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Case Report

A rare case of neuro regression in an Indian child: beyond the realm of nervous system

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ABSTRACT

When we encounter a child with dysmorphism and developmental delay or regression, we are prompted to think on lines of a disorder of nervous system. However, at times a disorder primarily involving another system, more importantly, a modifiable condition, could be responsible for same phenotypic presentation. A 6 years old male child with global developmental delay, dysmorphism, seizures and new onset regression appeared to be suffering from some neurodegenerative disorder on first impression. As detailed examination, lab investigations and imaging findings were noted, a rare endocrinal disorder was unravelled and a diagnosis of pseudohypoparathyroidism (PHP) type 1A was made and was genetically confirmed.

Keywords: Neuro regression, Seizures, Hypocalcaemia, Hyperphosphatemia, Soft tissue calcifications, PHP

INTRODUCTION

The aetiology spectrum for neuro regression in infants and toddlers is diverse.[1] In clinical practice, whenever we encounter a child with dysmorphism and developmental delay or regression, we are prompted to think of a disorder of nervous system. Rarely, a disorder primarily involving a system other than nervous system could be responsible for same phenotypic presentation. The nervous system and the endocrine system are closely interrelated and both involved intimately in maintaining homeostasis. At times, endocrine dysfunctions may lead to various neurologic manifestations and so, it is valuable to think about endocrine disorder as a cause of the neurologic manifestations in relevant clinical setting. Early diagnosis and treatment of hormonal imbalance can rapidly relieve the neurologic symptoms and help in achieving good outcome.[2]

CASE REPORT

A 6 years old, male child, with background of developmental delay and epilepsy was admitted with multiple episodes of breakthrough seizures. Seizure semiology was focal unaware type, with widening of eyes, shrill cry and stiffening of limbs, involving the right or left side. There was no history of fever, cough, vomiting or any other illness. Birth History revealed that the child was born at term by LSCS for fetal bradycardia and oligohydramnios, had cried immediately, with a birth weight of 2.5 kg. There was no NICU admission and neonatal period was uneventful (Figure 1). Developmental milestones were delayed according to parents as the child started standing independently at 2 years, walking at 2.5 years and running at the age of 3 years. Motor milestones were more delayed than language and social milestones. Detailed history also revealed that the child was shown to local paediatrician at 1 year of age for developmental delay and excessive

weight gain and at that time, the child was started on l-thyroxine for hypothyroidism in view of high TSH values (Figure 2). Seizures started at 3 years of age and child was given levetiracetam, however detailed work up was not done at that time. Parents also noted some motor regression in last 2 years in the form of difficulty walking with unsteady and broad-based gait. However, there was no regression in social interaction and language communication according to parents.

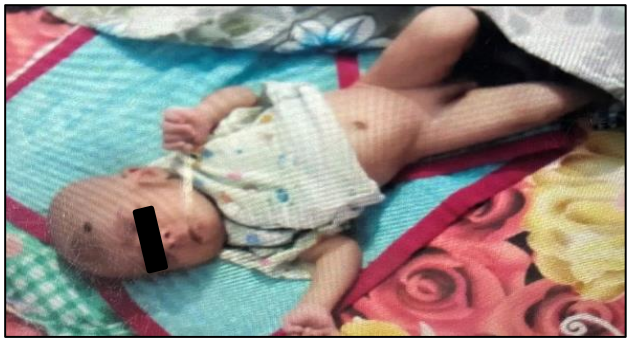

Figure 1: At 1 month of age.

Figure 2: At 1 year of age.

As the child was admitted with us with breakthrough seizures, a top up of injection levetiracetam was given and maintenance dose was increased. The seizures stopped and the child was back to baseline in few hours. VBG on admission, showed low ionised calcium (0.54 mmol/L), so injection calcium gluconate was also started. Later, on detailed examination, child had dysmorphic facies in the form of large head (box like), hypertelorism, low set ears, broad, flat nasal bridge and high arched palate (Figure 3 and 4). He had short broad hands and feet, normal spine, no neuro cutaneous marker and presence of bilateral cryptorchidism. Anthropometry showed a height of 107 cm (3rd-10th percentile), weight of 21 kg (50th-75th) and head circumference of 51 cm.

Figure 3: Dysmorphic facies.

Figure 4: Dysmorphic facies.

Higher function was good as child was aware of surroundings, responded socially, could comprehend and talk but speech was unclear. No cranial nerve abnormality was noted and motor examination was normal except that the gait of the child was unsteady and broad based. Cardiovascular system was normal and abdomen was soft with mild hepatomegaly. Based on history and clinical presentation, a possibility of neurodegenerative or metabolic disorder was suspected. Slit lamp examination was normal, but fundoscopy showed bilateral papilledema. Parents showed old papers of ophthalmic examination done 1 year ago and bilateral papilledema was noted at that time also. USG abdomen was normal.

