

Inflammatory Myelinoclastic Diffuse Sclerosis (Schilder's Disease): Neuroradiologic Findings

M. F. Mehler¹ and L. Rabinowich

Controversy has surrounded the rare clinicopathologic entity of inflammatory myelinoclastic diffuse sclerosis (IMDS) since the seminal description of Schilder in 1912 [1]. Since that time several distinct myelinoclastic and dysmyelinating conditions have been grouped under this eponym. To this newly described demyelinating disease, the author planted the seeds of an enduring controversy by including two additional cases (1913, 1924) [2, 3] that, in retrospect, were shown to be examples of a leukodystrophy and, possibly, subacute sclerosing panencephalitis, respectively. As a result, the evolving eponym "Schilder's" has come to represent a much wider spectrum of disease than the original 1912 description, including examples of adrenoleukodystrophy, acute disseminated encephalomyelitis, transitional sclerosis, and juvenile multiple sclerosis. In the context of recent advances in biochemistry, neuroimaging, and electrophysiology, it has been possible to more systematically separate related disorders of white matter. This diagnostic reappraisal has allowed the emergence of a rare IMDS that remains faithful to Schilder's original 1912 description. We present only the third fully documented case. The temporal profile spans the entire spectrum of clinical forms of IMDS previously defined by Lhermitte [4]. Because of the rapid and dramatic fluctuations in the patient's functional status, it has been possible to obtain sequential CT and comparative MR scans that graphically document the interplay of cavitary and diffuse white-matter lesions. This has allowed cliniconeuroradiologic assessment of this rare but distinctive inflammatory myelinoclastic condition, rigorously defined by biochemical, pathologic, and electrophysiologic criteria.

Case Report

A 12-year-old Ashkenazi Jewish girl was hospitalized in May 1985 with a 2-week history of progressive headaches, lethargy, and personality changes. Neurologic examination showed the patient to be lethargic but fully oriented when aroused. There was bilateral papilledema with left-sided facial and limb weakness associated with hyperactive reflexes and Babinski sign. Results of routine laboratory

tests were normal. An admission CT scan of the brain (Fig. 1) showed asymmetric bifrontal subcortical lucent lesions, larger on the right side. Lumbar puncture revealed elevated protein with no cells, normal glucose, negative cultures, and absence of oligoclonal banding. Dexamethasone, 60 mg daily, resulted in rapid improvement in arousal, attention, personality, and motor functioning.

The patient was transferred to another hospital where a right frontal-pole needle biopsy yielded 50 ml of serous, slightly hemorrhagic fluid under increased pressure. Cultures and staining were negative. She was promptly discharged and dexamethasone was discontinued.

In July 1985, she began to exhibit personality changes with aggressive behavior and poor attention span. A repeat CT scan was performed (Fig. 2). In the ensuing 2 months a progressive anterior perisylvian aphasia developed with a mild right hemiparesis and frontal lobe signs. The patient's condition continued to worsen. In September, she was readmitted with several generalized seizures. The CT scan obtained at this time is shown in Figure 3. CSF studies were unchanged with equivocal oligoclonal banding. An MR scan was also done 1 month later (Fig. 4). She was started on a regimen of diphenylhydantoin and phenobarbital. The patient was now mute but could follow simple commands. The fundi were normal. A right facial and marked right-sided weakness were present with bilateral hyperactive reflexes and Babinski signs. An EEG showed bifrontal slowing. A formal open craniotomy with deep frontal biopsy was performed. Microscopic studies revealed confluent areas of selective myelin breakdown with sparing of axons and contiguous subcortical U-fibers, perivascular inflammatory infiltrates (lymphocytes and plasma cells), and substantial edema. Ultrastructural studies revealed thinly and redundantly myelinated axons. Moderate clinical improvement in attention, language, and motor functioning followed the reinstitution of steroid therapy at the initial therapeutic dosage.

One month later, progressive left-sided weakness and gait instability ensued. The CT scan obtained at this time is shown in Figure 5. Over the next 6 months the patient's aphasia and hemiparesis continued to improve on maintenance corticosteroid therapy. However, progressive gait and postural instability and urinary and fecal incontinence supervened.

