Leukoencephalopathies in Adulthood

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Presentation of Leukoencephalopathies in Adulthood

The preceding articles in this issue have reviewed the basic genetic and metabolic background of leukoencephalopathies with their typical presentations, treatment, and prognosis. There is a wide phenotypical variance in the presentation and natural history of these disorders. The understanding of pathogenesis involving expression of genetic cofactors, modifier genes, residual enzymatic activity, and epigenetic factors are being further unraveled as the knowledge on each of these disorders increases. This development has coincided with discoveries of distinct etiologies for some leukoencephalopathies and the expectation is that further subclassifications and new disease entities will evolve as such discoveries are made. Some of the factors that play a role in this process have been outlined in the previous chapters of this issue. Most of the leukoencephalopathies have a spectrum of severity, and where often the disease takes a rapidly progressive course in the young pediatric patients, many of these can have a slowly progressive course with presentation in early or late adulthood. Though often this is an indolent slow course, there are reports of rapidly progressive leukoencephalopathies, which were either initially misdiagnosed or undiagnosed until further specific investigations were performed. In most of these disorders, it is expected that a preclinical stage precedes the presentation and details on this stage are largely unknown. Increased early detection may benefit as treatment options are improving. In addition, supportive management and in some instances halting disease progression, have improved life expectancy. This will increase knowledge and treatment options of these disorders, underlining the importance of increased awareness of these disorders. This article provides a brief overview of the current knowledge on the most prevalent adult leukoencephalopathies. Many of these disorders share a common presentation and although certain clues can direct the clinician toward specific diagnostic considerations, taken separately these conditions can present with nonspecific isolated features that are diagnostically challenging.

Metachromatic Leukodystrophy

Metachromatic leukodystrophy (MLD) usually has a slowly progressive course when onset is in adulthood. The cause of MLD is a deficiency in the activity of lysosomal arylsulfatase A. This results in the accumulation of 3-O-sulfogalactosylceramide in oligodendrocytes and microglia in the central nervous system (CNS) and Schwann cells in the peripheral nervous system. The autosomal recessive inherited genetic defect is the ARSA gene on chromosome 22q13.1 The adult form makes up only a small percentage of MLD patients. Presentation is typically in late adolescence to early adult years, although cases have been described with later onset.2

Symptoms at presentation can vary based on the specific common allelic mutations. P426L homozygous mutations are...
Typically associated with spastic paraparesis and other neurological symptoms, where I179S heterozygous patients often present with psychiatric symptoms. In the later stages of the disease these symptoms show more overlap. Motor symptoms include spastic paraparesis and frequently this is accompanied by cerebellar ataxia. In patients with I179S mutation, such symptoms eventually develop in the minority of cases where many of the patients with P426L mutation have these symptoms at onset and almost all have them later in the disease course. Psychiatric symptoms at presentation often involve alterations in behavior and can include frank psychosis and auditory hallucinations. These are more commonly encountered in patients with I179S mutation and rare in patients with P426L mutations. Cognitive dysfunction eventually is present in both mutations and often evolves into a progressive dementing picture. Demyelinating peripheral neuropathy is often present and there have been case reports of this as the sole initial manifestation. Seizures typically occur later in the course of the disease, although can occur at initial presentation.

The diagnosis is made by measuring arylsulfatase A activity in leukocytes or cultured skin fibroblasts in combination with elevated secretion of sulfatides in urine or positive genetic testing. Caution should be made to the presence of pseudodeficiency. In these patients, there is no urine or tissue accumulation of sulfatides. To our knowledge, saposin B defects have no described cases of adulthood presentation.

Magnetic resonance imaging (MRI) abnormalities include a periventricular predominant leukoencephalopathy with frontal predominance. In early stages, subcortical U fibers are typically spared. There is cerebral atrophy and deep gray matter involvement. The imaging pattern in adult onset had no clear difference from patients with P426L mutation. Cognitive dysfunction eventually is present in both mutations and often evolves into a progressive dementing picture. Demyelinating peripheral neuropathy is often present and there have been case reports of this as the sole initial manifestation. Seizures typically occur later in the course of the disease, although can occur at initial presentation.

