

OPHTHALMOLOGICAL AND RADIOLOGICAL PICTURE OF CROUZON SYNDROME – A CASE REPORT

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Crouzon syndrome (CS) accounts for about 4.8% of all cases of craniosynostosis. Crouzon syndrome occurs in approximately 1 per 25,000 births worldwide. It may be transmitted as an autosomal dominant genetic condition, but 25% of cases represent a fresh mutation. There is no race or sex predilection. The appearance of an infant with CS can vary in severity from mild presentation with subtle midface characteristics to severe forms with multiple cranial sutures, fused and marked midface and eye problems.

A ten-year-old girl suspected to have congenital glaucoma was sent to a consultative examination to the Ophthalmology Clinic, CC Nis. The very appearance of the girl indicated the diagnosis – Crouzon syndrome, which was confirmed by ophthalmological and radiological examinations. The patient was referred to the ophthalmologist in charge for further attendance and was recommended to undergo a surgical treatment by a maxillofacial surgeon.

Exophthalmus, hypertelorism, divergent strabismus, hypermetropia, head, orbit and jaw deformities, extremely illustrative, mostly rarely seen in everyday practice, are the elements of the clinical picture of Crouzon syndrome. It deserves our attention, taking into consideration ocular complications and multifactorial purblindness which it causes. *Acta Medica Medianae* 2009;48(2):37-40.

Key words: Crouzon syndrome, craniosynostosis, strabismus, purblindness

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Introduction

In 1912, a French neurologist, Octave Crouzon (1874-1938) (1) first described a hereditary syndrome of craniofacial dysostosis in a mother and son, which includes a triad – skull deformities, facial anomalies and exophthalmos (2,3).

Craniosynostoses (craniosynostoses) represent conditions of the premature fusion of one or more cranial sutures, resulting in skull deformities and the disturbances in the normal brain development, due to the reduced volume of the intracranial space (4). Their prevalence is estimated at 333-476 per million live births. Over 100 syndromes with craniosynostoses have been described, including autosomal dominant syndromes, such as Apert, Crouzon, Pfeiffer and Saethre-Chotzen syndromes (5).

Crouzon syndrome (dysostose cranio-faciale hereditare, dysostosis cranio-facialis, CS) accounts for approximately 4.8% of all cases of craniosynostosis, with the prevalence of approximately 1 per 25,000 live births worldwide (2).

The prevalence of this syndrome in the US is 1 per 60,000 live births (approximately 16.5 per million) (2,6) or 15-16 cases per million live births (5). It may be transmitted as an autosomal dominant genetic condition, but 25% of cases represent a fresh mutation. The molecular analysis of craniosynostosis syndromes identifies mutations in the fibroblast growth factor receptor 2 (FGFR2) gene, which is mapped to chromosome locus 10q25-q26 (8). In more than 50% of cases with Crouzon syndrome, mutations in the FGFR 2 gene (2,6,8), several mutations within the Ig III domain of FGFR 2 and a novel mutation, Tyr 281 Cys substitution at the exon IIIa of FGFR 2 (8) were observed. Based on the specific mutations of FGFR 2, other mutations of this and other still unidentified genes, it can be concluded that the Crouzon syndrome phenotype shows heterogeneity, while molecular analyses of the FGFR gene provide useful information and help with confirming the diagnosis and performing pre-natal diagnostics (8).

Crouzon syndrome has no sex or race predilection. The appearance of an infant with CS can vary in severity from a mild presentation with subtle midface features to severe forms with multiple fused cranial sutures and marked midface and ocular problems (2). Varieties of the ophthalmic findings of this syndrome include: proptosis – due to the shallow orbits, ocular hypertelorism – the consequence of the

widening of the sphenoid bone and the root of the nose, strabismus – exotropia, V syndrome, hypertrophy, which together with maxillary hypoplasia and the protrusion of the lower jaw (relative mandibular prognathism) contribute to a recognisable facial appearance of the affected (2-7). There have also been rare occurrences of aniridia, anisocoria, blue sclera, cataract, corectopia, ectopia lentis, glaucoma, iris coloboma, megalocornea and microcornea, nystagmus and optic nerve hypoplasia (6,7).

Ocular complications of CS include: chronic papillary edema, as a result of increased intracranial pressure with consequential optic nerve atrophy; keratopathy, as a consequence of qualitative changes of the tear film due to the exposure of the exposed part of the globe to external micro- and macroclimate factors of subluxated globes (2-7) and multifactorial porsightedness, which is, apart from the above-mentioned conditions, caused by astigmatism (particularly oblique astigmatism), anisometropia, strabismus (5).

Cranial X-ray of patients with Crouzon syndrome visualises the premature fusion of the coronal, sagittal and lambdoid sutures, cranial deformities, and maxillary hypoplasia. The upper part of the frontal bone is prominent, so that the head shows an oxycephalic, scaphocephalic or trigonocephalic shape. Increased intracranial pressure causes the dislocation and deformation of the sphenoid bone, shortening of the lateral orbital wall and dramatic reduction of the orbital volume. Maxillary hypoplasia results from the dislocation of the lower orbital floor, anterior cranial fossa and the shortening of the orbital floor. Mandibular prognathism is present. The nose is beaked (9).

