A NEW SYNDROME: MULTIPLE CONGENITAL ABNORMALITIES AND MENTAL RETARDATION IN TWO BROTHERS

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Summary: A new syndrome: multiple congenital abnormalities and mental retardation in two brothers: In this report we present two brothers with abnormal neurological development, hypotonia, short stature, pylorus stenosis, pectus excavatum, brachycephaly due to craniosynostosis, frontal bossing, depressed nasal bridge, high arched-wide palate, downslant palpebral fissures, low-set, large ears, thin upper lip and bilateral cryptorchidism. The brothers were born to a couple of second cousins and were the third and fourth pregnancies of the mother. The father, the mother and the eldest sibling were phenotypically and chromosomally normal. The clinical findings of the brothers were found to be similar. These clinical findings were compared with syndromes showing some of the symptoms, namely Apert, FG, Floating-Harbor, Shprintzen-Goldberg and Rett Syndromes. However, when the findings were detailed, we observed that they did not match completely any of the syndromes in a discernable way. The MECP2 gene mutation was analysed because of mental retardation, poor neurological evolution and large ears, but no mutation was found. So these cases are presented as a new syndrome with apparent autosomal recessive inheritance.

Key-words: New Syndrome – Multiple congenital abnormalities – Short stature – Hypotonia – Mental Retardation – Craniosynostosis.

CASE REPORT

The two-years-and-four-months old male child (Patient 1), who was (provisionally) diagnosed with pylorus stenosis, thalassemia intermedia, syndromic disorder, was the second living child born to the mother on her third pregnancy. The woman was married to a second cousin. The parents and the 6-year-old sister did not have any phenotypical abnormalities. The child was born at term by C-section delivery and weighed 3,100 g, stayed at the new-born unit for two days due to hypoglycemia, and underwent surgery for pylorus stenosis when he was one month old. He was diagnosed with thalassemia intermedia at seven months. The mother was a carrier of thalassemia.

The physical examination findings were: height 82 cm, weight 6.8 kg, occipitofrontal circumference 43.5 cm. All these measurements were under the 3rd percentile. The boy was diagnosed with low-set and large ears, thin upper lip, high arched-wide palate, crooked nose, brachy-
cephaly due to atypical craniosynostosis, pectus excavatum, bilateral cryptorchidism, micropenis, deformities of the toenails (Fig 1).

Neurological examination revealed hypotonia and loss of deep tendon reflexes, but no pathological reflexes. The patient was not able to walk, nor was able to sit without support. Ultrasound examination showed bilateral cryptorchidism and mild pelvi-calyceal ectasia. The Denver Developmental Screening Test scored 1-2 months. The Evoked Responsible Audiometry showed bilateral hearing loss. The patient’s urine and blood amino acids were normal. The Cranial CT showed craniosynostosis. Chromosomal analysis revealed 46, XY normal male karyotype.

His younger brother (Patient 2) was seen at our department in 2009 at the age of two years, and was diagnosed with symptoms such as inability to walk, inability to hold the head straight, mental and developmental retardation. During this consultation, we also found out that Patient 1 had died at the age of 4 years. Because the medical history report was not detailed, we were not able to determine the cause of
death of the older brother (Patient 1). Both brothers presented a similar clinical history. Patient 2 was born at term by C-Section delivery and weighed 3800 g. Following birth, he stayed at the hospital for twenty days due to the RDS diagnosis. He was operated at age one-month for pyloric stenosis, and at age six-months, for inguinal hernia and bilateral cryptorchidism. On the physical examination he was diagnosed with low-set, large ears, thin upper lip, high-arched, wide palate, brachycephaly due to atypical craniosynostosis, mid-facial hypoplasia, sparse eyebrows, pectus excavatum, and atypical simian line on the right hand (Fig. 2). On neurological examination, we found hypotonia and loss in deep tendon reflexes, but no pathological reflexes. He was not able to walk, nor was he able to sit without support. The EEG reported irregularities in the base rhythm, and sharp wave activities in both temporo-occipital lobes, whereas the Cranial MR imaging showed an increased occipito-frontal diameter, coronal-lambdoidal synostosis, larger than normal lateral ventricles, and dilatation in bilateral anterior temporal areas at the peripheral BOS distances. The Denver Developmental Screening Test score was at 4-5 months. Echocardiography was normal. Chromosomal analysis showed 46, XY normal male karyotype. Some of the

Figure 2: Patient 2 with a) dysplastic ears, thin lips, sparse eyebrows, upslant palpebral fissures; b) micrognatia, dysplastic ears, flat occiput, brachycephaly; c) pectus excavatus, increased internipple distance
findings including large ears, poor neurological evolution, and mental retardation overlapped with Rett Syndrome. No MECP2 duplication nor mutation was found at MECP2 sequencing (exon 1, 2, 3 and coding region of exon 4) and quantitative analysis by MLPA. Also the parents’ and the sister’s karyotyping and mutation analyses were found to be normal.

