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Involvement of the Pontomedullary Corticospinal Tracts: A Useful Finding in the Diagnosis of X-Linked Adrenoleukodystrophy

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PURPOSE: To determine whether pontomedullary corticospinal tract involvement is a common and specific finding of adrenoleukodystrophy on MR images. **METHODS:** MR images of 10 patients with biochemically proved adrenoleukodystrophy who were examined during the last 6 years were reviewed retrospectively to determine the frequency of corticospinal tract involvement in the medulla, pons, mesencephalon, internal capsules, and corona radiata. MR images of 10 patients with other leukodystrophies (three with Krabbe disease, two with Alexander disease, two with metachromatic leukodystrophy, two with Pelizaeus-Merzbacher disease, and one with Canavan disease) were reviewed with specific attention to the pontomedullary corticospinal tracts. **RESULTS:** Medullary and pontine corticospinal tract involvement was present in eight of the 10 patients with adrenoleukodystrophy. Mesencephalic and internal capsular involvement was present in three patients. The corona radiata portion of the corticospinal tracts was not involved in any of the 10 patients. No pontomedullary corticospinal tract involvement was identified in any of the 10 patients with other leukodystrophies. The difference in the frequency of pontomedullary corticospinal tract involvement between the two groups was highly significant. **CONCLUSION:** Pontomedullary corticospinal tract involvement is a common finding in adrenoleukodystrophy and is unusual in other leukodystrophies. Awareness of this finding can facilitate the radiologic diagnosis of this disease and may expedite management of affected patients.

Index terms: Adrenoleukodystrophy; Brain, magnetic resonance

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X-linked adrenoleukodystrophy is an uncommon disorder characterized by demyelination in the central nervous system. The underlying defect is in lignoceryl-coenzyme A ligase, a peroxisomal enzyme involved in the breakdown of very long chain fatty acids in the central nervous system, adrenal cortex, and testes (1–4). In the course of performing magnetic resonance (MR) imaging of several patients with adrenoleukodystrophy, we noted specific involvement of the corticospinal tracts in the pons and medulla. In one patient with atypical findings in the cerebral white matter, the finding of pontomedullary corticospinal tract involvement led to adrenoleukodystrophy as a possible diagnosis, which was confirmed by assessment of very long chain fatty acids in serum. To assess the specificity of the finding of T2 prolongation in the pontomedullary corticospinal tracts, we reviewed MR images of 10 patients with biochemically proved adrenoleukodystrophy examined over the past 6 years at our institutions.

Subjects and Methods

The MR imaging studies of 10 patients with X-linked adrenoleukodystrophy were reviewed retrospectively to determine the frequency of corticospinal tract involvement. These 10 patients composed the total of our experience in imaging patients with adrenoleukodystrophy during the past 6 years. The diagnosis of adrenoleukodystrophy was established in all patients by a combination of a typical clinical syndrome (1, 3) and the finding of elevated very long chain fatty acids in serum. All

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patients were boys; ages at the time of diagnosis ranged from 4 to 9 years (mean and median, 7 years).

The MR images consisted of sagittal 4- or 5-mm-thick spin-echo T1-weighted images; axial 5-mm-thick spin-echo or fast spin-echo images, including both proton density–weighted and true T2-weighted images; and, in five patients, axial 5-mm-thick T1-weighted images. In two of the patients, axial 5-mm-thick T1-weighted images were obtained after intravenous administration of paramagnetic contrast material.

The medulla, pons, mesencephalon, and cerebral hemispheres were assessed separately in each patient. Specifically, the images were analyzed for the presence of abnormal T1 and T2 prolongation along the corticospinal tracts in each region. In the cerebrum, the paracentral gyri, corona radiata, and posterior limbs of the internal capsules were assessed. In the mesencephalon, the middle portions of the cerebral peduncles were assessed. In the pons, the paracentral regions in the ventral pons were analyzed. In the medulla, the medullary pyramids were studied. In the two patients who received paramagnetic contrast agent, these regions on postcontrast images were compared with the precontrast images to determine whether an increase in signal intensity was present. If so, the regions were considered to have manifested contrast enhancement. The patients' charts were analyzed for the presence or absence of clinical corticospinal tract involvement (weakness, hyperreflexia, clonus, Babinski signs).