Clinical signs of CS also include epilepsy, headaches, dizziness, vertigo, hearing impairment (3,4,6,8,9), while, in establishing the final diagnosis, of relevant importance are ophthalmic and radiological examinations and laboratory analyses – molecular analyses of the FGFR gene.

Case report

A ten-year old girl from Vranje suspected of congenital glaucoma was sent to a consultative examination to the Ophthalmology Clinic, CC Nis. The heteroanamnesic data were provided by her father: the so-far healthy girl is the second of three children, from the third pregnancy out of six in total (three spontaneous abortions). Both the uncle and the father have "big" eyes. The girl was sent to our clinic, suspected of congenital glaucoma, after she had been examined by the primary pediatrician and ophthalmologist for the headaches and ocular redness occurring upon her return from the school excursion three weeks before. The very appearance of the girl indicated the diagnosis – Crouzon syndrome (Figure 1). An ophthalmic examination was carried out in accordance with the standard procedures and craniograms in postanterior (PA), and latero-lateral projections were made.



Figure 1. Appearance of a girl (aged 5) with Crouzon syndrome

Ophthalmic findings: Subjective visual acuity is bilaterally poor, BCVAs (best corrected visual acuities) were 0.2-0.3 logMAR units in the right eye (O.D) and 0.1-0.2 logMAR units in the left eye (O.S). The objective eye refraction (Sol. Homatropin 2%) indicates oblique astigmatism with the power difference between the principal meridians of up to +2.5 D. Intraocular pressure measured by the Schiötz impression tonometer was 18.0 mmHg bilaterally. The interpupillary distance was 69 mm, while the cornea diameter was 12.5 mm. Bilateral exophthalmos was observed (Hertel exophthalmometry readings were 22 mm in both eyes (OU) with a base of 110 mm). The ultrasonically measured axial length of bulbus was 20 mm OU. Apart from the bigger diameter of the cornea, biomicroscopic findings of the anterior segment of the eye were normal. Schirmer's test 1 values were normal (25 mm) OU, the BUT (break up time) test showed values of 10 seconds, while Rose Bengal staining was slightly positive in the interpalpebral zone and partly in the lower nasal quadrant of the bulbar conjunctiva. The ophthalmoscopic findings were consistent with the extant refractive error, hypermetropic fundus. Manifest divergent strabismus in the primary position was found, and the objective angle of strabismus was 25° (50 prism diopters).

Radiolographic findings: The craniograms (2a,b) in postanterior (PA) and latero-lateral projections visualise a variety of the child's skull deformity, scaphocephaly. The anteroposterior diameter of the cranium is widened. The anterior cranial fossa is short, with a steep floor. The parietal eminence (tuber parietale) is flattened. Calvarial bones are thin with deep digital markings. Orbits are shallow and widely spaced. The lower jaw is protruding. The teeth are deformed. Macrodonia of the central incisive teeth in the upper jaw is noticeable. Alveolar ridges are short and narrow. The girl displays dental malocclusion.

After the ophthalmic and radiological examinations had been carried out, the girl was diagnosed with Crouzon syndrome. The girl was prescribed appropriate vision correction with glasses, artificial tears eye drops and a gel for the future topical use. The father was introduced to the nature of his child's disease and the

consequential porsightedness. The girl was sent to the ophthalmologist in charge to further attendance and was recommended that she should undergo a surgical treatment by a maxillofacial surgeon in a reference health centre.

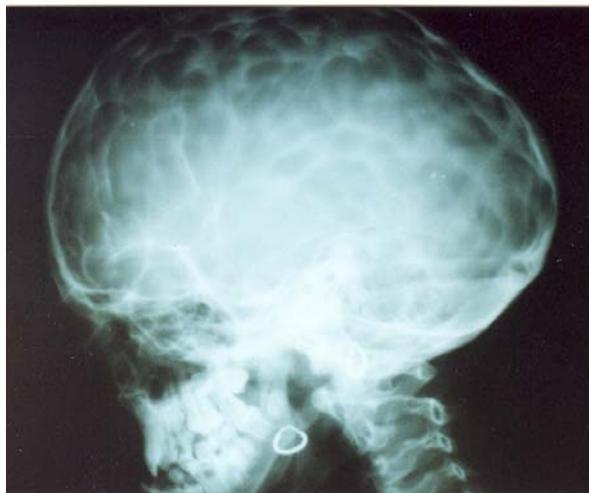


Figure 2. Radiological finding made at the time of examination

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Discussion

Congenital malformations of the orbit are usually a part of a complex syndrome which affects bones of the skull and face, i.e. the craniofacial region. According to the information provided by Roncevic (2003), congenital malformations of the craniofacial region can be seen in 42 cases per 1,000 live births, and one of the reasons for their presentation is premature synostoses of skull and facial bones (10).

