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Adult onset leukodystrophy with neuroaxonal spheroids: Clinical, neuroimaging and neuropathologic observations

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Abstract

Pigmented orthochromatic leukodystrophy (POLD) and Hereditary diffuse leukoencephalopathy with spheroids (HDLS) are two adult onset leukodystrophies with neuroaxonal spheroids presenting with prominent neurobehavioral, cognitive, and motor symptoms. These are familial or sporadic disorders characterized by cerebral white matter degeneration including myelin and axonal loss, gliosis, macrophages, and axonal spheroids. We report clinical, neuroimaging and pathological correlations of four women ages 34–50 years with adult onset leukodystrophy. Their disease course ranged from 1.5–8 years. Three patients had progressive cognitive and behavioral changes whereas one had acute onset. Neuroimaging revealed white matter abnormalities characterized by symmetric, bilateral, T2 hyperintense and T1 hypointense MRI signal involving frontal lobe white matter in all patients. Extensive laboratory investigations were negative apart from abnormalities in some mitochondrial enzymes and immunologic parameters. Autopsies demonstrated severe leukodystrophy with myelin and axonal loss, axonal spheroids, and macrophages with early and severe frontal white matter involvement. The extent and degree of changes outside the frontal lobe appeared to correlate with disease duration. The prominent neurobehavioral deficits and frontal white matter disease provides clinical-pathologic support for association pathways linking distributed neural circuits subserving cognition. These observations lend further support to the notion that white matter disease alone can account for dementia.

INTRODUCTION

Several forms of adult onset leukodystrophy of unknown etiology have been described in the literature. Hereditary diffuse leukoencephalopathy with spheroids (HDLS) was described by Axellson and found to have an autosomal dominant pattern of inheritance (4). Additional cases of HDLS have shown autosomal dominant patterns (27) as well as sporadic inheritance (14,31). The disease is characterized by a loss of myelin and axons, with lipid laden macrophages and gliosis. Pigmented orthochromatic leukodystrophy (POLD) another variant of adult onset leukodystrophy was defined by the presence of pigmented...
macrophages, myelin and axonal loss. Patients with adult onset leukodystrophies have presented with variable behavioral, cognitive, and motor changes (1,8,9,16,17,22,26,27). There is considerable overlap in the morphologic findings of the published cases of HDLS and POLD (17,18). Both entities have extensive myelin and axonal loss, gliosis and macrophages in the presence of axonal spheroids (17,18). A recent report examined five cases of HDLS and ten cases of POLD and demonstrated similarities between these diseases suggesting a possible link with oxidative injury (2). This overlap of clinical and pathologic features as well as a mechanism of injury suggests that these diseases with numerous synonyms may all be part of the same disease spectrum (2,17,18). Mariotti et al. suggested that POLD and HDLS be considered a single entity of adult onset leukodystrophy with neuroaxonal spheroids and pigmented glia. The adult onset leukodystrophies with neuroaxonal spheroids are rare diseases with hereditary and sporadic forms, encompassing both POLD and HDLS.

We report four patients with clinical histories and histopathologic changes characteristic of POLD and HDLS but not all have a family history or pigmented glia. All were women ranging in age from 34–50 years with a disease course of 1.5 to 8 years. Three presented with predominantly neurobehavioral symptoms while the fourth patient had an abrupt onset of neurological deficits resembling stroke but had a history of behavioral disorders. In this report we correlate the clinical, neuroimaging, and neuropathologic findings with emphasis on the pathophysiology of the cognitive impairment.

**METHODS**

All patients had been followed clinically by us (Case 1, JDS; Case 2 and 4, KBS; Case 3, BTH and JDS). MRI and CT scans performed at Massachusetts General Hospital as well as other institutions were reviewed (AV). Diagnoses were made at brain biopsy in one subject (case 3); and autopsy.

