Adrenoleukodystrophy: A Scoring Method for Brain MR Observations

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PURPOSE: To develop a scoring method for brain observations in patients with X-linked adrenoleukodystrophy. **METHODS:** One hundred seventy-five brain MR scans in 83 male subjects less than 20 years of age with proved biochemical defects were reviewed. A severity score (0 to 34), based on a point system derived from location and extent of disease and the presence of focal and/or global atrophy, was calculated for each exam. **RESULTS:** Fifty-five of the 83 patients showed MR findings consistent with adrenoleukodystrophy. Two major patterns were observed. A posterior pattern (mean score, 9; range, 0.5 to 25) was present in 80% of patients, and an anterior pattern (mean score, 10; range, 2 to 18) was present in 15% of patients. Serial MR imaging, positive for adrenoleukodystrophy in 34 patients (mean follow-up, 23 months; range, 2 months to 6 years 11 months), showed progressive disease in 52%, progressive disease with subsequent stabilization in 18%, stable disease in 24%, and minimal improvement in 6%. **CONCLUSION:** The adrenoleukodystrophy MR severity scoring method is a measure that can be used with standard MR images. When used in conjunction with clinical parameters, this scoring method may help define better the natural history of adrenoleukodystrophy and monitor response to developing therapies.

Index terms: Adrenoleukodystrophy; Brain, diseases; Brain, magnetic resonance; Pediatric neuroradiology

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Cerebral involvement in X-linked adrenoleukodystrophy can be detected by magnetic resonance (MR) imaging (1–4). To date, there is no adequate measure of MR brain involvement in patients with adrenoleukodystrophy to correlate with ongoing diagnostic and therapeutic research. Volume measurements are hampered by the fact that standard MR images are acquired in a two-dimensional data set with skip areas and are complicated by frequent presence of focal and/or global atrophy. We have developed a scoring system for brain observations in patients with adrenoleukodystrophy based on neuroanatomic involvement and the presence or absence of focal and/or global atrophy.

Methods

The patient study group was derived from a large pool of families with adrenoleukodystrophy seen at our institutions. One hundred eighty-two brain MR scans in 85 male patients younger than 20 years of age with proved biochemical defects for adrenoleukodystrophy were reviewed. The study included clinically symptomatic and asymptomatic patients. All patients have undergone clinical and laboratory testing at one or both of our institutions. MR of the brain was performed on a variety of scanners from around the world. Two patients with single MR scans were dismissed from the study. One patient had missing films, and the other patient had a suboptimal examination because of motion artifact. In addition, five other MR scans in patients with serial scans were excluded because of incomplete images or suboptimal quality. All post–bone marrow transplantation MR scans were also excluded in this study. The final patient population included 83 male patients and 175 MR scans. All MR scans included T1-weighted spin-echo images in the sagittal planes and T2-weighted spin-echo images in the axial planes.

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A severity score (0 to 34) was calculated for each MR scan based on a point system derived from location and extent of involvement and the presence of focal and/or global atrophy. The 33 MR scans performed at our primary institution were reviewed by three radiologists (D.J.L., S.H., and A.E.S.) with final scoring by consensus. The 142 MR studies performed at outside institutions were scored by one neuroradiologist (D.J.L.). The adrenoleukodystrophy MR severity score point system was designed to be all or nothing, with respect to each category, with a few exceptions. If involvement was unilateral for a specific location, a score of 0.5 was given for that location. If involvement was questionable in a specific location, and the patient had no other abnormalities, a score of 0.5 was given for that location. If involvement showed definite improvement on serial exam in a specific location, the score was halved with 0.5 points subtracted from that location. If a patient showed continual improvement on two follow-ups, the score was initially halved to 0.5 and then halved to 0.25.

MR involvement referred to any signal changes within the brain parenchyma that could be explained by adrenoleukodystrophy. Involvement could be caused by T2 hyperintensity, T1 hyperintensity, or enhancement. Small well-defined signal hyperintensities, referred to as unidentified bright objects, were not considered to be caused by adrenoleukodystrophy.