Premature craniosynostosis, midface hypoplasia and exophthalmos account for the triad of Crouzon syndrome. Premature closure of cranial sutures, most commonly the coronal and sagittal ones, results in abnormal skull growth, affects the growth and development of the orbits and maxillary complex. Other clinical features include hypertelorism, exophthalmos, strabismus, beaked nose, short upper lip, maxillary hypoplasia and relative mandibular prognathism, with no digital abnormalities.

Some other features commonly seen in these patients are visual disturbances related to an imbalance of the extraocular muscles, congenital damages due to exophthalmos, consequential refractive error (usually hypermetropic astigmatism), optic nerve complications. Hearing loss

owing to recurrent ear infections, ear canal stenosis or atresia are also possible. The mental capacity of Crouzon syndrome patients is usually in the normal range or there is a diminished mental function in 12% of patients (2).

In order to diagnose Crouzon syndrome, of relevant importance are a thorough ophthalmic examination (subjective visual acuity, objective eye refraction, biomicroscopy, ophthalmoscopy, tonometry, exophthalmometry, echosonography with ocular biometrics, the evaluation of the tear film quality with appropriate objective tests, strabologic examination), radiological examination – roentgenography, CT, cranial MR imaging, as well as genetic analyses.

As far as the differential diagnosis issue is concerned, Apert syndrome (Eugene Apert, a French pediatrician, 1868-1940) is the most similar to Crouzon syndrome and characterised by isolated coronal synostosis (acrocephaly) and syndactyly on all limbs (1-4,7).

The CS treatment implies a multidisciplinary teamwork with the family of the affected, aiming at staging reconstruction to coincide with facial growth patterns, visceral function, and patient's psychosocial development. Satisfactory results may be reached by plastic surgery and CS is one of the few syndromes in which the cosmetic results of the surgery can be strikingly effective (2).

Multifactorial porsightedness caused by Crouzon syndrome makes CS specific and relevant to early diagnostics. Considering the fact that it represents a rarity, there is little information in reference literature about the prevalence of ophthalmic sequelae in patients with CS. According to the Australian Craniofacial Unit database, 70 people with CS were operated on in the period between 1984 and 2000. Among these patients, 35% had reduced monocular visual acuity, 9% had reduced binocular visual acuity, primarily owing to amblyopia (21% of patients) and optic atrophy (7% of patients). 77% of patients had ametropia, out of whom 57% patients suffered from hypermetropia and 20% from myopia. Manifest strabismus is present in child population aged between 4 to 10, and makes up 2.7% of patients, while in patients with CS, it accounted for 39% ($p < 0.001$); keratopathy was observed in 15% of cases (6). In the period between 1979 and 2000 Khan et al. (2003) examined 141 patients with craniosynostotic syndromes and 40.3% of patients had astigmatism (64% had oblique astigmatism in at least one eye); anisometropia was found in 18% of patients, while strabismus was found in 70% - 38% exotropia and 32% esotropia (5).

An early detection of Crouzon syndrome is a precondition for the reduction of amblyopia by means of refractive error correction and an appropriate treatment of strabismus, while optic nerve atrophy remained the main cause of the decrease of a patient's visual acuity prior to decompressive craniectomy.

Conclusion

The ophthalmological-radiological picture of a 10-year-old girl with Crouzon syndrome was

presented. Exophthalmos, hypertelorism, divergent strabismus, hypermetropia, amblyopia, megalocornea, skull deformities, the very illustrative orbits and jaw, usually rarely seen in everyday work,

are part of the clinical picture of this syndrome. Timely diagnostics of Crouzon syndrome contributes to the reduction of ophthalmic complications

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OFTALMOLOŠKO-RENDGENOLOŠKA SLIKA SYNDROMA CROUZON - PRIKAZ BOLESNIKA

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Sindrom Crouzon (CS) čini približno 4,8% svih kraniostenozaza. Sa prevalencom od 1 na 25000 rođenih širom sveta, nasleđuje se autozomno dominantno, a u 25% slučajeva nalaze se sveže mutacije. Nema predilekcije prema polu i rasi, varira u težini forme u kojoj se manifestuje od lakših sa diskretnim promenama na licu, do teških formi sa multiplo sraslim kranijalnim suturama i приметnim promenama na licu i očima.

Desetogodišnja devojčica, pod sumnjom na kongenitalni glaukom, poslata je na konsultativni pregled na Oftalmološku kliniku KC Niš. Već sam izgled devojčice upućuje na dijagnozu – Sindrom Crouzon, koja je potvrđena oftalmološkim i radiološkim sagledavanjem. Bolesnica je upućena nadležnom oftalmologu na dalje praćenje, uz preporuku za pokušaj operativnog lečenja od strane maksilofacijalnog hirurga.

Egzoftalmus, hipertelorizam, divergentni strabizam, hipermetropija, megalokornea, deformiteti glave, orbite i vilica vrlo ilustrativni, uglavnom ređe viđani u svakodnevnom radu, deo su kliničke slike sindroma Crouzon. Zavređuje našu pažnju, s obzirom na okularne komplikacije i multifaktorijalnu slabovidost koju sa sobom nosi *Acta Medica Mediana* 2009;48(2):37-40.

Ključne reči: Sy Crouzon, craniosinostosis, strabizam, slabovidost