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ORIGINAL CONTRIBUTION

Clinical Symptoms of Adult Metachromatic Leukodystrophy and Arylsulfatase A Pseudodeficiency

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Objective: To determine the clinical symptoms in adult metachromatic leukodystrophy and in adult pseudodeficiency for arylsulfatase A.

Design: Case series.

Setting: University hospital.

Patients: Twenty-five adult patients with very low arylsulfatase A activity.

Results: In 13 patients, a diagnosis of adult metachromatic leukodystrophy was made. The main symptoms were dementia, behavioral abnormalities, ataxia, and polyneuropathy. In 12 patients, a diagnosis of arylsulfatase A pseudodeficiency was made. No characteristic clinical syndrome could be detected in these patients.

Conclusions: Adult metachromatic leukodystrophy is a progressive metabolic disease with symptoms of demyelination of the central and peripheral nervous systems. Diagnosis must be confirmed by determination of arylsulfatase A activity and accumulation of sulfatides. Pseudodeficiency for arylsulfatase A can be confirmed or excluded by means of DNA analysis.

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METACHROMATIC leukodystrophy (MLD) is an autosomal recessive lysosomal disorder characterized by demyelination of the white matter in the central nervous system and the peripheral nerves. The gene is located on chromosome 22q13.[1] Accumulation of sulfatides can be found in the brain, peripheral nerves, and nonneural organs. The disease is caused by a deficiency of the enzyme arylsulfatase A (ASA), which hydrolyzes various sulfatides, including galactosyl sulfatide and lactosyl sulfatide, the major sulfate-containing lipids of the nervous system. The diagnosis of MLD is based on decreased ASA activity in leukocytes or fibroblasts and accumulation of sulfatides in urinary sediment or various tissues, eg, sural nerve.

Clinically different forms of MLD can be distinguished according to the severity and the age at onset of the disease. The late-infantile form (age at onset, 1 to 2 years) is characterized by gait and behavioral disturbances; the disease course is rapid and the outcome is fatal.[2] The juvenile form of MLD (age at onset, 3 to 15 years) has a more protracted course.[3] The adult form of MLD (age at onset older than 16 years) has a slowly progressive course. Compared with the late-infantile and juvenile forms of MLD, the adult variant appears to be quite rare. Until now, to our knowledge, only 24 patients with adult MLD have been described in the literature. In these patients, a low ASA level was accompanied by accumulation of sulfatides.[4-6]

The determination of ASA deficiency alone is insufficient for a diagnosis of MLD, because a pseudodeficiency (PD) state has also been observed.[7] In the PD state, low ASA activity is not accompanied by accumulation of sulfatides in the organs, because the residual activity is supposedly sufficient to ensure normal sulfatide metabolism. This PD state is a common genetic polymorphism, with an estimated gene frequency of 7.3% in central Europe,[8] and is caused by a mutation affecting the polyadenylation of the ASA mRNA.[7]

Until now, eight different MLD alleles have been described.[9] The three dif-

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PATIENTS AND METHODS

During the period from 1972 to 1992, 25 patients aged older than 16 years were found to have very low ASA activity in the leukocytes, ranging from 1 to 25 nmol/h per milligram of protein (reference range, 35 to 110 nmol/h per milligram of protein).

PATIENTS WITH MLD

The diagnosis of MLD was confirmed in 13 patients by morphologic demonstration of storage material in the sural nerve or brain and/or increased amounts of sulfatides in urinary sediment (**Table 1**). Two patients (patients 2 and 3) have been described previously.[10] In patient 3, ASA activity was not determined, but we can be sure of the diagnosis because he was the brother of patient 2; they presented with similar clinical features, and a postmortem neuropathologic examination revealed accumulation of sulfatides in the brains of both patients. A survey of technical measurements performed in the patients with adult MLD is presented in Table 1. Electromyography (EMG) was performed in 11 patients, and analysis of cerebrospinal fluid was performed in 10 patients. Neither computed tomography (CT) nor magnetic resonance imaging (MRI) was available during the lifetime of patients 1 through 4. Peripheral nerve biopsy specimens from four patients (patients 2, 4, 5, and 6) were studied in our department, and the morphologic changes were compared with the features in late-infantile and juvenile cases. Pathologic examination of the sural nerve of patients 9, 12, and 13 was performed in other hospitals.

