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Leukodystrophy, Methylenetetrahydrofolate Reductase Deficiency (MTHFR), Heriditary Spastic Paraplegia

A RARE TREATABLE CAUSE OF ADULT ONSET SPASTIC PARAPARESIS

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ABSTRACT

Spastic paraparesis refers to weakness and stiffness of both lower limbs caused by lesions affecting the Pyramidal tract. It could be due to genetic or acquired etiology. Genetic causes include leukodystophies, Heriditary Spastic Paraplegia (HSP), metabolic disorders etc,. Acquired causes include B12 and folate deficiency , infections like HTLV-1 virus, HIV, neurosyphilis , vascular malformations and so on. Here we encounter a rare treatable cause of spastic paraparesis. A 28 year old male born out of 3o Consanguinous parents with normal developmental history came with insidious onset slowly progressive spastic paraparesis for the past 4 years. Initially at onset he noticed difficulty in getting up from squatting position, which was associated with stiffness of lower limbs. Then he noticed there was slippage of slippers while walking and he was aware about it. Physical examination revealed marfanoid Habitus ,increased tone and exaggerated reflexes involving both lower limbs .Motor power was MRC Grade 4/5 in both lower limbs in both proximal and distal muscles. Ocular Examination revealed Ectopia Lentis. MRI Spine screening was normal. MRI Brain revealed symmetric T2/FLAIR hyperintensities involving periventricular and deep white matter of bilateral frontoparietal region. Possibilities of Primary demyelinating diseases and genetic/degenerative leukoencephalopathies were considered. CSF examination was normal and oligoclonal bands were absent. Clinical Exome sequence testing was done in suspicion of Adult onset leukodystrophy which showed Homozygous MTHFR gene mutation on exon4. Plasma Homocysteine levels were elevated (60 µmol/L).Patient was started on Oral Vitamin B12 1500mcg/day, Folic acid and pyridoxine supplementation. Patient showed symptomatic improvement and is under follow up. MTHFR deficiency in adults is a mimicker of leukodystrophies and other white matter disease. It is a potentially treatable disease. Before considering degenerative diseases like HSP, treatable diseases should be considered.

INTRODUCTION:

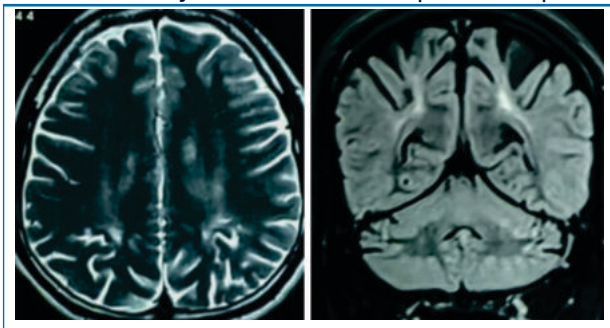
Spastic paraparesis refers to weakness and stiffness of both lower limbs caused by lesions affecting the Pyramidal tract. It could be due to genetic or acquired etiology. Genetic causes include leukodystophies, Heriditary Spastic Paraplegia (HSP), metabolic disorders etc,. Acquired causes include B12 and folate deficiency , infections like HTLV-1 virus, HIV, neurosyphilis , vascular malformations and so on.. Methylenetetrahydrofolate Reductase Deficiency (MTHFR) is an inherited autosomal recessive disorder which mostly affects children but can very infrequently affect adults. When homocysteine is combined with the B vitamins (B12, B6, and folate) with the help of enzyme Methylene Tetrahydrofolate Reductase (MTHFR) , it becomes cysteine and methionine . Homocysteine levels are higher than normal when this reaction's components are disrupted[1] . White matter lesions frequently observed in cerebral MRIs of these individuals speak to the possibility that hypomethioninemia may reduce overall methylation responses in the central nervous system, potentially damaging myelin[2]. Tall (Marfanoid habitus with arachnodactyly), with blonde hair, osteoporosis, a higher risk of fractures, pectus excavatum, and scoliosis are common characteristics of patients with MTHFR deficiency leading to hereditary homocysteinemia. The patients typically have psychological issues, seizures, and learning and intellectual disabilities (together, 50%)[3]. Clinical symptoms of adult-onset enzyme deficiency include psychotic episodes, cognitive dysfunction, stroke, peripheral neuropathy, recurrent encephalopathy and spastic paraparesis resembling hereditary spastic paraplegia[4]. Here we encounter a rare case of adult onset spastic paraparesis secondary to hyperhomocysteinemia.

