

MR Findings in Adult-Onset Adrenoleukodystrophy

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PURPOSE: To describe the MR findings of brain and spinal cord in adult-onset adrenoleukodystrophy. **METHODS:** One hundred sixty-four adult patients ranging from 19 to 74 years of age (119 men and 45 women) with clinically and biochemically proved adrenoleukodystrophy underwent MR of the brain. In 30 patients the spinal cord also was evaluated with MR. **RESULTS:** The brain MR findings were abnormal in 54 of 119 males and in 9 of 45 female heterozygotes and consisted of varying degrees of demyelination of the cerebral white matter in 40 patients, corpus callosum in 25 patients, corticospinal tracts in 46 patients, visual tracts in 31 patients, and auditory tracts in 18 patients. The thoracic spinal cord showed diffuse atrophy in 18 of 20 men and in 8 of 10 women. **CONCLUSION:** It is important to recognize the MR findings of adult-onset adrenoleukodystrophy, because not uncommonly the clinical and MR findings of adrenoleukodystrophy are misdiagnosed as multiple sclerosis, olivopontocerebellar or spinocerebellar atrophy, amyotrophic lateral sclerosis, or dementia. Analysis of the MR findings and correlation of the clinical findings has permitted a tentative subdivision of adult-onset adrenoleukodystrophy population into four subtypes that appear to differ in respect to prognosis and possibly pathogenesis. MR evaluation of the brain in adrenoleukodystrophy also is helpful in patient selection for experimental therapy, which is most effective if offered in the early stage of the disease.

Index terms: Adrenoleukodystrophy; Brain, magnetic resonance; Spinal cord, magnetic resonance

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Adrenoleukodystrophy (ALD) is an X-linked disorder that involves mainly the nervous system white matter, the adrenal cortex, and the testis (1). It is associated with the abnormal accumulation of very long chain saturated fatty acids in the brain and adrenal gland (2), red blood cells (3), and plasma (4) attributable to impaired capacity of peroxisomes to degrade them (5). The defective gene has been isolated

recently. It maps to Xq28, the terminal segment of the long arm of the X chromosome, and codes for a peroxisomal membrane protein (6).

The phenotypic expression of ALD varies widely. It ranges from the most severe childhood cerebral form, which often is fatal during the first decade of life (7), to milder adult forms that are compatible with survival to the eighth decade (8). The childhood cerebral phenotype has a mean age of onset of 7.1 years and often leads to an apparently vegetative state within 2 years and death at various times thereafter. It is associated with large regions of demyelination in the cerebral hemispheres.

The adult neurologic variants of ALD, which are the topic of this paper, affect approximately 30% of the males and 15% to 20% of female heterozygotes. Adrenomyeloneuropathy (AMN) is the most common form (9). It involves mainly the spinal cord and peripheral nerves, and the inflammatory response in cerebral white matter is mild or absent. Mean age of onset is 27.6 years, with spasticity and weakness of the legs and sphincter and sexual dysfunction that progress slowly over decades. Adrenal insuffi-

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TABLE 1: Pattern of brain involvement in 54 adult male ALD patients

Brain Region or Tract	ALMN 1 (n = 16)	ALMN 2 (n = 32)	Adult Cerebral (n = 3)	OPCA-like (n = 3)	Total (n = 54)
Cerebral hemisphere	2	32	3	3	40 (74%)
Frontal lobes	0	11	0	2	13
Temporal lobes	0	14	2	1	17
Parietooccipital lobes	2	27	3	3	35
Atrophy	1	10	1	3	15
Corpus callosum	0	19	3	3	25 (46%)
Cerebellum					
Demyelination	1	2	2	0	5 (8%)
Atrophy	0	2	2	3	7
Visual tract	4	22	3	2	31 (57%)
Auditory tract	2	14	2	0	18 (33%)
Corticospinal tract	16	24	3	3	46 (85%)

Note.—ALMN indicates adrenoleukomyeloneuropathy and OPCA, olivopontocerebellar atrophy.

ciency may be noted before or concurrent with the neurologic disturbance, although adrenal function is normal in up to 30% of AMN patients. About 50% to 60% of AMN patients also show subtle neuropsychological abnormalities, most commonly with the pattern of subcortical dementia (10). The purpose of this paper is to describe magnetic resonance (MR) findings in adult-onset ALD and to categorize them into four subgroups. MR has helped in choosing proper patient selection to evaluate the efficacy of dietary interventions (8, 11–12).

Patients and Methods

One hundred sixty-four adult patients (119 symptomatic men and 45 symptomatic women) with clinically and biochemically proved ALD underwent MR imaging of the brain; in 30 patients (20 men and 10 women) MR of the spine also was performed. The patients were recruited from a pool of 571 families with ALD around the world. The patients were selected on the basis of their willingness to participate in the research therapy and their physical capacity to make frequent follow-up examinations to our institution.

One hundred forty-eight (90%) patients were examined in the Department of Radiology using a high-field 1.5-T General Electric Signa system. The imaging protocol for spin-echo T1-weighted sagittal images was 600/20/2 (repetition time/echo time/excitations) and for axial proton density-weighted images and T2-weighted images was 3000/30-100/2 with a section thickness of 5 mm and a 2.5-mm gap. In some patients additional coronal sections were obtained. The spin-echo multisection images were generated by two-dimensional Fourier transformation with a 256 × 256 matrix (256 × 192 matrix in a minority of cases) with a field of view of 24 cm and flow compensation. A small number of patients were examined using different scanners in various institutions with similar techniques.