On examination, the patient appeared well developed with difficulty sitting upright and moderate kyphoscoliosis. She was euphoric and had rapid, imprecise speech. Her attention was mildly impaired, and her short-term memory and visuospatial reasoning were poor. There was a mild left ideomotor apraxia. Muscle tone was reduced through-

Received August 13, 1987; accepted after revision December 9, 1987.

This work was supported in part by Teacher-Investigator Development Award (NS00856) from the National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health.

¹ Both authors: Saul R. Korey Department of Neurology (F, G-9), Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461. Address reprint requests to M. F. Mehler.

Fig. 1.—Admission CT scan with contrast shows asymmetric bifrontal predominantly subcortical cystic lesions, larger on the right side with absence of contrast enhancement.

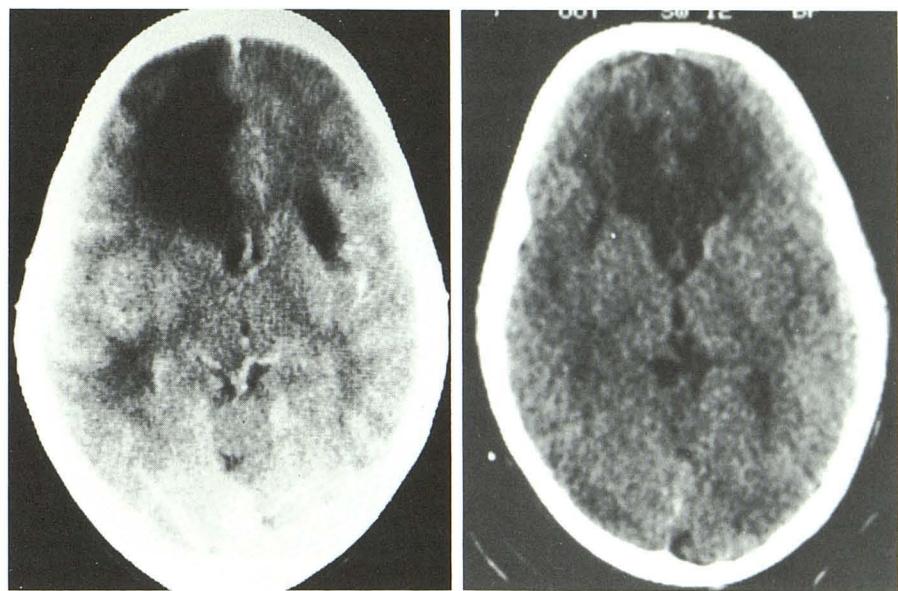


Fig. 2.—CT scan 2 months after admission shows large bifrontal white-matter hypodensities involving the anterior corpus callosum.

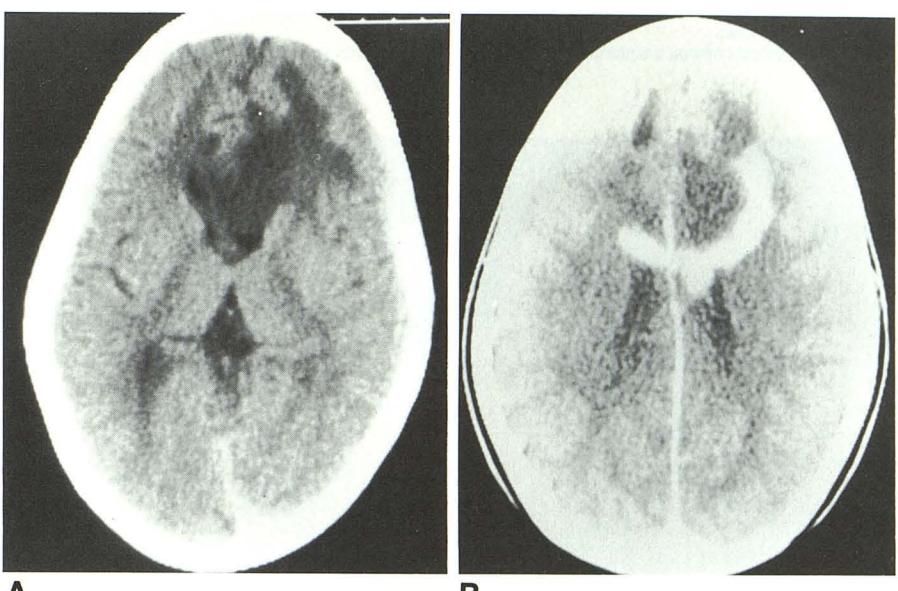


Fig. 3.—*A*, CT scan 2 months after Fig. 2 reveals bifrontal extension of the areas of white-matter attenuation, with left-sided predominance and further compression of frontal horns.