PATIENTS WITH PD

Twelve patients with low ASA activity were found to be homozygotic for the PD mutation. Lysosomal enzyme determination in these patients was requested based on progressive neurologic or psychiatric signs and symptoms of unknown etiology. Examination of the sural nerve was performed in two patients. In the other 10 patients, biopsy was not performed because they showed no neurophysiologic or radiologic symptoms of leukodystrophy, and DNA analysis for PD became available. In all patients, DNA analysis was performed. In three patients, urinalysis was performed. Ten patients underwent EMG, nine underwent CT, and three underwent MRI. The cerebrospinal fluid from five patients was analyzed.

Arylsulfatase A activity was measured in leukocyte supernatants after sonification with use of *p*-nitrocatecholsulfate as substrate, as described by Galjaard.[11] Urinary sulfatides were extracted from sediments, separated by thin-layer chromatography from other glycolipids, and estimated semiquantitatively after naphthol staining. Leukocyte genomic DNA was initially typed for the PD allele by the method of Gieselmann[12] and later by the method of Nelson et al.[13]

ferent forms of the disease can be explained by the existence of two types of alleles: type 0 alleles without and type R alleles with some residual activity. Homozygosity for type 0 alleles is associated with the late-infantile form. Homozygosity for the type R alleles is present in adult forms, while type 0/type R compound heterozygotes have intermediate (juvenile) phenotypes.[9]

Herein, we describe 25 adult patients with low ASA activity. In 13 patients, the diagnosis of adult MLD was confirmed by demonstration of sulfatide accumulation. In 12 patients, no accumulation could be demonstrated. In the latter group, a diagnosis of PD was established by means of DNA analysis. The data from both groups are compared with data from the literature.

RESULTS

The range of ASA activity in the leukocytes of the 13 patients with adult MLD was 1 to 12 nmol/h per milligram of protein (reference range, 35 to 110 nmol/h per milligram of protein) (**Figure 1**). The mean age at onset in the adult MLD group was 23 years (range, 16 to 31 years). The presenting clinical symptoms were behavioral abnormalities (n=4), ataxia (n=4), polyneuropathy (n=2), dementia (n=2), and paraparesis (n=1) (**Table 2**). The behavioral abnormalities consisted of aggressiveness, irritability, impaired social awareness, and inappropriate behavior. The interval between age at onset and age of occurrence of the second symptom was, on average, 3.7 years (range, 1 to 20 years). The third symptom occurred, on average, 2.0 years (range, 0 to 7 years) after the second symptom. The development of the main symptoms is graphically presented in **Figure 2**. In the final stage of the disease, most of the patients were suffering from mental deterioration (n=10) and showed severe ataxia (n=8) and behavioral abnormalities (n=6). Three patients developed epilepsy. None of the patients became psychotic, except for patient 3, who suffered from auditory hallucinations. Plantar response was flexor in six patients and extensor in seven patients. In three patients, paraparesis was evident.

All of the patients with MLD who underwent EMG showed a slowing of the nerve conduction velocities (NCVs) (Table 1). The mean NCV of the peroneal nerve was 24.4 m/s (range, 15 to 39 m/s; reference range, 44 to 57 m/s).

