

CSF1R-related leukoencephalopathy

A major player in primary microgliopathies

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Abstract

Since the discovery of *CSF1R* gene mutations in families with hereditary diffuse leukoencephalopathy with spheroids in 2012, more than 70 different mutations have been identified around the world. Through the analyses of mutation carriers, *CSF1R*-related leukoencephalopathy has been distinctly characterized clinically, radiologically, and pathologically. Typically, patients present with frontotemporal dementia-like phenotype in their 40s–50s, accompanied by motor symptoms, including pyramidal and extrapyramidal signs. Women tend to develop the clinical symptoms at a younger age than men. On brain imaging, in addition to white matter abnormalities, thinning of the corpus callosum, diffusion-restricted lesions in the white matter, and brain calcifications are hallmarks. Primary axonopathy followed by demyelination was suggested by pathology. Haploinsufficiency of colony-stimulating factor-1 receptor (*CSF1R*) is evident in a patient with a frameshift mutation, facilitating the establishment of *Csf1r* haploinsufficient mouse model. These mice develop clinical, radiologic, and pathologic phenotypes consistent with those of human patients with *CSF1R* mutations. In vitro, perturbation of *CSF1R* signaling is shown in cultured cells expressing mutant *CSF1R*. However, the underlying mechanisms by which *CSF1R* mutations selectively lead to white matter degeneration remains to be elucidated. Given that *CSF1R* mainly expresses in microglia, *CSF1R*-related leukoencephalopathy is representative of primary microgliopathies, of which microglia have a pivotal and primary role in pathogenesis. In this review, we address the current knowledge of *CSF1R*-related leukoencephalopathy and discuss the putative pathophysiology, with a focus on microglia, as well as future research directions.

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Glossary

AARS2-L = AARS2-related leukoencephalopathy; **ALSP** = adult-onset leukodystrophy with neuroaxonal spheroids and pigmented glia; **bvFTD** = behavioral variant frontotemporal dementia; **CI** = confidence interval; **CSF1R** = *CSF1R* gene encoding colony-stimulating factor-1 receptor; **HDLS** = hereditary diffuse leukoencephalopathy with spheroids; **HSCT** = hematopoietic stem cell transplantation; **IRB** = institutional review board; **MS** = multiple sclerosis; **NHD** = Nasu-Hakola disease; **POLD** = pigmentary orthochromatic leukodystrophy; **TKD** = tyrosine kinase domain; **TORCH** = toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex; **TREM2** = triggering receptor expressed on myeloid cells 2; **TYROBP** = TYRO protein tyrosine kinase-binding protein; **USP18** = ubiquitin-specific protease 18.

Owing to advances in molecular genetics, the complexity of hereditary leukoencephalopathies has been gradually unveiled in recent years. The discovery of a causative gene facilitates increasing recognition of the disease and understanding of its clinical, pathologic, and biologic characteristics. *CSF1R* gene encoding colony-stimulating factor-1 receptor (*CSF1R*) was identified in 1 of the hereditary leukoencephalopathies, hereditary diffuse leukoencephalopathy with spheroids (HDLS), in 2012.^{1,2} *CSF1R* is a transmembrane tyrosine kinase receptor that expresses in mononuclear phagocytic cells. In the brain, it mainly expresses in microglia. Binding of its ligands (*CSF1* and interleukin-34) to *CSF1R* leads to formation of a receptor homodimer on cell surface and subsequent activation of *CSF1R* through autophosphorylation.³ Activation is necessary to initiate signal transductions, which contribute to development, maintenance, and activation of microglia.⁴ Therefore, microglia are considered primarily affected in this inherited leukoencephalopathy, referred to as primary microgliopathies,^{2,5-7} as opposed to secondary microgliopathies, in which microglial activation occurs secondary to other CNS insults.^{7,8} In line with the recent understanding of this disease concept, we call this disease *CSF1R*-related leukoencephalopathy⁹ in this review. We review historical aspects of this unique disease and discuss clinical, radiologic, and pathologic characteristics and putative pathophysiology, with a focus on microglia.

Standard protocol approvals, registrations, and patient consents

We conducted all genetic analyses under approval of the institutional review board (IRB) of Mayo Clinic Florida and Niigata University. Written informed consent was obtained from all research participants. Brain autopsy was performed at the Mayo Clinic Florida with permission obtained from the legal next of kin. The Mayo Clinic IRB Committee exempts autopsy studies from human subject research.

Historical background and nosology

In 1936, pigmentary orthochromatic leukodystrophy (POLD) was reported as a subset of orthochromatic leukodystrophies in a Belgian family by van Bogaert and Nyssen.¹⁰ POLD is pathologically characterized by diffuse myelin and

axonal loss accompanied by pigmented macrophages. HDLS was first described in a Swedish family in 1984 by Axelsson et al.¹ Two neuropathologists, Røyttä¹¹ and Sourander, named HDLS based on its pathologic characteristics: loss of myelin sheaths and axons, widespread white matter degeneration, and numerous neuroaxonal spheroids. Marotti et al.¹² discussed the clinical and pathologic similarities between POLD and HDLS.¹⁰ Marotti et al.¹² reported 3 autopsy-confirmed HDLS cases from a single family, whose brain lesions also contained pigmented macrophages. These authors had a chance to review the original POLD case of van Bogaert and Nyssen and found abundant axonal spheroids in affected white matter reminiscent of HDLS. In the article by Marotti et al.,¹² the term adult-onset leukodystrophy with neuroaxonal spheroids and pigmented glia (ALSP) was coined as a comprehensive pathologic term for these conditions. Since then, the similarity between POLD and HDLS has been repeatedly discussed by others and the term “leukoencephalopathy” has been often used alternatively for “leukodystrophy.”¹³⁻¹⁵ A year after the discovery of the *CSF1R* gene in HDLS, Nicholson et al.¹⁶ identified *CSF1R* mutations in 2 pathologically diagnosed POLD families (1 mutation had already been found in HDLS²), providing genetic evidence that POLD and HDLS can be categorized as a single disease entity.

There have been several cases in which clinical and pathologic findings were consistent with ALSP, but *CSF1R* mutations were not identified.¹⁷⁻¹⁹ Notably, no *CSF1R* mutation has been found in the original Swedish family,²⁰ implying that other genes may be associated with these cases. In 2016, homozygous or compound heterozygous mutations in *AARS2* gene encoding mitochondrial alanyl-transfer RNA synthetase were identified in 5 patients who were clinically suspected to have ALSP, but were negative for *CSF1R* mutations.²¹ Importantly, pathologic findings similar to those of ALSP carrying *CSF1R* mutation were obtained in 1 of those patients with *AARS2* mutation by brain biopsy. However, there are several clinical and radiologic differences between ALSP caused by *CSF1R* mutation and *AARS2*-related leukoencephalopathy (*AARS2-L*).^{22,23} *AARS2-L* is not always an adult-onset disease.²⁴ Furthermore, in another case of *AARS2-L*, no pathologic evidence of ALSP was obtained by brain biopsy.²⁵ Thus, further studies, including detailed analyses of autopsied brains, are required to characterize *AARS2-L*.

