Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia Can Present as Frontotemporal Dementia Syndrome

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Key Words

Early-onset dementia • Frontotemporal dementia • Histopathology • Neuropathology • Non-Alzheimer dementia • Systematic review • White matter hyperintensities • White matter disease • White matter pathology

Abstract

Background/Aims: We review the characteristics of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) and determine prevalence of behavioral variant of frontotemporal dementia (bvFTD) features in ALSP. **Methods:** Clinical and pathological information was abstracted from histopathologically confirmed ALSP cases identified by a systematic literature search. A new case of ALSP presenting as bvFTD was also described. **Results:** We retrieved 51 ALSP cases. Mean age of onset was 42.2 years. Mean disease duration was 6.2 years, with 24 cases lasting 4 years or fewer. Fourteen cases had 3 or more of the 6 key bvFTD features. White matter hyperintensities on T₂-weighted MRI, motor symptoms, seizures and amnesia were common. **Conclusion:** ALSP can underlie FTD syndrome, as well as rapidly progressive dementia.

Introduction

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare inherited or sporadic dementia affecting the white matter of the central nervous system, although it may be less rare than previously expected. ALSP is now thought to encompass previously distinct entities of hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) and familial pigmentary orthochromatic leukodystrophy (POLD) [1, 2]. ‘Adult-onset leukoencephalopathy with neuroaxonal spheroids’ and minor variations of this name have also been used interchangeably with ALSP or HDLS. A diagnosis that requires histopathological confirmation, ALSP has distinctive pathological features of both HDLS and POLD [1]. Accordingly, we refer to ALSP as the disease entity encompassing HDLS, POLD and adult-onset leukoencephalopathy with neuroaxonal spheroids. ALSP can be distinguished from other adult-onset leukodystrophies and leukoencephalopathies, which have been discussed elsewhere [3, 4].

An early case report of POLD was published in 1936 [5], and a HDLS familial kindred was described in 1984 [6]. Since then, several authors have qualitatively re-

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viewed pathological and clinical characteristics of ALSP [1], HDLS [2] and POLD [7]. We encountered a case of rapidly progressive frontotemporal dementia (FTD) that had ALSP at autopsy, raising the question of how often the neuropsychiatric manifestation of ALSP meets criteria for behavioral variant of FTD (bvFTD). FTD is the third most common cause of cortical dementia after Alzheimer's disease and dementia with Lewy bodies. FTD most commonly presents with progressive behavioral changes, which is known as bvFTD; the other variant presents with progressive language dysfunction with preservation of other cognitive domains [8]. Diagnosis of bvFTD has been based on the consensus report by Neary et al. [9] in 1998, but recently in 2011, newer bvFTD criteria were developed with improved diagnostic sensitivity [10]. We thus performed a systematic literature search for all histopathologically confirmed cases of ALSP from 1970 to 2011 to characterize clinical and pathological features of ALSP and determine the prevalence of bvFTD features in ALSP based on 1998 and 2011 criteria. We also describe our new illustrative case study of a patient with underlying ALSP which presented as bvFTD.

Methods

A National Institute of Health PubMed database search for case reports and case series in English from 1970 to 2011 was performed, using keywords 'adult-onset leukoencephalopathy with axonal spheroids and pigmented glia'; 'hereditary diffuse leukoencephalopathy with axonal spheroids'; 'pigmentary orthochromatic leukodystrophy' or 'orthochromatic pigmented leukodystrophy'; 'leukoencephalopathy OR leucoencephalopathy AND neuroaxonal spheroids' or 'leukodystrophy OR leucodystrophy AND neuroaxonal spheroids.' 'Neuroaxonal' and 'axonal' were also interchangeably searched. Medical Subject Headings proved too general for the objectives of this study. Reference lists from identified articles were then searched manually for additional case reports. Duplicated publications in the search were excluded. Publications were included if they were case reports or series addressing ALSP in human subjects aged ≥ 15 years old. All of these criteria were necessary for inclusion. After application of these inclusion criteria for publications, the following inclusion criteria were applied to select individual cases from these publications: (1) histopathologically confirmed (biopsy or autopsy) ALSP, and (2) availability of a descriptive clinical history.

The following data were abstracted from each case: (1) patient information: sex, age of disease onset, age of death, clinical diagnosis, pathological diagnosis, earliest symptom and family history of neurodegenerative disease; (2) pathological features of ALSP: features characteristic of HDLS and POLD, white matter changes and concomitant pathology; (3) presence of bvFTD criteria based on 1998 [9] and 2011 [10] criteria; (4) clinical signs or symptoms not included in bvFTD criteria: whether cognitive, motor, behavioral or psychiatric; and (5) imaging results: atrophy,

Fig. 1. Flow chart of systematic literature search for histopathologically-confirmed cases of ALSP from 1970 to 2011.