Neuropathologic examination of the sural nerve in three patients (patients 2, 4, and 5) revealed, with acidic cresyl violet staining, the presence of brown metachromatic deposits in Schwann cells and in large perivascular macrophages. A process of segmental demyelination and remyelination with slight onion bulb formation was present, but this was less active than in the late-infantile and juvenile forms, and myelinated fiber density was only slightly reduced, in contrast to the more pronounced reduction in the earlier-onset cases. Myelin sheath thickness was clearly reduced, especially that of the large fibers. In patient 6, the myelinated fiber density, the percentage of large fibers, and the myelin thickness were normal. There were few signs of segmental demyelination and remyelination, but accumulation of metachromatic material was in the same range as in most adult and juvenile cases. Ultrastructural examination in all four patients revealed various types of inclusions, mainly lamellar zebralike bodies and tuffstone bodies. The specimens from the three patients whose biopsies were per-

Table 1. Technical Measurements in 13 Patients With Adult Metachromatic Leukodystrophy*

Variable	Patient 1	2	3	4	5	6	7	8
Sex	F	M	M	F	F	F	M	M
Age at onset, y	30	27	26	29	21	16	18	20
ASA activity, nmol/h per mg of protein								
Leukocytes (reference range, 35-110)	2	4	ND	1	3	4	10	3
Fibroblasts (reference range, 270-770)	ND	ND	ND	11	75	25	ND	19
Accumulation of sulfatides	Brain	Brain, sural nerve	Brain	Sural nerve	Sural nerve	Sural nerve	Urine	Urine
CT findings	ND	ND	ND	ND	Hypodensities	Hypodensities	Hypodensities	Hypodensities
MRI findings	ND	ND	ND	ND	ND	ND	ND	ND
CSF protein, g/L (reference range, 0.18-0.58 g/L)	ND	0.38	0.34	ND	0.50	0.26	0.50	ND
NCV of peroneal nerve, m/s (reference range, 44-57 m/s)	ND	15	ND	30	24	39	24	27

**ASA indicates arylsulfatase A; ND, not done; CT, computed tomographic; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; and NCV, nerve conduction velocity.*

formed in other hospitals were not available for review, but accumulation of metachromatic material was reported in all of them.

Computed tomography was performed in nine patients and revealed areas of hypodensity in the white matter, especially in the frontal lobes. Magnetic resonance imaging was performed in three patients and showed diffuse demyelination of the periventricular white matter (**Figure 3**).

Analysis of cerebrospinal fluid from 10 patients revealed normal (n=7) or slightly elevated (n=3) protein levels (range, 0.26 to 0.73 g/L) (reference range, 0.18 to 0.58 g/L).

At the time of this writing, nine of these patients have died. On average, death occurred 9.8 years (range, 3 to 24 years) after onset of the disease. Four patients are still alive an average of 16 years (range, 11 to 27 years) after disease onset.

In the 12 other patients with very low ASA activity, DNA analysis revealed homozygosity for the PD allele. The ASA activity in this group ranged from 6 to 25 nmol/h per milligram of protein. The levels of ASA activity for both groups are presented in Figure 1. The complaints of these patients were memory disturbances (n=6), ataxia (n=2), fatigue (n=2), tremor (n=1), and loss of vision (n=1). These patients were not related to patients known to have MLD. One patient was found to have multiple sclerosis, one was found to have Parkinson's disease, one was found to have Huntington's disease, and one was found to have an ischemic optic neuropathy. Neurologic and neuropsychological examinations of the six patients with memory complaints revealed no abnormalities. In addition, EMG, CT, and MRI yielded normal findings, while no evident abnormalities were found in the cerebrospinal fluid, with the exception of an elevated IgG index and oligoclonal bands in the patient with multiple sclerosis. Analysis of the urine revealed no evidence of accumulation of sulfatides. A sural nerve biopsy was performed in two patients with PD. In one, no abnormalities were found. In the second, acidic cresyl violet staining revealed a few deposits of brown metachromatic material perinuclearly in Schwann cells in addition to signs of chronic axonal degeneration and regeneration. The ASA activity in this patient was 10 nmol/h per milligram of protein.