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Globoid Cell Leukodystrophy (Krabbe’s Disease)
Globoid cell leukodystrophy or Krabbe’s disease is a rare autosomal recessively inherited leukodystrophy that typically has its onset early in life. Late onset is extremely rare and accounts for an estimated 10% of all cases, although regional variance exists with higher prevalence of late onset. The lysosomal enzyme β-galactocerebrosidase (GALC) deficiency is due to a mutation in the GALC gene, located on chromosome 14q31 and multiple different mutations have been described. The accumulation of galactosylsphingosine is thought to be toxic to oligodendrocytes. Extensive demyelination, loss of oligodendrocytes, and eventually axonal degeneration and gliosis is present on pathology. A recent review of late onset Krabbe’s disease noted that some of the mutations are responsible for the later onset of the disease. The reports of these are restricted to case reports and a few smaller series. The adult presentations consist of a slowly progressive pyramidal tract dysfunction with associated paraparesis and severe spastic gait. Other symptoms include a progressive cognitive dysfunction, visual loss, and peripheral neuropathy. MRI features include T2 hyperintense signal change along the corticospinal tracts and can be seen in the posterior corpus callosum. There have been case reports of spinal cord thinning and isolated spinal cord involvement. Treatment is supportive.

X-Linked Adrenoleukodystrophy and Adrenomyeloneuropathy
The presentation of X-linked adrenoleukodystrophy can have three distinct manifestations. The cerebral variant of adrenoleukodystrophy is extremely rare in adults. Adrenomyeloneuropathy is the most frequently encountered and has distinct neurologic features. Isolated adrenal failure (Addison’s only) is also more frequently encountered in adults and has no associated neurologic dysfunction, although adrenal dysfunction can precede the neurologic presentation. The disorder is a peroxisomal disorder that is caused by a defective ABCD1 gene located on Xq28. Very-long-chain fatty acids accumulate in the nervous system and adrenal cortex. Given the lack of genotype–phenotype correlation, modifier genes and epigenetic factors likely play a role in the unknown exact cellular mechanisms of phenotypical variance.

Adrenomyeloneuropathy is characterized by a slowly progressive development of spastic paraparesis, neurogenic bladder and bowel dysfunction, sexual dysfunction, and peripheral neuropathy. Pathologically, the predominant finding is an axonopathy within the spinal cord causing the spastic paraparesis. The myelopathy is typically sensorimotor. Somatosensory evoked potentials can be abnormal. Both axonal and demyelinating neuropathic changes are found electrophysiologically in the majority of the patients.

MRI findings vary and can range from the most commonly described subtle T2 hyperintensities in the corticospinal tracts to more extensive white matter involvement. Progressive cerebral forms had been described in patients that initially had negative brain MRIs in as high as 20%. Progression on MRI has been seen in the majority of patients that initially presented with mild corticospinal tract involvement on imaging. In this same study, patients with initially normal MRIs only had development of MRI lesions in 5%. Recent studies applying diffusion tensor imaging, magnetization transfer imaging, and MR spectroscopy have revealed pathologic changes beyond the typical lesions and atrophy, although clinical application of these techniques is still under investigation.

When adrenal dysfunction is present (70% of the patients are affected), ACTH levels are elevated and there is an impaired increase of plasma cortisol levels in response to administration of ACTH. Evaluation by an endocrinologist is...
warranted and there should be no other cause for adrenal failure. The diagnosis can be made by measuring (fasting) very long chain fatty acids, and an elevation in the (fasting) C26:0 very long-chain fatty acids and often elevated C26:0 and C24:0/C22:0 ratios.\(^\text{38}\)

Treatment is supportive and consists of corticosteroid replacement therapy for adrenal insufficiency, physical therapy, management of urological symptoms (both bladder and sexual dysfunction), and psychological as well as rehabilitation (vocational) support.\(^\text{39}\) Hematopoietic stem cell transplantation may be successful in adult males who develop cerebral disease if performed early.