MR imaging of the thoracic spinal cord was performed in 20 men and 10 women using a license plate surface coil. Sagittal T1-weighted images of the thoracic spine were obtained using a parameter of 600/20/2, with a thickness of 3 mm, 256 × 256 matrix, and a 26-cm field of view. Five-millimeter section thickness was used for the axial T1-weighted images with a field of view of 16 to 18 cm. Proton density-weighted and T2-weighted axial (5-mm section thickness) and sagittal (3-mm section thickness) images of the thoracic cord were obtained using a parameter of 3000/30-100/4 and 256 × 192 or 256 matrix with flow compensations. Because the thoracic cord bears the major brunt in AMN patients, the cervical cord was examined only in 10 patients using a similar protocol. In addition, in 1 patient, the thoracic and cervical cord was examined using a long-repetition-time fast spin-echo sequence. The parameters for the sagittal plane were 3000/100/4 with a section thickness of 4 mm, 512 × 256 matrix, and echo train of 16, and for axial plane were 4800/96/4 with a section thickness of 5 mm, 512 × 256 matrix, and echo train of 14.

The white matter lesions of the brain were recognized on MR as areas of bright signal intensity on both proton density-weighted and T2-weighted images. The diagnosis of thoracic spinal cord atrophy was based on computer measurements of the cord and subarachnoid space by placing a cursor around the margins of these structures on images as seen on the television console. The thoracic spinal cord was rated as markedly atrophic when it measured less than 30% of subarachnoid space, moderately atrophic when it measured 30% to 40% of subarachnoid space, and borderline atrophy when it measured 40% to 50% of subarachnoid space.

The MR images were read by two independent viewers (A.K., W.K.) who were not involved in the patients' treatment. Abnormalities of the brain were subdivided into different patterns of changes (lobar white matter involvement versus tract involvement) and the frequency of structural abnormality of the brain in each category (Table 1). The mean age at baseline examination was 35.2 years (± 10.9 SD) in the men and 47 years (± 10 SD) in the women,

ranging from 19 to 74 and 32 to 73 years, respectively. The mean age of onset of neurologic symptoms was 28.4 years (± 8.3 SD) in the men and 38 years (± 10 SD) in the women. All patients underwent a detailed clinical examination by a neurologist and psychomotor analysis by a clinical psychologist.

Results

The most common clinical presentation of all male patients are symptoms related to varying degrees of spinal cord affliction by this disorder.

The majority of male patients with AMN had progressive spastic paraparesis, hyperreflexia, and impaired vibration sense in the more distal aspect of the lower extremities and bladder-bowel or sexual dysfunction. Somatosensory evoked responses were abnormal in all patients. Twenty percent of the female heterozygotes had neurologic disability that resembled AMN but is somewhat milder and of later onset. Psychopathologic abnormalities were