COMMENT

We describe the signs and symptoms of 13 patients with adult MLD who demonstrated low ASA activity and accumulation of sulfatides and of 12 patients with PD. Until now, only 25 patients with confirmed adult MLD have been described in the literature. In 1991, the clinical signs and symptoms of 23 patients with MLD described in the literature were reviewed by Baumann et al.[4] One patient from their review was not included in our analysis because he was already included as patient 2 in the present study. Recently, two other patients with confirmed MLD have been described.[5,6] Table 2 summarizes the presenting symptoms of our patients with adult MLD and the symptoms of the disease in the developed state; it also outlines the clinical symptoms of the patients described in the literature. The mean age at onset in our patients was 23 years (range, 17 to 31 years), comparable with that reported in the literature (mean age at onset, 24 years; range, 16 to 62 years). Most of the patients described were younger than age 40 years at onset, with one exception, an elderly patient with an age at onset of 62 years.[14]

The most common presenting symptoms described in the literature are mental deterioration and behavioral abnormalities (Table 2). In our group, the most common presenting symptoms were ataxia and behavioral abnormalities, and only two of our patients presented with mental deterioration. In the early stages of the disease, the patients were not evaluated with neuropsychological testing, so we cannot rule out that the behavioral abnormalities represent early manifestations of

9	10	11	12	13
F	F	M	F	F
19	17	31	20	23
3	4	3	12	7
16	ND	14	43	ND
Sural nerve	Urine	Urine	Sural nerve	Sural nerve
Hypodensities	Hypodensities	Hypodensities	Hypodensities	Hypodensities
ND	Demyelination	Demyelination	Demyelination	ND
0.64	0.32	0.73	0.61	0.58
20	20	29	17	23

