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Letter to the Editor: New Observation

A Novel CSF1R Mutation Mimicking Frontotemporal Dementia: A Glimpse into a Microgliopathy

Francesco Misirocchi[1], Alessandro Zilioli[1], Alberto Benussi[2], Sabina Capellari[3,*], Carlotta Mutti[1,4], Irene Florindo[1], Marco Spallazzi[1] and Liborio Parrino[1,4]

[1]Department of Medicine and Surgery, Unit of Neurology, University of Parma, Parma, Italy, [2]Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, [3]Department of Biomedical and Neuromotor Sciences, University of Bologna, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy and [4]Sleep Disorders Center, Department of Medicine and Surgery, University of Parma, Parma, Italy

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CSF1R-related leukoencephalopathy (CRL), formerly defined as adult-onset leukoencephalopathy with axonal spheroids and pigmented glia, hereditary diffuse leukoencephalopathy with spheroids, and pigmentary orthochromatic leukodystrophy (POLD), is a rare autosomal dominant leukoencephalopathy due to mutations in the *CSF1R* gene.[1] This gene codes for the colony stimulating factor 1 receptor (CSF1R), a transmembrane tyrosine kinase receptor mainly expressed in microglia. The most accepted pathogenetic mechanism is CSF1R haploinsufficiency, causing a microgliopathy with primary axonopathy followed by demyelination.[2] Characteristic pathological findings are reduced, dysmorphic and pigmented microglia, giant neuroaxonal swellings (spheroids) and blood-brain barrier (BBB) impairment. Patients typically show cognitive decline and neuropsychiatric symptoms, accompanied by motor signs. The average age of onset of CRL is 43 years, with an age-dependent penetrance and a disease duration of almost 7 years. The most notable changes on brain magnetic resonance imaging (MRI) are corpus callosum thinning and white matter damage, which usually appears much earlier than symptom onset. We report a patient with rapidly worsening neuropsychiatric and motor symptoms and an undescribed mutation in the *CSF1R* gene, attempting to shed light on hallmarks that could lead to an early diagnosis and consequently to a possible etiologic therapy for this microgliopathy.

The index case was a highly educated 48-year-old Caucasian male with an 18-months history of social withdrawal and behavioral modifications (abulia and obsessive conducts), accompanied by progressive hesitating speech. Family history and the first neurological examination were unremarkable, and biochemical and serological tests were normal. Neuropsychological assessment highlighted a non-anamnestic mild cognitive impairment, with reduced frontal and executive function test scores. Brain MRI (Figure 1) showed mild to moderate bilateral periventricular

