Greig Cephalopolysyndactyly Syndrome: A Family Report

Greig Sefalopolisindaktili Sendromu: Bir Aile Sunumu

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ABSTRACT Greig cephalopolysyndactyly syndrome (GCPS) is an autosomal dominant condition characterized by distinct combination of craniofacial, hand and food malformations. It is caused by mutations of the gene GLI3, located on 7p13. The clinical features consistent with GCPS are typical craniofacial findings, post or preaxial polysyndactyly of the hands and feet. In this report we describe clinical and radiological findings of a Turkish family in which five members of three generations could be examined. Dysgenesis of the corpus callosum is diagnosed in one of the patients. A rare clinical manifestation, pectus excavatum, is also seen in two of the cases.

Key Words: GLI3 protein, human; polydactyly; syndactyly; funnel chest

ÖZET Greig sefalopolisindaktili sendromu (GSPS) otozomal dominant kalıtım gösteren ve belirgin kraniofasiyal, el ve ayak malformasyonları ile karakterize bir durumdur. GLI3 geninin 7p13 bölgesindeki bir mutasyondan kaynaklanır. GSPS'nin klinik özellikleri tipik kraniofasiyal bulgular, el ve ayaklarda post veya preaksiyal polisindaktilidir. Biz bu sunumda bir Türk ailesinde üç nesilden toplam beş aile üyesinin klinik ve radyolojik özelliklerini sunduk. Hastalardan birinde korpus kallozum disgenezisi vardı. Nadir klinik bulgulardan pektus ekskavatum da iki hastada görüldü.

Anahtar Kelimeler: Greig sendromu; polidaktili; sindaktili; pektus ekskavatum

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Greig cephalopolysyndactyly syndrome (GCPS) is a relatively rare disorder affecting limb and craniofacial development which was firstly described by Greig in 1926.[1] Craniofacial malformations usually consist of macrocephaly, frontal bossing, hypertelorism, down-slanting palpebral fissures and a broad nasal bridge. Associated skeletal characteristics include craniosynostosis, advanced bone age, syndactyly, broad thumbs and halluxes and postaxial polydactyly. In the feet there is often duplication of the hallux combined with syndactyly of toes 1, 2 and 3. In the hands usually postaxial and less frequently preaxial polysyndactyly can occur.[2-5] Other occasional abnormalities are mild mental deficiency, agenesisi of corpus callosum, craniosynostosis, mild degrees of hydrocephaly, advanced bone age, camptodactyly and pectus excavatum.[3] Also inter and intrafamilial variabilities of the phenotype have been described by several authors.[4-9]

GCPS is an autosomal dominant disorder caused by mutations of the gene GLI3, a human homologue of the Drosophila cubitus interruptus gene, has invoked haploinsufficiency as the mutational mechanism underlying the disease.[10] However only eight sporadic cases have been reported due to some of rare new mutations.[11-13]

In this report we described the syndrome in three generations of a Turkish family of which four cozens and a grandfather. We present a brother and a sister who were evaluated by the clinic of chest surgery because of pectus excavatum.

CASE REPORTS

The two patients described in this report were referred to our clinic for medical consultation by the clinic of chest surgery. The patients were a brother and a sister born of a consanguineous parent having mild dismorphic features including a prominent forehead, broad nasal bridge, down-slanting palpebral fissures, pectus excavatum, broad thumbs and big toes, operated polydactyly and syndactyly (Figure 1a, b, c, d, 2a, b). From their history it was learned that they have two cozens and a grandfather who have the same clinical features except pectus excavatum (Figure 3).

