Sporadic leucodystrophy with neuroaxonal spheroids: persistence of DWI changes and neurocognitive profiles: a case study

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ABSTRACT

Leucodystrophy with neuroaxonal spheroids (LNS) is rare. There have been fewer than 10 sporadic cases reported, all occurring in the fourth to sixth decades of life. Previously unreported diffusion weighted imaging (DWI) changes on brain imaging in LNS are described as well as the first neurocognitive profile of this disorder in a 24-year-old woman. Neuropsychological testing demonstrated a global cognitive decline, with deficits most representative of a frontal-subcortical dementia. Bright DWI and corresponding dark apparent diffusion coefficient changes were initially mistaken for acute cerebral infarction but then persisted for 19 weeks. Biopsy of a bright DWI lesion showed no evidence of vascular disease and confirmed this rare diagnosis. Given the number of patients with the diagnosis of cerebrovascular disease, supported by DWI findings, we propose other milder cases of LNS may be overlooked.

CASE REPORT

A 24-year-old student had a 7 month course of progressive mixed spastic–ataxic dysarthria and gait impairment. She could no longer play sports, primarily due to right leg spasticity. She developed ideomotor limb apraxia and was unable to use everyday items properly. She had emotional lability. Her speech was slow, aprosodic and hesitant. She drooled from the right side of her mouth. Her family history was negative. There was no history of medication or substance use.

She scored 33 out of 38 possible points on the Kokmen short test of mental status,7 with deficits in learning, construction and attention. Verbal responses were markedly slowed, with prominent dysarthria but no dysphasia. She was unable to perform the Luria manoeuvre (a patterned sequence of simple movements). There was right sided upper motor neuron facial droop and poor eye closure. She was unable to manipulate her tongue normally. There was symmetrical agraphia, stereognosis and dysdiadochokinesia. The lower extremities demonstrated asymmetric spasticity, hyperreflexia, plantar extensor responses and clonus, with mild unilateral proximal weakness. Gait was wide based and there was a prominent startle response.

Neuropsychological testing at the time of presentation revealed a global cognitive decline, compared with in-school testing, eight years earlier. She had a decrease in IQ of 50 points since grade 10. She had deficits in simple attention and concentration, and profound difficulty with rapid colour naming (table 1). Working memory score declined by 2 standard deviations since high school. Verbal concentration and word recognition each declined by 1 standard deviation.

Brain MRI at presentation showed T2 signal abnormality in periventricular and subcortical regions with confluent changes in the left frontal lobe and extension into the right internal capsule and cerebral peduncle. Several areas were also bright on diffusion weighted imaging with corresponding dark apparent diffusion coefficient (ADC) values consistent with multiple foci of acute infarction. This pattern of DWI and ADC signal persisted through an MRI examination 19 weeks later (figure 1). None of the T2 lesions demonstrated contrast enhancement. The biopsy site included one of these foci, biopsied 12 weeks following the initial neurological examination. Advanced axonal loss with abundant spheroid formation, myelin loss, mild macrophage infiltration and gliosis were seen microscopically (figure 2).
Table 1  Neuropsychological profiles in leucodystrophy with neuroaxonal spheroids

<table>
<thead>
<tr>
<th></th>
<th>Normal values (^{16, 17})</th>
<th>Patient reported here</th>
<th>Patient reported in Keegan et al ((2008)^{2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at testing (years)</td>
<td>24</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Education (years)</td>
<td>16</td>
<td>12</td>
<td></td>
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<tr>
<td>WAIS III verbal comprehension IQ/index</td>
<td>110 (75th percentile)</td>
<td>22 (18th percentile)</td>
<td></td>
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<tr>
<td>WAIS III perceptual organisation IQ/index</td>
<td>91 (27th percentile)</td>
<td>12 (65th percentile)</td>
<td></td>
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<tr>
<td>Mean cognitive speed (trails A) (s)</td>
<td>27.4 ± 9.6</td>
<td>50 and 81</td>
<td>78 and DC</td>
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<tr>
<td>Mean complex attention (trails B) (s)</td>
<td>58.7 ± 15.9</td>
<td></td>
<td></td>
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<tr>
<td>Mean language (Boston naming) (No of items)</td>
<td>55.9 ± 28.8*</td>
<td>54</td>
<td>52</td>
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<tr>
<td>Delayed recall after learning words (%)</td>
<td>60—71</td>
<td>89</td>
<td>50</td>
</tr>
<tr>
<td>WMS III logical memory (% retention)</td>
<td>33.7±1.6</td>
<td>25.5</td>
<td>Not tested</td>
</tr>
<tr>
<td>Visual spatial Rey Osterrieth complex figure</td>
<td>15 (1.5th percentile)</td>
<td>Not tested</td>
<td></td>
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<tr>
<td>Judgement of line orientation</td>
<td>7 ± 1.6 words (1st trial) †</td>
<td>5 words, 9 words (AVLT) (1st and 4th trials)</td>
<td>4 words, 6 words WMS III (1st and 4th trials)</td>
</tr>
<tr>
<td>Learning after 1st and 4th trials</td>
<td>11.7 ± 2.0 words (4th trial) †</td>
<td>AVLT: 10 of 15 words learnt, 6 retained at 30 min (59%)</td>
<td>WMS III: 6 of 12 words learnt, none retained at 30 min (0)</td>
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<tr>
<td>Delayed recall</td>
<td>11.2 ± 2.0 words †</td>
<td>Not tested</td>
<td></td>
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<tr>
<td>WAIS III working memory (^{16})</td>
<td>Not tested</td>
<td></td>
<td>71st percentile</td>
</tr>
<tr>
<td>WAIS III processing speed</td>
<td>Not tested</td>
<td></td>
<td>57th percentile</td>
</tr>
</tbody>
</table>

*Mean (SD) provided is for ages 25—34 years.
†Mean (SD) provided is for ages 20—29 years.
AVLT, Auditory-Verbal Learning Test; DC, discontinue as patient not able to do the test; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale.

