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Demyelinating and Gliotic Cerebellar Lesions in Langerhans Cell Histiocytosis

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PURPOSE: To describe the involvement of the cerebellum by a gliotic and demyelinating process in Langerhans cell histiocytosis. **METHODS:** A retrospective analysis of all (N = 30) cases of Langerhans cell histiocytosis followed at our institution since 1975 yielded four patients with CT and/or MR evidence of cerebellar abnormalities. **RESULTS:** Four patients manifested strikingly similar findings of symmetric nonenhancing hypodensities in the dentate nuclei region of the cerebellum, which were hypointense on short-repetition-time/short-echo-time MR and hyperintense on long-repetition-time/long-echo-time MR. Biopsy in one patient yielded areas of demyelination, cell loss, and gliosis without histiocytic infiltration. **CONCLUSION:** Langerhans cell histiocytosis involves the cerebellum in a specific and poorly understood manner. Lesions on imaging may precede clinical findings by years. Lesions may occur in patients who have never experienced radiation therapy and may act as a marker for eventual central nervous system deterioration.

Index terms: Histiocytosis X; Cerebellum, abnormalities and anomalies; Pediatric neuroradiology; Demyelinating disease

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Langerhans cell histiocytosis (formerly known as histiocytosis X) is a disease of unknown cause characterized by proliferation of histiocytic granulomas in tissues, the spectrum of which ranges from a solitary lesion of bone to a rapidly fatal multisystem infiltration. Cerebral manifestations, discovered primarily as hypothalamic infiltration causing diabetes insipidus, are a common occurrence in this disease. Cerebellar manifestations, although described in various case reports dating back to the 1930s, are not generally recognized, and some aspects are poorly understood.

Working at a regional oncology referral center, we have cooperated in the care of children with Langerhans cell histiocytosis. Over the years, we have cared for children with cerebellar dysfunction and/or central nervous system (CNS) deterioration and Langerhans cell histiocytosis. Four patients sequentially developed similar imaging abnormalities in the cerebellum on computed tomography (CT) and magnetic resonance (MR). This prompted us to review our records and the literature on this subject.

Materials and Methods

We retrospectively reviewed all 30 cases of Langerhans cell histiocytosis either diagnosed or followed at our institution since 1975. Three (10%) of these patients had cerebellar signs and symptoms with strikingly similar imaging findings on CT and/or MR within the deep nuclear region and corpus medullare of the cerebellum. One other patient has recently prospectively developed similar imaging abnormalities without initial cerebellar dysfunction. One patient was studied with radionuclide brain scanning; 2 patients underwent angiography; 1 patient received a CT scan on a second-generation scanner; and 2 patients underwent MR with a 1.5-T system. The case histories are summarized in the Table.

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Clinical, diagnostic, and imaging findings in four children with Langerhans cell histiocytosis

Patient	Age, y	Findings
1	7½	Diabetes insipidus and eczema. No radiation therapy.
	10	Intention tremor.
	11	Dysmetria. Dysdiadochokinesia MR/CT cerebellar abnormalities in dentate nuclei regions and white matter.
	12	No progression of clinical disease. New lesions in basal ganglia.
2	3½	Orbital mass and eczema. No radiation therapy initially.
	4½	CT: no cerebellar dysfunction. Hypodensities in bilateral corpus medullare.
	7½	Cerebellar dysfunction clinically first appears. Biopsy: demyelination, loss of Purkinje and granular cells.
3	2½	Orbital mass. Radiation therapy confined to orbit and frontal bone.
	3½	Clinical cerebellar signs. Normal cerebrospinal fluid; technetium brain scan; cerebral angiography.
	9	CT scan symmetric hypodensities in deep nuclei cerebellar regions and white matter.
	11-present	Progressive cerebral cortical, brainstem and corticospinal tract degeneration.
4	2½	Bone lesions and eczema.
	7	Zygomatic mass: Chemotherapy, low-dose radiation therapy, surgery.
	10	CT/MR: symmetric lesions in cerebellar white matter. Large extraaxial granuloma of posterior fossa.

