A rare case of 4H syndrome: A novel association

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Abstract

Hypomyelination, hypodontia, hypo gonadotropic hypogonadism (4H) syndrome is a rare syndrome which presents with varying degrees of developmental delay and ataxia with delayed eruption of teeth along with disruption in the eruption sequence and hypo gonadotropic hypogonadism. Here we describe a 13 year old girl with hypomyelination, hypodontia, and hypo gonadotrophic hypogonadism presented with progressive ataxia and developmental delay with MRI imaging suggestive of hypo myelination.

Key words: 4H syndrome,Hypodontia,Hypo gonadotropic hypogonadism,Hypo myelination.

Introduction:

Disorders of cerebral white matter can cause childhood neurologic disease, often with an unresolved etiology[1]. Recently, MRI has allowed the delineation of several new disease entities[2]. Still, hypomyelinating disorders often remain unsolved, although recently mutations in connexin 46.6 were described to cause a form of Pelizaeus–Merzbacher like disease.[3]

4H syndrome is a rare hypomyelination disorder, resulting from mutation in POLR3A and POLR3B genes with autosomal recessive inheritance grouped as pol III–related leukodystrophies. Around 105 cases are reported worldwide till now. It presents with spastic ataxic syndrome with fluctuations in clinical course and varying periods of stability along with hypodontia, hypo gonadotropic hypogonadism (figure:1) and characteristic magnetic resonance imaging findings.

We report a 13 year old girl with developmental delay, hypomyelination, hypodontia, hypogonadotropic hypogonadism with disruption in sequence of teeth eruption who presented with cerebellar ataxia.

Case report:

Here is a 13 year old girl born out of second degree consanguineous marriage presented to us with swaying to one side while walking since 3 months. She was noticed to have poor coordination and balance while walking since last 3 months along with head nodding and involuntary abnormal eye movements while fixing at objects. Her birth history was not significant, born through normal vaginal delivery with birth weight of 2.5kg with no perinatal asphyxia. She was having global development delay involving 3 domains mainly; gross motor, social and language where she is just able to walk upstairs and downstairs with jumping and she can ask questions to parents and is not able to sing songs or poems and knows her full name and gender with no group play or social activity with a development quotient of 42%.

At admission child had fever, cough and cold which was treated with intravenous antibiotics. Child gives history of repeated episodes of respiratory infection in the past. Her tooth eruption sequence was abnormal, with molars erupting first, followed by premolars, and till now her dentition is not complete. There was no history of altered sensorium, seizures, vision disturbances or hearing insufficiency. Family history was not contributory. Her head circumference was normal. She had short stature with height less than 3rd centile. There were no dysmorphism, no neurocutaneous markers, axillary and pubic hair were absent with Tanner staging B2P1 Her BMI was 17.5. She had absent lower central incisors (fig: 2) and there was no cataract and fundus examination was normal. She had bilateral gaze evoked nystagmus and cerebellar signs along with mild spasticity of both lower limbs. There was no organomegaly. Spine and cranium were normal. Her blood biochemistry, hemogram, and basic metabolic workup were normal. Her hormonal profile revealed normal thyroid hormone levels, low levels of luteinising hormone, and follicle-

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stimulating hormone (Table:1). USG abdomen showed small uterus (30*10*20mm) and ovaries (prepubertal size). Her brain MRI (Fig 3) showed hypomyelination, the degree of which varied between different regions of the brain, with Abnormal T2 hypo intensity and T1 hyper intensity involving basal ganglia, thalami and brain stem symmetrically and bilaterally. Subtle myelination noted in bilateral perirolandic whitematter and middle cerebellar peduncle, t2 hyper intensity in sub cortical and deep lobar white matter of cerebral hemispheres. There was mild cerebellar atrophy. Child was treated conservatively with amantadine and multivitamins, and there was mild improvement in symptoms on follow up at 6 months.

