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A Rare Prenatal Case: Greig Cephalopolysyndactyly Syndrome

Nadir Bir Prenatal Olgu: Greig Sefalopolisindaktili Sendromu

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ABSTRACT

Greig cephalopolysyndactyly syndrome (GCPS) is a rare genetic disorder characterized by macrocephaly, prominent forehead, hypertelorism, preaxial and/or postaxial polydactyly, and cutaneous syndactyly. Mutations that cause haploinsufficiency in the zinc finger protein family member 3 (*GLI3*) gene, which is located on the short (p) arm p14 region of chromosome 7 (Chr.7), have been associated with this syndrome. Here, a case of prenatal GCPS with haploinsufficiency of the *GLI3* gene is presented. A 32-year-old woman, in her 21st week of the first pregnancy, was referred to our center for cytogenetic analysis of amniotic fluid because of the detection of polyhydramnios, polydactyly, aortic stenosis, and the absence of vesica biliaris visualization on fetal ultrasound. Chromosome analysis was terminated with an interstitial short arm (p12-p15.1) deletion of chromosome 7 consisting of the *GLI3* gene region (7p14). The presence of the short arm terminal region of the relevant chromosome was confirmed by fluorescence *in situ* hybridization analysis. Array comparative genomic hybridization technique verified the breakpoint regions and revealed a 17.4 Mb deletion covering the *GLI3* gene. To date, reported prenatal cases with GCPS syndrome are very rare. Here we present a case of GCPS syndrome diagnosed in the prenatal period due to a *de novo* unbalanced chromosomal rearrangement.

Keywords: Chromosome 7, *GLI3* gene, greig cephalopolysyndactyly syndrome, deletion, polydactyly, prenatal

ÖZ

Nadir bir genetik hastalık olan greig sefalopolisindaktili sendromu (GCPS) makrosefali, belirgin alın, hipertelorizm, preaksiyel ve/veya postaksiyel polidaktili ve kutanöz sindaktili ile karakterizedir. Bu sendrom 7. kromozomun kısa kolunda (7p14 bölgesinde) yer alan çinko parmak gen ailesi 3 (*GLI3*) geninin haplo yetersizliğine neden olan mutasyonları ile ilişkilidir. Burada *GLI3* geninin haployetersizliği ile ilişkili bir prenatal GCPS olgusu sunulmaktadır. Fetal ultrasonografide polihidroamniyöz, polidaktili ve aort stenozu saptanması ve safra kesesinin izlenmemesi nedeniyle 32 yaşındaki kadının 21 haftalık ilk gebeliğine ait amniyon mayi sitogenetik analiz için merkezimize refere edilmiştir. Kromozom analizi 7. kromozomun *GLI3* gen bölgesini de (p14) içeren kısa kolunun (p12-p15.1) interstisyel delesyonu olarak sonuçlanmıştır. Floresan *in situ* hibridizasyon analizi, ilgili kromozomun kısa kol telomer bölgesinin korunduğunu göstermiştir. Karşılaştırmalı genomik hibridizasyon tekniği detaylı olarak kırık bölgelerini ve *GLI3* genini de içeren 17,4 mb'lik delesyonu teyit etmiştir. Bugüne kadar GCPS sendromlu prenatal olgu literatürde oldukça nadirdir. Burada *de novo* dengesiz kromozomal yeniden düzenlenmeye bağlı prenatal dönemde GCPS sendromu tanısı almış bir olgu sunulmaktadır.

Keywords: *GLI3* geni, greig sefalopolisindaktili sendromu, delesyon, kromozom 7, polidaktili, prenatal

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INTRODUCTION

Greig cephalopolysyndactyly syndrome [(GCPS), MIM #175700] is a disorder caused by mutations in the zinc finger gene family 3 (*GLI3* gene), which is crucial for limb, brain, and craniofacial development. It follows an autosomal dominant inheritance pattern. The prevalence of this syndrome is approximately 1-9/1,000,000 (1). The *GLI3* gene is located on the short arm of chromosome 7 (Chr.7-p14 band). The prominent clinical findings are macrocephaly, prominent forehead, hypertelorism, preaxial and/or postaxial polydactyly, and cutaneous syndactyly. In cases with multiple congenital anomalies, it is often assessed as a sequential gene syndrome (2,3).

The *GLI3* gene encodes a pivotal transcription factor essential for embryonic development. It also controls downstream targets of the sonic hedgehog pathway, which regulates cell proliferation and differentiation (4). Approximately 80% of GCPS cases linked to *GLI3* gene haploinsufficiency result from single nucleotide changes, whereas approximately 20% stem from copy number alterations (5).

The vast majority of the reported cases are postnatal with variable expression. Here, the presented case is a rare case of prenatal GCPS due to a *de novo* unbalanced chromosomal rearrangement belonging to the interstitial deletion of chromosome 7, covering the *GLI3* gene region.