The major locations assessed were supratentorial white matter, corpus callosum, visual pathway, and the frontopontine-corticospinal projection fibers. To allow for more discrimination in the scoring system, these major locations were subdivided. The supratentorial white matter was subcategorized into parietooccipital, anterior temporal, and frontal regions. The posterior temporal white matter, defined as being posterior to the anterior margin of the midbrain, was considered to be within the parietooccipital region, because early adrenoleukodystrophy involvement tends to be located at the junction of these three lobes. Each supratentorial white matter region was further subdivided into periventricular, central, and subcortical locations. The periventricular and subcortical white matter regions were defined as approximately equal in thickness to cortical gray matter, with the interposed parenchyma designated as central white matter. The corpus callosum was subdivided into genu, body, and splenium. The areas scored in the visual pathway included optic radiations, lateral geniculate body, and Meyer's loop. The locations evaluated in the auditory pathways were medial geniculate body, brachium to the inferior colliculus, lateral lemnis cus, and pons (trapezoid bodies). The frontopontine-corticospinal projection fibers were compartmentized into internal capsule and brain stem locations. In addition to these major categories and their subdivisions, the basal ganglia, cerebellum, and anterior thalamus were also evaluated and scored.

Focal atrophy was qualitatively assessed, and definite loss of brain parenchyma was required before a point was added to the severity score. The areas analyzed for the presence or absence of focal atrophy were the parietooccipital, anterior temporal, and frontal white matter, the genu and splenium of the corpus callosum, the cerebellum, and the brain stem. Global atrophy was both qualitatively and quantitatively assessed. Quantitative assessment was made by measuring the ratio between the maximum bifrontal horn diameter and the distance connecting the inner tables of the skull at the same level (5, 6). Maximum third ventricular width was also calculated. If subarachnoid spaces were prominent, the patient received one point for a third ventricular diameter between 5 and 10 mm, two points for a third ventricular diameter greater than 10 mm, one point for a bifrontal horn–to–inner table ratio greater than 40%, two points for a bifrontal horn–to–inner table ratio greater than 50%, up to a maximum score of three points. With regard to global atrophy, one point was considered mild, two points moderate, and three points severe.

MR severity scores were plotted with respect to the patients' ages at the time of the exams. Patients with serial MR studies were analyzed for changes over time.

Results

The age range of the 83 patients with adrenoleukodystrophy who had 175 brain MR examinations was 13 months to 20 years. Twenty-eight patients had negative MR exams (severity score, 0; mean age, 7 years 10 months; range, 1 year 1 month to 15 years 5 months).

Fifty-five of the 83 patients showed MR findings consistent with adrenoleukodystrophy. The severity scores of these patients with positive MR findings are plotted versus age in Figure 1. The youngest patient with a positive MR examination was 4 years 1 month of age. The three main patterns of MR disease in these 55 patients are as follows.

- Posterior white matter pattern (44 patients, 80%)
  - Parietooccipital white matter
  - Splenium of corpus callosum
  - Frequent visual and auditory pathway
  - Occasional corticospinal tract
- Anterior white matter pattern (8 patients, 15%)
  - Frontal white matter
  - Genu of corpus callosum
  - Frontopontine tract
  - Occasional cerebellar
- Other (3 patients, 5%)
  - Projection fiber abnormalities, isolated

The posterior white matter pattern of disease showed central to peripheral and posterior to anterior progression with development of posterior frontal or isolated frontal white matter MR changes in latter stages of disease. Two of the 8

