CSF1R Related Leukoencephalopathy - Rare Childhood Presentation of An Autosomal Dominant Microgliopathy!

Introduction

Colony-stimulating factor 1 receptor (CSF1R) is a tyrosine kinase receptor that helps in development, maintenance, and activation of microglia in central nervous system (CNS). CSF1R related leukoencephalopathy is an autosomal dominant inherited primary microgliopathy caused by heterozygous mutations in CSF1R present on surface of the microglia which leads to severely reduced number of microglia leading to secondary myelin loss, formation of axonal spheroids in neurons and demyelination. CSF1R related leukoencephalopathy usually presents in adults with a mean age of onset at fourth decade. Paediatric-onset CSF1R related leukoencephalopathy has not been reported. Herein we describe the clinical, radiological and pathological phenotype of a paediatric-onset CSF1R related leukoencephalopathy.

Case Discussion

A 12-year-old boy, born out of non-consanguineous parentage with normal perinatal history and development, was brought with complaints of progressive vision loss, behavioural disturbances and cognitive decline of 1-year duration. The patient developed gradual painless progressive vision loss in his right followed by left eye diagnosed during a routine school check-up a year back. Parents noticed behavioural disturbances in the form of stubbornness, irritability, and headbanging. Six months later, he developed rapid cognitive decline with worsening scholastic performance and memory disturbances with involuntary non-purposeful moments of right upper and lower limbs associated with emotional lability. He stopped recognizing his relatives and indicating toilet needs. He also developed multiple episodes of left focal motor seizures during admission. Family history was non-contributory. On examination, head circumference was normal. He was restless, irritable and was having continuous motor stereotypies of right upper and lower limb in the form of repetitive pronation-supination at elbow and flexion-extension at knee, which he was able to stop temporarily when asked to do so. He was able to comprehend simple commands and answer relevantly but had spastic dysarthria with pseudobulbar affect. Fundus examination and pupillary reflexes was normal. There was no Kayser–Fleischer ring. Motor examination showed spasticity in the left upper and lower limbs with brisk muscle stretch reflexes and flexor plantar responses bilaterally with motor stereotypes on right side with left hemiplegic gait. A possibility of childhood-onset cerebral white matter disease- demyelinating/dysmyelinating/neoplastic pathology was considered.

Investigations revealed a normal haematological and biochemical profile. Brain magnetic resonance imaging (MRI) done at first visit (12 years) showed frontal predominant asymmetric (right > left) leukoencephalopathy involving corpus callosum and internal capsule with extension of signal
intensity along corticospinal tract and posterior limb of internal capsule to medulla. Diffusion-weighted imaging (DWI) restriction was seen in all white matter structures described above only sparing the parietal lobar white matter. There was associated cerebral and callosal atrophy. There was no contrast enhancement or calcifications [Figure 1a-f and i]. Serum ammonia, lactate, very-long-chain fatty acids, arylsulfatase A and blood tandem mass spectrometry were normal. A possibility of leukodystrophy vs infiltrating lymphoma was considered and right frontal craniotomy with frontal brain biopsy was performed. Brain biopsy showed rarefaction of white matter changes with reduced staining and pallor on myelin stains, perivascular and interstitial histiocytes especially foamy histiocytes and reactive gliosis with intact but reduced density of axons suggesting a demyelinating versus dysmyelinating pathology with no features of neoplasm [Figure 2].

In view of dysmyelinating versus demyelinating pathology child received intravenous methylprednisolone. Child had initial transient improvement to steroids but had progressive worsening of clinical symptoms over the next few months. Neuroimaging done 6 months after the initial presentation showed progression with involvement of subcortical U fibres [Figure 1g-h]. Clinical exome sequencing showed a novel pathogenic heterozygous nonsense variant c.1717G > T (p.Glu573Ter) in exon 12 of CSF1R gene (ENST00000286301.3). The p.Glu573Ter variant results in a stop codon and premature truncation of the protein at codon 573. Parents were asymptomatic and genetic analysis couldn’t be performed due to financial constraints. A final diagnosis of paediatric-onset CSF1R related leukoencephalopathy was made.

