AJNR

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AJNR Am J Neuroradiol 1991, 12 (6) 1095-1098
http://www.ajnr.org/content/12/6/1095

MR Imaging of the Spinal Cord in 23 Subjects with ALD-AMN Complex

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Twenty-three subjects from two family groups with the adrenoleukodystrophy (ALD)-adrenomyeloneuropathy (AMN) complex were examined with MR imaging at 1.5 T to determine the presence and extent of brain and spinal cord abnormalities. Nineteen individuals were identified as having ALD or AMN, or as having carrier status on the basis of pedigree analysis and/or evaluation of serum very-long-chain fatty acids. In addition to the expected intracranial white matter changes for this disorder, decreased spinal cord diameter was found in seven (30%) of the 23 subjects. In three of these cases, atrophy was limited to the thoracic spinal cord, while atrophy of both the cervical and thoracic cord was identified in four patients. Two patients who did not have MR imaging of the spine were found to have spinal cord atrophy at autopsy.

The finding of decreased spinal cord diameter on MR examinations in individuals who are heterozygous for ALD-AMN, in patients with ALD or AMN, and in asymptomatic ALD-AMN patients may represent a new anatomic marker for the variable clinical presentations of this condition. In addition to cranial MR examination, MR imaging of the spine may be indicated in patients with suspected ALD or AMN, or in women with carrier status.

***AJNR* 12:1095–1098, November/December 1991; *AJR* 158: February 1992**

Adrenoleukodystrophy (ALD) is a sex-linked recessive disorder of childhood characterized by CNS demyelination and adrenal insufficiency [1, 2]. Phenotypes differ according to patterns of involvement of central and peripheral nervous systems and the endocrine systems [2, 3]. Adrenomyeloneuropathy (AMN) is manifested in young adulthood in members of families affected by childhood ALD, is also X-linked recessive, and is the second most common form of the ALD-AMN complex [2, 4]. Neonatal ALD is the rarest form and is autosomal-recessive. Survival is usually brief, and neonatal ALD has not been described in the same families as childhood ALD or AMN [2].

This study was undertaken to determine the frequency of MR-detectable spinal cord abnormalities in kindreds with the ALD-AMN complex, and the relationship between these abnormalities and the genetic and clinical status of the family members.

Subjects and Methods

Two family groups (23 individuals) were evaluated with MR imaging of the head and cervical and thoracic spine. One family had been included in a previous report [5]. Both kindreds contained pathologically proved cases of ALD-AMN. Carrier status was ascertained by pedigree analysis and/or by very-long-chain fatty acid (VLCFA) levels in 19 individuals.

MR imaging was performed on a 1.5-T superconducting magnet (Signa; General Electric, Milwaukee, WI) with spin-echo sequences. Various receiver-only surface coils were used for spinal examinations, which were performed as two or three overlapping scans from the level of the foramen magnum to the conus. Images of the head were acquired with a slice thickness

Received December 27, 1988; revision requested March 2, 1989; revision received May 7, 1991; accepted May 14, 1991.

Presented at the annual meeting of the American Society of Neuroradiology, Chicago, May 1988.

This work was supported in part by a grant from the University of New Mexico Medical Center, the Center for Non-Invasive Diagnosis, and the General Clinical Research Center.

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0195-6108/91/1206-1095

TABLE 1: Relevant Data for Two Family Groups (23 Individuals) with ALD-AMN Complex

Subject No.	Age (yr)	Sex	Genetic Status	MR Findings (Spinal Cord)	Clinical Status
Family 1					
1	56	F	Het	N	N
2	37	F	Het	CA	SD
3	36	F	Het	N	N
4	35	F	Het	CA	SD
5	33	F	Het	N	N
6	30	F	Het	N	N
7	26	M	N	N	N
8	23	M	Hem	N	N
9	20	F	Unk	N	N
10	15	M	Hem	CA	N[a]
11	15	F	Unk	N	N
12	7	M	Hem	N	N[a]
13	5	F	Het	N	N
14	7	F	Unk	N	N
15	4	F	Unk	N	N
Family 2					
1	75	F	N	CA	N[b]
2	55	F	N	N	N
3	49	F	Het	CA	N
4	47	F	Het	N	N
5	28	F	Het	CA	N
6	27	M	N	N	N
7	19	M	Hem	N	ALD
8	24	M	Hem	CA	AMN

Note.—N = normal, Unk = unknown, Het = heterozygote, Hem = hemizygote, CA = cord atrophy, SD = mild spastic diplegia, ALD = adrenoleukodystrophy, AMN = adrenomyeloneuropathy.

