**Introduction**

The term “Crouzon syndrome” describes an autosomal disease, which results from hereditary mutations identified in specific genes in the human DNA chain. The molecular deformities most customarily occur in FGFR2 gene and, in rare instances, in the FGFR3 gene. Moreover, recent studies have identified mutations in FGFR1, MSX2, TWIST1, EFnB1, NELL1, GLI3 and TCF12 genes. These mutations result in premature synostosis of several sutures of the craniofacial complex. Specifically, the fusion of the sagittal and coronal sutures begins, in the most of the cases, during the first year of life leading to the growth inhibition at the affected sutures and compensative growth at other sutures. It is one of the most frequent craniosynostosis syndromes, with estimated incidence of 1:60000 live births.

The aim of this study was to investigate the available information on the general characteristics, the therapeutic needs and the existing management protocols of patients with Crouzon syndrome.

**Clinical features**

**Craniofacial and dentoalveolar characteristics**

The syndromic patients are characterized by specific craniofacial characteristics. The main feature of Crouzon syndrome is the premature synostosis of craniofacial sutures, which leads to cranium deformity manifested as brachycephaly, scaphocephaly or oxycephaly with dolichocephalic growth pattern. Moreover, concave facial profile appears due to midfacial hypoplasia with implied retropositioned zygomaticomaxillary complex, while the exophthalmus and ocular proptosis are connected to shallow orbits. Part of the midfacial discrepancy includes the deviated nasal septum, which results in beaked nose.

The premature synostosis of several sutures of the middle third of the facial skeleton results in differentiation of the intraoral anatomy in Crouzon patients. The hypoplastic, narrow and high arched palate results in decreased upper dental arch dimensions. Also, severe crowding of the primary and secondary dentitions, anterior and posterior crossbite are usually diagnosed.
as well as malformed teeth, delayed dental eruption and impactions18-20. High risk of maxillary canine and premolar impactions is evident in patients who present severe lack of space in the upper arch. In some cases, about 40% of the patients with Crouzon syndrome, ectopic dental eruption of the upper first permanent molars is observed and also dental agenesis, especially of the lower second premolars and upper lateral incisors21-23. Class III malocclusion and Class III skeletal discrepancy is observed in all patients18-20.

Functional impairment

The above mentioned characteristics result in some functional complications. Eye exposure, as a result of shallow orbits, can result in corneal abrasions, scarring, exposure keratitis or luxation of the eyeballs in acute cases24. Additionally, increased intracranial pressure may lead to bilateral optic atrophy, which bring about nystagmus, strabismus or even blindness if the condition is not treated25,26. Bilateral atresia of auditory meatus often causes the deafness1. Factors contributing to the respiratory distress or obstructive sleep apnea syndrome would have included the retrusive location of the maxilla or a very long and fleshy soft palate, which is often observed in Crouzon syndrome28. These situations are usually linked to hypertension and cardiac arrhythmia or cardiac arrest27. As a consequence of the class III malocclusion, patients feel discomfort over the masseter region during eating.

General findings

Beside the functional problems, patients with Crouzon syndrome show some general clinical features such as cervical spine anomalies, acanthosis nigricans, increased intracranial pressure, hydrocephalus and occasionally mild mental retardation29-31. Developmental delays can also occur.

Diagnostic procedure

Craniosynostosis can be suspected prenatally based on indirect signs visualized using two or three dimensional ultrasound, magnetic resonance imaging (MRI) or computed tomography (CT) scan32. Prenatal 2D ultrasound diagnosis aims to visualize the cranium shape, allowing the calculation of the cephalic index33 [CI: Cephalic Index expresses the relationship between the biparietal and occipito-frontal diameters]. Abnormal values of the CI correspond to patients with brachycephaly, scaphocephaly or dolichocephaly. Regarding to the differentiated face morphology, common characteristics of Crouzon syndrome, such as hypertelorism, ocular proptosis and beaked nose can be identified by ultrasound scan. Nowadays, 3D ultrasound scan provides more accurate evaluation of fetal head, face and sutures, as well as detailed visualization of the whole fetal anatomy which contributes to the differential diagnosis between craniosynostosis syndromes34,35. In addition, MRI can be considered complementary to the above mentioned methods and seems to have negative predictive value36. The syndromic nature of craniosynostosis is, finally, confirmed by molecular diagnosis. Specifically, mutations in FGFR1, FGFR2 or FGFR3 genes are investigated by amniocenteses, chorionic villus sampling or pre-implantation diagnosis37.

