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A rare case of late adult-onset leukodystrophy due to CSF1R mutation

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ABSTRACT

The debilitating autosomal dominant inherited white matter illness known as CSF1R-related disorder (CSF1R-RD) is marked by a variety of symptoms including cognitive impairment, neuropsychiatric abnormalities, and motor symptoms such as ataxia, seizures, and pyramidal and extrapyramidal. Previously, CSF1R-RD was known as adult-onset leukoencephalopathy with pigmented glia and axonal spheroids. Between 0 and 11 years is the range for the mean duration of the disease from onset to incapacitation, and between 1 and 29 years is the range for the mean length of the disease from death. MRI shows diffusion-weighted anomalies, microcalcifications, progressive brain atrophy, and confluent white matter hyperintensities on T2W/FLAIR-weighted sequences. Although only around 300 cases of CSF1R-RD have been reported, this number may significantly underestimate the true prevalence. This misdiagnosis is often due to limited awareness, restricted access to genetic testing, and clinical manifestations resembling more common neurological conditions. According to the research currently in circulation, 10%–25% of adult-onset leukodystrophy patients are estimated to have CSF1R-related disorder. We present case of late-onset CSF1R-related disorder.

Keywords: CSF1R, adult onset leukodystrophy

Abbreviations:

CSF1R-RD – Colony stimulating factor 1 related disorder

BACKGROUND

The debilitating autosomal dominant inherited white matter illness known as CSF1R-related disorder (CSF1R-RD) is marked by a variety of symptoms including cognitive impairment, neuropsychiatric abnormalities, and motor symptoms such as ataxia, seizures, and pyramidal and

extrapyramidal indications. Previously, CSF1R-RD was known as adult-onset leukoencephalopathy with pigmented glia and axonal spheroids.

CASE REPORT

A previously healthy 31-year-old female with normal developmental milestones was brought to our hospital by her husband with complaints of slowness in her activities for a period of one year. The slowness began insidiously and was first noticed during cooking and household chores. Over the next three months, her condition worsened, and her husband observed that she walked slower than him. It was not associated with any involuntary movements. No history of incoordination in limbs. No imbalance while walking. No history of falls. No history of autonomic symptoms like light-headedness while standing, urinary disturbances, constipation, increased sweating. They did not seek any medical attention. 7 months later from the onset of illness, her husband noticed that she had difficulty concentrating while cooking and she would make errors in the portion of spices to be added while cooking. She began seeking help with cooking appliances that she previously operated with ease. Over the next few months, she lost the ability to cook, do household chores, and take care of her children. 10 months later from the onset of her illness, her husband noticed that she would laugh inappropriately, followed by episodes of unprovoked crying. At this point, they met a psychiatrist for her behavioral symptoms and started her on medications. Despite being on medications, there was no improvement. She was mobilized by her husband twice or thrice a day, while the rest of the day she was bedridden. All her activities of daily living required support. After a year and 2 months, her husband noticed that she had developed abnormal posturing of the right upper limb in the form of an extension of fingers. These symptoms were present continuously with no diurnal variation. It was neither suppressible nor painful. No triggers. It was not present during sleep. It was not abolished by any maneuvers. After one and half years, the husband noticed that she had slurring of speech. She could articulate but with difficulty. Her speech had distorted sounds. She made grammatical errors as well with a decline in vocabulary. Over the next few months, she had difficulty understanding the meaning of words. It worsened to the point where she couldn't follow instructions (oral or written). During this period, the patient also developed involuntary micturition and defecation. There was no history of fever, skin rash, mouth or genital ulcers or joint swelling. No history of mood disorder in the past, seizures, jaundice, sleep disturbances. No history suggestive of cranial nerve, or sensory involvement. There was no family history of neurodegenerative disease.

On examination Patient was conscious, but not oriented. No neurocutaneous markers. No Kayser-Fleischer ring. Higher mental function- Montreal Cognitive Assessment score 6. Frontal Assessment Battery score -2. Neuropsychological testing revealed impairments in attention, memory, language, and executive function. There was evidence of the pseudobulbar effect.

