A TURKISH FAMILY WITH GREIG CEPHALOPOLYSYNDACTYLY SYNDROME*

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Greig cephalopolysyndactyly syndrome is a very rare autosomal dominant disease characterized by postaxial polysyndactyly of hands, preaxial polysyndactyly of feet and peculiar facial features, and has been shown to be due to mutations in the GLI3 gene. We present clinical findings of a 39-year-old man and his nine-day-old daughter with Greig cephalopolysyndactyly who showed variable expression with regard to syndactyly of fingers and toes. The role of obstetric ultrasonography in the prenatal diagnosis of the syndrome is also dicussed. *Key words: polydactyly, syndactyly, macrocephly, prenatal diagnosis.*

Greig cephalopolysyndactyly (GCPS) is a very rare autosomal dominant syndrome which is characterized by peculiar skull shape and postaxial (occasionally preaxial) polydactyly of hands, preaxial polydactyly of feet and syndactyly of toes and fingers[1,2]. Only a few dozen cases have been reported and, as far as we know, no case with GCPS syndrome has been published previously from Turkey.

We report a 39-year-old man and his nine-day-old daughter with GCPS syndrome. Interestingly, prenatal ultrasonographic examination showed the enlargement of the lateral ventricles in the fetus at the 28th week of gestation. However, since the father was not diagnosed prior to the pregnancy, this observation did not lead to a prenatal diagnosis of GCPS. If the father's illness had been recognized, it would have been possible to conclude that the fetus was affected with GCPS syndrome.

Case Reports

Case 1

This nine-day-old female patient was the second child of a non-consanguineous couple. The first child was a five-year-old healthy boy. The patient was referred to the Clinical Genetics Department soon after birth with complex polysyndactyly of the hands and feet. Enlargement of the lateral ventricles was observed at the 28th week of gestation by obstetric ultrasonography. The birth was at the 40th week by cesarean section. Her weight at birth was 4000 g (90-97th percentile), length 52 cm (90th percentile) and head circumference 39.2 cm (> 97th percentile).

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Family history revealed that the mother had been epileptic since five years of age and was treated with carbamazepine during pregnancy. We learned that the father had similar hand, foot and facial features of the baby.

On physical examination, the striking feature of the baby was the complex polysyndactyly of hands and feet. She also had a peculiar facial appearance characterized by a high forehead, broad nasal root and midly downslanting palpebral fissures (Fig. 1). The anterior fontanel was 6 x 6 cm. On both hands, thumbs were duplicated and postaxial polydactyly with complete syndactyly between second, third and fourth fingers was also noted (Fig. 2). On both feet there was preaxial polydactyly and both halluces were broad. There was complete cutaneous syndactyly between the hallux and second and third toes (Fig. 3).

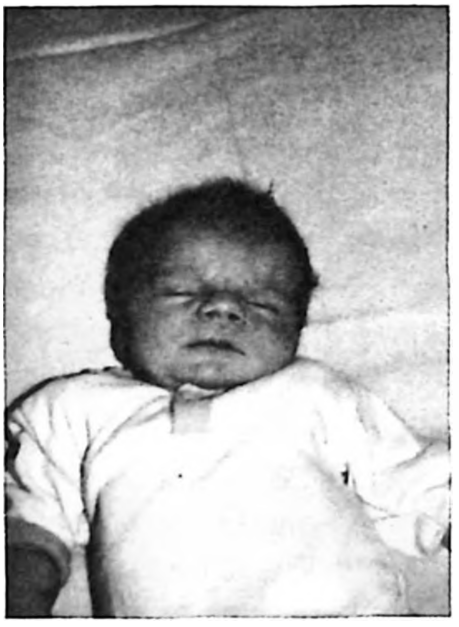


Fig. 1: Facial appearance of Case 1. Note prominent frontal region, hypertelorism and downslanting palpebral fissures.

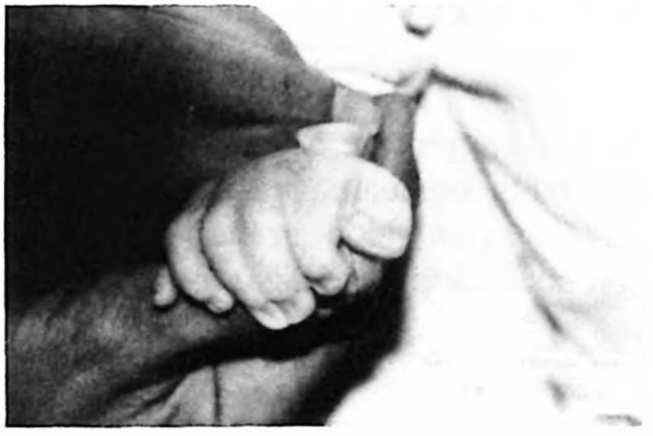


Fig. 2: Right hand of Case 1. Note bifid thumb, postaxial polydactyly and syndactyly betwen the second, third and fourth fingers.