Due to the evolving knowledge of pathology and genetics of this disease entity, its nomenclature is changing (figure 1). In our review, we use the term *CSF1R*-related leukoencephalopathy⁹ for descriptive purposes; however, if ALSP is further established as a consistent clinicopathologic entity determined by several genes, a prefix-gene style, as used for genetic movement disorders,²⁶ would be acceptable, such as ALSP-*CSF1R*. There is controversy which term—leukodystrophy or leukoencephalopathy—is more appropriate.²⁷ Recently, the GLIA Consortium defined leukodystrophies as heritable white matter disorders with neuropathology primarily characterized by involvement of non-neuronal cells.²⁸ According to this definition, ALSP could be categorized under leukodystrophies⁵ because microglia are considered to be primarily affected in this disease.²

Epidemiology

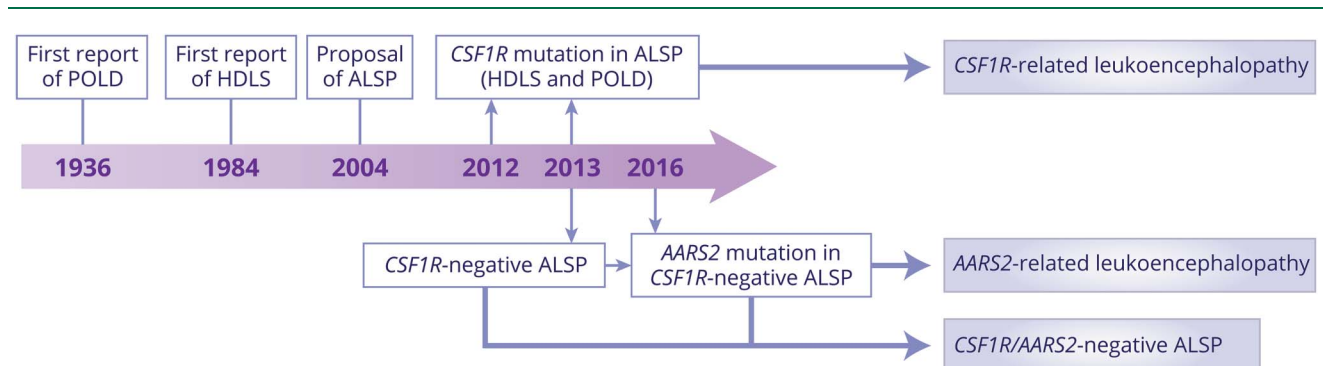
Since diagnosis of *CSF1R*-related leukoencephalopathy had depended on pathologic findings, the number of definitively diagnosed patients was extremely limited until discovery of the gene mutations. Since 2012, although still rare, genetically diagnosed patients have been increasingly recognized around the world (figure 2A), indicating that this disease has global distribution, and many patients may still be underdiagnosed. One study estimated the frequency of *CSF1R*-related leukoencephalopathy at 10% (5/48) of adult-onset leukoencephalopathies and implied that it is the most common type,²⁹ whereas in another study, using an MRI pattern-based approach, only 2 of 154 (0.6%) patients with adult-onset leukoencephalopathies were genetically diagnosed.³⁰ Approximately one-third of genetically proven patients have been reported in Japan.²³

Clinical features

The mean age at onset of *CSF1R*-related leukoencephalopathy is 43 years and disease duration is 6.8 years.²³ While

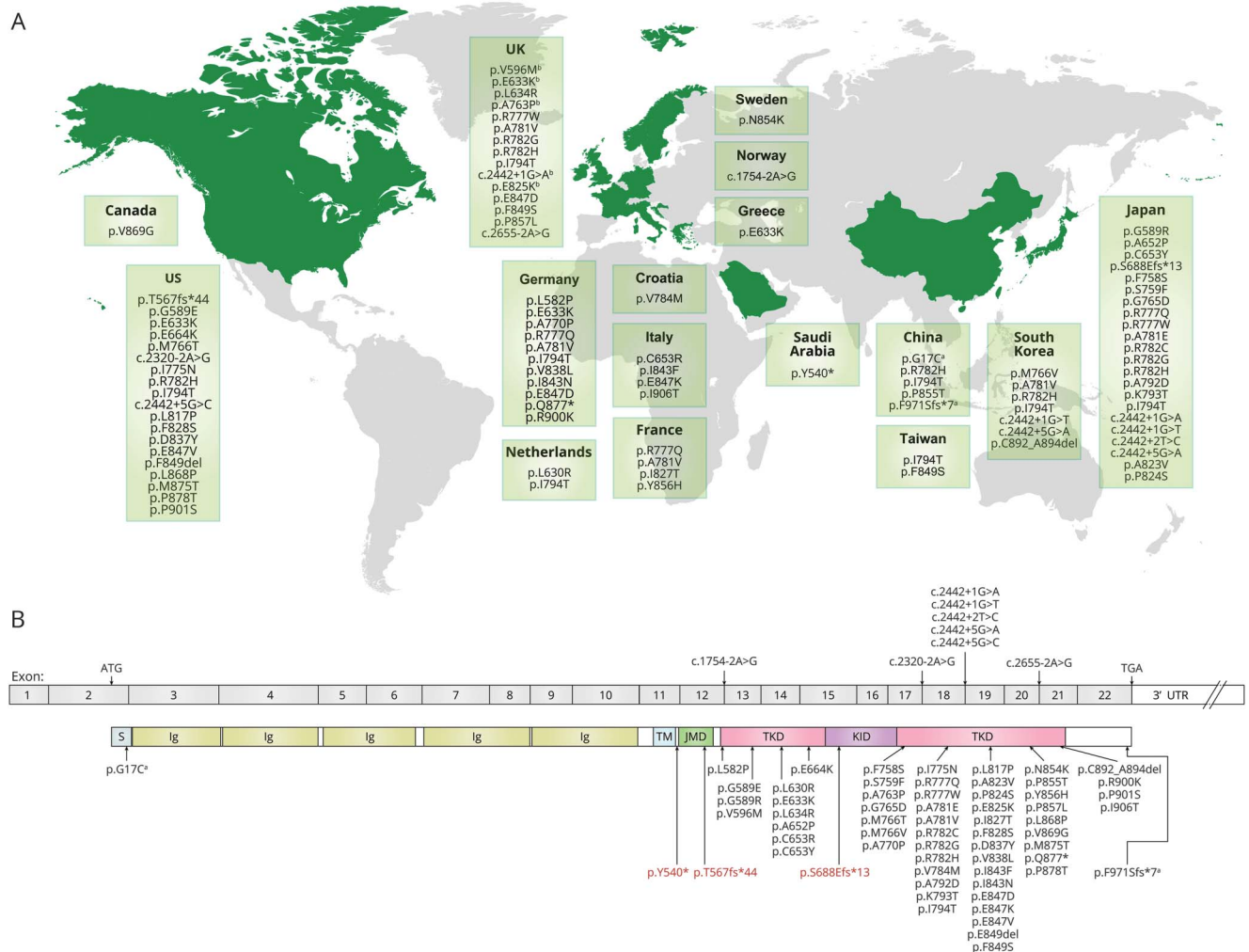
there is no sex difference in prevalence, women develop disease 7 years earlier than men (40 vs 47 years [95% confidence interval (CI) 3.158–11.177]).²³ The cumulative incidence is 10% at age 27 years, 50% at age 43 years, and rises to 95% by age 60 years.²³ This disease is clinically characterized by 2 major components: neuropsychiatric and motor symptoms.³¹ The former represents progressive cognitive decline, depression, apathy, anxiety, irritability, and other behavioral or personality changes, resembling behavioral variant frontotemporal dementia (bvFTD). The latter includes parkinsonian symptoms (i.e., tremor, rigidity, bradykinesia, and postural instability),²⁰ pyramidal signs (e.g., hyperreflexia, spasticity), bulbar signs (e.g., dysarthria, dysphagia), and ataxia. Some patients manifest gait disturbance as a cardinal symptom rather than cognitive and psychiatric symptoms.³¹ Apraxia, aphasia, and seizures can also develop in one-third of patients.²³ Like other leukoencephalopathies, there is no disease-specific clinical picture of *CSF1R*-related leukoencephalopathy; however, if patients manifest bvFTD at a relatively young age accompanied by motor symptoms and white matter abnormalities on MRI, *CSF1R*-related leukoencephalopathy should be included in the differential diagnosis. The progression of this illness is rapid. Some rare presentations have been described, such as stroke-like episodes,³² bone cysts,³³ and involvement of optic³⁴ and peripheral nerves.^{35,36} Further investigation is warranted to evaluate significance of these rare findings. Of note, motor symptoms can be more predominant than neuropsychiatric symptoms in young women, who are likely to be misdiagnosed with multiple sclerosis (MS).²³ In the literature, we found 24 patients (18 women, 5 men, and 1 whose sex was obscured) diagnosed with MS or demyelinating disorder.^{2,9,34,36–47} Eleven cases (45.8%) were sporadic. The mean age at onset was 32.1 years, 10 years younger than the overall average. Indeed, 14 (58%) patients initially presented with motor symptoms, including gait disturbance, limb weakness, hemiparesis, dysarthria, and dysphagia, regardless of whether or not they had cognitive impairment. These