CASE 1

On evaluation case 1 was a seven years old girl. Her mother described her at birth as having mild dysmorphic features and craniosynostosis. During the second year of life, a mild developmental delay was noticed. She was 25 kg (%50-75th) weighed and was 114 cm (%3-10th) tall. Her head circumference was 55.5 cm (> %97th). Several clinical anomalies were noticed upon physical examination including hypertelorism, frontal bossing, broad nasal bridge,

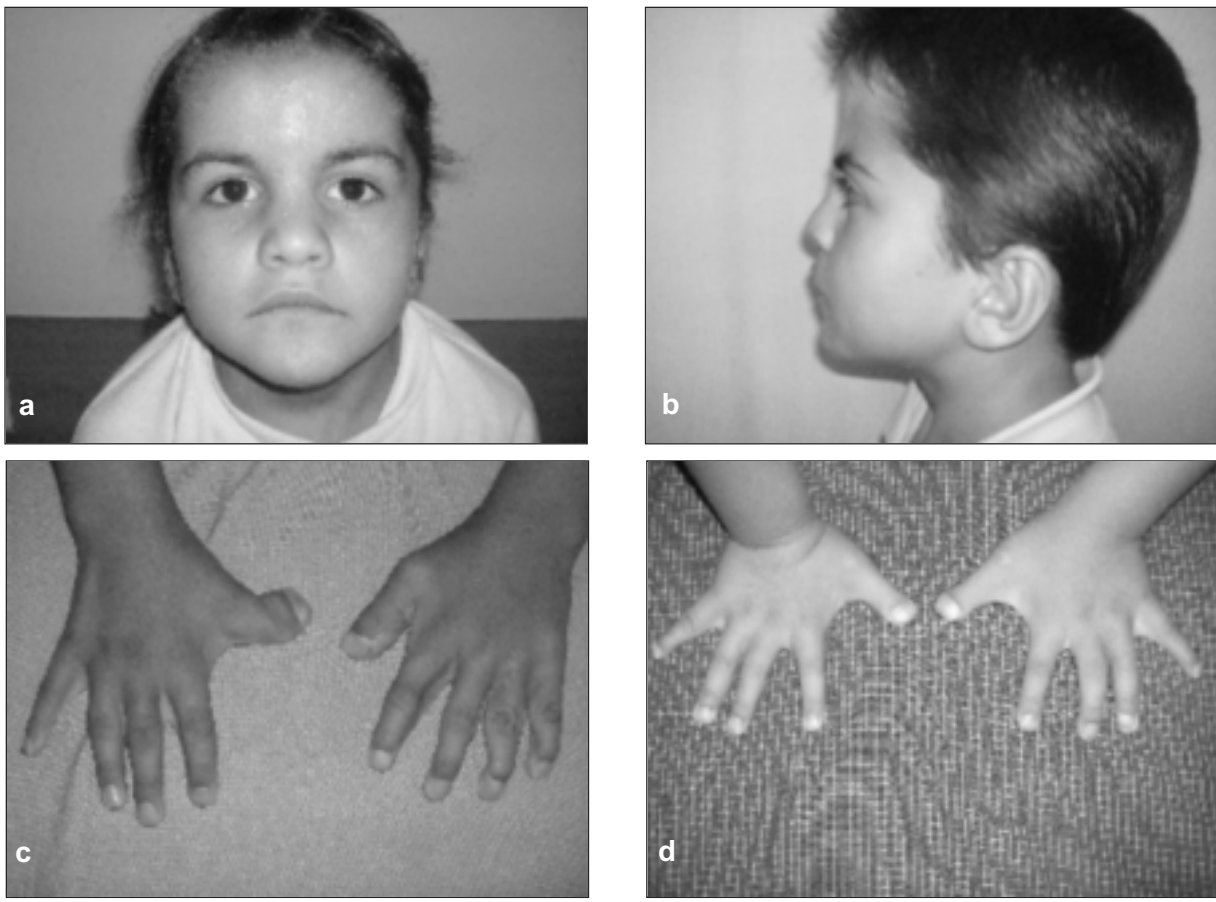

FIGURE 1: Craniofacial and hand anomalies; prominent forehead, broad nasal bridge, down-slanting palpebral fissures (a), low set ears (b), broad thumbs, operated syndactyly of fingers (c,d).