T₂-hyperintensities in MRI and abnormalities in single photon emission computed tomography (SPECT) and positron emission tomography (PET).

To fully illustrate one case for the reader, a retrospective chart review of clinical and pathological records of a patient from a tertiary academic center was performed. Informed consent was provided by the patient's family to publish his case.

Results

Literature Search Results

Results of the systematic literature search are summarized in figure 1. The literature search identified 51 individual cases that fulfilled the inclusion criteria, with absence of exclusion criteria, from 31 publications [2–4, 6, 7, 11–36]. Including the new case described in this study, a total of 52 individual ALSP cases were subsequently analyzed. Widening the range of keywords for the search made us aware that although ALSP is rare, there was a substantial number of ALSP cases already published.

Online supplementary Appendix A (see online at www.karger.com/doi/10.1159/000331422) lists specific information extracted from 31 publications and 1 case of ALSP. Overall, there were 30 women and 21 men (1 unrecorded). Pathological diagnoses were recorded as ALSP in 8 patients, HDLS in 12 patients, POLD in 17 patients,

Table 1. Number of 52 ALSP cases meeting clinical criteria for bvFTD, using 2011 and 1998 consensus clinical criteria

	Cases n (%)		Cases n (%)
2011 criteria [10]		1998 criteria [9]	
Progressive deterioration	52 (100.0)	Core features	
Early behavioral disinhibition	22 (42.3)	Insidious onset and gradual progression	37 (71.2)
Socially inappropriate behavior	22 (42.3)	Early decline in social interpersonal conduct	19 (36.5)
Loss of manners or decorum	7 (13.5)	Early impairment in regulation of personal conduct	22 (42.3)
Impulsive, rash or careless actions	4 (7.7)	Early emotional blunting	16 (30.8)
Early apathy or inertia	18 (34.6)	Early loss of insight	13 (25.0)
Apathy	17 (32.7)	Supportive diagnostic features	
Inertia	6 (11.5)	Behavioral disorder	
Early loss of sympathy or empathy	14 (26.9)	Decline in personal hygiene and grooming	6 (11.5)
Diminished response to other's needs and feelings	13 (25.0)	Mental rigidity and inflexibility	2 (3.8)
Diminished social interest, interrelatedness or personal warmth	6 (11.5)	Distractibility and impersistence	11 (21.2)
Early perseverative, stereotyped or compulsive/ritualistic behavior	9 (17.3)	Hyperorality and dietary changes	7 (13.5)
Simple repetitive movements	5 (9.6)	Perseverative and stereotyped behavior	6 (11.5)
Complex, compulsive or ritualistic behaviors	2 (3.8)	Utilization behavior	8 (15.4)
Stereotypy of speech	4 (7.7)	Speech and language	
Hyperorality and dietary changes	7 (13.5)	Altered speech output	30 (57.7)
Altered food preferences	1 (1.9)	Stereotypy of speech	4 (7.7)
Binge eating, increased consumption of alcohol or cigarettes	5 (9.6)	Echolalia	0 (0)
Oral exploration or consumption of inedible objects	1 (1.9)	Perseveration of speech	6 (11.5)
Neuropsychological profile ¹	1 (1.9)	Mutism	17 (32.7)
Deficits in executive tasks	24 (46.1)	Physical signs	
Relative sparing of episodic memory	2 (3.8)	Primitive reflexes	26 (50.0)
Relative sparing of visuospatial skills	2 (3.8)	Incontinence	27 (51.9)
Imaging results consistent with bvFTD		Akinesia, rigidity, tremor	11 (21.2)
Frontal and/or anterior temporal atrophy on CT or MRI	12 (23.1)	Low and labile blood pressure	1 (1.9)
Frontal hypoperfusion or hypometabolism on SPECT or PET	7 (13.75)	Investigations	
		Impairment on frontal lobe tests in absence of severe amnesia, aphasia, perceptuospatial disorder	14 (26.9)
		Electroencephalogram normal	3 (5.8)
		Frontal or anterior temporal abnormality	18 (34.6)
		Other supportive features	
		Onset before 65	50 (96.2)
		Bulbar palsy or dysfunction ²	27 (51.9)

¹ All 3 features required.² Dysarthria, dysphagia, tongue atrophy/fasciculations.

and adult-onset leukoencephalopathy with neuroaxonal spheroids in 15 patients. Eight diagnoses were confirmed by biopsy antemortem, while the rest were confirmed at autopsy. Mean age of onset was 42.2 ± 12.1 years, ranging from 15 to 78 years ($n = 52$). Initial symptoms of disease were highly varied and are listed in detail in online supplementary Appendix A. Patients could present with more than one initial symptom, which included personality or behavioral changes ($n = 15$), motor abnormalities ($n = 15$), depression or anxiety ($n = 9$), memory impair-

ment ($n = 9$), speech abnormalities ($n = 9$) and seizure ($n = 3$).

