A Unique Radiological Correlate of CSF1R Mutation: “Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia - Sine Leukoencephalopathy”

Dear Editor,

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is an unifying term encompassing the extremely rare and progressive disease of hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) and pigmentary orthochromatic leukodystrophy (POLD) that shares mutation in CSF1R gene.[1–5] Herein, we report a young male with novel variant of CSF1R mutation with its unique radiological correlate sparing the white matters.

A 28-year-old male, single child, presented with insidious onset, gradually progressive slowing of all activities and social withdrawal for last 1.5 years. This was followed by tremulousness for last 1 year, initially in left distal upper limb, later progressing to the right side. Subsequently, there

Figure 1: MRI Brain axial section T2 and T2 FLAIR sequence shows hypointensities in globus pallidus (a, g) and substantia nigra (b, h), respectively; GRE sequence reveals hypointensities in globus pallidus (c) and substantia nigra (d); T1 sequence is isointense in globus pallidus (e); and substantia nigra (f)
was abnormal posturing of limbs and trunks for last 6 months, with a few unproctected falls without loss of consciousness in last 2 months. Family history was unremarkable. Neurological examination revealed hypometric saccade, generalized rigidity, bradykinesia, dystonia, and orolingual dyskinesia. Cognitive assessment revealed impaired attention, execution, retrieval defects, and decreased information processing speed. Kayser–Fleischer ring was absent on slit lamp examination.

A brain MRI revealed non-enhancing deep GRE and long TR hypointensities in bilateral globus pallidus and substantia nigra [Figure 1] without any white matter abnormalities. Routine blood investigations were non-contributory. Ferritin was 57 mg/ml (Normal: 20-250 mg/ml), Ceruloplasmin was 26 mg/dL (Normal: 20-35 mg/dL), while 24-hour-urinary-copper excretion was 28 mg (Normal: 10-30 mg/24 hours). Whole exome sequencing revealed heterozygous mutation in intron 21 c. 2763+1G>A (5’splice site) of CSF1R gene in chromosome 5q. Clinically asymptomatic father was tested positive for same mutation, without any imaging abnormalities.

Dopamine supplementation and anti-cholinergics resulted in mild symptomatic improvement.

The clinical manifestations of ALSP are heterogeneous. Wide variability in clinical features and genotype-phenotype discordance frequently lead to misdiagnosis. ALSP usually manifests around the 4th decade (mean age of onset is 43 years), with neuropsychiatric abnormalities and cognitive impairments often in isolation or with features of Parkinsonism and diverse movement disorders. Seizure can be found in 50% cases.[1,3–5]

MRI changes in ALSP can precede symptom-onset. The common findings include (I) periventricular and deep white matter changes commonly involving frontal and parietal lobe (90%), (II) corpus callosum thinning (35%) and marked volume loss in splenium, (III) persistent diffusion restriction in the involved white matter (>66%), (IV) diffuse cerebral atrophy (marked in fronto-parietal region) with disproportionate dilatation of lateral ventricles (37%).[2,4,5] Symmetrical, tiny “stepping stone” calcification in pericallosal region (around frontal horns of lateral ventricles) and fronto-parietal white matter (54%), can be detected on thin section Non-contrast Computed tomography brain scan (NCCT), possibly specific to ALSP. Grey matter involvement (cortical or subcortical) is unheard of in ALSP.[2,4] The most noticeable feature in brain imaging in this index case was the bilateral globus pallidus and substantia nigra altered intensities in Gradient Echo (GRE) (considered typical of neurometabolic disorder) with relative absence of the white matter T2/FLAIR hyperintensities, most striking of ALSP; along with autosomal dominant inheritance pattern and variable penetrance, as his father harboring similar mutation was completely asymptomatic clinically and without any radiological abnormalities.

**Informed consent for participation in research study**

The patient’s legally authorized representative consented (written) to use of the information elaborated in the manuscript.

**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.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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Submitted: 31-Mar-2022 Revised: 02-May-2022 Accepted: 09-May-2022 Published: 14-Jul-2022

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**DOI:** 10.4103/aian.aian_300_22