Crouzon's Syndrome: Literature Review

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SUMMARY

Introduction: The Crouzon syndrome or craniofacial dysostosis type I is a rare disease that affects the craniofacial skeleton development. Although it is uncommon, it has a transmission risk of 50% when one of the parents is a carrier.

Objective: Performing a literature review about the Crouzon Syndrome, with emphasis on the current aspects.

Method: As a methodology, a search on databases on-line, such as Cochrane, LILACS, MEDLINE, OMIM and SciELO has been made, by applying for the search the key-word Crouzon's Syndrome for articles published until 2007, in addition to the literature already dedicated to the subject.

Literature Review: This syndrome is characterized by craniofacial anomalies caused by the early loss of the cranium flexibility, and present since the birth with tendency to aggravation in time. The main clinic signs are craniosynostosis, hypertelorism, exophthalmia, external strabismus, "parrot-beaked nose", short upper lip, hypoplastic maxilla and a relative mandibular prognathism determining a mid-facial hypoplasia aspect. It is a hereditary affection with an autosomal dominant transmission with 100% of penetrance and large phenotypic scale.

Final Considerations: The genetic advising and an individual study of each case are essential to promote the improvement of the diagnosis. An early multidisciplinary approach is necessary, with specific therapeutic program aiming at the prevention of late diagnosis effects.

Keywords: crouzon, otorhinolaryngology, genetics, Crouzon's disease, cranium.

Introduction

The Crouzon's Syndrome or Type I Crouzon's Disease is a rare affection that commits the craniofacial skeleton development and that, in spite of being uncommon, has 50% of risk for transmission when one of the parents has the disease, without dependence on the individual's sex (1,2,3).

The craniosynostoses are a heterogeneous group of syndromes characterized by a premature sutural fusion that occurs individually or relating to other anomalies (1,2,3). The Disease of Crouzon may be distinguished from the simple craniostenosis for its association with facial malformations (2). And out of the more than 70 syndromes described, the Crouzon's syndrome and the Apert syndrome are the most known ones, and several researches have been carried out in the last 10 years to allow for a better understanding of theses diseases etiology and pathogenesis (3,4).

Depending on the diagnosis methods and the population under study, the craniostenosis incidence is variable, and is between 1:50.000 and 1:1.000 children. There is no affection distinction as to sex, however when the craniostenosis are of sagittal and metopic types their predominance increases in the male sex, while coronal craniostenosis is more common in the female sex (1,3).

The day-by-day interdisciplinary actuation of the Hospital Universitário Bettina Ferro de Souza - Universidade Federal do Pará e Universidade do Estado do Pará has encouraged us as to a deeper study of the Crouzon Syndrome, that comprises the areas of Otorhinolaryngology, Ophthalmology, Pediatrics, Psychology, Social Service and Physiotherapy, specially regarding assistance to patients carrying several special needs. This work is justified by the need to alert the health professionals as to the occurrence of this rare syndrome that causes severe consequences to their carriers, mainly when they are faced with a late diagnosis.

Making a review of the literature about many aspects of the Crouzon's Syndrome, with emphasis on the clinical otorhinolaryngological manifestations.

Method

The research through on-line databases has supplied information and articles for the achievement of this bibliographic review, and they may be accessed at any time for research and updating, since they are renewed as the scientific literature is produced.

The databases Cochrane, LILACS, MEDLINE and SciELO have been searched by applying to the research the terms *Sindrome de Crouzon* for articles published until 2007, in addition to the literature dedicated to the subject.

The interested readers may deepen their studies in researches in Internet, by searching for recent articles. We suggest the free database (OMIM) Online Mendelian Inheritance in Man, which brings information and articles updated on a regular basis (3).

Literature Review

Overview and etiopathogenesis

The Crouzon's Syndrome is the most frequent of the craniofacial diseases and is characterized for being a rare genetic disorder that can be diagnosed upon the birth or during the childhood. The dominant transmission range is of 100% and the large scale penetrance with phenotypic expression is highly variable (3,4,5,6,7,8). It is responsible for about 4.8% of all the cases of craniosynostosis, and is the most common syndrome of a group of more than 100 types of craniosynostoses (6,9,10,11,12,13).

The mutation in the genes that codify receptor 2 of the (FGFR2) fibroblast growth factor (14), is responsible for the deformities observed (5,6,13,16). Twenty five mutations have already been identified in the FGFR2 and concern the Crouzon's Syndrome pathogenesis (14). However, 50% of the Crouzon's syndrome incidents are not inherited but result from new spontaneous mutations (5,6).