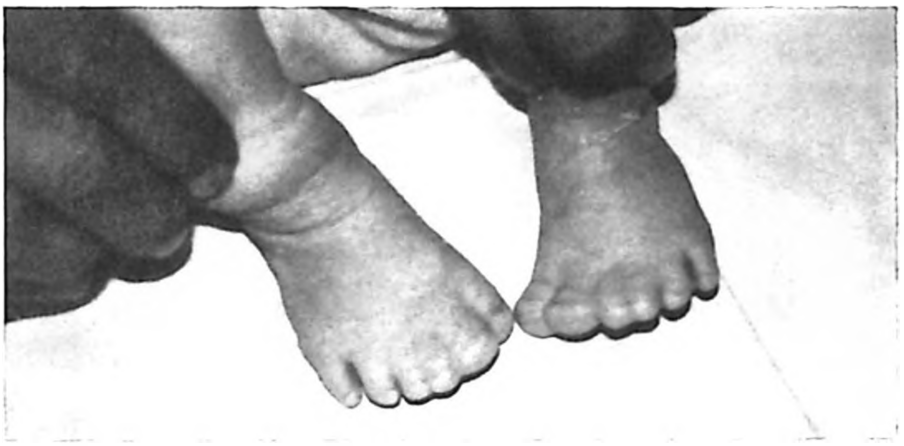


Fig. 3: Feet of Case 1. Note preaxial polydactyly on both feet. Halluces are broad and there is syndactyly between, the first, second and third toes.

Radiological examination, which was performed after removal of the supernumerary fingers in hands, showed duplication of te distal phalanges of both tumbs and fusion between the distal phalanges of the third and fourth fingers in both hands (Fig. 4). In feet, halluces were totally duplicated (Fig. 5). Cranial tomography showed mega cistema magna, enlargement of the lateral ventricles and variation of the cavum septi pellucidi (Fig. 6). Corpus callosum was present. High resolution chromosome analyses showed normal karyotype.

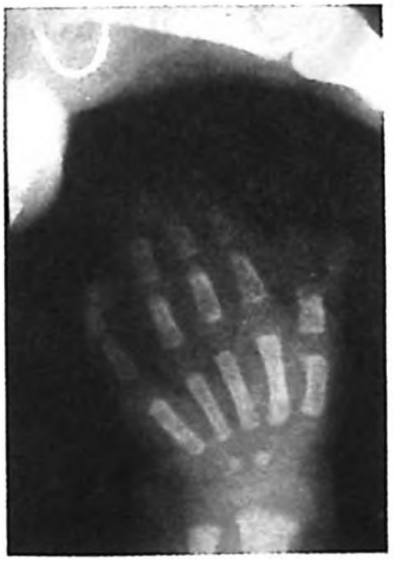


Fig. 4: X-ray of the left hand of Case 1. Note duplication of the distal phalanx of thumb and fusion of distal phalanx of third and fourth fingers.