Results

The clinical, diagnostic, and imaging findings are summarized in the Table. The four children ranged in age from 2.5 to 7.5 years at presentation of Langerhans cell histiocytosis. Of the three children who developed cerebellar dysfunction, the average time from initial presentation to dysfunction was 2.4 years. One child has not developed cerebellar dysfunction for more than 6 months after detection of imaging abnormalities. Patient 2 did not exhibit clinical cerebellar signs for 3 years after CT abnormalities. One child presented with diabetes insipidus, and another acquired diabetes insipidus 1 year later. When treated with chemotherapy, the children received standard doses of prednisone, vincristine, or vinblastine and/or cyclophosphamide. Radiation doses, when given, were fractionated in a standard regimen. Review of

radiation ports substantiated little probability of significant scatter to the cerebellum. Two children did not receive radiation therapy before imaging abnormalities. Brain stem auditory evoked responses were abnormal in all three patients in which this was performed. This physiologic aberration was reflected in imaging of the brain stem in only one of the patients (patient 1), who had been followed for years with MR.

At 7½ years of age, auditory evoked responses in patient 2 revealed bilateral upper and lower brain stem dysfunction. One month later, he underwent open cerebellar biopsy. Grossly this tissue had a rubbery consistency. Histologically, it revealed demyelination, gliosis, and loss of Purkinje and granular cells (see Fig 2). There was no evidence of histiocytic infiltration.

In all patients, imaging revealed strikingly similar abnormalities in the dentate and deep nuclei regions and corpus medullare of the cerebellum. On CT, these were manifested as non-enhancing, noncalcified hypodensities (Figs 1C and D and 2B). On long-repetition-time (TR)/short-echo-time (TE) and long-TR/long-TE conventional and fast spin-echo MR sequences the lesions were hyperintense (Figs 1A and B, 2A, and 3B). None of the lesions studied after gadopentetate dimeglumine administration enhanced. Patient 1 had even more unusual findings: repeat MR of the brain performed at 1.5 T (Fig 1) at 12 years of age revealed no significant changes in her cerebellar abnormalities, which centered symmetrically in the deep nuclei region of the cerebellum and extended into the adjacent deep white matter (Figs 1A and B), but she had developed multiple small lesions in the pons and basal ganglia and internal capsules. These were primarily hyperintense on T2-weighted images and nonenhancing. Some lesions were hyperintense on T1-weighted images (Fig 1E). One year later, some of the lesions had improved, and she clinically remained stable without evidence of pyramidal or extrapyramidal tract dysfunction. Of the two patients who underwent arteriography, no abnormalities were found. Of the two patients who underwent cerebrospinal fluid analysis, no abnormalities were found. The isotopic brain scan in our third patient was performed before the advent of CT scanning at our institution, and findings were normal.