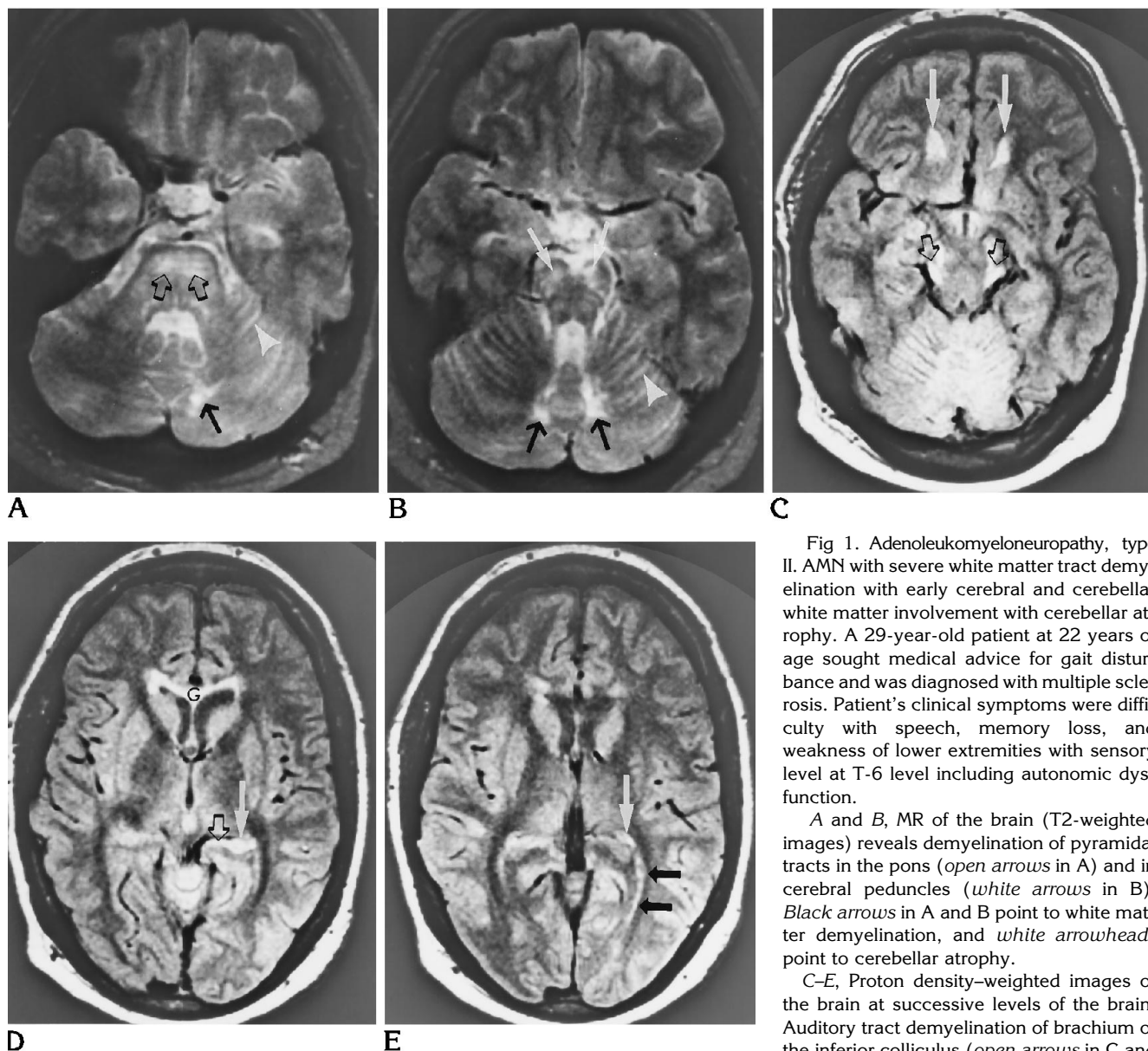


Fig 1. Adenoleukomyeloneuropathy, type II. AMN with severe white matter tract demyelination with early cerebral and cerebellar white matter involvement with cerebellar atrophy. A 29-year-old patient at 22 years of age sought medical advice for gait disturbance and was diagnosed with multiple sclerosis. Patient's clinical symptoms were difficulty with speech, memory loss, and weakness of lower extremities with sensory level at T-6 level including autonomic dysfunction.

A and B, MR of the brain (T2-weighted images) reveals demyelination of pyramidal tracts in the pons (*open arrows* in A) and in cerebral peduncles (*white arrows* in B). *Black arrows* in A and B point to white matter demyelination, and *white arrowheads* point to cerebellar atrophy.

C-E, Proton density-weighted images of the brain at successive levels of the brain. Auditory tract demyelination of brachium of the inferior colliculus (*open arrows* in C and

D) as it joins the demyelinated medial geniculate body (*large arrow* in D) is beautifully depicted. Visual pathway demyelination involving lateral geniculate body (*arrow*) and optic radiations (*black arrows*) is shown in E. Lobar white matter demyelination: In addition to specific tract demyelination, focal frontal lobe white matter demyelination (*white arrows* in C) and cerebellar white matter demyelination (*black arrows* in A and B) are observed. Genu of the corpus callosum (G in D) show demyelination. Cerebellum show diffuse atrophy (*white arrowheads* in A and B).

present in 50% to 60% of the patients and ranged from slightly abnormal behavior to severe dementing illness (10). Detailed clinical description of our patients and results of neurophysiologic testing have been reported elsewhere (8, 11, 13).

The brain MR findings were abnormal in 54 (46%) of the 119 male AMN patients and in 9 (20%) of the 45 female heterozygotes. The spinal cord findings were abnormal in 18 of 20 men and in 8 of the 10 women examined. MR abnormalities of brain and spinal cord in 7 patients are illustrated in Figures 1 through 7.

Brain Abnormalities in Male AMN Patients (Table 1)

Among the 54 men with brain MR abnormalities, involvement of the corticospinal tract was the most common finding. Eighty-five percent of these patients showed bilateral increased signal intensities in the projections of the cortico-

spinal tract fibers in the pons (Fig 1A), cerebral peduncles (Fig 1B), and internal capsule (Figs 2C and 3D). Demyelinating lesions in the visual pathway, mostly the optic radiations (Figs 2B, 4B, 1E, 3C) and lateral geniculate body (Fig 1E), were found in 31 (57%) patients. Auditory pathway involvement was observed in 18 (33%) patients. The involvement of auditory pathways, as demonstrated by MR images, included lesions of the lateral lemnisci (Fig 3B), brachium of the inferior colliculus (Fig 1C and D), medial geniculate body (Fig 1D), and acoustic radiations (Fig 3C).

Spinothalamic tract demyelination can be identified as the tracts go through the thalamic nuclei (Fig 2B), but at times it was difficult to distinguish between the spinothalamic and the corticospinal and audiovisual pathways as the tracts merge with each other.

Cerebral lobar involvement, resembling that seen in childhood ALD was present in 40 patients. As is true in the childhood cerebral