[a] Asymptomatic.

[b] Cord atrophy in clinically and genetically normal subject.

of 5 mm in sagittal, axial, and coronal planes. Cranial examinations included T1-weighted, 600/20 (TR/TE), sagittal and coronal sequences and T2-weighted (1500–2000/80) sequences in the axial plane. Cranial and spinal imaging was often performed at separate times owing to the length of the examinations. Spinal images were acquired at 3- to 5-mm slice thicknesses in sagittal and axial planes. Proton density–weighted (950–2000/20–35) sagittal images and T1-weighted (600/20) axial images were obtained in all spinal examinations. Some spinal examinations also included T2-weighted axial and/or sagittal images.

Scanning techniques such as cardiac gating, flow compensation, gradient echoes, 3-D imaging, fast scans, and oblique image planes were not available at the time the MR examinations were performed Consensus readings were obtained, and the diagnosis of spinal cord atrophy was based on a subjective decrease in the diameter of the spinal cord, either focally or diffusely. Autopsy results of two family members who did not undergo spinal MR examination were reviewed.

Results

In addition to the expected cranial white matter changes for this disorder, decreased spinal cord diameter was found in seven (30%) of the 23 patients (Table 1). Four of the 10 female heterozygotes had evidence of spinal cord atrophy on MR examinations of the spine. Two of these had mild spastic diplegia (Table 1) and had atrophic changes in the cervical and thoracic cord. The other two had normal neurologic examinations with MR evidence of atrophy limited to the

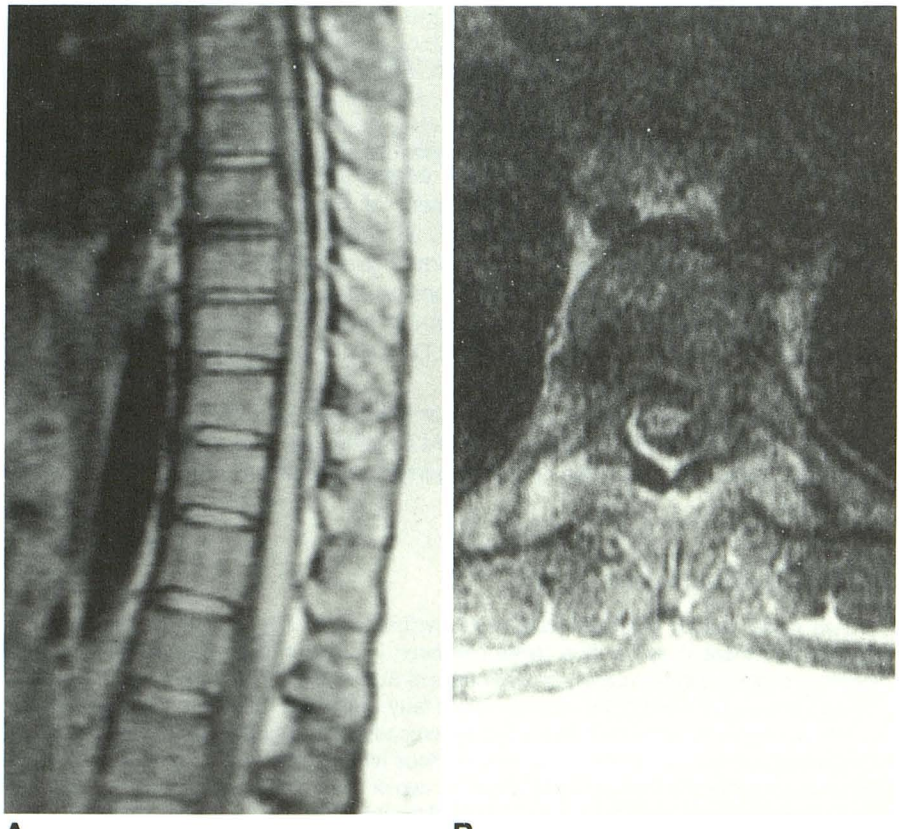

Fig. 1.—28-year-old clinically normal woman who is heterozygous for ALD-AMN syndrome.

