Leukoencephalopathy with spheroids (HDLS) and pigmentary leukodystrophy (POLD)

A single entity?

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ABSTRACT

Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) and familial pigmentary orthochromatic leukodystrophy (POLD) present as adult-onset dementia with motor impairment and epilepsy. They are regarded as distinct diseases. We review data from the literature that support their being a single entity. Apart from a slightly older age at onset, a more rapid course, and more prominent pyramidal tract involvement, familial POLD is clinically similar to HDLS. Moreover, the pathologic hallmarks of the two diseases, axonal spheroids in HDLS and pigmented macrophages in POLD, can be identified in both conditions. This supports HDLS and POLD being referred collectively as adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP). **Neurology**® 2009;72:1953-1959

GLOSSARY

ALSP = adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; **HDLS** = hereditary diffuse leukoencephalopathy with axonal spheroids; **OLD** = orthochromatic leukodystrophy; **POLD** = pigmentary orthochromatic leukodystrophy.

Nonmetachromatic or orthochromatic leukodystrophies (OLD) constitute a heterogeneous group of noninflammatory demyelinating disorders.¹ Peiffer^{1,2} distinguished pure forms, special forms, OLD combined with phakomatoses and other disorders, and symptomatic forms. In 1936, Van Bogaert and Nyssen³ described a family with adult-onset OLD associated with pigmented macrophages and other glia (POLD) corresponding to Peiffer's pure forms of OLD. Subsequently, the majority of reported POLD cases have been sporadic; however, no less than eight POLD families have been reported with both recessive and dominant inheritance. Fifty years later in Sweden, Axelsson and colleagues⁴ described a large family with adult-onset leukoencephalopathy characterized pathologically by the presence of numerous axonal dilations named spheroids. They coined the term hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS).

While POLD and HDLS are regarded as distinct conditions in the literature, recent reappraisal of clinical and pathologic features suggests they may be variants of the same disease.^{5,6} Herein we review the available literature on POLD and HDLS and provide a critical assessment that supports the hypothesis of a single clinicopathologic entity.

SEARCH STRATEGY References for this review were identified by searches of PubMed from 1966 until November 2008 with the terms HDLS, POLD, leukodystrophy, leukoencephalopathy, spheroids, and pigmented macrophages. Articles were also identified through searches of the authors' own files, and manual retrieval of articles published before 1966 was performed. Papers in English, French, and German were reviewed.

CLINICAL PRESENTATION The core symptoms of HDLS and POLD are behavioral changes, depression, dementia, motor impairment (parkinsonism; spastic hemiparesis, paraparesis, or tetraparesis; ataxia), and epilepsy. However, there is a wide variability in the occurrence and severity of each clinical phenotype. In the

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following section, we will discuss reported HDLS and POLD families, highlighting pedigrees, symptoms, progression, and treatments.

Existing pedigrees, inheritance. To date, there are 12 HDLS families reported with detailed clinical and pathologic data (including three familial probands described by Freeman et al.¹³) (table e-1 on the *Neurology*® Web site at www.neurology.org).^{4,5,7-14} In two of them, pathologic criteria were also deemed compatible with familial POLD.^{5,8} Given HDLS' complex clinical and pathologic presentations and similarity with more common adult-onset white matter diseases, underdiagnosis is likely. An unavailable/unreliable family history or low disease penetrance may also impede its recognition. The distribution of the disease is worldwide, with reported families from Sweden, the Netherlands, the United States, Japan, and Australia. HDLS pedigrees display apparent autosomal dominant disease inheritance. Apart from the original Swedish family in which there were 71 family members and 17 patients over four generations (four patients pathologically verified), reported pedigrees are small, with two to six affected individuals over one to three generations. In the 38 patients for whom this information was available, the age at onset ($\pm$ SD) was 39 ± 15 years (range, 8–78); disease duration was 9 ± 10 years (range, 1–34) in 31 of them. When removing patients from the over-represented Swedish family, figures were age at onset 40 ± 15 years (range, 15–78; 24 patients) and 5 ± 5 years disease duration (range, 1.5–17; 17 patients). The gender ratio was 0.81 with (58 patients; 26 men) and 0.64 without (41 patients; 16 men) the Swedish family.