To determine whether pontomedullary corticospinal tract involvement is a specific finding in adrenoleukodystrophy, MR images of 10 patients with other leukodystrophies (three with Krabbe disease, two with Alexander disease, two with metachromatic leukodystrophy, two with Pelizaeus-Merzbacher disease, and one with Canavan disease) were reviewed with specific attention to the pontomedullary corticospinal tracts. The diagnoses in these patients were proved either biochemically or by brain biopsy. Analysis of the MR studies in these patients was restricted to a determination of whether abnormal hyperintensity was present in the pontomedullary corticospinal tracts on standard spin-echo or fast spin-echo T2-weighted images.

After analyzing the frequency of pontomedullary corticospinal tract involvement in adrenoleukodystrophy and the other leukodystrophies, we used standard methods to determine the sensitivity and specificity of the pontomedullary corticospinal tract involvement (5). Fisher's Exact Test was then used to determine whether the difference in pontomedullary corticospinal tract involvement between the adrenoleukodystrophy patients and the patients with other leukodystrophies was a chance occurrence.

Results

Adrenoleukodystrophy Patients

Cerebral Hemispheric White Matter.—The cerebral hemispheric white matter showed a typical pattern of T2 and T1 prolongation in the occipital white matter and splenium of the corpus callosum in nine of the 10 patients in this study (Fig 1A). In all of these patients, the retrolenticular portion of the posterior limb of the internal capsule was involved contiguously with the occipital white matter; however, the involvement spared the corticospinal tracts, which are located farther anteriorly. One patient had an atypical pattern in which the anterior limbs, genus, and anterior portions of the posterior limbs of the internal capsules were involved, showing abnormal T1 and T2 prolongation in the absence of any occipital white matter abnormality (Fig 2). A typical pattern of contrast enhancement around the periphery of the affected white matter was noted in both patients in whom paramagnetic contrast material was administered.

Corticospinal Tracts.—The corticospinal tracts in the pons and medulla showed abnormal hyperintensity on both T2- and proton density–weighted images (Figs 1 and 2) in eight of the 10 patients. The pontomedullary signal abnormality was seen without mesencephalic or cerebral corticospinal involvement in five of the patients (Fig 1), indicating that this was not merely wallerian degeneration. In two patients, abnormal hypointensity was seen on T1-weighted images; in one patient, minimal contrast enhancement was seen in the pontine portion of the corticospinal tracts.

The corticospinal tracts in the mesencephalon and internal capsules showed abnormal hyperintensity on T2- and proton density–weighted images (Fig 2) in three of the 10 patients. Abnormal hypointensity was seen on T1-weighted images in one patient. Contrast enhancement was not present in either patient in whom paramagnetic contrast agent was administered.

No abnormal signal intensity or contrast enhancement was seen in the corticospinal tracts within the corona radiata or in the paracentral regions of the cerebral hemispheres in any of the patients.

Review of the charts showed no evidence of signs or symptoms of corticospinal tract involvement in any of the patients in this series at the time the initial MR studies showed the pontomedullary corticospinal tract involvement, although all patients eventually exhibited spasticity in the extremities.