Figure 1 Changing nomenclature with a growing understanding of pathology and genetics



We currently have at least 3 different leukoencephalopathies from this adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) axis: colony-stimulating factor-1 receptor (*CSF1R*)-related leukoencephalopathy, alanyl-transfer RNA synthetase 2 (*AARS2*)-related leukoencephalopathy, and *CSF1R/AARS2*-negative ALSP. It is controversial whether *AARS2*-related leukoencephalopathy can be classified under ALSP. HDLS = hereditary diffuse leukoencephalopathy with spheroids; POLD = pigmentary orthochromatic leukodystrophy.

Figure 2 World distribution of colony-stimulating factor-1 receptor (*CSF1R*) mutations and *CSF1R* gene/protein diagram with reported mutations



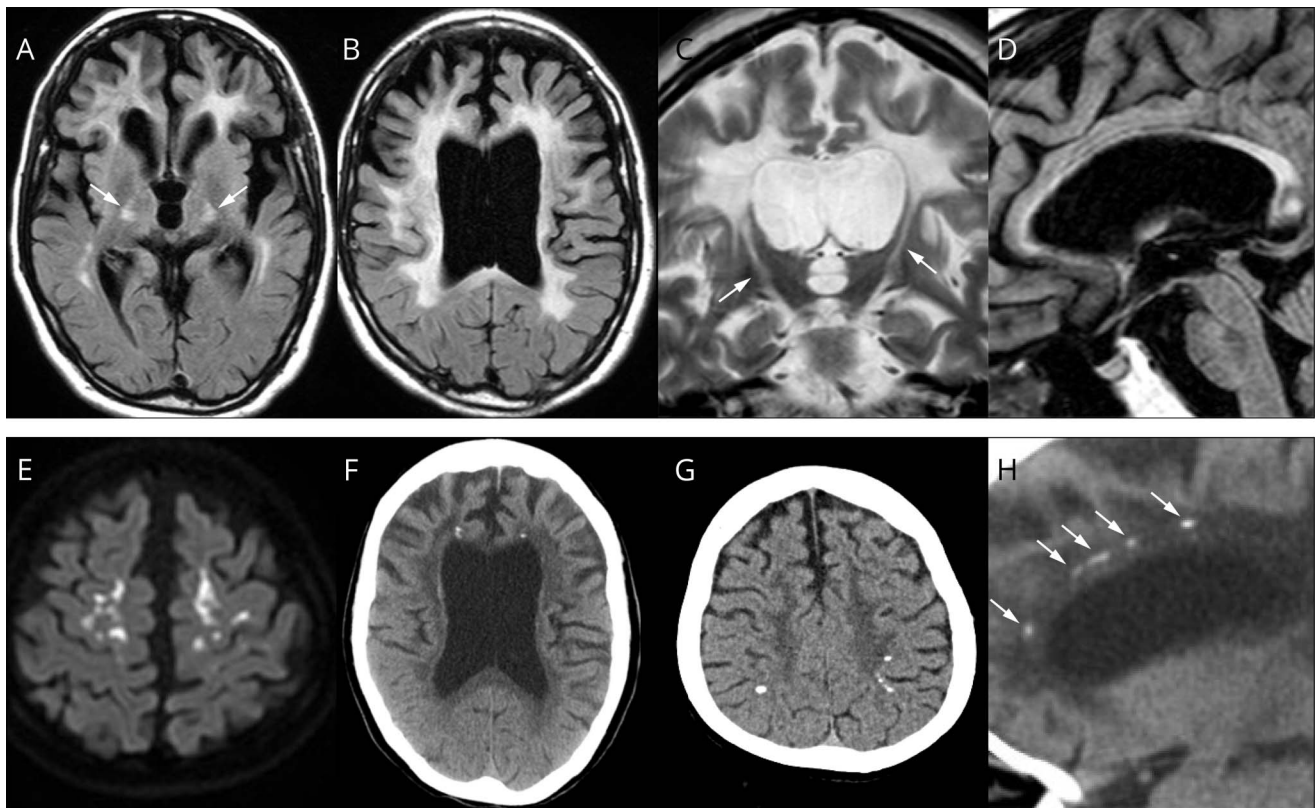
(A) World distribution of *CSF1R* mutations. The countries in which the mutation was reported are shown in green. This world map was created using mapchart (<http://mapchart.net/>). (B) Diagram of *CSF1R* gene and protein with reported mutations. All mutations are found within the tyrosine kinase domain (TKD) of *CSF1R* except for a nonsense mutation, p.Y540*, and 2 frameshift mutations, p.T567fs*44 and p.S688Efs*13, shown in red. These are located in the intervening sequence between transmembrane domain (TM) and juxtamembrane domain (JMD) and in the kinase insert domain (KID). ^aThese 2 variants, located outside the TKD, have been reported recently in Chinese patients.⁴⁰ One (p.G17C) is in the signal peptide sequence of *CSF1R* and the other (p.F971Sfs*7) is at the C-terminal sequence. The former variant does not change the TKD, but might fail to express *CSF1R* on the cell surface if it influences the signal peptide function, resulting in loss of *CSF1R* function. The latter induces subtle changes in a couple of the last amino acids of *CSF1R*, but the TKD remains unchanged. This has been reported as a rare variant in an East Asian population (rs766047383; allele frequency is 0.0004641 based on The Genome Aggregation database, gnomad.broadinstitute.org/). Therefore, the pathogenicity of these variants remains to be determined. ^bThese 5 mutations were identified in a mixed cohort from the United Kingdom, Greece, and Ireland.⁴⁹ Ig = immunoglobulin-like domain; UTR = untranslated region.

features may drive MS diagnosis over *CSF1R*-related leukoencephalopathy.