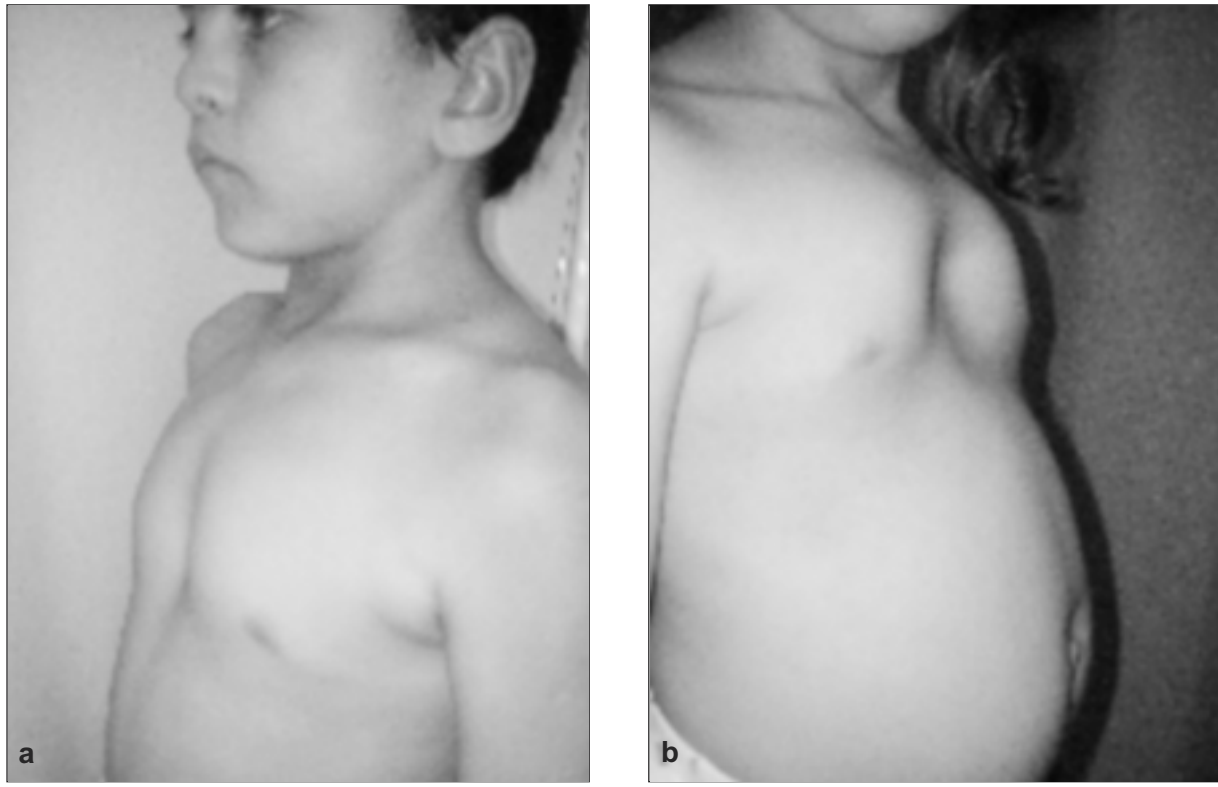

FIGURE 2: Pectus excavatum (a,b).

down-slanting palpebral fissures, low set ears, pectus excavatum, broad thumbs and big-deformated toes and polysyndactyly. Her hands had broad thumbs and she was operated two years ago because of the syndactyly of fingers 3 and 4 bilaterally. In the feet there are broad halluces, bilateral syndactyly of toes 2, 3 and 4 and also she was operated on lateral preaxial polydactyly of two feet (Figure 4a, b, c). On cardiac examination she had a 12 mm. ASD. Her intelligent quotient (IQ) was 75 and on magnetic resonance imaging of the brain dysgenesis of corpus callosum was detected (Figure 5a, b). X-ray examination revealed markedly advanced bone age.