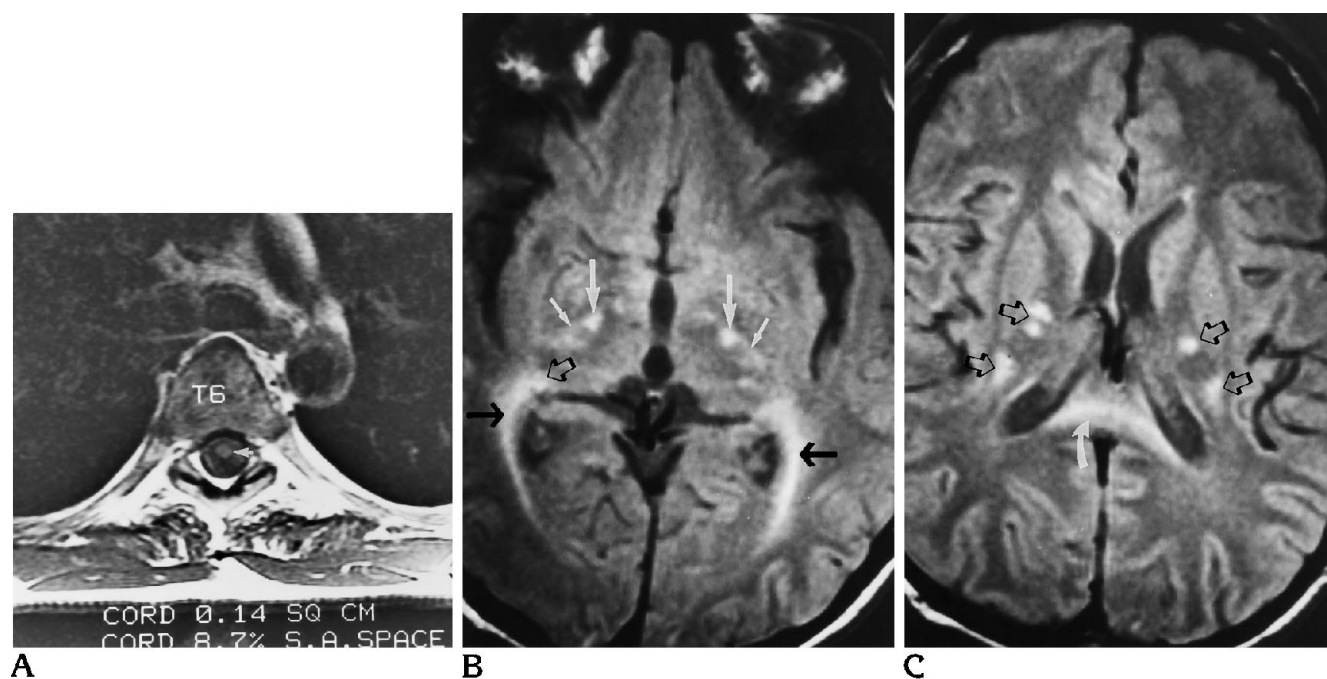


Fig 2. AMN with cerebral abnormalities limited to long tracts (type 1). A forty-three-year-old patient with spastic paraparesis since 29 years of age.

A, Axial T1-weighted image of the thoracic cord at T-6 level shows severe cord atrophy (*arrow*), the cord occupying only 8.7% of the subarachnoid space.

MR of the brain (T2-weighted images) reveals spinothalamic tract, pyramidal tract, and visual pathway demyelination (B and C). B, Section at the level of the third ventricle and thalamus. Abnormal hyperintensity involving the thalamic nuclei (*large white arrows*) and spinothalamic tracts (*small white arrows*) bilaterally correlating with abnormal somatosensory evoked responses. Visual pathways show evidence of demyelination with abnormal hyperintensity involving the lateral geniculate body (*open arrow*) and optic radiations (*black arrows*). In this patient, MR abnormalities of optic radiations were detected before clinical symptoms.

C, Section at the level of frontal horns. Pyramidal fibers in the internal capsule (*open arrows*) show areas of demyelination. Splenium of the corpus callosum (*curved white arrow*) also is abnormal.

form, in the adult form the diffuse demyelinating lesions were most prominent in the parietooccipital regions (35 patients; Fig 3 C and D) but were also present in the frontal (13 patients; Figs 1C and 3D) and temporal lobes (17 patients; Fig 3B). The lesions were usually bilateral, but asymmetries were not uncommon. Patients in whom there were diffuse lobar cerebral hemisphere lesions also showed the tract involvement (Figs 1 and 3). However, 16 patients with tract involvement showed no diffuse cerebral lobar involvement (Figs 2 and 4).

Demyelination of the corpus callosum was present in 25 patients (Figs 1D, 3D, 5B). Cerebral atrophy was diffuse or focal secondary to severe adrenoleukodystrophy. Twelve patients showed cerebellar abnormalities, either demyelination (Fig 3A) or atrophy (Figs 1 A and B).

Three patients had olivopontocerebellar atrophy. In two of these, it was combined with white matter lesions.

Brain MR in Female Heterozygotes

Nine (20%) of the 45 women showed brain MR abnormalities. The most common finding was a mild diffuse increase of signal intensity in the parietooccipital (8 patients) or frontal (4 patients) lobe white matter (Fig 5). In four women, the changes were very mild. Four women showed bilateral involvement of the corticospinal tracts similar to that in the male patients.

Spinal Cord Findings

Diffuse spinal cord atrophy, mainly in the thoracic regions, was present in 18 of 20 male