Eight families with POLD have been described in the Netherlands, France, Spain, Germany, Japan (two families), Switzerland, and the United States (table e-2). Assessment of published pedigrees shows the disease displays either autosomal dominant¹⁵⁻¹⁷ or recessive^{3,18-21} inheritance. The pedigrees are small, with one to five affected individuals over one to three generations. In the 15 patients for whom this information was available, the age at onset ($\pm$ SD) was 43 ± 13 years, disease duration was 6 ± 3 years, and gender ratio was 0.7 in 22 patients (13 men).

First symptoms. In HDLS, the initial symptoms are most commonly psychiatric, with depression often being recognized several years before other disease manifestations.⁵ In the original Swedish family,⁴ patient II-8 presented with generalized convulsions, reduced spontaneity and initiative, and emotional blunting. Patient III-18 presented with fatigue, apathy, indifference, and lack of initiative, and was diagnosed with depression. Patient III-19 began with

personality changes and memory impairment, followed by emotional and intellectual deterioration, whereas patient III-20 presented with right upper limb stiffness and paresthesias, followed by anxiety and gait difficulties. In the other families, four patients manifested depression^{5,7,9}; one had depression and gait impairment⁵; four had cognitive and behavioral symptoms^{13,14}; two had mental and motor impairment¹²; one had anxiety, clumsiness, confusion, and stiffness⁵; four had memory loss^{7,8,11}; one had behavioral changes and gait impairment⁸; three had parkinsonism^{7,10}; three had hemiparesis^{10,13}; and two had epilepsy.^{10,12}

Initial symptoms in POLD families included depression and anxiety, executive dysfunction, euphoria and apathy,^{3,15,17,19-21} memory impairment,¹⁹ headache,¹⁵ and pyramidal dysfunction.¹⁶

Psychiatric and neuropsychological symptoms. Neuropsychiatric symptoms have been reported in all identified HDLS families to date (table e-1). The most common psychiatric symptoms are depression and anxiety, described in 70% and 65% of the patients from the Swedish family⁴ and in several other pedigrees.^{5,7,9} Depression may be severe, with two patients from the Swedish family committing suicide. Substance abuse such as alcoholism has also been reported.^{4,12} Disorientation is also a prominent symptom, as are confusion, agitation, irritability, aggressiveness, and memory impairment.^{4,5,7-14} Most HDLS patients develop dementia, which may be misdiagnosed as Alzheimer disease^{4,5,7-9,11} or frontotemporal dementia.⁸ A frontal syndrome, mainly of the apathetic and emotionally blunted type, has been described in several patients,^{5,7-9,11,13} although a more disinhibited phenotype has also been reported.^{8,13} Additional symptoms include apraxia^{5,7,11,13} and mutism.⁸

Similarly, most familial POLD patients present with neuropsychiatric symptoms (table e-2). Depression and anxiety are particularly common,^{3,17} as are behavioral changes including disinhibition, aggressiveness, euphoria, and apathy.^{3,15,18} In the family described by Constantinidis and Wisniewski,¹⁵ patients displayed a frontotemporal dementia phenotype consistent with a diagnosis of Pick disease. Psychosis (e.g., paranoid delusions) may occur.³ Diffuse cognitive decline, including memory impairment, but with frontal predominance, eventually occurs in all patients, leading to end-stage dementia.^{3,16,21}

Neurologic symptoms. Gait impairment and epilepsy are common neurologic symptoms in both HDLS and familial POLD (tables e-1 and e-2). Gait impairment may stem from parkinsonism, ataxia, pyramidal dysfunction, or a combination of these.^{5,7,9,10,12} Asymmetric parkinsonian signs exist in some patients

with HDLS, mostly rigidity, bradykinesia, and postural instability.^{5,7,10} In the family described by Baba and colleagues,⁷ notably asymmetric parkinsonism with apraxia was consistent with corticobasal syndrome and strong family history suggested a diagnosis of frontotemporal dementia–parkinsonism linked to chromosome 17 (FTDP-17). A postural or rest tremor may occur.^{4,5,7} In contrast, motor impairment in familial POLD is commonly due to prominent pyramidal tract involvement producing spastic paraparesis, tetraparesis, or hemiparesis.^{3,15–20} An unspecified tremor occurred in one family,¹⁵ and an action tremor was noted in another patient.¹⁷

