

## CASE REPORT

## Apert syndrome – clinical case

MIRELA ANIȘOARA SIMINEL<sup>1)</sup>, CRISTIAN OVIDIU NEAMȚU<sup>2)</sup>, DAMIAN DIȚESCU<sup>3)</sup>,  
 MIRCEA-CĂTĂLIN FORTOFOIU<sup>4)</sup>, ALEXANDRU-CRISTIAN COMĂNESCU<sup>5)</sup>, MARIUS-BOGDAN NOVAC<sup>6)</sup>,  
 SIMONA-DANIELA NEAMȚU<sup>7)</sup>, ADRIAN GLUHOVSCHI<sup>8)</sup>

<sup>1)</sup>Department of Neonatology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

<sup>2)</sup>Faculty of Chemistry, University of Craiova, Romania

<sup>3)</sup>Department of Obstetrics and Gynecology, "Constantin Brâncuși" University of Târgu Jiu, Romania

<sup>4)</sup>Department of Internal Medicine, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

<sup>5)</sup>Department of Obstetrics and Gynecology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

<sup>6)</sup>Department of Anesthesiology and Intensive Care, University of Medicine and Pharmacy of Craiova, Romania

<sup>7)</sup>Department of Hematology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania

<sup>8)</sup>Department of Obstetrics and Gynecology, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania

## Abstract

Apert syndrome – acrocephalosyndactyly – is a rare autosomal dominant disorder representing 1:65 000 cases of living newborns. Characteristic malformations of the Apert syndrome are early craniostenosis, microviscerocranium and II–V finger syndactyly of hand and toes with proximal phalanx of the bilateral thumb “in delta”. It is difficult to determine prenatal diagnosis in the second quarter, when examining the morphology of fetal signs; the dysmorphism signs appeared in the third pregnancy quarter. We present here the case of a newborn with Apert syndrome that was born prematurely in our Clinic after a monitored pregnancy, where there was issued a suspicion of cranio-facial dysmorphism, malposition and malformation of the feet and hands in the third quarter of prenatal pregnancy. The diagnosis of Apert syndrome was placed on clinical signs, laboratory and genetic tests. The clinical outcome of the baby in the maternity was favorable, the therapeutic management being established by a multidisciplinary team. Immediate complications were due to the case of prematurity: respiratory distress syndrome and the characteristics of the syndrome: micrognathia and naso-facial dysmorphism, syndactyly, bilateral foot metatarsus adductus.

**Keywords:** early craniostenosis, microviscerocranium, II–V fingers syndactyly.

## Introduction

Apert syndrome – acrocephalosyndactyly – is a rare autosomal dominant disease characterized by craniostenosis due the synostosis of the bilateral coronal suture, the hypoplasia in the middle of the viscerocranium, severe symmetrical syndactyly on both hands and feet. Over 98% of cases come from new mutations, the syndrome being the best described of all the craniostenoses.

With an incidence of 1:65 000 cases [1, 2] and 3% of all the craniostenoses [3], the syndrome affects boys and girls equally, with an Asian breed predisposition.

Mutations cause is exclusively of paternal origin [4, 5] and it is represented by two amino acid mutations in exon 7 of the protein receptor 2 of the growth hormone – fibroblast growth factor (FGFR2) and c.755>G resulting the mutation p.Ser252Trp and c.758>G resulting p.Pro 253Arg [6–8]. The growth and development of these children in the first years of life is linear and enrolls between 5% and 50% percentile, resulting in short stature with short upper limbs and short lower limbs [9, 10].

We present the clinical case of a newborn with Apert syndrome not diagnosed before birth and with a suspicion of facial dysmorphism and limbs modifications after the fetal morphology was examined by an echography.

## Case presentation

We present the clinical case of a newborn with Apert syndrome arising from a monitored pregnancy, as the first child.

