracheostomy, who presented between 1987 and 2006. Their records were analyzed for clinical symptoms of OSA, results of polysomnography (PSG) and endoscopy of the upper airways, and the different treatment modalities for OSA. CT scans were used to measure the airway volume before and after midface advancement. For this case series, sufficient data and follow-up were available in 11 patients.

Obstructive sleep apnea

The clinical symptoms of OSA scored were snoring, difficulty in breathing, apnea during sleep, perspiration, and daytime sleepiness. PSG was carried out ambulatory or during admission to hospital and the following criteria for analysis were used. Apnea was defined as absence of airflow for more than 2 breaths and hypopnea as reduction by $\geq$50% in nasal flow signal amplitude for more than 2 breaths. The analysis was expressed in an apnea-hypopnea index (AHI), the number of obstructive apneas in combination with hypopneas followed by desaturation per hour, and an oxygenation-desaturation index (ODI), the number of desaturations ($\geq$4% decrease with respect to the baseline) per hour. A score $<$1 is considered to be normal, 1–5 is defined as mild OSA, 6–25 as moderate OSA, and $>$25 as severe OSA[6,7,19,20].

Respiratory outcome of midface advancement

The timing, type and outcome of the following interventions were evaluated: oxygen, NPT, CPAP, adenotomy and tonsillectomy, tracheostomy and midface advancement. The different interventions in each patient were added to evaluate the total number of procedures carried out to improve the breathing.

The efficacy of treating OSA was determined on the basis of clinical symptoms and PSG before and after midface advancement. Midface advancement was considered to be effective on respiration, in the short term, if oxygen, CPAP, NPT or tracheostomy were discontinued within 1 year after midface advancement. Relapse of OSA was defined as the need for respiratory support again. Long-term effectiveness was defined as independence of respiratory support at least 2 years after midface advancement.

Endoscopy of the upper airway

Endoscopies were carried out under general anesthesia in a supine position. In 2 patients an additional endoscopy was carried out at the outpatient clinic in a sitting position. The endoscopies were carried out to identify the possible level of obstruction including anatomical malformations in the rhino- and hypopharynx.

Volume measurements of the upper airway

A software program (MevisLab) was used to import and analyze the CT scans by means of a custom-designed tool. Preoperative and postoperative scans were analyzed on transversal slices. The maxillary, ethmoidal, frontal and sphenoidal sinuses, concha bullosa and the oral cavity were manually excluded. The respiratory active air-holding cavities were segmented using semi-automatic region growing. The volumes of 2 separate anatomically defined areas were measured in mm^3, taking the scale into consideration: nasal cavity and rhinopharynx (defined to range from the most caudal point of the frontal sinus to the cranial point where the soft palate transformed into the uvula); and oro- and hypopharynx (ranged from the most cranial point where the soft palate transformed into the uvula, to the most caudal point of the hyoid bone). The total volume was calculated by adding the volumes of the 2 areas. All patients were scanned according to a protocol, using the same CT scan, and the thickness of the transversal slices was similar.

Statistical analysis

The results were analyzed using SPSS 14.0 for Windows 2000. All numbers are expressed as median and range.

Results

Eleven patients with Apert (n = 3), Crouzon (n = 6) or Pfeiffer (n = 2) syndrome who had moderate or severe OSA, requiring treatment with nocturnal oxygen, CPAP, NPT, or tracheostomy, were included. Four of the 11 patients were boys (36%), aged 14.9 years (range 4.1–23.1 years). All patients had midface hypoplasia. Six of the 11 patients underwent PSG before the start of treatment for OSA; this showed moderate OSA in 3 patients and severe OSA in 3 (median ODI 25, range 10–66). In the other patients, no PSG was performed due to the severity of the respiratory distress at presentation, which necessitated instant airway management, namely intubation or insertion of a tracheostomy. Airway treatment after diagnosis of OSA involved tracheostomy in 4 patients, oxygen in 3, CPAP or NPT in 3, and monobloc with NPT in 1. All patients underwent a midface advancement with distraction followed by a control PSG; in 3 a monobloc was performed; and in 8 a le Fort III.

