Greig Cephalopolysyndactyly Syndrome: A Case Report

Greig Sefalopolisindaktili Sendromu: Bir Olgu Sunumu

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SUMMARY

Introduction: The Greig cephalopolysyndactyly syndrome (GCPS) is a pleiotropic, multiple congenital anomaly syndrome.

Case Report: The patient had high forehead, frontal bossing, macrocephaly, apparent hypertelorism, down-slanting palpebral fissures and a broad nasal root. The feet showed bilateral polydactyly with cutaneous syndactyly of the fifth digits.

Conclusion: GCPS is a rare condition with an autosomal dominant mode of inheritance. The primary findings include hypertelorism, macrocephaly with frontal bossing, and polysyndactyly. Presented here is a case of a 1 week old female with typical clinical manifestations of GCPS. *(Journal of Current Pediatrics 2011; 9: 47-9)*

Key words: Greig cephalopolysyndactyly syndrome, macrocephaly, polysyndactyly

ÖZET

Giriş: Greig sefalopolisindaktili sendromu (GCPS), çoklu konjenital anomalili bir pleiotropik sendromdur.

Olgu Sunumu: Hasta yüksek alın, frontal şişlik, makrosefali, belirgin hipertelorizm, aşağı eğik palpebral fissürler ve geniş bir burun köküne sahipti. Ayakları bilateral kutanöz sindaktilili polidaktili gösterdi.

Tartışma: GCPS otozomal dominant genetik modelli nadir bir durumdur. Primer bulguları, hipertelorizm, frontal şişliği olan makrosefali ve polisindaktiliyi içerir. Burada, GCPS'nin tipik klinik bulguları ile 1 haftalık kız bir olgu sunuldu. *(Güncel Pediatri 2011; 9: 47-9)*

Anahtar kelimeler: Greig sefalopolisindaktili sendromu, makrosefali, polisindaktili

Introduction

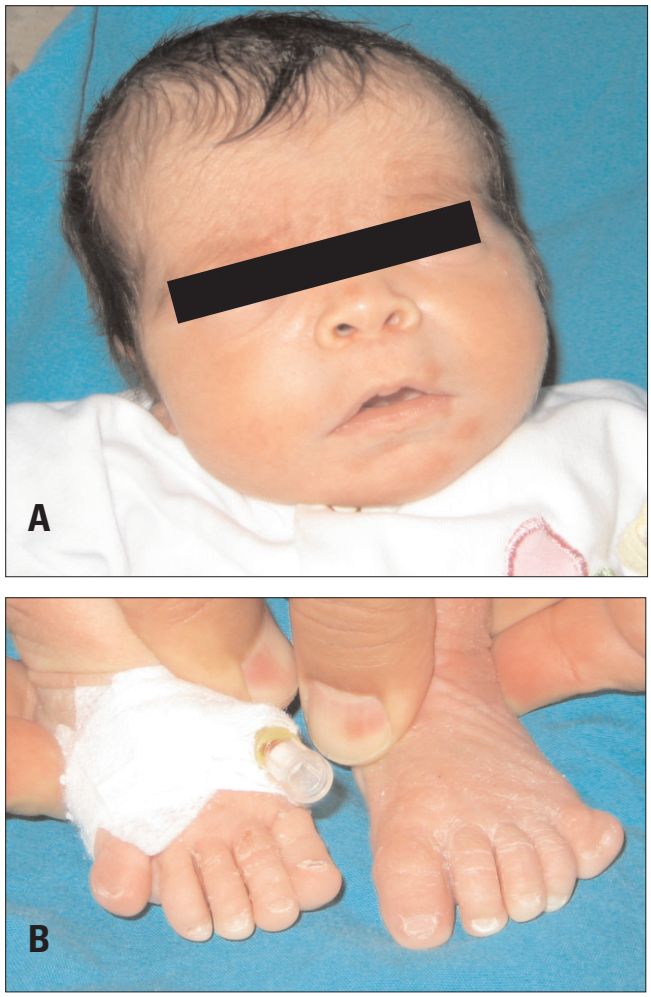
Greig cephalopolysyndactyly syndrome (GCPS) is characterized by polydactyly, macrocephaly, and hypertelorism. Patients with severe GCPS can also present with mental retardation, seizures, and hydrocephalus. Mutations or deletions in GLI3 at the 7p13 locus have been shown to cause GCPS (1,2,3). Here we report a case of a 1 week old female with GCPS.

Case Report

History revealed that the female newborn is the first child of nonconsanguinous parents. Delivery was uneventful, birth weight was 3400g, length 49cm, and occipitofrontal head circumference 41cm. When first examined at 7 days of age the patient showed the following dysmorphic features: high forehead, frontal bossing, macrocephaly, apparent hypertelorism, down-slanting palpebral fissures and a broad nasal root (Figure 1A). The feet showed bilateral polydactyly with cutaneous syndactyly of the fifth digits (Figure 1B). Cranial magnetic resonance graphy (MRG) indicated a structurally normal corpus callosum. Echocardiography, chest radiograph and ultrasound examination of the abdomen were normal. Karyotype analysis was a normal (46,XX). There was no history of similar clinical profile in any of the relatives of the case.