Figure 1  MRI demonstrating bihemispheric regions of abnormality by (A) fluid attenuated inversion recovery and (B) T2 weighted fast spin echo. The findings were stable for months. There were prominent foci of high diffusion weighted imaging signal (arrows) (C), many of which have corresponding low apparent diffusion coefficient values (D).
The following tests were normal or negative: complete blood count; serum electrolytes; liver, renal and thyroid function tests; sedimentation rate; C reactive protein; international normalised ratio; activated partial thromboplastin time; rheumatoid factor; antinuclear antibody; SSA and SS-B antibodies; p- and c-antineutrophil cytoplasmic antibodies; C3 and C4 complement levels; angiotensin converting enzyme; homocysteine and methylenetetrahydrofolate reductase; Russell viper venom test; β-2-glycoprotein; amino acid screen; very long chain fatty acid screen; acylcarnitine; arylsulfatase A; HIV, toxoplasmosis and B burgdorferi antibodies; PCR testing for herpes simplex virus 1 and 2 and varicella zoster virus; thyroid peroxidase antibodies; paraneoplastic antibody panel; mitochondrial DNA analysis; molecular testing for Canavan disease; notch 3 mutation analysis and skin biopsy for cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; CSF studies (protein 30, glucose 56, white cells <5, zero oligoclonal bands, bacterial and viral cultures, total IgG); electromyogram with nerve conduction studies; right quadriceps muscle biopsy; and four vessel cerebral angiogram. Skeletal survey demonstrated no evidence of dystrophic lesions. EEG demonstrated mild bifrontal slowing.

DISCUSSION
Sporadic leucoencephalopathy with neuroaxonal spheroids can present in young adults. Current reports include patients between 36 and 54 years of age. Familial cases, including a large Swedish kindred with 17 affected family members over four generations, found onset to occur between 8 and 60 years of age. Although severe dementia and psychiatric disorders were prominent in this first large kindred and reported in every case thereafter, cognitive deficits have not been outlined in detail. Both our case and one additional biopsy diagnosed patient at this institution have undergone neurocognitive testing. A global pattern of cognitive decline was found with prominent deficits in

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**Figure 2** Left frontal lobe biopsy occurred at one of the diffusion weighted imaging-bright, apparent diffusion coefficient-dark foci, demonstrating swollen axonal profiles by nerve fibre staining ×200 (A) with corresponding white matter pallor on Luxol fast blue ×200 (B). Haematoxylin–eosin stain ×200 (C) and ×400 (D) show axonal spheroids (arrows), rarefaction gliosis, white matter pallor and pigmented macrophages.
Attention, concentration and learning, representative of a frontal-subcortical predominant dementia. Patient No 2 in table 1 was a 54-year-old woman tested 13 months after symptom onset with a more marked, moderate to severe dementia, inconsistent with Alzheimer’s disease. She died 17 months later.

Neuroimaging in diffuse LNS is not diagnostic. Our patient had DWI bright foci in the cerebral white matter with decreased signal on ADC mapping, and therefore was initially considered to have had multiple acute cerebral infarctions in a background of more chronic appearing T2 signal increase. Diffusion signal abnormality from acute infarction lasts up to six days on average, followed by pseudonormalisation and eventually increased ADC values. In this case, diffusion signal abnormality persisted for 19 weeks, leading to brain biopsy of a DWI bright, ADC dark focus in the deep left frontal lobe. Biopsy showed no evidence of acute infarction.

Bright DWI and dark ADC values persisting for 6 weeks and 19 weeks are highly atypical for infarction but have been described secondary to intramyelinic oedema in regions of demyelination or in leucodystrophies with high grade myelin oedema. This combination of chronic DWI and ADC findings is described in metachromatic leucodystrophy. However, metachromatic leucodystrophy in adults is dissimilar, with preferential frontal lobe and corpus callosum involvement on brain imaging although the two may be indistinct on imaging alone. Similar findings have been ascribed to restricted diffusion of extracellular water intimately associated with degraded myelin sheaths termed ‘intramyelic oedema’, with an element of oligodendrocyte cytotoxic changes. Three of the five initially reported cases of sporadic onset diffuse LNS from this institution have smaller more subtle areas of bright DWI and dark ADC signal evident in retrospect (images not shown). None of the other patients have had comparable follow-up MR examinations to assess chronicity of signal abnormality.

In summary, we have reported the youngest case of sporadic diffuse LNS to date in a 24-year-old woman presenting with dysarthria and spastic gait. Although hereditary cases of diffuse LNS may present in childhood, all known cases of diffuse LNS of sporadic onset have occurred later in the fourth to seventh decades of life. We have demonstrated that the predominant cognitive deficits in this disorder represent a frontal-subcortical dementia with a multi-domain, global cognitive loss. Finally, we have described the persistence of DWI changes on MRI in our patient, and retrospectively in other patients with biopsy proved diffuse LNS at this institution. Given this, we propose that milder cases of LNS could be similarly mistaken for cerebrovascular disease.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Mayo Clinic Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES
