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Case Report

Familial isolated hypoparathyroidism type 2: a case report with review of literature

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ABSTRACT

Familial isolated hypoparathyroidism (FIH) is a rare group of genetic disorder associated with dysregulation of parathyroid hormonal axis characterized by refractory hypocalcaemia. Herein we report a 1 month 4 days old baby born out of consanguineous marriage presented with respiratory distress with single episode of convulsion, cause pointing towards hypocalcaemia. The hypocalcaemia symptoms were refractory despite repeated calcium gluconate. Laboratory parameters yielded evidence of hypoparathyroidism which was further strengthened by neuroimaging and skeletal imaging. The hypoparathyroidism was treated by oral calcitriol and calcium supplementation along with institution of phosphate binder. Whole genome exome sequencing revealed a novel nonsense mutation of glial cell missing transcription factor 2 (GCM2) gene variant c.109C>T (p.Gin37Ter) establishing the diagnosis as FIH type 2. The calcium and phosphate normalized in further follow up. The new found locus and the novel variation of GCM2 gene adds another feather to the ever-evolving genetic conundrum of the disease.

Keywords: Hypoparathyroidism, Hypocalcaemia, GCM2

INTRODUCTION

Familial isolated hypoparathyroidism (FIH) is a rare heterogenous group of inherited disorder which manifests due to dysregulation of calcium metabolism due to insufficiency of bioactive parathormone without other coexisting endocrinal pathologies often attributed to symptoms of refractory hypocalcaemia which shows varying pattern of mendelian inheritance like autosomal dominant, autosomal recessive or X linked recessive type.[1] Sporadic cases has been reported throughout the world yet so little is known about the natural course and management of the disease. Herein we report a case of FIH caused by a novel nonsense mutation of Glial cell missing transcription factor 2 (GCM2) gene in a 34 days old male baby showing autosomal recessive inheritance that can help future clinicians to think beyond the usual aspects of refractory hypo-calcaemic seizures and also aid to diagnosis and successful management of the same.

CASE REPORT

A 34 days old exclusively breastfed baby who was a first order child out of a consanguineous wedlock, presented with one episode of bilateral tonic-clonic convulsion not associated with fever. The baby had uneventful antenatal, natal and postnatal period and without any family history of epilepsy.

Initial investigations ruled out hypo-glycaemia and no organomegaly and gross dysmorphism, no specific urinary odour noted. Blood gas analysis showed severely low ionic calcium (iCa) 0.68 mmol/l and ECG showed QT prolongation (505 msec). He was treated with anti-convulsant phenobarbitone loading dose (20 mg/kg), and calcium bolus as 10% calcium gluconate (2 ml/kg with equal volume of 5% dextrose over 10 mins) with infusion (8 ml/kg/day for 2 consecutive days followed by 4 ml/kg/day on 3rd day under cardiac monitoring.

Sepsis screening came negative and a repeat blood gas analysis showed persistence of low calcium (iCa-0.58 mmol/l) and the Serum calcium came out to be 6.1 mg/dl with normo-albuminemia. Meanwhile the baby started having multiple episodes of tonic-clonic convulsion with appearance of carpopedal spasm which was again treated with another bolus of 10% calcium gluconate followed by maintenance infusion followed by 50% magnesium sulphate intramuscular 100 mg/kg 12 hours apart to treat the refractory hypocalcaemia.

Further investigations showed high level of serum phosphate (8 mg/dl), with normal alkaline phosphatase, Serum magnesium, serum urea, creatinine, vitamin D. Concurrently thyroid function test, anti-thyroid peroxidise (TPO) antibody assay, 2D echocardiography, urine 24 hr calcium and spot calcium creatine ratio, sleep electroencephalogram (EEG) were done but no abnormalities were detected. Subsequently the serum intact parathormone (iPTH) level was found to be very low (1.10 pg/ml) and a diagnosis of hypoparathyroidism was made. On stabilisation non contrast CT brain was done and it revealed right basal ganglia calcification (Figure 1) and skeletal x ray of hand were also suggestive of osteosclerosis of metacarpal bones (Figure 2). Later the baby was started on oral calcitriol (150 ng/kg/day), oral calcium (200 mg/kg/day), oral sevelamer (150 mg/kg/day), with continuation of breast-feeding and whole exome sequencing was planned.