**CADASIL**

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common hereditary multiinfarct leukoencephalopathy. After an initial description in 1977,\(^\text{40}\) the term hereditary multiinfarct dementia was introduced.\(^\text{41}\) Multiple reports followed describing similar patients with familial pattern of recurrent subcortical cerebrovascular ischemic events presenting in young adults lacking the typical vascular risk factors.\(^\text{42}\) The genetic defect was mapped to 19q12 in 1993.\(^\text{43}\) Shortly thereafter, the acronym CADASIL was introduced.\(^\text{44}\) The autosomal dominantly inherited Notch3 gene\(^\text{45}\) has

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*Figure 1* Magnetic resonance imaging of a patient with adult-onset metachromatic leukodystrophy demonstrating (A) diffuse abnormalities of the periventricular white matter associated with cerebral atrophy, and (B) atrophy of the corpus callosum.
numerous different described mutations. The pathophysiology is related to abnormal expression of Notch3 in the smooth muscle layers of small vessels with formation of granular osmophilic inclusion material in the smooth muscle layer of small arteries, although the exact mechanism is still under investigation. The degeneration of the vascular smooth muscle layer in small vessels leads to reduced compliance, reduced blood flow, and eventually small vessel ischemia.

The clinical presentation is variable and the age of onset varies based on presentation. When present, migraine headaches are often the first presenting symptom, median age of onset is in the late 20s. Migraines are frequently with aura or atypical variants. The clinical picture may be indistinguishable from other migraineurs prior to the onset of ischemic disease.

Ischemic events typically present in the mid to late forties, although this has been described with a very wide age range. In many patients, these are recurrent strokes and clinical progression is related to the impact of each ischemic event. Eventually, microvascular changes lead to cognitive impairment. Psychiatric symptoms, often mood disorders and apathy, have been well described as common features. Occasionally, seizures are seen, rarely as the presenting symptom.

Typical early MRI features (Fig. 2) include small periventricular T2 hyperintensities, eventually evolving into a diffuse confluent pattern of abnormal T2 hyperintensity. Changes within the anterior white matter of the temporal lobe, extreme capsule signal changes are often encountered features and should raise the suspicion of CADASIL. Lacunar infarcts are commonly seen. MRI features have been described in asymptomatic carriers and have been described to precede the clinical features by many years. The small vessel pathology can be visualized on skin biopsy, and either typical changes or molecular confirmation of the genetic defect is diagnostic.

Interestingly, the initial cases of hereditary multi-infarct dementia that were described did not have the Notch3 mutation. There have been multiple genetic etiologies for familial forms of (recurrent) cerebrovascular disease. Several single-gene disorders that can cause recurrent strokes should be in the differential diagnosis. These include mitochondrial causes (e.g., mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]), connective tissue disorders, such as Ehlers-Danlos and Marfan’s disease, disorders associated with vasculopathies, such as Fabry’s disease, moyamoya disease, and cerebral amyloid angiopathies and polycystic kidney disease. Others may include retinal involvement (cerebroretinal vasculopathy [CRV], hereditary vascular retinopathy [HVR], COL4A1 mutations). These small vessel diseases can have an indistinguishable appearance on MRI and work-up will rely on possible other clues from the clinical picture.

**Alexander’s Disease**

The course of Alexander’s disease with adult onset is typically milder than in pediatric patients. The onset of the adult variant is from late teens to early adulthood. It is caused by an autosomal dominant (often de novo) mutation in the gene coding for the glial fibrillary acidic protein (GFAP), located on chromosome 17. Pathologically, the eosinophilic Figure 2  Magnetic resonance imaging of a patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) demonstrating a diffuse confluent pattern of periventricular T2 hyperintensity.
Rosenthal fibers within the astrocytic cytoplasm have been described in adults.54 The typical perivascular distribution with prominence in periventricular and subpial locations55 in children has been described to be more sparse in adults with predominant presence in the brainstem and cerebellum.56 The pathogenesis is believed to be cytotoxicity due to gain of function in the affected GFAP gene.50 It is unclear how the different mutations across the GFAP coding region result in phenotypical variance61; (epi)genetic cofactors may be responsible for this. Specific mutations have been described in many sporadic cases62 and in larger families.57 Even within adult presentations of the disease, courses have varied from rapidly progressive disease to an indolent slow progression.57,60,62

