Carpenter syndrome – acrocephalopolysyndactyly – A case report

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Abstract
Carpenter syndrome, also called ACPS type2, belongs to a group of rare genetic disorder known as acrocephalosyndactyly, (ACPS). This condition is characterized by the premature fusion of certain skull bones (craniosynostosis), abnormalities of the fingers and toes, and other developmental problems. Mutations in the RAB23 gene, located on chromosome 6 and mutations in MEGF8 gene, located on chromosome 19 at 19q13.2, have been identified as primary causes of Carpenter syndrome. Pattern of inheritance is autosomal recessive. We report a case of Carpenter Syndrome in a male baby, 2 months old, born of consanguineous parents.

Keywords: Craniosynostosis, Acrocephaly, Postaxial Polydactyli

Introduction
Carpenter syndrome belongs to a group of rare genetic disorders known as "acrocephalopolysyndactyly" (ACPS) disorders, characterized by craniosynostosis, causing the top of the head to appear pointed (acrocephaly); syndactyly of certain fingers or toes; and/or polydactyly). Carpenter syndrome is also known as ACPS type II.

Case
A 2-month-old male baby, born of 3rd degree consanguineous parents, was referred by the pediatrician for dysmorphism. Delivered full term, by LUCS, cried at birth, b. wt was 2.5kg. On examination, there was macrocephaly (38cm), brachycephaly, asymmetric skull, pancraniosynostosis, ossified anterior fontanelle, excess and wrinkled skin between the eyes., very sparse hair, low set crumpled ears, smooth wide philtrum and progeroid look of the face [Fig. 1]. The fingers were short, and each finger had missing middle phalanx. The feet had b/l preaxial polydactyly, all toes showed cutaneous syndactyly [Fig. 2,3]. There was prominent umbilical hernia, and b/l undescended testes. There was no history of convulsions, the baby was hypotonic in all 4 limbs. Cardiac echo did not show any abnormality. Vision, hearing assessment was not done.

Previous child had similar features, but developed hydrocephalous at 4 months of age and died at 4.5 months.

Investigation reports
Whole exome sequencing was done for the proband.

There was homozygous pathogenic variant c.145C>T in the RAB23 gene, which is disease causing for Carpenter syndrome.

Genetic counseling
The couple was advised sanger sequencing for the target variant found in the proband. They were asked to do prenatal testing in their next pregnancy, by sanger sequencing of the same variant in the family, to see what was the status of the fetus - normal, unaffected heterozygous or affected homozygous (25% recurrence risk).

Fig. 1: Acrocephaly and brachycephaly

Fig. 2: Syndactyly polydactyly

Fig. 3: Brachydactyli

Discussion
Primary findings associated with Carpenter syndrome include premature closure of the cranial sutures (craniosynostosis), characteristic facial abnormalities. Craniosynostosis initially involves the sagittal and lambdoidal sutures; this is often followed by early closure of the coronal sutures. Such abnormalities may cause severe malformation of the skull -

pointed head (acrocephaly) or unusually short and broad head (brachycephaly).[1] Unilateral involvement of lambdoidal and/or coronal sutures may cause cranial asymmetry. Rarely, due to involvement of multiple cranial sutures (Kleeblattschadel type craniosynostosis), the skull appears to be abnormally divided into three lobes (cloverleaf skull deformity). Sometimes early closure of certain cranial sutures may lead to abnormally increased intracranial pressure.

Affected individuals present with malformations of the fingers and toes - brachydactyly (due to shortness or absence of the middle bones of the digits), cutaneous fusion between certain fingers & certain toes (syndactyly), supernumerary digits (preaxial polydactyly, less commonly, postaxial polydactyly). There may also be abnormal flexion (camptodactyly) and deviation (clinodactyly) of certain fingers. Hip deformity (coxa valga) may be present along with knees close together (genu valgum); and/or an abnormally curved spine (kyphoscoliosis).

Mild short stature and obesity, mild intellectual disability are common findings. There maybe hearing loss, both conductive and sensorineural hearing loss, congenital heart defects and/or talipes varus. Additional abnormalities may also be present, including abnormal skin ridge patterns of the hands.

Carpenter syndrome may be associated with eye (ocular) abnormalities- improper development, and/or clouding of the corneas, degeneration of the optic nerves (optic atrophy). Hypogoadism, undescended testes may be accompanying findings.

Sudden deaths have been reported, possibly due to acute and chronic cardiac complications[2]

Genetics

Carpenter syndrome is mainly caused by a mutation in the RAB23 gene, although mutation in the MEGF8 gene is found in a few individuals.[3-6] The mutations that cause Carpenter syndrome are inherited in an autosomal recessive manner. The risk of recurrence is 25% affected off springs, 50% carrier and 25% normal off springs.

Treatment

Specific therapies for Carpenter syndrome are symptomatic and supportive. Early surgery is advised to correct craniosynostosis which can cause increased intracranial pressure[7]. Reconstructive surgery is recommended to correct additional craniofacial malformations, polydactyly and syndactyly. Hearing aids for correcting deafness.

Source of Funding

None.

Conflict of Interest

None.

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