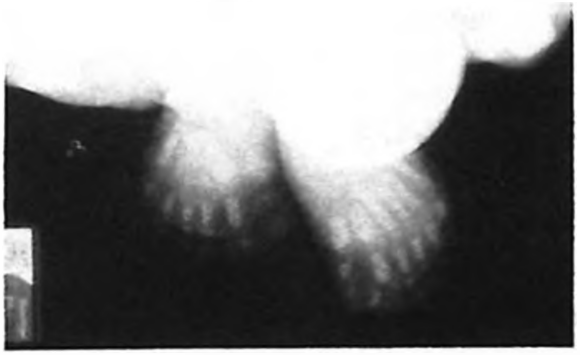
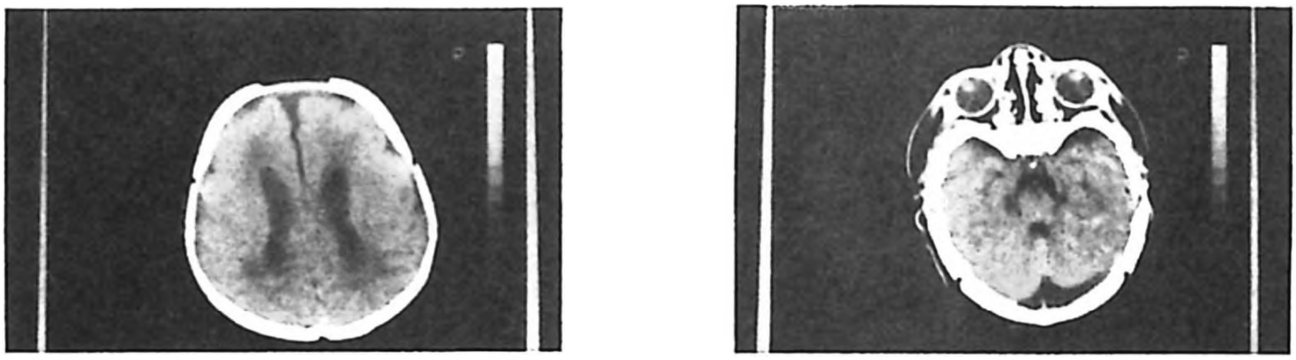


Fig. 5: X-ray of feet of Case 1. Note preaxial polydactyly in both feet.



(a) (b)

Fig. 6: Computerized tomography of the brain of Case 1. a) Note enlargement of the lateral ventricles and interhemispheric fissure b) Note mega cisterna magna.

Case 2

Case 2 was the 39-year-old father of Case 1. His facial and digital features were very similar to his daughter's. He mentioned that the postaxial polydactyly of his hands and preaxial polydactyly of his feet were excised in infancy and that did not have any other health problem. He was normal mentally.

On physical examination frontal bossing, high forehead and downslanting palpebral fissures were the characteristic facial features (Fig. 7). Head circumference was 58 cm. His right hand was normal but on the left hand the thumb was larger and shorter than normal and there was partial cutaneous syndactyly between the third and fourth fingers (Fig. 8). Scars due to excision of postaxial extra finger were visible on the ulnar side of both hands.

Fig. 7: Facial appearance of Case 2. Note prominent forehead and frontal region and downslanting palpebral fissures.

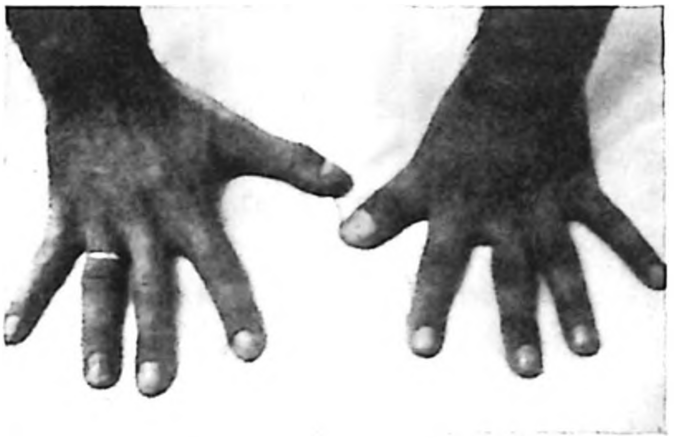


Fig. 8: Hands of Case 2. Note the short and broad thumb and partial syndactyly between the third and fourth fingers of the left hand.

The right hallux was larger than normal and there was a visible scar due to excision of preaxial extra finger. The left hallux and the preaxial extra toe were removed together. The other toes of both feet had normal appearance except for the syndactyly between the second and third toes on the left foot (Fig. 9). High resolution chromosome analyses showed normal karyotype.

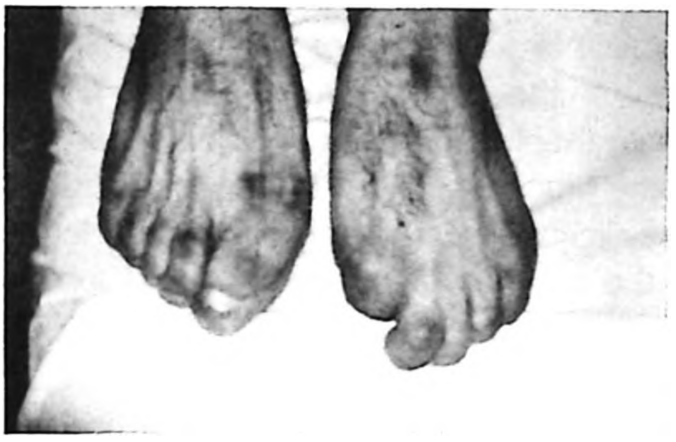


Fig. 9: Feet of Case 2. Preaxial polydactyly in both feet and hallux of the left foot were surgically removed in infancy. Note incision scar on the right hallux. There is an incomplete cutaneous syndactyly between the second and third toes.