At the time of autopsy, one cerebral hemisphere was sliced fresh in the coronal plane, frozen and stored at −80°C. The other hemisphere with attached half brainstem was fixed in 10% formalin (29). Five to eight micrometer thick paraffin sections from all cortical regions, underlying white matter, basal ganglia, hippocampus, amygdala, thalamus, cerebellum, midbrain, pons, medulla and spinal cord were stained with Luxol fast blue hematoxylin and eosin (LFB/H&E). Sections from selected areas were stained with modified Bielschowsky silver, Prussian blue, Bodian, PAS, cresyl violet and Oil red O. Immunohistochemistry was performed manually for ubiquitin (Dako, Glostrup, Denmark, 1:200), tau (Dako, Glostrup, Denmark, 1:3,000), alpha-synuclein (Zymed, Carlsbad, CA, 1:1600) or on the Ventana auto-stainer (Ventana, Tucson AZ) using Ventana reagents for GFAP, neurofilament proteins and CD68 (Ventana, Tucson, AZ). Electron microscopy was performed on the glutaraldehyde fixed biopsy in case 3 and on postmortem formalin fixed tissue in case 1.

**CASE PRESENTATIONS**

**Case 1**

**Clinical features**—A 40 year-old-woman with a history of juvenile rheumatoid arthritis for 26 years, presented with a 3-year history of cognitive and behavioral decline, including feeling forgetful, and losing track of time, followed by memory loss. She had difficulty learning new tasks which required spatial orientation. She became unable to manage her finances, and required prompting for personal hygiene. She was oriented to person and location but not the date and had deficits in memory, concentration, logical sequencing, visual spatial function, and praxis.
Over the ensuing 3–4 months she had rapid decline in function, becoming unable to dress herself, and doubly incontinent, and offered no spontaneous conversation. She became unable to identify the date, time or place, and became increasingly abulic with occasional emotional outbursts. She developed cortical blindness with no blink to threat, no eye contact during the examination and no response to oculokinetic testing. She walked with small shuffling steps and a stooped posture. Treatments with immune modulating agents, vitamins and antioxidants were ineffective. Aspiration became frequent and she died at age 43, five years into the illness. Autopsy was limited to the brain.

The patient’s father and paternal uncle developed memory impairment in their 60s. A paternal uncle died age 55 after a dementing illness of approximately 10 years duration, with a clinical diagnosis of Pick disease, but no autopsy was performed. Her two siblings were healthy.

Case 2

Clinical features—A 31-year-old woman with a remote history of behavioral problems in high school awoke with inability to speak, imbalance and right hemibody dysesthesia. Symptoms worsened over the next 3 days. Examination revealed slight right facial droop, dysarthria, right-sided weakness, hyperreflexia, extensor plantar response and normal sensation.

Nine months into her illness she developed hypophonia, severe dysarthria, right hemiparesis and urinary incontinence. She had a flat affect, “la belle indifférence” and impaired short-term memory. Three years into the course, she was mute, able to turn her head to voice but unable to follow simple commands or perform purposeful movements. She died one year later.

Both maternal grandparents had carried the diagnosis of Alzheimer disease. The maternal grandfather had onset of dementia at age 45 and died at age 52. He had no history of gait problems, abnormal speech or psychiatric problems, and an autopsy was not performed. The patient’s mother at age 60, presented with a progressive change in her personality, behavioral, cognitive symptoms and white matter changes similar to her daughter. A maternal aunt had a history of sudden onset of speech loss, dementia and gait difficulties similar to the patient, at age 38, and died at age 48 with no autopsy. The patient had 2 sisters, one whom died in a car accident at age 16, and a second who was healthy at the age of 36.

Case 3

A 49 year-old female with rheumatoid arthritis for 4 years, treated with prednisone and hydroxychloroquine, presented with personality changes, including aggression over the preceding 6 months resulting in termination of her long term employment. General medical and neurologic exam was normal. Neuropsychological testing demonstrated poor attention and concentration, and deficits in spatial processing and short-term memory. She was unconcerned and had no insight into her behavioral changes. Language and long term memory were preserved. One month later she was abulic with a flat affect, emotional response inappropriate to context, and disinhibited. Declarative memory was poor. Over the next few months she became increasingly disoriented to time, place, and person. She was inappropriately jocular, disinhibited, and flippant. Language, comprehension and repetition were intact. She had visual spatial impairments and could not cooperate with memory testing. She had bilateral positive palmar grasp reflexes and a snout reflex. She continued to decline with dysphagia and seizures and succumbed to aspiration pneumonia one and a half years into the illness.
Her father had a history of cognitive impairment and died at age 55. An older brother had trisomy 21. Her mother was reported to be cognitively intact at the time of death, aged 79. There was no other known family history of neurologic disease.

