# APERT SYNDROME WITH AGENESIS OF THE CORPUS COLLOSUM - CASE REPORT

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Received: 08.12.2019.
Accepted: 17.02.2020.

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DOI: 10.2478/sjecr-2020-0010

## ABSTRACT

*Apert syndrome (Acrocephalosyndactylia type 1) belongs to the group of extremely rare congenital dysmorphic syndromes. It is characterized by craniostenosis with very early fusion of the skull and / or cranial base sutures, facial hypoplasia, symmetrical syndactyly of the fingers and toes and other systemic malformations. Multiple CNS abnormalities are common, but simultaneous occurrence of Apert syndrome and agenesis of corpus callosum is estimated about 10%.*

*We present a male patient born after first, normal and controlled pregnancy and term, naturally birth, in which the Apert syndrome was diagnosed, based on the clinical presentation of the skull and face and syndactyly of fingers and toes. Neurological examination established generalized hypotonia and aggravated provocation of the primitive reflexes. Neurosonography showed complete agenesis of the corpus callosum, which makes this case a rare form of this syndrome. The head X-rays showed turricephalic skull shape and suture's synostoses, which is demonstrated in more detail at computed tomography finding. The hands and feet X-rays showed bone synostosis of fingers and toes. The video-electroencephalogram recorded intermittent depression of electrocortical activity. There was conducted the multidisciplinary examination in order to examine the possibility of reconstructive and plastic surgical correction of the anomalies.*

*The neurodevelopmental disorders in patients with Apert syndrome can be manifested by a variety of congenital malformations, but considering its rare occurrence, the significance of these abnormalities remains unknown.*

***Keywords***: *Acrocephalosyndactylia type 1, syndactylia, agenesis of corpus callosum.*

## INTRODUCTION

Apert syndrome (AS), called Acrocephalosyndactylia type 1, is a congenital complex dysmorphic syndromes with the cranio-mandibular-facial dysostosis and syndactyly of fingers and/or toes [1, 2]. AS is inherited as an autosomal dominant disorder, but most often manifested sporadically, indicating fresh mutations and/or environmental effects on the genome [3]. The syndrome is characterized by premature synostosis of the coronal suture in the first place, and then all the sutures with a protuberance of the skull towards the frontal fontanelle, where the skull becomes high and peaked [1, 2]. A typical facial appearance is tall and dominant forehead, flat back of the skull, shallow orbits, broadly spaced eyes, low-set ears, high-arched palate, irregularity in the dentition and mandibular prognathism. The syndactyly of fingers and/or toes is visible at the extremities (skin or skin-bone fusions) [4, 5]. The syndrome is accompanied with difficult or mild developmental delay [6-8].

A cerebral dysgenesis of various degrees is usually present. Main cerebral abnormalities are prominent convolutional markings, ventriculomegaly, crowded foramen magnum and more rarely deficient septum pellucidum and corpus callosum agenesis (ACC) [6, 8]. AS with complete ACC is extremely rare, and only a dozen of cases have been described so far [9-12].

Aetiology of the ACC is unknown. The agenesis can be partial, complete or atypical, isolated, syndromic and non-syndromic, it is significantly more common in male children, and often associated with abnormalities of the septum pellucidum. It is also described by other congenital malformations and found in people with mental health disorders, epilepsy, neurologic manifestations, visual impairment, although it may be asymptomatic or accompanied by minimal functional disorders [9-13].

The AS with or without ACC could be diagnosed prenatally using the fetal ultrasonography, nuclear magnetic resonance and amniocentesis in the early neonatal period. After birth the diagnosis is based on the typical clinical appearance documented by additional X-ray and CT diagnostics, while molecular genetic tests, unavailable and expensive in our country, confirm the diagnosis [14, 15]. Apert Syndrome has no specific treatment. Numerous non-surgical methods are used, surgical correction of abnormal connections between the bones of the skull, face and extremities, antibiotic therapy for frequent infections of the inner ear and sinus etc [16, 17].

## CASE REPORT

Male child, born after the first, normal, controlled and term pregnancy, with no history of the trauma, infection or drug use during the term, delivered naturally, with birth weight of 4310 g, birth body length of 60 cm and head circumference of 37 cm. The family does not have history of the hereditary diseases. Immediately after birth, the child transferred to the Center of Neonatology, Clinical Centre of Kragujevac due to suspicion of craniosynostosis.