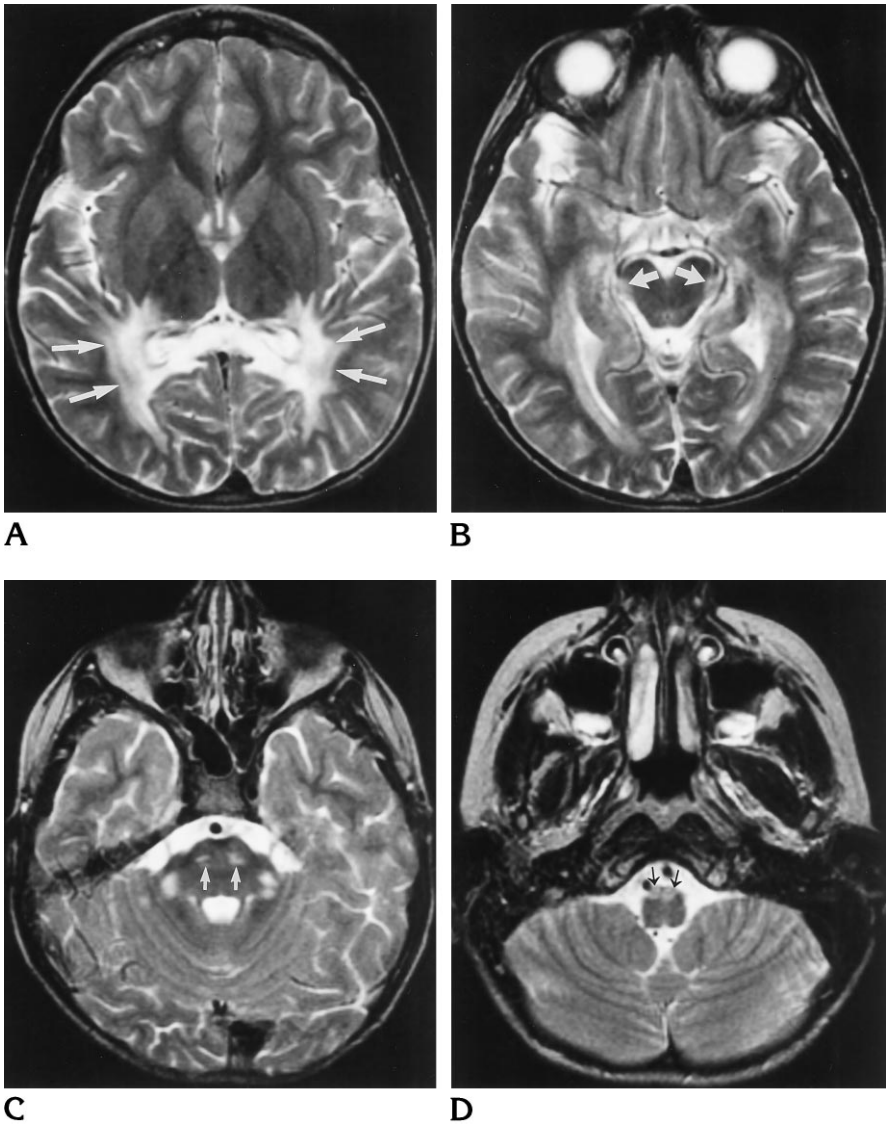

Fig 1. Axial spin-echo MR images (2500/80) in an 8-year-old boy with progressive decline in behavior.

A, Image at the level of the basal ganglia shows T2 prolongation (*arrows*) in the callosal splenium and the periventricular occipital white matter with extension into the posterior aspects of the external and internal capsules.

B, At the level of the mesencephalon, a small amount of T2 prolongation (*arrows*) is seen in the lateral aspects of the cerebral peduncles. The corticospinal tracts, which run through the middle third of the cerebral peduncle, are spared.

C, At the level of the pons, the corticospinal tracts show T2 prolongation bilaterally (*arrows*). T2 prolongation is also present in the middle cerebellar peduncles.

D, At the level of the medulla, the medullary pyramids show T2 prolongation (*arrows*).

Corticospinal Tract Involvement in Other Leukodystrophies

Although the corticospinal tracts were involved at the level of the corona radiata, internal capsules, or cerebral peduncles in four of the 10 patients in this group, the pontomedullary corticospinal tracts were not involved in any patients.

Statistical Analysis

On the basis of the data generated in this study, the sensitivity of the finding of corticospinal tract involvement for the diagnosis of adrenoleukodystrophy in children is 80% and the specificity is 100%. The likelihood of the difference we noted in the frequency of pontomedullary corticospinal tract involvement between adrenoleukodystrophy patients and other leukodystrophy patients occurring by chance is one in 10 000 ($P = .0001$). Thus, the finding of pontomedullary corticospinal tract involvement in a child with a leukodystrophy strongly suggests a diagnosis of adrenoleukodystrophy.

Discussion

In this study, we documented the frequent involvement of the pontomedullary corticospinal tracts in patients with X-linked adrenoleukodystrophy. Involvement of these structures has been observed previously (6), and we be-