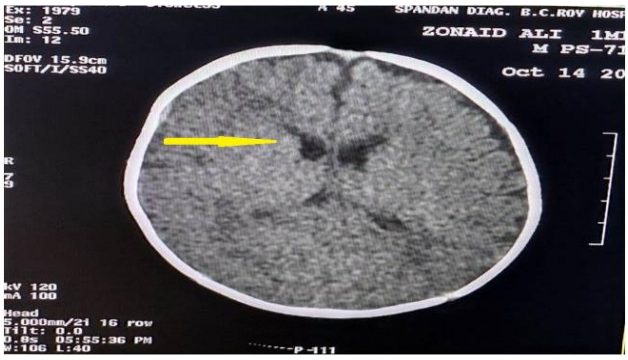

Figure 1: NCCT brain revealing right sided basal ganglia calcification (marked by yellow arrow).

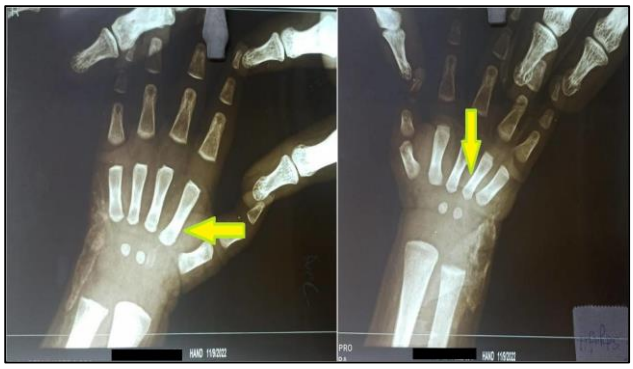

Figure 2: X ray of hand showing features of osteosclerosis (marked by yellow arrow).

Whole exome sequencing report yielded presence of a homozygous novel variety of nonsense mutation in the GCM2 gene located in the exon 2. The mutated variation of [p.Gln37Ter] in the GCM2 gene has not yet been addressed in any medical literature and presence of such pathogenic mutation leads to a final diagnosis of FIH type 2 which shows a pattern of autosomal recessive inheritance. Parental sanger sequencing could not be done due to financial constraint.

On follow up after 3 months' serum calcium, iCa, serum phosphate has been found to be normalized with a value of 10.2 mg/dl, 1.1 mol/lit, 4.3 mg/dl respectively and the baby is free from any new onset convulsions or carpopedal spasm with age-appropriate achievement of normal developmental milestones.

DISCUSSION

Hypoparathyroidism is an unusual metabolic pathology characterized by features of hypocalcaemia, hyperphosphataemia due to absence or reduction of circulating parathormone concentration. Hypoparathyroidism can either exist as an isolated endocrinopathy named as isolated hypoparathyroidism attributed to different familial genetic variations or can be secondary to different diseases. Anterior neck surgery is the most common cause of acquired hypoparathyroidism contributing almost 75% of cases followed by non surgical causes attributed to autoimmune disease involving multiple endocrinal glands like autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome, Di-george syndrome, hypoparathyroidism, sensorineural deafness, renal anomaly (HDR) syndrome, Barakat syndrome, Kenney-Caffey disease, Sanjad-Sakati syndrome, Kearns-Sayre syndrome and can be also due to metastatic infiltration, iron or copper overload or radiation exposure.[2-4] Based on genetic heterogeneity, FIH-1 (OMIM #146200) is caused by heterozygous, homozygous, or compound heterozygous mutation in the parathyroid hormone gene (PTH) located on chromosome 11p15.[3] In our case FIH 2 was attributed to homozygous nonsense mutation of GCM2 (OMIM #618883).

