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Case Report

NEB Gene Novel Mutation Leading to Arthrogryposis Multiplex Congenita with Partial Corpus Callosum Partial Agenesis: A Case Report with Review of Literature

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Abstract

Arthrogryposis multiplex congenita (OMIM# 619334), involves a variety of non-progressive conditions that are characterized by multiple joint contractures and muscle weakness. Here we report a case of 8months male, case of Arthrogryposis multiplex congenital(AMC) type VI with partial corpus callosum agenesis having novel gene mutation pTyr5262His of the NEB gene on Exon 101, who presented to us with global developmental delay with multiple joint contractures.This child has been managed by a multidisciplinary team. AMC type VI with partial corpus callosum agenesis is rare and NEB gene mutation causing both has not been reported in any Indian setting.

Keywords: Arthrogryposis Congenita; Corpus Callosum; Agenesis; Mutation

Introduction

Arthrogryposis multiplex congenita (AMC) [OMIM# 619334] is a non-progressive disease characterized by multiple joint contractures and generalised muscle weakness since birth. Arthrogryposis is the medical term for joint crooking or bending. It is an uncommon condition that affects 1 in every 3,000 live births [1]. Reduced fetal movements and polyhydramnios are common complications during pregnancies. It can be detected antenatally using ultrasound. Reduced fetal movement during development can have a number of causes, including environmental factors (maternal illness, restricted space in utero), pathology of the central nervous system, including brain and anterior horn cells, chromosomal abnormalities, single gene changes, and various syndromes [2]. More than 400 genetic alterations have been associated to arthrogryposis [2]. These children often present with congenital joint contractures, dysmorphic facial characteristics, and distal skeletal deformities. Respiratory insufficiency, hypotonia, and numerous pterygia are seen. Typically, these children have normal speech and learning capabilities. Although co-existing abnormalities in the central nervous system is high, AMC type IV with partial callosal agenesis has not been reported from India.

Case Report

Eight months male born out of a non-consanguineous marriage presented to us with complaints of multiple joint contractures, gross and fine motor delay and delayed speech. Antenatal history suggested polyhydramnios with reduced fetal movement. Child's mother had history of 4 recurrent spontaneous abortions before the birth of this child. He was delivered at term by emergency caesarean section due to fetal distress. Child was kept in NICU for observation.

On examination, child had multiple contractures in bilateral lower limbs with syndactyly of 2nd and 3rd toes of both feet, bilateral simian crease, wrist stiffness, fisting of thumb, talipes equinovarus, clubfoot. Facial dysmorphism with frontal bossing, depressed nasal bridge, hypertelorism, epicanthal folds, arched eyebrows, retrognathia were also present. Anthropometry revealed microcephaly. Hearing and fundus examination were within normal limit. Examination of cranial nerves was normal including extraocular and facial movements. Tone was mildly increased with normal deep tendon reflexes and planters were extensor. Child was managed conservatively with cast, splinting devices and physiotherapy. Contractures have resolved to some extent and the child is better now. Child is regularly followed up in Pediatrc OPD.

Complete hemogram, thyroid profile and Karyotyping was normal (46, XY). X-rays lower limb revealed curved fibula and clubfoot. MRI Brain revealed upward extension of 3rd ventricle above the level of body of lateral ventricles in continuity with inter-hemispheric fissure and the frontal horns had a crescentic shape because of the impressions on the medial aspects made by the bundles of Probst bundles, suggestive of partial agenesis of corpus callosum (Figure 1). A provisional diagnosis of Arthrogryposis with partial corpus callosum Agenesis was made.

Clinical exome detected heterozygous missense mutation in exon 101 of NEB gene causing substitution of Histidine for Tyrosine at codon 5262 (Tyr5262His) leading to autosomal recessive condition known as Arthrogryposis multiplex congenita VI.

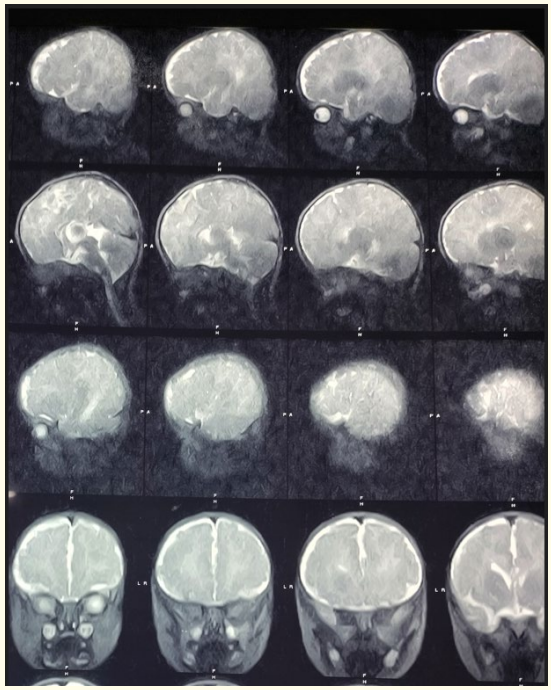

Figure 1: MRI Brain showing upward extension of 3rd ventricle with crescentric frontal horns suggestive of partial agenesis of corpus callosum.

Discussion

Arthrogryposis multiplex congenita VI (*OMIM #619334*) is caused by homozygous or compound heterozygous mutations in NEB gene on chromosome 2q23. This gene encodes a protein nebulin, which is present in the sarcomeres of skeletal muscles and plays an important role in muscle contraction. Cerebral dysplasia has been reported at autopsy in children with AMC and includes proliferation of subependymal glial elements, micropolygyria, cerebral gray matter heterotopias, lateral ventricular dilatation and absent corticospinal tracts [3,4]. Agenesis of the corpus callosum is often associated with other congenital malformations [4,5].

Although the reported co-existing abnormalities in the central nervous system are numerous but AMC has not been routinely associated with callosal agenesis. Hanga et al reported a similar case, where the infant had AMC, callosal agenesis, cerebellar vermis agenesis and smallness of muscle fibers [6]. Neu et al reported absence of the corpus callosum in one of three siblings with AMC,

however muscle biopsy was not done [7]. Neurogenic muscle changes have been reported in three unrelated families of French-Canadian descent, several members having complete agenesis of the corpus callosum and biopsy evidence of anterior horn cell disease [8]. Fenichel studied muscle biopsies of seven infants with AMC in an effort to differentiate the relative importance of brain damage versus disuse atrophy of muscle morphology. Muscle biopsies were normal on the two patients, who had no evidence of cerebral anomalies and normal developmental milestones. The remaining five patients with evidence of central nervous system disease (microcephaly, hypotonia, psychomotor retardation) had abnormal muscle biopsies [9].

Conclusion

Fenichel concluded that the integrity of the nervous system had a greater influence than did fetal mobility on maturation of muscle fiber types. Voorhies et al in their study observed pyramidal tract maldevelopment with callosal agenesis in 63%. The absence of the normal central influence, hypothetically pyramidal tract influence on the development of the lower motor unit and may presumably have resulted in muscle abnormalities and secondarily fixed joints [10]. None of the previously mentioned studies had any genetic work-up done. The fact that arthrogryposis multiplex congenita VI is manifesting in a heterozygous genotype in combination with partial corpus callosum agenesis makes it a unique case.

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