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Case Report

Multiple congenital anomalies-hypotonia-seizures syndrome 3 secondary to phosphatidylinositol glycan class T mutation: a neonatal case report

Ankit Ranjan*, M. Shahbaz Alam, Vinod Kumar, Snigdha Samanta, Rajesh Kumar, Khalid M. Saifullah

Department of Neonatology, Rani Hospital, Ranchi, Jharkhand, India

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***Correspondence:**
Dr. Ankit Ranjan,
E-mail: ankitranjan96@gmail.com

ABSTRACT

Multiple congenital anomalies-hypotonia-seizures syndrome 3 (MCAHS3) is caused by genetic defects in glycosyl-phosphatidylinositol transamidase complex synthesis due to mutations in the PIGT gene. The disease encompasses dysmorphism, cardiac, genito-urinary and skeletal anomalies, developmental delay and epilepsy in variable severity. Only 39 such cases have been reported till date in literature. We reported the first Indian case with neonatal presentation and overall the sixth case of MCAHS3 to present in neonatal age. The pro-band was a male baby born to non-consanguineous parents. He had perinatal depression, craniofacial dysmorphism, epileptic encephalopathy, left radio-ulnar congenital fractures and respiratory failure managed with multiple anti-epileptics, invasive ventilation and limb splinting. Clinical exome sequencing revealed an autosomal recessive homozygous PIGT gene mutation on exon 6 of chromosome 20 with a variant nomenclature of C.709G>C with heterozygous parents confirming MCAHS3. This report expands the range of information available on MCAHS3. It highlights the need to elaborately investigate dysmorphic newborns with severe hypotonia along with the described neurological symptoms, so as to pin point this potentially diagnosable entity.

Keywords: Congenital fracture, MCAHS3, PIGT, Homozygous mutation, Hypotonia

INTRODUCTION

Eukaryotic proteins require specific anchor molecules for their expression on the plasma membrane. Glycosylphosphatidylinositol (GPI) acts as a lipid anchor to more than 150 such protein moieties which play a crucial role in embryogenesis and neurogenesis along with cellular adhesion, signalling, intracellular transport and enzymatic activities.[1]

The mammalian GPI-TA is a hetero-pentameric complex comprising of 5 known subunits; namely PIGK, PGAA1, PIGU, PIGS and PIGT. Loss of function mutation in these genes leads to an amalgamation of neurological impairment, hypotonia, complex seizure semiology, multiple congenital anomalies of the cardiovascular, genitourinary and skeletal system, craniofacial dysmorphism and psychomotor retardation.[2]

Homozygous or compound heterozygous mutations in the PIGT gene presenting with the above spectrum are classified as MCAHS3 (OMIM#615398).[3] With only 39 cases of MCAHS3 reported till date, we describe a case of a floppy neonate with upper limb fractures, facial dysmorphism, neonatal onset intractable epilepsy who was diagnosed as MCAHS3 with a missense novel PIGT variant.

CASE REPORT

A 2900 g male neonate born at 38 weeks of gestation was referred to our hospital in a limp state on oxygen support at 4 hours of life. The baby was born out of a non-consanguineous marriage by emergency LSCS for decreased fetal movement with recurrent decelerations on cardiotocography.

The maternal and paternal age at this pregnancy were 30 and 31 years respectively. It was a poorly supervised pregnancy with limited ultrasound examinations. Mother was a known case of hypothyroidism managed with oral thyroxine supplementation. There was no history of fever with rash and lymphadenopathy in the first trimester, medical illness, any history of drugs and teratogen exposure or any liquor abnormality. Family history was not suggestive of repeated abortions, dysmorphism, delay in motor milestones and any premature death. This baby was born limp requiring positive pressure ventilation for 30 sec. Apgar scores and cord blood gas were not available. There was an alarming history of early male sibling death at 30 minutes of life around four years back. He was also born limp with severe bradycardia which didn't respond to resuscitation. However, genetic testing or autopsy could not be done due to non-availability at the delivery center.

Baby was referred to our hospital at four hours of life on oxygen by nasal cannula. On examination, he had a Downe's score of 5 requiring escalation of respiratory support to heated humidified high flow nasal cannula (HHHFNC) with a flow of 6 l/min and FiO_2 of 30%. Weight, head circumference and length were at 30th, 80th and 60th percentile respectively as per modified Fenton chart.[4] Baby was dysmorphic with brachycephaly, high forehead, bitemporal narrowing, depressed nasal bridge, long and deep philtrum, wide open mouth, sagging of the lower jaw, high arch palate and pectus excavatum. He had a strikingly swollen and erythematous left forearm with crepitus on palpation raising a clinical suspicion of fracture. Proximal and distal upper limb and lower limb pulses were intact. Clinodactyly with dynamic contractures of second to fifth meta-carpophalangeal and inter-phalangeal joints were noted in both the upper limbs. Genitalia, spine and lower limb examinations were unremarkable.