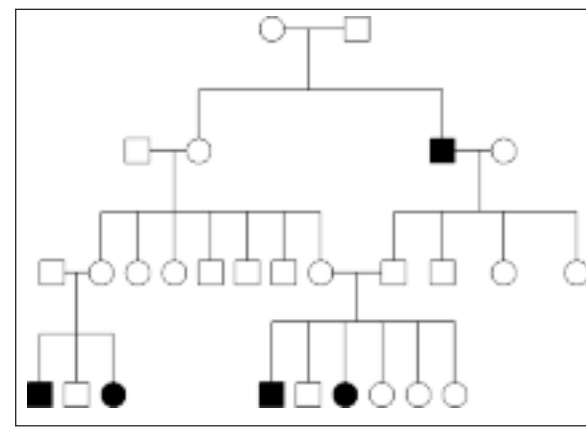

FIGURE 3: Pedigree of the family.

CASE 2

Case 2 was a nine years old boy with the same craniofacial findings of his sister and his history revealed craniosynostosis at birth. He was 35 kg (%75-90th) weighed, 139 cm (%75th) tall and head circumference was 56 cm (%97th). On physical examination, he had hypertelorism, frontal bossing, broad nasal bridge, down-slanting palpebral fissures, low set ears, pectus excavatum, broad thumbs and halluces and polysyndactyly of the hands and feet. He was operated on the hands because of the syndactyly of fingers 2, 3 and 4 of the left hand and the fingers of 3 and 4 of the right hand. In the feet there are broad and deformated halluces, bilateral

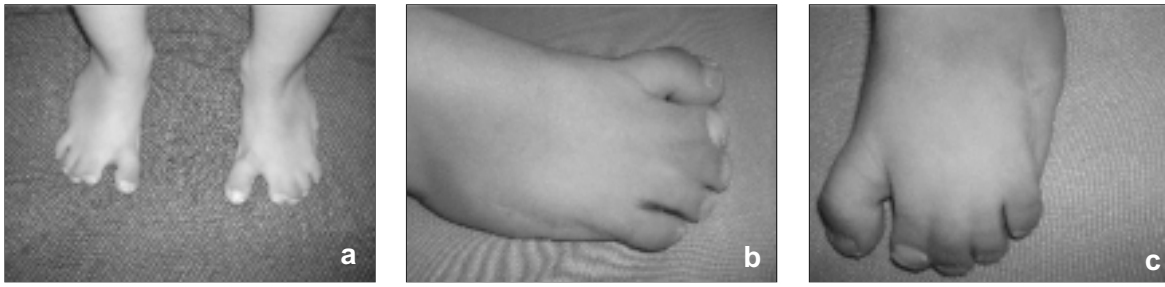

FIGURE 4: Bilateral syndactyly of toes 2, 3 and 4 (a) and operated preaxial polydactyly of two feet (b,c).

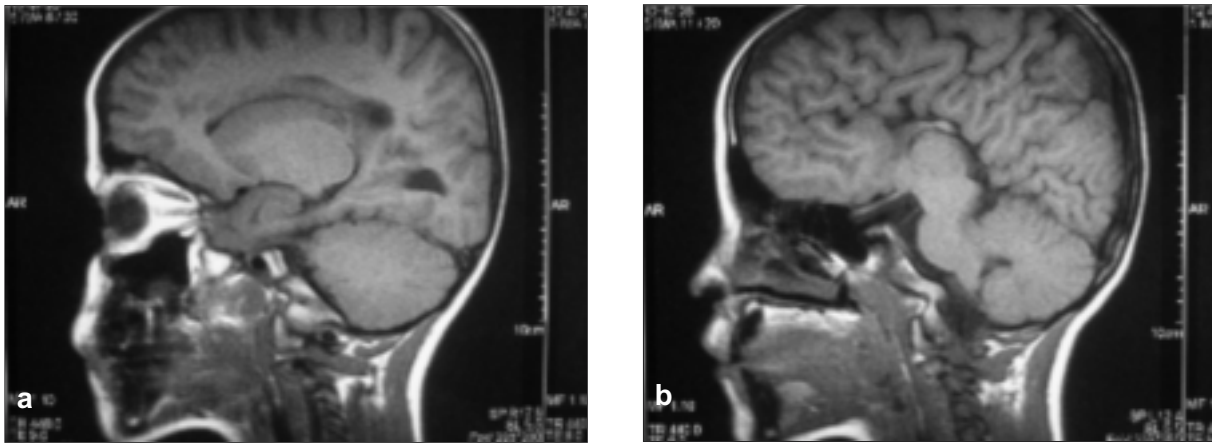

FIGURE 5: Dysgenesis of corpus callosum on magnetic resonance imaging (a,b).