Speech mixed type- spastic dysarthria with aphasia. Motor system- Bulk was normal, Tone- spasticity in all limbs (right more than left). Power- Right side upper and lower limb 4/5, and left side upper and lower limb 4/5. Reflexes DTR- exaggerated in both upper and lower limb with bilateral plantar extensor. Cerebellum- no gross incoordination. EPS- Right upper limb- Repeated, sustained, tonic posturing and twisting. There is an extension at the elbow, and wrist joint with extension of 4 fingers and flexion of thumb. There were signs of bradykinesia in both upper limbs. Geste antagoniste absent. Release reflex- glabellar tap present, palmomental reflex present, Sensory examination- unable to perform.

Investigations:

The patient had chronic progressive neurocognitive decline associated with speech disturbances, pyramidal and extrapyramidal symptoms. Our differentials were Wilsons, demyelinating disorders, NBIA, mitochondrial disorders, leukodystrophies, inborn errors of metabolism, young onset Parkinson's, atypical parkinsonism, including corticobasal degeneration, multiple system atrophy, progressive supranuclear palsy, and frontotemporal lobal degeneration.

Routine investigations, including CBC, ESR, CRP, RFT, and LFT, were normal. Serum ammonia, Serum lactate, Serum vitamin B12, and Serum homocysteine. ANCA, ANA, and LIA 23 are negative. Serum Ceruloplasmin – Normal, 24 hr urinary copper- 86.3. Viral markers (HIV, HCV, Hep-B) were non-reactive. 2D echo is normal. The CSF analysis revealed no cells with a protein level of 28 mg/dl. OCB was negative. MOG and NMO were negative. IgG4 was negative.

Brain neuroimaging revealed symmetrical T2 FLAIR hyperintensities, diffusion restriction, and a decrease in ADC with T1 Hypo intensities in the periventricular matter of the frontal and parietal region, as well as corpus callosal atrophy. There was no contrast enhancement, and the MR angio was normal.

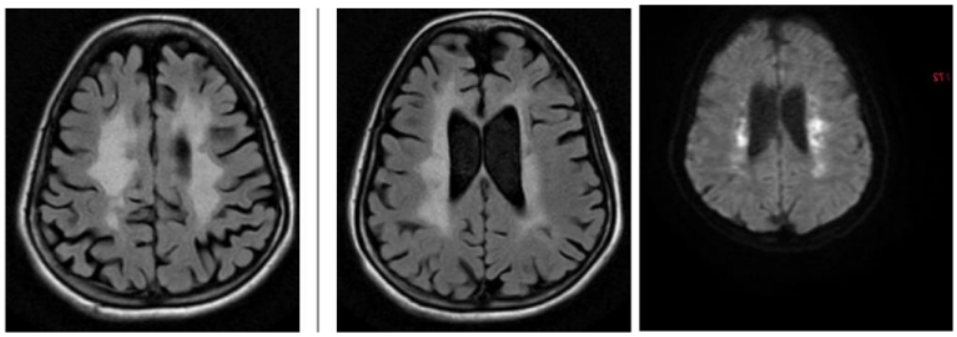

Figure 1-MRI Brain shows confluent T2/FLAIR hyperintensities with DWI restriction are noted predominantly involving the periventricular white matter of bilateral frontal and parietal lobes.

