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REVIEW ON VANISHING WHITE MATTER DISEASE

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ABSTRACT
Vanishing white matter (VWM) disease is a type of disorder which mainly affects the brain and spinal cord. This disorder mainly causes deterioration of white matters in Central nervous system specifically the nerve fibres covered with myelin. The basic defect of the disease is caused by mutations in one of the five genes eIF2B1, eIF2B2, eIF2B3, eIF2B4 and eIF2B5 that encodes the five subunits of a protein called eukaryotic translation initiation factor (eIF2B), which is essential for the protein synthesis and regulations in all cells of the body under different stress conditions. VWM disease is characterised by chronic progressive and episodic worsening with ataxia (loss of control of body movements), spasticity (abnormal muscle tightness) and optic atrophy (worsening of vision). This disease is diagnosed on the basis of clinical symptoms in amalgamation with the results of a Magnetic Resonance Imaging (MRI) scan of the brain which shows distinctive pattern of abnormalities in the white matter of the brain.

KEYWORDS: Gene, Myelin, Mutation, Magnetic Resonance Imaging,

INTRODUCTION
Vanishing White Matter (VWM) disease belongs to a group of rare, genetic neurologic diseases called leukodystrophies. Leukodystrophies largely affect white matter region of the brain.[1,2] White matter disease is usually seen in childhood but may alarm patients of other groups as well.[5] VWM Disease is also known as Childhood ataxia with central hypomyelination (CACH) is considered a major form of leukoencephalopathy associated with autosomal recessive inheritance inherited mostly in Caucasian populations.[7] Typically, Hypomyelination is due to some disturbances caused by myelin protein insufficiency. Mutations in gene eIF2B1-5 are also claimed to be the potential reason for the onset of the disease. eIF2B 1-5 are the genes belonging to the class of subunits of eukaryotic translation initiation factors.[1,3,5] A hallmark feature of this disease is the sudden and activity worsening neurological condition after an encounter with provoking factors. There is also prevalence of accelerated neurological damage which is mediated via conditions like infections, pyrexia, minor head injury and also acute fright.[3,5,14]

Usually, the clinical signs of this disease are not specific.[9] Some patients have their cognitive and rational skills adhered where as other don't. The disease is characterized by movement disorders which are considered the most prevalent. Patients with considerably elder age groups are said to have rational or psychiatric disorders.[3]

The disease is classified into three groups based on its observable characteristics and the age of onset. One is the classical phenotype, appearing in children at an age between 2-6 years. A severe phenotype, appearing in infants with onset at age of less than 2 years including before birth. A Mild Phenotype appearing in adults aswell as children more than 6 years of age.[15]

This disease was first presented in woman aged 36 years with the complaints of movement difficulties, secondary

amenorrhea and ataxia. VWM disease has a grim prognosis with treatment including supportive therapy only.[1,4,5] Patients having their symptoms onset at an early age less than 1 year are said to have hastily worsening of the disease and succumb within few months. Patients die because of various excuses in VWMD which includes respiratory failure, discontinuation of life support, coma.[3]

ETIOLOGY

VWM Disease belongs to the genetical disorder which is heterogenous in nature. Based on linkage study, the genetic mutation is usually associated to a chromosomal region 3q27, but there are about more than 100 different mutations that are related to VWM.[4,5,15] The gene belonging or present at 3q27 site of chromosome is eIF2B5. The disease is associated with missense mutations in any one of the 5 subunits of eIF2B1-5. Based on some studies, it is evident that a great portion of patients had mutation in eIF2B5.[4,18] eIF2B and its encoding genes play an essential part in translation of mRNA into proteins. Translation of proteins involve three main steps: Initiation, Elongation and Termination. eIF2, tRNA linked with methionine, GTP and ribosomal subunit is combined in initiation process. Upon the presence of start codon, GTP breaks down to GDP. GDP binds to eIF2 to form an inactive complex. eIf2 again gets activated under conversion of GDP to GTP which is mediated by eIF2B, a catalyst. eIF2B is an important agent that suppresses protein synthesis in stressful conditions like pyrexia, head injury.[8] Any faults in the eIF2B drops the activity of eIF2B complex, deteriorating the cell's response for stress which yields VWM Disease genotype expression.[14] It is also evident that homozygous mutated patients have mild disease condition then heterozygous mutated ones.[18]

