

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.elsevier.com/locate/radcr](http://www.elsevier.com/locate/radcr)

## Case Report

# Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia: A case report

Seongsu Kang, MD, Da Mi Kim, MD\*, In Ho Lee, MD, Chang June Song, MD

Department of Radiology, Chungnam National University Hospital, Chungnam National University School of Medicine, 282, Munhwa-ro, Jung-gu, Daejeon 35015, Republic of Korea

### ARTICLE INFO

#### Article history:

Received 12 December 2018

Revised 25 January 2019

Accepted 27 January 2019

Available online 18 February 2019

#### Keywords:

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia  
Calcification  
Diffusion-weighted imaging

### ABSTRACT

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare neurodegenerative disorder characterized by cerebral white matter abnormalities, myelin loss, and axonal swellings. ALSP is caused by mutations in colony stimulating factor 1 receptor gene. We report an ALSP patient with asymptomatic intracranial calcifications distributed in white matter found incidentally in a health screening.

© 2019 The Authors. Published by Elsevier Inc. on behalf of University of Washington.

This is an open access article under the CC BY-NC-ND license.

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

## Introduction

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare white matter disorder. ALSP was previously known to be 2 neurodegenerative disorders: hereditary diffuse leukoencephalopathy with spheroids and familial pigmentary orthochromatic leukodystrophy [1]. However, hereditary diffuse leukoencephalopathy with spheroids and familial pigmentary orthochromatic leukodystrophy should be regarded as a single clinicopathologic entity. Colony stimulating factor 1 receptor gene (CSF1R) mutations have been identified in families with both these diseases [1,2].

To the best of our knowledge, there have only been few reports regarding imaging appearance of ALSP in Korea [3]. We

present a case of ALSP with computed tomography (CT) and magnetic resonance (MR) imaging findings.

## Case report

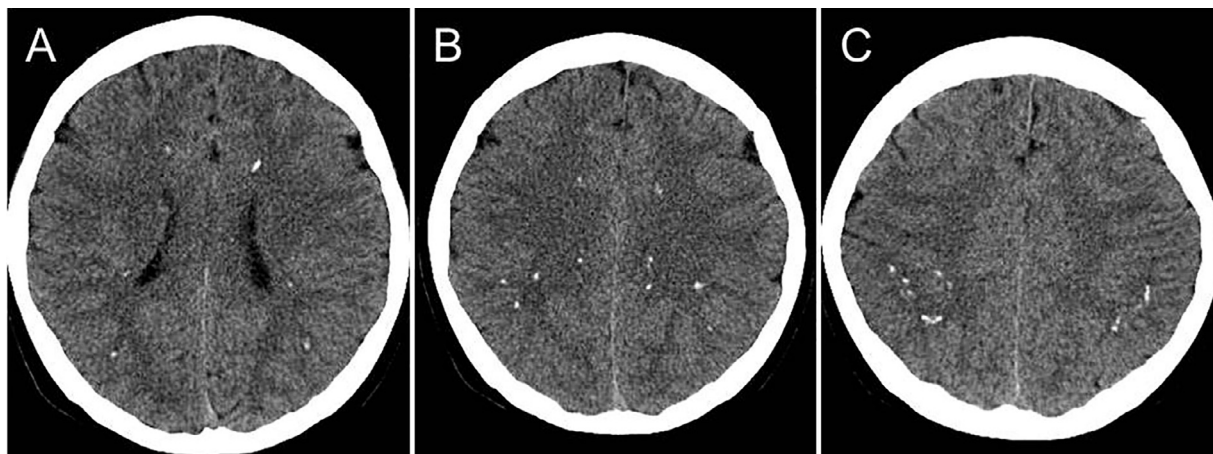
A 31-year-old woman had intermittent headaches over 10 years. She did not have any neurological symptoms except headache. She received conservative treatment. Laboratory investigations for infectious, inflammatory, vitamin deficiency, mitochondrial, and rheumatological etiologies were negative. Cerebrospinal Fluid (CSF) analysis was negative for oligoclonal bands and antiaquaporin-4 antibody. Seoul Neuropsychological Screening Battery revealed mild to moderate impairment of language function (difficulty of naming). Patient's clinical

\* Corresponding author.