It is worth to mention that due to the less severe phenotype of Crouzon syndrome in relation to other craniosynostosis syndromes the prenatal diagnosis is confoundedly difficult38. The postnatal diagnosis of the Crouzon syndrome requires extensive clinical and radiological examination. Cephalometric analysis of the anteroposterior and lateral radiographies and CT scans confirm clinical findings and shows the premature suture closure39,40. Patients are usually examined by geneticists in order to detect the associate mutations.

Treatment management

Patients with Crouzon syndrome present complex abnormalities, which require early clinical management of multidisciplinary teams. These teams should consist of craniofacial surgeons, oral and maxillofacial surgeons, neurosurgeons, plastic surgeons, ENT (ear, nose and throat) surgeons, orthodontists, dentists, dental technicians, speech pathologists, psychologists, ophthalmologists, nurses, speech-language pathologists, anesthesiologists, geneticists, pediatricians and radiologists41,42.

Surgical intervention in the craniofacial region

The surgical treatment of the syndromic patients consists of two phases. The first phase takes place in the first year of life and is limited to the correction of the cranium deformity and prevention of the cranial pressure increase and optic nerve damage43-45. The midfacial advancement, the second phase, takes place in older age. To achieve the desired result a combination of Le Fort III osteotomy, or frontofacial Monobloc osteotomy with distraction osteogenesis is required46,47. The use of distraction osteogenesis overcomes the complications of the osteotomies, such as increased operative time, relapse of midface protrusion, need for bone grafting and severe blood loss48,49. In cases of severe sleep apnea, tracheostomy may be required as additional intervention50. Interventions on the lid occlusal suture or tarsorrhaphy are part of the ophthalmologic management, while plastic surgery is usually performed in adulthood to restore patients appearance51.
Several protocols have established through the years. McCarthy et al.\textsuperscript{51} published the parameters of care of craniostenosis established in a multidisciplinary meeting titled “Craniostensosis: Developing Parameters for Diagnosis, Treatment, and Management” in 2010. Generally, according to this protocol the surgical interventions are divided in six treatment periods. The first period includes early operative treatment for synostosis and for selected suture fusion, aiming to cranial vault decompression and suture release. Common surgical procedures for this stage are the craniectomy or craniotomy and fragmentation of the cranium, the anterior or posterior skull expansion, the endoscopic strip-craniectomy with external molding, spring, or distraction and the open cranial vault procedure which take place between birth and the first year of life. At the same time, airway and ophthalmologic management are strongly suggested. The second period (between 6 months to 4 years) aims to the fronto-orbital advancement and reshaping inclusive of cranial vault remodeling, strip craniectomy and midface or monobloc distraction osteogenesis. The correction of midface deformities, as well as secondary cranial vault procedures and adjunct procedures are made during the third or the fourth phase (between 4 to 12 years). Conventional monobloc or Le Fort III combined with distraction osteogenesis are suggested for the midfacial advancement. Hypertelorism correction is necessary in this period. Phase five (between 13 and 17 years) consists of adjunct procedures such as lateral canthopexy, rhinoplasty and cranioplasty and secondary – complementary procedures when needed. The last period begins after 17 years of living and includes orthognathic surgery for craniofacial dysmorphology or malocclusion for skeletally mature patients. It is noticeable that several of the aforementioned surgical procedures can be performed in different periods depending on the functional, aesthetic, and psychological needs of each patient.