The fibroblast growth factors are intrinsically related to the extracellular matrix. When the extracellular matrix presents FGFR2's mutation, it begins to secrete cytokines both in autocrinous and paracrinous manner and these may modify the very matrix. It is allegeable that such changes are in the osteogenic process change genesis, which explains the pathologic variations found (1,17).

It is also postulated that a cranium basis malformation causes the premature fusion of the cranial sutures evolving with midfacial hypoplasia and cranium shape changing according to the sutures involved (2,4,8).

The abnormalities found change too much from case to case including variations between members affected of the same family. The suture fusion order and range determine the degree of deformity and inability (6).

The triad composed by cranium deformities, facial

anomalies and exophthalmia, described by Crouzon in 1912, forms today the Crouzon's syndrome (5,6,7,19). In this disease, the premature closure of cranial sutures and midfacial sutures and the cranium basis premature sinostosis give it a branchiocephalic configuration (1,4,6,12,18).

Since the suture becomes cast, the growth perpendicular to it becomes restrict and the cast bones act like a sole osseous structure (6). Compensatory growth occurs in the remaining open sutures to allow continuity to the brain development causing abnormal osseous growth and production of facial deformities (6,18).

Such syndrome is progressive, from the beginning in the first year of life appearing frequently only at two years of age (5,6,9).

There are also congenial premature forms in which the sinostosis begins inside the uterus and is manifested at the birth with facial deformities like upper maxillary hyperplasia, responsible for respiratory difficulties and exophthalmia (1,5,6).

Otorhinolaryngologic manifestations

In the affected individuals there are almost always a high and large forehead, with convexity in the region of the anterior fontanelle, flattening of the occipital region and a certain front occipital protuberance. This gives the cranium an aspect of a tower (4,5,12). Hypoplastic maxilla, midfacial and maxillary hypoplasia are responsible for a number of alterations in the face aspect (6).

The mouth shows a bad occlusion and maxillary dental arch in V shape with to much spaced teeth. There are reports of individuals with narrowing or congenital cleft in the roof of the mouth, ogival palate and cleft uvula (2,4,6). The upper lip is short and the inferior lip, along with the tongue, are prominent; the maxilla is hypoplastic and there is relative maxillary prognathism and micrognatia (1,2,6,11).

The conductive hearing loss is common due to the medium ear deformities. Alterations to the clamp with consequent fusion in the promontory, hearing ossicle ankylosis heading to the epitympanus external wall, distortions and narrowing of the medium ear space, absence of tympanic membrane and external channel stenosis or atresia are possible due to deforming growth (6,12) Recurrent infections are common in the hearing system (6).

Acoustic meatus atresia, hypacusis and malformations of the medium ear are, therefore, the main manifestations of the disease concerning the hearing system (20). We can observe conductive non-progressive hearing loss in a third of the cases, in addition to mixed hearing loss (12).

The nose shows an aduncous aspect, due to the strong maxillary hypoplasia, recalling a "parrot beak" due to the frontal shortening of the dorsum of nose (4,5,6,12).

The obstruction of the upper respiratory passages develops, following the septal diversion, abnormalities to the center of the nose and epipharynx narrowing (1,6). It can lead to acute respiratory anxiety (6), dyspnea of the type polypnea and even sleep apnea, mainly when connected to upper maxillary hypoplasia (5).

Other clinical manifestations

There are several ocular abnormalities and the most common already reported for such disease are: shallow orbits, bilateral ocular proptosis, hypertelorism, divergent strabismus, optical atrophy, conjunctivitis or exposure keratoconjunctivitis and a non-explained loss of visual accuracy (4,5,6,12). There rarely may occur nystagmus, coloboma of the iris, anisocoria, microcornea or megalocornea, cataract, blue sclerae, glaucoma and globe luxation (6).

Despite the exophthalmia is constantly verified in the patients affected by the Crouzon's disease, the ocular proptosis is not clearly present at birth and develops gradually in the first years of life (9).

The optical atrophy may be a complication resulting from the narrow optical channel. Blindness following the optical atrophy by the intracranial hypertension may also occur. Other characteristics generally seen in these patients are visual disturbances relating to a muscular unbalance (6).

An early craniosynostosis, evidenced by the existence of intracranial hypertension, is present in 60% of the cases and furnishes a reserved visual prognostic (5). The patients have hyperemia, bilateral ocular irritation and sensation of long-term nuisance for being constantly rubbed (6).

Acanthosis nigricans, a disorder that causes brown to black velvet stains, generally on the neck, under the arm or in the groin region is the main Crouzon's syndrome dermatologic manifestation, and it is detectable after the childhood (6).

Generally, the psychomotor development is normal and the mental ability of these patients is usually within the normality (5,6). However, some reports of mental retardation have been related to the increased intracranial

pressure, which develops due to the brain growth restriction by the several synostoses (1,6,9).