Other symptoms in HDLS and familial POLD include ataxia,^{4,5,7,12,15,17} dysphagia,^{3,5,10,12,16} and dysarthria,^{3,5,7,9,10,15} whereas in HDLS families, cortical blindness,¹³ oral dyskinesia,⁴ dystonia,^{4,9} myoclonus,¹³ apraxia,^{7,13} and tremor, atrophy, and fasciculations of the tongue⁵ have been reported. Other symptoms described within POLD families include an afferent pupillary defect,³ apraxia,²¹ myoclonus,¹⁹ and severe headaches.¹⁵ Epilepsy has been reported in 7 of the 12 HDLS families and in 5 of the 8 POLD families at variable times during the illness course. In affected patients, generalized tonic-clonic seizures are most common, although partial seizures with⁷ or without^{4,16} secondary generalization also have been described.

Disease progression. HDLS and familial POLD typically manifest with neuropsychiatric symptoms, which progress to dementia. In most cases, a frontotemporal phenotype remains predominant with marked personality changes and aberrant behavior, but more diffuse cognitive impairment occurs as well. After a few years, motor dysfunction develops, notably gait impairment. Eventually, most patients with HDLS and patients with POLD become wheelchair-bound or bedridden, with end-stage dementia. In HDLS, the average life expectancy is 9 years and in POLD 6 years. For practical purposes, disease onset was defined as occurrence of either neuropsychiatric or motor symptoms if progressive, excluding a single episode of seizure or depression that would have occurred years before.

Treatments. Few details have been reported on therapeutic interventions. Depression has been treated with limited benefit using selective serotonin reuptake inhibitors,⁹ and parkinsonism has responded poorly, or not at all, to carbidopa/levodopa.⁷

Discriminating clinical features. As pointed out in the table, familial POLD and HDLS have very similar clinical presentations. In familial POLD, the age at onset is slightly older, the course of disease is more rapid, and there is more prominent pyramidal tract

involvement than in HDLS. Conversely, parkinsonism is more common in HDLS families.

LABORATORY AND IMAGING WORKUP Extensive laboratory evaluations in patients with HDLS, including serum electrolytes; complete blood counts; liver and thyroid function tests; vitamin B12 and folate; vitamin E; cholesterol and triglycerides; amino acids (serum and urine); syphilis and HIV serologies; arylsulfatase A; galactocerebrosidase; sialic acid; α - and β -glucosidase; α - and β -galactosidase; α -mannosidase; α -fucosidase; very long chain fatty acids; antinuclear, antineutrophil cytoplasmic, and antineuronal nuclear antibodies; erythrocyte sedimentation rate; lead and copper; and cortisol, as well as urine organic acids and lactate (blood and CSF), have not revealed any abnormalities.^{9,10,12}

Likewise, in POLD, no abnormality was found in electrolytes, complete blood count, liver and thyroid function tests, vitamin B12, folate, arylsulfatase A and B, glucosidase, galactosidase, mannosidase, fucosidase, xylosidase, nitro-catechol sulfatase A and B, very long chain fatty acids, hexosaminidase A and B, and sphingomyelinase.^{16,19}

CSF studies were normal in HDLS and in POLD, including cell counts, protein, glucose, and oligoclonal bands.^{4,9,16,19} No studies reported on neuronal markers such as enolase and tau; however, one study found normal CSF levels of protein 14-3-3.⁹