Pagnoni et al.\textsuperscript{44} suggested correction of cranio-synostosis between the ages of three and six months and midfacial advancement with distraction procedures between the age of 4 to 5 years depending on the extremity of malocclusion, psychological factors and the existence of obstructive sleep apnea. According to this protocol, hypertelorism is corrected in conjunction with the midfacial advancement or separately between the ages of 4 and 6 years. Le Fort I or II combined with mandibular osteotomy is performed after full maturity to normalize appearance.

Kahnberg et al.\textsuperscript{43} suggested the use of distraction osteogenesis by the age of 7 to 8 years in patients with severe form of deformity or psychological burden. In the rest of the cases the midfacial advancement took place between the ages of 16 and 18 years. The surgical procedure consisted of Le Fort I or II osteotomy for the correction of the midface retrusion (single jaw maxillary surgery) and the additional set-back of the mandible or segmental osteotomy of the mandible when needed. (bimaxillary surgery). Rhinoplasty was performed in some cases to refine the result.

Won Lee et al.\textsuperscript{52} treated midfacial hypoplasia using dual midfacial distraction osteogenesis in 6 patients with mean age 7.2 years. Le Fort III or frontofacial monobloc was performed in these patients and a rigid distraction device was placed.

In contrast with the above mentioned protocols, Mithlbauer et al.\textsuperscript{53} suggested the correction of the midfacial hypoplasia alongside with the fixing of the cranial deformity in the first months of life in order to improve severe exorbitism, obstruction of nasal airways and implied functional problems. Additional advantages of this technique are the reduction of the psychological effect on the patient and the technical advantages of the surgery due to the elasticity of bones and tissues and the anatomical characteristics in infancy. Nowadays, it is generally accepted that early distraction of the hypoplastic midface usually requires secondary procedures in older age\textsuperscript{54, 55}.

**Orthodontic and Orthognathic procedures**

Orthodontist specialists can evaluate and manage the patient’s growth pattern through various diagnostic and therapeutic procedures. In that way, they play an important role in the timing of craniofacial surgery. Thus, it is generally recommended for each patient to be monitored by an orthodontist from infancy to adulthood.

Orthodontic treatment can be, also, divided into two periods, the preoperative and postoperative period. In the preoperative period, early evaluation allows guidance of teeth eruption, expansion of the maxilla with suitable appliances, alignment of dentitions and preparation for orthognathic surgery\textsuperscript{52}. The creation of interdental spaces for osteotomies is a common procedure\textsuperscript{56}. Moreover, surgical prediction tracings and splints are created\textsuperscript{57, 58}. After the orthodontic preparation, the midfacial advancement is performed in adolescence. The postoperative orthodontic procedure involves occlusion settlement and functional guidance, which are essential after the surgery. These are arranged using intermaxillary elastics or orthodontic appliances such as reverse activators\textsuperscript{59}.

In cases where an additional orthognathic surgery is needed in adulthood, the orthodontist in cooperation with the maxillofacial surgeon will choose the appropriate time for the secondary surgery\textsuperscript{10}.

Vargervik et al.\textsuperscript{10} published the dental and orthodontic perspectives of craniosynostosis resulted from the multidisciplinary meeting mentioned above. The orthodontist, as stated by the participants of the meeting, is obligated to obtain and maintain photographic, radiographic and other imaging records from infancy to early adulthood. Additionally, growth monitoring and dental extractions coordination with pediatric dentists are necessary until the age of 7 years, as well as orthognathic procedures in coordination with surgeons. Between the ages of 7 and 12 years, the first phase of the orthodontic treatment is carried
out. Specifically, alignment of dentitions, active guidance of permanent teeth eruption, insertion of intraoral appliances and midface advancement planning, with cephalometric analysis prediction tracings, images and splints are necessary. The second phase of orthodontic treatment takes place between the ages of 12 and 21 years and includes orthodontic preparation for craniofacial and orthognathic surgery (midfacial advancement or distraction osteogenesis or Le Fort I osteotomy or facial bipartition procedure or 2-jaw surgical correction) using the same procedures mentioned in phase 1. In addition, management of dental impactions with surgical exposure and orthodontic assisted eruption, cooperation with other dental specialties for general dental treatment objectives (prosthodontics, periodontal care, extractions and preventive dental care) and intraoral soft tissue procedures are made at this stage. After surgery, the orthodontic treatment is completed, retention is placed and final records are obtained. Since the 21st year of life onwards a follow up assessment is obligatory at appropriate intervals.