Recent review of 215 cases in the literature63 proposes to divide the disease into two subtypes rather than three. The juvenile and adult variants have substantial overlap and are likely on a spectrum/continuum of the disease. The variant with later onset (in adolescence or adulthood) can present at any age. The variance in symptoms is larger and common clinical features include cerebellar ataxia, bulbar dysfunction (including dysarthria, dysphonia, and dysphagia), pyramidal symptoms (spastic paraparesis and hyperreflexia), sleep abnormalities, bladder dysfunction, autonomic dysfunction, ocular movement abnormalities, and palatal myoclonus. Where seizures, macrocephaly, encephalopathy, and cognitive dysfunction/delay are typical in the early course, this is rarely encountered in adult presentations.62,63

MRI findings have been described in detail and criteria for diagnosis have been developed.64 These typical findings (mostly young onset) include symmetric T2 hyperintensities with a frontal predominance, a periventricular rim of T2 hypointensity and T1 hyperintensity, and signal change in the basal ganglia, thalamus, and brainstem. Gadolinium contrast enhancement may be present in the periventricular regions and brainstem.65 In adult patients, these can be present, but often to a lesser extent or even with minimal subtle abnormalities with more frequently present atypical features, including predominance of signal change in the posterior fossa and atrophic changes within the spinal cord, cerebellum, or brainstem.63,66

Adult-Onset Autosomal Dominant Leukodystrophy
Adult-onset autosomal dominant leukodystrophy (ADLD) is a slowly progressive leukoencephalopathy. The first descriptions from 1984 included a family of American-Irish background with progressive neurologic symptoms.67 Since then, multiple case reports have been reported. In 2000, the clinical phenotype was linked to chromosome 5q31.68 Further linkage studies in 2006 revealed the cause of this disorder was genetically linked to a duplication of the lamin B1 gene (LMNB1) on chromosome 5q23.2.69 although the large duplications included other less likely candidate genes. In a recently described patient, a much smaller duplication was described.69 This further strengthened the hypothesis that LMNB1 is the pathologic cause for the disease, although the exact pathogenic pathways of duplication of LMNB1 resulting in these changes remain unknown. Pathologic studies have revealed widespread demyelination with relatively preserved axons and there is an abundance of astrocytic and macrophages with inclusions.71,72

The typical presentation starts in the fourth or fifth decade, with autonomic abnormalities, followed by pyramidal motor symptoms and cerebellar ataxia.67,68,73,74 Cognitive features are common and slowly progressive dementia has been described.

MRI changes include symmetric, often extensive white matter T2 signal hyperintensities.71,75 The frontal lobe, followed by the parietal lobe and middle cerebellar peduncle, are affected. Often the signal change along the longitudinal tracts can be followed into the brainstem. There is atrophy of the brainstem and corpus callosum. Lesions typically do not enhance with gadolinium contrast.71 MRI features have been described in nonaffected mutation positive family members.70,71 Longitudinal spinal cord T2 hyperintensities and cord atrophy have been described.75,76

**Adult Polyglucosan Body Disease**

Adult polyglucosan body disease (APBD) is a rare degenerative disorder that can have clinical features and MRI findings indistinguishable from other leukoencephalopathies. The disease is most commonly seen in Ashkenazi Jews and is related to a mutation in the glycogen branching enzyme GBE1.77 There have been a few reports of patients of non-Jewish descent with defects related to different parts of the GBE1 gene.78–80 This gene had been previously described in glycogen storage disorder type IV (fructokinase deficiency), which also has PAS positive deposits. In APBD these deposits have been described in the brain.80

The disease clinically presents with bladder dysfunction, pyramidal dysfunction (spastic paraparesis), and a mixed sensory and motor neuropathy, resulting in a mixed pattern of pyramidal and lower motor neuron weakness. There may be cognitive impairment, cerebellar ataxia, and extrapyramidal signs and symptoms.