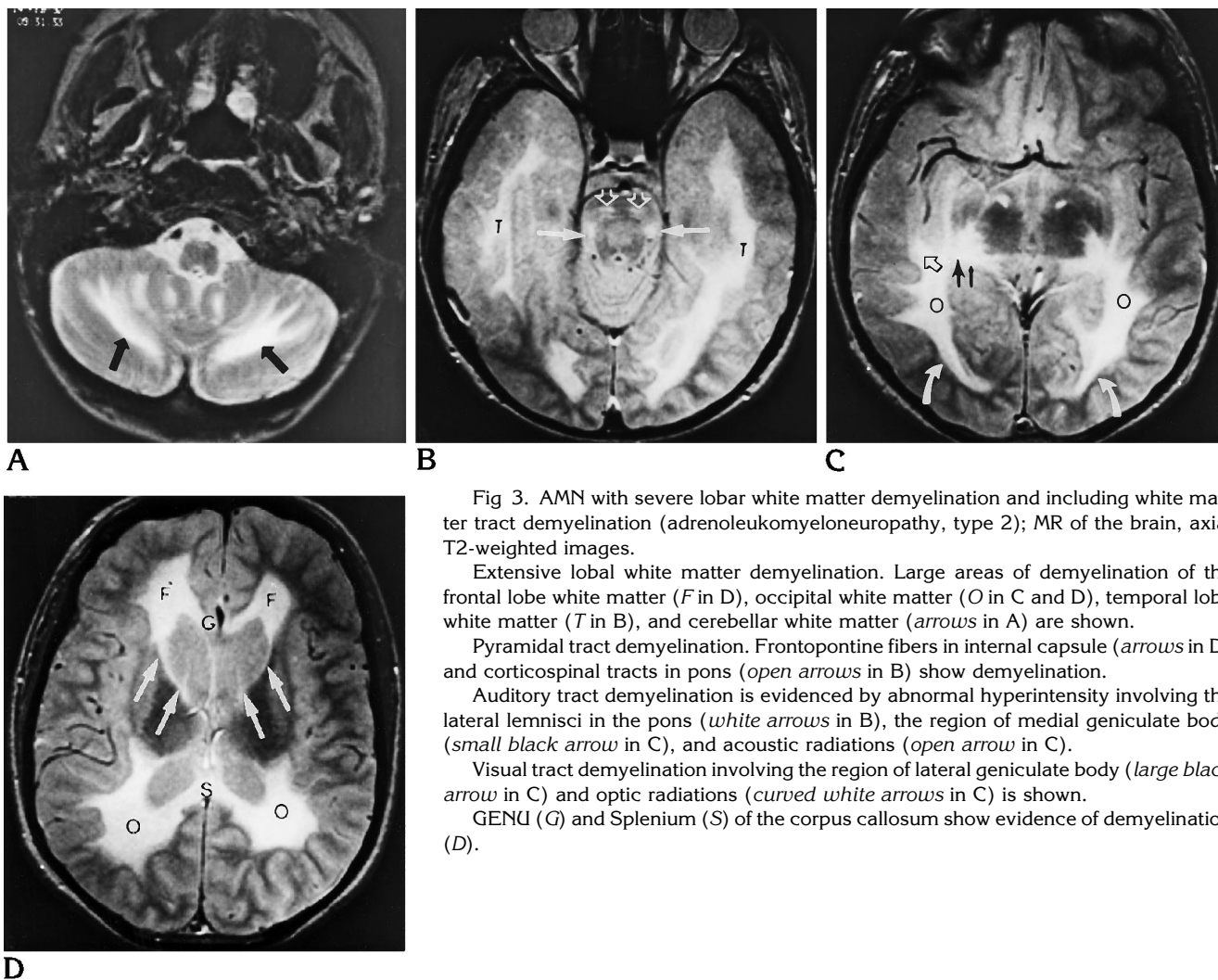


Fig 3. AMN with severe lobar white matter demyelination and including white matter tract demyelination (adrenoleukomyeloneuropathy, type 2); MR of the brain, axial T2-weighted images.

Extensive lobar white matter demyelination. Large areas of demyelination of the frontal lobe white matter (F in D), occipital white matter (O in C and D), temporal lobe white matter (T in B), and cerebellar white matter (arrows in A) are shown.

Pyramidal tract demyelination. Frontopontine fibers in internal capsule (arrows in D) and corticospinal tracts in pons (open arrows in B) show demyelination.

Auditory tract demyelination is evidenced by abnormal hyperintensity involving the lateral lemnisci in the pons (white arrows in B), the region of medial geniculate body (small black arrow in C), and acoustic radiations (open arrow in C).

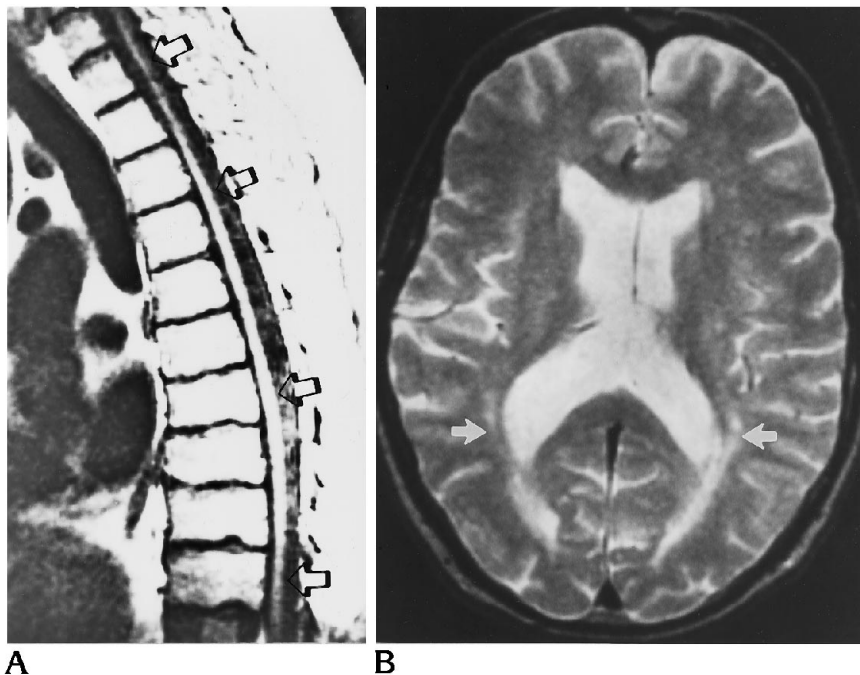
Visual tract demyelination involving the region of lateral geniculate body (large black arrow in C) and optic radiations (curved white arrows in C) is shown.

GENU (G) and Splenium (S) of the corpus callosum show evidence of demyelination (D).

Fig 4. Adrenoleukomyeloneuropathy type 1 in a 73-year-old man with spastic paraparesis, with difficulty in walking since 35 years of age. At 53 years of age, Addison disease was diagnosed.

A, MR of the spinal cord in sagittal plane (T1-weighted image) shows diffuse thoracic cord atrophy (arrows).

B, MR of the brain (T2-weighted image). Abnormal hyperintensity involving the optic radiations (arrows) secondary to demyelination.



AMN patients who were examined (Figs 2, 4, 6, 7). Borderline atrophy was present in the other two. Among the 10 heterozygote women who were examined, there was thoracic cord atrophy in 6 (Fig 5A); 2 showed borderline atrophy, and findings were normal in 2. In all patients, the cord showed no evidence of abnormal hyperintensity in T2-weighted images. The cervical cord showed atrophy in 4 of 8 patients studied (Fig 7B).