Mean duration of progression was 6.2 ± 6.0 years, ranging from 2 months to 34 years ($n = 45$). Excluding the two extreme cases of 2 months and 34 years of progression, which were both reported by Axelsson et al. [6], mean duration was 5.7 ± 4.2 years ($n = 43$). Of the 45 patients who were followed until death, 24 had a disease duration of 4 years or less. Mean age of death was 48.6 ± 14.3 years, ranging from 17 to 89 years ($n = 45$). Of the 44

Table 2. Non-bvFTD clinical characteristics of 52 ALSP cases

	Cases, n (%)
Cognitive	
Amnesia	27 (51.9)
Early amnesia ¹	7 (13.5)
Disorientation ¹	11 (21.2)
Motor	
Pyramidal signs	31 (59.6)
Postural or gait disturbance	31 (59.6)
Seizures	22 (42.3)
Abrupt seizure onset with ictal events ¹	3 (5.8)
Dysarthria or mutism	22 (42.3)
Cortical signs ²	20 (38.5)
Extrapyramidal symptoms	16 (30.8)
Cerebellar ataxia ¹	6 (11.5)
Myoclonus ¹	4 (7.7)
Chorea	2 (3.8)
Behavioural or psychiatric	
Emotional lability	21 (40.3)
Depression	13 (25.0)
Irritability or aggression	12 (23.1)
Anxiety	6 (11.5)
Sleep disturbance	4 (7.7)
Other	
Abnormal electroencephalogram ¹	15 (28.8)
Blindness or visual disturbance	8 (15.4)
Emaciation or weight loss	7 (13.5)
Infertility	4 (7.7)
Past medical history of hypertension ¹	3 (5.8)
Autonomic symptoms	3 (5.8)
Headache	3 (5.8)
Sensory symptoms	2 (3.8)

¹ bvFTD 1998 diagnostic exclusion features [9].

² Frontal release signs, apraxia, graphesthesia, tactile agnosia.

cases that did not have brain biopsies performed, 14 listed antemortem diagnoses, none of which accurately diagnosed ALSP: Pick's disease, bvFTD or FTD (n = 4), Alzheimer's disease (n = 2), corticobasal degeneration (n = 2), presenile dementia (n = 2), psychiatric disorder (n = 2), microvascular leukoencephalopathy (n = 1) and Binswanger leukoencephalopathy (n = 1).

Twenty-five patients had at least one family member with histopathologically confirmed ALSP, belonging to 10 unique kindreds; 24 had family histories of neurodegenerative diseases, which are listed in online supplementary Appendix A.

Features of bvFTD

Table 1 shows the prevalence of bvFTD features in ALSP patients according to the 2011 and 1998 criteria [9,

10]. All cases had progressive deterioration, fulfilling the first criteria for bvFTD according to 2011 criteria [10]; 14 cases had 3 or more of 6 clinically discriminating features, fulfilling the criteria for possible bvFTD [3, 6, 7, 10–12, 18, 20, 23, 27, 28, 33, 36]; 9 cases had 3 features [6, 7, 18, 20, 23, 27, 33, 36], 4 cases had 4 features [3, 11, 12, 28] and our case had 5 features. Of these 14 cases, 6 went on to fulfill criteria for probable bvFTD with imaging consistent with bvFTD (frontal and/or temporal atrophy on CT or MRI, or frontal hypoperfusion or hypometabolism on SPECT or PET) and significant functional decline [7, 10, 12, 23, 28, 33]. These cases also fulfilled the requirement for possible or probable bvFTD diagnoses that other non-degenerative nervous system, medical or psychiatric disorders could not better account for the disease, and the requirement for probable bvFTD diagnosis that biomarkers indicative of another neurodegenerative process were absent [10]. None of the ALSP cases had frontotemporal lobar degeneration pathology or a known pathogenic mutation, thus none had a diagnosis of definite bvFTD [10].

From a total of five 1998 core features [9], the mean number of core features exhibited was 2.0 ± 1.6 (n = 52); 3 cases had all 5 core features [11, 12, 23] and 10 cases had 4 core features [3, 4, 6, 7, 27, 30, 33, 36]. The most common core feature was insidious onset and gradual progression. Mean number of supportive features exhibited was 3.7 ± 2.5 , ranging from 0 to 11 out of a total of 18 supportive features (n = 52) [9]. Common supportive diagnostic features included altered speech output, primitive reflexes, incontinence, frontal or anterior temporal abnormality on imaging, and mutism. Notably, 50 patients had onset of disease before age 65 years.