syndactyly of toes 1, 2 and 3 and he was operated on medial preaxial polydactyly of left foot two years ago (Figure 6a, b). Radiography showed the dublication of halluces and advanced bone age (Figure 7). Cardiac and brain imaging were normal. His IQ was 80.

The clinical features of the individuals are summarized in Table 1.

DISCUSSION

The combination of craniofacial abnormalities and broad thumbs and halluces, preaxial polydactyly of the hands and feet, variable syndactyly of fingers and toes is known as GCPS. It was firstly described by Greig in 1926.[11] GCPS is an autosomal dominant disease caused by mutations of the gene GLI3 loca-

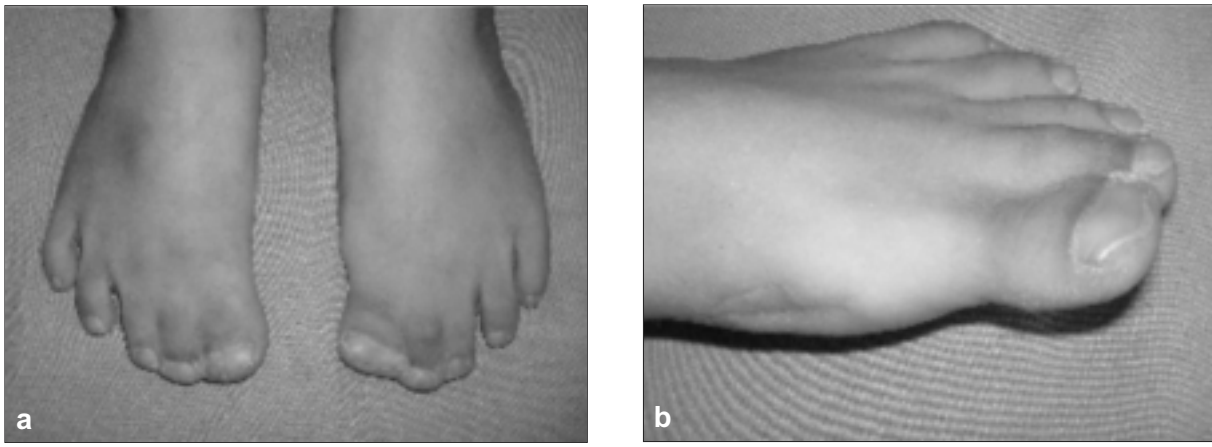

FIGURE 6: Bilateral syndactyly of toes 1, 2 and 3 (a) and operated preaxial polydactyly of left foot (b).

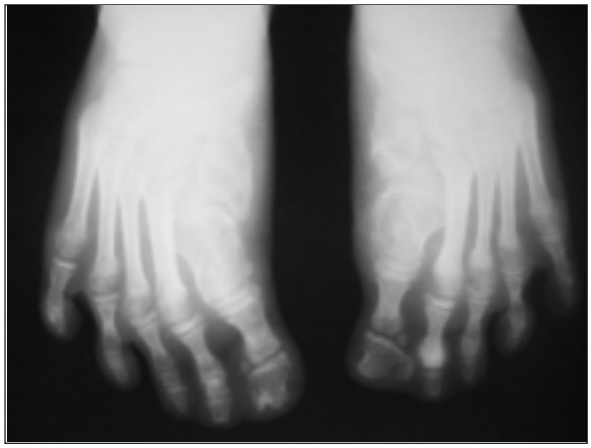

FIGURE 7: Bilateral dublication of halluces.