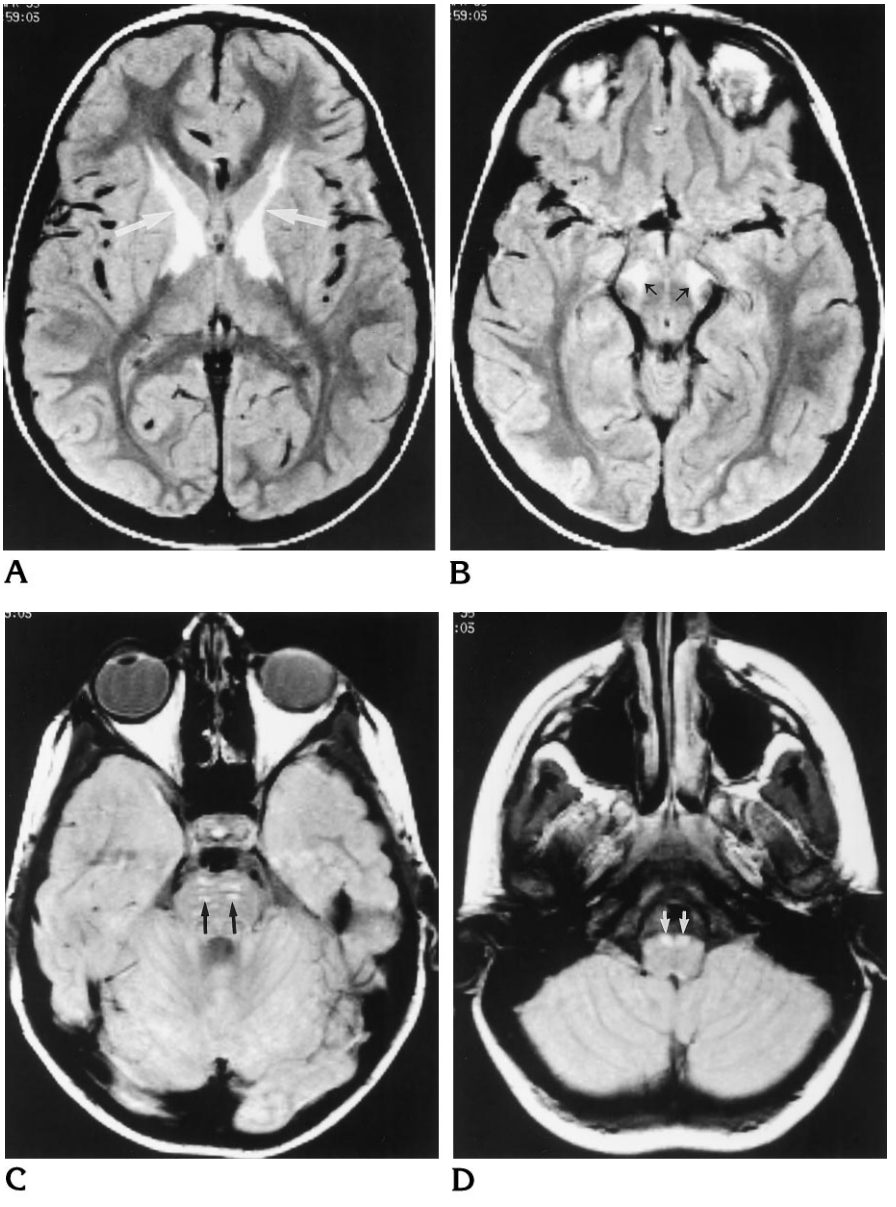

Fig 2. Axial fast spin-echo MR images (2540/19) in a 7-year-old boy with progressive decline in school performance.

A, Image at the level of the basal ganglia shows T2 prolongation (*arrows*) in the anterior limbs, genus, and anterior portion of the posterior limbs of the internal capsules. The occipital white matter is spared.

B, At the level of the mesencephalon, T2 prolongation (*arrows*) is seen in the middle portion of the cerebral peduncles, the region of the corticospinal tracts.

C, At the level of the pons, the corticospinal tracts show T2 prolongation bilaterally (*arrows*).

D, At the level of the medulla, the medullary pyramids show T2 prolongation (*arrows*).

lieve that this finding can be extremely useful in the diagnosis of adrenoleukodystrophy, particularly in patients who have unusual supratentorial manifestations of this disorder, such as the patient illustrated in Figure 2. The pattern of bilateral occipital white matter involvement in adrenoleukodystrophy is so well known that cases with atypical patterns of white matter involvement are often misdiagnosed, or diagnosis is significantly delayed (7, 8). However, atypical supratentorial manifestations of adrenoleukodystrophy, although uncommon, occur with some frequency, as demonstrated by multiple reports in the literature (7–10). Patterns of brain stem involvement in adrenoleukodystrophy have also been reported (11, 12), although these studies concentrated primarily on lateral lemnisci and corticopontine tract involvement rather than the pontomedullary corticospinal tracts. Indeed, most authors have considered pontomedullary involvement to be a manifestation of adrenomyeloneuropathy, a possibly related peroxisomal disorder that occurs in adolescents and adults, rather than of adrenoleukodystrophy itself (11, 13).