Other Clinical Features

Table 2 demonstrates the prevalence of clinical signs and symptoms in ALSP patients that have not been covered by the bvFTD criteria. Motor findings of pyramidal signs, postural or gait disturbance, seizures, and dysarthria or mutism were most frequently reported. Mean age of seizure onset was 45.3 ± 14.8 years, ranging from 21 to 83 years (n = 22). There were no signs of epileptiform activity on electroencephalogram (EEG) investigations, but slow or δ -wave activity seen across all dementias was observed.

Pathological Features

Table 3 demonstrates the prevalence of specific gross and microscopic pathological features. Almost all cases featured myelin loss. The majority of cases also had gliosis and axonal spheroids. Macrophages with pigmented

Table 3. Pathological features of the 52 ALSP cases

	Cases, n (%)
HDLS features	
Myelin loss	49 (94.2)
Gliosis	45 (86.5)
Neuroaxonal spheroids	40 (76.9)
Macrophages with lipid granules	9 (17.3)
POLD features	
Macrophages with pigmented granules	27 (51.9)
Iron-positive macrophages	18 (34.6)
‘Fingerprint’ pattern, electron microscopy	6 (11.5)
White matter affected	
Frontal	32 (61.5)
Corpus callosum	24 (46.2)
Parietal	19 (36.5)
Basal ganglia	19 (36.5)
Pyramidal tracts in medulla	18 (34.6)
Temporal	14 (26.9)
Generalized	12 (23.1)
Occipital	9 (17.3)
Cerebellar	8 (15.4)
Spinal cord	6 (11.5)
Other	
Sparing of subcortical U-fibers	32 (61.5)
Ventricular dilation	24 (46.2)

granules were frequently found, as were iron-positive macrophages. Some cases had macrophages with lipid granules or intracytoplasmic ‘fingerprint’ patterns. White matter was most often affected in the frontal lobe and corpus callosum. Sparing of subcortical U-fibers and ventricular dilation were common findings. Only two cases had concomitant pathology of senile plaques and amyloid angiopathy with Braak neurofibrillary tangle stage III-IV in one case and stage I in the other case [25].

Imaging

Imaging findings are summarized in table 4. CT or MRI often showed brain atrophy regionally or diffusely. White matter hyperintensities on T₂-weighted MRI were most frequently observed diffusely. Of note, despite histopathological descriptions of subcortical U-fiber sparing, 2 cases had reported white matter hyperintensities in this tract [14, 30]. On PET, generalized reduced metabolism was exhibited predominantly in the frontal lobes of one case [28] and parietal lobes of another [25].

Illustrative Case Study

A 60-year-old right-handed Caucasian man with 17 years of formal education presented to a specialty mem-

Table 4. Imaging features of the 52 ALSP cases

	Cases, n (%)
Atrophy	
Regional	14 (26.9)
Diffuse cortical	13 (25.0)
Ventriculomegaly	8 (15.4)
Not otherwise specified	2 (3.8)
White matter hyperintensities on T ₂ -weighted MRI	
Diffuse	22 (42.3)
Periventricular	15 (28.8)
Regional	8 (15.4)
SPECT abnormalities	7 (13.7)
Frontal hypoperfusion	7 (100.0) ¹
Parietal hypoperfusion	5 (71.4) ¹
Temporal hypoperfusion	1 (14.3) ¹
PET abnormalities	2 (3.8)
Generalized decreased metabolism	2 (100.0) ²
¹ n = 7. ² n = 2.	

ory clinic after 2 years of cognitive decline that had accelerated in the past year. The history of emotional blunting, poor interpersonal conduct, amotivational syndrome, new preference for sweets, and distractibility – against relative preservation of spatial orientation and short-term memory – raised the highest suspicion of bvFTD. At presentation, he required prompting for activities of daily living, yet maintained fluent speech. His family denied dysarthria, dysphagia, new weakness or falls. He had no stroke risk factors, no significant neurological or psychiatric past medical history, and no relevant family history. Mental status testing showed abnormal executive functions of sustained attention, set-shifting and self-monitoring. Elemental neurological examination was normal.

Brain MRI on previous work-up for presumed depression showed symmetrical cerebral atrophy with frontal predominance (fig. 2a). There were hyperintensities in deep white matter of bilateral frontal lobes, left temporal lobe, subcortical regions and splenium of the corpus callosum. On a SPECT scan the same year, perfusion in the right anterior frontal lobe was decreased. Brain MRI repeated 6 months later showed increased volume of the previously identified hyperintensities (fig. 2b). Frontal cerebral atrophy had also worsened and progressed dorsally. Hippocampal atrophy was not apparent.

Two and a half years into the illness, he lost spontaneous speech. There was no parkinsonism, loss of vertical saccades or gait abnormality. Brain MRI at that time

showed further progression of all white matter changes, including involvement of the entire inferior corpus callosum. The patient developed incontinence and falls, then dysphagia in the third year of illness.