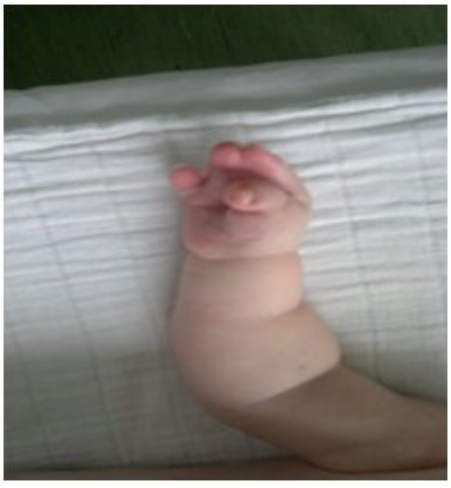
The newborn had normal vital functions and weak cry. Upon inspection, turricephalic head shape was determined. The palpation was used to determine that the frontal fontanelle was shifted forward, widely open and connected via expanded sagittal suture with posterior fontanelle, making improper formation of diameter 15x4 cm, above the level of the bony framework. The examination showed numerous malformations: hypertelorism, exophthalmos, high-arched palate, low-set ears, and short neck (Figure 1).

**Figure 1.**



The bilateral syndactyly on hands and feet was noticed (Figure 2). The neurological examination revealed a moderate generalized hypotonia, while primitive reflexes were harder to provoke. We suspected on the Apert syndrome because of the typical anomalies that were noticed, and detailed diagnostics had begun.

**Figure 2.**



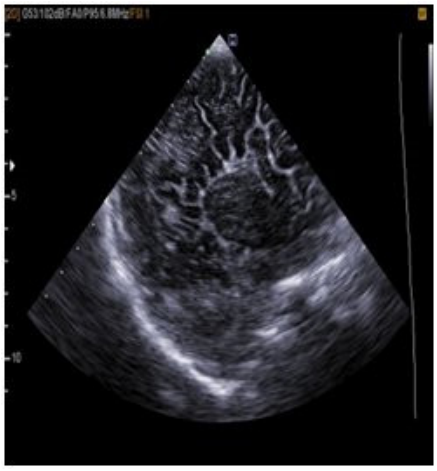
The transfontanelle neurosonography revealed the complete ACC. The coronal sections showed that the interhemispheric fissure was enlarged and it continued onto the third ventricle. The frontal horns of lateral ventricles were widely separated, because there was no corpus callosum above them, while the back parts of the lateral ventricles were grossly dilated (trigone, occipital and temporal horns) (Figure 3).

**Figure 3.**



The parasagittal scans showed a lack of the corpus callosum and pericallosal artery and radial (not parallel) propagation of sulci on the inner side of the hemispheres (Probst bundles) (Figure 4).

**Figure 4.**



The head X-rays showed the turricephalic shape of the skull and the synostoses of the sutures (Figure 5). The hands and feet X-rays showed the multiple bone synostosis of fingers and toes (Figure 6).

**Figure 5.**

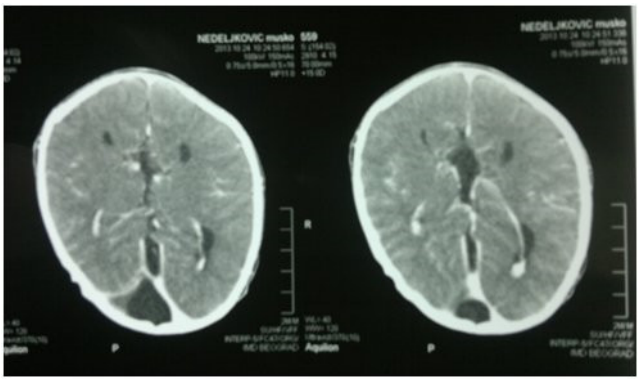


**Figure 6.**



The CT examination of the head (native, followed by IV administration of contrast media) showed parallel lateral ventricles, with emphasized dilatation of the occipital and temporal horns. The frontal horns are oriented upwards and give an image characteristic for the ACC. The third ventricle is elevated and dilated to 12 mm, normal appearance of the fourth ventricle. It was also observed mega cisterna magna (Figure 7).