In 10 of the 11 patients, an endoscopy of the upper airway was performed to identify the level of obstruction; this was done preoperatively in 5, postoperatively in 1, and both in 4. In 4 patients, a CT scan carried out before and after midface advancement was available. After advancing the midface for at least 20 mm the occlusion was corrected from class III in class II with overcorrection in all patients (Fig. 1). Clinically, a sufficient advancement of the midface was achieved in all patients. Final adjustment of the level of occlusion is performed in patients aged 18 or older. So far, an additional Le Fort I has been performed in 2 patients, no patient

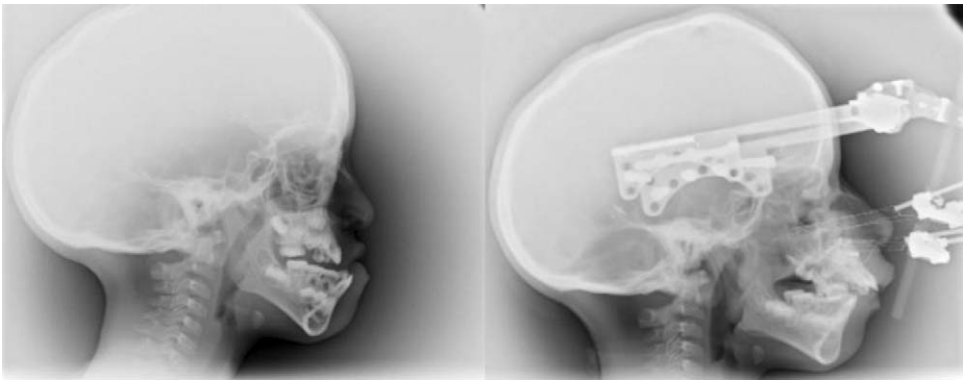

Fig. 1. Sufficient correction was achieved in all patients; after advancing the midface for 20 mm the occlusion changed from class III to class II including the overcorrection.

Table 1. Respiratory outcome of midface advancement in the short term.

Treatment	Number of treatments	Effect	Insufficient effect
Monobloc without distraction	3	1	2
Monobloc with distraction	3	2	1
Le Fort III with distraction	8	4	4
Total view (N patients)	14 (11)	7 (6)	7 (5)

underwent mandibular correction. The follow-up time after midface advancement was 3.5 years (range 2.4–11.4 years, mean 5.7 years).

Respiratory outcome of midface advancement

The follow-up of the 11 OSA patients at different ages is shown in Fig. 2. The respiratory outcome of each treatment option was considered. Adenotomy and tonsillectomy had a temporary beneficial effect on respiration in 1 of 5 patients, and no effect in 4.

In 6 of the 7 patients, oxygen and CPAP or NPT were effective in bridging time to the midface advancement. In the other patient, tracheostomy was required despite monobloc and NPT. Midface advancements were carried out in 3 different modes: monobloc with and without distraction, and le Fort III with distraction.

The patients with moderate or severe OSA underwent a median number of 5 (2–8) invasive or non-invasive treatment procedures to improve their breathing. Midface advancement in the short term had a good or improved respiratory outcome in 6 patients (patients 1, 2, 8, 10, 11 and patient 9, respectively), and was unsatisfactory in 5 (patients 3, 4, 5, 6 and 7) (Table 1). In 2 patients (patients 1 and 11) OSA relapsed. In the long term, 4 of the 11 patients (patients 3, 4, 6 and 7) were still dependent on CPAP (2.5, 8.1 and 8.2 years after advancement) or tracheostomy (10.6 years) in spite of a surgically successful midface advancement and 1 (patient 11) had severe OSA without treatment (following a parental decision).

Endoscopy and volume measurements of the upper airway

Anatomical malformations of the rhino- and hypopharynx were a common feature in nearly all patients, causing a functional obstruction at this level. Only one patient did not have this feature and had a good respiratory outcome after midface advancement. All patients had a narrow nasal cavity.