Case 4

A 38-year-old previously healthy woman began having difficulty performing familiar tasks and complained of depression. She had an episode of blindness that lasted several hours, lost multiple jobs, became increasingly forgetful, and began wearing soiled clothing.

Within 3 years, her cognition was markedly impaired, her gait was slow and unsteady, and she required assistance with all activities of daily living. She was incontinent of urine.

Four years into the course of her illness, speech was fluent and she could read without difficulty, but did not comprehend the material. Tone was increased in the legs and her gait was wide based with spasticity. Reflexes were exaggerated. She had plantar flexor responses and palmar grasps. A year later, she would smile when approached, but could not follow commands, and had no spontaneous volitional movements. She had frequent, generalized, brief myoclonic jerks. Six years into the illness she had bilateral optic atrophy with no visual fixation or tracking and only minimal response to light. She drooled continuously and a gastric feeding tube was placed for severe dysphagia. She died age 46.

Her maternal grandparents were first cousins. A maternal aunt and uncle had died in their 40’s within 3 to 5 years of the onset of a neurologic disease that included dementia. (No autopsies were performed).

Laboratory Investigations

Laboratory studies on all four patients included an extensive search for hematologic and chemical abnormalities which were unrevealing. Test included normal CBC, thyroid function, vitamins B6, B12, RPR, Lyme antibodies, lactate (serum and cerebrospinal fluid), very long chain fatty acids, arylsulfatase A, hexosaminidase A, galactocerebrosidase, β-galactosidase and phytic acid.

ANA was only positive in cases 1 and 3. In case 1 ANA was 1:2560 with a speckled pattern and Anti-Ro antibody was positive at 0.838 (cut off of 0.328). This patient also had 3 oligoclonal bands in her otherwise normal cerebrospinal fluid. In case 3 ANA was positive at 1:5120 with a homogenous pattern.

Muscle Biopsy and Mitochondrial Evaluation—In case 1 biochemical analysis of skeletal muscle showed decreased activity of cytochrome c oxidase, succinate cytochrome c reductase, and NADH cytochrome c reductase. In case 2 muscle biopsies showed mild variation in fiber size with rare atrophic type II fibers and results of electron microscopy and histochemistry for mitochondrial disorders were normal. In case 4 a muscle biopsy revealed type 2 fiber atrophy and a small number of mitochondrial paracrystalline inclusions. Mitochondrial DNA analysis for mutation at position 8993 (associated with NARP and Leigh syndrome) were negative. Southern blot analysis of mitochondrial DNA isolated from muscle showed no re-arrangements. Electron transport chain analysis was abnormal on one analysis, and showed an equivocal complex 1 deficiency on another analysis.

Neuroimaging—In all four patients, neuroimaging demonstrated volume loss with bilateral, symmetrical, confluent abnormal T2 hyperintense and T1 hypointense MRI signal involving the periventricular, deep, and subcortical white matter of the frontal lobes (Figures 1 and 2). These same areas demonstrated low attenuation on CT scanning. There was
variable involvement of the white matter of the parietal, occipital, and temporal lobes. Subcortical U-fibers were generally spared, but in two patients there were scattered areas in which the white matter signal abnormality extended to the cortical margin, indicating partial involvement of U-fibers (cases 1 and 3). The abnormality extended into the corpus callosum in three patients. High T2 signal was seen within the descending corticospinal tracts in one case. Scattered foci of decreased diffusion with isointense apparent diffusion coefficient (ADC) within the larger areas of white matter abnormality in the frontal lobes was evident in the 3 patients in whom diffusion imaging was performed. No patients demonstrated contrast enhancement with gadolinium or areas of abnormal susceptibility. MR spectroscopy demonstrated increased choline to creatine ratio in the cortex/subcortical regions of the frontal lobes, but no abnormally increased lactate in the areas sampled. Positron emission tomography (PET) scanning demonstrated diffuse glucose hypometabolism in the frontal and parietal lobes.