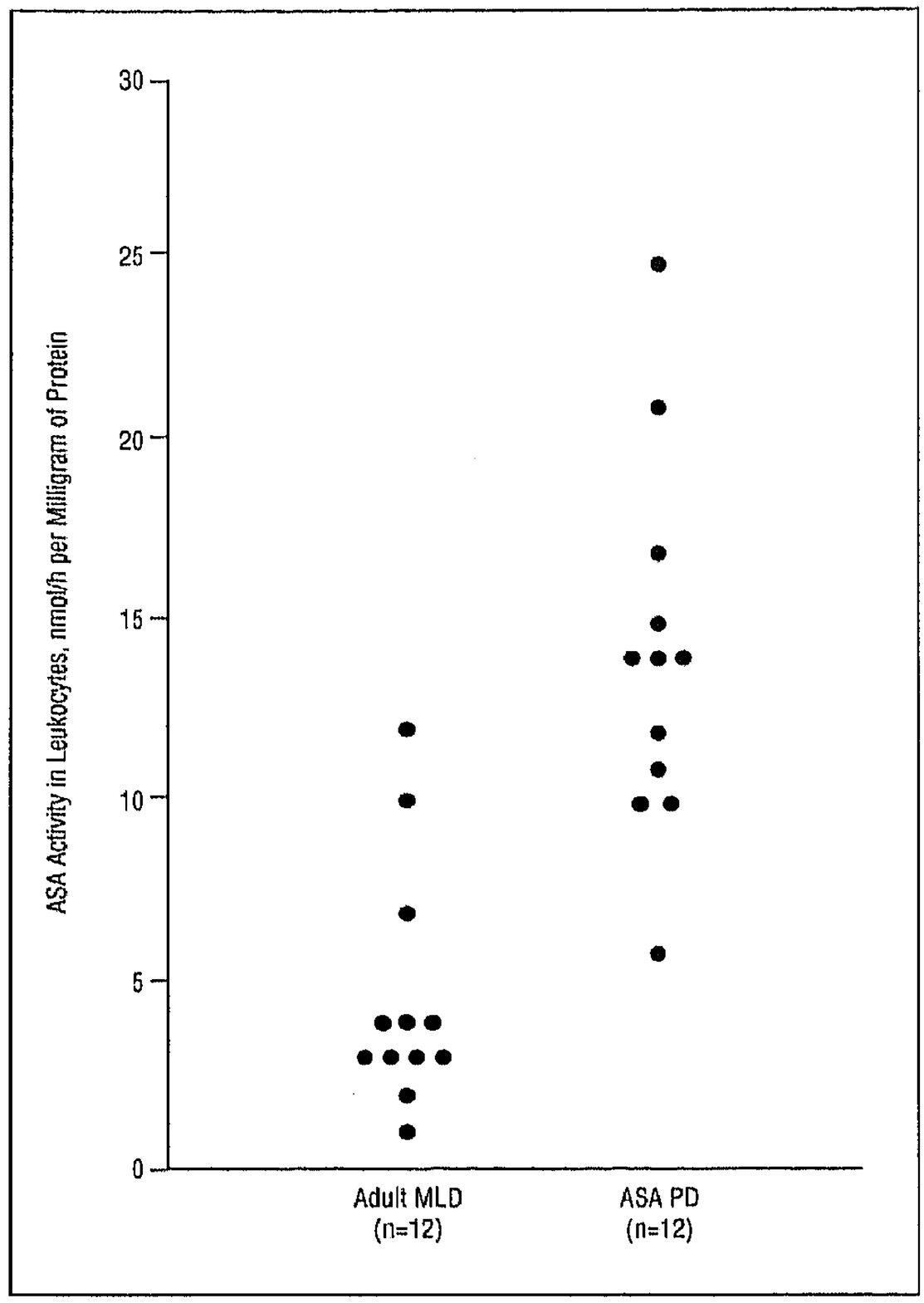

Figure 1. *Arylsulfatase A (ASA) activity in the leukocytes of patients with adult metachromatic leukodystrophy (MLD) and ASA pseudodeficiency (PD) (reference range, 35 to 110 nmol/h per milligram of protein).*

mental deterioration. Compared with late-infantile MLD, in which the motor symptoms predominate in the early stage,[1] it seems that a combination of mental and behavioral symptoms and ataxia predominate in the adult form of MLD.

The course of the disease is slowly progressive, and the variability in progression is remarkable. Sometimes the patients developed the second and third symptom within 1 year. On the other hand, in one patient, the second symptom did not become evident for 20 years. In the developed state of the disease, most of the patients showed mental deterioration, and about half exhibited behavioral abnormalities and ataxia. Sometimes behavioral abnormalities and dementia[15] or polyneuropathy[6] are the only symptoms for many years; this might be why adult MLD is probably underdiagnosed. As in late-infantile and juvenile MLD, epilepsy tends to be a late feature.[2] Only one of the 13 patients became psychotic. On the other hand, in a review of the literature, Hyde et al[16] suggested that in 53% of patients with adult MLD, psychosis is present and often the initial manifestation. In most of these patients, however, only ASA activity was determined, while sulfatide accumulation was not demonstrated, and DNA analysis to exclude PD was not performed. Of the group of 24 patients with confirmed MLD in the literature, only four were psychotic.[5,17-19] Apparently, psychosis is a less common symptom than formerly suggested.

The course of adult MLD is not as rapidly fatal as the late-infantile and juvenile forms of MLD. Although some of our patients are still alive, we have calculated the mean survival to be at least 12 years, which is longer than the survival in late-infantile MLD (3 to 4 years[2]) and juvenile MLD (7 to 9 years).[2,3]

In all the patients who underwent cerebral CT, bilateral areas of hypodensity were found in the white matter, especially in the frontal lobes. In addition to the areas of hypodensity, cerebral atrophy can be seen as a result of the loss of myelin.[20] In the three patients who underwent MRI of the brain, the areas of hypodensity were more diffuse and pronounced than on CT scans (Figure 3). Analysis of the cerebrospinal fluid revealed normal protein levels in seven patients and only slightly elevated protein levels in three patients, which is in contrast with late-infantile and juvenile MLD, in which the CSF protein level is usually more markedly elevated (0.44 to 2.25 g/L).[2,3]

Polyneuropathy is seldom the first clinical symptom (Table 2). Only two of our 13 patients showed overt clinical symptoms of polyneuropathy. The NCVs, on the other hand, were markedly slowed in all of our patients, suggesting a demyelinating process. In the literature, only one patient with adult MLD with normal NCVs has been described.[21] The decreased NCVs in the peroneal nerve (mean, 24.4 m/s; range, 15 to 39 m/s) is not so marked as in late-infantile MLD (range 0 to 30 m/s) or in juvenile MLD (range, 10 to 28 m/s).[2]