E-mail address: [damirad@cnuh.co.kr](mailto:damirad@cnuh.co.kr) (D.M. Kim).

<https://doi.org/10.1016/j.radcr.2019.01.021>

1930-0433/© 2019 The Authors. Published by Elsevier Inc. on behalf of University of Washington. This is an open access article under the CC BY-NC-ND license. (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)



**Fig. 1 – Axial CT images (A-C) show multiple symmetric small-sized discrete calcifications in the bilateral frontal and parietal subcortical and periventricular white matter.**

past history was unremarkable. Her father had early onset of memory loss and unexplained muscle weakness. He died at the age of 58 of unknown cause.

Brain CT showed multifocal discrete calcifications in bilateral frontal and parietal white matter (Fig. 1). MR imaging showed multifocal small nodular high signal intensities in bilateral frontal white matter on T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging. These lesions showed high signal intensity with or without restricted diffusion on diffusion-weighted imaging (DWI) (b value = 1000 s/mm<sup>2</sup>), with apparent diffusion coefficient (ADC) map. In addition, these lesions were iso- to hypointensity on T1-weighted images. There was no contrast enhancement of any of these lesions. Sagittal T2-weighted imaging showed normal appearance of corpus callosum and normal calloseseptal interface area. Follow-up MR imaging after a month showed no change of high signal intensity lesions on T2-weighted imaging and FLAIR imaging with persistent high signal intensity on DWI (Fig. 2).

Genetic analysis of the CSF1R gene was performed due to a suspected diagnosis of ALSP; a c.1780G>C mutation was identified.

## Discussion

ALSP is an autosomal dominant disease [4], resulting from mutations in the tyrosine kinase domain of the CSF1R gene which is mainly expressed on the surface of microglia and in neurons to a lesser extent [2]. The mutation in the current case is present in exon 13, CSF1R:p.G594R.

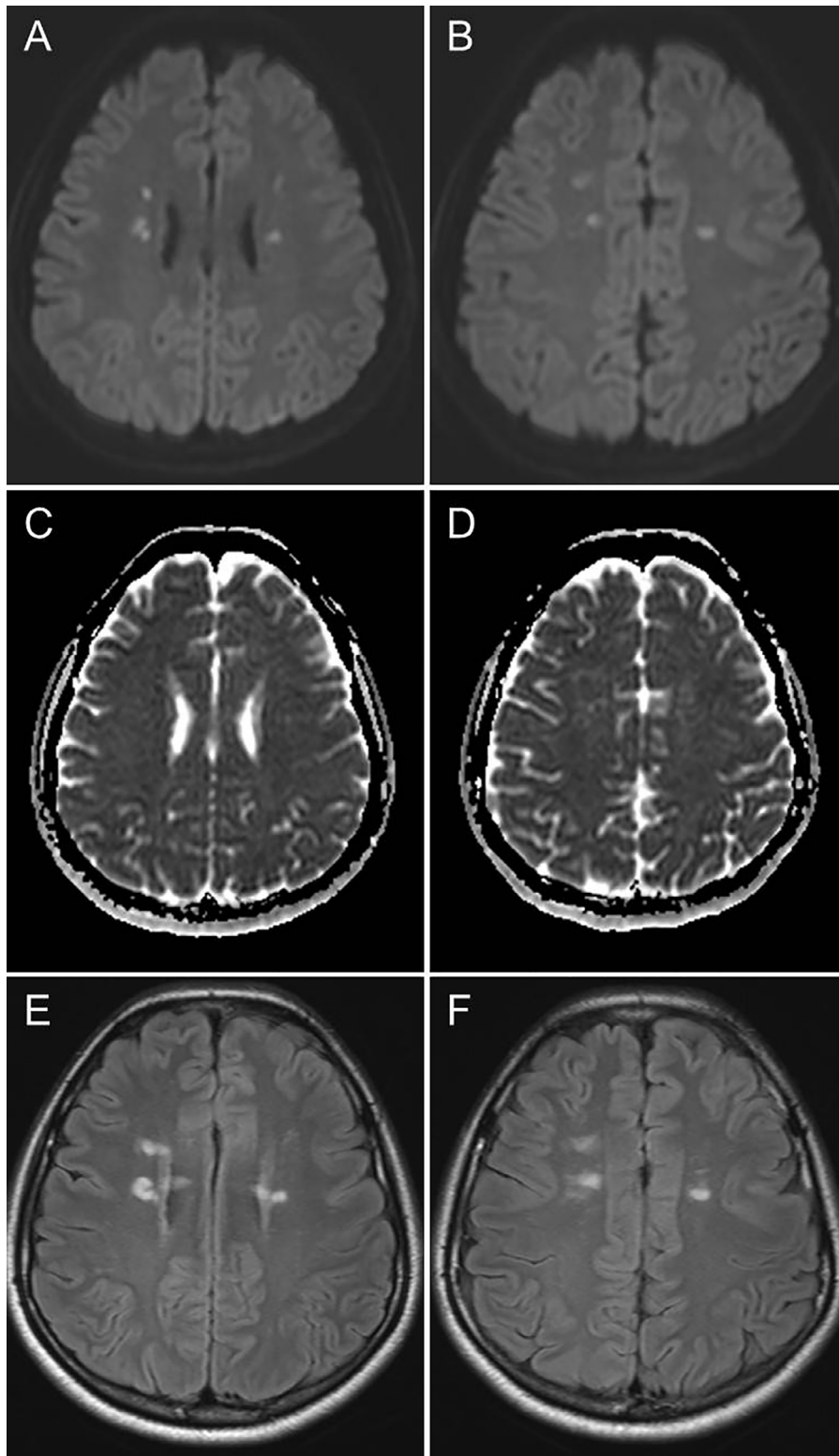
The mean age at onset of ALSP is 42 years (range, 15-78 years) [1]. Disease onset is often marked by neuropsychiatric features including behavioral changes, executive dysfunction, depression, anxiety, psychosis, and progressive cognitive decline [1]. Motor and gait disturbances, including ataxia, apraxia, and pyramidal dysfunction may appear as the disease