Neuropathology—Gross examination of all 4 brains revealed diffuse atrophy (brain weights for case 1 was 470g, (right hemisphere); case 2, 880g; case 3, 1224g; case 4, 950g) The white matter in the affected regions was discolored and yellow-brown and spongy in all cases. The U-fibers were relatively preserved. There was some disruption of the U-fibers present at the crowns of the gyri in case 3, where the grey-white junction was indistinct. The corpus callosum was markedly thinned in all cases. This was most severe in the 2 cases of longest duration (case 1 and case 4). In cases 1, 2, and 3 the callosal thinning was most severe rostrally with separate lesions in the splenium in cases 1 and 3. Case 4 had thinning throughout the corpus callosum with some preservation of the splenium (Figure 3).

Microscopic examination of the cerebral cortex in all cases demonstrated mild gliosis most severe overlying the regions of extensive white matter damage. Cases 2 and 3 had rare ballooned neurons in the cingulate and in case 3 ballooned neurons were also identified in the parietal cortex. Patchy neuronal loss was present in case 1. The other cases showed no evidence of neuronal loss. Axonal spheroids were present in the deep cortical layers in cases 2 and 3.

Microscopic examination of the cerebral white matter in all cases demonstrated severe myelin loss and axonal damage (Figure 4). Regions beneath the association areas were most severely affected, and white matter axonal spheroids were most frequent in areas adjacent to areas of severe white matter injury (Figure 5). The pattern of white matter involvement was similar in all case but varied based on disease duration (Table 1). In all cases frontal white matter was devastated. In case 3 a brain biopsy preformed early in the disease course, 10 months prior to death, demonstrated ill-defined areas of white matter destruction with numerous axonal spheroid and scattered macrophages. The autopsy in case 3, who had the shortest duration of illness, demonstrated severe involvement of frontal white matter with only patchy involvement of parietal lobe white matter. In cases 1, 2, and 4, white matter in the frontal and parietal regions was most severely affected with less severe and patchy involvement of the temporal and occipital regions.

In the brain stem, all cases except for case 3 demonstrated degeneration of the corticospinal tract. In case 4, asymmetric degeneration of the corticospinal tracts was also seen to involve the spinal cord. The cerebellum was spared in all cases except for case 4 which demonstrated astrocytosis, white matter and neuronal loss of both Purkinje and granule neurons. In cases 1, 2, and 3 only rare scattered lymphocytic cuffing was present around blood vessels. No other inflammatory changes were present.

The thalamus, showed neuronal loss in case 1, 3 and 4. In case 1 the centromedian nucleus, medial dorsal, lateral dorsal and lateral posterior nuclei of the thalamus had neuronal loss
with astrocytosis. In case 3 the anterior nucleus and medial thalamus had severe gliosis and extensive neuronal loss and vacuolation. In case 4 the thalamic damage involved the anterior and lateral nuclear groups and the lateral aspect of the lateral geniculate nucleus, particularly in the parvocellular layers.

Staining pattern—In all cases Bodian silver staining and neurofilament immunohistochemistry highlighted axonal spheroids (Figure 5). No tau, ubiquitin or alpha-synuclein inclusions were present in any of the cases. Scattered foamy macrophages were present in the white matter in all and stained with CD68 (Figure 5). They also demonstrated strong staining for PAS. Scattered pigmented macrophages present in case 2 also stained for Fontana-Masson and only rare cells were positive for iron stains in cases 2 and 4. Oil red-O performed on case 2, revealed scattered positive cells but not the pigmented cells. No metachromatic material was present on toluidine blue stain. GFAP demonstrated strong white matter staining.