Discussion

Greig cephalopolysyndactyly syndrome (GCPS) is named after David Middleton Greig for his 1926 manuscript describing a patient with this disorder (4). The Greig cephalopolysyndactyly syndrome (GCPS) is a rare (estimated range 1-9/1000.000), pleiotropic, multiple congenital anomaly syndrome characterized by the primary clinical triad of polysyndactyly, macrocephaly, and hypertelorism (5). Our patient had high forehead, frontal bossing, macrocephaly, apparent hypertelorism, down-slanting, palpebral fissures and a broad nasal root. Her feet showed polydactyly with cutaneous syndactyly of the fifth digits. Cranial magnetic resonance graphy (MRG) indicated a structurally normal corpus callosum.



Figures 1. A patient with Greig cephalopolysyndactyly syndrome. A. Facial view of the patient. Note the hypertelorism, down-slanting palpebral fissures, a broad nasal root and macrocephaly. B. The feet of this patient shows a postaxial duplication with cutaneous syndactyly of fifth digits.

Other, less common anomalies in GCPS include craniosynostosis, mental retardation, agenesis of the corpus callosum, and umbilical and diaphragmatic hernias. There have been several case reports of patients with GCPS and malignancies, such as leukemia and gliomas (6,7). Again, it is difficult to assign relative risks for such a putative association, especially considering ascertainment biases.

More than 75% of patients with clinically recognizable GCPS who have been evaluated in the National Institutes of Health (NIH) study have been found to have mutations in GLI3 (1). GCPS is caused by mutations that lead to haploinsufficiency for GLI3 and, as is typical for this mode of pathogenesis, the spectrum of mutations is very large. The recurrence risk for affected persons is 50%. The penetrance of GCPS is high, but is not 100% (8). Therefore, unaffected persons from multiplex families have a risk for affected children that is probably less than 1% per conception. Apparently, unaffected parents of simplex patients should be examined carefully for subtle signs of the disorder and molecular testing is indicated. If they manifest no signs of the disorder and do not carry the mutation seen in the affected child, they should be advised of a small recurrence risk, again probably less than 1% per conception. Gonadal mosaicism for GCPS has not been reported.

The differential diagnosis for polydactyly is enormous, comprising more than 100 disorders and is beyond the scope of this paper (9,10). Therefore, the careful assessment of subtle dysmorphic features of a patient with polydactyly is key to making a correct diagnosis. The spectrum of GCPS overlaps with that of the so-called non-syndromic preaxial polydactylies such as preaxial polydactyly type 4 (11). A few disorders have substantial overlap with GCPS. The acrocallosal syndrome comprises preaxial polysyndactyly, macrocephaly, agenesis of the corpus callosum, mental retardation, seizures, and hernias (12). It is inherited in an autosomal recessive pattern; however, this fact is of little use in the differential diagnosis of a simplex case. There are two further complicating factors with acrocallosal syndrome. First, there is a single case of a patient with a phenotype indistinguishable from acrocallosal syndrome who has a p.A934P GLI3 mutation (8). Second, patients with Greig cephalopolysyndactyly contiguous gene syndrome (GCPS-CGS) have substantial phenotypic overlap with acrocallosal syndrome (13). In these situations, molecular diagnostics are essential to

arrive at a correct diagnosis. The Teebi hypertelorism syndrome shares craniofacial manifestations with GCPS, although the polydactyly is typically not preaxial (14). Pallister–Hall syndrome shares with GCPS the key features of postaxial polydactyly and developmental delay but does not include hypertelorism or macrocephaly (2). Carpenter syndrome manifests polysyndactyly and craniosynostosis with mental retardation and has recently been shown to be caused by mutations in the RAB23 gene (15). The Gorlin syndrome (nevoid basal cell carcinoma syndrome) also manifests macrocephaly, and occasionally manifests hypertelorism and polydactyly. Gorlin syndrome is caused by mutations in PTCH1, another gene in the GLI-SHH pathway (16).

Antenatal diagnosis is technically straightforward to perform (via amniocentesis or chorionic villus biopsy) on at risk pregnancies in families where a causative point mutation has previously been determined. However, some unique mutations detected in patients with GCPS can be difficult to interpret and in such cases, prenatal molecular diagnosis should be approached with caution. Antenatal ultrasound may also be used to assess polydactyly. The ultrasound finding of macrocephaly is probably not sufficiently specific to be used for antenatal diagnosis of GCPS. High-resolution ultrasound can detect fetuses with polydactyly (17).

The present report is a rare newborn with typical clinical manifestations of Greig cephalopolysyndactyly syndrome.

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