On neurological examination, baby was mildly stuporous with lack of habituation response. Cranial nerve examinations revealed an intact pupillary response with normal red reflex. There was presence of vertical nystagmus with esotropia. Rooting and sucking reflexes were absent. Weak startle and gag response were appreciated. Facial and hypoglossal nerve examinations were normal. Motor examination was suggestive of gross axial and appendicular hypotonia. Lower limb reflexes were just elicitable. Moro's reflex was incomplete with partial palmar and plantar grasp response. Cardiovascular examination revealed a grade two systolic murmur on auscultation with normal heart sounds. Gastrointestinal system examination was insignificant.

After initial stabilization, baby was shifted to NICU. Multiple seizure episodes of mixed semiology including generalized tonic-clonic, myoclonic and tonic seizures with ocular and oral deviation were noticed at 7 hours of life. A brief control was achieved on sequentially introduced quadruple therapy with phenobarbitone, fosphenytoin, levetiracetam and clonazepam. Baby was subsequently initiated on tube feeds which he tolerated well. An infantogram revealed generalized osteopenia with fracture of left mid shaft of radius and ulna without any vertebral malformation. A splint was applied from the left elbow till the left wrist joint after an orthopedic consultation (Figure 1).

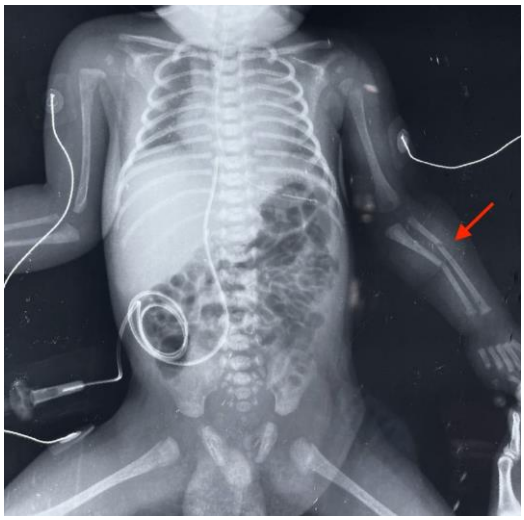

Figure 1: X-ray of the chest, abdomen and upper limbs showing generalized osteopenia with left sided radio-ulnar fracture.

Baseline blood investigations revealed hypophosphatasia, a mildly raised creatine phosphokinase with a normal serum calcium and phosphorus (ALP= 182 IU/l, CPK= 503 µg/l, serum calcium 8.5 mg/dl, serum phosphorus 5.3 mg/dl). Hemogram, sepsis screen and blood gas were within normal limits. An echocardiography was done as a part of syndromic work up, which was suggestive of a small ostium secundum atrial septal defect (OS-ASD) of 3 mm size with left to right shunt with normal biventricular function. Renal ultrasonography was unremarkable however serial cranial ultrasound did show mild ventriculomegaly without any other structural abnormality. Owing to a vast phenotypic constellation of symptoms under consideration with a similar history in sibling, high suspicion of a genetic etiology was kept for which Clinical Exome Sequencing was ordered.

Baby could be gradually weaned off from the respiratory support with escalating feeds which he tolerated well over the subsequent 10 days. On day 12 of life, he had acute respiratory deterioration requiring invasive mechanical

ventilation secondary to right sided lower zone consolidation requiring intravenous antibiotics. Culture of endotracheal aspirate grew multidrug resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* which was treated with appropriate sensitive antibiotics. Multiple extubation trials were attempted over the next three months, but the baby failed to sustain a normal respiratory pattern requiring re-intubation within 12 hours of extubation owing to respiratory muscle hypotonia. Hearing and retinopathy of prematurity screenings were normal. Patient remained hemodynamically stable throughout the subsequent hospital stay and was managed on minimal ventilatory support and tube feeding. Occasional myoclonic seizures continued to be noted which were controlled after addition of 100 mg of oral pyridoxine.

Clinical exome sequencing result revealed an autosomal recessive homozygous PIGT gene mutation on exon 6 of chromosome 20 with a variant nomenclature of C.709G>C (p.Glu237Gln) fitting into the diagnosis of multiple congenital anomalies-hypotonia-seizure syndrome 3 (MCAHS3). Sanger sequencing confirmed the presence of previously detected homozygous c.709G>C (p.Glu237Gln) variant (pathogenic) in exon 6 of PIGT gene (NM_015937.6) via next generation sequencing. With the backdrop of homozygous gene defect in the index case, parental clinical exome sequencing was conducted. Both the parents were heterozygous for the above tested PIGT variant; thus, confirming the diagnosis of MCAHS3 in this case.