progresses [1]. Some patients develop Parkinson like symptoms, including resting tremor, rigidity, bradykinesia, and postural instability [5]. Epilepsy is a common neurologic symptom, especially at late stages of disease [6].

Brain CT shows multifocal calcifications in cerebral white matter. Radiologists can make a diagnosis of sequelae of perinatal (TORCH) or previous infection (tuberculosis, neurocysticercosis, etc.) [7]. However, calcifications in TORCH infections are commonly seen in periventricular white matter, basal ganglia, cerebral cortical areas, and subependymal sites [7]. A “target sign” representing a central nidus of calcification surrounded by a ring of enhancement is usually associated with intracranial tuberculosis [7]. In our case, calcifications tend to be distributed in the subcortical white matter than periventricular area. Calcifications are usually symmetric. They have “stepping stone appearance” in sagittal view. They are often observed bilaterally in the frontal white matter adjacent to the anterior horn of the lateral ventricle and the subcortical region of the parietal lobe [8]. In most patients with genetic and metabolic disorders, calcifications are usually observed in the basal ganglia, thalamus, and cerebellum on CT scans [8]. However, these regions are not typical in ALSP patients [8].

Typical MR imaging findings are bilateral patchy, diffuse, or confluent T2 hyperintensities in the white matter [1,9]. Serial MR imaging of an asymptomatic CSF1R mutation carrier suggests that white matter lesions may be asymmetric initially, small-sized nodular hyperintensities in presymptomatic early states, becoming more widespread, patchy, confluent, and more symmetric distribution in later stages [10]. Frontal and parietal lobe predominance with involvement of the periventricular deep white matter without abnormal gadolinium enhancement has been observed [5, 9]. Subcortical U-fibers are generally spared [1].

DWI hyperintensities are punctate with restricted diffusion or normal intensity on ADC maps [9]. These abnormalities are typically located in the centrum semiovale and/or corona radiata and sometimes enlarging and coalescing [9].



**Fig. 2** – DWI (A and B) and ADC maps (C and D) show multiple small nodular high signal intensities in the bilateral frontal white matter on DWI with/without restricted diffusion, compatible with the areas of cytotoxic/vasogenic edema in the lesions. Also FLAIR images (E and F) show multiple small nodular high signal intensities in the bilateral frontal periventricular white matter.

