Journal of Cranio-Maxillo-Facial Surgery xxx (2017) 1–5

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

The effect of early fusion of the spheno-occipital synchondrosis on midface hypoplasia and obstructive sleep apnea in patients with Crouzon syndrome

Caroline Driessen [a, *], Bianca F. Rijken [a], Priya N. Doerga [a], Marjolein H. Dremmen [b], Koen F. Joosten [c], Irene M. Mathijssen [a]

[a] Department of Plastic, Reconstructive and Hand Surgery, Dutch Craniofacial Centre, Rotterdam, The Netherlands
[b] Department of Radiology, Dutch Craniofacial Centre, Rotterdam, The Netherlands
[c] Intensive Care Unit, Department of Paediatrics and Pediatric Surgery, Dutch Craniofacial Centre, Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Paper received 28 December 2016
Accepted 30 March 2017
Available online xxx

Keywords:
Craniosynostosis
Crouzon
Synchondrosis
Obstructive sleep apnea

ABSTRACT

Introduction: The investigators hypothesized that patients with Crouzon syndrome and premature fusion of the spheno-occipital synchondrosis (SOS) more often have, or have more severe midface hypoplasia and obstructive sleep apnea (OSA).
Methods: A prospective cohort study was performed among patients with Crouzon syndrome to analyze SOS closure, midface hypoplasia represented by the sella-nasion angle (SNA) and OSA.
Results: Forty patients were included in whom the OSA-prevalence was 65%. Kaplan Meier analyses suggest a trend towards earlier closure of synchondrosis in patients with OSA ($p = 0.066$). The mean SNA was 74.7°. There was a positive effect of age on the SNA ($p = 0.020$). There was no difference in SNA for patients with an open SOS as compared to patients with a closed SOS after correction for age.
Conclusions: The longitudinal data are suggestive of a trend towards earlier fusion of the SOS in patients with Crouzon syndrome and OSA as compared to patients with Crouzon syndrome without OSA. Although the SNA increases with age, our results suggest that this increase in independent closure of the SOS.

1. Introduction

The spheno-occipital synchondrosis (SOS) facilitates growth and development of the cranial base and face (Fig. 1). In otherwise healthy children, the intra-occipital synchondroses fuse in childhood, whereas the spheno-occipital synchondrosis remains open up to adulthood. Normative data from the literature suggest that average fusion normally occurs around puberty at an age of 14–16 years (Powell and Brodie, 1963; Ingervall and Thilander, 1972; Tahiri et al., 2014). Since FGFR genes are expressed in the synchondroses, it is likely that they close prematurely in patients with syndromic craniosynostosis, just like the calvarian sutures have FGFR expression and are affected by premature fusion. This was previously shown for the intra-occipital synchondroses (Matsushita et al., 2009). More recently, this hypothesis was confirmed for the spheno-occipital synchondrosis in patients with Crouzon and Apert syndrome (McGrath et al., 2012). This may be related to mutations in the FGFR1, 2 or 3 gene. The FGFR genes may also contribute to anatomical abnormalities in the upper airway, which is derived from the first and second branchial arch (Trokovic et al., 2005). Since obstructive sleep apnea (OSA) in patients with Crouzon syndrome has a prevalence as high as 63% (Driessen et al., 2013), results in major physical and functional impairment (Guilleminault et al., 2005), and is only partially understood, it is of great importance to unravel this problem.

Premature fusion of the SOS has been associated with midface hypoplasia in animal models (Schmidt et al., 2013). Previous studies have also confirmed the association of premature closure of the SOS with midface hypoplasia as measured by the sella-nasion-A point angle (SNA) in human subjects with syndromic craniosynostosis

* Corresponding author. Dutch Craniofacial Centre, Erasmus MC Sophia Children's Hospital, Department of Plastic Surgery, Sk-1202, Post office box 2060, 3000 CB Rotterdam, The Netherlands. Fax: +31 10 7036844.
E-mail address: c.driessen@erasmusmc.nl (C. Driessen).