**Figure 7.**



The multi slice CT (MSCT) with three dimensional reconstruction of the scull showed the asymmetrical turricephalic shaped skull, with a wide sagittal suture and open metopic suture as a result of coronal craniosynostosis and the bilateral exophthalmos (Figure 8).

**Figure 8.**




The video-electroencephalogram recorded intermittent depression of electrocortical activity. The karyotype was normal male, 46XY. The AS with ACC was diagnosed based on the clinical findings and examinations.

The additional tests were conducted for eventual reconstructive surgical corrections and plastic surgeries. The fiberoptic nasolaryngoscopy showed bilateral narrow nasal passages and choanae, with deformation of the septum. During the oropharyngoscopy it was determined laryngomalacia and elongated epiglottis. The genetic testing was not carried out due to poor cooperation from the parents (material costs).

At the age of 3 months, the child had normal vital functions and the basic laboratory analyses were within reference ranges. Due to anomalies, the child required regular aspiration of secretions from the upper respiratory tract, not dependent on oxygen therapy, without the apnea crises. He was transferred to the competent reception center at the age of 6 months (Figure 9).

**Figure 9.**



## DISCUSSION

The first clinical description of Apert syndrome dates from 1906, the work of the French physician Eugene Apert, who described 9 patients with similar abnormalities [4, 5]. Considering that the syndrome occurs sporadically, new mutations and/or the influences of environmental factors on genome blamed for its occurrence [3]. Prevalence is estimated at 1:64.500, which makes 3-4% of all craniosynostoses or 10-20% of syndromic craniosynostoses [2]. There is no difference in the occurrence of the syndrome in relation to sex [1]. The abortive cases show an autosomal dominant form, and the results in about 98% cases are point mutations of the fibroblast growth factor receptor 2 (FGFR2) gene, which is located on the long arm of chromosome 10, most commonly derived from the father, which explains the higher incidence in older fathers [1, 2]. The suture progenitor cells with mutated FGFR2 (different expression of mutations of the three isoforms) can not transduce signals from extracellular FGF, as a result they do not produce the fibrous material required for the normal calvarias sutures. There are mutation of the gene for FGFR2-isoforms for keratinocyte growth factor receptor, active in metaphysis and interphalangeal joints, FGFR1 in bone diaphysis, and FGFR2-Bek isoform in metaphysis, diaphysis and in interdigital joint syndactin. When gene mutations for FGFR2 are activating, FGFR2 loses its specificity, and so is activated by other FGF, causing increased osteoblast proliferation and differentiation and early fusion of multiple skull sutures, and other facial bone abnormalities. FGF also suppresses mesenchymal cell apoptosis, the interdigital mesenchyme is not resorbed, and that causing syndactyly [1, 2].

The karyotype is usually normal, or there are separate findings of deletions - translocation (from chromosome 2 to chromosome 11 or 12) [3].

The coronal suture is the most commonly first affected and after that all the sutures with a protuberance of the skull towards the frontal fontanelle, where the skull becomes high (acrocephaly), tower (turricephaly) or conical (oxycephaly) [1, 2]. In our patient the head shape was the closest form of towers. In addition, he had all the characteristic facial malformations and syndactyly of fingers and toes, so that diagnosis or at least suspicion of the diagnosis was not so difficult to set up quickly after birth. The diagnostic dilemma has been Crouzon syndrome, but according to the literature, Apert and Crouzon syndrome seem to be variant of the same syndrome, with the exception of the syndactyly of hands and feet in AS. Cleft or pseudo cleft palate is a frequent finding in Apert syndrome (our patient did not have them), whereas these traits are extremely rare in Crouzon syndrome [1].

On the other hand, the lack of corpus callosum leads to the clinical findings of hindered transfer of information from one to another side of cerebral cortex. The corpus callosum is the largest commissure of the brain and because it's specific structure and topographical organization, the lesions of some parts result in the predictable deficit in

interhemispheric transfer of information. This defect is described in the context of mental disorders, epileptic seizures, neurologic manifestations, optical damages, and may be asymptomatic or accompanied by minimal functional disorders, in which case it can be diagnosed accidentally [11, 13].