There are multiple MRI case reports that describe periventricular white matter changes that are typically nonenhancing.78,81–83 The electrophysiologic findings can be consistent with an axonal neuropathy. Clinical diagnosis can be established with nerve biopsy or sometimes skin biopsy, which shows PAS positive deposits, measuring glycogen brancher enzyme activity in cultured fibroblasts. This can be confirmed by genetic testing. Treatment is supportive.

**Cerebrotendinous Xanthomatosis**

Cerebrotendinous xanthomatosis (CTX), an autosomal recessive disease, has its genetic defect in the gene for sterol 27-hydroxylase, resulting in a deficiency in this mitochondrial active enzyme.86,87 Due to abnormal conversion of cholesterol into cholic and chenodeoxycholic acids, elevated cholesterol levels in plasma, and bile are found.88 Cholesterol accumulation occurs in the brain, tendons, eyes, and other tissues.89 Normal lipoprotein levels can be found despite the biochemical abnormality.
Presentation often is with juvenile onset of cataract. In children, unexplained chronic diarrhea is reported in as high as half of the cases.\textsuperscript{90,91} In adulthood, this can be followed by gradual development of neurologic manifestations, including spastic paraparesis, pyramidal tract signs, cerebellar ataxia, peripheral neuropathy, and bulbar symptoms. Myelopathic presentations have been described in a spinal variant of CTX.\textsuperscript{92} The majority of the patients have a low baseline intellectual quotient and the disease eventually leads to a progressive dementia when left untreated. Seizures, myopathy, extrapyramidal, and psychiatric symptoms may be present.\textsuperscript{93} The examination in addition to the neurologic symptoms can reveal the tendon xanthoma, typically on the Achilles tendon. Variability of symptoms has been described, including the absence of xanthomas.\textsuperscript{93,94} Other extracerebral manifestations include atherosclerosis, osteoporosis,\textsuperscript{95} and respiratory, endocrine, and liver abnormalities.\textsuperscript{91}

MRI findings include increased T2 signal in and around the dentate nucleus, and the supratentorial white matter changes can often have periventricular distributed mild confluent T2 hyperintensities.\textsuperscript{96–99} Both cerebellar and cerebral atrophy has been described. MR spectroscopy can show low NAA to choline ratio with mild lactate peaks.\textsuperscript{97} Choroid calcifications have been described.\textsuperscript{99}

Treatment is with chenodeoxycholic acid, which inhibits the synthesis of abnormal bile acids, reducing the cholesterol levels.\textsuperscript{88,100} Treatment with addition of statins (HMG-CoA reductase inhibitors) has been suggested, though clear evidence-based prospective studies are lacking.\textsuperscript{101,102}

**Diffuse Leukoencephalopathies With Neuroaxonal Spheroids**

Leukoencephalopathy with neuroaxonal spheroids or hereditary diffuse leukoencephalopathy with spheroids (HDLS) are disorders pathologically defined by the presence of neuroaxonal spheroids. HDLS was first described in a large Swedish family in 1984.\textsuperscript{103} Inheritance is autosomal dominant, with many thought to be sporadic mutations. No genetic marker has been found and no linkage studies have identified the locus. Pathologically, both myelin loss and axonal loss are present with neuroaxonal spheroids on Bielschowsky, Bodian, and antineurofilament stain.\textsuperscript{104–107} Affected areas are centrum semiovale, corpus callosum, frontal, frontoparietal, and temporal lobes.\textsuperscript{108,109} The main clinical manifestations include cognitive dysfunction, seizures, ataxia, retropulsion, gait apraxia, spasticity, and urinary incontinence.\textsuperscript{110,111} Extrapyramidal symptoms have been described.\textsuperscript{112} Symptoms of cognitive decline have been described in a range of speed of progression.\textsuperscript{105,111,113} Psychiatric symptoms are common, ranging from mood disorders to psychotic episodes.\textsuperscript{111} The heterogeneity of symptomatology can make the presentation difficult to distinguish from other neurodegenerative or frontal lobe predominant dementias, or immune-mediated, metabolic, or vascular CNS diseases.

