

Hereditary Diffuse Leukoencephalopathy with Spheroids: Diffusion Restriction on Magnetic Resonance Imaging and Novel Mutation in an Indian Patient

Dear Editor,

A 43-year-old woman, well educated and craft teacher by occupation presented with a history of progressive cognitive decline over 10 years. Initially, there were mild behavioral disturbances in the form of irritability and compulsive hand washing. But there has been significant cognitive deterioration since the last 3 years. She can no longer take the craft classes. She lost interest in carrying out religious rituals and daily chores. She makes mistakes while praying and cooking. She is not able to do daily routine activities such as bathing and dressing, and needs assistance for same. She is having bladder and bowel incontinence since the last 1 year. Oral exploration of inedible objects, palilalia, and echolalia were noticed recently. There was a family history of similar illness in her father and paternal uncle in the sixth decade of life [Figure 1].

On examination, echolalia and palilalia were noted. Her attention span was poor with a forward digit span of 3 and backward of 0. Mini-mental state examination score was 4/30 and frontal assessment battery score was 2/18. Further, domain-based cognitive testing was not possible due to very poor attention span. Assessment of cranial nerves was normal. Face was hypomimic. There was axial rigidity; her gait was slow and ataxic. Speech was hypophonic (the score of Unified Parkinson's Disease Rating Scale-III was 10).

Hemogram, biochemistry, vitamin B12, and thyroid profile were within normal limits. Magnetic resonance imaging (MRI) brain showed bilateral symmetrical T2 hyperintense signals with true diffusion restriction in bilateral frontoparietal periventricular and deep subcortical white matter involving centrum semi ovale, corona radiata, and corpus callosum [Figure 2a and b]. Cerebrospinal fluid (CSF) routine microscopy was normal. CSF oligoclonal band, neuromyelitis optica, myelin oligodendrocyte antibody, and IgG4 index was negative. Electroencephalography was normal.

Three years ago, MRI brain showed true diffusion restricting signals in same areas as given in Figure 2a and b. There was no contrast enhancement. The possibility of clinical isolated syndrome was considered. She was advised further work up for same. But she was lost to follow up.

The patient had significant white-matter disease with persistent diffusion restriction on two MRIs 3 years apart. Hence, the possibility of adult-onset leukodystrophy especially hereditary diffuse leukoencephalopathy with spheroids (HDLS) was considered based on the recent review of the literature.^[1]

Next-generation sequencing identified a previously unreported novel heterozygous single base pair deletion in exon 21 of *CSF1R* gene (chr5:g.149433963delC, c.2686delG, p.Glu896SerfsTer56:ENST00000286301.3) that results in a frameshift and premature truncation of the protein. The variant was validated by Sanger sequencing. The truncated protein is predicted to have a length of 950 amino acids as opposed to the original length of 972 amino acids. The resultant protein is likely to lack the C-39 terminal region of the protein; this will likely result in loss of function. [Figure 2c]

HDLS, also known as adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), is a hereditary autosomal dominant neurodegenerative disease with age of onset between 30 and 50 years.^[2] HDLS is the most common cause of adult-onset leukodystrophy (approximately 10%).^[3]

It manifests as progressive cognitive impairment such as aphasia and frontal lobe predominant dementia. Motor impairments such as dyskinesia, Parkinson's disease, ataxia, and seizures are described.^[2]

CSF1R has been determined as a causative gene. It encodes a polypeptide containing 972 amino acids, and is a type III tyrosine kinase receptor that belongs to the platelet-derived