We recently proposed diagnostic criteria for *CSF1R*-related leukoencephalopathy.²³ The criteria yield high sensitivity (more than 96% of cases fell into probable or possible criteria) and can successfully exclude cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, which is one of the main differential diagnoses and a major cause of adult-onset leukoencephalopathies.³⁰ If a patient fulfils the probable criteria, genetic testing for *CSF1R* is recommended.

Radiologic features

Consistent radiologic findings on brain MRI are white matter abnormalities and enlargement of the lateral ventricles, reflecting the intensive white matter damage (figure 3, A–C). Thinning of the corpus callosum is characteristic and best observed in a sagittal view (figure 3D). These MRI findings develop insidiously⁴⁸ and are usually seen at the time of symptom onset. White matter changes have been observed 6 years prior to symptom onset.⁴⁹ White matter lesions are initially patchy, but later confluent and distributed predominantly in the frontal and parietal areas. These are usually



(A–D, F, H) A 44-year-old woman with *CSF1R* p.G589R. (E) A 27-year-old woman with *CSF1R* c.2442+5 G > A. (G) A 31-year-old woman with *CSF1R* p.A652P. All of these patients have been reported previously.⁴¹ (A, B), Bilateral diffuse white matter hyperintensity with pyramidal tract involvement (arrows in A), cortical atrophy, and enlarged lateral ventricles on fluid-attenuated inversion recovery MRI. (C) Longitudinal pyramidal tract involvement (arrows) on coronal T2-weighted image. (D) Thinning of the corpus callosum with hyperintensity on sagittal fluid-attenuated inversion recovery image. (E) Hyperintensity lesions in the subcortical white matter on diffusion-weighted image. (F) Small calcifications located bilaterally near the anterior horns of the lateral ventricles on brain CT image. (G) Calcifications in parietal subcortical white matter. (H) Stepping stone appearance of calcifications (arrows) in the frontal pericallosal region on sagittal CT image.

bilateral, but not always symmetric. The lesions also involve projection fibers, including pyramidal tracts in the internal capsule and brainstem (figure 3, A and C),^{23,43} whereas U-fibers are likely spared until the terminal stage of disease. Cortical atrophy over the frontal and parietal lobes becomes evident with disease progression. Diffusion-restricted lesions with reduced apparent diffusion coefficient can be observed in the white matter of some patients (figure 3E). Unlike ischemic lesions, these are persistent for several months or more, presumably reflecting intramyelinic edema.^{50,51} No contrast enhancement is observed.^{51,52} Cerebellar dentate nuclei and cerebellar peduncles are spared. An MRI scoring system for assessing severity of white matter lesions and brain atrophy (total severity score ranges from 0 [minimum] to 57 [maximum]) has been proposed.⁵² Lakshmanan et al.²² were aware of the high incidence (63% of their cohort) of a cavum septum pellucidum and cavum vergae. Consistent with their observation, we found the same findings in our patients.^{41,48,52} Given that the cavum septum pellucidum and cavum vergae can be seen as normal variants in the general population, comparison studies between *CSF1R*-related leukoencephalopathy, other neurologic diseases with white matter involvement, and normal controls are required to validate.

Brain CT scan is also useful for diagnosing *CSF1R*-related leukoencephalopathy. It can depict brain calcifications in the white matter that are possibly specific to this disease. Based on a review of 25 patients who had CT-confirmed brain calcifications (table)^{22,40,41,47,48,53–60,e1,e2} (doi.org/10.5061/dryad.498j63f), there were 7 men and 18 women with a mean onset age of 38 years, though significantly younger in women than in men (34.6 vs 46.1 years, respectively, 95% CI 2.580–20.530). The calcifications always distributed in the frontal white matter adjacent to the anterior horns of lateral ventricles (25/25, 100%, bilaterally in most patients) (figure 3F), and to a lesser extent, in the parietal subcortical white matter (12/25, 48%) (figure 3G).^{41,48} On a sagittal view, a striking pattern of the calcifications can be seen bilaterally in the frontal pericallosal regions, called stepping stone appearance (10/25, 40%) (figure 3H).⁴¹ The calcifications can be found at an asymptomatic stage of *CSF1R* mutation carrier,^{56,58} even at birth,⁴¹ indicating that the calcifications may not be related to clinical symptoms or white matter damages. The size and distribution of the calcifications usually remain stable over time,^{54,56} but occasionally the calcifications may be reduced in size.⁴¹ The calcifications are usually very small, and thus, very easily overlooked; therefore, thin-section (1 mm) CT scan and reconstructed sagittal images are

Table List of 25 colony-stimulating factor-1 receptor (*CSF1R*)-related leukoencephalopathy patients with CT-confirmed brain calcifications

Reference	Sex	Origin	FH	<i>CSF1R</i> mutation	Age at onset, y	Age at first detection of calcifications, y	Location of calcifications		Stepping stone appearance on sagittal CT
							Frontal	Parietal	
Konno et al. ⁵⁶	F	US	+	p.G589E	Asymptomatic ^a	23	+	+	+
Konno et al. ⁴¹ Fujioka et al. ⁵⁴	F	US	+	p.G589E	47	52	+	+	NA
Konno et al. ⁴¹	M	US	+	p.G589E	58	60	+	-	NA
Konno et al. ⁴¹	F	Japan	-	p.G589R	37	44	+	+	+
Daida et al. ⁵³	F	Japan	-	p.G589R	44	46	+	+	+
Konno et al. ⁴¹	F	Japan	-	p.A652P	30	31	+	+	NA
Imai et al. ⁴⁷	F	Japan	-	p.F758S	23	24	+	+	+
Konno et al. ⁴⁸	F	Japan	+	p.G765D	37	41	+	-	NA
Konno et al. ⁴¹	F	US	+	p.M766T	18	30	+	-	+
Konno et al. ⁴⁸	F	Japan	+	p.A781E	36	39	+	+	NA
Okamoto et al. ⁵⁸	M	Japan	-	p.R782C	43	33	+	+	+
Ueda et al. ^{e2} (doi.org/10.5061/dryad.498j63f)	M	Japan	+	p.A792D	41	43	+	ND	+
Meyer-Ohlendorf et al. ⁵⁷	F	Germany	-	p.I794T	29	29	+	ND	NA
Lan et al. ^{e1}	F	Taiwan	+	p.I794T	32	34	+	ND	NA
Konno et al. ⁴⁸	M	Japan	-	p.I794T	40	44	+	+	NA
Lakshmanan et al. ²²	F	UK	-	c.2442+1 G > A	45	NA	+	ND	NA
Konno et al. ⁴⁸	M	Japan	-	c.2442+1 G > T	53	56	+	-	NA
Konno et al. ⁴¹	M	Japan	+	c.2442+5 G > A	58	61	+	+	+
Konno et al. ⁴¹	F	Japan	+	c.2442+5 G > A	27	28	+	-	+
Konno et al. ⁴¹	F	US	-	c.2442+5 G > C	23	0	+	+	+
Terasawa et al. ⁵⁹	F	Japan	+	p.A823V	50	50	+	ND	NA
Konno et al. ⁴⁸	F	Japan	-	p.P824S	45	47	+	-	NA
Blume and Weissert ⁶⁰	F	Germany	-	p.E847D	32	33	+	ND	NA
Gore et al. ⁵⁵	F	US (African American)	-	p.E847V	33 ^b	5	+	+	NA
Wu et al. ⁴⁰	M	China	-	p.F971Sfs*7	30	32	+	ND	NA

Abbreviations: *CSF1R* = colony-stimulating factor-1 receptor; FH = family history; NA = not available for sagittal images; ND = not described (unable to fully assess because only a few slides were provided in the relevant articles).