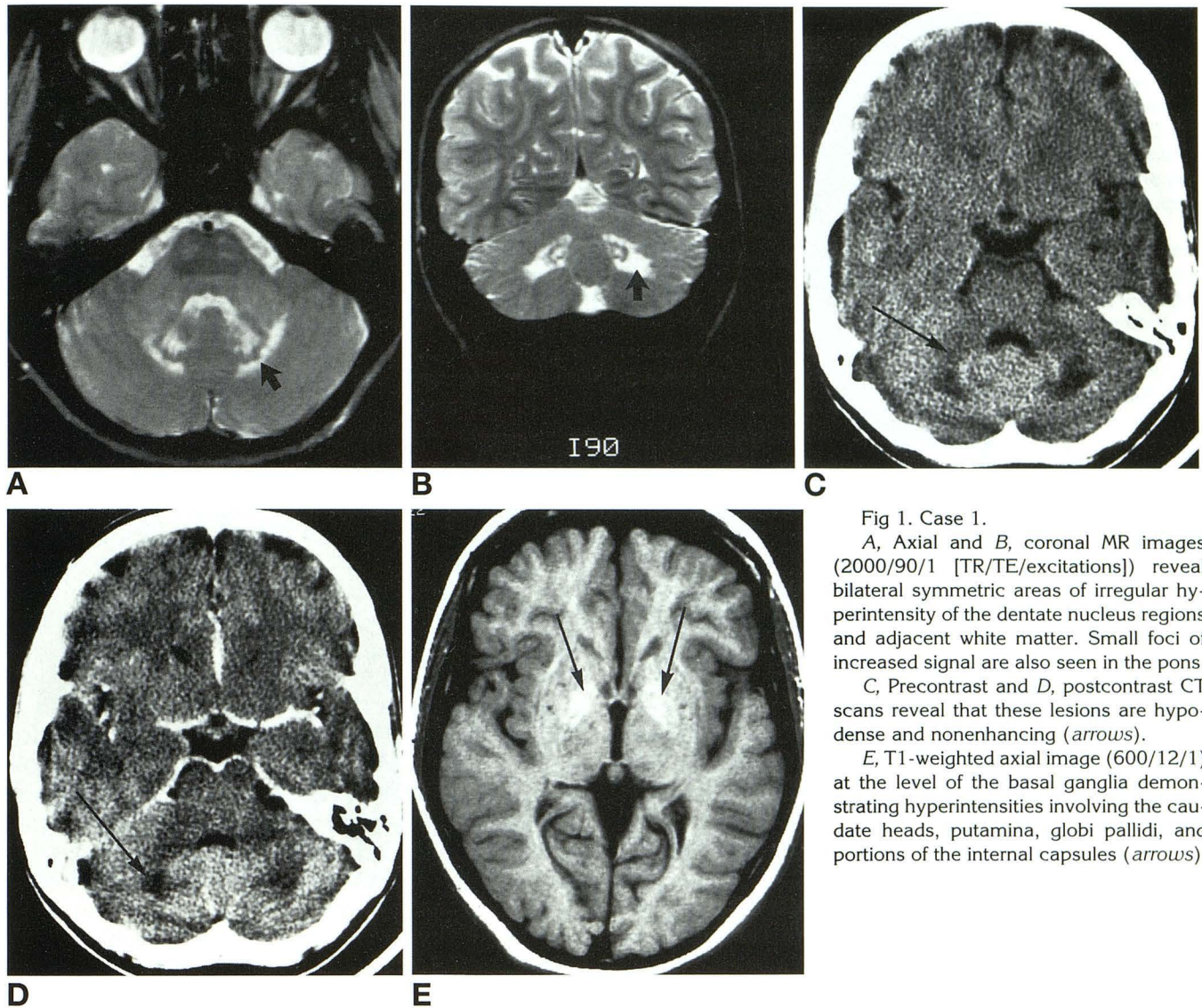


Fig 1. Case 1.

A, Axial and B, coronal MR images (2000/90/1 [TR/TE/excitations]) reveal bilateral symmetric areas of irregular hyperintensity of the dentate nucleus regions and adjacent white matter. Small foci of increased signal are also seen in the pons.

C, Precontrast and D, postcontrast CT scans reveal that these lesions are hypodense and nonenhancing (arrows).

E, T1-weighted axial image (600/12/1) at the level of the basal ganglia demonstrating hyperintensities involving the caudate heads, putamina, globi pallidi, and portions of the internal capsules (arrows).

Discussion

The term *histiocytosis X* was coined by Lichtenstein in 1953 (1) to consolidate infiltrative granulomatous conditions variously called *Letterer-Siwe disease*, *Hand-Schuller-Christian syndrome*, and *eosinophilic granuloma* under one name. In 1987, the Writing Group of the Histiocyte Society proposed that the term *Langerhans cell histiocytosis* replace *histiocytosis X*, because the Langerhans-type histiocyte is a unique identifier for this disease (2).