Lab reports showed normal complete blood picture, liver function test, kidney function test (urea, creatinine, electrolytes). Serum calcium was low, 5.1 mg/dl, vitamin D was 81.3, serum magnesium was 1.54 mg/dl, ALP was 173, TSH and T4 were 4.98 and 8.79 respectively, and serum phosphorus was very high at 11 mg/dl. Parathormone levels was also very high to the tune of 627. At this point, we considered the possibility of vitamin D resistant rickets (but no alopecia and serum

phosphorus were high) or PHP. X-ray of hands and legs were done which showed osteopenia, short and deformed phalanges, early epiphyseal fusion, exostosis and soft tissue calcification (Figure 5 and 6). MRI brain was done and it revealed subtle basal ganglia and deep white matter calcification (Figure 7 and 8). Based on the clinical features, lab and imaging findings, a final diagnosis of PHP, likely type 1 A (presence of Albright's hereditary osteodystrophy (AHO) features) was made. Genetic test was sent. The child was treated with oral calcium, calcitriol, phosphate binders, L-thyroxine and levetiracetam and was discharged to follow up from OPD. On follow up after 4 weeks, there was significant improvement in gait, motor functions and cognitive function. Repeat blood test showed improvement in all parameters (serum phosphorus-7.2, calcium-8.9, PTH-601, vit D-57, creatinine-0.59).

Clinical exome sequencing showed that a heterozygous 3 base pair insertion in exon 1 of the GNAS gene (chr 20), that results in the in-frame insertion of amino acid leucine at codon 46 (p.Leu46dup), was detected (Table 1). This variant was a deep intronic variant and was confirmed by sanger sequencing. Child is doing well on medicines and is advised IQ testing to assess the degree of intellectual disability. Parents have been advised to undergo genetic testing also.

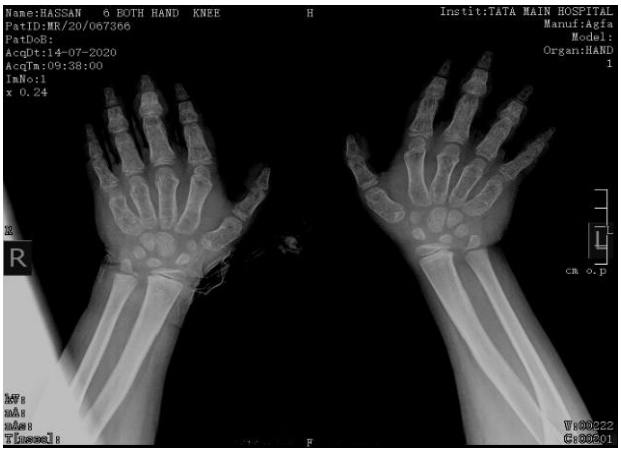

Figure 5: X-ray of hands.

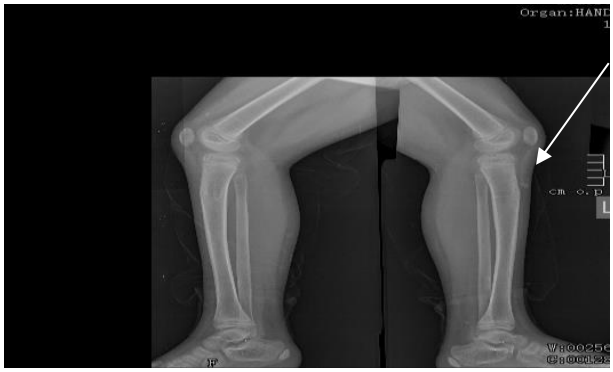

Figure 6: X-ray of legs of calcifications.

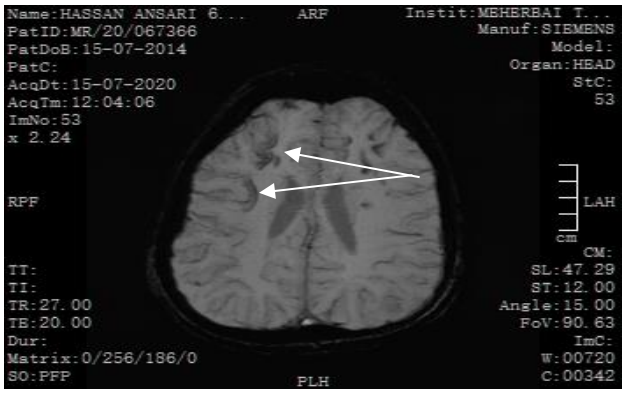

Figure 7: MRI (SW) of gyral calcification.