Ultrastructure—Electron microscopic examination of formalin fixed entorhinal cortex, superior frontal and inferior parietal white matter of case 1, revealed occasional mitochondria with preservation artifact, non-specific electron dense inclusions and possibly abnormal cristae patterns. In the frontal white matter large aggregates of mitochondria and vesicles probably representing the axonal spheroids were present. Intracytoplasmic inclusions with myelin figures were also present (Figure 6).

Electron microscopy of the brain biopsy of case 3 demonstrated dystrophic axons surrounded by a myelin sheath (Figure 6).

**DISCUSSION**

Our four patients with adult onset leukodystrophy with neuroaxonal spheroids, illustrate the clinical, neuroradiologic, and neuropathologic similarities as well as the differences that characterize this disorder. The illness commenced with changes in personality, disorganization and forgetfulness and progressed to devastation across multiple domains of cognition, with elementary neurological functions impaired only late in the course. These clinical features were matched by early destruction in the deep white matter of the prefrontal cortex, followed by the white matter deep to the association areas of the parietal and temporal lobes and secondary degeneration in the thalamus as demonstrated by neuroimaging and post-mortem examination.

The differential diagnosis for subacute confluent white matter disorders in adults is wide, including metabolic disorders (metachromatic leukodystrophy, adrenoleukodystrophy, adult-onset Krabbe’s disease) infectious causes including (HIV, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis), vascular disease (vasculitis, lupus cerebritis, Behçet’s disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and small vessel ischemia) and neoplastic (primary cerebral lymphoma) (7,10,21). Adult onset leukodystrophy with neuroaxonal spheroids can be an autosomal dominant disease with variable age of onset (4,9,27), or a sporadic disease (14,27,31). The diagnosis depends on the presence of degeneration of white matter including loss of myelin and axons, neuroaxonal spheroids, gliosis, and macrophages (18). Presenting symptoms have included early psychiatric changes (16,24,26) or motor symptoms that progress to memory loss and a more generalized cognitive decline.

In our cases the duration of disease ranged from 1.5 to 8 years and correlated well with the extent and degree of cerebral damage seen on imaging and pathologic examination. The subject with the shortest duration, 1.5 years, showed predominantly frontal lobe involvement
while the patient with the longest course, 8-years, had more widespread involvement of white matter, as well as cerebellar white matter, and corticospinal tracts, together with neuronal loss in cerebellum and medulla. As the clinical disease progressed there seemed to be a temporal pattern of involvement beginning in the frontal lobe white matter and extending to the corpus callosum and white matter of the somatosensory and eventually visual cortices. The white matter of the primary motor, sensory, and visual cortices were preserved until late in the course of the disease. Our patients reflect the published accounts of this condition, in that the heralding symptoms are generally neuropsychiatric (16,24,26), progressing later to dementia and motor impairment, although case 2 initially presented with motor symptoms as has been previously reported (1,8,9). Three of our patients had at least one other family member with similar symptoms and the fourth had a parent with early cognitive decline, but none of these family members had come to autopsy.

The distribution of white matter disease in our patients corresponds to that described previously (1,8,22,23,26,27,32). The more recent white matter lesions had more abundant macrophages and more frequent axonal spheroids. Older lesions showed near total loss of all axons, with only U-fiber preservation, and fewer spheroids and macrophages. As the disease progressed there was secondary involvement of other structures such as the thalamic nuclei. This pattern of disease progression is illustrated by case 3. At the time of the biopsy 8 months into the disease course, the white matter had ill-defined regions of myelin sheath and axon loss with frequent axonal spheroids. Ten months later the autopsy revealed, well defined, more severe white matter loss and gliosis with fewer axonal spheroids. Neuroaxonal spheroids indicate axonal damage (23,27) and can be seen in many conditions including trauma, neurodegenerative diseases, metabolic diseases, and tumors. The presence of neuroaxonal spheroids in the cortex in cases of short duration supports the speculation that this may be a primary axonal process with early axonal degeneration and resulting myelin loss (17,27,32). The finding of rare ballooned neurons in two cases, located near areas of more acute white matter damage, perhaps represent ‘axonal reaction’ (5,17) also supports the notion of a primary axonal injury.