Imaging. Cranial CT scans may be normal in the early stages of HDLS,⁴ but eventually show moderate, frontal-predominant atrophy with enlarged lateral and third ventricles both in HDLS^{4,5,9–11} and in POLD.^{16,18,19,21} In HDLS, MRI shows frontal-predominant atrophy with periventricular, callosal, and deep white matter lesions, which may be patchy,¹² confluent,^{7,8,12,13} or diffuse,^{5,9,12} and have a frontal or frontoparietal predominance (table). Occipital involvement rarely occurs. Our group recently reported serial presymptomatic and symptomatic MRI scans of one patient showing subtle patchy abnormalities (presymptomatic) becoming widespread and confluent (symptomatic).¹⁴ Although they are characteristic, MRI features in HDLS are nonspecific and may suggest several alternate diagnoses. Those include white matter diseases such as multiple sclerosis, cerebrovascular diseases (e.g., Binswanger disease, cerebral autosomal dominant arteriopathy with subcortical infarcts), late-onset metachromatic leukodystrophy and Krabbe disease, membranous lipodystrophy, X-linked adrenoleukodystrophy, or chronic exposure to toxic substances (e.g., chemotherapy).¹² Most of these conditions can usually be ruled out by appropriate clinical and biologic tests; however, pathologic verification may be required. Magnetic resonance spectroscopy in

Table	Clinical, imaging, and pathologic features found in familial cases of HDLS and POLD	
	HDLS	Familial POLD
Demographics		
Age at onset, y, mean (range)	39 (8–78)	43 (11–70)
Duration, y, mean (range)	10 (1.75–34)	6 (2–11)
Neuropsychiatric symptoms		
Depression	+++	+++
Aggressiveness	+	+
Anxiety	++	+
Behavioral changes	+++	+++
Frontal release signs	+++	+++
Memory impairment*	+	+
Neurologic symptoms		
Parkinsonism	++	+
Pyramidal signs	++	+++
Epilepsy	+++	+++
Apraxia	+	+
Ataxia	++	++
MRI findings*		
White matter lesions	+++	(+++)
Frontal/frontoparietal predominance (PV, SC)	+++	NA
Corpus callosum	++	NA
Pyramidal tract (IC, BS)	++	NA
Cerebellum	–	NA
Initially asymmetric/patchy, later symmetric/confluent	++	NA
Enhancement	–	NA
Cortical atrophy	+++	(+++)
Frontal/frontoparietal predominance	+++	NA
Corpus callosum	++	NA
Lateral ventricles enlargement	++	(++)
Pathology		
Myelin/axon destruction	+++	+++
Axonal spheroids	+++	++
Pigmented macrophages	++	+++

*Very common in end-stage disease.

*Parentheses denote CT scan studies.

HDLS = hereditary diffuse leukoencephalopathy with axonal spheroids; POLD = pigmentary orthochromatic leukodystrophy; + = occasional; ++ = common; +++ = very common; PV = periventricular; SC = subcortical; NA = not available; IC = internal capsule; BS = brainstem.

one study identified an increased choline to creatine ratio in frontal subcortical regions, but with no increase of lactate signal.¹³ No data are available in the literature on MRI in patients with familial POLD.

SPECT (99mTc-ECD) showed frontoparietal hypoperfusion in one patient with POLD¹¹ and frontotemporal hypoperfusion in one patient with HDLS (tracer not specified in the second study).⁸ ¹⁸F-2-fluorodeoxyglucose PET in one patient with HDLS showed generalized hypometabolism, with

asymmetric parietal predominance.⁷ Another study found diffuse frontal and parietal hypometabolism.¹³

Electrophysiology. In HDLS, EEGs may be normal,^{4,7,11} slightly abnormal with intermittent slow activity,⁵ or show diffuse^{4,5,10} or paroxysmal slowing.⁴ Similar normal¹⁹ or abnormal¹⁸ EEG findings have been reported in patients with POLD, which are sometimes asymmetric¹⁶ or with frontal or temporal predominance.¹⁵ No clearcut interictal epileptiform patterns were described in either one of the diseases despite epilepsy being a prominent symptom. Nerve conduction studies, visual and somatosensory evoked potentials, and electroretinograms were normal in HDLS^{4,12} and in POLD.¹⁹

