Published in final edited form as:

J Neurol. 2013 October ; 260(10): . doi:10.1007/s00415-013-7093-x.

An adult-onset leukoencephalopathy with axonal spheroids and pigmented glia accompanied by brain calcifications:

A case report and a literature review of brain calcifications disorders

Shinsuke Fujioka, M.D.¹, Daniel F. Broderick, M.D.², Christina Sundal, M.D., Ph.D.^{1,*},
Matthew C. Baker, Ph.D.³, Rosa Rademakers, Ph.D.³, and Zbigniew K. Wszolek, M.D.¹

¹Department of Neurology, Mayo Clinic, Jacksonville, Florida

²Department of Radiology, Mayo Clinic, Jacksonville Florida

³Department of Neuroscience, Mayo Clinic, Jacksonville Florida

Keywords

adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; CSF1R; calcification; computed tomography; white matter; differential diagnosis

Sir

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) also known as hereditary diffuse leukoencephalopathy with spheroids is a rare inherited neurodegenerative disorder caused by mutations in the *CSF1R* gene [1, 2]. ALSP is clinically characterized by cognitive, behavioral, and language impairment, movement disorders, pyramidal signs, seizures, and ataxia [3]. Brain magnetic resonance imaging (MRI) is a useful diagnostic tool that shows bilateral and predominantly frontal lobe generalized brain atrophy and white matter signal changes [4]; brain computed tomography (CT) has provided less useful information [5]. During a recent international symposium on ALSP held in Tokyo, Japan, in February 2013, Japanese researchers demonstrated the presence of brain calcification in several ALSP cases [6]. To confirm this observation, we reviewed the available clinical charts from our collection of ALSP and identified a single familial case with brain calcification demonstrated by CT. The family was previously reported [1, 3]. The study was approved by Mayo IRB committee. The patients signed informed consent.

The patient (IV-1) developed progressive symptoms at age 47 years. She initially presented with dysarthria, loss of balance, falls, and hand tremor. On neurological examination at age 52 years, she had left-side hemiparesis. Brain CT revealed mild diffuse brain atrophy and sparse hyperdense areas in subcortical white matter of the frontal and parietal lobes (Figure 1A–C). Brain MRI detected extensive hyperintensity in the white matter of the right parietal lobe on T2-weighted images and fluid attenuated inversion recovery images without contrast

Correspondence: Zbigniew K. Wszolek, MD, Department of Neurology, Mayo Clinic Florida, 4500 San Pablo Road, Jacksonville, FL 32224, Tel.: (904) 953-2498, Fax: (904) 953-0757, Wszolek.zbigniew@mayo.edu.

*Current address: Department of Clinical Neuroscience and Rehabilitation, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden.

Conflict of interest

SF, DFB, and MCB have no conflict of interest. CS is supported by Anna Lisa och Bror Björnsson foundation for neurological research 2013/2014. RR is supported by NIH/NINDS P50 NS072187. ZKW is partially supported by the NIH/NINDS P50 NS072187, Mayo Clinic Center for Regenerative Medicine, and the gift from Carl Edward Bolch, Jr., and Susan Bass Bolch.

enhancement. At age 54 years, she experienced seizures and developed contracture in her legs. She required assistance with standing and walking. At age 54, she had predominantly left-side spasticity, hyperreflexia, and ankle clonus. Her gait was spastic. Brain CT obtained at that time revealed no significant changes (Figure 1D–F). She eventually developed impulsive and inappropriate behavior. Brain MRI at age 57 years demonstrated more pronounced brain atrophy. Later in the course of her illness, she was not able to speak clearly, and she died at age 58 years. The cause of death was not noted. Genetic sequencing identified the CSF1R p.G589E mutation. Her family tree is demonstrated in Figure 1G. Clinical, pathological, and genetic characteristics of this family are summarized in Table 1.