The etiology of POLD and HDLS is uncertain. As pigmented cells were a minimal to absent component in all but one case, POLD is not the best category in which to consider our cases. Since not all of our cases show a definite family history of this disease, the term HDLS is similarly not ideal. The evolution of the neuropathology correlates with the clinical and radiological severity, pointing perhaps toward an underlying metabolic derangement. In cases 1 and 4, we detected changes in mitochondrial function lending support to the possibility of a mitochondrial derangement resulting in oxidative injury seen in both POLD and HDLS (2). Elevated pre-mortem ANA levels found in cases 1 and 3 raised the possibility of an autoimmune process, but lack of an inflammatory component on neuropathologic examination makes this mechanism seem less likely.

**Clinical-pathological correlations**

The clinical manifestations of the white matter disease in these patients may be understood in the light of the organization of the fiber tracts that course through the white matter of the cerebral hemispheres. Every cerebral cortical area gives rise to short, neighborhood and long association pathways, as well as striatal fibers, and a cord system of fibers with two distinct fiber populations - one destined for the opposite hemisphere in the corpus callosum or anterior commissure and the other to thalamus and pons in the subcortical bundle (21).

Disconnection syndromes were originally described as neurobehavioral impairments following focal white matter lesions of the cerebral hemisphere (11,12). More recently, dementia resulting from microvascular ischemia (e.g., (6)) and the cognitive effects of white
matter lesions on MRI in otherwise healthy aged individuals and monkeys have been increasingly recognized (e.g., (15,19).

Our cases support the concept of white matter dementia (3,10,21), as the cognitive and behavioral changes occurred early in the course of the illness generally in the absence of weakness, sensory loss or blindness. The areas containing the long association tracts interconnecting the parietal, temporal and occipital lobes with the frontal lobe were the most severely affected in our cases. In contrast, projection pathways such as the corticospinal projections from peri-Rolandic cortices were spared until later in the illness. This is exemplified by case 1 in whom cortical blindness corresponded to the late pathological changes in the sagittal stratum that contains the optic radiations. This dichotomy of early dementia with preservation of gait, strength, dexterity and sensation until later in the illness provides an interesting glimpse into the clinicopathological distinction between association and projection fiber tract involvement, and the functional contributions of these different white matter tracts.

The location of the damage in the corpus callosum fibers also reflects the association-projection dichotomy seen in these cases. Case 1 had minimal sensorimotor deficits, and sector 3 of the corpus callosum that conveys sensorimotor fibers between the hemispheres (21) was spared whereas sectors 1, 2, and 4 of the corpus callosum that convey association fibers between the hemispheres were devastated. In case 4 with progressive motor impairment as the disease evolved, almost the entire corpus callosum was degenerated, except for sector 5 that conveys fibers between the caudal parts of the temporal lobes which were relatively less devastated.

Whereas cerebral cortical neurons were spared in our cases, there was marked neuronal dropout in thalamus which could reflect the loss of sustaining cortical/subcortical projections (30). In patient 3, damage was concentrated in the white matter of the prefrontal cortex and this patient had the characteristic frontal lobe syndrome. Thalamic degeneration was confined to the anterior thalamic nuclear complex which has reciprocal interconnections with medial prefrontal and cingulate cortices (13,25,28), and the medial dorsal thalamic nucleus projections to cortex essentially define the frontal lobe with strict reciprocal thalamocortical topography (13,25). Similarly, in patient 1, neuronal loss in the medial dorsal thalamic nucleus likely reflects destruction of projection fibers between prefrontal cortex and thalamus; the neuronal loss in the lateral dorsal thalamic nucleus likely reflects paralimbic association cortical interaction with thalamus, particularly cingulate gyrus and posterior parietal cortex (20,28,30,33,34); and the lateral posterior thalamic neuronal dropout reflects the white matter devastation in parietal association areas (20,33).