B, With contrast administration, CT scan shows area of maximal partial ring enhancement at border of parenchymal lesion.

out, with quadriplegia. Deep tendon reflexes were exaggerated throughout with left Babinski sign. Lower extremity proprioceptive and vibratory loss, bilateral frontal release signs, and double incontinence were present.

There was no family history of neurologic disease. Perinatal history and developmental milestones were normal. There was no history of recent immunizations or toxin or pet exposure. The patient had traveled to the Middle East (Israel) 1 year before initial presentation.

Normal ratios of long chain (C26/22) fatty acids were obtained in plasma and cultured skin fibroblasts. CSF cultures and viral titers, collagen vascular survey, and HIV screening were all negative. Visual and brainstem auditory evoked responses and nerve conduction studies were normal. Biochemical studies to exclude lysosomal enzyme deficiencies and disorders of amino acid metabolism were unrevealing. Formal neuropsychologic evaluation revealed a verbal

I.Q. score of 84 with evidence of poor short-term verbal memory and abstract reasoning.

Between April 1986 and September 1988 the patient exhibited examples of both slowly progressive and rapid functional improvement. Gait, postural stability, and strength have shown steady improvement to the point where ambulation with minimal assistance is possible. Recent (past 3 months) rapid gains have occurred in the control of bladder and bowel function so that the patient is now fully continent. Although evidence of disinhibited, indifferent behavior with a poor attention span, indicative of frontal lobe dysfunction, is still present, she has made significant affective gains that have warranted reenrollment in a special education program. (Formal schooling had been curtailed for more than 2 years because of intractable behavioral problems.) During this interval the family has refused further neurologic assessment.

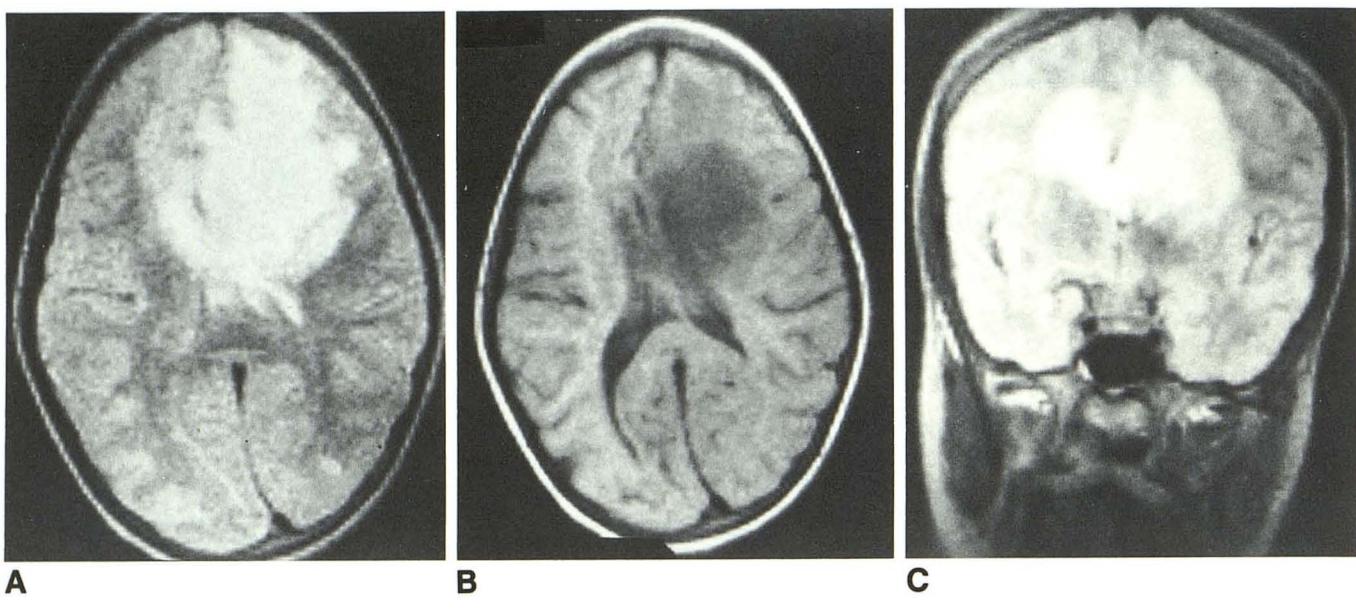


Fig. 4.—MR images taken 3 months after Fig. 2.