http://dx.doi.org/10.1016/j.jcms.2017.03.024
1010-5182/

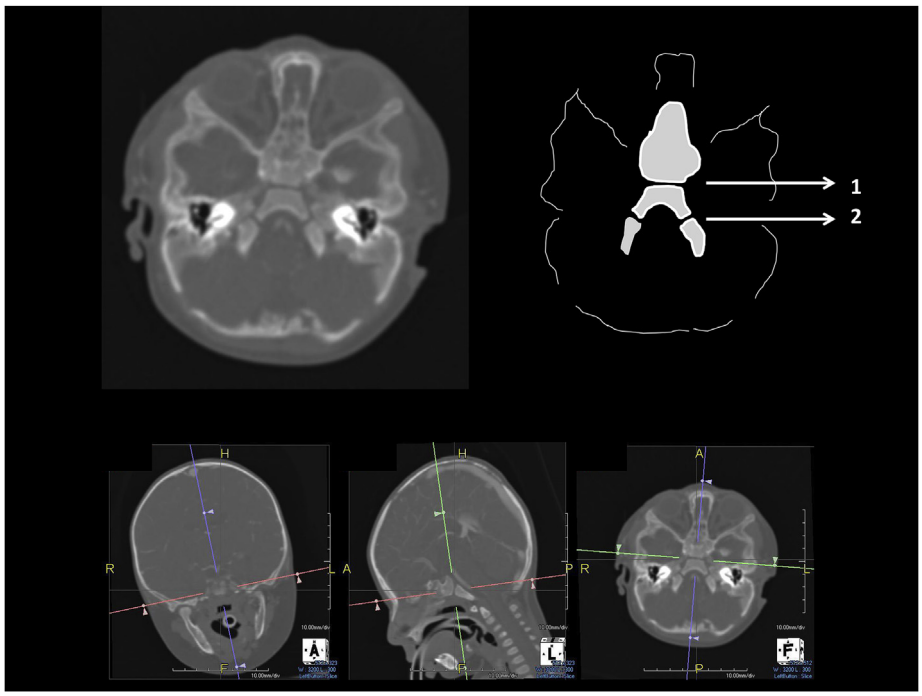

Fig. 1. Cranial synchondroses on CT scan. 1: Spheno-occipital synchondrosis; 2: anterior intra-occipital synchondroses.

(Goldstein et al., 2014). However, it is currently unknown whether there is a causal relation between OSA and premature SOS closure. This study will addresses the following questions:

1) whether there is a premature closure of the SOS in patients with Crouzon syndrome;
2) whether patients with Crouzon syndrome and OSA have an earlier closure of the SOS than those without; and
3) whether patients with Crouzon syndrome and OSA have a smaller SNA than patients with Crouzon without OSA.

2. Materials and methods

Patients with Crouzon syndrome were evaluated. We included all sleep studies and all computed tomography (CT) scans that were taken to the age of 8 years during these patients' participation in our prospective cohort study. This is an ongoing study that is based on our medical protocol, which follows the Declaration of Helsinki. Approval of our local ethical committee was received.

OSA was evaluated by repetitive sleep studies according to our research protocol, which includes an annual sleep study during the first 6 years of life and once every 3 years thereafter. We analyzed the obstructive apnea–hypopnea index (oAHI) and oxygen desaturation index (ODI), which represent the number of events per hour. Stratification to the OSA or non-OSA group was performed after analyzing all sleep studies and OSA treatments performed in the duration of the study. If any one of the sleep studies during the study period showed an oAHI > 5 or if a child was treated for OSA during follow-up, the child was stratified to the OSA group. Children with an oAHI < 5 at all sleep studies and no OSA treatment whatsoever were stratified to the non-OSA group. This group also contained children with features of mild OSA in whom sleep studies did not show more than five events per hour and no treatment was performed at any time to improve breathing.

CT scans were performed in the first year of life preoperatively and during follow-up in the case of craniofacial problems or planning of surgery. Scans were analyzed using a multiplane platform (AquariusNET). The researchers were blinded to the outcome of the sleep study. A dedicated team (C.D. and B.R.) standardized the scans in a coronal plane based on an exact horizontal position of the mastoid and in the sagittal plane based on the plane of the foramen magnum, using the position of its anterior and posterior borders. Thereafter they agreed upon the extent of closure of the SOS based on the classification according to Madeline and Elster (1995) (Table 1). Grade 1 and 2 were regarded as "open" synchondrosis.

A second team (C.D. and P.D.) aligned the CT scans to the caudal edge of the mastoid bone in the coronal plane and to the nasal septum in the axial plane. The sella-nasion angle (SNA) was used to measure midface hypoplasia. It was measured on CT scans before any advancement of the midface was performed. Next, in the midsagittal image, a line was drawn from the center of the sella to the most concave part of the nasion and a second line to the most concave part of the maxilla (A point). The angle between these lines represents the SNA (Fig. 2). The SNA is normally around 82 ± 3° (Hurst et al., 2007).

Table 1
Spheno-occipital synchondrosis closure based on the classification according to Madeline and Elster (1995).

Grade	Character
1	Margins of the synchondrosis are clearly separated on all sections
2	Clear separation of the synchondrosis is seen along most sections, except for some areas that are indistinct or suspicious for bony bridging
3	There is a fusion or bridging across a portion of the synchondrosis
4	There is complete fusion of the synchondrosis with remnant sclerotic margin
5	Complete closure is seen with no apparent vestige remaining

Please cite this article in press as: Driessen C, et al., The effect of early fusion of the spheno-occipital synchondrosis on midface hypoplasia and obstructive sleep apnea in patients with Crouzon syndrome, Journal of Cranio-Maxillo-Facial Surgery (2017), http://dx.doi.org/10.1016/j.jcms.2017.03.024