Nurko et al.56 splitted orthodontic therapy in two periods: (1) orthodontic treatment during childhood and (2) orthodontic treatment during adolescence. During childhood, the orthodontic therapy aims to deal with ectopic eruptions, delayed tooth emergence, crowding and posterior crossbite in patients with mixed dentition (5 to 12 years old). Recommended methods are the extractions, the use of a lingual arch and/or fixed appliances and the palatal expansion. In patients with suture closure in the palate, segmental surgery in Le Fort I level is proposed as alternative to palatal expansion with orthodontic appliances. The preparation for midfacial advancement, which usually takes place between 6-10 years, requires extractions of the primary teeth, fixed orthodontic appliances for acrylic surgical splint holding and full dimension rectangular arch wires, while a removable retainer is suggested after surgery to prevent dental relapse.

Later, during adolescence, the patient is prepared for orthognathic surgery which requires full permanent dentitions and skeletal maturity (13-15 years for girls and 15-17 years for boys). The orthodontist aligns the teeth of each jaw without worrying about reverse overjet or dental occlusion using fixed appliances and arch compatibility is checked on dental casts. Full dimension rectangular arch wires are placed and final records should be taken (panoramic and lateral cephalogram radiographs, dental casts, facial and intraoral photos and posteroanterior cephalometric radiograph for asymmetry evaluation). Root separation (4 to 5mm) is required to facilitate osteotomies. Final, predictions and surgical splints are created. Postsurgical orthodontic therapy starts approximately 4 to 6 weeks after the surgery. Vertical elastics are used to settle occlusion and prevent relapse or shifts different from centric relation. This procedure lasts about 6 months and then a retainer is used full time for 12 months.

Kahlberg et al.43 used fixed orthodontic appliances in order to align dentitions preoperatively. Sectional orthodontic arches were put in position, 4 to 6 weeks before the operation to facilitate transverse maxillary expansion. A wafer was constructed for the final planning of the surgery. Postoperatively, minor corrections were made using intermaxillary elastics. The retention period duration varied between 6 and 24 months and removable orthodontic appliances with a grid to avoid tongue thrust were used during this period.

### Dental management

Supervision by a pediatric dentist in early childhood is critical in order to ensure satisfactory oral hygiene of patients with syndromic craniosynostosis. Because of the anatomical discrepancies, these patients present decreased upper arch dimensions which lead to crowding, delayed and ectopic eruptions with implied propensity for periodontal disease60.

Furthermore, the morphological abnormalities of teeth, lower levels of calcium, phosphorus and magnesium in dentine in combination with the difficulties in maintaining the adequate oral hygiene, usually, lead to dental caries61,62. Fluoride supplementation, pit or fissure sealants, restorative treatment and oral hygiene guidance are recommended after caries risk assessment51. The early localization of missing teeth is an important part of general treatment planning. Therefore, the dentist is obligated to keep baseline diagnostic records such as full head CT scans, cephalograms, intraoral and facial/head photographs. The oral examination needs to be repeated every 6 months or as indicated by the risk status of each syndromic patient51.

Post-surgery patients with Crouzon syndrome refer to a prosthodontist in order to replace missing teeth and restore full anatomical dimension of peg or abnormally shaped teeth10. A life-long follow up evaluation is mandatory for all these patients. Critical knowledge and understanding of the craniofacial growth are required for the dental specialist in order to treat syndromic patients effectively.

### Conclusions

Patients with Crouzon syndrome need long term management by scientists of various specialties. Facial and functional malformations in individuals with Crouzon syndrome could be significantly improved after a series of surgical and orthodontic procedures in almost all the cases. According to the above mentioned protocols, the surgical treatment of craniofacial hypoplasia is obligatory. However, the role of orthodontist is crucial both before and after surgery to reach the desired treatment plan goals.

### References