CASE REPORT

At 32 years of age, a primigravida at 21-week of gestation underwent amniocentesis because of abnormal ultrasonographic (USG) findings. USG revealed polydactyly in the feet, polyhydramnios, and aortic valve stenosis, whereas the vesica biliaris could not be visualized. The parents are non-consanguineous.

Interphase fluorescent *in situ* hybridization (I-FISH) analysis for common euploidies (Chr.13, 18, 21, and gonosomes) of uncultured amniocytes showed a normal hybridization pattern. Cytogenetic analysis from long-term tissue cultures revealed an interstitial deletion on the short arm of Chr.7, and metaphase FISH analysis confirmed the presence of telomeric regions [(46,XX,del(7)(7pter→7p15.1::7p12→7qter)] (Figure 1a, b).

Array comparative genomic hybridization (array-CGH) (Human Genome G3 SurePrint 8x60K ISCA Array; Agilent Technologies, Santa Clara, California) verified the deletion [17.4 megabase (Mb) deletion], including the *GLI3* gene located on the 7p12.3-14.3 (hg19:7:30307418-47765428) (Figure 1c). Cytogenetic analysis was also carried out on the parents, and their karyotypes were normal. The detected unbalanced chromosomal rearrangement was considered a *de novo*.

After unbiased genetic counseling was given in terms of GCPS, the family decided to continue the pregnancy. Because of fetal cardiac arrest, the mother had a stillbirth at 25 weeks of gestation. Prominent forehead, biparietal narrowing, hypertelorism, flat and wide nasal bridge, broad thumbs in the hands and feet, and preaxial polydactyly in the foot were observed in the clinical examination of the exitus fetus, all consistent with GCPS (Figure 2). Written consent was obtained from the family.

DISCUSSION

GCPS is primarily caused by single nucleotide or copy number changes in the *GLI3* gene. Rarely, chromosomal alteration within the deletion of related genes can cause GCPS syndrome, as in the present case. Considering other allelic disorders of the *GLI3* gene, such as Pallister Hall syndrome (midaxial/postaxial polydactyly,

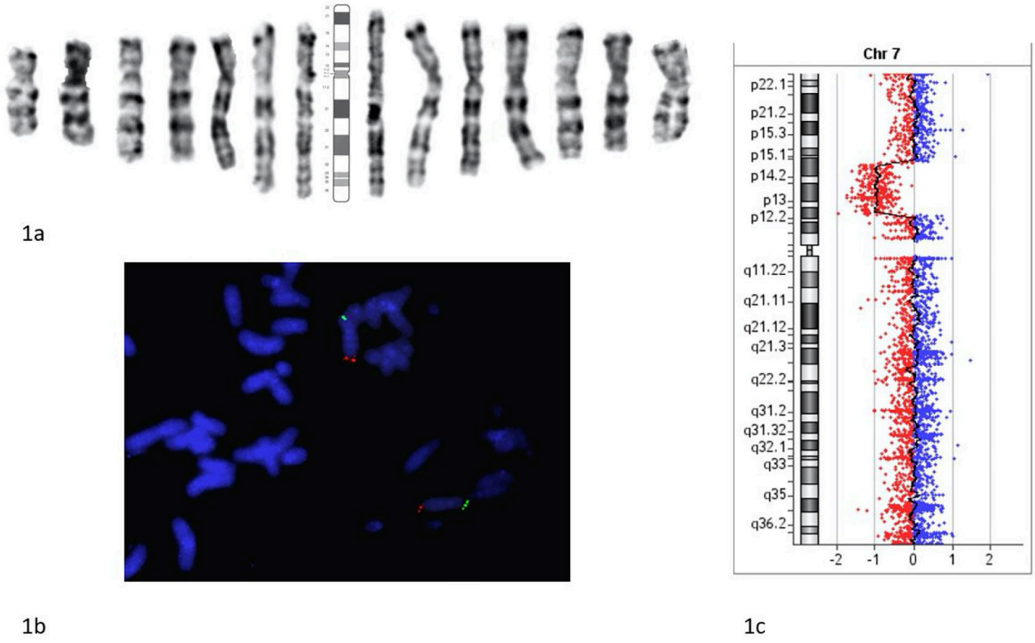

Figure 1. Comprehensive analysis of the fetus; partial karyotype, metaphase FISH image, and array-CGH image. (a) Partial karyotypes of deleted Chr.7 (left side) and normal Chr.7 (right side). (b) Metaphase FISH images displaying Chr.7 pter and qter regions (green and red signals respectively). (c) Array-CGH image showing the breakpoint region 7p12.3-14.3, revealing a 17.4 Mb deletion on chromosome 7 (Human Genome G3 SurePrint 8x60K ISCA array).