Langerhans cell histiocytosis is a disease of unknown cause created by a proliferation of nonmalignant Langerhans-type histiocytes into various tissues of the body. The cells have specific biochemical and ultrastructural definition, including the electron-microscopic presence of

Birbeck granules (3). Clinical manifestations are variable and range from a nonprogressive solitary eosinophilic granuloma of bone to a rapidly progressive and fatal multisystem involvement (previously referred to as Letterer-Siwe disease). Langerhans cell histiocytosis is more common in white children and usually appears in the first decade. Bone lesions are the most common site of the disease, with prognosis relating to age of presentation and the number of organ systems involved (4-7). Specific organ system involvement sometime during the course of this disease may be approximated in descending order of frequency as follows: bone (80%); skin (45%); liver, spleen, and lymphatic (35%); hematopoietic (30%); CNS (10-50%); pulmonary (25%); orbital (25%); otologic

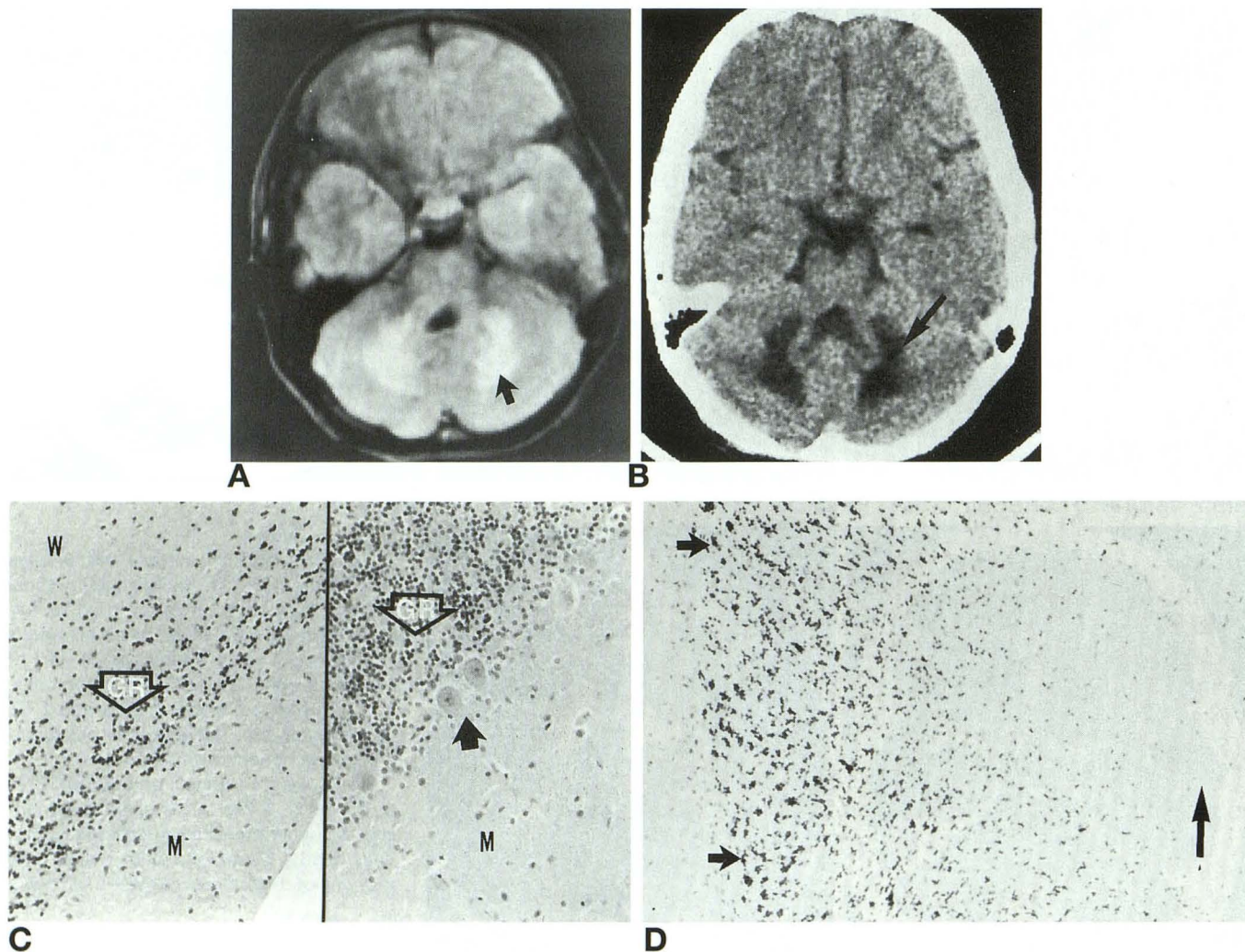


Fig 2. Case 2.