Within the next year, he manifested a generalized tonic-clonic seizure. Cerebrospinal fluid analysis did not support viral encephalitis, multiple sclerosis, Lyme's disease or active inflammatory processes. This seizure heralded a rapid decline into nursing home admission for palliative care. Motor weakness rapidly worsened to the point of immobility and full dependence for nutrition. The patient died before completing a fourth year of illness. The family deferred an electromyogram study, but requested an autopsy.

The postmortem brain weighed 1,600 g. Cortical atrophy was pronounced at bilateral frontal tips, but not in other regions. Frontal coronal sections revealed bilateral atrophy of deep white matter, corpus callosum and internal capsule (fig. 2c–d). Subcortical U-fibers were intact. White matter atrophy was observed in temporal and subcortical regions and cerebellar peduncles. Occipital white matter was relatively spared. Ventricles appeared enlarged with a preserved but flattened head of the caudate nucleus.

Microscopic examination confirmed myelinated white matter loss with sparing of subcortical U-fibers. There were gliosis and reactive astrocytosis (fig. 2e), axonal spheroids (fig. 2f) and macrophages with pigmentation (fig. 2g) in white matter regions. Microcalcifications and vacuolations were observed in some sections. Electron microscopy revealed intracytoplasmic 'fingerprint' patterns in white matter regions (fig. 2h).

Discussion

Analysis of clinical features from 52 histopathologically confirmed cases of ALSP revealed a high frequency of clinical bvFTD features. Four patients were diagnosed antemortem with a FTD syndrome. Using 2011 bvFTD criteria, 26.9% of ALSP cases could have been diagnosed with possible bvFTD and 11.5% could have been diagnosed with probable bvFTD [10]. Furthermore, undocumented bvFTD features may have existed in some cases included in our review. For example, psychiatric symptoms of emotional lability, depression, irritability or aggression could have contributed to features typical of bvFTD – such as decline in interpersonal or personal conduct and loss of sympathy or empathy – that were not explicitly documented.

Fig. 2. Typical imaging, gross pathology and histopathology samples of ALSP in one patient. **a** Axial T₂-weighted FLAIR MRI of the patient's brain reveals frontal lobe hyperintensities bilaterally in deep white matter. **b** Axial T₂-weighted FLAIR MRI 6 months later reveals increased hyperintensities in the same region, and more pronounced and dorsal frontal atrophy. **c** Coronal section shows intact subcortical U-fibers at the arrow, along with extensive demyelination in the frontal lobe. **d** Coronal section shows white matter loss limited to the temporal lobes, again with preservation of subcortical U-fibers. **e** HE and Luxol Fast Blue stains show macrophages with pigment (arrows) and large reactive astrocytes. **f** HE and Luxol Fast Blue stains show an axonal spheroid (arrow) and large reactive astrocytes. **g** Macrophages with Periodic acid-Schiff stain-positive pigment (arrows). **h** Transmission electron microscopy shows an intracytoplasmic 'fingerprint' pattern, which is characteristic of pigmentary orthochromatic leukodystrophy macrophages.

There were key distinguishing features of ALSP that are not commonly seen in bvFTD. First, the prominent white matter hyperintensities on T₂-weighted MRI of ALSP cases were not consistent with 'routine' bvFTD imaging findings. In bvFTD, distinct atrophy is expected in frontal and temporal lobes with limited white matter damage [3, 37]. Secondly, many ALSP patients had seizures. Interestingly, despite the prevalence of seizures, no patients showed epileptiform activity on EEG investigations. Abnormal EEG results are also unsupportive of bvFTD, and most ALSP patients who underwent EEG investigations had abnormal slow wave activity. Thirdly, the mean age of onset in ALSP patients (42.2 years, ranging from 15 to 78 years) was younger than that in FTD patients (60.4 years, ranging from 30 to 82 years) [38]. Finally, ALSP progressed more rapidly (mean 74.4 months) than FTD (mean 89.1 months) [38]. Common pathologies underlying rapidly progressive dementia include Creutzfeldt-Jakob disease, frontotemporal lobar degeneration, tauopathies, diffuse Lewy body disease and Alzheimer's disease [39]. While ALSP is a comparably rare pathology, it nevertheless should be considered in the differential diagnosis of rapidly progressive dementia.

ALSP is pathologically distinguished by myelin loss, gliosis, neuroaxonal spheroids, macrophages with pigmented granules, sparing of subcortical U-fibers and varied but frontal-predominant white matter damage. Some cases had macrophages with intracytoplasmic 'fingerprint' patterns. These patterns have been observed in previous case reports and are suggestive of ceroid [12, 15, 18]. Since oxidative stress or decreased lysosomal proteolytic activity can lead to ceroid or lipofuscin accumulation in human glial cells [40], these patterns raise the possibility that oxidative damage plays a role in the pathogenesis of ALSP. Macrophages with granular inclusions may also be associated with solvent inhalation, but none of the ALSP cases had a recorded history of solvent exposure [41].