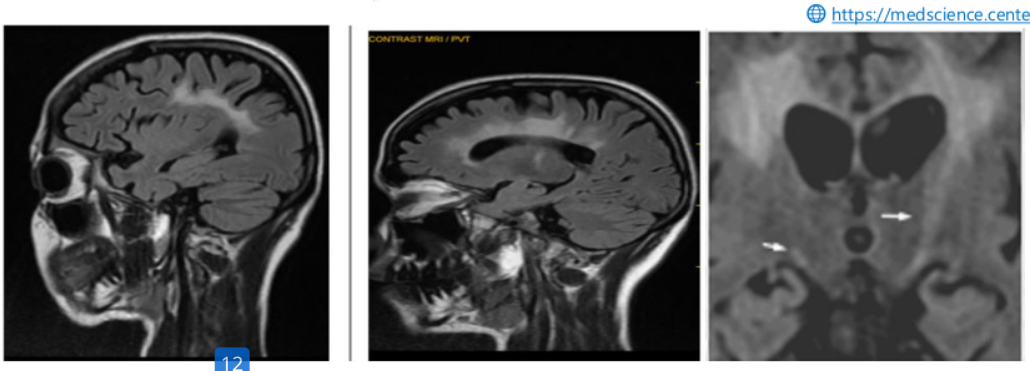

Figure 2-Confluent symmetrical T2/FLAIR hyperintensities involving the periventricular white matter of bilateral cerebral hemispheres and bilateral pyramidal tracts. Diffuse cerebral and corpus callosal atrophy.

The MRI was suggestive of a leukodystrophy pattern. Also, other possibilities were ruled out with above investigations. Hence we proceeded with Genetic testing by Whole-exome sequencing showed a mutation in the CSF1R gene.

DISCUSSION

CSF1R is a cell surface receptor for the cytokine macrophage colony-stimulating factor1 (CSF1). CSF-1 is known to help control the differentiation and proliferation of mononuclear phagocytic cells, such as microglia in the brain and spinal cord. There is no cure for CSF1R-related leukoencephalopathy. Despite limited expected benefits, we provided symptomatic treatment, including antidepressants for depression, muscle relaxants for spasticity, and antiepileptic drugs for seizures. The literature has described the role of hematopoietic stem cell transplantation but found no significant benefit. Our patient received a multidisciplinary treatment from a physiotherapist, occupational therapist, and speech-language therapist, in addition to family counselling.

Axonal Spheroids and Pigmented Glia (ALSP) is a rare neurodegenerative disease characterized by myelin sheath loss in the white matter, axonal spheroids, and pigmented glial cells. CSF1R-related leukoencephalopathy is a type of primary microgliopathy that is caused by a genetic pathogenic mutation heterozygous variant in CSF1R. It was previously called Hereditary Diffuse Leukoencephalopathy with Spheroids (HDLS) or Pigmentary Orthochromatic Leukodystrophy (POLD). Mutations in the CSF 1R gene are the most common, with over 106 different mutations discovered. Symptoms usually occur during the early 40s and progress rapidly, with an average disease duration of 6.8 years. Early symptoms include neuropsychiatric manifestations similar to behavioral variant frontotemporal dementia, such as depression, anxiety, apathy, irritability,

personality changes, and cognitive decline. Motor symptoms of both pyramidal and extrapyramidal occur ranging from spasticity, progressive rigidity, dyskinesia, tremors, ataxia, and seizures. In rare presentations, motor symptoms may predominate without significant behavioral or personality changes. Earlier onset of symptoms is seen mostly in women, although the disease duration is similar in both genders. When symptoms appear earlier in women, it is the motor symptoms that predominate leading to a misdiagnosis of immune-mediated disease multiple sclerosis due to overlapping clinical and imaging characteristics. MRI shows asymmetric white matter changes in the subcortical, deep, and periventricular regions with changes in signals and thinning of the corpus callosum, as well as cerebral atrophy, lateral ventricles that are prominent, and convexity in the subarachnoid spaces, especially in the frontal and parietal areas. Prominent findings in MRI Brain include signal changes along the corticospinal tract in the posterior limb of the internal capsule and brainstem. The affected white matter tracts shows high signal intensity on DWI sequences, likely indicating intramyelinic edema. Contrast-enhanced studies typically do not show enhancement. It is important to note that the posterior fossa is typically spared. The calcification that happens in the pericallosal white matter, appear as patter known as a steppingstone appearance, is a characteristic finding in the sagittal view. Potential biomarkers include Neurofilament Light Chain proteins, which are indicative of neuron death and axonal deterioration, as well as tau proteins and glial fibrillary acidic proteins, which indicate neuronal and astrocytic pathology. Researchers have not found a potential cure for CSF1R-related disorder. When a young patient presents with FTD like presentation like phenotype with pyramidal, and extrapyramidal features and MRI showing DWI restriction after ruling out the differentials considered we need to suspect CSF1R-related disorder.