Other less frequent characteristics are associated. The diminished mental function is present in about 12% of the patients; headaches and apprehensions are ascribed to the high intracranial pressure; a progressive hydrocephaly occurs in 30% of these patients (6); and accompanying the cephalea there also may be vomits and/or convulsions (1).

There are reports of children with Crouzon's Syndrome with stenosis of the jugular foramen. This kind of affection produces brain venous congestion, failure of the cephaloraquidian liquid absorption and hydrocephaly. However, by making the ventricle peritoneal diversion aiming at solving the hydrocephaly, we can verify the brain congestion persistence, evolving to a tonsillar herniation. We still do not have an exact percentage of this affection in this syndrome (13,21).

The Crouzon's syndrome early diagnosis is critical to avoid cranial hypertension, as well as visual disturbances and blindness, etc. Therefore, it is important to pay close attention to the patients that have some Crouzon's syndrome carrier relative precedent or that have a certain level of exophthalmia. We must be attentive to the cerebriform impressions development in the cranium-occipital region, cranial hypertension and the appearing of other characteristics of the syndrome (6).

The cranium radiographies are used to evidence craniofacial deformities, moderate brachycephalism, cerebriform impressions, hypophyseal cavity enlargement, small paranasal sinuses and the maxillary hypoplasia with shallow orbits (5,6).

Cervical region radiologic abnormalities include butterfly-shaped vertebra and fusion of the posterior bodies and elements, present in about 18% of the patients. C2-C3 and C5-C6 are equally affected (5,6). The magnetic resonance is used to view corpus callosum occasional agenesis and optical atrophy (6).

Differential diagnosis

The Apert syndrome has statements similar to those found in the Crouzon's syndrome associated to malformation of the hands and feet, with symmetric syndactylus generally including the second, third and fourth digits (6,9).

Differential diagnosis is also made with the syndromes of Pfeiffer, Carpenter and Sayre-Chotzen.

An important information is that more than 50% of the patients with Crouzon's syndrome have mutations in FGFR2, and these mutations are also observed in the syndromes of Apert, Pfeiffer and Jackson-Weiss, highlighting the importance and complexity of this factor in the development of the cranial sutures and their pathologies (6,9).

Treatment

The treatment is multidisciplinary, and it allows for acceptable results (6). The surgical procedure for the Crouzon's syndrome was one of the main therapeutic advances, with high complexity surgeries and in many steps (6). Considering this point, the symptomatic treatment and the treatment with hearing aid, phonotherapy, psychopedagogy, family orientation, genetic advise, teaching of speech, labial reading and LIBRAS, special school or a good quality school contribute for improving the quality of life of this syndrome carriers (1).

Generally, the several surgical techniques are employed to prevent the early craniofacial sutures fusion and thus reduce the head pressures, and avoid or reduce the cranium and face bones deformities (1,3,19). The surgical procedures may benefit the patients, by providing them with a normal life (1).

The goal is to act the reconstruction so that it coincides with the standard tests of facial growth, visceral function and psychosocial development (6). The front-orbital region remodeling, for instance, is able to prevent functional disturbances and the normal development of the cranium shape.

The proper moment to carry out a surgery is before 1 year of life of the child, since the bones are more flexible and there will be a major facility to work with them. In the first year of life, it is preferable to release the cranium synostosis sutures to provide that an adequate cranial volume allows for the brain growth and expansion.

If necessary, the midfacial surgery may be carried out to provide the adequate orbital volume, reduce the exophthalmia and allow a more harmonious appearance (6).

The plastic surgery may also be beneficial (1). The methylmetacrilate is a polymer that has been used in the cosmetic surgery to smooth and harmonize the facial contour. This aloplastic implant can also be used in the Crouzon's and Apert's syndromes (16).

The experience of some authors with a long-term follow-up of their patients has shown great advantage of methylmetacrilate compared with autogenic engraftments,

with absence of long-term complication and safety in its use. In the other hand, this material cellular toxicity has been described in experimental studies with extrusion and local infection (16).

It is one of the few syndromes in which the surgery cosmetic results may be very effective (6).

The prognostic depends on the malformation severity. It varies from an exclusively aesthetic problem (scaphocephaly or trigocephaly) up to malformations with possible cranial hypertension.

Final Considerations

The rarity of the Crouzon Syndrome and its spectra heterogeneity show this pathology multifactor nature. For being characterized by cranial-facial anomalies and being a multifactor digenetic syndrome, it is necessary to maintain the genetic advising and the detailed study in each individual affected by this syndrome. Therefore, the study has to be continuous to promote the progress in the required diagnosis to an early multidisciplinary approach and the beginning of the specific treatment, thus preventing the late diagnosis effects.

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