

Greig Syndrome: A Rare Disease - Case Report

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Abstract

Grieg cephalopolysyndactyly syndrome (GCPS) is a rare congenital genetic disorder present at birth, characterized through physical abnormalities, primarily affecting the development of the limbs, head, and face (craniofacial malformations). We report a case of a full term, newborn female, large for gestational age with 4.2 kg. Symptoms included transient tachypnea of the newborn and craniofacial dysmorphism. The mother was G5P4 with gestational diabetes, and a reported case of polyhydramnios but did not have any previously affected babies. The craniofacial dysmorphism anomalies consisted of macrocephaly (Head circumference of 39 cm with a standard deviation of 2+ for her age), frontal bossing with a broad forehead, a groove between the frontal bone, widely spaced eyes, bilateral polysyndactyly, a thumb and an extra digit fused bilaterally in the toes. However, imaging such as CXR & skeletal survey were normal. Her tachypnea partially improved and only occurred intermittently during feeds, maintained her vital signs well and remained at room air, feeding on demand. Consults with neurology, ENT and ophthalmology specialists in hospital did not add any new findings. She was then discharged from the hospital with referral to genetics to assess the child and counsel the family as an outpatient.

Background



Figure 1: Clinical photograph showing polysyndactyly.

Typical Grieg cephalopolysyndactyly syndrome (GCPS) is characterized by a preaxial polydactyly or a mixed pre- and/or

postaxial polydactyly, true wide spaced eyes, and macrocephaly. Individuals with mild GCPS may have subtle craniofacial findings. The mild end of the GCPS spectrum is a continuum with preaxial polysyndactyly type IV and crossed polydactyly (preaxial polydactyly of the feet and postaxial polydactyly of the hands plus syndactyly of fingers 3-4 and toes 1-3). Individuals with severe GCPS may have seizures, hydrocephalus and intellectual disability. This condition is rare and its prevalence is unknown. Grieg syndrome has a wide range of varieties depending on the Mutations in the GLI3 gene related to chromosome 7, and the presence of continuous intermittent tachypnea did not report as a primary feature. Certain cranial sutures may close prematurely (craniosynostosis). Such irregular closure of the sutures may cause the head to appear shaped abnormally (scaphocephaly, trigonocephaly, or plagiocephaly). Rarely, less than 10% of affected individuals may have more serious medical problems including seizures, delayed development, and intellectual disability, build-up of fluid inside the

skull (hydrocephalus), and abnormalities affecting the nerve fibers (corpus callosum) that connect the two cerebral hemispheres of the brain, may be present (Figures 1 & 2).

fluid resuscitation, supplemental oxygen. Neonatal sepsis was ruled out though sepsis work-up. Later nasogastric tube feeding was initiated and 5 days later was transitioned to oral feeding gradually as tolerated. However, she continued to have intermittent tachypnea which appeared to improve gradually but was still evident during & after her feeds. This continued until her discharge, which was on Day-37 (Figures 3-6).

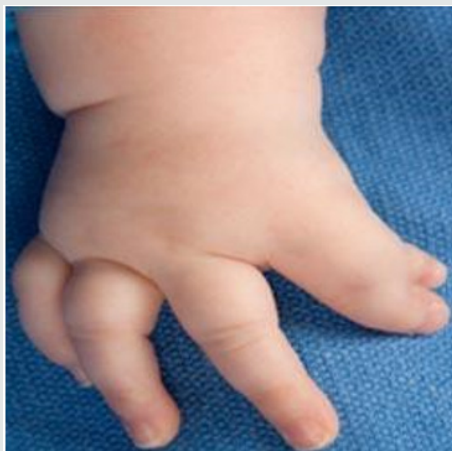


Figure 2: Polysyndactyly.

Case Presentation



Figure 3: Macrocephaly on skeletal survey.

A full term, newborn female, large for gestational age weighing 4.2kg. Her symptoms included transient tachypnea of the newborn and craniofacial dysmorphism. The mother was a G5P4 with gestational diabetes and polyhydramnios with a history of shoulder dystocia in her previous baby, which was delivered by caesarean section. The Apgar score was 7 at 1 minute and 9 at 5 minutes. The craniofacial dysmorphism anomalies consisted of macrocephaly (Head circumference of 39 cm with a standard deviation of 2+ for her age), frontal bossing with a broad forehead, a groove between the frontal bone, widely spaced eyes, bilateral polysyndactyly, extra thumb, and an extra digit fused bilaterally in the toes. The parents did not have a family history of any reported inherited diseases. At birth, the baby was distressed, tachypneic with subcostal & intercostal retractions. Therefore, she was managed in Neonatal intensive care unit in an incubator with suitable heat, meticulous cardiorespiratory monitoring. She was kept NPO, provided with



Figure 4: Macrocephaly with frontal bossing and broad forehead.



Figure 5: Right feet polysyndactyly.



Figure 6: Left sided polysyndactyly, extra thumb and extra digit fused.