**DISCUSSION**

The similar findings between the two brothers were as follows: developmental and mental retardation, hypotonia, brachycephaly with craniosynostosis, pyloric stenosis, bilateral cryptorchidism, low-set and large ears, high-arched wide palate, pectus excavatum, thalassemia intermedia, inability to hold the head straight, inability to sit. These findings led us to think that both brothers might have Apert syndrome, which is characterized by autosomal dominant inheritance, brachycephaly due to craniosynostosis, mid-facial hypoplasia, cutaneous and progressive bone syndactyly that can be observed in both hands and feet (9). Apert syndrome is one of the most serious craniosynostosis syndromes. Fifty percent of the patients have mental retardation (7). Neuropathological studies have also demonstrated that cases might have polymicrogyri, hypoplastic white matter, gray matter heterotopy, corpus callosum agenesis, septum pellucidum abnormalities (1). Moreover, all cranial sutures are abnormal at birth.

The findings in the present male siblings that do not match Apert syndrome are as follows: absence of syndactyly, cardiovascular pathologies, skeletal deformities, and central nervous system pathologies. Moreover, most of the findings did not dysmorphically match with Apert syndrome.

FG Syndrome is a rare syndrome also known as Opitz and Kaveggia Syndrome (OKS), which is characterized by mid-line defects, anal and GIS defects, hypertelorism, developmental and mental retardation and inherited as X-linked recessively. Among the clinical findings of FG are: macrocephaly, anal stenosis, constipation, Hirschprung disease, severe mental retardation, corpus callosum agenesis, frontal cowlick, high-frontal hairline, frontal bossing, dysplastic ears, low-set and small ears, sensorineural deafness, hypertelorism, macrocornea, small mandible, prominent lower lip, delayed speech, sacral dimple, congenital heart defects, inguinal hernia, pylorus stenosis, abnormal GIS motilities, broad thumbs, cryptorchidism, joint contractures, hypotonia, craniosynostosis, hydrocephaly, and wide ventricles (8, 11). The findings in our patients that match FG Syndrome are: hypotonia, mental retar-
craniosynostosis, frontal cowlick, dysplastic ears, micrognatia, sensorineural deafness, cryptorchidism. However, corpus callosum agenesis, macrocephalia, anal stenosis, severe constipation, Hirschprung disease or gastrointestinal system motility disorder, joint contractures, cardiac malformations were not observed in our patients. These brothers also bring to mind the Floating Harbor Syndrome (FHS). Our patients were diagnosed with short stature, developmental delay, triangular face, thin lips, joint hyperlaxity (4, 5). These findings match those of FHS. However, the motor development that we expect to be generally normal in FHS was extremely delayed in both patients. Besides that, there were a number of additional findings such as pyloric stenosis, craniosynostosis, chest deformities, cryptorchidism, and sensorineural hearing loss.

Shprintzen-Goldberg Syndrome is one of craniosynostosis syndromes. Although there are similar findings such as craniosynostosis, hypotonia, developmental retardation, chest deformity, pyloric stenosis, cryptorchidism, the absence of the following dysmorphic findings eliminated the possibility of SGS in our patients: severe exophthalmos, marfanoid habitus, finger abnormalities, skeletal deformities, soft-tissue hypertrophy, and cardiac pathology (10).

Rett Syndrome (RTT) is a rare, progressive neuro-developmental disorder with X-linked dominant inheritance and causes progressive severe mental retardation (6). Classical RTT cases are sporadic and are caused by mutations in the Methyl-CpG-binding protein-2 (MECP2) gene located at Xq28 (12). Mutations and duplications in MECP2 cause multiple neuro-developmental disorders including mental retardation, severe neonatal encephalopathy, and autism (2, 3). MECP2 consists of four exons with two isoforms and encodes a protein of 486 aminoacids. The sequencing analysis of exon 1,2,3, the coding region of exon 4, and quantitative analysis by MLPA of MECP2 were done. No mutations were found in the analysed region.

In conclusion, we were not able to diagnose our patients as presenting with any of the existing, known syndromes clinically, neurologically, or by molecular study. The patients most likely represent a distinct condition caused by an autosomal recessive gene defect. The increase in the incidence of autosomal recessive diseases in countries like Turkey where consanguineous marriages are common is noteworthy.
REFERENCES


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