These DWI findings are mimics of internal border zone infarction. However, DWI lesions in ALSP are persistent with progression over months to years [3,9]. In the early stage of disease, MR imaging findings may mimic common demyelinating disease of the brain, such as multiple sclerosis. However, there is no white matter lesion in calloseseptal interface in ALSP. Brain calcification in multiple sclerosis has never been reported until now. Our presymptomatic patient's MR imaging showed bilateral small nodular T2 hyperintensities in the frontal lobe and similar distribution on DWI for a month.

Thinning of the corpus callosum is a characteristic of ALSP. It can be observed even in the early stages of the disease [1]. However, in the current case, this finding did not show on MR imaging.

Another adult-onset leukoencephalopathy due to autosomal recessive mutations in the mitochondrial alanyl-transfer RNA synthetase 2 gene (AARS2-L) shows clinical, imaging, and pathologic characteristics similar to ALSP [9]. Differentiating features on imaging are marked restricted diffusion on ADC map in AARS2-L; however, in ALSP, ADC values appear similar to or slightly lower than normal white matter [9]. The suppression of rarefied periventricular white matter signal on T2-weighted and FLAIR imaging in AARS2-L has not been described in ALSP [9]. Another feature to differentiate ALSP and AARS2-L is the presence of calcifications in the frontal periventricular white matter in ALSP but not in AARS-L [9].

---

## Conclusion

In summary, characteristic distribution of calcifications with bilateral small nodular hyperintensities in the white matter on T2-weighted image and persistent DWI lesions should alert a radiologist to possible ALSP.

## REFERENCES

---

- [1] Adams SJ, Kirk A, Auer RN. Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP): integrating the literature on hereditary diffuse leukoencephalopathy with spheroids (HDLS) and pigmentary orthochromatic leukodystrophy (POLD). *J Clin Neurosci* 2018;48:42–9.
- [2] Nicholson AM, Baker MC, Finch NA, Rutherford NJ, Wider C, Graff-Radford NR, et al. CSF1R mutations link POLD and HDLS as a single disease entity. *Neurology* 2013;80(11):1033–40.
- [3] Kim EJ, Shin JH, Lee JH, Kim JH, Na DL, Suh YL, et al. Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia linked CSF1R mutation: report of four Korean cases. *J Neurol Sci* 2015;349(1-2):232–8.
- [4] Mitsui J, Matsukawa T, Ishiura H, Higasa K, Yoshimura J, Saito TL, et al. CSF1R mutations identified in three families with autosomal dominantly inherited leukoencephalopathy. *Am J Med Genet B Neuropsychiatr Genet* 2012;159B(8):951–7.
- [5] Konno T, Yoshida K, Mizuta I, Mizuno T, Kawarai T, Tada M, et al. Diagnostic criteria for adult-onset leukoencephalopathy with axonal spheroids and pigmented glia due to CSF1R mutation. *Eur J Neurol* 2018;25(1):142–7.
- [6] Wider C, Van Gerpen JA, DeArmond S, Shuster EA, Dickson DW, Wszolek ZK. Leukoencephalopathy with spheroids (HDLS) and pigmentary leukodystrophy (POLD): a single entity? *Neurology* 2009;72(22):1953–9.
- [7] Kiroglu Y, Calli C, Karabulut N, Oncel C. Intracranial calcifications on CT. *Diagn Interv Radiol* 2010;16(4):263–9.
- [8] Konno T, Broderick DF, Mezaki N, Isami A, Kaneda D, Tashiro Y, et al. Diagnostic value of brain calcifications in adult-onset leukoencephalopathy with axonal spheroids and pigmented glia. *AJNR Am J Neuroradiol* 2017;38(1):77–83.
- [9] Lakshmanan R, Adams ME, Lynch DS, Kinsella JA, Phadke R, Schott JM, et al. Redefining the phenotype of ALSP and AARS2 mutation-related leukodystrophy. *Neurol Genet* 2017;3(2):e135.
- [10] Van Gerpen JA, Wider C, Broderick DF, Dickson DW, Brown LA, Wszolek ZK. Insights into the dynamics of hereditary diffuse leukoencephalopathy with axonal spheroids. *Neurology* 2008;71(12):925–9.