**Introduction**

ALSP is a rapidly progressive and debilitating neurodegenerative disorder that results in diminished quality of life and eventual demise and remains an unmet medical need with no approved symptomatic or disease-modifying treatments.

ALSP is attributable to loss of function mutations in the CSF1R gene that result in structural abnormalities and physiopathology of axons and microglia, demyelination of white matter of the brain and accelerated development of neurological symptoms (cognitive impairment, motor dysfunction, peripheral neuropathy).

Although accurate diagnosis of ALSP has been shown to improve outcomes by delaying disease progression, there is a high rate of initial misdiagnosis of ALSP which remains problematic.

**Objective**

To determine frequency of initial misdiagnosis of ALSP through a comprehensive, systematic literature review of published case reports.

**Methods**

Data for initial misdiagnosis of ALSP were obtained from a comprehensive, systematic review of clinical manifestations and genetic features of ALSP through a MEDLINE search (January 1, 1980 through March 22, 2022) of published case reports using prespecified selection criteria for ALSP.

Systematic review protocol was entered in the Registry Database under UIN 1251.

Inclusion criteria: 1. Published in or press case reports identified by MEDLINE. 2. Clinical diagnosis confirmed by genetic testing for CSF1R and/or histopathology. 3. Adult (18 years of age or older) male or female patients of any race, ethnicity or country. 4. Publications that describe neurological symptoms, clinical symptoms, brain images and neuropathology from living or deceased patients.

Exclusion criteria: 1. Presence of AARS2 gene mutation confirmed by genetic testing. 2. Unconfirmed clinical diagnosis of ALSP. 3. Case reports not written in English or not fully translated into English.

Continuous data (age of onset, disease duration, age at death, survival time) and categorical data (genetic findings, first suspected differential diagnosis, inheritance, country, family history, sex, initial and advanced symptoms, brain imaging and histopathology) from each of the patients in eligible case reports were extracted, entered electronically into a Master Excel Table under specific demographic and clinical characteristic headings, independently reviewed and examined for accuracy.

**Results**

The mean (SD) age (years) of patients in this systematic review was 43.2 (11.6) with a median (minimum, maximum) of 42.0 (18.0, 86.0) years. Table 1 demographic data show 58.9% of patients with a family history of ALSP, a greater number of females with ALSP (48.3%) compared to males (42.5%) and a slightly greater number of Asian patients with ALSP (34.2%) compared to Europe (32.2%) and North America (28.1%).

Table 1 indicates that the majority of CSF1R genetic mutations were within exon numbers 18-21 (55.5%) compared to outside of exons 18-21 (44.5%).

Table 2 reveals that misdiagnosis of ALSP involved a broad spectrum of neurodegenerative, neuroimmune and vascular disorders and, due to phenotypic heterogeneity at disease onset, accurate initial diagnosis was observed in only 31.5% of ALSP patients.

Table 2 also shows that the most frequent misdiagnoses were frontotemporal dementia (11.6%), multiple sclerosis (11.3%), Alzheimer’s disease, Parkinson plus syndrome, hereditary spastic paraplegia, leukodystrophies (6.8%) and familial leukoencephalopathy (6.8%).

The high rate of initial misdiagnosis of ALSP emphasizes the inclusion of early genetic testing of CSF1R gene mutations to enhance the accuracy of initial diagnosis of ALSP.

Given the large number of misdiagnosed patients reported in the literature, the prevalence of ALSP may be greater than estimates that are currently cited.

Family history and early-onset cognitive impairment with behavioral and/or motor impairment were identified as key markers of ALSP and should be used in combination with definitive genetic testing for improvement in initial diagnostic accuracy of ALSP.

Larger, prospective clinical studies are recommended for further investigating presenting symptoms and increased awareness of ALSP as a neurodegenerative disease that requires early, safe and effective therapies.

**Conclusions**

This systematic review demonstrated a high incidence of initial misdiagnosis of ALSP and confirmed the need for early, accurate diagnosis to allow rapid therapeutic intervention for potential cessation or slowing of the progression of this devastating disorder and improvement of survival time.

The high rate of initial misdiagnosis of ALSP requires early, accurate diagnosis to allow rapid therapeutic intervention for potential cessation or slowing of the progression of this devastating disorder and improvement of survival time.

**References**


4. NORD Rare Disease Database 2021 Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia.