Cerebro-oculo-facio-skeletal syndrome: report of two cases from Turkey with postmortem findings

C. Nur Semerci[1], Neşe Onat[2], Sevil Günçe[3], Nihal Demirel[4], Murat Becer[5] Yankı Yılmazer[6], İzlem Öznur[7], Canan Türkyılmaz[4], Sevim Balcı[8]

Departments of [1]Genetics, [2]Pediatrics, [3]Pathology, and [6]Radiology, Zübeyde Hanım Maternity Hospital, Departments of [4]Neonatology, and [5]Pathology, Dr. Sami Ulus Children's Health and Disease Hospital, [7]Med-Mar Imaging Center, and [8]Genetics Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

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We describe two cases of COFS (cerebro-oculo-facio-skeletal) syndrome in two newborn females of consanguineous parents. The clinical, radiological and pathological features of the patients are presented. One of the two cases had 11 pairs of ribs (Case 1) and the other had three-lobed left lung (Case 2), neither of which has been described in COFS syndrome previously . To our knowledge, these are the first reported cases of COFS syndrome from Turkey.

Key words: cerebro-oculo-facio-skeletal syndrome, microcephaly, contractures of the extremities.

Cerebro-oculo-facio-skeletal (COFS) syndrome, or Pena-Shokeir syndrome type II, was first described by Pena and Shokeir[1] in 1974. COFS syndrome is an autosomal recessive disorder characterized by hypotonia, microcephaly, microphthalmia, cataracts, blepharophimosis, large auricles, prominence of the nasal bridge, micrognathia, widely set nipples, camptodactyly, flexion contractures on the elbows and knees, generalized osteoporosis, dysplastic acetabula, coxa valga and rocker-bottom feet[1-3]. We report the clinical and postmortem findings of two newborn girls with COFS syndrome having some new abnormalities in addition to the ones reported previously.

Case Report

Case 1

A female infant was born at 38 weeks of gestation by cesarean section because of transverse position. Unfortunately her mother had never admitted to hospital for obstetric examination during pregnancy. The mother (36 years old) and the father (42 years old) were first cousins. The previous obstetric history included four surviving children, a premature delivery who had died at 18 days and two induced abortions.

Birth weight was 2,200 g (<10th percentile), length was 43 cm (<10th percentile), Clinical examination showed bilateral microphthalmia, nystagmus, blepharophimosis, prominent nasal bridge, high and narrow palate, micrognathia, overhanging upper lip, low set and large auricles, hirsutism, short neck, camptodactyly, flexion contractures of the lower limbs, and rocker-bottom feet (Fig. 1). Laboratory tests showed normal levels of serum biochemical values, and karyotype was 46, XX. Radiological findings included eleven ribs, bilaterally flexion contractures of the proximal interphalangeal joints bilaterally, ulnar deviation of the hands (Fig. 2), and congenital vertical talus deformity of the foot (rocker-bottom feet) bilaterally (Fig. 3). The patient died at the 8th day of age exhibiting feeding and breathing difficulties. Before the postmortem examination, brain magnetic resonance imaging (MR) was performed, which demonstrated overall decrease in white matter of both cerebral hemispheres, marked dilatation of the left and slight dilatation of the right lateral ventricle, and choroid plexus hemorrhage in both lateral ventricles (Fig. 4). The genu of corpus callosum was present; however, its body and splenium could not be demonstrated.

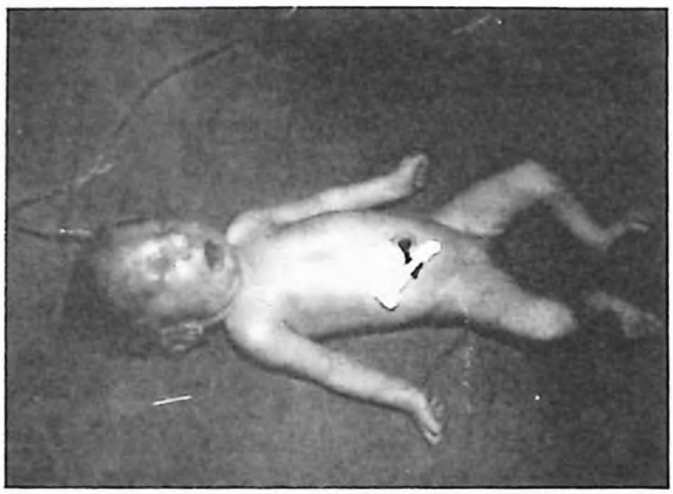

Fig. 1. General apearance of Case 1.