A, Long-TR/long-TE axial MR image (1800/110/1) reveals bilateral symmetric areas of irregular hyperintensity of the dentate nucleus regions, including the corpus medullare (arrow).

B, Axial CT scan with symmetric hypodensities in the corpus medullare (arrow).

C, Photomicrograph comparing a biopsy specimen in patient 2 (left) to normal cerebellar cortex (right). The granular cell layer (GR) is much thinner and more sparsely populated in our patient. There is a conspicuous absence of Purkinje cells compared with normal (arrow). (Micrographs taken at different magnifications to demonstrate a large area of granular and Purkinje cell loss: right magnification, $\times 110$; left, $\times 270$.) W indicates white matter; M, molecular layer.

D, Photomicrograph of a biopsy specimen in patient 2 stained for myelin and counterstained with hematoxylin and eosin. There is gross demyelination with minimal myelin staining in the white matter (long arrow). There is near-complete absence of Purkinje cells, which should be seen just superficial to the granular cell layer (short arrows) (Luxol fast blue and hematoxylin and eosin stains, low power).

(20%); and dental (20%) (5, 6, 8–13). CNS manifestations occur most frequently with multisystem disease; only rarely do they present initially or solely in the CNS (14, 15). When present, these granulomas are most commonly in the subarachnoid space. Infiltration into the hypothalamus or posterior pituitary, creating diabetes insipidus, is overwhelmingly the most commonly identified premortem CNS focus of disease (4). In the brain, the granulomas are

believed to begin as periaxonal infiltrations around small vessels (4). These CNS granulomas are composed of Langerhans histiocytes, microglial cells, fibrillary astrocytes, and other inflammatory cells, such as plasma cells, leukocytes, and fibroblasts (4, 16, 17).

There have been several reports in the last 25 years in which patients with various manifestations of histiocytosis X exhibited signs and symptoms of cerebellar dysfunction (14, 17–

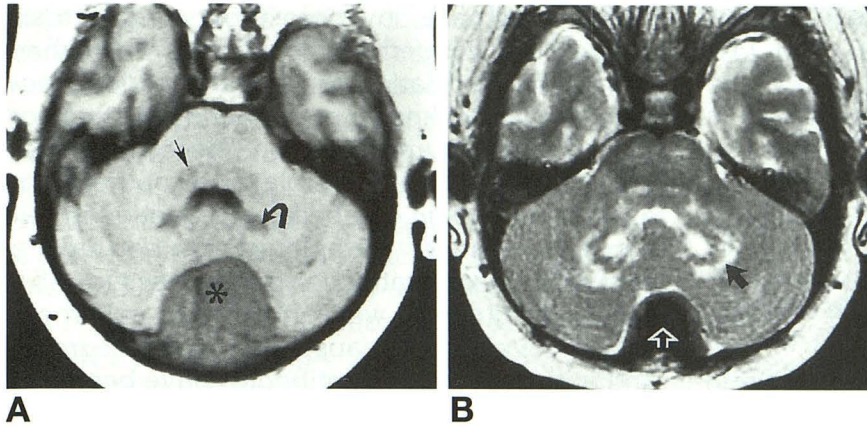


Fig 3. Case 4.

A, Axial T1-weighted image at the level of midpons (600/15/2). There are symmetric areas of hypointensity deep to the brachium pontis in the region of the dentate nuclei (*curved arrow*). Notice confluent hypointensity within the pontine tegmentum (*straight arrow*). The posterior midline extraaxial granuloma (*asterisk*) is well circumscribed and hypointense to white matter.