From the anamnesis, we know the parents are without suggestive changes of Apert syndrome, positively healthy without significant family history. When examining the fetal morphology, we observed a facial dysmorphisms, with the protrusion of the eyeballs, a short nose and wide basis clogged, a wide metopical suture, bilateral hallux position and bilateral thumb and congenital bilaterality foot position, reasons for us to guide the case to the laboratory of human genetics.

Pregnancy progresses to the third quarter and before the genetic consultation the premature birth of a baby boy occurs, at a gestational age (GA) of 35–36 weeks, with 2900 g weight, extracted by Cesarean section with cranial presentation, indicated for the beginning of fetal suffering with APGAR score 8.

At birth, we have a boy with facial dysmorphism, limb malformations: II–V toes and fingers syndactyly that develops respiratory distress syndrome in the first minutes after birth, reasons to guide him to neonatal intensive care.

Clinically, the infant shows: flattened antero-posterior head, flat occiput with wide and prominent forehead, and wide-opened metopic suture, bilateral coronal suture craniostenosis, the anterior fontanelle is large and wide, protrusion of the eyeballs, hypertelorism, oblique slot eyelid, short nose and wide base clogged with stenosis;



**Figure 1 – Flattened antero-posterior head.**

the oral cavity has a trapezoidal form, the hypoplasia of the middle of the mouth (Figures 1 and 2); mimic cleft palate but piece rates palace image given by two sides swellings of the palate, II–V fingers and toes syndactyly hand and feet, and proximal phalanx police and hallux shaped as “delta” (Figures 3 and 4).



**Figure 2 – Facial dysmorphism.**



**Figure 3 – II–V toes syndactyly.**



**Figure 4 – II–V fingers syndactyly.**

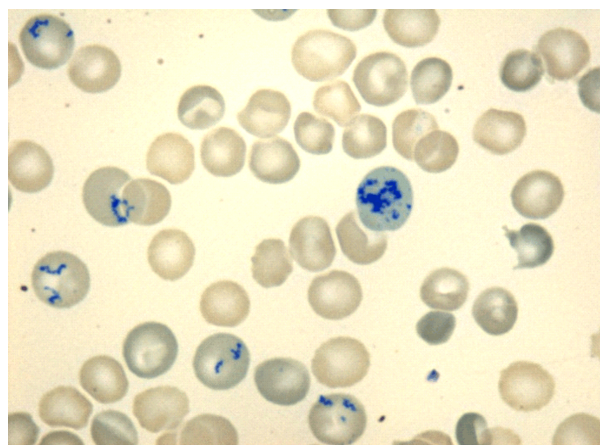
Five minutes after birth, the groaning expiratory appears, thorax with clogging sternum, subcostal movements and thoraco-abdominal balance suggestive for respiratory distress syndrome in the context of prematurity (premature later), for which we begin initial non-invasive nasal continuous positive airway pressure (NCPAP) ventilation that was ineffective due to deformed nostrils with obstructive effect and to choanal stenosis, reasons why it is given oxygen through the Venturi mask.

Paraclinically, the infant shows a slight anemia and mild respiratory acidosis (Table 1; Figure 5).

The transfontanelar ultrasonography test in the third day of life reveals a post-hemorrhagic cyst of 0.89 cm in the anterior horn of the left ventricle, discrete hypoplasia in the posterior septum pellucidum (Figures 6 and 7).

Echocardiography and cardiology exam did not show any malformation. Abdominal and renal ultrasound were normal.

Head radiography revealed bone changes in the skull: bilateral coronal suture craniostenosis, orbits in the form of a drop, maxillary hypoplasia.



**Figure 5 – Reticulocytosis. Brilliant cresyl blue staining,  $\times 1000$ .**

Hands radiography revealed full syndactyly to II–V fingers, short distal phalanx and diverted bilateral radial and proximal phalanx of the thumb in a distorted “delta” form.

Feet radiography revealed complete syndactyly of the



II–V fingers “sock” foot form together with the fusion of the tars, metatars and interphalanx joints and bones, proximal phalanx of the hallux delta distorted.

