Phenotypic Features of Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP): Presenting Symptoms and Clinical Course

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**Introduction**

- ALSP is a neurodegenerative disease characterized by accelerated development of neurological symptoms such as cognitive impairment, moderate to severe motor dysfunction and neuropsychiatric complications
- ALSP is an undiagnosed disorder and often misdiagnosed in the early stages as Alzheimer’s disease, frontotemporal dementia, multiple sclerosis, adult-onset leukoencephalopathy or familial leukoencephalopathy
- ALSP is an unmaintained medical with no approved symptomatic or disease modifying treatments
- ALSP is a rare, global disease with a NORD 2021 estimated prevalence of 10,000 in the United States and a similar point prevalence and incidence in Europe and Japan
- ALSP is a rapidly progressive, debilitating, autosomal dominant inherited disorder that results in diminishing quality of life and early demise
- ALSP is caused by loss of function mutations in the CSF1R gene that elicit structural abnormalities and pathophysiology of axons and microglia and demyelination of white matter of the brain
- Since there are no published prospective studies on the natural history of ALSP, descriptions of phenotypic features are limited and derived primarily from small case series and single case reports

**Objective**

To gain a better understanding of the phenotypic characteristics of ALSP through a comprehensive, systematic review of published case reports

**Disclosures**

This systematic review was financially supported by Vigil Neuroscience, Inc.

**Methods**

- A systematic review of the initial and advanced clinical symptoms reported in case studies and case series was conducted to construct a cohort of patients with ALSP
- A MEDLINE search was limited to English language literature from January 1, 1980, through March 22, 2022 and 90 published case reports were identified with data extracted from a cohort of 292 patients with ALSP: this cohort represents the largest case series to date of ALSP; the number of case reports and patients recently increased due to expansion of the literature search to March 22, 2022
- The systematic review protocol was entered in the Research Registry database under UN 1251
- Inclusion criteria: 1. Published or in press case clinical case reports identified by MEDLINE. 2. Clinical diagnosis confirmed by genetic testing for CSF1R gene mutation, brain imaging and/or pathophysiology. 3. Adults, 18 years of age or older, male or female patients of any race, ethnicity or country. 4. Publications that describe neurological symptoms, clinical manifestations, brain imaging and neuropathology from living or deceased patients
- Exclusion criteria: 1. Presence of ALSP at birth in the published case studies and this may have resulted in inconsistent interpretation of the results. 2. Published in English language literature from January 1, 1980, through March 22, 2022

**Conclusions**

- The findings of this comprehensive, systematic literature review confirmed and expanded the previous, smaller case reports on the phenotypic characteristics of ALSP
- It is anticipated that these phenotype data will lead to improved understanding of the onset and rapid progression of some symptoms in patients with ALSP
- The clinical symptoms at disease onset in this study reflected ALSP phenotype heterogeneity, a significant contributor to frequent misdiagnosis as Alzheimer’s disease or frontotemporal dementia
- Due to rapid progression of symptoms and accelerated demise of patients with ALSP, it is important that patients with ALSP are excluded from clinical trials of Alzheimer’s disease and frontotemporal dementia
- Since cognitive impairment, behavioral and psychiatric dysfunction and extrapyramidal and pyramidal motor abnormalities were identified as the most frequent clinical symptoms in this systematic review, endpoints that quantify these symptoms should be considered in the design of future interventional trials of ALSP
- The high frequency of family history of ALSP in the patients of this study suggests that inheritance is a key marker for early and accurate diagnosis of the disorder and genetic testing for CSF1R mutations should be used to confirm diagnosis of ALSP
- The large number of patients with ALSP in this study from Asia, Europe and North America provides further support for the global presence of this neurodegenerative disease
- A limitation of this systematic review is the lack of patient medical records that may lead to inaccurate, incomplete or missing medical assessments
- Another limitation involves the sampling procedure for the cohort that was limited to cases published in peer-reviewed journals and, therefore, the phenotype produced by this cohort may not be a true representation of the overall population of patients with ALSP
- Another limitation was the considerable variation in geographic location of the clinics involved in the published case studies and this may have resulted in inconsistent interpretation of the clinical manifestations

**Table 1: Demographic Data of Patients With ALSP**

<table>
<thead>
<tr>
<th>Age (Years) at Onset of Symptoms, Mean (SD), Minimum, Maximum</th>
<th>N (%)</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 14.0</td>
<td>45 (16.8)</td>
<td>42 (20.0)</td>
<td>3 (1.5)</td>
</tr>
</tbody>
</table>

**Table 2: Initial Symptoms of Patients With ALSP**

<table>
<thead>
<tr>
<th>Cognitive Impairment, N (%)</th>
<th>No</th>
<th>Yes</th>
</tr>
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<tbody>
<tr>
<td>38 (30.1%)</td>
<td>134 (49.0%)</td>
<td>80 (24.0%)</td>
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**Table 3: Advanced Symptoms of Patients With ALSP**

<table>
<thead>
<tr>
<th>Extrapyramidal Motor, N (%)</th>
<th>No</th>
<th>Yes</th>
</tr>
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<tbody>
<tr>
<td>149 (51.0%)</td>
<td>143 (49.0%)</td>
<td>56 (19.2%)</td>
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**Results**

- Table 1 shows that the mean (SD) age of onset (years) of symptoms was 43.2 (11.6), survival time (years) was 6.1 (4.7), age of death (years) was 52.2 (11.1) and the number of deaths was 118
- Table 1 also reveals that the percent of females (48.3%) was slightly greater than males (42.5%), family history was considerably more frequent (38.9%) than absence of family history (28.4%) and there was a slightly higher percentage of Asian patients (34.2%) compared to those from Europe (32.6%) and North America (28.1%)
- Table 2 demonstrates that the most common initial symptoms were cognitive impairment (45.9%), behavioral and psychiatric dysfunction (26.4%), extrapyramidal and pyramidal motor abnormalities (15.4%, 11.4% respectively) and speech difficulty (11.5%)
- Table 3 demonstrates that the clinical symptoms associated with progression of ALSP were more prevalent compared to the same initial symptoms and consisted of cognitive impairment (80.8%), behavioral and psychiatric dysfunction (72.9%), extrapyramidal and pyramidal motor abnormalities (61.5, 49.0%, respectively), speech difficulty (41.1%) and extrapyramidal motor symptoms (26.3%)
- Less frequent clinical findings in this study were pseudo-hallucination with percentages < 25% (data not shown)

**Note:**

1. The use of the term “Alzheimer’s disease” or “frontotemporal dementia” in the conclusions is a key marker for early and accurate diagnosis of the disorder and genetic testing for CSF1R mutations should be used to confirm diagnosis of ALSP.