Investigations

Imaging such as skeletal survey, Abdominal ultrasound, transfontanelle ultrasonography and a CT brain were done which were all normal except for macrocephaly without any hydrocephalus. Blood work included CBC, extended electrolyte panel and sepsis work-up including blood cultures were all negative. Echocardiography was also done to check for any valvular abnormalities but did not show any anomalies. Consultation with specialists in neurology, ophthalmology and ENT did not add any other findings. Although, genetic counseling was recommended but there were no facilities available for this and therefore, mutation analysis could not be performed.

Treatment

Managed in the neonatal intensive care unit in an incubator with suitable heat and meticulous cardiorespiratory monitoring. She was kept NPO, provided with fluid resuscitation, supplemental oxygen. Surgical consultation was done for elective repair of polydactyly with follow-up with the outpatient department.

Outcome and Follow-Up

The baby was treated in the NICU for 30 days for intermittent tachypnea especially during & after feeds. She was then shifted to PICU according to our admission and discharge policy, managed there for 8 days and was then discharged on breast feeding with proper education of the parents, and referral for Outpatient Department appointment follow-up for further surveillance. This was done to monitor for any changes in the occipitofrontal circumference (OFC) and continuous evaluation and treatment as needed for developing hydrocephalus or any other CNS abnormalities showing signs of increased intracranial pressure, developmental delay, loss of milestones, and/or seizures. On follow-up with neurology, the growth, and rest of the neurological workup remained normal.

Discussion

Grieg cephalopolysyndactyly syndrome (GCPS) is a rare congenital genetic disorder present at birth, characterized through physical abnormalities, primarily affecting the development of the limbs, head and face (craniofacial malformations). The features of this syndrome are highly variable, ranging from mild to severe. Patients with this condition typically have one or more extra fingers or toes (polydactyly), or an abnormally wide thumb, or a big toe (hallux). The skin between the fingers and toes may be fused (cutaneous or osseous syndactyly). In some individuals, the syndrome may include permanently flexed fingers (camptodactyly), dislocation of the hip, protrusion of a portion of the large intestine through an abnormal opening in the muscular wall that lines the lower abdominal cavity (inguinal hernia). This disorder is also characterized by an abnormally large head size (macrocephaly), and

a high, prominent or protruding forehead (frontal bossing), high anterior hairline; a broad nasal bridge; and/or widely spaced eyes (ocular hypertelorism). In some cases, the fibrous joints (sutures) between certain bones in the skull may be abnormally wide and may close unusually late in development; but, in rare individuals, certain cranial sutures may close prematurely (craniosynostosis). Such irregular closure of the sutures may cause the head to appear unusually shaped (scaphocephaly, trigonocephaly, or plagiocephaly). Rarely, less than 10% of affected individuals may have more serious medical problems including seizures, delayed development, and intellectual disability, build-up of fluid inside the skull (hydrocephalus), and abnormalities affecting the nerve fibers (corpus callosum) that connect the two cerebral hemispheres of the brain may be present.

We have to consider these related disorders:

- a. Acrocallosal syndrome (ACLS): A rare genetic disorder typically inherited in an autosomal recessive pattern.
- b. Oro-facial-digital syndrome: A rare genetic disorder includes split tongue, splits in the jaw, midline cleft lip.
- c. Pfeiffer syndrome (acrocephalosyndactyly type V) is generally accepted to be the same as Noack syndrome inherited in an autosomal dominant pattern.

Mutations in the GLI3 gene related to chromosome 7 can cause Grieg cephalopolysyndactyly syndrome In most cases. This gene provides instructions for making a protein that controls gene expression, which plays a role in the normal shaping or patterning of many organs and tissues before birth, so it is inherited in an autosomal dominant pattern from either parent, or in rare instances of this disorder are sporadic, and occur in people with no history of the condition in their family result of a new mutation (gene change) in the affected individual. The risk of passing the abnormal gene from an affected parent to an offspring is 50% for each pregnancy regardless of the gender of the child. In most individuals with the severe form of the disorder, it is caused by a deletion of the entire GLI3 gene. The larger the deletion encompassing GLI3 gene is (greater than 300 kb), the more likely the individual will show these uncommon symptoms.

Learning Points

- a) The diagnosis of GCPS is based on clinical findings and family history.
- b) An Enlarged skull (macrocephaly) in ultrasound imaging during a pregnancy have to be considered.
- c) The diagnosis at birth is based upon clinical evaluation, identification of characteristic physical findings. (Head circumference greater than a 97th centile, distance between the pupils).

d) Procedures including X-rays and transfontanyl ultrasound and CT scanning reveals the extent of bone fusion in several occurrences of osseous syndactyly.

e) In future significant development delay or intellectual disability should have genetic testing through sequence analysis to detect possible changes in GLI3 gene.

f) Treatment may require the efforts of a team of such as pediatricians, orthopedists, plastic surgeons, physical and occupational therapists, and/or other health care professionals.

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