Discussion

Biochemistry of ALD

The term *adrenoleukodystrophy* has evolved to refer to two distinct hereditary traits: sex-linked recessive adrenoleukodystrophy and autosomal recessive (neonatal) forms. Clinical subtypes of the sex-linked recessive trait (Table 2) have been recognized in 1475 men whose biochemical tests showed the characteristic abnormality of adrenoleukodystrophy consisting of elevated, very long chain fatty acids in plasma, cultured skin fibroblasts, and other tissues, attributable to defective peroxisomal fatty acid oxidation. Also noticed was a striking abnormality in the fatty acid composition of cholesterol esters and gangliosides from the

brains and adrenal cortices of patients with adrenoleukodystrophy (2). Cholesterol esters in normal brain contain mostly carbon 16 to carbon 20 fatty acids, whereas cholesterol esters in brain tissue in adrenoleukodystrophy contain large amounts of very long chain fatty acids (carbon 24 to 30 or more); these fatty acids compose 20% to 67% of all fatty acids compared with 0% to 5% in normal brain tissue (14). The abnormal fatty acids are saturated and unbranched.

Pathology of ALD

Schaumburg et al (15) have reported the histologic abnormalities of brain and spinal cord in postmortem examination of two men with adrenoleukodystrophy. Cerebral white matter dis-

TABLE 2: Phenotypes among X-linked ALD hemizygotes (N = 1475)

Type	Frequency, %
Childhood cerebral phenotype	48
Adolescent cerebral phenotype	5
Adult cerebral phenotype	3
Adrenomyeloneuropathy	25
Addison disease only	10
Asymptomatic and presymptomatic	8

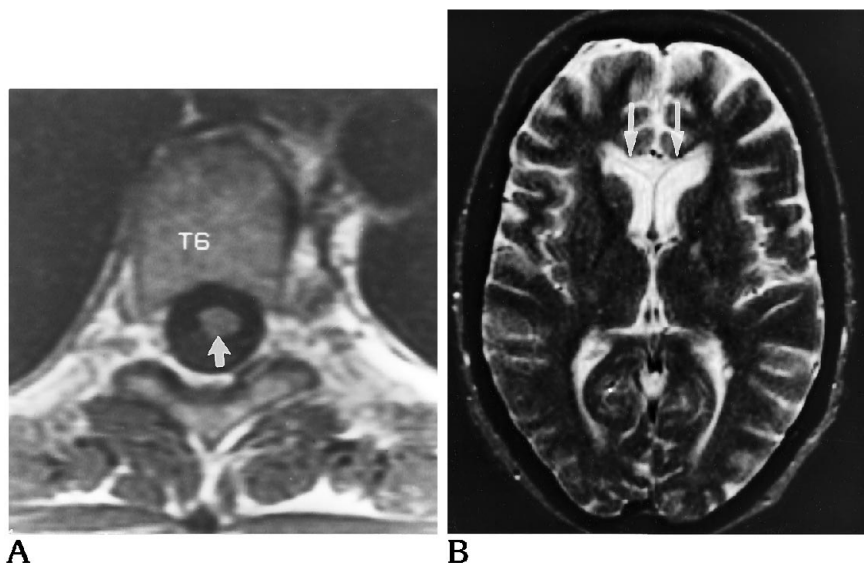


Fig 5. MR of the brain and spinal cord in a 40-year-old female symptomatic heterozygote.

A, MR of the thoracic cord in axial plane (T1-weighted image) at T-6 level with severe thoracic cord atrophy (*arrow*).

B, MR of the brain shows severe demyelination involving the genu of corpus callosum (*arrow*).

played a moderate, diffuse pallor throughout both hemispheres. Cerebral white matter abnormalities consisted of diffuse loss of myelin with mild gliosis and many perivascular periodic acid-Schiff-positive cells. Geniculocalcarine radiations exhibited consistent loss of myelin and axons. The optic nerves displayed loss of myelin and axons. Sections of the brain stem revealed severe degeneration of corticospinal tracts in the medulla, pons, and midbrain. There was a moderate loss of fibers in the dorsal spinocerebellar tracts and the medial lemnisci in the medulla.

Sections of the spinal cord revealed a striking loss of axons and myelin throughout the entire length of the lateral corticospinal tracts.

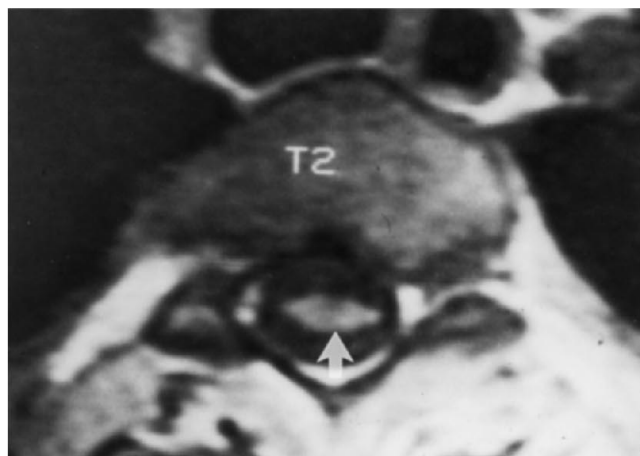
Clinical-MR Correlation in Adult-Onset ALD

The MR abnormalities in the childhood cerebral type have been well described recently (16–18). The characteristic MR findings consist of large bilateral, symmetric parietooccipital lobe abnormal signal intensity correlating with the diffuse white matter demyelination seen histopathologically. Specific tract demyelination in childhood ALD consisting of corticospinal pathway, visual pathway, and auditory pathway was described by Kumar et al (17). Contrast enhancement with gadopentetate dimeglumine occurs at the advancing edges of the lesions and in the areas of active demyelination (16–20).