**Discussion**

CSF1R-related leukoencephalopathy initially was described as two separate entities called pigmented orthochromatic leukodystrophy (POLD) and hereditary diffuse leukoencephalopathy with spheroids adult-onset leukoencephalopathy (HDSL). The first case of POLD was reported in 1936 and the first case report of HDSL came in 1984. In 2004, both POLD and HDSL were identified as a single entity and renamed as axonal spheroids and pigmented glia (ALSP). In 2012, dominant CSF1R mutation was found in ALSP and the name “CSF1R related leukoencephalopathy” was proposed.

The mean age of symptom onset in CSF1R related leukoencephalopathy is 43 years (18-78 years) with earlier age of onset in females and rapid progression to death in mean duration of 6.8 years. Cognitive decline (59%), psychiatric (44%) and motor symptoms (38%) are the most common initial symptoms. Other clinical features are stroke-like episodes, seizures, frontal lobe dysfunction, pathological reflexes, aphasia, apraxia, parkinsonism, pyramidal signs, dysthria, dysphagia, ataxia, myelopathy, sensory symptoms and peripheral neuropathy. Konno et al. proposed diagnostic criteria for definitive, probable and possible ALSP based on clinical, imaging, pathological findings after ruling out other causes for leukoencephalopathy. The exclusion criteria were age of presentation <10 years. Our patient had clinical symptoms starting at 11 years of age and satisfies the criteria for definitive ALSP. There are no paediatric cases described previously with this condition and the youngest case reported was an 18-year-old patient. Vision loss as one the initial manifestations as in our patient is less described in the literature.

![Figure 1](image-url)
MRI findings of adult-onset CSF1R related leukoencephalopathy include T2 white matter hyperintensities with frontal or frontoparietal predilection, with asymmetry noted in one-third cases, callosal involvement with prominent atrophy (81%), patchy restriction on DWI (75%) and deep punctate calcifications on CT (67%).[6,7] Calcifications are bilateral frontal and have a characteristic stepping stone appearance with symmetrical alignment along upper edges of lateral ventricles (40%) in pericallosal region on sagittal view.[8] Cerebral atrophy and corticospinal tract involvement are often present. Deep grey matter nuclei, brain stem is rarely involved. Gadolinium enhancement is absent. Similar brain MRI findings were noted in our patient with exception of intense diffusion restriction in most of the involved white matter. The diffusion restriction is due to intramyelin oedema.

Neuropathological findings described in CSF1R related leukoencephalopathy include myelin pallor and axonal loss in the white matter with axonal spheroids containing neurofilaments, staining positive with phosphorylated neurofilament, amyloid precursor protein and ubiquitin along with CD68 positive pigmented macrophages that are autofluorescent and periodic Schiff (PAS) positive.[9] Our patient brain biopsy showed characteristic findings of myelin pallor with mild axonal loss, CD68 positive histiocytes and neurofilament staining was positive though axonal spheroids were not seen. Till date, 81 different CSF1R mutations (51 missense, 6 nonsense, 6 splice site, 2 frameshift mutations) have been detected with no significant genotype phenotype correlations. Though pattern of inheritance is autosomal dominant, sporadic cases are seen in 40% families due to de novo mutations.[14] Our patient had a heterozygous nonsense mutation at exon 12 c. 1717G > T (p.Glu573Ter) of the CSF1R gene, with no family history. Homozygous mutations in CSF1R gene cause severe leukoencephalopathy, corpus callosal agenesis, pontocerebellar hypoplasia and skeletal changes of metaphyseal dysplasia with rapid demise in neonates.[10] The novelty of this case is the paediatric-onset (11 years) which has not been reported so far and the report of novel nonsense mutation at exon 12 c.1717G > T of the CSF1R gene.

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.

Conclusion
This case highlights the earlier age of onset, novel mutation in CSF1R gene in CSF1R related leukoencephalopathy thus expanding the phenotype-genotype spectrum.

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Conflicts of interest
There are no conflicts of interest.
Letters to the Editor

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