Case Report:

A 28 year old male born out 3° Consanguinous parents with normal developmental history came with insidious onset slowly progressive spastic paraparesis for the past 4 years. Initially at onset he noticed difficulty in getting up from squatting position, which was associated with stiffness of both lower limbs.

Two years into the illness he noticed difficulty in walking particularly on uneven surfaces with slippage of chappals while walking with awareness. No history suggestive of sensory disturbances, upper limb, bowel , bladder or cranial nerve involvement or cognitive decline. There was no history of similar illness in the family. General examination revealed Marfanoid Habitus. CNS examination revealed spasticity and exaggerated reflexes involving both lower limbs ; Motor power was MRC Grade 4/5 proximal and distal muscles in both lower limbs symmetrically; Abdominal reflex was absent. Patient was able to sit with support. He had normal bowel and bladder habits. His sensory system, spine and cranium examination were unremarkable. Ocular Examination revealed Ectopia Lentis.

Routine hematological and biochemical blood tests were normal. Serology testing for HIV and VDRL were negative. MRI Spine was normal. CSF analysis was unremarkable. MRI Brain revealed symmetric T2/FLAIR hyperintensity involving periventricular and deep white matter of bilateral frontoparietal region. Clinical Exome sequence testing was ordered in view of suspicion of Adult onset Leukodystrophy which showed Homozygous MTHFR gene mutation on exon4 c.469G>A variant. Fasting plama Homocysteine levels were significantly elevated (60 µmol/L; normal -3.3 -11.3). Patient was started on Oral Vitamin B12 1500mcg/day, Folic acid and pyridoxine supplementation. Genetic testing of the parents was advised. Patient showed symptomatic improvement and is under follow up.



Mri brain showing symmetrical T2/Flair hyperintensities involving periventricular and deep white matter in bilateral frontoparital region

DISCUSSION:

The MTHFR C677T variant is referred to as the most prevalent MTHFR mutation. Just 30% of the normal enzyme function is present in those who are homozygous for the MTHFR C677T mutation[5]. Saraswathy KN et al published a case study on 23 population groups in India and found that Indo-European-speaking inhabitants of north India were found to have the highest levels of the 677T gene variant, whereas the Dravidian-speaking tribes of east and south India had the highest levels of the 1298C allele[6]. The average age at which neurological symptoms first appeared was 22.4 years. In a study done by Gales et al , among the 24 individuals whose records were analysed ; Gait disturbance (46%), epilepsy (29%), cognitive decline (21%), psychosis (12%), encephalopathy (4%), and stroke (4%), were among the initial neurological symptoms. 21% of patients had thrombosis overall (venous or arterial). Gait disturbance was the most common symptom mostly brought on by lower limb weakness (91%) or central causes. Ataxia (35%) was less frequent. 71% of the individuals had periventricular white matter lesions in imaging. All patients had markedly elevated homocysteinemia. 18 individuals with metabolic conditions were treated, and 83% of them improved, with the other 17% remaining stable without improvement or deterioration[7]. The reason for non improvement after therapy is due to the irreversible changes that occur over time and hence early diagnosis is essential in achieving good prognosis.. Elderly people frequently have white matter changes(WMC), and they are not benign. Many negative clinical effects are linked to WMC that are more comprehensive. Although small vessel disease, age, and other vascular risk factors have been demonstrated to be linked with WMC, the precise processes behind these associations are yet unknown[7]. Although young patients have subtle white matter changes on imaging ; those are to be considered important in the setting of patients with neurological symptoms .

CONCLUSION:

Detailed physical examination aids in identifying inherited disorders. Central causes of spastic paraparesis are a rare etiology.MRI brain can be done to aid in diagnosis. White matter lesions can be pathological especially in young age. A potentially treatable genetic condition like MTHFR mutation should be considered in cases of spastic paraparesis before considering degenerative conditions like HSP. Serum Homocysteine is a useful screening tool for suspected MTHFR mutation in patients with non compressive spastic paraparesis.

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