Discussion

Greig cephalopolysyndactyly syndrome was first decsribed by Greig[3] in 1926. to date more than fifty cases have been published by several authors[4-7]. Major findings of GCPS are postaxial polydactyly (pedinculated postminimi) of hands, preaxial polydactyly of feet, cutaneous syndactyly of fingers and toes, and minor craniofacial abnormalities such as high forehead, macrocephaly, frontal bossing, broad nasal root and oblique palpebral fissures. Megalencephaly and enlargement of the lateral ventricles are also reported in patients with this

syndrome[1, 2]. Various authors have caled attention to the similarities between acrocallosal syndrome and GCPS and have proposed that they were same entity[4, 5, 8]. The main clinical distinction between these two syndromes is the presence of mental retardation in patients with acrocallosal syndrome, whereas patients with GCPS are usually normal mentally[4]. Linkage analysis has also confirmed that these two syndromes are not allelic[9]. Greig cephalopolysyndactyly syndrome, which has been shown to be due to mutations in the GLI3 gene[10], has an autosomal dominant mode of inheritance with high penetrance and variable expression[6]. Recognition of these findings and consideration of variable expression are very important for the diagnosis. The two patients in this report showed variable expression. Both of them had polydactyly of the hands and feet to a similar extent, but the daughter had more severe syndactyly of fingers and toes than her father. Mild craniofacial features and mild syndactyly of the father probably resulted in the diagnosis of uncomplicated polydactyly. Braitser et al.[4] (1983) proposed that some patients within the same family might have an indistinguishable phenotype from uncomplicated polysyndactyly (preaxial polydactyly type 4) due to very mild presentation of the facial features of GCPS syndrome. The father in this report is such a case with mild facial features. Since he had three corrective surgeries he never knew that he was a Greig cephalopolysyndactyly syndrome patient. If the father had been diagnosed correctly, it might have been possible to diagnose the baby prenatally in view of the ultrasonographic findings. Although intelligence is often normal in GCPS patients, some cases do have mild mentalretardation. For this reason, it might be important to diagnose this syndrome prenatally. Prenatal diagnosis of GCPS might be possible if there is a history of the disease in family members and there are specific prenatal ultrasound findings of the central nervous system and extremities.

REFERENCES

1. Johns KL. Greig cephalopolysyndactyly syndrome. In: Johns KL (ed). Smith's Recognizable Patterns of Human Malformations (5th ed). Philadelphia: W.B. Saunders Co; 1997; 426-427.
2. Online Mendelian Inheritance in Man, OMIM (TM). Baltimore: Johns Hopkins University, MD. MIM Number: 175700: 6/2/1997.
3. Greig DM. Oxycephaly. Edinb Med J 1926; 33: 189-218.
4. Baraitser M, Winter RM, Brett EM. Greig cephalopolysyndactyly: report of 13 affected individuals in three families. Clin Genet 1983; 24: 257-265.
5. Chundley AE, Houston CS. The Greig cephalopolysyndactyly syndrome in a Canadian family. Am J Med Genet 1982; 13: 269-276.
6. Fryns JP, Van Noyen G, Van Den Berghe H. The Greig polysyndactyly craniofacial dysmorphism syndrome: variable expression in a family. Eur J Pediatr 1981; 136: 217-220.
7. Gollop TR, Fontes LR. The Greig cephalopolysyndactyly sydrome: report of a family and review of the literature. Am J Med Genet 1985; 22: 59-68.

8. Legius E, Fryns JP, Casaer P, Boel M, Eggermont E. Schinzel acrocallosal syndrome: a variant example of the Greig syndrome? Ann Genet 1985; 28: 239-240.

9. Brueton LA, Chotai KA, van Herwerden L, Schinzel A, Winter RM. The acrocallosal syndrome and Greig syndrome are not allelic. J Med Genet 1992; 29: 635-637.

10. Vortkamp A, Gessler M, Grzeschik KH. GLI3 zinc-finger gen interrupted by translocations in Greig syndrome families. Nature 1991; 352: 539-540.