It is difficult to understand why the pontomedullary corticospinal tracts are preferentially involved in this disorder. It is noteworthy that the corticospinal tracts have some characteristics that are different from other white mat-

ter tracts of the brain. De Coene et al, for example, have noted that the corticospinal tracts in the brain stem have a different signal intensity than other brain stem white matter tracts on fluid-attenuated inversion recovery images (14). Others have noted that the corticospinal tracts have different signal intensity on heavily T2-weighted images (15). In addition, the pontine corticospinal tracts are relatively spared in central pontine myelinolysis (16). Thus, it is possible that the myelin surrounding the pontomedullary corticospinal tracts is in some ways different from the myelin of other brain stem tracts. This possibility is to some extent related to the postulation of van der Knaap that patients with dysmyelinating diseases form intrinsically unstable myelin because the myelin is intrinsically unstable, the oldest myelin breaks down first (M. van der Knaap, *Myelination and Myelin Disorders,* Utrecht, the Netherlands: University of Utrecht; 1991, thesis). This theory is proposed to explain why central cerebral myelin, which forms early, breaks down sooner than peripheral cerebral myelin, which forms later. It would also explain why the pontomedullary corticospinal tracts, which begin the process of myelination before birth (17), are often involved in adrenoleukodystrophy whereas other pontine and medullary white matter tracts are not. However, if this theory were the sole factor, the posterior limbs of the internal capsules should undergo demyelination before the occipital white matter, and we should not see cases in which the demyelination develops in atypical patterns, such as the frontal white matter demyelinating before the occipital white matter (7–10). Furthermore, this rationalization does not explain why the pontomedullary corticospinal tracts were not affected in two of our 10 patients. Because the exact causes and mechanisms of the demyelination are poorly understood, it is not fruitful to speculate further on them. Unfortunately, pathologic descriptions of pontomedullary corticospinal tract involvement in adrenoleukodystrophy are vague and not helpful in this context (16, 18).

Other diseases in which corticospinal tract demyelination is reported include primary lateral sclerosis, amyotrophic lateral sclerosis, and adrenomyeloneuropathy. Amyotrophic lateral sclerosis is a degenerative disease that affects the anterior horn cells of the spinal cord in adults. MR imaging may show T2 prolongation along the corticospinal tracts, most typically in the posterior limbs of the internal capsules and the corona radiata of the cerebral hemispheres (19, 20). In primary lateral sclerosis, another degenerative disorder seen in adults, the cellular loss and damage are confined to the pyramidal neurons of the motor cortex, and hyperintensity of the corticospinal tracts, presumably a consequence of wallerian degeneration, is seen along the entire extent of the corticospinal tracts (21). Dramatic T2 prolongation and contrast enhancement of the pontomedullary corticospinal tracts has not been reported in either of these diseases. Adrenomyeloneuropathy is a peroxisomal disorder, possibly a variant of adrenoleukodystrophy, that manifests in adolescents and adults with prominent involvement of the cerebellum, brain stem, spinal cord, and peripheral nerves (1, 22). Involvement of the corticospinal tract and cerebellum is a prominent component of the clinical syndrome (1). Our patients were younger, had more cerebral involvement than in typical adrenomyeloneuropathy, and did not have prominent cerebellar or corticospinal tract symptoms on clinical examination. Thus, both their clinical and radiologic manifestations appear to be more compatible with those of adrenoleukodystrophy than with those of adrenomyeloneuropathy.

Pontomedullary corticospinal tract involvement has not, to the best of our knowledge, been reported in any pediatric disorders of myelination other than peroxisomal disorders; moreover, our examination of MR images of 10 children with various myelination disorders revealed that none had involvement of the pontomedullary corticospinal tracts. Thus, we believe that this neuroimaging sign is potentially specific when found in children. Further studies will be necessary to prove such specificity.

We believe that the finding of pontomedullary corticospinal tract involvement, when found in boys with developmental delay, impaired attention, or worsening school performance, can be extremely useful in making a diagnosis of adrenoleukodystrophy. It can be used to dramatically reduce the cost of the metabolic screen (a series of biochemical tests for inborn errors of metabolism) in the workup of the patients. Moreover, by making the workup more focused, it can reduce the time needed to establish the diagnosis and thus the time before potential treatment is initiated.

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