B, T2-weighted (fast spin-echo) axial image at similar level as A (3500/108/1). Hyperintensities define the areas of presumed demyelination and gliosis in the cerebellum and pons (*dark arrow*). For unclear reasons, the posterior extraaxial granuloma (*white arrow*) is very dark on long-TR sequences. (It was not calcified on CT.)

26). In most of these cases pathologic correlations were not made. In 1979, Adornato et al (20) published clinical follow-up and the CT scans of four patients previously described by Braunstein et al (21). All four had abnormal cerebellar function. Two patients had calcification in the region of the cerebellar dentate nuclei. One patient had bilateral hypodense areas in the medial portions of both cerebellar hemispheres. In the fourth patient, the fourth ventricle and posterior fossa cisterns were prominent, and there was a "suggestion" of decreased absorption in the right cerebellar hemisphere.

Kristenssen (25) described a 3-year-old boy presenting with cerebellar ataxia and multiple skull and other bone lesions. He was treated with irradiation (specifics not given), with regression of the bone lesions. He deteriorated neurologically over the next 2 years, progressing to spastic tetraplegia. The patient died at age 6 of a respiratory infection. Autopsy revealed lesions most marked in the cerebellum. Histologically, demyelination, gliosis, and Purkinje cell loss were found similar to the pathologic results in our patient 2. No histiocytic infiltration was seen in the CNS, although there was granulomatous infiltration in several other organs. Elian et al (18), Braunstein et al (21), and Yamaguchi et al (23) reviewed the literature and found reports of a total of 27 patients with clinically evident cerebellar signs and pathologic findings at autopsy. Twenty-five of these cases were reported before 1960. There is no mention of any possible cranial irradiation in these cases. It is difficult to be certain that all these early descriptions of posterior fossa involvement are attributable to the same disease, because Langerhans cell histiocytosis is only

one type of infiltrating granulomatous disorder that might be described as a reticuloendotheliosis (23, 27).

Considering pathologic information from the reports we have summarized, combined with information from Elian et al's (18), Braunstein et al's (21), and Yamaguchi et al's (23) reviews of autopsy cases before 1960, several forms of pathologic involvement of the cerebellum and brain stem emerge. Cases have been reported of leptomeningeal infiltration, meningeal-based nodules, parenchymal infiltrates of histiocytes and inflammatory cells, focal areas of demyelination with gliosis, dentate nucleus degeneration with or without calcification, loss of cells in the granular and Purkinje and layers of the cerebellar cortex, and granulomatous infiltration of cranial nerve sheaths. Autopsy reports indicate the most common pathologic site of infiltration in the brain is in the leptomeninges. These might be clinically and radiographically undetected if not large enough to create symptoms. We present four patients who have CT and/or MR lesions that are striking in their similarity and may be attributable to demyelination, cell loss, and gliosis (Figs 1A, 2A, and 3B). Pathologic substantiation was made in one of our cases at open biopsy. These findings have been described in the pathology literature but are rare. This process is manifested as low attenuation on CT (Figs 1C and 2B) and hyperintensity on long-TR/long-TE MR in the deep nuclei regions and deep white matter of the cerebellum symmetrically. They are not apparently associated with long-term blood-brain-barrier breakdown, because they do not enhance. Although it might be argued that demyelination or gliosis in the cerebellum could be a consequence of ther-

apeutic irradiation, we believe that this is not the situation. Our patients received 1000 cG or less of external-beam radiation therapy before cerebellar dysfunction or imaging abnormalities. In the more recently reported cases in which this information is available in prior reports (19, 20, 25), most patients received less than 1000 cG, usually to the anterior calvarium or orbit. This amount of radiation seems unlikely to routinely create the clinical signs or pathologic findings that have been reported (20, 28–30). Two of our patients did not receive cranial irradiation before imaging abnormalities developed. Our third patient received multiple small doses of external-beam radiation to the anterior cranium and orbit over years. The radiation ports were felt to be too anterior to allow significant scatter to the cerebellum. Our fourth patient received small doses to the face. Specifically, as a “model” to refute the idea that changes found in our patients can be attributable to radiation damage, there is a large group of children with acute lymphoblastic leukemia who have received even larger doses of whole-brain irradiation (up to 2400 cG) who have been followed for years without development of the specific symptom and imaging complex we describe (29–33).