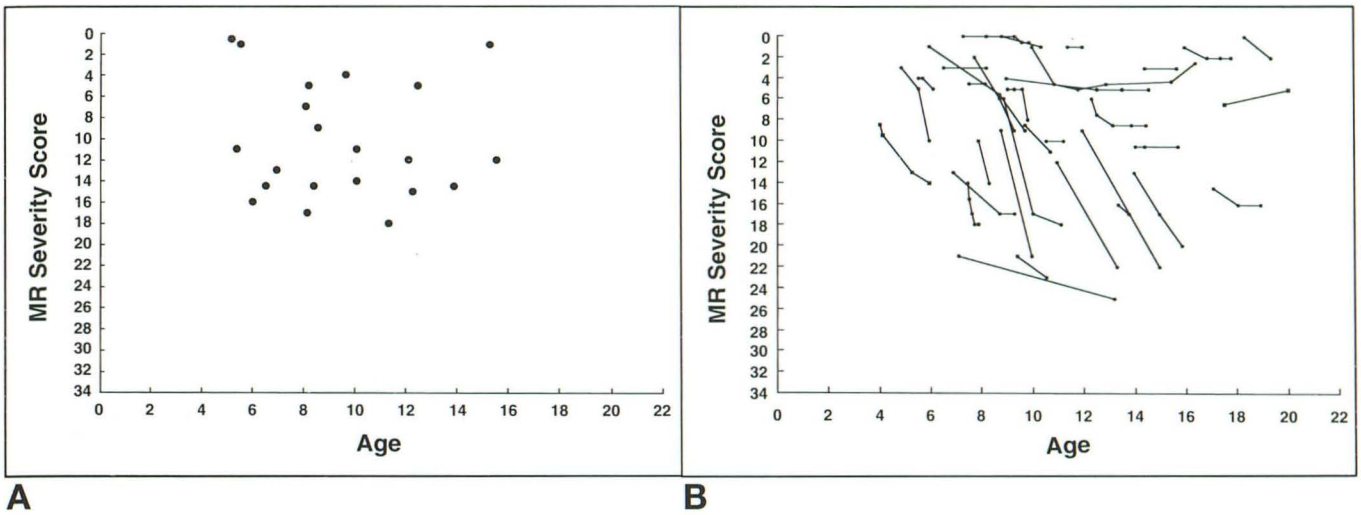

Fig 1. Adrenoleukodystrophy severity score versus age: isolated (*A*) and serial (*B*) MR analyses.

patients with the anterior white matter pattern had isolated, less-severe posterior white matter disease. Cerebellar white matter disease, which was present in 2 patients with the anterior white matter pattern, was not seen in the patients with the posterior pattern. The mean MR severity score for the posterior pattern was 9 with a range of 0.5 to 25. The mean severity score for the anterior pattern was 10 with a range of 2 to 18. The three patients with isolated projection fiber abnormalities all had MR severity scores of 1.

Serial brain MR scans were available in 48 patients. Fourteen of these patients had negative serial exams (mean scan number, 3.0; mean follow-up interval, 18 months; range, 3 months to 3 years 10 months). Thirty-four patients with serial brain MR exams had positive MR findings for adrenoleukodystrophy (mean scan number, 2.9; mean follow-up interval, 23 months; range, 2 months to 6 years 11 months). Based on MR severity scores, serial MR examinations in the MR-positive group of patients with adrenoleukodystrophy showed progressive disease in 52%, progressive disease with subsequent stabilization in 18%, stable disease in 24%, and minimal improvement in 6%.

Discussion

X-linked adrenoleukodystrophy can produce serious and lethal damage to the central nervous system (7). The biochemical defect for X-linked adrenoleukodystrophy can be diagnosed in asymptomatic and symptomatic persons by a plasma assay that detects elevated, saturated, very-long-chain fatty acids in affected patients (8). It is believed that asymptomatic patients with the biochemical defect will eventually develop either the devastating childhood-onset cerebral adrenoleukodystrophy or the later-onset less severe form known as adrenomyeloneuropathy (7). Childhood-onset cerebral adrenoleukodystrophy is characterized by early onset, between the ages of 5 and 8, progressive cerebral inflammatory demyelination with or without prior adrenal insufficiency, and rapid neurologic deterioration leading to death (7). Adrenomyeloneuropathy (adult-onset adrenoleukodystrophy) has a more protracted course and is characterized by spinal cord and peripheral nerve involvement out of proportion to cerebral disease (7, 9, 10). Childhood-onset cerebral adrenoleukodystrophy and adrenomyeloneuropathy have overlapped phenotypic variants and some overlap with regard to age at clinical onset.