ted on 7p13.[14] However at least two further disorders are caused by point mutations or truncating mutations of GLI3; polydactyly Type 1 and Pollister-Hall syndrome.[15,16] But clinical apperance of these syndromes are different from each other. Also craniosynostosis is thought to be determined by mutations in a gene on 7p.[17] Moreover, agenesis of the corpus callosum is found to be associated with the gene ZFHX1B located at 2q22.[18]

Craniofacial abnormalities usually consist of frontal bossing, hypertelorism, down-slanting palpebral fissures, broad nasal bridge and high forehead. Usually craniosynostosis is observed in the cases at birth. In GCPS, postaxial polydactyly is common in the hands while preaxial polydactyly preminates in the feet. Thumbs are usually broad and a misshapen distal phalanx can be occured. Only in one case a complate bilaterally dublication of the thumbs was reported.[19] Also in the hand bony fusion was reported.[20] Other digital malformations include camptodactyl, clinodactyly, brachydactyly and radial deviation of digits.[21] In the feet with the dublication of the hallux preaxial polydactyly, broad halluces with broad nails are common. Separately dublication of the fifth toe and broadening are usual. Usually, GCPS patients have advanced bone age on radiographs.[19]

TABLE 1: Clinical features in our GCPS patients.

	Case 1	Case 2	Cozen 1	Cozen 2	Grandfather
Age/sex head	7/F	9/M	8/F	9/M	89/M
Macrocephaly	+ (55.5)	+ (56)	+ (55.8)	+ (56.2)	+ (58 cm)
Prominent forehead	+	+	+	+	+
Hypertelorism	+	+	+	+	+
Broad nasal bridge	+	+	+	+	+
Down-slanting palpebral fissures	+	+	+	+	+
Low set ears	+	+	+	-	-
Hand					
Syndactyly	+ (3, 4) bilateral, operated	+ (2, 3, 4) left (3, 4) right operated	+ (2, 3, 4) bilateral	+ (2, 3) bilateral	+ (2, 3, 4) bilateral perated
Broad thumbs	+	+	+	+	+
Polydactyly	-	-	+ (right)	+ (right)	-
Foot					
Syndactyly	+ (2, 3, 4) bilateral	+ (1, 2, 3) bilateral	+ (1, 2, 3) bilateral	+ (2, 3, 4) bilateral	+ (2, 3, 4) bilateral
Broad halluces	+	+	+	+	+
Polydactyly	+ (bilateral) (operated)	+ (left) (operated)	+ (right)	+ (right)	+ (left)
Other clinical features					
Mental deficiency	-	-	-	-	-
Malformed thorax (pectus excavatum)	+	+	-	-	-
Cardiac anomalies (ASD, i.e)	+	-	-	-	-
Corpus callosum agenesis	+ (dysgenesis)	-	-	-	-

GCPS: Greig cephalopolysyndactyly syndrome.

Mental retardation is an uncommon clinical finding.[22] However mild degrees of hydrocephaly, megalencephaly, aqueduct stenosis, dysgenesis or agenesis of corpus callosum can be seen on brain imaging.[22-24] In some patients EEG anomalies have been observed and seizures can be occurred.[8] Other unusual clinical findings of GCPS includes; cardiac findings such as ASD, supravalvular aortic stenosis and sinus node disease, umblical hernia, metabolic anomalies, cryptorchism, delayed puberty, hirsutism and moderate psychomotor retardation.[8,25]

The clinical findings in our patients are compatible with the diagnosis of GCPS. The most interesting observations in our cases are the presence of pectus excavatum and dysgenesis of corpus callosum which are the rare findings of GCPS. The association of these clinical features has not been reported yet in the literature. There may be a relation between the gene GLI3 and ZFHX1B in spite of locating on different chromosomes. We need more new studies to prove this estimation. Otherwise prenatal diagnosis of GCPS with genetic analysis or prenatal ultrasonography is possible especially if there is a history of the disease in family members.

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