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Review article

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP): Integrating the literature on hereditary diffuse leukoencephalopathy with spheroids (HDLS) and pigmentary orthochromatic leukodystrophy (POLD)

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ABSTRACT

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a progressive degenerative white matter disorder. ALSP was previously recognized as two distinct entities, hereditary diffuse leukoencephalopathy with spheroids (HDLS) and pigmentary orthochromatic leukodystrophy (POLD). However, recent identification of mutations in the tyrosine kinase domain of the *colony stimulating factor 1 receptor* (*CSF1R*) gene, which regulates mononuclear cell lineages including microglia, have provided genetic and mechanistic evidence that POLD and HDLS should be regarded as a single clinicopathologic entity. We describe two illustrative cases of ALSP which presented with neuropsychiatric symptoms, progressive cognitive decline, and motor and gait disturbances. Antemortem diagnoses of autopsy-confirmed ALSP vary significantly, and include primary progressive multiple sclerosis, frontotemporal dementia, Alzheimer disease, atypical cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), corticobasal syndrome, and atypical Parkinson disease, suggesting that ALSP may be significantly underdiagnosed. This article presents a systematic review of ALSP in the context of two illustrative cases to help integrate the literature on HDLS and POLD. Consistent use of the term ALSP is suggested for clarity in the literature going forward.

1. Introduction

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a progressive degenerative white matter disorder. The term encompasses two clinicopathologically similar entities previously known as hereditary diffuse leukoencephalopathy with spheroids (HDLS) and pigmentary orthochromatic leukodystrophy (POLD) [1]. Van Bogaert and Nyssen first described POLD in 1936 in a family with adult-onset leukodystrophy [2]. Since then, most cases of POLD described in the literature have been sporadic. Axelsson et al. coined the term HDLS in their 1984 paper describing a Swedish family with adult-onset leukoencephalopathy in which axonal dilatations (spheroids) were a prominent feature [3]. Several cases of POLD have been described in the literature which fulfill all criteria for HDLS except heritability; these may represent sporadic cases or reduced disease penetrance [4]. The identification of common mutations in the kinase domain of *CSF1R*, a gene which regulates mononuclear cell lineages including microglia, in both HDLS and POLD [1] provided additional evidence that HDLS and POLD should be regarded as a single disease entity, echoing previous reports [4–6]. This article presents a systematic review of ALSP in the context of two illustrative cases to help integrate the literature on HDLS and POLD.

2. Literature search

A systematic review of published literature using MEDLINE/PubMed and Google Scholar using combinations of the search terms "adult-onset leuk[c]odystrophy", "adult-onset leukoencephalopathy", "[neuro]axonal spheroids", "pigmented [micro]glia", "pigmentary orthochromatic leukodystrophy", "hereditary diffuse leukoencephalopathy with spheroids" and "*CSF1R*" was carried out for all publications related to ALSP, POLD, or HDLS. Addi-

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tionally, references obtained from these publications were reviewed.

3. Illustrative cases

3.1. Case 1

A 26-year-old male with longstanding developmental delay due to perinatal hypoxic-ischemic injury presented with new-onset dysarthria, inability to release the grasp of his left hand, dragging of his left foot, and verbal aggression. Developmental history revealed he had a birth weight of 2951 g and spent 84 days in neonatal intensive care following possible prenatal Epstein-Barr virus infection and resulting respiratory distress syndrome. He had delayed milestones of speech, motor function and intellect, and attended a special education school from grade 2 onwards.

On examination he was significantly dysarthric with slight facial asymmetry and bilateral gaze-evoked nystagmus. Tone was increased in all four limbs, especially in his left arm and left leg, with clenching of his left finger flexors and dystonic, flexed positioning of his left arm. Reflexes were brisk with the left being greater than the right. His gait had a shuffling characteristic and he dragged his left leg in an extended posturing. Finger-nose coordination was slow with mild intention tremor and poor heel-shin coordination on the left.

Cerebrospinal fluid analysis, ceruloplasmin, serum copper, very long chain fatty acids, mitochondrial studies, L-aspartic acid, arylsulphatase, acylphosphatase, hexosaminidase A&B, β-galactosidase, glucocerebrosidase, and galactocerebroside levels were all normal. Urine for glycosaminoglycans showed trace chondroitin and heparan sulfate.