^a This patient was asymptomatic at age 43 years.

^b This patient had had complex partial seizures and been treated with phenytoin from 5 to 14 years old. After a healthy period after remission of the seizures, she developed slow gait and concentration problems at age 33 years.

recommended to locate them.⁴¹ An exceptional patient has been reported in whom large calcifications were observed.⁵⁵ In our experience, *CSF1R* mutations were always found in patients who had these calcifications, suggesting that the brain calcifications if present have extremely high diagnostic value. Of additional

interest is that a pericallosal brain calcification distribution pattern is very similar to the distribution of Iba1- and CD68-immunopositive cells in the human fetal brain,^{e3,e4} raising the possibility of a causal relationship between formation of calcifications and some mutant microglia dysfunction.

SPECT demonstrates hypoperfusion in the frontal and parietal cortices^{37,45,53,59,e5} (doi.org/10.5061/dryad.498j63f). [¹⁸F]-fluorodeoxyglucose PET reveals diffuse cortical hypometabolism predominantly in fronto-parietal areas.^{16,46, e6,e7} These findings are not disease-specific, but may well reflect the affected brain areas. In studies using magnetic resonance spectroscopy, increased choline and decreased N-acetylaspartate levels are constantly observed in white matter lesions,^{32,34,51,57,e8} indicating demyelination and axonal damage, respectively. The change of metabolite levels can be detected prior to development of symptoms.^{e8}

Pathologic features

A key neuropathologic finding is the combination of widespread white matter degeneration with a loss of myelin and axons, abundant neuroaxonal spheroids, and lipid-laden and pigmented macrophages (figure 4).¹ White matter degeneration affects the centrum semiovale, the periventricular white matter, and the corpus callosum, predominantly in the frontal and parietal lobes, with relative sparing of the temporal and occipital lobes. Reactive bizarre astrocytes that appear irregular and hypertrophic are observed in the affected white matter^{e9} (doi.org/10.5061/dryad.498j63f). While cortical neurons are relatively preserved, ballooned neurons are frequently observed in the overlying cortex. The significance of ballooned neurons remains unknown, but may be associated with impaired axonal transport^{e10} or dying-back degeneration.¹⁵ Interestingly, in contrast to the prominent involvement in the cerebral white matter, other fibers, including arcuate fibers (U-fibers), pencil fibers in the putamen, anterior commissure, fornix, and optic nerves, are generally preserved. Projection fibers, including frontopontine and corticospinal fibers, can be involved. In some patients, pyramidal tract degeneration is observed continuously through the brainstem to the spinal cord.^{e11}

Two pathologic hallmarks, axonal spheroids and pigmented macrophages, are vastly observed in the affected white matter. The spheroids are immunostained with phosphorylated neurofilament, amyloid precursor protein, and ubiquitin^{e9} (doi.org/10.5061/dryad.498j63f). The pigmented macrophages are CD68-positive and contain brown granular pigments that are autofluorescent and stained with periodic acid-Schiff.^{e9} Electron microscopy reveals heterogeneous appearances of spheroids with combinations of aggregated neurofilaments, mitochondria, vesicles, and dense bodies.^{1,e9,e12-e17} Thickness of the myelin sheath varies and intramyelinic vacuolations are frequently seen.^{e14} Macrophages contain ceroid-like ultrastructure with lamellated or fingerprint bodies.^{e14,e18,e19} The abundance and distribution of spheroids and macrophages seem to be related to the severity of the white matter pathology. According to pathologic staging proposed by Alturkustani et al.,^{e17} numerous spheroids appear prior to the white matter change. Then the number of spheroids is decreased along with white matter damage. Importantly, any

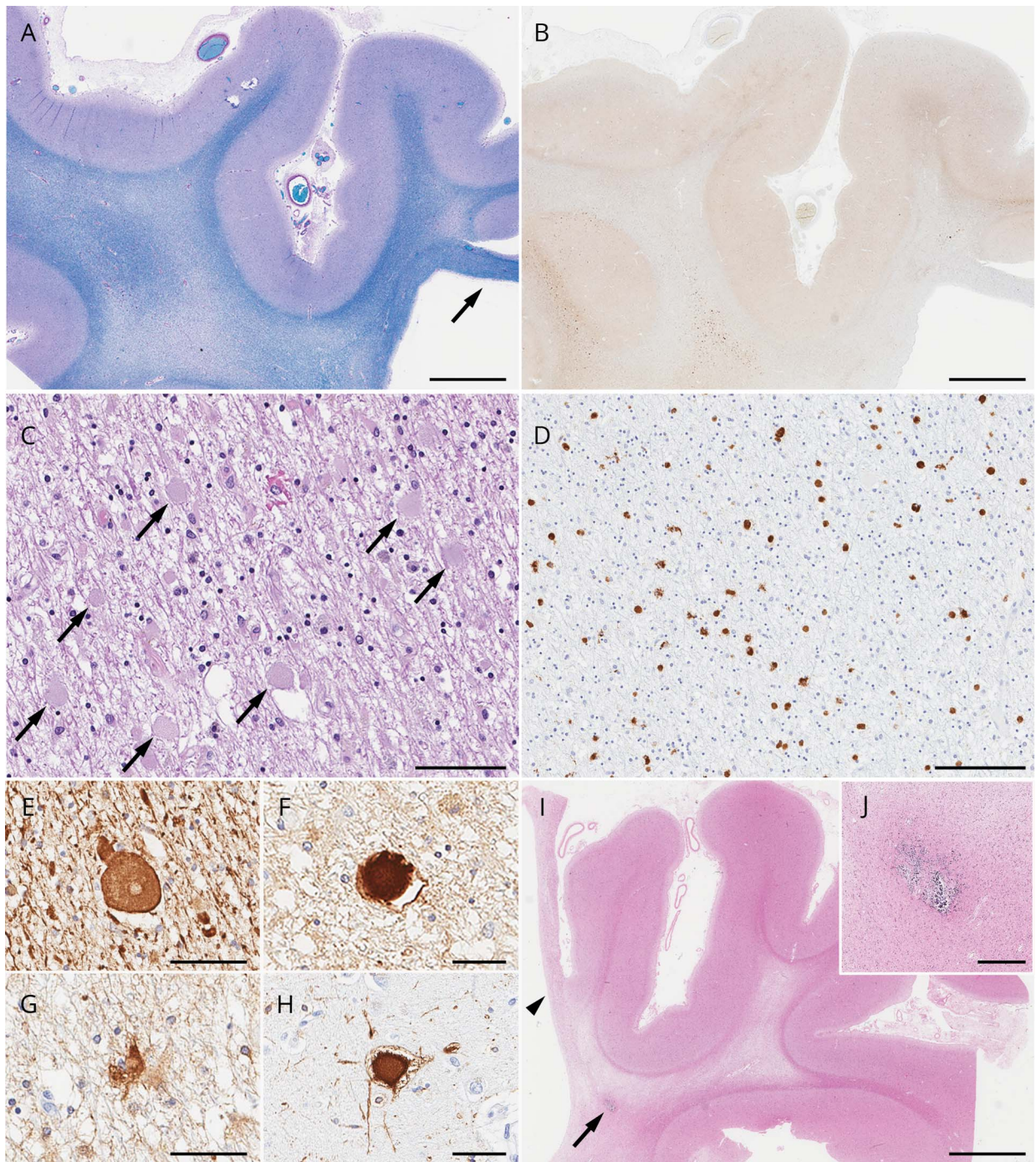
stages can be observed simultaneously in a single patient, implying that lesions may occur multifocally, and thus, only 1 biopsy specimen could fail to detect typical findings.⁵⁵ This temporal and spatial association between spheroids and white matter lesions supports the idea of primary axonopathy; axonal damage occurs prior to myelin loss.^{12,15,e5,e17,e17,e20,e21} The pigmented macrophages also become sparse in severely affected white matter.^{e5,e13,e17} Alturkustani et al.^{e17} described that CD68-positive macrophages were rarely observed in early stages, whereas others argued that the emergence of these cells precedes axonal injury.^{e5,e21} In general, there are no pathologic structures immunostained with tau, α -synuclein, and TDP-43.