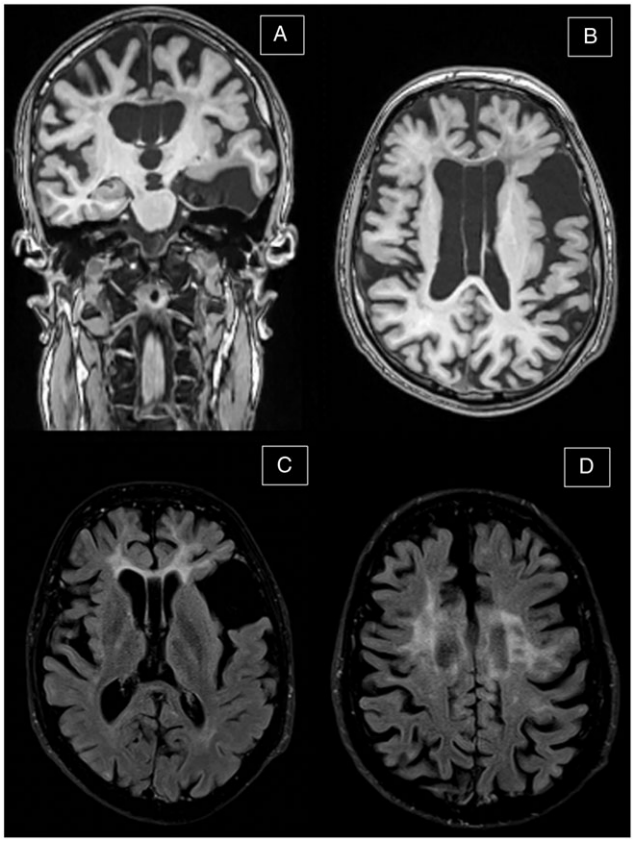


Figure 1: Index case MRI. On top, coronal (A) and axial (B) T1-weighted MRI showing frontoparietal atrophy, cavum vergae, and right temporopolar arachnoid cyst. On bottom, two different axial (C, D) T2-weighted fluid attenuated inversion recovery (FLAIR) MRI showing symmetrical mainly periventricular prominent frontal leukoencephalopathy.

Corresponding author: Francesco Misirocchi, Department of Medicine and Surgery, Unit of Neurology, University of Parma, Hospital of Parma, Via Gramsci 14, Parma, 43126, Italy. Email: francesco.misirocchi@unipr.it

*Sabina Capellari's name has been corrected. A corrigendum detailing this change has also been published (doi: 10.1017/cjn.2022.302).

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Table 1: Comparison of epidemiologic, clinical, cerebrospinal fluid, and radiological characteristics between CSF1R-related leukoencephalopathy (CRL), frontotemporal dementia (FTD), and the index case

		CRL	FTD	Index case
Epidemiology	Family history	65%	30%	N
	Sex ratio	M:F = 1:1	M:F = 1:1	M
	Age at onset	40–50 years	45–64 years	48 years
	Life expectancy	6–8 years	5–12 years	
Clinical features	Neuropsychiatric symptoms	+++	+++	Y
	Cortical motor symptoms	+++	++	N
	Extrapyramidal symptoms	+++	++ (mainly in *MAPT* mutations and FTD parkinsonism)	Y
	Seizures	30%	5%	Y
CSF	ATN profile	(No data)	A-T-N-/+	A-T-N+
Imaging	Atrophy	+++	+++	Y
	Atrophy pattern	Fronto parietal. Symmetrical	Mainly Fronto temporal. Symmetrical/asymmetrical (asymmetrical in *GRN* mutations, mainly temporal in *MAPT* mutations, parietal involvement in *C9orf72* mutations)	Fronto parietal. Symmetrical
	White matter disease	+++	+ (common in *GRN* mutations)	Y
	Peculiar hallmarks	1. Corpus callosum thinning 2. Brain calcifications 3. Cavum vergae 4. DWI lesions		1. Corpus callosum thinning 2. Cavum vergae 3. Arachnoid cyst

+: rare; ++: in about 50% cases; +++: frequent; Y: present; N: absent.
CSF: cerebrospinal fluid; MAPT: microtubule-associated protein Tau; GRN: progranulin; C9orf72: chromosome 9 open reading frame 72.

leukoencephalopathy, prominent frontoparietal atrophy, thinning of the corpus callosum, a voluminous left arachnoid cyst, and cavum vergae. CSF analysis showed a slight protein increase and was consistent with an A-T-N+ biomarker profile. Subsequent evaluations revealed a clinical progression to dementia, rapidly declining speech, and extrapyramidal signs. A diagnosis of probable behavioral variant frontotemporal dementia was made according to the diagnostic criteria, but the subsequent next-generation sequencing (NGS) panel showed a heterozygous *CSF1R* mutation. The genetic variant was a previously undescribed missense mutation (G > C, c.2509, p. Asp837His) in the tyrosine kinase domain (TDK), the critical CSF1R domain. The mutation was absent in the control database (Varsome) and likely pathogenic according to the American College of Medical Genetics and Genomics guidelines. The patient had core clinical and radiological features of CRL, and a definite diagnosis could be made according to current diagnostic criteria.[3,4] Due to the symptoms' severity, symptomatic and supportive therapy was proposed, and 1-year follow-up showed speech deterioration up to a complete speaking inability, with several seizures worsening his clinical status.