FISH: Fluorescent *in situ* hybridization, CGH: Comparative genomic hybridization.

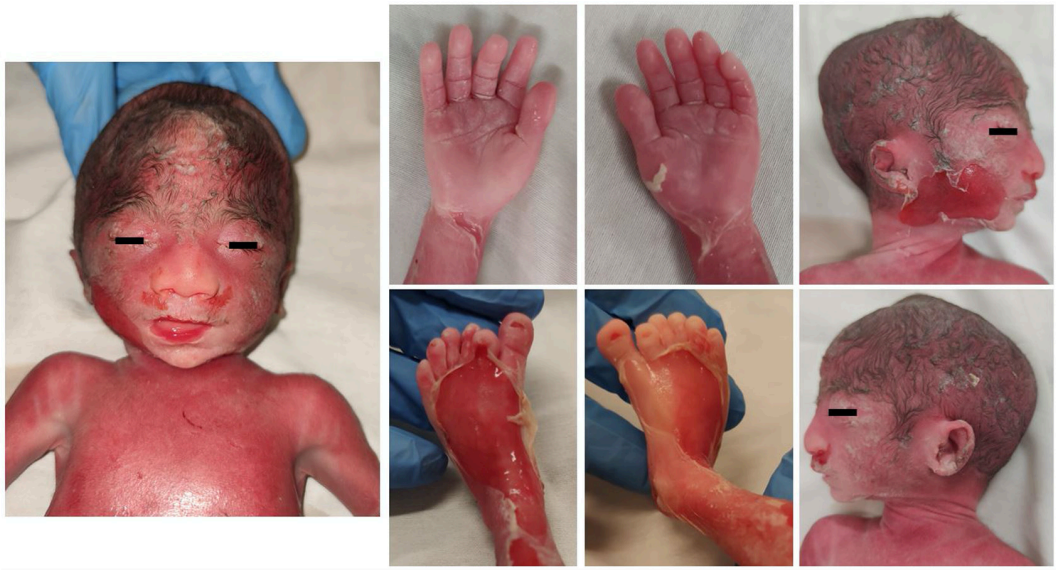

Figure 2. Clinical findings of the exitus fetus were a prominent forehead, biparietal narrowing, hypertelorism, flat and wide nasal bridge, broad thumbs in the hands and feet, and preaxial polydactyly in the foot.

asymptomatic bifid epiglottis, imperforate anus, and hypothalamic hamartoma), evaluation of the individual's genetic and phenotypic characteristics pattern is essential (6). Fortunately, genetic and phenotypic correlations are well documented and can be used to diagnose each condition more accurately (5,7,8). Similar to the present case, large deletions of the *GLI3* gene are more commonly associated with GCPS than with Pallister Hall syndrome.

Array-CGH analysis of this case revealed a 17.4-Mb deletion, resulting in the loss of genes such as *POU6F2, GCK, TBX20, CDK13, CAMK2B,* and *GARS,* besides the *GLI3* gene. *POU6F2* gene deletion may increase the risk of Wilms tumor, whereas the deletion of the *GCK* gene may lead to MODY (9,10). The family was informed that intellectual influence was unpredictable because of the involvement of other genes. The deletion interval of the fetus was interpreted on the DECIPHER database, and most of the dysmorphic signs were common, except for the absence of vesica biliaris.

During pregnancy, polydactyly can be diagnosed earlier, whereas macrocephaly and hypertelorism can mainly be detected in the third trimester. Fetal USG plus genetic testing make prenatal diagnosis feasible, allowing early diagnosis and appropriate management of the newborn (8). It allows the potential medical and surgical interventions that the newborn may need to follow birth. Beyond that, diagnosis is also essential for the family's subsequent pregnancies. If chromosomal alteration is familial, counseling should be given regarding preimplantation genetic diagnosis and invasive prenatal testing. Even if the parental karyotype analysis is normal and considered *de novo*, the risk of recurrence exists, albeit low, because of possible changes that cannot be detected by conventional cytogenetic analysis, such as gonadal mosaicism and familial micro-inversions.

In sum, this case holds significance as it was prenatally diagnosed on the basis of suspicious fetal ultrasound findings and subsequently confirmed through genetic testing. GCPS syndrome can be challenging to diagnose prenatally (11). As in this case, families should be briefed on the condition, its potential causes, and prenatal diagnosis and management options.

Ethics

Informed Consent: The parent of the case signed the written informed consent form.

Authorship Contributions

Surgical and Medical Practices: T.N., P.T.C., Concept: T.H., G.K., M.Y.K., Design: T.H., G.K., M.Y.K., Data Collection or Processing: T.H., M.Y.K., Analysis or Interpretation: T.H., G.K, M.Y.K., Literature Search: T.H., Writing: T.H., M.Y.K.

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