The predominance of the pathologically found abnormalities are confirmed by the distribution seen on MRI. There are T2 hyperintensities that may be patchy or confluent; these are most pronounced in the pre/post central gyri and can extend through the internal capsule into the pyramidal tracts.\textsuperscript{106,110} Subcortical U-fibers seem relatively spared. Atrophy can be found and the corpus callosum can be thin and may contain areas of abnormal signal. MRI findings in itself are not specific and do not allow definite diagnosis. With the absence of specific genetic testing, the certain diagnosis needs to be confirmed by histopathology.

Axonal spheroids are pathologic findings characteristic of the neuroaxonal dystrophies, a rare disorder. Other neuroaxonal dystrophies with spheroids include infantile neuroaxonal dystrophy (Seitelberger’s disease) and pantethein kinase associated neurodegeneration (PANK). Rare leukodystrophies have been reported with spheroids (such as lipomembranous osteodysplasia with sclerosing leukoencephalopathy [PLOS]) and pigmentary orthochromic leukodystrophy (POLD).

**Fragile X Associated Tremor/Ataxia Syndrome**

Recently described fragile X associated tremor/ataxia syndrome (FXTAS) is a progressive disorder that is seen in patients that have premutations of the FMR1 gene on chromosome X. These consist of 50 to 200 CGG triplet repeats, less than the patients with classical fragile X syndrome with >200 copies. This is most frequently seen in male carriers over the age of 50, but female patients have been described.\textsuperscript{114,115} Pathology studies have revealed an extensive and distinct degenerative pattern with both subcortical cerebral and cerebellar white matter involvement with patchy loss of axons and myelin, and there is relative sparing of the cortex. There are eosinophilic intranuclear inclusion bodies within astrocytes and neurons. These can be found in the brain and spinal cord.\textsuperscript{116} There is a loss of Purkinje cells and spongiosis of the middle cerebellar peduncle. The inclusions typically are negative for staining for tau or synuclein; they contain FMR1 (m)RNA.\textsuperscript{116}

Clinically, FXTAS is characterized by progressive ataxia and intention tremor, with frequent presence of cognitive dysfunction. Other parkinsonian features may be present as well as peripheral neuropathy and autonomic dysfunction.\textsuperscript{116–119} Cognitive dysfunction can be mild, with most frequent mild executive dysfunction and memory deficits and less often global dementia.\textsuperscript{120} Many of the patients are initially diagnosed with other varied neurologic disorders.\textsuperscript{121}

Neuroimaging can show typical lesions of T2 hyperintensities in the middle cerebellar peduncles (MCP sign) and surrounding the dentate nuclei.\textsuperscript{122} Cerebral T2 hyperintensities have been reported in the subcortical and periventricular white matter. Both cerebellar and cerebral atrophy can range from mild to prominent atrophy.\textsuperscript{122–124} Both pathologic, symptomatic, and neuroimaging severity have been shown to correlate to the number of CGG copies.\textsuperscript{125}

Diagnosis can have important implications as the patient’s male grandchildren (via daughter offspring) are at risk of developing fragile X syndrome. Treatment is symptomatic.

**Future Directions**

The diagnoses of the above-reviewed disorders make up a large percentage of adult leukoencephalopathies, but still
many remain unclassified. The overlap in symptoms makes differentiation between the possibilities difficult; sometimes brain biopsy has to be considered. Currently, the majority of these progressive disorders have no curative treatment. It is hoped that better classification and understanding of the underlying pathogenetic pathways will lead to improved understanding and possible treatment.

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