Tada et al.^{e22} (doi.org/10.5061/dryad.498j63f) focused on microglia by detailed pathologic analyses. They showed that microglia had relatively small and narrow cytoplasm with thin processes in *CSF1R*-related leukoencephalopathy (n = 6) compared to controls (n = 6) and other white matter-involved disorders, including Alzheimer disease (n = 1), Nasu-Hakola disease (NHD) (n = 1), adrenoleukodystrophy (n = 1), and Binswanger disease (n = 2).^{e22} The number of microglia was decreased in brains with *CSF1R* mutations. Interestingly, distribution of activated microglia (immunopositive for Iba1, P2ry12, and GLUT5) is spatially restricted; more abundant in relatively preserved areas, but sparse in devastated areas, which is consistent with the previous observation by Alturkustani et al.^{e17, e22} In contrast to the activated microglia, Tada et al.^{e22} showed that macrophages (immunopositive for Iba1, but negative for P2ry12 and GLUT5) accumulated in the damaged white matter and are involved in phagocytosis. These cells were distinguishable from activated microglia and likely derived from peripheral circulation. They seemed to compensate for the insufficient function of microglia. Ultrastructurally, vesiculation of rough endoplasmic reticulum and disaggregated polyribosomes is observed in microglia.^{e22} These observations lend support to the concept of primary microgliopathy in which distinct microglial abnormality has a principal role in neurodegeneration. Microglia might lose their normal physiologic function by *CSF1R* mutation.

Management

Like most other hereditary leukoencephalopathies, there is no cure for *CSF1R*-related leukoencephalopathy. Although expected benefit is limited, symptomatic therapies should be offered, including antidepressants for depression, muscle relaxants for spasticity, and antiepileptic drugs for epilepsy if tolerable. *CSF1R*-related leukoencephalopathy may mimic Alzheimer disease in some cases^{2,46,52,e7,e23,e24} (doi.org/10.5061/dryad.498j63f); however, given that the nucleus basalis of Meynert is usually preserved, cholinesterase inhibitors are unlikely to be beneficial for cognitive impairment. Likewise, for parkinsonian symptoms, levodopa may not be beneficial since dopaminergic neurons in substantia nigra are usually

Figure 4 Pathologic findings of colony-stimulating factor-1 receptor (*CSF1R*)-related leukoencephalopathy



(A–H) A 78-year-old man with *CSF1R* p.M875T who was a member of a previously reported family (VA-27 in reference 2),^{2,e60} (doi.org/10.5061/dryad.498j63f) At 71 years of age, he developed cognitive impairment followed by personality and behavior change, depression, executive dysfunction, apraxia, parkinsonism, and pyramidal weakness. He died with 7 years disease duration. (A) Luxol fast blue stain shows severe myelinated fiber loss in the superior frontal and cingulate white matter, whereas the U-fibers are relatively spared. Note the thinning of the corpus callosum (arrow). (B) The axonal spheroids in the affected white matter are stained with amyloid precursor protein (APP). (C) Numerous axonal spheroids (arrows) are seen within the frontal white matter (hematoxylin & eosin). (D) CD68-immunopositive macrophages in the frontal white matter. (E, F) An axonal spheroid in the white matter depicted by phosphorylated neurofilament (SMI31) (E) and APP (F). (G) A bizarre astrocyte in the white matter (α B-crystallin). (H) A ballooned neuron in the superior frontal cortex (α B-crystallin). (I, J) A 55-year-old woman with autopsy-confirmed adult-onset leukodystrophy with neuroaxonal spheroids and pigmented glia, but genetic testing was not performed because DNA was unavailable. (I) Note the small calcified lesion (arrow) located in the pericallosal region. An arrowhead indicates the paper-like atrophy of the corpus callosum. (J) An enlarged image of the calcification. Bars in A, B, and I = 5 mm; C and D = 100 μ m; E, F, G, and H = 50 μ m; and J = 400 μ m.

preserved.²⁰ Rehabilitation may be helpful for patients to maintain their physical performance. While mouse disease model showed some evidence of neuroinflammation,^{e25} no patients have shown positive response to immunotherapies like steroids, interferon β -1a/1b, cyclophosphamide, and plasmapheresis.

As shown for metabolic leukodystrophies, including adrenoleukodystrophy, Krabbe disease, and metachromatic leukodystrophy^{e26} (doi.org/10.5061/dryad.498j63f), hematopoietic stem cell transplantation (HSCT) might be an effective treatment for *CSF1R*-related leukoencephalopathy. There has been only 1 patient treated with HSCT.^{e27} The patient did not gain clinical improvement, but no more progression was observed after HSCT. The patient's neurologic condition was described as stable for at least 15 years, suggesting HSCT could be beneficial for this disease.^{e27} However, how the HSCT works remains to be determined. Unlike the metabolic disorders, *CSF1R*-related leukoencephalopathy is not associated with an essential enzyme deficiency. In addition, given that microglia are not originally derived from bone marrow and are intrinsically maintained by a self-renewal manner independent of circulating monocytes,^{e28} it is questioned whether the transplanted bone marrow-derived cells can sufficiently compensate for microglial function and its longevity and self-renewal ability.^{e29} Although intense investigation is required to validate the utility of HSCT, it is worth noting that HSCT might be an optimal treatment option for this fatal disease.

Pathophysiology

Genetic perspective

As of January 2018, 71 different *CSF1R* mutations (56 missense mutations, 8 splice-site mutations, 3 frameshift mutations, 2 nonsense mutations, and 2 small deletions) were found in more than 100 cases around the world (figure 2B). Apparently, there is no phenotype-genotype correlation. While this disease is an autosomal dominant trait, sporadic cases have often been reported. This may be partially explained by incomplete penetrance^{e30} (doi.org/10.5061/dryad.498j63f) and genetic mosaicism^{e27}. In addition, de novo mutations have been identified in sporadic cases, including a monozygotic twin pair.^{2,42, e30-e32} Almost all mutations were located in the tyrosine kinase domain (TKD) of *CSF1R*.²³ While mutations have been found in any exons encoding the TKD, so far, they have been most frequently identified in exons 18 and 19. In vitro, ligand-induced autophosphorylation of *CSF1R* was not detected in cells expressing mutant *CSF1R*, indicating loss of *CSF1R* signaling is relevant to the disease.^{2,16,47,48,e33} Splice-site mutations produce aberrant splice variants lacking a part of TKD, supporting the loss of function hypothesis.^{2,41,44,48,e34,e35} Flow cytometry analysis showed that cell surface expression of mutant *CSF1R* was decreased compared to that of wild-type *CSF1R* in transfected cells,^{e33} but another study yielded

sustained expression of mutant *CSF1R*.^{e36} Our cell surface biotinylation assay revealed that mutant *CSF1R* (p.I794T and an aberrant splice variant produced by c.2442+1 G > T) expressed on the cell surface comparable to the wild-type (Konno et al.,⁴⁸). Mutant *CSF1R* does not inhibit autophosphorylation of wild-type *CSF1R* when the mutant *CSF1R* is transfected in cells stably expressing the wild-type *CSF1R*, suggesting that dominant-negative mechanism is unlikely.