In adult MLD, the process of segmental demyelination in the peripheral nerves is less active than in the juvenile and especially the late-infantile forms. The amount of metachromatic deposits does not differ clearly from that of the juvenile form. The moderate to marked slowing of NCVs in adult MLD is in accordance with the pathologic changes in the nerve biopsy specimen indicating demyelination and reduction of myelin sheath

Table 2. Clinical Symptoms in Adult Metachromatic Leukodystrophy

	At Presentation			Developed		
	Patients (n=13)	Literature (n=24*)	Total (%) (N=37)	Patients (n=13)	Literature (n=24*)	Total (%) (N=37)
Dementia	2	13	**15** (40.5)	10	21	**31** (83.8)
Behavioral abnormalities	4	8	**12** (32.4)	6	8	**14** (37.8)
Ataxia	4	4	**8** (21.6)	8	12	**20** (54.1)
Paraparesis	1	3	**4** (10.8)	3	9	**12** (32.4)
Polyneuropathy	2	2	**4** (10.8)	2	2	**4** (10.8)
Epilepsy	0	1	**1** (2.7)	3	6	**9** (24.3)
Psychosis	0	0	**0** (0)	1	4	**5** (13.5)

**Patients from the literature include those described by Baumann et al,[4] Sadeh et al,[5] and Fressinaud et al.[6]*

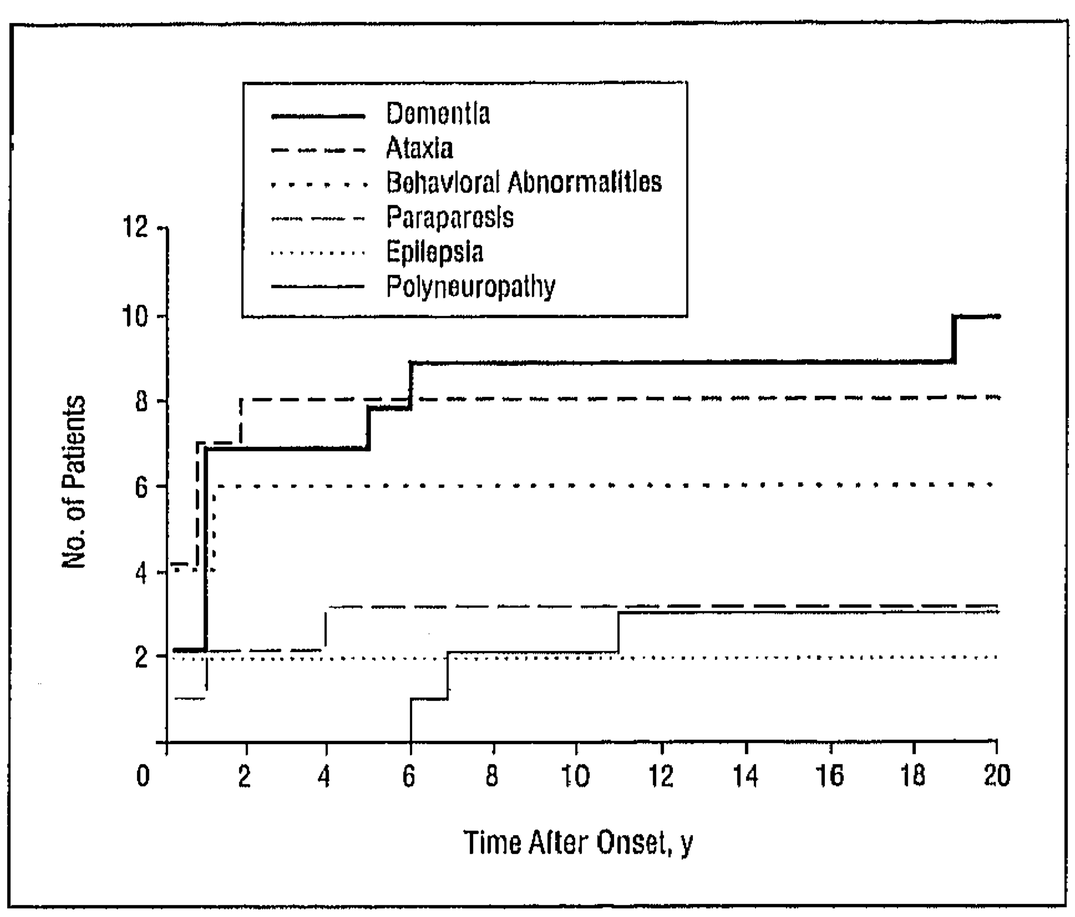

Figure 2. *Development of clinical symptoms in 13 patients with adult metachromatic leukodystrophy.*