The past decade featured an increasing number of ALSP cases diagnosed antemortem by brain biopsy, whereas previous diagnoses had largely relied on autopsies. Historically, other diagnostic techniques in ALSP also evolved. Since the 1970s, CT imaging has revealed regional or generalized atrophy in brains of ALSP patients. EEG tests have also been used for investigations, but have not been definitively diagnostic. MRI became commonplace since the late 1990s; T₂-weighted MRI has been especially important in revealing white matter changes. Functional imaging such as SPECT or PET may provide more opportunities for antemortem diagnosis of ALSP in the future.

Limitations

Systematic literature reviews are more commonly performed for randomized control or cohort studies, but we pursued a systematic literature review for case reports, which had several limitations. First, case selection in this review was based on fulfillment of inclusion criteria, and not on any additional parameters for study quality. Some case reports of ALSP were excluded due to lack of clinical information about an individual case [42, 43]. Secondly, while we used a quantitative approach in order to provide an accurate description of ALSP, definitive conclusions could not be drawn about disease etiologies or correlations, due to the heterogeneity of authors' qualitative descriptions in case reports. Thirdly, although we selected cases with adequate clinical descriptions, the majority of cases did not explicitly record signs or symptoms of bvFTD. Thus, omission of recorded features of bvFTD did not necessarily mean that they were not present. Furthermore, our assessment of fulfillment of bvFTD criteria was based solely on published clinical histories; optimally, full neuropsychological testing would have supported the bvFTD diagnosis. Finally, we limited this systematic literature search to English articles, but there are also French [5, 44–48], German [49, 50] and Japanese [51] reports that describe ALSP.

Conclusions

Based on the results of this systematic literature review on ALSP presenting as bvFTD, we recommend that ALSP should be considered in the differential diagnosis when white matter hyperintensities on T₂-weighted MRI are noted in an FTD workup, or dementia is rapidly progressive. An increased autopsy rate for clinically diagnosed bvFTD can help elucidate its pathological basis. An increased biopsy rate can help rule out treatable conditions (e.g. vasculitis); avoid medications with potentially harmful side effects for diseases with no known treatment, such as ALSP; and provide definitive antemortem diagnoses for patients and their families.