Table1:INVESTIGATIONS

HB	12.5 gm%
TLC	14800 cells/cu.mm
RBC	4.5million cells/cu.mm
PLATELET	2.1lakh cells/cu.mm
CRP	6mg/L
SODIUM	142 mEq/L
POTTASIUM	4.5 mEq/L
CHLORIDE	103 mEq/L
UREA	35 mg%
CREATININE	0.8 mg%
CALCIUM	10 mg%
MAGNESIUM	2.5 mg%
THYROID PROFILE	NORMAL
FSH	2.32mIU/ml
LH	0.97mIU/ml

Figure 1: 4H syndrome; schematic diagram

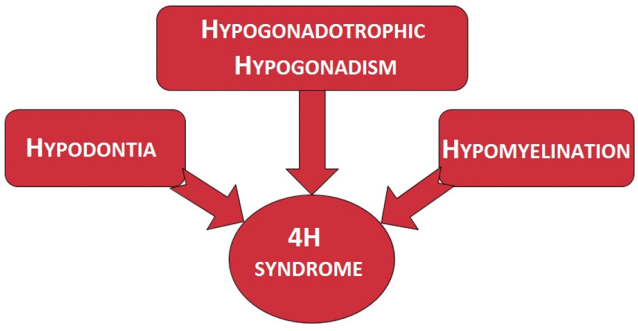


Figure 2: Hypodontia present in the child

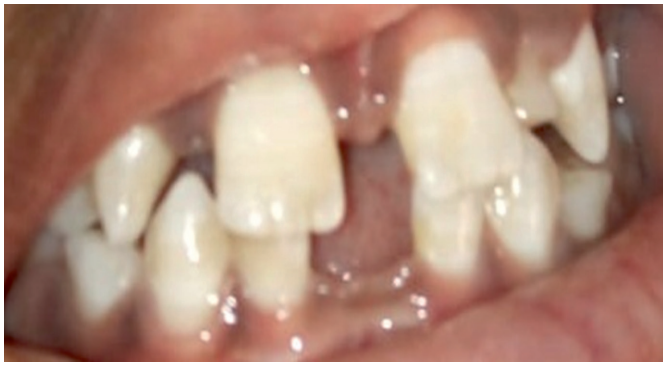
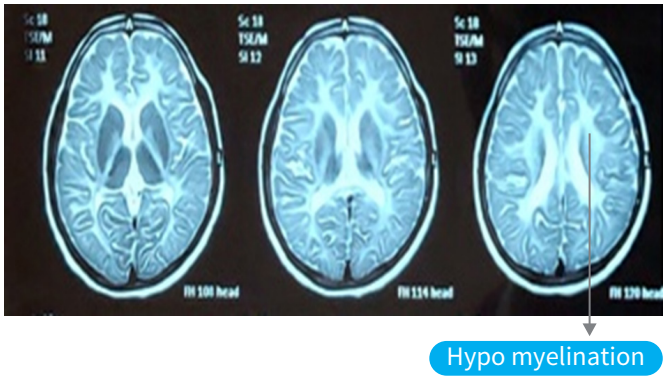


Figure 3: MRI Brain showing hypo myelination



Discussion:

Hypomyelination, hypodontia, hypo gonadotropic hypogonadism syndrome is a rare leukodystrophy with hypomyelination first described by Timmons et al[4]. Age of onset of symptoms varies from infancy to late childhood. Clinical picture is dominated by cerebellar signs and a variable degree of spasticity with varying periods of clinical stability in the course of their illness. The clinical presentation with prominent cerebellar signs and pyramidal involvement with fluctuations were similar to the previously reported cases[5-7]. Refractive error and cataract[8] reported were not seen in our patient. Brain MRI of these children show hypomyelination along with relative T2 hypo intensity of optic radiation, posterior limb of internal capsule, anterolateral thalamus, and involvement of cerebellar white matter[9] as seen in our patient.

Child had disruption in tooth eruption sequence as reported previously. The first teeth to erupt are the mandibular medial incisors; the deciduous molars, which in our patient erupted first, usually erupt after the incisors[10]. Our patient showed no peripheral nerve impairment. Although peripheral nerve abnormalities observed by electron microscopy and immunohistochemical studies have been included previously in the distinguishing features of 4H syndrome[4], these abnormalities were not supported by the clinical and physiological evidences

of peripheral neuropathy. The other reports of 4H syndrome made no statement on peripheral nerve involvement.

4H syndrome is caused by mutations in POL3A and POL3B, with autosomal recessive inheritance[11]. Genetic workup was not done in our case because it is not available in our country.

Conclusion: In conclusion, we present a case of 4H syndrome, in which peripheral nerve impairment was not found. Taken together with the previous reports on 4H patients, 4H syndrome can be regarded as a spectrum disorder, the cardinal signs of which are central hypomyelination, ataxia, hypo gonadotropic hypogonadism, and hypodontia.

There is wide variation in presentation but disorders due to POLR3A gene mutations are very severe. The disorder is not limited to brain parenchyma but involves structures arising from neural ectoderm. Paediatricians and paediatric neurologists should be aware of this entity to look out for non-neurological features that provide clue to the diagnosis.

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