The infant had to be discharged against medical advice on oxygen support at an age of 12 months due to personal issues in the family. At the final evaluation in hospital; the weight, head circumference, and length were at 30th, 66th and 75th centiles respectively as per the WHO growth charts. The infant was still floppy with spontaneous eye opening, just elicitable deep tendon reflexes with marked axial and appendicular hypotonia. He had an abnormal visual fixation with inability to follow objects, though a startle response to auditory stimulus was present with a normal oto-acoustic emission in both the ears. Unfortunately, he succumbed to death after 8 hours of leaving the hospital (as per telephonic conversation with parents).

DISCUSSION

The first case involving biosynthetic defect in GPI-AP was described in 1970 by Mabry et al with four siblings presenting with mental retardation, seizures and raised ALP levels.[5] The PIGT subunit plays a critical role in generation of carbonyl intermediates facilitating protein attachment and confers stability to the GPI-TA complex by linking the PIGS subunit to the PGAA1 subunit. PIGT mutation presents as a constellation of seizures, hypotonia, psychomotor retardation and congenital anomalies. A homozygous PIGT gene mutation was first described by Kvarnung et al in 2013 (PIGT variant c.547A>C, p.Thr183Pro) in a consanguineous Turkish family of 4 patients presenting with hypotonia, craniofacial dysmorphism, intellectual disability, renal cysts and restrictive cardiomyopathy with generalized osteopenia.[6] Bayat et al reported the largest case series of MCAHS3 patients with 15 novel patients with homozygous and compound heterozygous pathogenic variants. This study described a milder phenotype with treatable epilepsy in cases with the missense c.1582G>A variant (p.Val528Met) seen till date only in Caucasians.[2,7] A recent series of seven novel Polish patients, all having the same variant have supported the conclusion of less severe phenotype with Val528Met variant.[8] The missense pathogenic PIGT variant in our index case (c.709G>C; p.Glu237Gln) is novel with only 3 such cases reported in literature till date. It was first reported in an Afghanistani male by Pagnamenta et al in a homozygous state.[9] Subsequently, the same variant was found in a pair of Bangladeshi female siblings in Bayat et al cohort pointing to an Asian origin. In all the 4 cases (including the index case), neonatal onset epileptic encephalopathy was the norm. This differed from the infantile onset seizures often provoked by febrile episodes which were previously reported with other variants. Another striking finding of congenital fractures as seen in our case was reported only once in one of the Bangladeshi siblings in the Bayat et al cohort.[2,7] This points to a probability of severe phenotypic correlation with the C.709G>C (p.Glu237Gln) PIGT variant as epileptic encephalopathy was noted as early as the neonatal period along with congenital fractures; never described with any other variant.

Seizure semiology ranged from generalized tonic-clonic, myoclonic, atonic and dyscognitive seizures in most of the published cases. However, episodes of epileptic apnea have been described by Kohashi et al, Nakashima et al and Bayat et al.[2,10,11] Multifocal epileptiform activity was observed as the most common preliminary EEG finding. Surprisingly, two patients with intractable epilepsy presented with normal EEG patterns at the onset of epilepsy.[2] This supports an ongoing continuum of changes in the EEG pattern as the disease evolves. MRI brain illustrated cerebral, cerebellar and brainstem atrophy as prominent findings. Out of the four cases reported with the C.709G>C variant (index variant), neuroimaging was feasible only in one patient. This patient showed white matter immaturity without any evidence of cerebellar atrophy.[7] Unfortunately, MRI brain and EEG study were not available in our index case due to logistic constraints and sick status of the infant posing risk of life during transport. Majority of the cases were intractable and necessitated the use of zonisamide, topiramate, high doses of phenobarbitone and ketogenic diet, although with poor results. We found pyridoxine therapy to be effective in the index patient reducing the seizure duration as well as frequency. Only one case describing PIGO mutation reported intractable epilepsy responding to pyridoxine as noted in our case.[12] Congenital anomalies involving the skeletal, genitourinary, and cardiovascular and respiratory system have been noted in varying proportions across the

reported cases. However, no critical cardiac or renal malformations were noted in the 4 cases with the index PIGT variant c.709G>C (p.Glu237Gln). Low ALP values were noted in the index case along with seven other reported cases. This could be explained by ALPL protein dysfunction due to reduced GPI anchoring leading to hypophosphatasia, generalized osteopenia and skeletal manifestations as severe as bony fractures.

CONCLUSION

This report expands the umbrella of information regarding PIGT variants. As the genotype-phenotype correlation is still evolving, it highlights the need to elaborately investigate dysmorphic newborns with severe hypotonia along with the described neurological symptoms, so as to pin point this potentially diagnosable entity. Large population based, multicentric studies would help decipher distribution and predisposition of specific dysmorphic, clinical, laboratory features according to subtypes of genetic mutations.

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