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References

- 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;72:1953–1959.
- Marotti JD, Tobias S, Fratkin JD, Powers JM, Rhodes CH: Adult onset leukodystrophy with neuroaxonal spheroids and pigmented glia: report of a family, historical perspective, and review of the literature. *Acta Neuropathol* 2004;107:481–488.
- Mascalchi M, Gavazzi C, Morbin M, Giacccone G, Arnetoli G, Zappoli R, Bugiani O: CT and MR imaging of neuroaxonal leukodystrophy presenting as early-onset frontal dementia. *AJNR Am J Neuroradiol* 2006;27:1037–1039.
- Knopman D, Sung JH, Davis D: Progressive familial leukodystrophy of late onset. *Neurology* 1996;46:429–434.
- Van Bogaert L, Nyssen R: Le type tardif de la leukodystrophie progressive familiale. *Rev Neurol (Paris)* 1936;65:21–45.
- Axelsson R, Roytta M, Sourander P, Akesson HO, Andersen O: Hereditary diffuse leukoencephalopathy with spheroids. *Acta Psychiatr Scand* 1984;314(suppl):1–65.
- Verghese J, Weidenheim K, Malik S, Rapin I: Adult onset pigmentary orthochromatic leukodystrophy with ovarian dysgenesis. *Eur J Neurol* 2002;9:663–670.
- McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ: Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol* 2001;58:1803–1809.
- Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF: Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;51:1546–1554.
- Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EG, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini ML, Rosen H, Prioleau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman J, Capa SF, Freedman M, Grossman M, Miller BL: Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* DOI: 10.1093/brain/awr179.
- Pietrini V, Tagliavini F, Pilleri G, Trabattini CR, Lechi A: Orthochromatic leukodystrophy with pigmented glial cells: an adult case with clinical-anatomical study. *Acta Neurol Scand* 1979;59:140–147.
- Gray F, Destee A, Bourre JM, Gherardi R, Krivosic I, Warot P, Poirier J: Pigmentary type of orthochromatic leukodystrophy (OLD): a new case with ultrastructural and biochemical study. *J Neuropathol Exp Neurol* 1987;46:585–596.
- Tunon T, Ferrer I, Gallego J, Delgado G, Villanueva JA, Martinez-Penuela JM: Leukodystrophy with pigmented glial and scavenger cells (pigmentary type of orthochromatic leukodystrophy). *Neuropathol Appl Neurobiol* 1988;14:337–344.
- Okeda R, Matsuo T, Kawahara Y, Eishi Y, Tama Y, Tanaka M, Kamaki M, Tsubota N, Yamadera H: Adult pigment type (Peiffer) of sudanophilic leukodystrophy: pathological and morphometrical studies on two autopsy cases of siblings. *Acta Neuropathol* 1989;78:533–542.
- Constantinidis J, Wisniewski TM: The dominant form of the pigmentary orthochromatic leukodystrophy. *Acta Neuropathol* 1991;82:483–487.
- Calandriello L, Matteucci C, Bertini E, Medolago Albani L, Antonelli A, Manfredi M, Palladini G: Biopsy diagnosis of a case of adult onset orthochromatic leukodystrophy: clinical and brain biopsy findings. *Ital J Neurol Sci* 1992;13:787–792.
- Yazawa I, Nakano I, Yamada H, Oda M: Long tract degeneration in familial sudanophilic leukodystrophy with prominent spheroids. *J Neurol Sci* 1997;147:185–191.
- Shannon P, Wherrett JR, Nag S: A rare form of adult onset leukodystrophy: orthochromatic leukodystrophy with pigmented glia. *Can J Neurol Sci* 1997;24:146–150.
- van der Knaap MS, Naidu S, Kleinschmidt-Demasters BK, Kamphorst W, Weinstein HC: Autosomal dominant diffuse leukoencephalopathy with neuroaxonal spheroids. *Neurology* 2000;54:463–468.
- Hancock N, Poon M, Taylor B, McLean C: Hereditary diffuse leukoencephalopathy with spheroids. *J Neurol Neurosurg Psychiatry* 2003;74:1345–1347.
- Browne L, Sweeney BJ, Farrell MA: Late-onset neuroaxonal leukoencephalopathy with spheroids and vascular amyloid. *Eur Neurol* 2003;50:85–90.
- Moro-de-Casillas ML, Cohen ML, Riley DE: Leukoencephalopathy with neuroaxonal spheroids (LENAS) presenting as the cerebellar subtype of multiple system atrophy. *J Neurol Neurosurg Psychiatry* 2004;75:1070–1072.
- Terada S, Ishizu H, Yokota O, Ishihara T, Nakashima H, Kugo A, Tanaka Y, Nakashima T, Nakashima Y, Kuroda S: An autopsy case of hereditary diffuse leukoencephalopathy with spheroids, clinically suspected of Alzheimer's disease. *Acta Neuropathol* 2004;108:538–545.
- Itoh K, Shiga K, Shimizu K, Muranishi M, Nakagawa M, Fushiki S: Autosomal dominant leukodystrophy with axonal spheroids and pigmented glia: clinical and neuropathological characteristics. *Acta Neuropathol* 2006;111:39–45.
- Baba Y, Ghetti B, Baker MC, Uitti RJ, Hutton ML, Yamaguchi K, Bird T, Lin W, DeLucia MW, Dickson DW, Wszolek ZK: Hereditary diffuse leukoencephalopathy with spheroids: clinical, pathologic and genetic studies of a new kindred. *Acta Neuropathol* 2006;111:300–311.
- Keegan BM, Giannini C, Parisi JE, Lucchinetti CF, Boeve BF, Josephs KA: Sporadic adult-onset leukoencephalopathy with neuroaxonal spheroids mimicking cerebral MS. *Neurology* 2008;70:1128–1133.
- 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;71:925–929.
- Levin N, Soffer D, Biran I, Gomori JM, Bocher M, Blumen SC, Abramsky O, Segal R, Lossos A: Leukoencephalopathy with neuroaxonal spheroids presenting as frontotemporal dementia. *Isr Med Assoc J* 2008;10:386–387.
- Maillart E, Rousseau A, Galanaud D, Gray F, Polivka M, Labauge P, Hauw JJ, Lyon-Caen O, Gout O, Sedel F: Rapid onset frontal leukodystrophy with decreased diffusion coefficient and neuroaxonal spheroids. *J Neurol* 2009;256:1649–1654.
- Freeman SH, Hyman BT, Sims KB, Hedley-Whyte ET, Vossough A, Frosch MP, Schmahmann JD: Adult onset leukodystrophy with neuroaxonal spheroids: clinical, neuroimaging and neuropathologic observations. *Brain Pathol* 2009;19:39–47.
- Mendes A, Pinto M, Vieira S, Castro L, Carpenter S: Adult-onset leukodystrophy with axonal spheroids. *J Neurol Sci* 2010;297:40–45.
- Boisse L, Islam O, Woulfe J, Ludwin SK, Brunet DG: Neurological picture. Hereditary diffuse leukoencephalopathy with neuroaxonal spheroids: novel imaging findings. *J Neurol Neurosurg Psychiatry* 2010;81:313–314.
- Sohn SY, Ko YJ, Hong JM, Kim SH, Kim HS, Kim JH, Chi JG, Moon SY: A case of pigmentary orthochromatic leukodystrophy with findings of proton MR spectroscopy and serial brain MRIs. *J Neurol Sci* 2010;295:23–26.
- Mateen FJ, Keegan BM, Krecke K, Parisi JE, Trenerry MR, Pittcock SJ: Sporadic leukodystrophy with neuroaxonal spheroids: persistence of DWI changes and neurocognitive profiles: a case study. *J Neurol Neurosurg Psychiatry* 2010;81:619–622.
- Tan K, Brewer J, Rowe DB, Jenkins B, Powers JM, Buckland ME: Adult onset leukodystrophy with neuroaxonal spheroids and pigmented glia (ALSP): report of a new kindred. *Neuropathol Appl Neurobiol* 2011, E-pub ahead of print.

