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# Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia associated with an A792D mutation in the CSF1R gene in a Polish patient

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## To the Editors

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare cerebral white matter disease characterised by motor and neuropsychiatric symptoms, including pyramidal and extrapyramidal signs, personality changes, cognitive impairment, depression and seizures.

Cognitive impairment and psychiatric symptoms are the most common initial symptoms. It is prevalent in both sexes equally. The mean age at disease onset is 43, with women developing the disease approximately seven years earlier than men. The most commonly reported magnetic resonance imaging findings in patients with ALSP are: bilateral white matter lesions (96% of cases), thinning of the corpus callosum (88%), abnormal signal of the pyramidal tracts (58%), calcifications in the white matter (54%), and diffusion-restricted lesions (38%). No apparent phenotype-genotype correlations have been found [1].

Colon-stimulating factor-1 receptor (CSF1R) is a transmembrane tyrosine kinase receptor that is expressed in phagocytic cells, including microglia in the brain. The activation of CSF1R through auto-phosphorylation contributes to signal transduction, maintenance, and activation of microglia [2]. ALSP is also known as *CSF1R*-related leukoencephalopathy, and is representative of primary microgliopathies.

Microglia are resident macrophages of the central nervous system, and their unique molecular signature is dependent upon CSF-1 signalling. It has been proved that microglial populations in affected frontal white matter in ALSP differ from microglia in unaffected frontal grey matter and cerebellar white matter. This finding suggests a potential mechanism of disease pathogenesis by linking aberrant CSF-1 signalling to altered microglial phenotype [3].

To date, many different mutations of *CSF1R* have been reported including missense, splice-site, nonsense and deletion mutations. Almost all are located in the tyrosine kinase domain [1]. Furthermore, it has been suggested that frameshift mutations outside the tyrosine kinase domain are able to cause ALSP by haploinsufficiency [4]. This condition is inherited in an autosomal dominant pattern, with sporadic cases due to *de novo* mutation also reported [1].

In 2015, a novel A792D mutation in the *CSF1R* gene was described in two Japanese family members. Their initial symptoms, including cognitive impairment, were likely to correspond with previously reported clinical characteristics. The disease profile of the cases was late onset (age 51 on average), and long duration (> 12 years on average) [5].

We here present the case of a Polish Caucasian patient with A792D mutation and rapid disease progression.

A 35-year-old male, with no family history of neurological disorders, developed gait and postural disturbances, dysarthria and bradykinesia. These were followed by cognitive decline and emotional lability at age 36, and urinary incontinence and erectile dysfunction at age 37.

On neurological examination three years after the onset of symptoms, he demonstrated psychomotor slowing,

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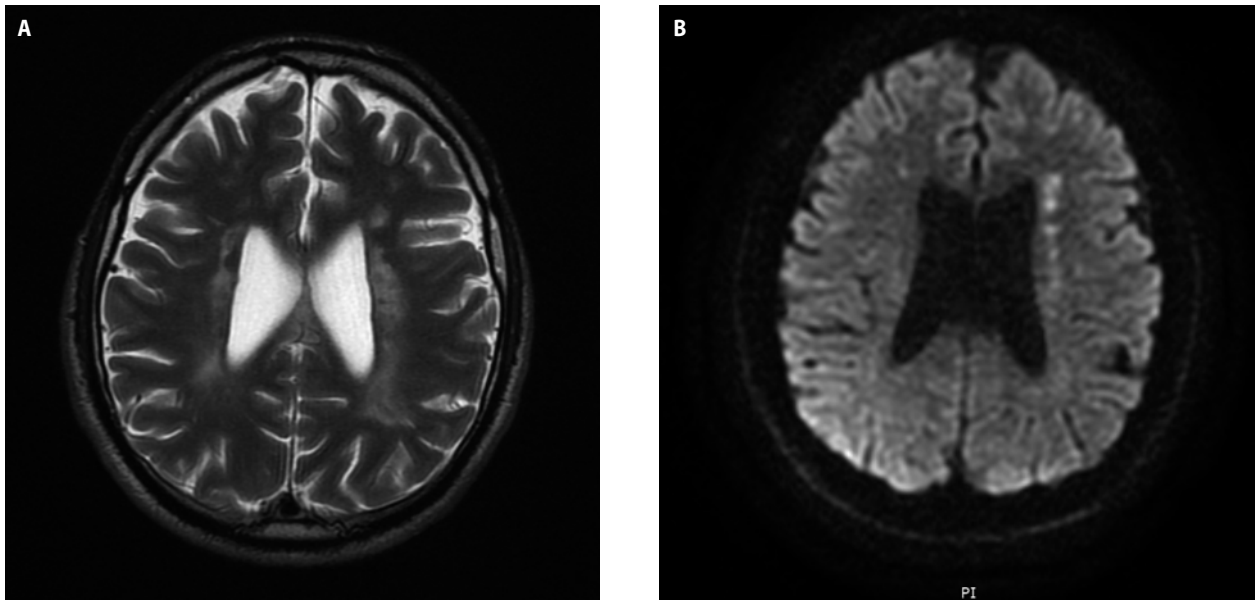


**Figure 1. A.** Magnetic resonance T2 imaging. Extensive, multifocal signal abnormalities in periventricular and deep white matter. Lateral ventricles and spaces are enlarged; **B.** Diffusion-weighted magnetic resonance images reveal multiple foci of diffusion restriction

a mask-like expression, dysarthria with monotonous speech, spasticity of the lower limbs symmetrically with bilateral positive Babinski sign, rigidity, ataxia of all four extremities, and postural instability. After three years of symptoms, his EDSS (Expanded Disability Status Scale) score was 5 (range 0–10). [Supplementary materials: Video 1–3].

A neuropsychological examination performed three years after the onset of symptoms showed mild cognitive dysfunction, especially in terms of memory, attention and articulacy. In addition, executive and behavioural disorders were revealed, as well as problems with cognitive inhibition, working memory and mental flexibility.

MR imaging showed confluent multiple patchy and confluent T2 hyperintense foci in the deep cerebral white matter bilaterally with associated atrophy. Diffusion-weighted images revealed punctuate foci of restricted diffusion in the deep left frontal white matter with normal signal on ADC maps. Sagittal T2-weighted scanning showed the corticospinal tract to be affected, with thin appearance of corpus callosum [Fig. 1].

Due to the suspicion of ALSP, genetic analysis of the *CSF1R* gene was performed. A c.2375C > A mutation in exon 18 of *CSF1R* was identified. This variant in the *CSF1R* gene was not detected in the patient's parents.

Recently, a case with clinical features suggestive of CSF1R-related leukoencephalopathy was described in the Polish population, but without a genetic confirmation of CSF1R gene mutation status [6, 7]. However, our case is the first genetically confirmed CSF1R-related leukoencephalopathy patient in Poland.

The clinical features of the affected Japanese family members with the A792D mutation in the *CSF1R* gene did not vary from previous reports. However, their age at onset was 51 years on average (range 43–54) and disease duration was > 12 years on average (range 6–29) suggesting a possible link between this type of mutation and the clinical profile of late-onset and long duration of ALSP [5].

We present a Caucasian patient with a *de novo* A792D mutation and different clinical manifestation. With initial symptoms of motor dysfunction at the age of 35 and serious decline within three years of first symptoms, his clinical profile can be described as rapidly progressive.

We believe further studies are required to reveal the phenotype-genotype correlation and to establish risk factors of a rapidly progressive clinical course of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia.

**Search terms:** *gene expression studies, leukodystrophies*
**Conflict of interest:** *All authors declare no conflict of interest*
**Ethical permissions:** *No ethical permissions were required*

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