The volumes of the upper airway on CT scan before and after midface advancement were calculated in patients 1, 4, 6 and 8 (Table 2). In Fig. 3 the changes in these volumes are shown. In patient 1 the CT scan 4 months post-surgery showed an increase in airway volume (1.4 times), mostly in the region nasal cavity and rhinopharynx (1.6 times). One year after midface advancement the CT scan illustrated the narrow hypopharynx seen with endoscopy, with a volume decrease in the region oro- and hypopharynx (0.7 times). The CT scans of patient 4, made 7 months before and 1 year after midface advancement, showed no increase in the total volume of the upper airway. The volume of the oro- and hypopharynx increased 1.2 times. Patient 6 showed no change in total volume of the upper airway 4 months after midface advancement in comparison with 1 year before, which matches the clinical presentation. After midface advancement the nasal cavity and rhinopharynx volume increased, but the oro- and hypopharynx region was 0.7 of the volume before. In patient 8, with a good clinical result, the volume of the upper airway increased by a factor of 1.6, 13 months after midface advancement in comparison with 3 months before. The volume of the nasal cavity and rhinopharynx increased 1.6 times and the volume of the oro- and hypopharynx was 1.7 times larger.

Discussion

In the general population, adenotonsillectomy is the treatment of choice, as adenotonsillar hypertrophy is an important cause of OSA[5,20]. In this study, in patients suffering from Apert, Crouzon or Pfeiffer syndrome with moderate or severe OSA, neither tonsillectomy nor adenotomy had a significant effect on respiration.

Table 2. Measurements of airway volume on CT scan before and 4 months and/or 1 year after midface advancement in mm^3.

Patient	Nasal cavity and rhinopharynx			Oro- and hypopharynx			Total airway volume		
	Before	After 1	After 2	Before	After 1	After 2	Before	After 1	After 2
1	20.109	32.850	33.544	13.287	14.772	9.620	33.396	47.622	43.164
4	35.909	33.166		6.408	7.913		42.317	41.078	
6	19.639	20.327		9.166	6.252		28.804	26.578	
8	20.147	32.671		3.683	6.081		23.830	38.751	