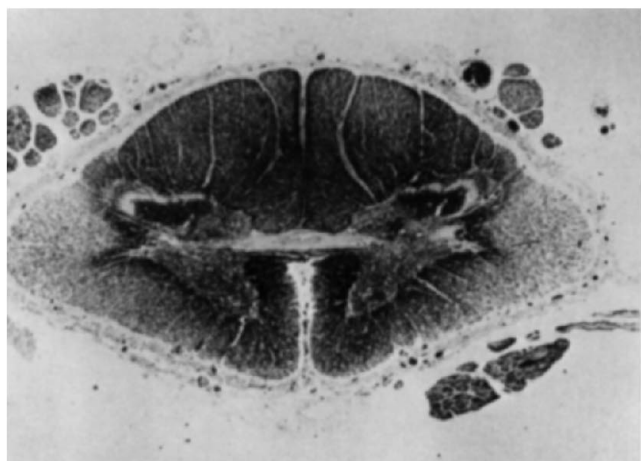
The main purpose of this study was to define the brain MR abnormalities in a large series of

men with ALD and in women who were manifesting heterozygotes. Most of the patients had been admitted to the Clinical Research Center at our institution as part of a study to evaluate the effectiveness of dietary therapy with glyceryl trierucate and trioleate oils (also referred to as “Lorenzo’s oil”). The male patients ranged from 19 to 74 years of age, showed a wide range of clinical severity at baseline, and are considered representative of the total adult ALD population. All of the heterozygote women, who ranged from 32 to 73 years of age, had clinical evidence of spinal cord involvement and are considered representative of the 20% or more of ALD heterozygotes who have neurologic disability. Eighty percent of the men and none of the women had primary adrenocortical insufficiency and were treated with appropriate steroid replacement therapy. Adrenal function was normal in all women.

Because the spinal cord is known to bear the brunt of the disease both in men with ALD and in manifesting heterozygotes, the finding of atrophy is not surprising; thoracic cord is more severely affected than cervical cord. MR findings of the spinal cord mainly consisted of diffuse atrophy with severe loss of cord tissue. No focal T2-weighted abnormalities were seen, probably attributable to AMN’s reflecting a more indolent degenerative process with a less intense reaction to the breakdown of myelin and axons than does ALD as postulated by Schaumburg et al (15). The spinal cord atrophy in AMN probably represents a degenerative disease of dying back phenomenon with distal cord af-



A



B

Fig 6. AMN with thoracic cord atrophy in a 25-year-old patient.

A, Axial T1-weighted image of the thoracic spinal cord at T-2 level. The thoracic cord is markedly atrophic (*arrow*), occupying 20% of the subarachnoid space. The entire thoracic cord was found to be atrophic in this patient.

B, Pathologic section of the thoracic spinal cord in a postmortem examination of an individual with AMN revealed striking loss of myelin in lateral columns, Heidenhain stain (from Schaumburg et al [15]).

ected first, secondary to interruption of corticospinal tracts in the cerebral hemisphere (15). We focused here mainly on the brain MR findings, because clinical signs of brain involvement appear to be not infrequent, and reports on brain MR findings in a large and representative series of patients are not available. Furthermore, as options on counseling and therapy for ALD are becoming available, information about the natural history of the disorder becomes increasingly important.

Analysis of the MR findings and correlation with clinical findings has permitted us to



A

B

Fig 7. AMN with normal brain. A 35-year-old man, a member of pedigree with mother and sister who are carriers and a brother who died of ALD at 5 years of age. A nephew is biochemically positive for ALD but asymptomatic. He experienced difficulty in running at 26 years of age with progressive gait disturbance. The diagnosis of ALD was made at 30 years of age by biochemical analysis.

A, MR of the thoracic cord in axial plane (fast spin-echo sequence). Thoracic cord is markedly atrophic (*arrow*) with no focal intrinsic signal abnormality.

B, MR of the cervical cord (sagittal fast spin-echo sequence). Diffuse atrophy of the cervical cord (*arrows*) also is shown.

achieve a tentative subdivision of the adult ALD population into four subtypes that appear to differ in respect to prognosis and possibly pathogenesis (Table 3).

AMN with normal brain (Figs 6 and 7). These are patients in whom the brain MR findings are normal, and demonstrable disease is confined to the spinal cord and peripheral nerves. Sixty-five (55%) of our 119 male AMN patients belong in this category.

AMN with brain abnormalities limited to long tracts (Figs 2 and 4). In 16 of the AMN patients, the brain MR abnormality was confined mainly to the long fiber tract systems. We refer to this group as having adrenoleukomyeloneuropathy type 1 (ALMN 1). Bilateral involvement of the corticospinal tract is a characteristic feature. Because we have identified patients in whom there was a greater than 25-year interval between onset of neurologic symptoms and tract degeneration demonstrable by MR, we propose that this represents a "dying-back" mechanism of these long tracts, possibly attributable to a defective axonal protein transport secondary to metabolic alterations of the perikarya (21). The pathoanatomic description of a 24-year-old pa-