In this case study, we identified a novel mutation in *CSF1R* gene in a patient without a family history, as it happens in about 30% cases. Thanks to the expanding use of NGS, CRL has been recognized as one of the leading causes of adult inherited leukoencephalopathy and its typical features have been increasingly elucidated.[5] Clinically, patients show frontal lobe and executive functions decline with depression, apathy, and other personality changes. In addition, motor engagement is distinctive, with parkinsonian, bulbar, or pyramidal signs. CRL is marked by a broad phenotypic variability, and a genetic–phenotypic correlation has never been established to date, suggesting how other heritable or environmental factors might modulate clinical expression. Given the wide clinical spectrum, a considerable diagnostic delay is common, and an initial frontotemporal dementia (FTD) diagnosis is occasionally established (Table 1).[6] Besides neuropsychiatric and motor features, our patient presented epilepsy, observed in approximately 30% cases.

Computed tomography (CT) scan detection of small brain calcifications in the frontal white matter could be evocative. MRI hallmarks are white matter disease, lateral ventricles enlargement, and corpus callosum thinning. White matter abnormalities are initially patchy but later confluent, bilateral, with greater frontal and parietal involvement, affecting both projection tracts and U fibers. Furthermore, characteristic findings are progressive cortical frontoparietal atrophy, long-lasting diffusion restricted lesions, and the presence of cavum vergae. Advanced MRI analysis shows decreased volume of bilateral thalami and hippocampi and impaired white matter microstructure, particularly in midline associations' fibers. Together with functional MRI resting-state alterations in bilateral caudate nuclei, hippocampi, and thalami, these results highlight the wide connective fibers alterations in CRL and the subsequent impact on key structures in integrating widespread neural activity.[5]

CSF1R is a crucial factor for the survival, proliferation, and activation of microglia, especially in the cortex, hippocampus, and striatum. These cells play a prominent role in central nervous system (CNS) development and homeostasis, regulating neuronal environment, implementing non-inflammatory phagocytosis,

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and taking part in synaptic pruning. Relying on the haploinsufficiency mechanism, it is hypothesized that about half of functional cells might be sufficient in heterozygous patients to reach adulthood unimpaired. Rare subjects with biallelic mutations show a variable conjunction of structural brain abnormalities, progressive neurologic deterioration with seizures and bone dysplasia, evident from childhood (BANDDOS: brain abnormalities, neurodegeneration, and dystosteosclerosis).[7]

Microglia cells are brain-resident macrophages creating a niche where repopulation is tightly regulated by local self-renewal, mainly thanks to the CSF1R signaling pathway, without further precursor colonization due to the BBB impermeability. Being CRL a primary microgliopathy and taking advantages of BBB disease-related impairment, microglial replacement with hematopoietic stem cells transplantation has been suggested as a promising therapy. Despite the absence of longitudinal studies, early findings seem encouraging, at least in terms of symptoms stabilization. Drawing inspiration from preclinical research and other inherited leukodystrophy therapy, a new cutting-edge approach might consist in the pharmacological depletion of affected microglia followed by replacement with resident microglia proliferation and microglia-like cells infiltration.[8]

In conclusion, CRL is often a delayed diagnosis. Given the extensive clinical overlap between FTD and CRL, an imaging evaluation seeking specific hallmarks such as brain calcifications, cavum vergae, and corpus callosum thinning is essential, coupled with a wider use of NGS in early-onset dementias. This approach is even more crucial considering how current and future therapies might have a narrowed therapeutic window during the first stages of the disease.

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Statement of Authorship. Conceptualization FM, AZ, and MS; Writing – original draft preparation, FM, AZ, MS and IF; Writing – review a editing, MS, IF, AB, SC, CM, LP.

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