We have described the clinical, neuroimaging and neuropathological features that characterize adult onset leukodystrophies with neuroaxonal spheroids and related the functional impairments in our patients to the pattern of morphologic damage identified in their cerebral hemispheres. Our cases of white matter disruption in adult onset leukodystrophy with neuroaxonal spheroids underscore the critical importance of cerebral white matter for cognition and emotion, as the fiber pathways they contain link cerebral cortex with other cortical and subcortical regions and are a key element in the anatomic underpinning of the distributed neural circuits that subserve higher order behavior.

**Acknowledgments**

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References


Figure 1.
MRI images of patient 1 with adult onset leukodystrophy with neuroaxonal spheroids. A and B: Axial and sagittal T1-weighted MRI demonstrating hypointense signal in the white matter underlying the prefrontal cortex and mildly enlarged lateral ventricles, and atrophy of the anterior corpus callosum (C) FLAIR image showing confluent high signal in the periventricular, deep, and subcortical white matter of the frontal, and parietal lobes extending through the posterior corpus callosum.
Figure 2. MRI imaging of patient 3 (A) T2-weighted fast spin echo images (TR/TE=8200/108) demonstrate confluent high signal in the periventricular, deep and subcortical white matter with sparing of the u-fibers and volume loss in both frontal lobes. (B) Diffusion-weighted image (DWI) demonstrates small foci of high signal within the area of high T2 signal abnormality. (C) ADC map confirming the DWI abnormality and showing isointense signal corresponding to the foci of DWI hyperintensity. (D) T2 weighted image showing voxel placement location for MR spectroscopy. (E) Multi-voxel MR spectroscopy demonstrates high choline-to-creatine ratio in the cortical/subcortical region of the abnormal left frontal lobe. (F) Post-contrast T1-weighted image (TR/TE=800/25) demonstrates lack of contrast enhancement in the abnormal white matter areas in the frontal lobes.
Figure 3.
Postmortem findings in the brain. (A) Mid-sagittal section of case 1 demonstrating extensive thinning and brown discoloration of the corpus callosum with relative sparing of sector 3 and enlarged lateral ventricle. (B) Coronal section of the parietal lobe from case 4 demonstrating gray discoloration of the white matter with U-fiber preservation at the level of the hippocampus. The parietal is more severely affected than the temporal lobe white matter.
Figure 4.
Paraffin section of the frontal lobe from case 4 stained with luxol fast blue hematoxylin and eosin demonstrates loss of white matter myelin and axons with only a rim of preserved U-fibers; (original magnification 4×).
Figure 5.
(A) Microscopic section of the frontal white matter in case 2 demonstrating several axonal spheroids (original magnification 20×). (Luxol fast blue hematoxylin and eosin stain). (B) Neurofilament immunostain of the white matter; reveals a milder loss of axons compared to myelin and an axonal spheroid; (original magnification 20×). (C) Scattered macrophages containing luxol fast blue material in white matter (case 4) (Luxol fast blue hematoxylin and eosin stain; original magnification 40×). (D) CD68 immunostain, demonstrates scattered macrophages (brown) within the white matter; (original magnification 40×).
Figure 6.
Ultrastructure: (A) The brain biopsy from case 3 revealed enlarged axons filled with neurofilaments characteristic of axonal spheroids. Epoxy embedded brain; (original magnification 4500×). (B) Large aggregates of mitochondria, some with preservation artifact, and large number of vesicles consistent with an axonal spheroid; (original magnification 3400×). (C and D) Cell containing intracytoplasmic coiled filamentous inclusions, a myelin figure and dilated endoplasmic reticulum (original magnification 4500×). (D) Enlarged area highlighted by rectangle in image (C) demonstrating coiled filamentous inclusions and a myelin figure.
Table 1

Distribution of White Matter Changes

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Extent of damage scored from 0–3+: (0 = rare, 1+ = patchy white matter loss, 2+ = confluent white matter loss, 3+ = almost complete absence of myelin and axons)