The karyotype examined by the GTG (G-banding using Trypsin and Giemsa) technique revealed a normal karyotype (46,XY), in the metaphases examined there were not observed chromosomes abnormalities concerning the form and the structure.

Two days after birth, the distress syndrome improves and intense jaundice appears with high bilirubin values with reticulocytosis (Table 1), which responds well to treatment with phototherapy.

The clinical outcome of the newborn is favorable and it includes the remission of the neonatal distress syndrome, with transient tachypnea of the newborn, the jaundice resolves, the weight curve is upward and the child is fed by bottle, two weeks after birth it meets the discharge criteria and leaves the hospital.

## Discussion

The Apert syndrome is caused by two gene mutations in tyrosine kinase receptor 2 (FGFR2) – Ser252Trp and Pro253Arg located on chromosome 10q26 and by the effect of the keratinocyte growth factor receptor (KGFR) fact that was noticed from the correlation between the KGFR expression in fibroblasts and the syndactyly severity.

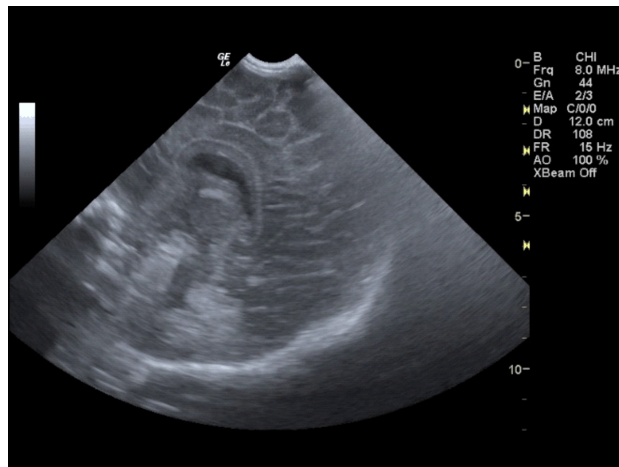


Figure 6 – Septum pellucidum hypoplasia.

The FGFR2 functions are the stimulation of the embryonic functions: mesoderm induction, anterior–posterior advancing, developing limb ossification, neural induction, development and of the neural tube and tissue maturation: angiogenesis, organization of keratinocytes, the healing of wounds [11, 12]. At the molecular level, increases the affinity for ligand and decreases binding specificity of the ligand. Patients with Pro253Arg mutation show predominant severe syndactyly, unlike those with the mutation Ser252Trp where the eye changes prevail [13].

In our case, syndactyly was evidenced bilateral, both in hand and foot, being correlated with the presence of the mutation Pro253Arg, namely the proline replacement with arginine. The protein signal is amplified and causes rapid bone fusing.

FGFR2 sends signals to undifferentiated cells to turn into bone cells or other areas cells causing early skull ossification.

Table 1 – The laboratory investigations

Parameter	Result	Biological reference values
Blood smear	Erythrocyte anisocytosis, macrocytic polychromatophils	May–Grünwald–Giemsa staining: normocytes
Leukocytes	$10.17 \times 10^3/\text{mm}^3$	$5-9 \times 10^3/\text{mm}^3$
Erythrocytes	$3.65 \times 10^6/\text{mm}^3$	$4-5.5 \times 10^6/\text{mm}^3$
Hemoglobin	14.4 g/dL	14.5–19 g/dL
Hematocrit	41.5%	42–54%
MCV	113.7 fL	88–95 fL
MCH	39.5 pg	28–32 pg
MCHC	34.7 g/dL	32–36 g/dL
Platelets	288	150–400
Lymphocytes	33.6%	20–40%
Monocytes	9.6%	0–8%
Neutrophils	55.3%	50–75%
Eosinophils	1.1%	0–3%
PDW	11 fL	11–16 fL
MPV	10 fL	7.4–10.4 fL
Total bilirubin	22.8 mg/dL	0.4–1.2 mg/dL
Direct bilirubin	1.2 mg/dL	0.2–0.4 mg/dL
Reticulocytes	9%	0.5–2%

MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; PDW: Platelet distribution width; MPV: Mean platelet volume.