A, T2-weighted sequence at level of maximal pathologic change reveals the extent of parenchymal involvement.

B, T1-weighted sequence at same level shows relationship of lesion to ventricular system and accurately identifies the extent of mass effect and subfalcial herniation.

C, T2-weighted coronal sequence at level of maximal pathologic change demonstrates the extent of subcortical and callosal involvement.

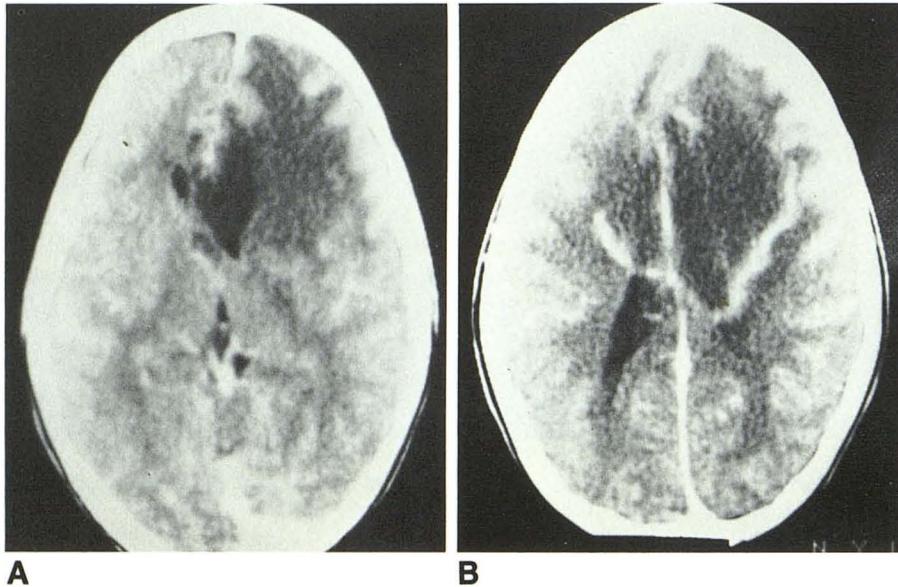


Fig. 5.—A, CT scan 4 months after Fig. 2 shows further progression of left frontal hypodense focus and the appearance of a large midline subcortical cystic lesion, further obliterating the lateral ventricles.

B, With contrast administration, CT scan shows area of thinner but more extensive contrast enhancement near the border of the parenchymal lesion. Both this and Fig. 3B may be compared with the mid-sequence MR image of Fig. 4A. All images are at the level of maximal pathologic involvement.

Discussion

A severe, subacute encephalopathy developed in a 12-year-old girl, and during a brief but dramatic temporal course, recapitulated the entire clinical spectrum attributed by Lhermitte [4] to Schilder's disease: psychiatric predominance, acute intracranial hypertension, intermittent exacerbations, and progressive deterioration. The MR and serial CT scans are the first neuroimaging studies of this variety reported in

IMDS and provide a unique perspective on the interplay of cavitary and diffuse subcortical white-matter lesions that accompanied the rapidly evolving clinical profile. The pathologic findings of severe, selective myelinoclasia, inflammatory changes, exquisite subcortical U-fiber sparing, and extensive myelin regenerative capacity establish the disease process as a primary inflammatory demyelinating disorder. In arriving at a diagnosis of IMDS, a number of clinicopathologic entities had to be considered, including adrenoleukodystrophy (ALD),

the Lowenberg-Hill form of Pelizaeus-Merzbacher disease, several disseminated scleroses (transitional, Balo's concentric, acute Marburg), childhood multiple sclerosis, progressive multifocal leukoencephalopathy (PML), the acute encephalomyelitis, and rare toxic and vascular conditions. These neurologic disorders were excluded by a variety of clinical, paraclinical, ultrastructural, viral, immunological, and biochemical tests. Definitive diagnosis of IMDS requires exclusion of ALD by findings of normal ratios of long-chain fatty acids in plasma/cultured skin fibroblasts. The absence of precise biochemical testing prior to 1980 has contributed to the diagnostic confusion between the two diseases. Rigorously defined cases have only been described in children (both sexes) [5, 6], although incompletely studied patients suggest that adults may also be affected.