In the literature, we found only four reports that demonstrated brain CT of ALSP patients [5, 7–9]. However, brain calcification has not been identified radiologically and/or pathologically in any of the previously reported ALSP cases. This may be due to the punctate nature of the calcification in ALSP, as well as the decreased sensitivity of MRI in detection of calcification compared with CT. Additionally, pathological assessments were performed for only small parts of available brains, which may have prohibited identification. Some of the disorders and conditions that can manifest brain calcification can be seen in Online Resource 1. The distribution of brain calcification in our case was not identical to that typically seen in any of the disorders listed in Online Resource 1. Brain calcification was confirmed one year after the symptomatic disease onset, and the distribution and severity had not changed during the course of our patient's illness. This fact indicates that the calcification had potentially existed before symptomatic disease onset dependently or independently and may have been due to another underlying etiology. Calcification is thought to occur due to inflammation [10], mineralizing microangiopathy [11], dystrophic process [12], abnormal metabolism of calcium [13], superoxide production by mitochondria [14], and others; however, the mechanism of brain calcification in our case remains unknown. To confirm our result, further clinical, radiological, pathological, and biological assessment on additional ALSP cases are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank all those who have contributed to our research, particularly the patients and families who donated DNA samples for this work. We also would like to thank Ann S. Martin for her assistance in genealogical research and administrative efforts, and Kelly E. Viola for editorial assistance.

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Figure 1.

Brain computed tomography (CT) images at age 52 (A–C), brain CT images at age 53 (D–F), and a pedigree of the CSF1R p.G589E (G). This family was previously described [1], and additional genealogical details are provided in this manuscript. Brain axial CT at age 52 shows lateral ventricle enlargement and calcification in the deep left frontal white matter (A) and the subcortical white matter of the bilateral parietal lobes (B, C). No significant changes are seen on brain axial CT at age 53 (D–F). An arrowhead indicates the proband. Squares represent males, circles represent females. Darkened symbols indicate affected individuals. A diagonal line through a symbol means deceased. A number indicates number of offspring. A hash sign indicates an autopsied case. To protect patient confidentiality, gender is portrayed using a diamond for all individuals except affected individuals and their

spouses. A number in a square indicates a number of family members. A plus sign indicates that DNA was examined for the *CSF1R* sequencing analysis.

Table 1

Demographics, clinical, pathological, and genetic characteristics of our ALSP family

	IV-1 (proband)	IV-2	IV-3	III-3
Demographics				
Age at onset (years)	47	46	58	59
Disease duration (years)	11	2	3	3
Sex	Female	Female	Male	Male
Clinical features				
Cognitive impairment	–	+	+	+
Behavioral abnormalities	+	–	+	+
Language problems	Unknown	+	+	Unknown
Movement disorders	+	–	P, myoclonus, action tremor, dystonia, dyskinesia	Unknown
Pyramidal signs	+	+	–	Unknown
Cerebellar ataxia	Unknown	–	–	Unknown
Sensory impairment	Unknown	+	–	Unknown
Seizures	+	–	+	+
Dysphagia	Unknown	+	Unknown	+
Bladder dysfunction	Unknown	+	+	+
Radiological findings				
Brain CT	<ul style="list-style-type: none"> Mild diffuse brain atrophy Hyperdense foci in subcortical WM of frontal and parietal lobes 	N/A	<ul style="list-style-type: none"> Mild diffuse brain atrophy* 	N/A
Brain MRI	<ul style="list-style-type: none"> Extensive hyperintensity in WM of right parietal lobe on T2WI and FLAIR without enhancement 	<ul style="list-style-type: none"> Multiple bilateral plaques in periventricular WM, BG, corona radiata, cerebral peduncle, right cerebellar peduncle 	<ul style="list-style-type: none"> Severe WM gliosis in frontal and parietal lobes 	N/A
Clinical diagnosis	Cerebrovascular disorder/epilepsy	Progressive multiple sclerosis	Frontotemporal dementia	Probable Alzheimer disease
Pathological diagnosis	N/A	N/A	Adult onset leukodystrophy*	N/A
Genetic testing	CSF1R p. G589E mutation	N/A	CSF1R p. G589E mutation	N/A

ALSP=adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; BG=basal ganglia; CT=computed tomography; FLAIR= fluid attenuated inversion recovery; MRI=magnetic resonance imaging; N/A=not available; P=Parkinsonism; T2WI=T2-weighted image; WM=white matter;

*=no evidence of brain calcification was identified.