PATHOPHYSIOLOGY

eIF2B is a group of 5 subunits of Guanine Exchange Factors (GEF). GEF converts GDP into GTP in order to form a complex between eIF2 and GTP, this complex then binds to tRNA which carries methionine, which collectively forms eIF2-GTP-Met-tRNA, which is lately called as ternary complex. The formation of ternary complex is a step which regulates the translation rate which is based on phosphorylation of eIF2α. Four protein kinases like eIF2AK4, eIF2AK2, eIF2AK3 and eIF2AK1 mediate the phosphorylation of eIF2α. Deficiency of amino acids, unfolded protein storage in Endoplasmic reticulum, infection, thermal shock, stress can activate any one of the above-mentioned kinases. Hence, the influence of eIF2 with eIF2B gets inhibited which contributes in decreasing the translation in cell. Mutations in any one of the five subunits of eIF2B results in narrow deficiency of GEF activity.[4]

Glial cells like oligodendrocytes are more liable for infection, stress and trauma which conclude in myelin impairment. Protein synthesis is under halt when the cells are subjected to stress and after the stress condition is lowered.[10] Oligodendrocytes are more susceptible because of Endoplasmic reticulum (ER) stress that is caused by accumulation of misfolded proteins. Whenever an unfolded or misfolded protein accumulates inside the Endoplasmic reticulum, it causes ER stress by initiating cellular response called Unfolded Protein Response (UPR). UPR is stimulated by thermal, physical or metabolic stress indirectly by disturbing the folding of protein within ER.[4] Activation of UPR increases the activity of various kinases like eIF2α, phosphorylated eIF2α, ATF4 (Activating Transcription Factor 4), CHOP (C/EBP Homologous Protein).[5]

Accumulation of misfolded protein inside the endoplasmic reticulum stimulates PERK which in turn sends signals to phosphorylated eIF2α. Phosphorylated eIF2α gets bound to eIF2B irreversibly and inhibits the process of translation. Phosphorylation of eIF2α leads to increase in levels of ATF4 which in turn stimulates CHOP and GADD protein 34. The increased and abnormal expression of CHOP induces programmed cell death. On the other hand, GADD reverses the phosphorylation of eIF2α and promotes the recovery of cell. Continuous overexpression of GADD and CHOP in VWM disease may lead to cellular abnormalities and cell damage. Oligodendrocytes are more vulnerable to such conflicting expressions and are prone to cell damage.[5]

CLINICAL MANIFESTATIONS

Patients diagnosed with VWMD will have normal development at an early stage. This disease usually presents as a chronic neurologic degeneration with loss of neuro-muscular coordination and mild cognitive decline. In some patient's onset of symptoms can be either spontaneous or can be induced by minor trauma like stress, pyrexia and febrile infections. [4] Following the onset of provoking factors, patient may be loose coordination in motion and also may become hypotonic. Patients may even experience increased difficulty in walking, tremor, spasticity and seizures.[4,5] Seizures include non-motor seizures, focal onset with or without altered consciousness, myoclonus seizures.[3,16]

Childhood ataxia with central hypomyelination also affects extracerebral organs also. In most of the case, optic atrophy develops with vision loss as a late onset. Disease onset after the age of 5 years linked to ovarian underdevelopment is often termed as ovarian leukodystrophy syndrome. Also, there are cases of encephalopathy along with reduced growth rate or failure in growth, cataracts, renal hypoplasia. There are no significant evidences of involvement of peripheral nerves mentioned.[4,5,6,17]