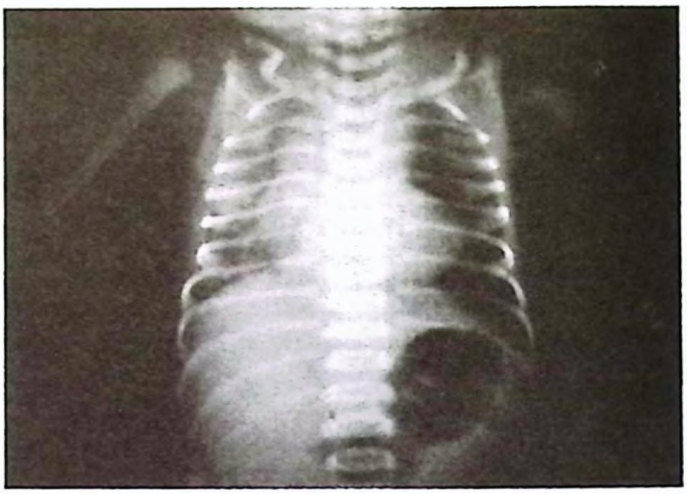

Fig. 2. X-ray: eleven pairs of ribs and ulnar deviation of the hands (Case 1).

Fig. 3. X-ray: dorsoflexion of the hands and camptodactyly, flexion contractures of the lower limbs, and vertical talus deformity (Case 1).

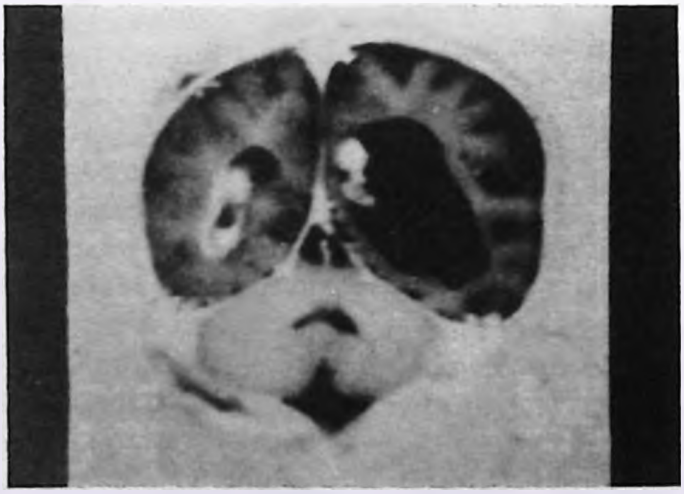

Fig. 4. Cranial MRI showing marked dilatation of left lateral ventricle and choroid plexus hemorrhage in both ventricles. White matter is decreased on both sides (Note. The superior sagittal sinus is hyperintense due to postmortem imaging) (Case 1).

Autopsy findings showed craniosynostosis, decrease in white matter of cerebral hemispheres, choroids plexus hemorrhage in both ventricles and pneumonia.

Case 2

Our second case was a four-day-old female infant. She had a healthy male sib. Her female sib, who had died at two days of age, had the same phenotype as the patient. The mother (25 years old) and the father (35 years old) were first cousins. Before delivery, ventriculomegaly, rocker-bottom feet and polyhydramnios were detected at 22 weeks of gestation by ultrasonography, but the parents did not accept to terminate this pregnancy. At birth, weight was 2,100 g (<10th percentile), length was 45 cm (<10th percentile) and head circumference was 31 cm (<10th percentile). Physical examination revealed microcephaly, micrognathia, prominent and large nasal bridge, low-set ears, overhanging upper lip, hairy frontal region, widely set nipples and camptodactyly (Fig. 5). The hips and knees showed severe flexion contractures. There was bilateral talipes equinovarus deformity (Fig. 6). Neurological examination revealed generalized mild hypotonia. Chromosome analysis revealed 46, XX, inv (9) (p11;q13). She had difficulty in breathing and feeding as in the first case, and died at the 9th day of life.

At autopsy, ventriculomegaly and a three-lobed left lung were found. On microscopic examination there were generalized gliosis and congestion in the brain and bronchopneumonia.

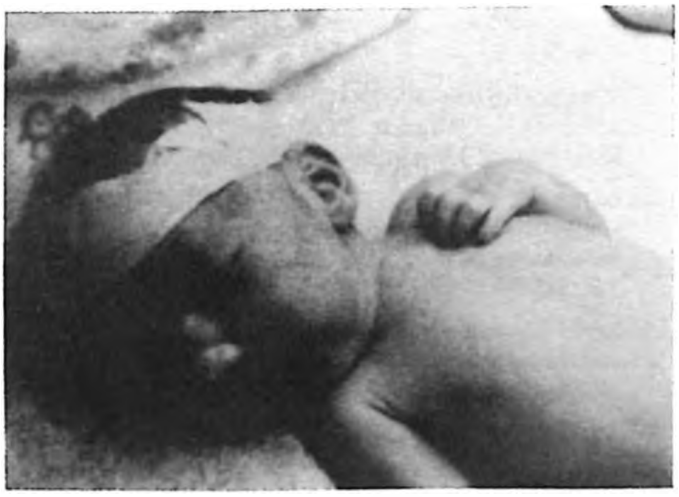

Fig. 5. Note prominent and large nasal bridge, micrognathia, widely set nipples and camptodactyly (Case 2).