Non-contrast CT imaging at age 28 years showed diffuse cerebral atrophy and sulcal and ventricular dilatation. Confluent hypodensities were noted bilaterally in the white matter of the frontal lobes from subcortical to periventricular regions. Areas of calcification were noted bilaterally in the white matter around the trigone. MR imaging of the head was performed at age 30 years. It confirmed the CT imaging findings of diffuse cerebral atrophy and white matter changes. Confluent T1 and T2 prolongation of the frontal white matter was noted extending from subcortical to periventricular regions (Fig. 1A) with thinning of the corpus callosum. Periventricular calcifications appeared as punctate foci of signal void admixed with increased signal on T2-weighted and FLAIR images. No signal abnormality was detected in the cortex, basal ganglia, thalami, brainstem and cerebellum. The confluent periventricular and deep white matter abnormalities with focal calcifications and loss of bulk of the white matter were thought to represent periventricular leukomalacia due to perinatal hypoxic-ischemic injury.

Over the course of four years, the patient's cognition continued to deteriorate and a pseudobulbar palsy developed with significant dysarthria and reduced palatal movements bilaterally. He developed rigidity, weakness and spasticity, with dystonia prominent in his left upper limbs, and became wheelchair bound. At age 30 the patient died from aspiration pneumonia following multiple hospital admissions for the same.

Autopsy showed predominantly right-sided white matter disease of the hemispheres which correlated with the clinical asymmetry (Fig. 2). Loss of myelin was seen in the deep hemispheric white matter, sparing subcortical U-fibers. Areas of myelin loss had a diffuse edge suggestive of dysmyelination rather than demyelination, and subcortical U-fibers were spared. Blood vessels appeared normal, effectively ruling out a secondary leukoencephalopathy due to small vessel disease. Pigmented glia were observed with brown granular cytoplasm (Fig. 3). Granules stained positive with Periodic acid–Schiff and were positive for iron on Prussian Blue staining. Numerous neuroaxonal spheroids were seen with Bielschowsky staining, consistent with ALSP. Coarse calcification of the white matter was observed, with no calcification seen in the leukodystrophic lesion (Fig. 4). A concurrent diagnosis of periventricular leukomalacia was made, consistent with the patient's neonatal presentation and developmental delay. Electron microscopy revealed discontinuous myelin sheaths with myelin debris, consistent with ALSP (Fig. 5).

3.2. Case 2

A 46-year-old male presented with progressive dementia and abnormal gait. Symptoms were first appreciated by his family at age 43; at that time, the patient developed a stooped posture and docile personality, decreased concentration, and difficulty managing his finances. During the three years from symptom onset, his gait became shuffling, his speech became paraphasic and slurred, and he developed urinary incontinence. He had a history of binge drinking. Family history was unclear, though his grandfather had a "brain illness" and died in his 70 s.

On neurological examination, he scored 3/30 on the Montreal Cognitive Assessment. Prominent grasp responses were noted bilaterally. He had a stooped posture and shuffling gait, with great difficulty turning in a circle. Coordination was intact, though slowed. He seemed disinclined to move his right limbs, despite being right handed. No myoclonus, tremor, bradykinesia, or rigidity was appreciated. Neuropsychological assessment showed global abnor-

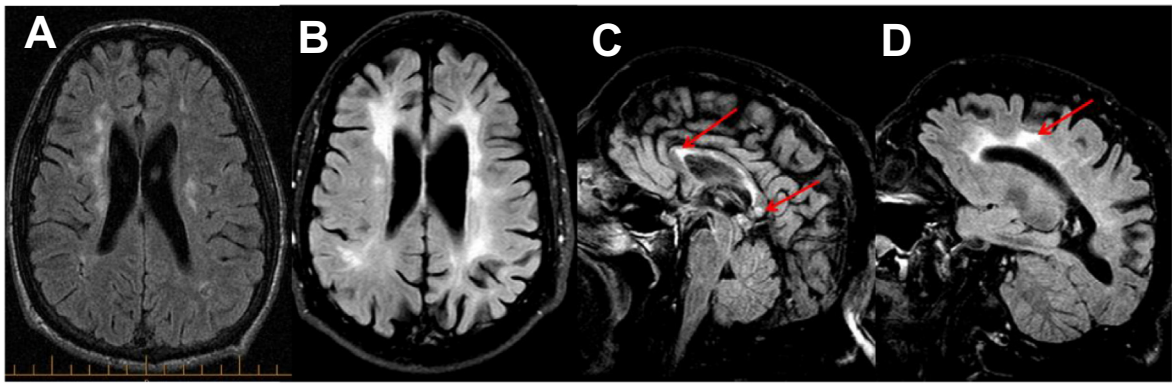

Fig. 1. Axial FLAIR images of (A) Case 1 and (B) Case 2 reveal confluent periventricular and deep white matter lesions, with diffuse cerebral atrophy most prominent in Case 2. Sagittal FLAIR images of Case 2 show (C) notable atrophy of the corpus callosum and increased signal intensity particularly at the genu and splenium and (D) periventricular T2 hyperintensities most prominent within the frontal lobes. Subcortical U-fibers are spared and no enhancement is seen post-gadolinium.

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