Etiology of the ACC remains unknown. It is linked to chromosome aberrations, infection, errors of metabolism and the influence of various harmful toxins (e.g. fetal alcohol, cigarettes and drugs exposure) from 12-22 week of gestation. The agenesis may be associated with other congenital malformations or syndromes (Down, Aicardi, Andermann, macrocephaly, arhinencephaly, lissencephaly etc), where a more severe psychomotor retardation and epileptic seizures are expected. Our patient has not expressed the loss of consciousness, but due to the possible occurrence of it, the electrophysiological monitoring must be regularly done. There are indications in the literature that epilepsy may occur in early childhood until the age of 3 years or later [11, 13].

Thanks to the early use of neurosonography, which is done as a screening in a maternity ward of Clinical Centre of Kragujevac, we diagnosed brain malformations in all neonates in the 2nd day of life, even when they were not symptomatic as well as the described defect in our patient. The ACC in combination with the AS is an extremely rare anomaly. Breik et al. found the prominent convolutional markings (67%) as most frequent CNS abnormality associated with Apert syndrome, after that ventriculomegaly (48%), crowded foramen magnum (36%), deficient septum pellucidum (13%), and ACC in only 11% [8]. There is described a familial occurrence of ACC, but it is not confirmed in our patient [11]. The course of pregnancy was completely normal, in family does not have heredodegenerative diseases, also father is in late twenty years (some authors indicated on paternal age effect [16]), so that we believe that our patient's anomalies are result of new mutations of the genome.

The recent neurobiological evidence have demonstrated that L1 cell adhesion molecule (L1CAM) gene plays a major role in the development of the white matter and its mutation in humans causes similar defects of the corpus callosum, septum pellucidum and cortico-spinal tracts. L1CAM need interactions with FGFR. It seems logical to assumes that the FGFR defects generate both the skull abnormalities and, by lack of interaction with L1CAM, the primary defect of the white matter. The mental deficiency that is common in these patients therefore is likely to be part of the disease, rather than a consequence of the skull size or of the associated hydrocephalus [3, 8].

The children with AS without visible cerebral malformations, if they survive early childhood, can have a normal life expectancy. That was achieved by a considerable improvement in quality of care for these children, and multidisciplinary approach of experts from different medical specialties (primarily reconstructive and plastic surgery). The main treatment is the surgical correction of abnormal connections between the bones of the skull, face and extremities, which is usually performed in 3 phases. The craniotomy is often performed during 6 months of age to treat the craniosynostosis. In the second phase the corrective surgery for syndactyly is done in first year of life and completed by 3 to 4 years of age. The cosmetic corrections for midface deficiency are at 4 to 6 years age. The treatment goals focused on the prevention of avoidable developmental delays (from raised intracranial pressure and sleep apnea) and reducing operative interventions may potentially improve developmental outcomes. Non-surgical methods are symptomatic measures that include: 1. Eye drops that prevent the mucous membrane of the conjunctiva from drying out, with incomplete closure of the eyelids. 2. Continuous positive airway pressure for present obstructive sleep apnea, possibly tracheostomy and intubation 3. Antibiotic therapy for frequent infections of the inner ear and sinus, with possible implantation of aeration tubes, etc [17].

The contribution of the family in order to achieve a better psychomotor development and quality of life is also significant. Some studies showed that grew up in a family environment increased the possibility of normal psychic development (normal IQ), as opposed to children who lived in residential institutions. Therefore, there is a wide variability in IQ of these children [7]. For now, it is not clear why mutation in the same gene can lead to such large variations [3, 8, 16]. Unfortunately, our patient has associated anomalies and psychomotor retardation, which will undoubtedly go to the progression, so the prognosis is very uncertain.

## CONCLUSION

We present the experience during the diagnosis and further treatment plan of a male infant with extremely rare Apert syndrome, especially associated with corpus callosum agenesis, which can be qualitative contribution to a broader knowledge of the issue. For now, there is no successful treatment of this disease, besides multidisciplinary approach. Severe psychomotor retardation is always present. It should be noted the important role of the fetal ultrasonography, magnetic resonance imaging and amniocentesis early in the prenatal period, and after birth, ultrasound, CT and MSCT, in order to establish an early diagnosis of the AS with or without associated anomalies. Certainly, the question remains of molecular genetic confirmation of the diagnosis, which, as in many other cases in our country, cannot be made, both because of its unavailability and the high cost of testing. The long term care of children with Apert syndrome as well as other dysmorphic syndromes that carry less or greater morbidity and require a great deal of commitment from both the family and the wider community remains an open question.

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