***A*, Sagittal proton density–weighted MR image (2000/35) shows evidence of thoracic spinal cord atrophy.**

***B*, Axial proton density–weighted MR image (2000/35) shows spinal cord atrophy in mid-thoracic region.**

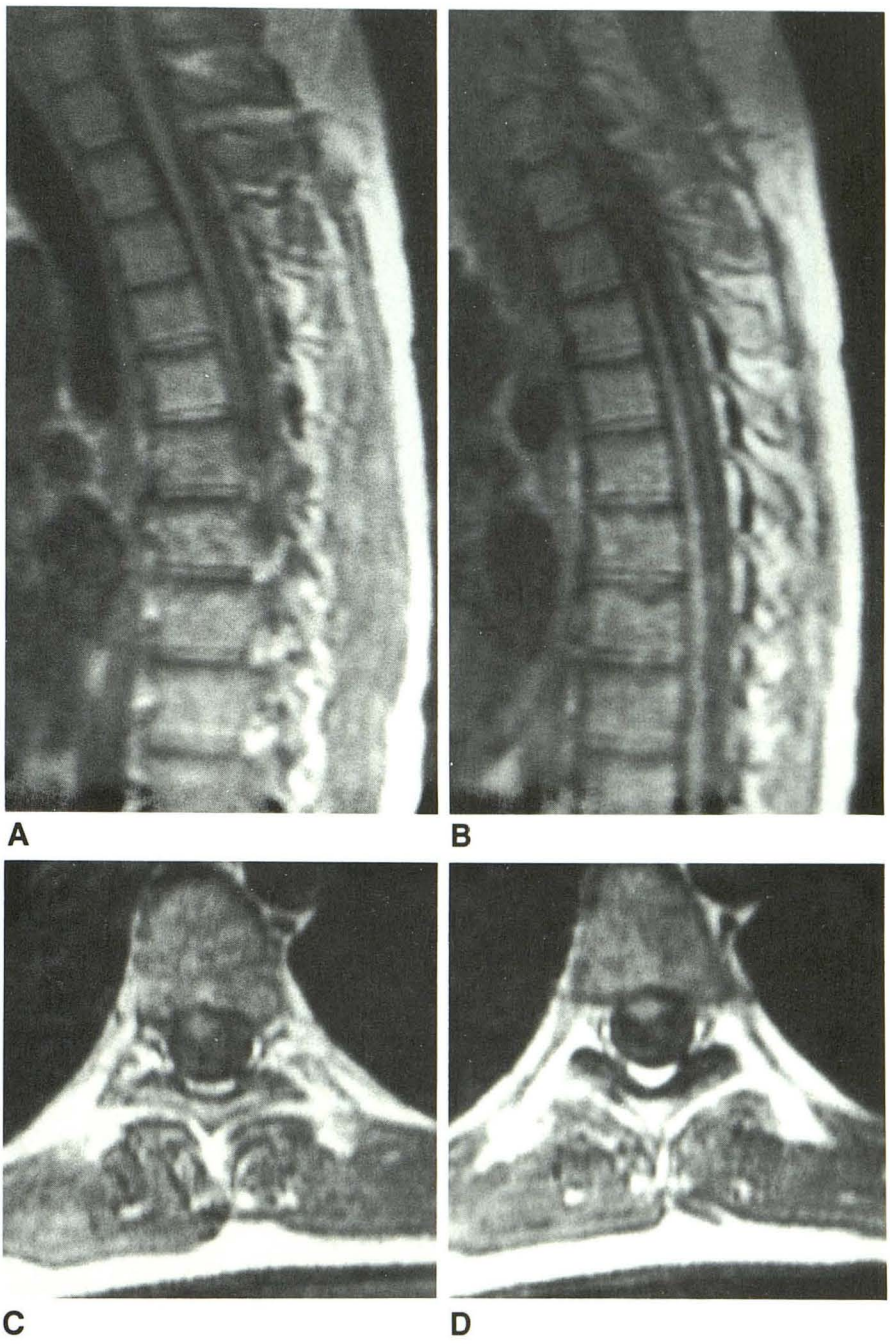

Fig. 2.—24-year-old hemizygous man with adrenomyeloneuropathy.

***A* and *B*, Sagittal spinal T2-weighted MR images (1500/20) show diffuse atrophy of lower cervical and thoracic spinal cord.**

***C* and *D*, Axial T1-weighted MR images (600/20) show decrease in size of thoracic spinal cord.**

thoracic cord (Fig. 1). Diffuse atrophy of the cervical and thoracic spinal cord was found on MR examination in one patient with AMN (Fig. 2). Clinically, he had spasticity and hyperreflexia in his lower extremities, sensory deficits below the mid-thoracic level, and no neurologic deficits in his upper extremities. One asymptomatic 15-year-old male hemizygote with a normal neurologic examination had MR evidence of atrophy involving the lower cervical and upper thoracic cord. His cranial MR examination demonstrated the findings typical of ALD. A 75-year-old woman with normal genetic status and normal neurologic examination had MR evidence of diffuse thoracic spinal cord atrophy.