TABLE 3: ALD classification

ALD types	Clinical and pathologic findings	MR findings
"Pure" AMN (n = 65)	Slowly progressive spastic paraparesis, sensory disturbances, and bladder dysfunction; demyelinating myelopathy	Thoracic cord atrophy; normal brain MR findings
AMN with tract involvement (ALMN 1) (n = 16)	Severe spastic paraparesis with chronic progression; centripetal tract demyelination, mainly corticospinal ("dying-back" mechanism)	Thoracic cord atrophy; evidence of tract demyelination (corticospinal, spinothalamic, visual, and auditory pathways)
AMN with lobar involvement (ALMN 2) (n = 32)	Initially severe spastic paraparesis acceleration of clinical course in later stages, frequently in combination with dementing illness; inflammatory demyelination of white matter	Thoracic cord atrophy, tract involvement and/or severe lobar white matter demyelination
Adult cerebral (n = 6)	Primarily psychopathological disturbance; rapid progressive inflammatory disease	Severe lobar white matter demyelination and/or severe atrophy
Symptomatic heterozygotes (Females) (n = 45)	Very slowly progressing spastic paraparesis; chronic demyelinating myelopathy	Thoracic cord atrophy; brain MR abnormalities in rare cases

tient with AMN by Budka et al (22) emphasized a "pseudosystematic" involvement of the entire pyramidal tract as well as similar symmetric demyelination in ascending tracts such as the medial lemnisci, spinocerebellar tracts, or the medial parts of the posterior fasciculi. These findings, which were later confirmed by Schaumburg (21) and Powers (7), could well be the pathologic basis of the MR findings in the present study.

AMN with diffuse lobar cerebral involvement (Figs 1 and 3). In this group of patients, the brain MR lesions are not confined to tract boundaries but extend diffusely. We refer to this group as adrenoleukomyeloneuropathy type 2 (ALMN 2). Thirty-two patients belonged to this category. The findings in our patients conform to those described in the literature (20, 23–28) and resemble those in childhood cerebral ALD. The most common pattern is a bilateral parietooccipital involvement extending across the splenium of the corpus callosum in combination with bilateral pyramidal tract involvement in the brain stem and internal capsule. We hypothesize that in this group, the brain inflammatory process characteristic of childhood cerebral ALD has been superimposed on a "pure" AMN, or ALMN 1. Unlike the adult cerebral patients, these ALMN 2 patients start with the same neurologic disturbances as in "pure" AMN but with an accelerated clinical progression and frequent impairment of cortical functions in later stages (10).

Adult cerebral ALD. Adult cerebral ALD is a severe and rapidly progressive disorder in which there is widespread involvement of cerebral hemispheres in a patient who is 21 years of age

or older, and in whom there has been no clinical evidence of preceding AMN. Six of our patients belonged to this group. Changes resembled those reported previously (24, 29–33). They show severe white matter lesions and brain atrophy. The corpus callosum was severely involved in all six patients. In contrast to the childhood cerebral form, the white matter signal hyperintensities were diffuse without the typical occipital or frontal pattern seen in childhood cerebral ALD. Another difference from the childhood cerebral form is the presence of atrophic changes in the cortex, subcortical regions, and brain stem.

In three of the adult cerebral patients, the clinical and MR features resembled olivopontocerebellar atrophy. These patients showed some degree of intellectual dysfunction before the onset of dysarthria, ataxia, and mild spasticity. These patients resembled those described previously, particularly in the Japanese literature (34–40), except that some of the previously described patients did not have cognitive deficits. Their experience and ours reemphasize the importance of including ALD in the differential diagnosis of olivopontocerebellar atrophy, however, without the common MR features of olivopontocerebellar atrophy consisting of abnormal increase signal intensity involving transverse pontine fibers, middle cerebellar peduncles, and putamen as seen as T2-weighted images (41). Although the presence of adrenal insufficiency represents an important lead to the diagnosis of ALD, it must be recalled that as many as 30% of adults with ALD have normal adrenal function and that definitive diagnosis depends on the demonstration of abnormally

high levels of very long chain fatty acids in plasma, red blood cells, or cultured skin fibroblasts.

Symptomatic Female Heterozygotes

In 20% of female heterozygotes develops a neurologic disability that resembles AMN but is somewhat milder and of late onset (42). Only a few symptomatic heterozygote women show MR abnormalities attributable to ALD, even though severe white matter lesions in young girls have been observed (43). Diffuse signal increases predominantly in parietooccipital brain regions were seen in eight patients.

A preliminary comparison of our data indicates a close correlation of severe lobar white matter lesions or atrophy with an impairment of cortical functions and the overall prognosis of ALD phenotypes (W. Köhler, E. Edwin, and H. W. Moser, unpublished observation). Severe disability develops more frequently and earlier in AMN patients with lobar involvement (ALMN 2) than in AMN patients without these lesions ("pure" AMN; ALMN 1).

Our overall results demonstrate a high percentage of demyelinating and atrophic brain and spinal cord abnormalities that are not adequately reflected in the term *adrenomyeloneuropathy*. The recognition of MR findings of the brain and spinal cord in adult ALD is important because they mimic other disease process such as dementia, schizophrenia, olivopontocerebellar atrophy, multiple sclerosis, and amyotrophic lateral sclerosis. We suggest that the term *AMN* should be restricted to patients with normal brain MR findings. The common MR finding of severe cord atrophy underlines the myelopathic character of this most frequent form of adult X-ALD. ALMN 1 may reflect a further progression of AMN to more proximal parts of the affected long spinal tracts. In contrast, the pathology and prognosis of patients with cerebral lobar white matter lesions appears to be different. Further clinical investigations and the study of the natural history of the various phenotypes are needed to confirm our hypothesis that ALMN 2 is a separate adult variant of X-ALD.

We conclude that the clinical course in the various adult phenotypes differs significantly. Delineation of brain MR abnormalities is valuable for the differentiation of adult ALD phenotypes for prognostic considerations and also

helps patient selection for experimental dietary therapy and bone marrow therapy (44).

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