The major use of the adrenoleukodystrophy MR severity scoring system is to provide a measure for brain involvement. It was designed to be applicable to standard MR exams and reproducible by any neuroradiologist or other individual familiar with neuroanatomy and MR of the pediatric brain.

The adrenoleukodystrophy MR severity scoring system capitalizes on the neuroanatomic locations that are exquisitely illustrated when involved by the disease process (1). The primary neuroanatomic compartments involved by adrenoleukodystrophy include supratento-

rial white matter, the corpus callosum, the auditory and visual pathways, and major projection fibers such as the pyramidal tract and the frontopontine tract. These primary locations were subcompartmentalized to allow for more discrimination in the scoring system. Areas of less-frequent involvement, such as the cerebellum, basal ganglia, and anterior thalmus, were also included in the scoring system but were not further subdivided.

The adrenoleukodystrophy MR severity scoring system also takes into consideration the presence or absence of focal and/or global atrophy. Atrophy, either selective or diffuse, can mimic improvement on MR. Two other major pitfalls in diagnosing adrenoleukodystrophy MR involvement also exist. One must be cautious not to overinterpret subtle symmetric parietooccipital signal hyperintensity on T2-weighted images, which may represent normal incom-

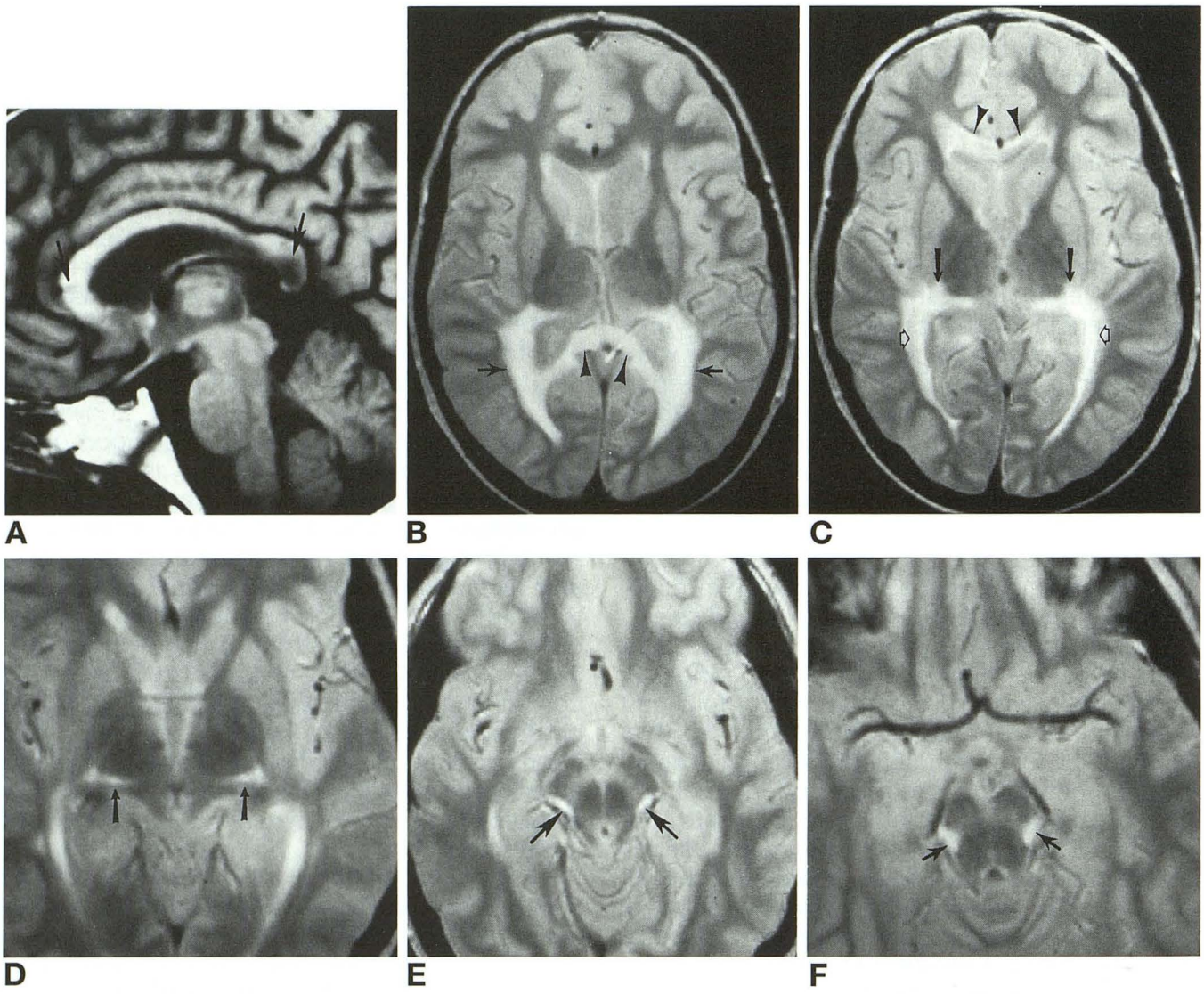

Fig 2. MR images in a 9-year-old boy with a parietal pattern of adrenoleukodystrophy.

A, Sagittal T1-weighted image (800/20/1 [repetition time/echo time/excitations]) shows involvement of the splenium and subtle involvement of the genu of the corpus callosum (*arrows*) without focal atrophy.

B–F, Sequential axial proton density–weighted images (2500/45) through brain and brain stem from cephalad to caudal confirm involvement of the splenium and genu of the corpus callosum (*arrowheads* in *B* and *C*) and show involvement of periventricular parietooccipital white matter (*arrows* in *B*), lateral geniculate bodies (*arrows* in *C*), optic radiations (*open arrows* in *C*), medial geniculate bodies (*arrows* in *D*), brachium of the inferior colliculus (*arrows* in *E*), and lateral lemniscus (*arrows* in *F*) for a total MR severity score of 8. In the middle to late stages of the posterior pattern, isolated anterior involvement (as seen in this case by involvement of the genu of the corpus callosum) or direct frontal progression is frequently seen.

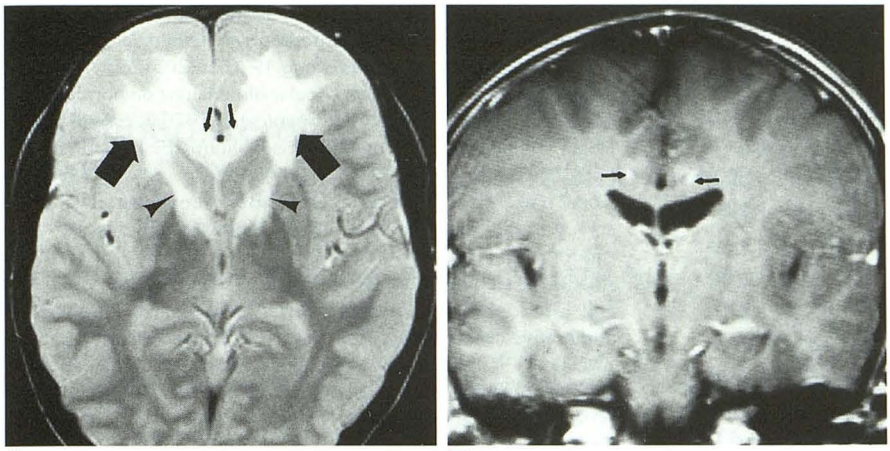

Fig 3. MR images in an 11-year-old boy with a frontal pattern of childhood-onset cerebral adrenoleukodystrophy.