Biopsy. Skin and muscle biopsies revealed no red ragged fibers or Lafora bodies in HDLS or in POLD.^{9,13,19} Atrophy of type II muscle fibers and decreased activity of cytochrome *c* oxidase, succinate cytochrome *c* reductase, and NADH-cytochrome *c* reductase were reported in one study of muscle tissue.¹³ A sural nerve biopsy showed minimal pathologic changes of an unspecified nature in one patient with POLD.¹⁰

PATHOLOGY The pathologic hallmark of HDLS is widespread loss of myelin sheaths and axonal destruction, numerous axonal spheroids, gliosis, and autofluorescent sudanophilic lipid-laden macrophages (table e-3, figure). Ultrastructural and immunohistochemical studies showed that the spheroids contain phosphorylated neurofilaments, ubiquitin, amyloid precursor protein, and mitochondria.^{5,9–11,22} Lesions predominate in the frontal lobe, variably in the parietal or temporal lobes, and in the descending pyramidal tracts at the midbrain, brainstem, and spinal cord levels. U-fibers are spared, as are the cortical mantle and the cerebellum. However, abnormalities in the frontal cortex have been described, including neuronal loss¹⁰ and ballooned neurons,⁷ and cerebellar atrophy may occur.⁴

In familial POLD, there is widespread myelin and axon destruction in a similar distribution, the distinctive feature being the presence of pigmented macrophages and other glia (table e-4, figure).^{3,16} The sudanophilic pigment is autofluorescent and stains with periodic acid-Schiff, Masson-Fontana coloration, and variably for iron. Ultrastructurally, the pigmented granules are similar to the lipopigment ceroid, with fingerprint, multilamellar, and granular morphology.

As pointed out by Marotti and colleagues,⁵ there are striking similarities between the POLD and HDLS pathologies. First, in several HDLS families, pigmented macrophages similar to those found in POLD can be

Figure Neuropathologic features of three patients

(A, B) Patient III-67 diagnosed with hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS). (C, D) New patient, a 31-year-old woman with a 6-year history of depression and personality changes, followed by dementia and seizures, who was diagnosed with features of HDLS and pigmentary orthochromatic leukodystrophy. (E, F) Patient IV-5,¹⁴ diagnosed with HDLS. Immunohistochemistry for amyloid precursor protein (APP; 22C11, Chemicon, Temecula, CA) (A) and neurofilament (NF; SMI-31, Sternberger Monoclonals, Lutherville, MD) (B), and staining with hematoxylin-eosin (H-E) (C) and Luxol fast blue (F) show axonal spheroids in the white matter of all three patients (arrows). Pigmented macrophages are seen on H-E (D, E, arrows) in two patients.

identified (figure),^{13,14} sometimes fulfilling the pathologic criteria for both diseases.^{5,8} Second, in a study of the original POLD family reported by Van Bogaert and Nyssen, Marotti and colleagues⁵ demonstrated the presence of numerous axonal spheroids, compatible with HDLS. This is consistent with several POLD families in which pathologic descriptions of axonal dilations correspond morphologically to spheroids.^{3,5,16,18}

PHYSIOPATHOLOGIC MECHANISMS In both HDLS and POLD, the mechanism of myelin and axonal damage remains unclear. Brain biopsy results from one of the patients described by Marotti and colleagues⁵ 2.5 years before postmortem examination may be instructive. Abundant spheroids were found on the biopsy, and much less at autopsy, favoring the hypothesis of a primary axonal disease. This view is supported by other authors.¹² In POLD, several authors have hypothesized a primary myelin defect,¹⁸ and this has recently gained some support by the finding of a defect in the myelin-associated glycoprotein in one family with OLD.²³ However, several authors have consistently reported markedly reduced number of oligodendroglial cells, particularly at the periphery of white matter lesions in HDLS and in POLD cases.^{6,24} These findings suggest a primary oligodendroglialopathy, with secondary myelin and axonal damage. This view is further supported by the reactive rather than dystrophic aspect of axonal spheroids.⁶

As in other neurodegenerative conditions such as Parkinson disease, the primary biochemical defect in

HDLS and POLD may involve oxidative stress.⁶ First, as pointed out by Ali and colleagues,⁶ the ceroid found in macrophages and other glia is thought to be an end-product of oxidative damage of various cellular compounds. Second, iron, also found in many HDLS and POLD cases, may increase levels of toxic free radicals, thus leading to cellular energy failure.