FIH, with the exception of male exclusive X-linked form, affects males and females equally. The prevalence of overall nonsurgical hypoparathyroidism is 2.3/100 000 person-years which clearly states the rarity of the isolated hypoparthyroidism.[5] The onset of symptoms of the disease is usually during early childhood or infancy but may occur at any period from birth to adulthood. Hypocalcaemic seizures during infancy may be the initial sign of the underlying disorder. The symptoms of hypoparathyroidism are primarily due to subnormal levels of serum calcium leading to neuromuscular irritability and characterized by numerous symptoms including numbness, tingling, carpopedal and facial spasms, and seizures.[3]

Diagnosis of hypoparathyroidism from laboratory parameters is pretty straight-forward however, eliciting nonsurgical cause behind isolated hypoparathyroidism needs clinical exome sequencing as this yields a genetic background. In our case the gene identified was glial cells missing 2 and variant reported c.109C>T (p.Gin37Ter). This gene acts as binary switch between glial cell and neuronal differentiation in Drosophila. An ortholog of the gene, GCM2 serves as embryological regulator for parathyroid gland which contains a conserved n-terminal GCM motif that possess DNA binding activity. GCM2 gene localized to chromosome 6p24.2 and its five exons encodes a transcription factor constituting of 509 amino acids mainly expressed in developing and mature PTH secreting cells that mediate the activity of calcium on parathyroid hormone expression.[1] Various mutation of GCM2 like gene single nucleotide variation, missense, nonsense, frameshift mutations have been identified in previous cases of FIH2 depicted in Table 1. In our case the novel variant c.109C>T (p.Gin37Ter) is a stop gained variant which causes nonsense mediated decay along with another pathogenic loss of function variant 99 residues. Other genetic variations leading to this disease are gain-of-function mutations of calcium-sensing receptor gene (CASR), gene encoding Gα11 protein (GNA11), X-linked inheritance due to SOX3 gene.[1]

Table 1: Summary of identified GCM2 mutations in different studies.

Author	Year	Number	Mutation	Locus
Ding et al[2]	2001	1 case	Deletion	NG_008970.1:g.3172_(10967_10971)
Baumber et al[6]	2005	1 family (4 pts)	Missense	NM_004752.4(GCM2):c.140G>T (p.Arg47Leu)
Thomee et al[7]	2005	2 siblings	Missense	NM_004752.4(GCM2):c.187G>A (p.Gly63Ser)
Mannstadt et al[8]	2008	2 families	Frameshift	NM_004752.4(GCM2):c.1400del (p.Pro467fs)
Canaff et al[9]	2009	2 families	Frameshift	NM_004752.4(GCM2):c.1389del (p.His465fs)
Bowl et al[10]	2010	8 families	Frameshift	NM_004752.4(GCM2):c.893del (p.Ile298fs)
Guan et al[11]	2016	7 patients	2 variants	p.[Gln251Glu; Leu379Gln] p.Tyr394Ser
Castano et al[12]	2021	5 patients	Frameshift missense	c.1185_1186insGCCTACCAG c.1460C>T
Index case	2022	1 case	Nonsense	NM_004752.4(GCM2):p.Gln37Ter (c.109C>T)

Treatment is aimed at raising serum calcium level without inflicting hypercalcuria and food and drug administration (FDA) has approved vitamin D analogs and calcium supplements as the conventional therapy for all types of hypoparathyroidism. The main form of active vitamin D used is 1,25 OH vitamin D3, calcitriol whether other synthetic forms often used are cholecalciferol and dihydrotachysterol which have a longer duration of action than calcitriol. Patients with hypoparathyroidism are often supplemented with calcium rich diet like dairy products, breakfast cereals, fortified orange juice and green, leafy vegetables.[3,13] In our patient Sevelamer, a phosphate binder is also added along with calcitriol as the patient showed significant hyperphosphataemia. Elkattawy et al. has described the efficiency of sevelamer in managing hyperphoshataemia in a patient with acquired hypoparathyroidism.[14] Another study by Constantin et al. also supported concomitant use of calcitriol and sevelamer to combat the effects of hypoparathyroidism.[15] Parathormone (PTH) replacement therapy has been new adjunctive therapy in treatment of the disease and long-term controlled studies done in both adults and children comparing recombinant PTH 1-34 analog teriparatide with conventional therapy have passed in both safety and efficacy domain when once or twice daily PTH injections used subcutaneously and many patients of hypoparathyroidism have shown drastic improvement worldwide.[16,17] It has also been observed that if well treated, normal life expectancy can be achieved but quality of life may be negatively influenced.[18]

CONCLUSION

This is a detailed case review of FIH type 2 due to a nonsense mutation of GCM2 along with review literature which boasts upon a novel variant identification along successful management of the disorder.

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