A, Axial proton density–weighted image (2500/45) shows involvement of the genu of the corpus callosum (*small arrows*), the anterior limb and genu of the internal capsules (*arrowheads*), and the periventricular, central, and subcortical frontal white matter (*large arrows*). Because there was additional brain stem involvement (not shown), the patient received an MR adrenoleukodystrophy severity score of 6.

B, Coronal postcontrast T1-weighted images (800/20) show involvement of the lateral longitudinal fasciculus (*arrows*).

pletely myelinated white matter, as definite adrenoleukodystrophy (11, 12). Small well-defined punctate supratentorial white matter hyperintensities (unidentified bright objects) also should not be overinterpreted as representing definite disease. Although unusual in children, unidentified bright objects rarely are caused by adrenoleukodystrophy. Serial examinations are especially useful in both of these groups of patients.

The MR signal changes in adrenoleukodystrophy are caused by an inflammatory demyelinating process resulting in prolongation of T1 and T2 relaxation times (13). Areas of involvement on MR are best seen as foci of hyperintense signal on T2-weighted images. In a few patients, brain stem involvement was better depicted on postcontrast T1-weighted images as abnormal areas of enhancement. Involvement of the splenium or genu of the corpus callosum was frequently better seen as areas of hypointense signal on noncontrast sagittal T1-weighted images, probably because the corpus callosum is more easily evaluated in the sagittal plane than in the axial plane. Ideally, a T2-weighted sagittal sequence would be the best method to evaluate the corpus callosum in patients with adrenoleukodystrophy.

Our series confirms the predominance of the posterior pattern of parietooccipital white matter disease of X-linked adrenoleukodystrophy, which frequently involves the auditory and visual pathways and the corticospinal tracts (Fig 2). MR abnormalities in these patients progressed from central to peripheral and posterior to anterior cerebral white matter involvement with subsequent development of focal and global atrophy. An anterior pattern involving frontal white matter, the genu of the corpus callosum, the frontopontine tract, and occasionally the cerebellum was observed in 15% of MR-positive patients (Fig 3). Isolated projection fiber abnormalities were present in 5% of MR-positive patients. Adrenoleukodystrophy has the propensity to spread longitudinally along white matter tracts. Interestingly, three of the eight patients with frontal disease showed involvement of the lateral longitudinal fasciculus, which is a tiny vestigial white matter tract along the superior lateral surface of the corpus callosum (Fig 3).

The severity score was designed to compare serial MR exams among individual patients. Because adrenoleukodystrophy may have at least two different patterns of disease and possibly more, we do not believe that this scoring system can be used to compare patients with different disease patterns. It may be cautiously used as a method to compare those with the same disease pattern. It is important to emphasize that subtle changes did not usually result in a change in severity score. This system was adopted because volume averaging and differences in scan planes could readily result in pseudoimprovement or pseudodeterioration. At our institution, we use a standard angle acquired from sagittal images to reproduce nearly identical axial images on serial examinations.

A slight majority of patients with positive MR exams showed progressive disease on subsequent serial imaging, although almost an equal number showed stabilization of their disease on MR. Although not reflected in the MR severity score, the edges of stable lesions occasionally appeared better defined on follow-up examinations, and the areas of involvement question-

ably improved. This finding may be attributable to a reduced inflammatory component, retraction from focal atrophy, or minimal remyelinization. The two patients who improved had resolution of brain stem abnormalities. They were in their middle and late teenage years; hence, they had adrenomyeloneuropathy or an overlap phenotype rather than childhood-onset cerebral adrenoleukodystrophy. Five other patients also showed slight or questionable improvement in selective areas, but because other areas worsened, their MR severity scores did not improve.

There is a need to categorize better the phenotypic variants of adrenoleukodystrophy (14). MR imaging and neuropsychologic testing are the primary tools currently being used to evaluate asymptomatic and symptomatic patients with adrenoleukodystrophy and monitor their responses to therapy (15–18). The adrenoleukodystrophy MR severity scoring method, when used in combination with neuropsychologic and neurologic parameters, may improve our characterization of the natural history of the disease and monitoring of therapeutic interventions.

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