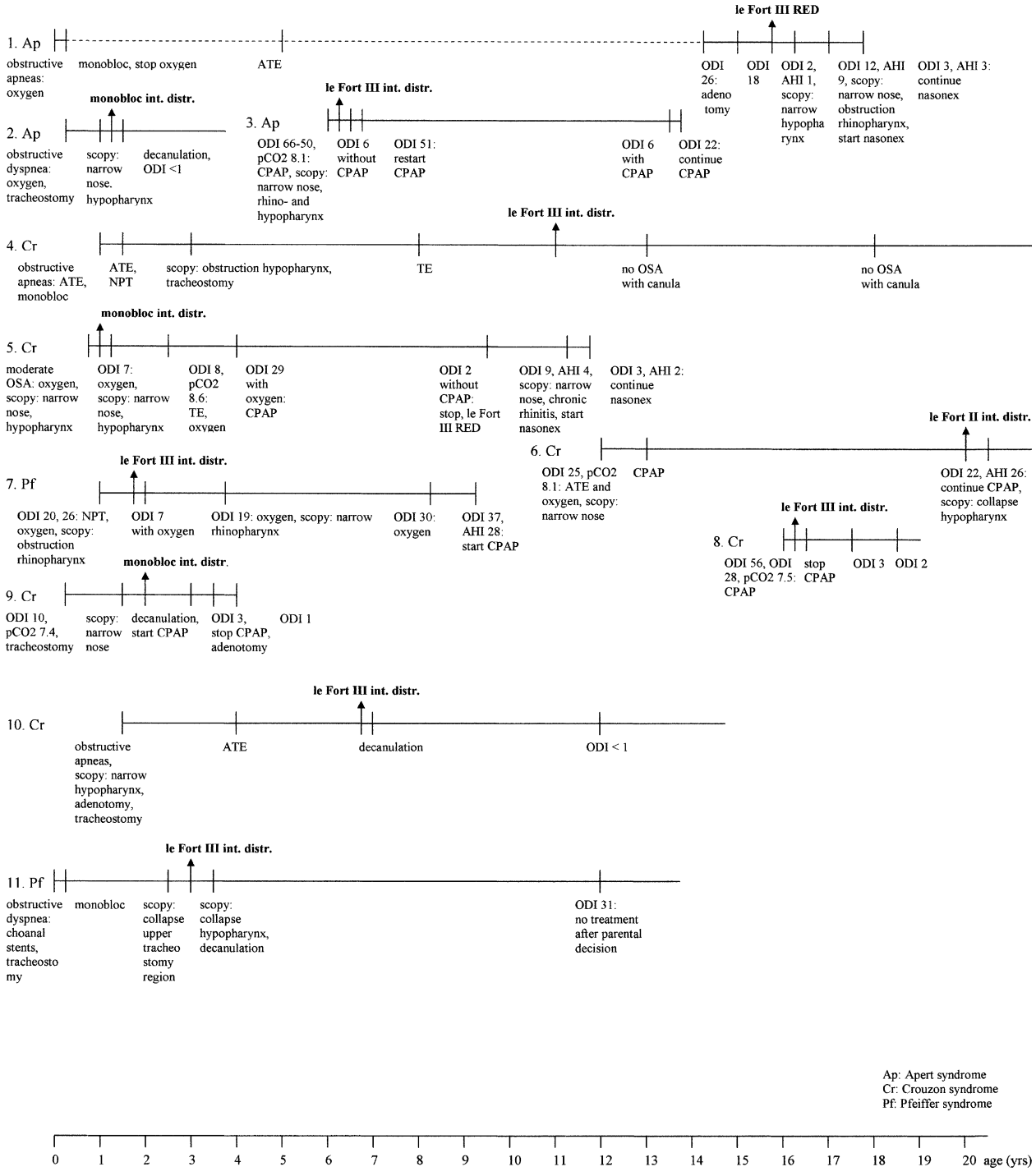

Fig. 2. Follow-up of OSA in 11 patients at different ages.

In patients with syndromic craniosynostosis, midface hypoplasia is generally considered to be the major cause of upper airway obstruction[13]. All children in this study also had midface hypoplasia. Although, midface advancement seemed to be a good treatment modality for compromised airways at the level of the midface[13,14], in this study 6 of 11 patients (55%) had a favourable effect in the short term after monobloc or le Fort III with distraction. WITHEROW et al.[21] found an improvement in all patients suffering from Apert, Crouzon or Pfeiffer syndrome with abnormal PSG after monobloc with external distraction. Of the 14 patients with severe OSA, treated with tracheostomy or CPAP, OSA was resolved after surgery in 6 (43%). The other 8 patients remained dependent on tracheostomy or CPAP. The mean follow-up was 24 months[21]. ARNAUD et al.[2] showed a respiratory improvement measured by oxygen level in 14 of 16 patients with Apert, Crouzon or Pfeiffer syndromes after monobloc with internal distraction. In the severe cases, removal of tracheostomy was possible in 4 of 6 (67%). In 1 patient a tracheostomy was needed 6 months after removal of distractors because of relapse of OSA. The mean follow-up after surgery was 2.5 years[2]. NELSON et al.[15] studied 18 patients with syndromic bilateral coronal synostosis and