CLINICOPATHOLOGIC CORRELATION In both HDLS and POLD, the frontal predominance of white matter damage is consistent with prominent psychiatric and behavioral symptoms. The common frontotemporal dementia phenotype is also explained by this distribution, and by the associated temporal or parietal involvement. Neuropsychiatric symptoms in HDLS and POLD reflect the disconnection of the temporal, parietal, and occipital cortices from the frontal lobe, mainly affecting associative pathways (discussed in ¹³). Gait impairment likely has several pathologic correlations. In addition to spastic gait secondary to pyramidal tract lesions, frontal subcortical damage could produce lower body parkinsonism. Ataxia is often present even in patients without cerebellar involvement, which could reflect either minimal cerebellar damage, or diffuse cerebral white matter lesions. As in other leukodystrophies, seizures may be caused by diffuse or patchy white matter lesions.

GENETICS The genetic cause of HDLS and familial POLD remains unknown, and current families are

not large enough for powerful linkage studies. Mutations in one of the five subunits of eukaryotic translation initiation factor *eIF2B* have been causally implicated in vanishing white matter disease²⁵; however, a mutation in this gene was excluded in one HDLS family, as were mutations in the tau gene (*MAPT*).⁷ Similarly, duplications at the chromosome 5q23 locus containing three genes including the *LMNB1* gene were identified in families with adult-onset autosomal dominant leukodystrophy.^{26,27} The discrepant modes of inheritance of HDLS (autosomal dominant) and familial POLD (autosomal dominant or recessive) suggest both diseases are caused by distinct genetic defects. The implication of different genes in one clinicopathologic entity is not uncommon and is exemplified by Parkinson disease due to mutations in the *LRRK2* and *SNCA* genes. Alternatively, the apparent recessive inheritance in some POLD families may reflect reduced penetrance as suggested by the report of sporadic cases (see below).

SPORADIC FORMS Several sporadic patients have been described who fulfill clinical and pathologic criteria for HDLS except heritability.²⁸⁻³⁴ Similarly, most of the patients with POLD reported so far are sporadic.^{1,19,22,24,35-41} Until the genetic basis for familial aggregation is identified, it remains unknown whether these sporadic cases truly are sporadic or reflect reduced disease penetrance. Conversely, the genetic cause of POLD and HDLS may include the interplay of several genetic factors, some of which may be lacking in sporadic cases.

NOSOLOGIC CONSIDERATIONS In a comparative morphologic study of 5 patients with HDLS and 10 patients with POLD, Ali and colleagues⁶ reported no distinctive pathologic features between the two diseases. In particular, they found spheroids, iron, and ceroid accumulation in the white matter of patients with HDLS and patients with POLD. Further, Marotti and colleagues⁵ reviewed the literature of reported POLD cases, and found descriptions of axonal spheroids in most of them. This adds to the striking clinical similarities between familial POLD and HDLS discussed in the present review (table). Familial POLD and HDLS have more similarities than differences, and likely belong to the same disease spectrum. In addition, the myelinic, axonal, or oligodendroglial origin of white matter disruption remains contentious, thereby complicating the distinction between leukodystrophy (POLD) and leukoencephalopathy (HDLS). As suggested before, evidence supports HDLS and POLD being collec-

tively referred to as adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP).⁶

CONCLUSIONS There is compelling evidence that HDLS and familial POLD belong to the same disease spectrum. Grouping them together as ALSP may foster their heightened recognition as it is conceivable that they are underrecognized. In so doing, identifying their genetic causes may be enhanced.

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