The present case demonstrates a remarkable array of temporospatial and parenchymal density changes with serial CT scans over a brief but dramatic clinical course. Extensive, bilateral, anterior hemispheric, subcortical white-matter lesions are constantly present but show a rapidly changing pattern of cystic and diffuse low-density predominance. No noncontiguous foci are demonstrable by neuroimaging or paraclinical testing. With contrast administration at different times, one demonstrates either absence of (Fig. 1) or dramatic partial ring enhancement (Figs. 3B and 5B). This is different from the type-II pattern of selective parenchymal enhancement in ALD and the uniform hyperdense foci seen in Balo's concentric and other diffuse sclerosis [7-11]. Although the parenchymal location and rapidity of the initial clinical course may be similar to PML, IMDS also differs from this condition by several imaging features. In PML, there is an enduring CT-clinical dissociation in both the location and the latency of correlative lesions, and progressive, multifocal white-matter involvement, with relative absence of mass effect and contrast enhancement [12-17]. Thus, IMDS can be seen to exhibit an unusual constellation of neuroimaging features: extensive bihemispheric white-matter lesions with dramatic temporospatial density changes. These parenchymal changes show mass effect, fluctuating forms of contrast enhancement, excellent clinical correlation with absence of a unimodal course, and absence of noncontiguous foci. When coupled with specific biochemical (normal plasma ratios of long-chain fatty acids to eliminate ALD), electrophysiologic (trimodal evoked potentials to confirm the absence of noncontiguous parenchymal demyelinating foci) and pathologic (appearance of acute inflammatory demyelination) criteria, the neuroimaging findings are diagnostic for IMDS.

Despite the large pathologic foci, there is excellent clinico-radiologic correlation. Initially, the bifrontal but predominantly right-sided foci (Fig. 1) are compatible with the observed personality changes and left hemiparesis. As the lesions become deeper, more diffuse, and midline (Fig. 2), diencephalic and paralimbic areas mediating emotional expression, including anger, become involved. As the pattern of predominant white-matter involvement shifts to left frontal and perisylvian areas (Fig. 3A), a right hemiparesis and Broca's aphasia ensue. The pattern of agrammatical, effortful speech progressing to mutism is opposite to the pattern usually

documented with vascular infarction, and emphasizes the progressive involvement of anterior perisylvian areas illustrated by serial CT scans (Figs. 3A and 5A) and confirmed by MR (Fig. 4A).

This case and a review of the literature, suggest that, rigorously defined, IMDS is a subacute or chronic inflammatory myelinoclastic disorder resulting in extensive, often cavitary, bilateral hemispheric white-matter lesions with mass effect, the absence of noncontiguous foci, and histologic resemblance to acute multiple sclerosis (i.e., inflammatory demyelination with exuberant myelin regeneration). Diagnostic dilemmas in the field of demyelinating disease have directly resulted from the inconsistencies of Schilder's early reports and the absence of definitive biochemical analysis prior to 1980 [7]. Neuroimaging is crucial in establishing the temporospatial and parenchymal pattern of white-matter involvement and in documenting the absence of additional foci in the neuraxis. When the latter is combined with paraclinical data, the accuracy of assessment is excellent. In the future, as more cases of IMDS are diagnosed, neuroimaging will be invaluable in charting the natural history of the disease process and the neuroanatomic and physiologic responses to various therapeutic manipulations.

ACKNOWLEDGMENTS

We thank Donna Platyan, Rosemary Cafarelli, and Carmela Fucci for their skill and patience in the preparation of the manuscript.

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Editor's Note.—An abbreviated report of this case, titled "Inflammatory Myelinoclastic Diffuse Sclerosis," appeared in the April 1988 issue of *Annals of Neurology* (*Ann Neurol* 1988;23:413-415).