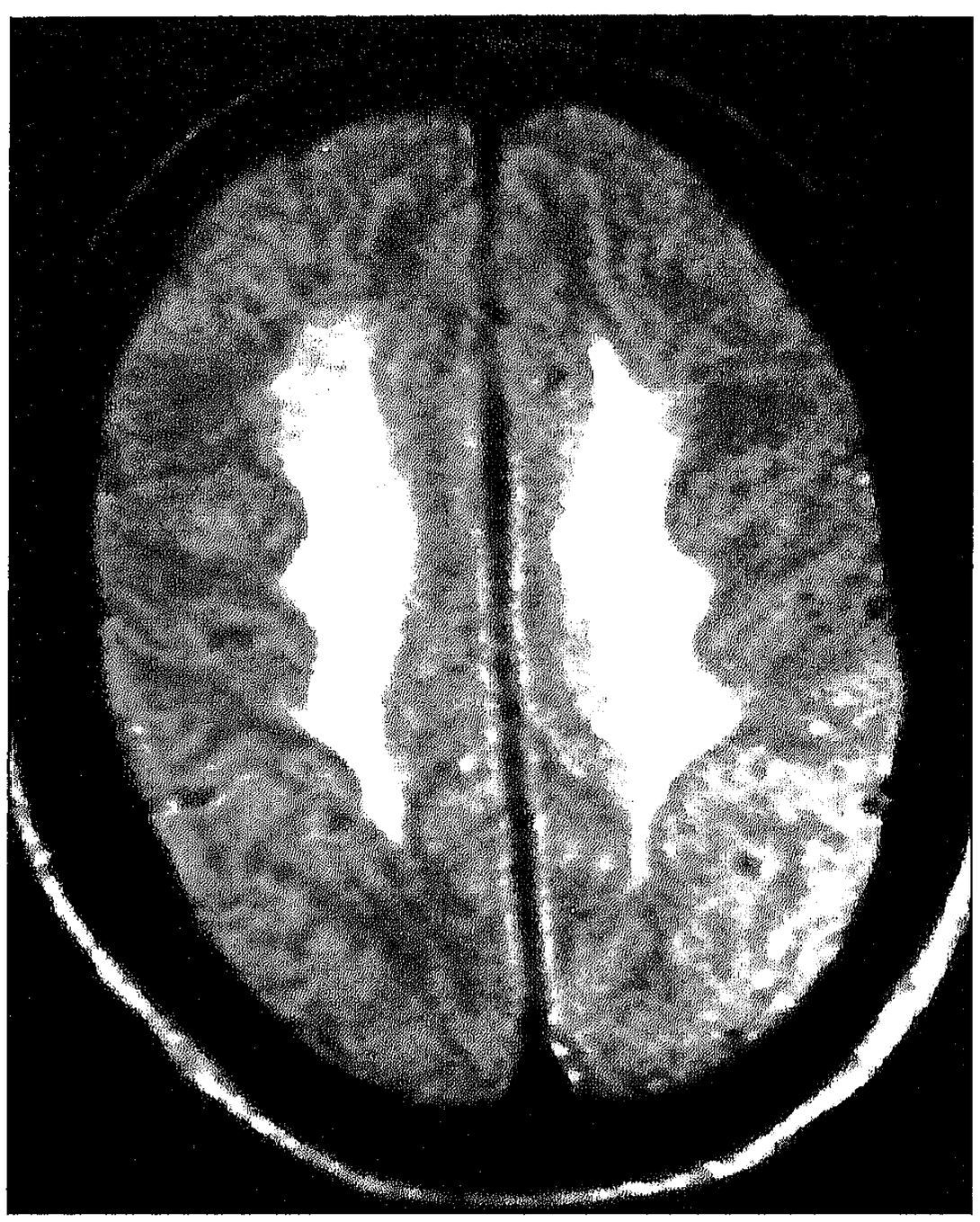

Figure 3. *Magnetic resonance image of a patient with adult MLD, showing diffuse demyelination of the white matter.*

thickness.[22-25] In one patient (patient 6) who showed the best-preserved NCVs in our series of patients with adult MLD, accumulation of sulfatides could be seen on light and electron microscopic examination, but signs of a demyelinating process were minimal, no substantial fiber loss had occurred, and sheath thickness was normal. Comparable findings were reported by Martin et al[26] in a patient with adult MLD with moderate slowing of NCVs whose nerve biopsy specimen revealed mild demyelination and normal sheath thickness. On the other hand, Fressinaud et al,[6] in their report of a patient with adult MLD with an isolated neuropathy, noted marked slowing of NCVs and conduction blocks, as well as widespread demyelinating lesions in the nerve biopsy specimens. There are apparently marked differences in the severity of the neuropathy within the group of patients with adult MLD. This is also reflected by the electrophysiologic and morphologic features. No correlation exists between the NCV and the amount of storage material in the peripheral nerve.

Treatment of late-infantile MLD with bone marrow transplantation has produced conflicting results,[1] but incidental success has been claimed in a few patients whose motor and cognitive development were almost normal during several years after bone marrow transplantation.[27,28] As far as we know, bone marrow transplantation has not been reported in cases of adult MLD.

In the 12 patients with PD, no characteristic clinical syndrome could be detected. An association with multiple sclerosis[29] and dystonia[30] has been suggested, but no causal relationship has been proved. Only one of our patients with PD turned out to have multiple sclerosis. The symptoms and signs of the other 11 patients revealed no abnormalities as seen in