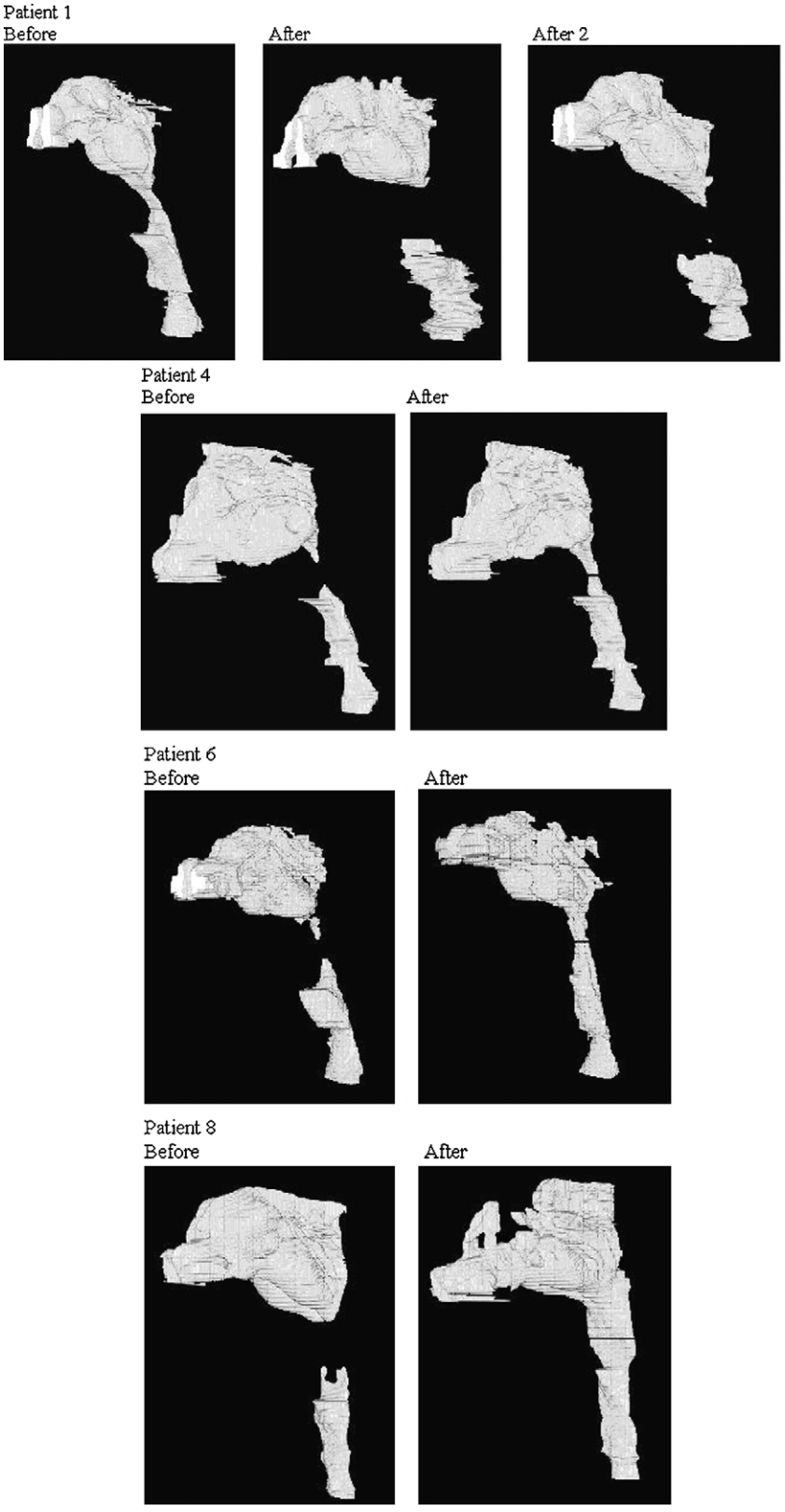

Fig. 3. Volume measurements of the upper airway before and after midface advancement.

OSA, in 15 of them a tracheostomy or CPAP was required before midface advancement. After midface advancement, 5 patients were decanulated and in 6 CPAP was discontinued (73%). The mean time of follow-up was 3.2 years. In these 3 studies, midface advancement did not result in good respiratory outcome in all (similar to the present study). These studies and the present one showed that respiratory outcome after midface advancement in syndromic craniosynostosis patients who need it the most is not as successful as is generally thought. Inclusion of patients with mild OSA in other studies has given the impression that midface advancement with distraction gives a guaranteed improvement of OSA.