- 36 Yamashita M, Yamamoto T: Neuroaxonal leukoencephalopathy with axonal spheroids. *Eur Neurol* 2002;48:20–25.
- 37 Savoiardo M, Grisoli M: Imaging dementias. *Eur Radiol* 2001;11:484–492.
- 38 Forman MS, Farmer J, Johnson JK, Clark CM, Arnold SE, Coslett HB, Chatterjee A, Hurtig HI, Karlawish JH, Rosen HJ, Van Deerlin V, Lee VM, Miller BL, Trojanowski JQ, Grossman M: Frontotemporal dementia: clinicopathological correlations. *Ann Neurol* 2006;59:952–962.
- 39 Josephs KA, Ahlskog JE, Parisi JE, Boeve BF, Crum BA, Giannini C, Petersen RC: Rapidly progressive neurodegenerative dementias. *Arch Neurol* 2009;66:201–207.
- 40 Thaw HH, Collins VP, Brunk UT: Influence of oxygen tension, pro-oxidants and antioxidants on the formation of lipid peroxidation products (lipofuscin) in individual cultivated human glial cells. *Mech Ageing Dev* 1984; 24:211–223.
- 41 Al-Hajri Z, Del Bigio MR: Brain damage in a large cohort of solvent abusers. *Acta Neuropathol* 2010;119:435–445.
- 42 Ali ZS, Van Der Voorn JP, Powers JM: A comparative morphologic analysis of adult onset leukodystrophy with neuroaxonal spheroids and pigmented glia – a role for oxidative damage. *J Neuropathol Exp Neurol* 2007;66:660–672.
- 43 Lin WL, Wszolek ZK, Dickson DW: Hereditary diffuse leukoencephalopathy with spheroids: ultrastructural and immunoelectron microscopic studies. *Int J Clin Exp Pathol* 2010;3:665–674.
- 44 Gille M, Brucher JM, Indekeu P, Bisteau M, Kollmann P: Kufs disease with leukoencephalopathy (in French). *Rev Neurol (Paris)* 1995;151:392–397.
- 45 Belec L, Gray F, Louarn F, Gherardi R, Morelot D, Destee A, Poirier J, Castaigne P: Pigmentary orthochromatic leukodystrophy. Van Bogaert and Nyssen disease (in French). *Rev Neurol (Paris)* 1988;144:347–357.
- 46 Dousset V, Tison F, Vital A, Henry P: Fulminant orthochromatic leukodystrophy in an adult (in French). *Rev Neurol (Paris)* 1998; 154:415–418.
- 47 Chretien F, Servan J, Elghozi D, Fontaine B, Brion F, Ereau T, Chesneau AM, Henin D, Gray F, Duclos H: Familial orthochromatic leukodystrophy: clinicopathological study of two cases (in French). *Rev Neurol (Paris)* 2001;157:178–186.
- 48 Graveleau P, Gray F, Plas J, Graveleau J, Brion S: Cavitory orthochromatic leukodystrophy with oligodendroglial changes: a sporadic adult case (in French). *Rev Neurol (Paris)* 1985;141:713–718.
- 49 Peiffer J: On non-metachromatic leukodystrophy (in German). *Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr* 1959;199: 417–436.
- 50 Oepen H: Clinical, Anatomopathologic and genealogic study of a late adult leukodystrophy (in German). *Arch Psychiatr Nervenkr* 1964;206:115–130.
- 51 Yamadera H, Okeda R, Amakawa T, Murofushi K, Eishi Y, Yamamoto K, Ishiguro T, Takahashi Y, Kojima T, Shimazono Y: 3 autopsy cases of adult pigment type (Peiffer) of familial sudanophilic leukodystrophy (in Japanese). *Seishin Shinkeigaku Zasshi* 1985; 87:93–113.