Antenatal manifestations include cases with low amniotic fluid than required, Retardation of foetal growth, cataracts, pancreatitis, hepatosplenomegaly, renal hypoplasia, defective development of ovaries, decreased movement of foetus, microcephaly. After birth manifestations include hypotonicity in limbs, improper

feeding, emesis, apathy, seizures, coma, respiratory arrest and sudden demise within few months.[4,5] They often come up with complaints of encephalopathy with or without seizures, irritability and lethargy. Acquired motor skills being absent is considered a hallmark in all the age groups.[3] Juvenile or adult onset of clinical symptoms of VWMD usually involves enuresis as the disease progresses.[13]

There are alternative forms of VWMD. One of them is "Cree leukoencephalopathy" present among the patients of Cree Indian Origin with onset at an age of 3 months to 9 months followed by death before 2 years of age.[5]

DIAGNOSIS

Laboratory evaluation of patient with VWMD is done by MRI of head and also by fluid attenuated inversion recovery (FLAIR) imaging. The definitive MRI reading of patients with VWMD include hypo-intensity signals in cerebral white matter in T1 weighted images and hyper-intensity signals in subcortical white matter under T2 weighted images. MRI suggests that there is gradual decline in white matter which is then replaced by fluid. Under FLAIR imaging there are evidences of cavities or cystic breakdown in white matter. In adult patients with abiding disease with ovarian leukodystrophy, lateral ventricle dilatation is seen. At an advanced stage, complete vanishing of cerebral white matter takes place with only the ventricular membrane and cortex filled with fluid.[4,5] Localized proton Magnetic resonance spectroscopy (MRS) helps in obtaining the complete in-vivo spectrum of signals that quantifies the number of metabolites to check for normal cortical metabolism.[6] Proton MRS shows abnormalities in all the metabolites and is conclusive for the reduced white matter in cerebral region. Phosphorous MRS suggests the abnormalities in metabolites involved in synthesis of membrane phopholipids. There is a comparative decrease in glycerphophoethanolamine and increase in phosphoethanolamine.[4]

By using proteomic studies, biochemical abnormalities of VWM Disease can be identified. This technique involves evaluation of several functional proteins present in Cerebrospinal fluid. Patients with VWMD had a remarkable decline in asialo-transferrin in CSF whereas plasma concentrations of the same was normal. Asialo-transferrin in brain is said to be produced by oligodendrocytes and astrocytes and reduction in its levels indicates severe abnormalities in those cells. This biochemical parameter can be considered a biomarker and a diagnostic tool.[4] Experimental analysis of corpus callosum suggested thin myelin in VWM patients compared to that of normal. Examination of many patients suggested normal axon under those tissues which has mild exposure and thin axons in tissues where there was moderate to severe exposure to injury.[11]

TREATMENT AND PREVENTION

There are no evident treatment strategies suitable to treat this disease. Supportive therapy is advised to improve the motor dysfunction. Rehabilitation therapy, physical therapy is suitable for motor problems. Patients complaining hypotonia in lower limb can be given with Ankle Foot Orthosis, which improve walking patterns. Prevention of provoking factors can be followed to reduce the recurrence of neurological deterioration. Prevention strategies include, use of antibiotics, antipyretics, vaccinations, avoiding contact sports. These preventive strategies can be practiced but are not enough for the complete prevention of the disease.[4,5] Seizures being a frequent symptom of this disease can be treated with an optimal anti-convulsant.[12]

CONCLUSION

VWM disease being a prevalent form of leukodystrophy is a genetic disorder affecting patients from childhood to adulthood. Onset of symptoms can be found from infantile stage to adult stage. It is caused by mutation in translation initiation factors (eIF2B 1-5), which play an important role in synthesis of protein from mRNA in stressful conditions. Clinical manifestations usually are not specific. It differs in different age groups, major being motor dysfunction, ataxia and cognitive reduction. The gold standard diagnosis is MRI others like Proton MRS, FLAIR imaging and proteomic techniques are also considered. There is no permanent curative therapy for VWMD, but supportive therapy and preventive measures are useful.

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