Autopsy of two family members with ALD who did not undergo MR examination of the spinal cord revealed cord atrophy. An 11-year-old boy had symmetrical areas of demyelination in the anterior and lateral corticospinal tracts at multiple levels, and a 9-year-old boy had marked demyelination in the lateral corticospinal tracts of the cervical spinal cord. Cranial MR of the 11-year-old revealed findings typical of ALD (Fig. 3).

Discussion

Childhood ALD appears in boys, usually between 4 and 8 years of age, in the form of behavioral disorders, dementia, and visual/hearing impairment. Adrenal insufficiency may fol-

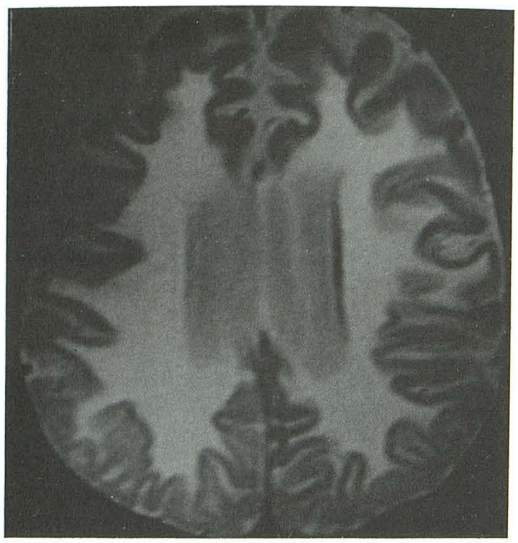

Fig. 3.—Axial T2-weighted MR image (2000/80) in 11-year-old boy with ALD shows diffused, abnormally increased signal intensity in white matter and associated atrophy. At autopsy, this patient also had atrophy of the spinal cord.

low CNS symptoms [2]. Death usually occurs within several years [5]. AMN commonly has its onset between the ages of 20 and 30 years, with progressive spastic paraplegia, peripheral neuropathy, and ataxia. Hypoadrenalism may be present [2]. Female heterozygotes are usually asymptomatic, but approximately 12% are symptomatic, most often with a spastic paraparesis [2, 6]. Rarely, these carriers can manifest more widespread involvement of the CNS and/or adrenal insufficiency [2, 7]. Excessive amounts of VLCFAs are found in the Schwann cells and adrenocortical cells of affected individuals and heterozygotes [2, 6, 8]. Definitive diagnosis is made by gas-liquid chromatography of serum, or by fibroblast assays of tissue for elevated VLCFAs [2]. A peroxisomal enzymatic defect, probably causing impairment of oxidation of VLCFAs, may be the cause of ALD-AMN [2, 9, 10].

Spinal cord disease in ALD may involve degeneration of the entire length of the corticospinal tracts, possibly from interruption of the tracts in the cerebral hemispheres [11] (Fig. 3). In AMN, loss of axons and myelin occurs throughout the entire length of the lateral corticospinal tracts, dorsal spinocerebellar tracts, and gracile tracts [11]. These processes likely account for our finding in the hemizygotes who had MR evidence of spinal cord atrophy. Since the two symptomatic female heterozygotes had MR evidence of spinal cord atrophy in the thoracic and cervical areas, and the two asymptomatic female heterozygotes had MR evidence of atrophy in the thoracic cord only, it may be that atrophy involving the cervical cord is necessary to cause symptoms in female heterozygotes. The finding of a diffusely small spinal cord in the 75-year-old woman with normal genetic status and normal neurologic examination may be attributed to her advanced age or to a subclinical disease state.

The finding of decreased spinal cord diameter in some female ALD-AMN carriers, in patients with AMN, and in asymptomatic individuals with ALD-AMN may represent an anatomic marker for the variable clinical presentations of the ALD-AMN complex. However, further study of a larger number of patients, with age-matched controls, is needed to support this conclusion. In addition to a cranial MR examination, MR imaging of the spine may be helpful in patients with suspected ALD or AMN, or in women with carrier status.

ACKNOWLEDGMENT

The analyses of VLCFAs were kindly performed by Hugo Moser and associates, John F. Kennedy Institute, Baltimore, MD.

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