Haploinsufficiency of *CSF1R*

Haploinsufficiency of *CSF1R* was evident in a patient with a frameshift variant (p.S688Efs*13) not located within the TKD, but within the kinase insert domain.⁴⁸ Theoretically, the mutant mRNA was supposed to be degenerated by nonsense-mediated mRNA decay^{e37} (doi.org/10.5061/dryad.498j63f). To support this, mRNA and protein expression levels of *CSF1R* were indeed reduced in the patient's brain.⁴⁸ Accordingly, frameshift or nonsense mutations that induce premature stop codon have been found outside the TKD.^{37, e38} Reduced expression of *CSF1R* was also observed in patients' brains with missense and splice-site mutations by immunohistochemistry,^{35,48,57,e5,e22} indicating that any type of *CSF1R* mutation may cause quantitative and functional loss of *CSF1R*, which underlies the pathogenesis of *CSF1R*-related leukoencephalopathy. A heterozygous truncating *CSF1R* mutation (p.Y540*) was identified in first-cousin parents from a study of consanguineous families.^{e38} Two of their children had lethal phenotype showing generalized osteopetrosis, Dandy-Walker malformation with agenesis of the corpus callosum, and extensive subependymal and periventricular calcifications. Homozygosity was not confirmed in these children due to unavailable samples; however, their phenotypes were similar to those of *Csf1r*-knockout mouse (*Csf1r* -/-).^{e39, e40} This report further supports the concept that the quantitative loss of *CSF1R* plays a crucial role in human brain integrity; the smaller the amount of *CSF1R*, the more severe the phenotype becomes.

Mouse model

A *Csf1r* haploinsufficient mouse model (*Csf1r* +/-) has been established^{e25} (doi.org/10.5061/dryad.498j63f). In adulthood, these mice develop similar clinical findings observed in patients with *CSF1R* mutations, including cognitive decline, behavioral changes, and motor symptoms. By 12 months of age, white matter abnormalities, enlargement of the lateral ventricles, and thinning of the corpus callosum become evident on MRI. In addition, dysmyelination and axonal spheroids are revealed by electron microscopy. This mouse model provides strong evidence that *CSF1R* haploinsufficiency is enough to cause white matter degeneration.^{48,e25} However, there are several differences between human disease and the mouse model. Olfactory dysfunction, hypermyelination in the presymptomatic stage, and increased oligodendrocyte precursors in the cortex observed in the mouse model^{e25} have not been described or fully investigated in patients with *CSF1R* mutation. Interestingly, microglial density was increased in

this *Csf1r* haploinsufficient mouse, inconsistent with findings in human patients.^{e22} An increased microglia in *Csf1r* +/- mice might induce microglial-mediated inflammation.^{4, e25} To our knowledge, no clear evidence of neuroinflammation has been shown in the brains of patients with *CSF1R*-related leukoencephalopathy. Therefore, this should be assessed further in human autopsied brains.

Putative mechanism by *CSF1R* mutations

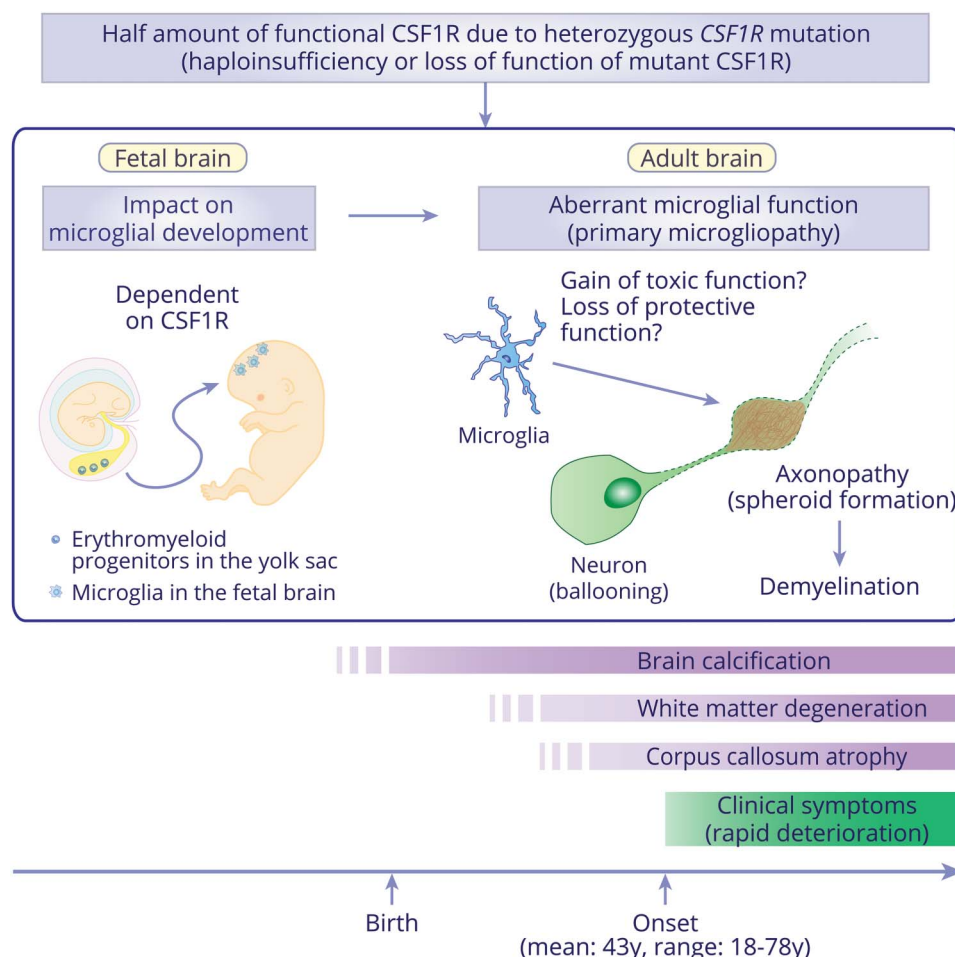
In mice, microglia originate from *CSF1R*-expressing erythromyeloid progenitors that appear in the yolk sac and migrate into the fetal brain during early embryogenesis^{e41, e42} (doi.org/10.5061/dryad.498j63f). A recent study showed that a somatic mutation in erythromyeloid progenitors causes postnatal neurodegeneration through the activation of mutant microglia,^{e43} providing evidence that microgliopathy could stem from an early event in the erythromyeloid progenitors. *CSF1R* is an essential factor for development and maintenance of microglia.^{4,7} *Csf1r*-knockout mice showed nearly total loss of microglia, but peripheral monocytes were preserved, suggesting that microglial development is dependent on *CSF1R*.^{e39, e42} Taking these facts into account, we assume

that microglial development and maturation in the fetal brain comprise quantitative and functional loss of *CSF1R* due to *CSF1R* mutations (figure 5). Given the heterozygous state of mutation carriers, a half amount of functional microglia may be sufficient to grow the carriers to adulthood; however, certain damages are presumed to insidiously accumulate in the brain white matter, or perhaps, only aging may affect the physiologic conditions of the brain with aberrant microglia. Once the threshold is exceeded, clinical symptoms develop in the 40s–50s and progress rapidly. Aberrant microglia that acquire toxic function or lose protective function may play a pivotal role in white matter degeneration (figure 5).