MLD, suggesting that PD is not related to demyelination of the central or peripheral nervous systems. In the sural nerve of one patient, small amounts of metachromatic material were found. Chronic axonal degeneration of undetermined cause may have induced a slight accumulation of sulfatides owing to an increased turnover of myelin and low ASA activity (10 nmol/h per milligram of protein) in this patient. Unfortunately, EMG, CT, MRI, or urinary sul-

fatide determination were not performed in this patient, and the patient is unavailable for further studies. That this patient has an as yet unobserved MLD mutation in his ASA gene in addition to the PD mutation cannot be excluded.

An overlap exists between the ASA activity levels of patients with MLD (1 to 12 nmol/h per milligram of protein) and patients with PD (6 to 25 nmol/h per milligram of protein) (Figure 1), confirming that determination of ASA activity level is not sufficient for differentiation between MLD and PD. In patients aged 17 to 40 years with progressive symptoms of mental deterioration, behavioral abnormalities, or ataxia, in combination with hypomyelination of the central nervous system and slowing of NCVs, a diagnosis of MLD should be considered. Diagnosis of adult MLD can be confirmed by determination of ASA activity in leukocytes or fibroblasts and accumulation of sulfatides in different tissues or urine, and PD should be confirmed or excluded by means of DNA analysis.

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Conversion From Système International (SI) Units to Traditional Units (Modified From *The SI Manual in Health Care*)

System	Component	SI Reference Interval*	SI Unit	Conversion Factor (Divide by)	Traditional Reference Interval*	Traditional Unit
Cerebrospinal fluid	Protein, total	<0.40	g/L	0.01	<40	mg/dL

**These reference values are not intended to be definitive since each laboratory determines its own values. They are provided for illustration only.*