Fig. 6. Flexion contractures of the lower limbs and talipes equinovarus deformity are seen (Case 2).

Discussion

Cerebro-oculo-facio-skeletal syndrome was first described by Pena and Shokeir[1] in 1974. This syndrome is caharcterized by neurogenic arthrogryposis, microcephaly, microphthalmia, cataracts, prominent root of nose, overlapping upper lip, rocker-bottom feet, hirsutism, camptodactyly, osteoporosis and osteopetrosis[1-3]. The diagnosis of COFS syndrome is difficult because it is variable even within a family and has many variants. The mode of inheritence of this rare syndrome is autosomal recessive, but X-linked recessive form may also present[4-7]. While our patients had the most characteristic features of this syndrome, Case 1 also had eleven pairs of ribs and Case 2 a three-lobed left lung.

In COFS syndrome, may skeletal anomalies are observed, such as camptodactyly, limb contractures, rocker-bottom feet, kyphoscoliosis, longitudinal foot groove, hip dysplasia, craniosynostosis, osteoporosis and osteopetrosis[1-3,8]. The 11 pairs of ribs found in Case 1 had previously been reported in trisomy 18, trisomy 21, femoral hypoplasia-unusual facies syndrome, Ritscher-Schinzel syndrome, spondylocostal dysostoses, and cerebro-costo-mandibular syndrome[9-10], but never in association with COFS syndrome.

Postmortem examination of Case 2 showed bilateral three-lobed lungs. Abnormalities of lung lobation have been reported in asplenia/polysplenia syndrome[11] but not in COFS syndrome previously.

Other important findings in COFS syndrome are those related to the central nervous system. These are microcephaly, callosal agenesis,

polymicrogyria, neuronal heterotopia, white matter hypoplasia, optic tract abnormalities, small pons, reduced myelination and hypoplastic dentate nucleus[1,2,8,12-16]. In our cases, microcephaly, partial agenesis of corpus callosum, white matter hypoplasia and ventriculomegaly were present.

Pulmonary infections and degenerative changes of spinal cord are the main causes of death in children with COFS syndrome as in the presented cases[17]. However, the etiology of COFS syndrome has not been clearly understood. Temtamy et al.[18] described an Egyptian girl with phenotypic abnormalities of COFS syndrome who had balanced translocation of 46, XX,t (1;16) (q23;q13) in all cells, and thus suggested that the gene for COFS syndrome may be located on chromosome 1q23 or 16q13. We described heterozygous pericentric inversion of chromosome 9 in Case 2. Pericentric inversion of chromosome 9 is a commonly observed structural variation in many healthy people[19]. At the same time, this inversion has also been reported in some patients with different phenotype and ophthalmological abnormalities, mental retardation, psychiatric problems and schizophrenia. Recently, Baltacı et al.[20] reported homozygous pericentric inversion 9 in a case with Walker-Warburg syndrome. They reported that further observations were needed in order to explain the causal association of these two conditions.

Patton et al.[21] and later Hamel et al.[22] noticed for the first time that there are some phenotypic similarities between early-onset Cockayne's (CS) syndrome and COFS syndrome. Recent molecular studies by Meira et al.[23] in COFS syndrome demonstrated a mutation identical to the one detected in Cockayne's syndrome group B (CSB). They suggested that COFS syndrome and CS might share a common pathogenesis.

Well known clinical findings of COFS syndrome can facilitate early prenatal diagnosis. Paladini et al.[24] were the first to prenatally diagnose a case of COFS syndrome, at 21 weeks of gestational age by ultrasonography. They demonstrated that the fetus had micrognathia, multiple joint contractures and rocker-bottom feet. The diagnosis was also confirmed on the basis of postmortem findings after termination of the pregnancy. In our second case, ventriculomegaly and rocker-bottom feet were prenatally diagnosed by ultrasonography at 22 weeks of gestation, but the parents refused termination of the pregnancy.

In conclusion, this report presents the first two cases of COFS syndrome from Turkey. The eleven pairs of ribs and three-lobed lungs have not previously been described in this syndrome.

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