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First Polish case of *CSF1R*-related leukoencephalopathy

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In this issue of the *Polish Journal of Neurology and Neurosurgery*, Żur-Wyrozumska, et al. describes the very first genetically proven case of *CSF1R*-related leukoencephalopathy in Poland [1]. *CSF1R*-related leukoencephalopathy (due to mutations in *CSF1R* gene [2]) has been reported in multiple countries around the world (reviewed in Konno, et al. [3]); however, despite its worldwide occurrence, *CSF1R*-related leukoencephalopathy is still an underdiagnosed condition [4].

There are three primary reasons for this diagnostic difficulty. The disease was first recognized by Van Bogaert and Nyssen back in 1936 [5] as a subset of orthochromatic leukodystrophies. They identified it as a pigmentary orthochromatic leukodystrophy (POLD). However, until the discovery of causative *CSF1R* gene mutations in 2011 [2], only a handful of sporadic and familiar POLD cases were published (reviewed in Marotti, et al. [6]). To diagnose it with certainty, either brain biopsy or autopsy had to be done.

The second reason relates to a nomenclature confusion leading to labeling many cases of POLD as hereditary diffuse leukoencephalopathy with spheroids (HDLS). For example, in our own first publication on this subject from 2006, we erroneously named a POLD family as an HDLS family [7]. HDLS was first describe by Axelsson et al in 1984 [8] in a Swedish family with clinical and pathologic similarities to POLD families. Recently, this family was found to carry mutations in *AARS2* gene [9]. Even before this genetic discovery, we found that families mislabeled as HDLS were indeed POLD families [10]. Fortunately, these nomenclature difficulties stemming from similarities in clinical and pathologic presentations have been solved by advances in genetic technology. The nomenclature introduced by Konno et al. [3] simplifies it, and now we identify these two separate conditions as *CSF1R*-related leukoencephalopathy, formerly POLD families, and *AARS2*--related leukoencephalopathy, formerly HDLS families (Tab. 1). Unfortunately, there are also published and unpublished cases/families suspected for *CSF1R*-related leukoencephalopathy or *AARS2*-related leukoencephalopathy with negative genetic testing for both *CSF1R* and *AARS2* gene mutations [11, and personal observation]. Thus, the concept of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), initially introduced by Marotti et al. [6] and further popularized by Wider et al. [11], is still quite useful. Konno et al. [3] make this distinction even more specific by introducing the term, *CSF1R/AARS2*-negative ALSP. It is very likely that there are other so far unidentified genes in which mutations are responsible for clinical and pathologic phenotypes currently indistinguishable from those seen in *CSF1R*-related leukoencephalopathy and *AARS2*-related leukoencephalopathy.

The third and most important reason is that clinical features of *CSF1R*-related leukoencephalopathy are very broad, encompassing headaches, seizures, spasticity, rigidity, tremors, psychiatric features, dementia, among others, thus leading to misdiagnosis or delayed diagnosis. Fortunately, a much wider availability of clinical genetic testing at this juncture makes

Table 1. Current and previously used nomenclature

Current nomenclature	Previously used nomenclature
CSFIR-related leukoencephalopathy	POLD cases/families
	Previously mislabeled HDLS cases/families
AARS2-related leukoencephalopathy	HDLS cases/families
CSF1R/ANRS2-negative ALSP	Genetically negative for *CSF1R/AARS2* mutation cases/families

CSF1R-related leukoencephalopathy — colony stimulating factor 1 receptor-related leukoencephalopathy; POLD — pigmented orthochromatic leukodystrophy; HDLS — hereditary diffuse leukoencephalopathy with axonal spheroids; *AARS2*-related leukoencephalopathy — alanyl tRNA synthetase-related leukoencephalopathy; ALSP — adult-onset leukoencephalopathy with axonal spheroids and pigmented glia

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the diagnosis easier and faster as demonstrated in the case presented by Żur-Wyrozumska et al. [1]. I congratulate Żur-Wyrozumska et al. for their diagnostic success and for bringing this case to the attention of the readership of the *Polish Journal of Neurology and Neurosurgery*. It is very likely that more cases of this disease will be identified in Poland.

At the present time, *CSF1R*-related leukoencephalopathy is an incurable disease. However, a better understanding of the pathophysiology and molecular biology of this illness makes development of a halting progression therapy a possibility [4]. In fact, hematopoietic stem cell transplantation has already been used to treat several patients (briefly discussed in Tipton, et al. [12]).

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