CONCLUSION

Adult-onset leukodystrophies are rare disorders characterized by diverse clinical and pathological variations. Extensive degenerative and demyelinating lesions in the cerebral cortical white matter distinguish these conditions pathologically. Clinical expression can span widely, including behavioral or mood changes, seizures, dementia, Parkinsonism, dystonia and spasticity. Mostly brain MRI changes can help determine the cause of leukodystrophy, but they are not always definitive. Recently, researchers have associated mutations in the Colony-Stimulating Factor 1 Receptor gene (CSF1R) with hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) and pigmentary orthochromatic leukodystrophy. Our 31-year-old previously healthy female patient presented with a one-year history of cognitive decline associated with pyramidal and extrapyramidal involvement. An MRI revealed features suggesting leukoencephalopathy. Further genetic testing revealed the CSF1R mutation. Our case highlights the importance of

considering adult-onset leukodystrophies in young patients presenting with rapidly progressive dementia with pyramidal and extrapyramidal involvement.

Patient consent: Patient Consent - obtained

Conflict of interest: The authors declare that they have no competing interests

Authors' contributions:

Dr. Anusha Mekala - data curation, interpretation, drafting

Dr. Lavanya Kunkala- Conception and design, data acquisition, interpretation, drafting and validation, supervision

Dr. Sundar Shanmugam- Revising and editing it for critical intellectual content

Dr. Rithvik Ramesh - Conception, supervision, final approval.

Dr. Lakshmi Narasimhan- review and editing, supervision, final approval

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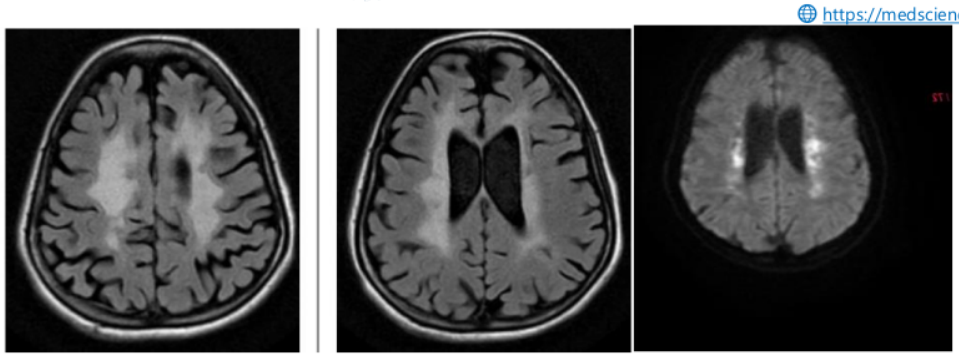

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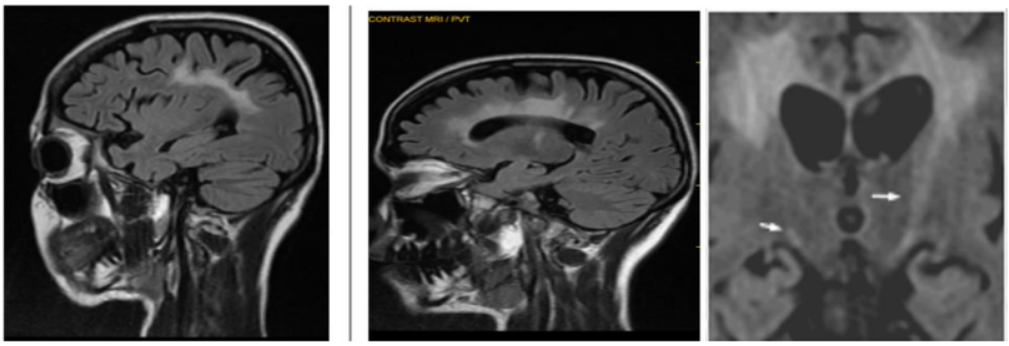

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