Endoscopy of the upper airway can show the level of obstruction and the dynamic influence of breathing. In the 4 patients with persistent OSA after advancement and in the patient with a relapse of OSA an obstruction of the rhino- or hypopharynx was seen. In Apert, Crouzon and Pfeiffer syndrome, the anatomy of the upper airway is different and there seems to be a dynamic function problem regarding the airway, possibly related to the mutation of the fibroblast growth factor receptor[11]. The nasal cavity is narrow in all patients; this is common in these syndromes. Collapse of the pharynx is a dynamic problem that may or may not improve with midface advancement. In the non-responders, the pharyngeal walls collapsed with each breath, and resulted in an airway obstruction. So the advancement did not result in a larger airway volume and could not overcome the tendency of the pharyngeal walls to collapse. The changes in airway volume on CT scan after midface advancement were similar to the results of endoscopy, and thus seem to illustrate the dynamic situation of the airway, including the level of obstruction. An improvement of airway volume on CT correlated with a good respiratory outcome. The authors consider that the degree of functional obstruction of the rhino- or hypopharynx correlates with respiratory outcome after midface advancement: a mild tendency for collapse can be overcome with midface advancement. This hypothesis could not be substantiated in this retrospective analysis.

Measurement of airway volume on CT scan has some limitations, in particular the difficulty of manually defining the borders of the nasal cavity because of anatomical anomalies. A cold can affect the thickness of the mucosa and the size of the tonsils, and the position and respiration state of the patient in the CT scan can influence the

volume of the airway at the moment of scanning. The influence of growth in volume changes is not likely in patients with syndromic craniosynostosis since they have growth retardation of the maxilla[4] and restriction of normal transverse growth of the mandible, possibly secondary to cranial base abnormalities[3].

Previous studies on airway changes after advancement were based on tracing of cephalograms[10,12]. ISHII et al.[10] studying 16 patients with Apert or Crouzon syndrome found an improvement on cephalogram in the nasopharyngeal airway after Le Fort III osteotomy, but no change in hypopharyngeal airway was found. In 12 'normal' adults who underwent maxillary and mandibular advancement for OSA LI et al.[12] found an increase in the airway dimension after surgery measured by cephalometric imaging. Fiberoptic nasopharyngoscopy with the Müller maneuver (take a breath while the mouth is closed and the nostrils are plugged) showed a decrease in collapsibility of the upper airway, mostly the lateral pharyngeal wall. They suggested a reduction of the thickness of the muscular wall. Mandibular advancement seemed to be needed to enlarge the pharyngeal airway. In the present study group no mandibular advancement was carried out. Mandibular advancement is generally not considered in children with syndromic craniosynostosis to treat their OSA, although this may be an option in patients with disappointing results following midface advancement and remaining obstruction at the hypopharynx.

This study showed that moderate or severe OSA in children with syndromic craniosynostosis is a major problem and difficult to treat. It is not only directly correlated with midface hypoplasia. Endoscopy showed anomalies at different levels throughout the upper airway. Dynamic pharyngeal collapse can affect the respiratory outcome of midface advancement; endoscopy of the upper airway before midface advancement may predict respiratory improvement. It may be possible to treat obstructions at another level with other procedures, such as widening of the palate to enlarge the nose and mandibular advancement to create more space at the level of the hypopharynx. Long-term follow-up is important because OSA may relapse.

To implement these findings and to improve the prognostic information on respiratory outcome after midface advancement, the authors recommend performing an endoscopy of the upper airway before midface advancement to identify all levels of obstruction (also stated by NELSON et al.[15]). Treatment of OSA will then be better focussed on its cause. The volume measurements of the upper airway will be continued in further research as a tool to investigate the effect of midface advancement on airway volume and to specify the level of largest gain on respiration.

In conclusion, despite midface advancement, long-term dependence on, or indication for, CPAP or tracheostomy was maintained in 5 of 11 patients in whom Apert, Crouzon or Pfeiffer syndrome was combined with moderate or severe OSA. In the patients with persistence of OSA despite optimal surgical treatment, pharyngeal collapse appeared to play a role in obstruction of the airway. Endoscopy makes it possible to identify a static or dynamic airway obstruction that may interfere with respiratory improvement, enabling a prediction of respiratory improvement and treatment to be adapted to the specific level of obstruction. Long-term follow-up is needed because of the chance of relapse.

Conflict of interests

None declared.

Funding

This research project was funded by the Carolien Bijl foundation and sponsored by Trustfonds Erasmus University Rotterdam.

Ethical approval

Ethical approval was given by the medical ethics committee of the Erasmus Medical Center Rotterdam with the following reference number: MEC-2005-273.

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