Other cell contribution

Not as much as microglia, the *CSF1R* also expresses in other brain cells. It has been reported that *CSF1R* is expressed in a small number of neurons in the hippocampus and cortex, and its expression level is increased by brain injury. The upregulated *CSF1R* in neurons exerts a neuroprotective effect^{e44} (doi.org/10.5061/dryad.498j63f). Mutant *CSF1R* in neurons might fail to induce this neuroprotective effect and eventually exaggerate neurodegeneration. Nandi et al.^{e45}

Figure 5 Microglia-oriented hypothesis for colony-stimulating factor-1 receptor (*CSF1R*)-related leukoencephalopathy



Based on the haploinsufficiency or loss of function of mutant *CSF1R*, it is thought that microglia possess a half amount of functional *CSF1R* in patients with *CSF1R*-related leukoencephalopathy. This may influence not only microglial physiologic function in adult brains, but also microglial development in fetal brains since embryonic microglial development and maturation are dependent on *CSF1R*. Therefore, the character of microglia in patients may be somewhat different from individuals with a full amount of functional *CSF1R*, even at the time of birth. In adult brains, aberrant microglia may have a pivotal role in the white matter degeneration, which is characterized by primary axonopathy (spheroid formation shown in brown) and following demyelination (shown as dot lines surrounding the neuronal axon). Ballooned neurons are frequently found in the overlying cortex. Given that patients develop clinical symptom in adult, a half amount of functional *CSF1R* is considered to be sufficient for surviving to adulthood; however, white matter degeneration and corpus callosum atrophy could precede symptom onset. Importantly, brain calcification can be observed at birth, implying that the calcifications are independent of white matter degeneration or clinical symptoms.

showed that during early postnatal development, CSF1R expressed in neuronal progenitor cells and contributed to regulation, proliferation, and neuronal differentiation of these cells. It is of interest whether *CSF1R* mutations affect neurogenesis and neuronal survival even at the beginning of life.⁴ Considering that the subventricular zone, where neurogenesis occurs, is close to the place where the brain calcifications are observed in *CSF1R*-related leukoencephalopathy,^{e45,e46} there might be a pathophysiologic link between neuronal progenitor cells and calcifications. *Csf1r* haploinsufficient mouse model would provide further insights regarding this point.

Other microgliopathies in humans

In recent years, the relatively new concept of microgliopathies⁶ has attracted attention since the role of microglia-related genes in neurologic disorders has been elucidated^{7,e47} (doi.org/10.5061/dryad.498j63f). In addition to *CSF1R*-related leukoencephalopathy, there are at least 2 human disorders in which microglia are likely to be affected primarily: NHD caused by homozygous or compound heterozygous mutations of triggering receptor expressed on myeloid cells 2 (*TREM2*) or TYRO protein tyrosine kinase-binding protein (*TYROBP*)^{e48,e49} and pseudo-toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex (TORCH) syndrome caused by homozygous or compound heterozygous mutation of ubiquitin-specific protease 18 (*USP18*).^{e50}

TREM2 is a cell-surface receptor that expresses in myeloid cells and interacts with a transmembrane adaptor protein *TYROBP*. In the brain, the *TREM2*–*TYROBP* complex exclusively expresses in microglia^{e51} (doi.org/10.5061/dryad.498j63f). In NHD, loss-of-function mutations in *TREM2*/*TYROBP* are considered to result in malfunction of microglia and osteoclasts, leading to brain pathology and bone manifestations, respectively.^{e52-e54} *USP18* negatively regulates type I interferon signaling.^{e55} In the mouse brain, *USP18* abundantly expresses in microglia in the white matter and has a role in microglial quiescence.^{e56} In pseudo-TORCH, loss of function of *USP18* is thought to induce white matter abnormality through type I interferon-mediated neuroinflammation following microglial activation.^{e56,e57} Both diseases, as well as *CSF1R*-related leukoencephalopathy, are clinically heterogeneous, but can be characterized by distinct white matter abnormalities, indicating that primary microglial malfunction may directly involve white matter changes. Moreover, brain calcifications are commonly seen in these diseases. In NHD, brain calcifications are usually observed in the basal ganglia, but occasionally found in the fronto-parietal subcortical white matter, reminiscent of those of *CSF1R*-related leukoencephalopathy.^{e58,e59} The subcortical and periventricular white matter are favorite sites of calcifications in pseudo-TORCH. These calcifications may occur secondary to brain damage, so-called dystrophic calcifications. However, given that calcifications in *CSF1R*-related leukoencephalopathy can be detected before clinical manifestation even early in life, it

would be worth investigating whether mutant microglia are also primarily associated with the formation of calcified lesions independent of white matter change.

Discussion

Since the discovery of *CSF1R* mutations, *CSF1R*-related leukoencephalopathy has been increasingly recognized as a unique disease among adult-onset hereditary leukoencephalopathies. Moreover, it has attracted attention in terms of primary microgliopathy.^{5,7} Clinical, radiologic, and pathologic characteristics have since been elucidated; however, there are still many questions to be answered. Why do clinical symptoms of this disease only manifest in adults? What is the determinant yielding clinical difference between the sexes? Are there any biochemical or imaging biomarkers for predicting disease onset or progression? Are brain calcifications observed in the mouse model? How is the spheroid formation initiated? Are microglia truly dysfunctional? How do microglia and other cells contribute to pathogenesis? Are there any other possible treatments?

There are only a few studies focusing on molecular mechanism of this disease. Given the rarity of this illness, international collaboration should be encouraged to solve the questions and find an effective treatment. If the concept of microgliopathy is established without doubt for *CSF1R*-related leukoencephalopathy, development of microglia-targeted therapy will be an ideal and attractive approach that might be applicable in other microgliopathies. In addition, preventive interventions are desirable because asymptomatic mutation carriers can be found, even occasionally, by head CT scans showing the specific brain calcifications. In line with this, a longitudinal follow-up study of asymptomatic carriers is required not only to clarify the natural course of *CSF1R*-related leukoencephalopathy, but also to find biochemical or imaging biomarkers related to disease progression. Finally, there is no doubt that other genes are associated with *CSF1R*/*AARS2*-negative ALSP. A causative gene is still missing in the first Swedish family. Identifying these genes will open a new research field and facilitate understanding of adult-onset hereditary leukoencephalopathies.

Author contributions

T. Konno: drafting the manuscript, design and conceptualization of the review, acquisition, analysis, and interpretation of data, and final approval of the manuscript. K. Kasanuki: reviewing the manuscript, acquisition and interpretation of data, creating a pathologic figure, and final approval of the manuscript. T. Ikeuchi: reviewing the manuscript and final approval of the manuscript. D.W. Dickson: reviewing the manuscript, creating a pathologic figure, and final approval of the manuscript. Z.K. Wszolek: reviewing the manuscript, design and conceptualization of the review, interpretation of the literature, and final approval of the manuscript.

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