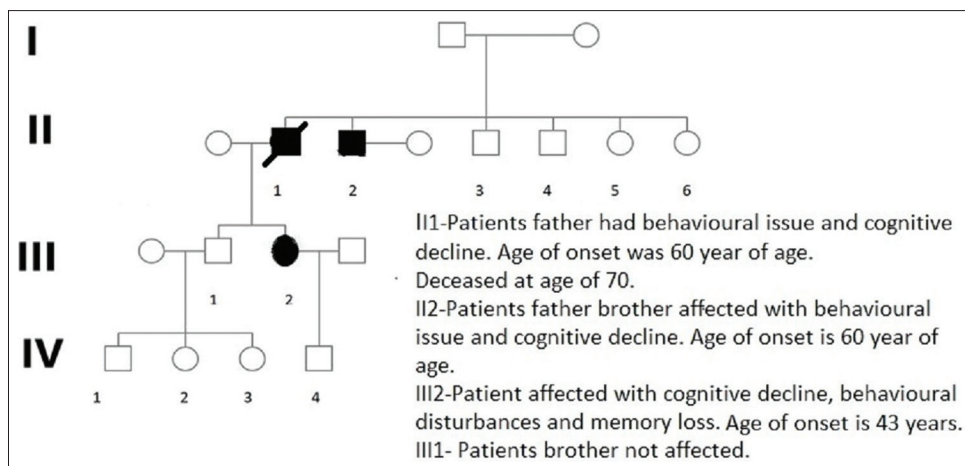


Figure 1: Pedigree-family tree of a family with hereditary diffuse leukoencephalopathy with neuroaxonal spheroids. Circles represent females and squares represent males. Black symbols indicate affected family members. Arrow indicates the deceased. Roman numbers indicate generation

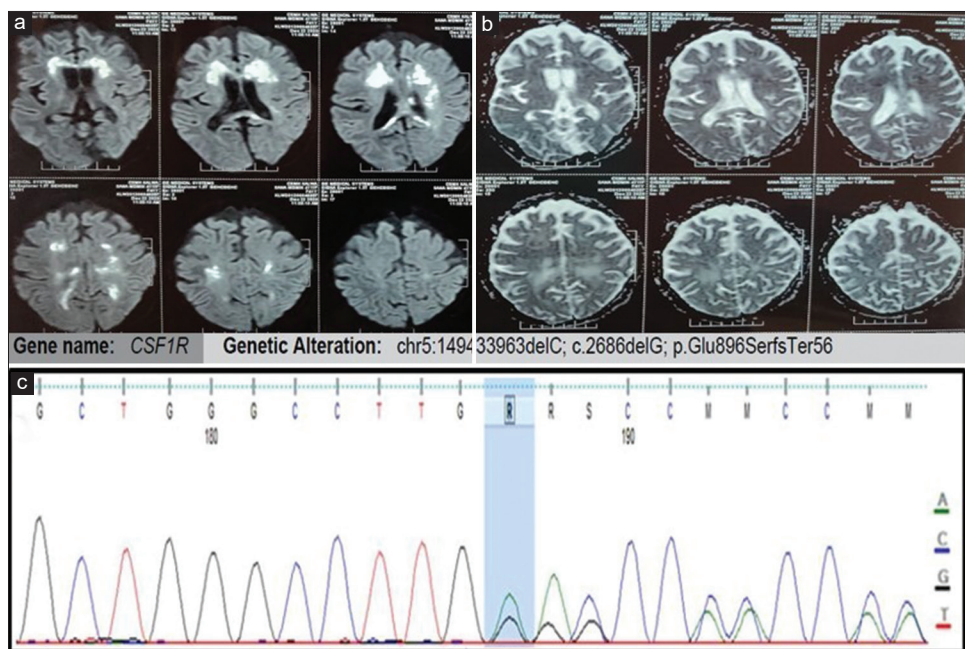


Figure 2: (a, b) Diffusion, ADC MRI show bilateral symmetrical hyperintense signals in periventricular and subcortical white matter of bilateral fronto-parietal, periventricular, corona radiata, genu and splenium of corpus callosum with ADC drop. (c) Sanger sequencing data (electropherogram) showing a heterozygous deletion of the nucleotide G at position c.2686 in the *CSF1R* gene. This variation was confirmed by sequencing with both forward and reverse primers

growth factor (PDGF) receptor family.^[2] This receptor mainly influences the proliferation and differentiation of mononuclear macrophages, microglia, and neurogliaocytes. Inhibition of signaling through *CSF1R* was found to lead to the rapid depletion of microglia via apoptosis, hence affecting white-matter myelination in the brain.^[4] The presence of vacuoles in the white-matter tracts leads to splitting of myelin causing intramyelin edema.^[5] Dysfunction of oligodendroglia may also cause myelin splitting. Intramyelin edema may be the mechanism of diffusion restriction rather than cytotoxic edema.^[6]

HDLS can be misdiagnosed as atypical multiple sclerosis, central nervous system vasculitis, or vascular dementia

based on MRI findings. Hence, the knowledge of clinical and radiological manifestations of various adult-onset leukodystrophies is crucial. Persistent white-matter diffusion restriction in our patient re-emphasizes the conclusion noted in the article by Onder *et al.*^[1] It is a useful sign for suspecting HDLS.^[1]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published

and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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