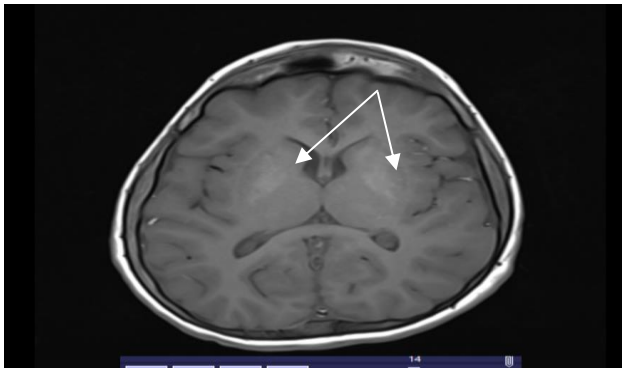

Figure 8: MRI (T1) of basal ganglia calcification.

Table 1: Genetic test report of GNAS mutation.

Likely pathogenic variant causative of the reported phenotype was detected.						
Gene (Transcript)*	**Location**	**Variant**	**Zygosity**	**Disease (OMIM)**	**Inheritance**	**Classification**
GNAS (+) (ENST00000354359.11)	Exon 1	c.136_138dup (p.Leu46dup)	Heterozygous	Pseudo hypoparathyroidism Pseudo hypo parathyroidism la, lb and lc	Autosomal dominant	Likely Pathogenic

*The GNAS variant was found to be genuine by Sanger sequencing.

DISCUSSION

In 1942, Fuller Albright et al. described a disorder characterized by end-organ resistance to parathyroid hormone (PTH) resulting in increased serum PTH levels, hypocalcaemia and hyperphosphatemia.[3] The patients lacked the appropriate response to administration of PTH and had blunted urinary cAMP and phosphate excretion. The condition was named 'pseudohypoparathyroidism' (PHP). It's a rare disorder with estimated prevalence being 0.34-1.1 in 100.000.[4,5] There are different types of PHP. The classical form of PHP, pseudohypoparathyroidism type 1A (PHP1A), which is associated with Albright's hereditary osteodystrophy (AHO), is caused by de novo or autosomal dominantly inherited inactivating mutations within the Gsα-coding GNAS gene.[6] AHO is characterized by short stature, brachymetaphalangism, subcutaneous ossifications, cognitive/behavioural impairments, obesity and metabolic disturbances.[7] Many patients with PHP 1a present with subclinical hypothyroidism in infancy because of resistance to TSH action.[8,9] The biochemical profile in patients with PHP 1a shows evidence of PTH resistance, with elevated serum concentrations of PTH and phosphate, and low or normal serum levels of ionized calcium. Resistance to PTH action could lead to hypocalcaemia which could be complicated by hypocalcaemia seizures. Learning disabilities and psychomotor retardation have been described in PHP 1a.[8,10] Our child described above also demonstrated the clinical, biochemical and imaging abnormalities similar to PHP 1a and was also detected to have hypothyroidism in infancy for which he received thyroid replacement therapy. The goals of pharmacotherapy are to correct calcium deficiency and to reduce morbidity. Intravenous calcium is the initial treatment for all patients with severe symptomatic hypocalcaemia followed by oral calcium and 1alpha-hydroxylated vitamin D metabolites, such as calcitriol. Aim of therapy is to maintain serum total and ionized calcium levels within the reference range, supress PTH levels to normal range and avoiding development of hypercalciuria. If the serum phosphate levels are high, then diet with low phosphorus is suggested and phosphate binders are also used as treatment. The child should be regularly monitored and resistance to other hormones e.g., TSH, gonadotropins, growth-hormone-releasing hormone, and glucagon should be identified and treated appropriately.[11]

CONCLUSION

So, on first impression, based on appearance and clinical presentation of seizures, dysmorphic facies and neuro regression, it was thought to be a case of a neurometabolic disorder but as detailed history was revealed and lab investigation reports came to light, a rare endocrinal disorder, PHP 1a, was diagnosed. Presence of severe hypocalcaemia which was seen on first line investigation (as blood sugar, serum calcium and electrolytes are done in all children presenting with acute seizures) and presence of long-standing papilledema was a clue to investigate further into the cause of hypocalcaemia. Further lab tests like serum phosphorus, PTH, vitamin D and X-ray of limbs and MRI brain helped in making the final diagnosis. Positive response to treatment was noted on follow up.

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