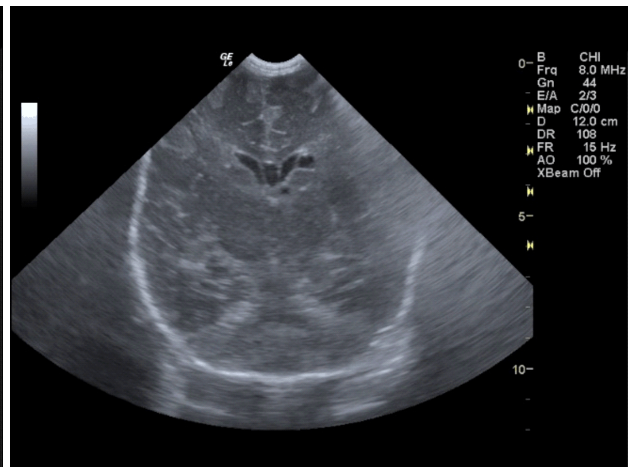


Figure 7 – Post-hemorrhagic cyst in left ventricle.

Genetic counseling shows that there is a 50% risk for Apert syndrome if it was determined at a previous abortion or if a parent is affected, the advanced age of the father was incriminated in causing mutation *de novo* [5]. In our case, the paternal age was not known so it cannot be incriminated as a determining factor [14].

The prenatal diagnosis is difficult to the new mutations characteristic changes not being able to be routinely determined in the second quarter but sporadically and could be highlighted only in the third quarter [7, 15]. By using some clues given by three-dimensional (3D) ultrasound, as there are the premature closure of the coronal suture, the wide metopic suture, limb and facial abnormalities can help in preparing the genetic counseling and in further investigation by molecular genetic after amniocentesis.

In our case, amniocentesis has not been performed anymore, the pregnancy being in evolution in the third

quarter, triggering the mechanisms of fetal distress and giving birth mechanisms.

The whole evolution of the child in hospital was overseen by a multidisciplinary team of neonatal pediatric surgery, pediatric cardiology, ophthalmology, otorhinolaryngology, kinesiology, neuro-pediatric surgery, pediatric neurology, imaging, laboratory, genetics, in order to establish the diagnosis of certainty and the therapeutic management.

The prognosis depends on the age when craniostenosis is surgically performed, the first intervention occurs earlier than three months.

The surgical management consists of: coronal suture release of the infancy period to the completion of the brain development, cosmetic facial reconstruction for dysmorphism, exophthalmia correction between 6–11 years, surgical separation of the fingers providing a very small improvement in functional terms [16]. Psychological tacking of child and family is part of the integrated management plan in Apert syndrome. Orthodontic reconstruction and all the submitted surgical procedures are aimed to built his self-esteem and confidence and to integrate the person in the society.

## ✉ Conclusions

In our case, the Apert syndrome was diagnosed post-natally based on clinical genetic and imaging examination. The determining factor was the FGFR2 gene mutation – the substitution of proline with arginine in sequence of Pro253Arg. The therapeutic management was a multidisciplinary one. It is a rare disorder, but with severe effects in terms of social and psychomotor development of the child. The prenatal diagnosis and the genetic counseling are recommended in choosing a responsible management of the Apert syndrome cases.

## Conflict of interests

The authors declare that they have no conflict of interests.

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## Corresponding author

Simona-Daniela Neamțu, Lecturer, MD, PhD, Department of Hematology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Clinical Laboratory, "Filantropia" Municipal Hospital, 3 Constantin Brâncuși Street, 200136 Craiova, Romania; Phone +40745–574 308, e-mail: simona\_0712@yahoo.com

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