There is little evidence that Langerhans cell histiocytosis is a true neoplasm (3). Despite this fact, traditional therapy has included the use of chemosuppressive agents. None of the chemotherapeutic agents administered to our patients have been reported to cause the clinical signs or imaging abnormalities described. The agents used to treat Langerhans cell histiocytosis as recommended by the Children’s Cancer Study Group (prednisone, vinblastine, G-mercaptopyrine, and intravenous methotrexate) are widely used to treat childhood neoplasms. The cerebellar deterioration and imaging abnormalities are not recognized by the literature of the Children’s Cancer Study Group or the Pediatric Oncology Group to be attributable to these chemotherapeutic drugs (32–34). The recent understanding that dysfunction of the immune system has an important role in the pathophysiology of this disease has opened a new avenue of therapeutic research (3, 28) and may explain the curious pathologic findings of cerebellar degeneration and demyelination without granulomas that were found in one of our patients and in Kristensson’s case (25). Theoretically, the cerebellar degeneration and demyelination could be created by an autoimmune “paraneo-

plastic syndrome,” by more direct phagocytosis of myelin by Langerhans histiocytes, which then reenter the circulation or die and escape detection, or by an unknown neuropathologic toxin or other released humoral factor. These are all theories that have been postulated at one time or another to explain cerebellar dysfunction in patients with cancer. Pathologists do not have a compelling explanation for this process (4, 25), and unfortunately, we cannot offer any more solid evidence of its cause. Serum antineuronal and anti-Purkinje cell antibodies have been discovered in patients with various cancers, including small-cell lung and ovarian carcinoma. These antibodies are felt to be associated with subacute cerebellar degeneration, but the exact relationship to the syndrome is unclear, because many patients circulate these antibodies without expressing dysfunction. Although sensory neuropathies felt to be secondary to circulating autoantibodies unassociated with malignant neoplasms are well described, apparently only a few patients without malignant neoplasms with similar antibodies and cerebellar degeneration have been previously reported (35).

It is curious that our first patient later developed imaging abnormalities in the basal ganglia and internal capsules without neurologic dysfunction referable to these areas. Some of these lesions were transitory, further suggesting an “autoimmune” process. Some of the lesions were slightly hyperintense on T1-weighted images. We do not know what accounts for these hyperintense signals on T1-weighted images. They may represent an uncommon manifestation of calcification (36) or demyelination/remyelination of axonal sheaths, as have been described with multiple sclerosis (37, 38) and central pontine myelinolysis (39). A CT study was not performed to look for calcifications in this patient; however, a CT scan taken 1 year previously did not reveal calcifications. We were struck by the large number of scattered small lesions that were not creating symptoms. Two other patients eventually developed “more global” dysfunction, including corticospinal tract involvement. It is possible that the lesions within the corpus medullare and deep nuclei of the cerebellum may serve as a marker for progressive CNS abnormalities.

Some patients with Langerhans cell histiocytosis may have incidental posterior fossa find-

ings on autopsy. Despite abnormalities in the cerebellum on CT and MR, cerebellar signs did not develop in our second patient for more than 3 years. When patients present with clinical abnormalities referable to the cerebellum and brain stem, they are likely to have at least one of the described manifestations demonstrable on CT and/or MR. Dentate nucleus degeneration and cerebellar white matter disease may or may not be seen with CT but should be demonstrated on MR because of high contrast resolution and lack of bone-generated artifacts. However, if a patient presents with a cerebellar mass or signal abnormality as the initial or sole finding, differential diagnostic confusion is to be expected and may require a biopsy for resolution.

In autopsy reports, posterior fossa disease in Langerhans cell histiocytosis is not an uncommon finding. Nevertheless, this pathologic site is not widely publicized and is poorly described in the radiologic literature. Kepes (4) has stated that the cerebellum is the second most common site of disease in the CNS. Yet a review of the radiology literature yields numerous cases of parenchymal eosinophilic granulomas reported almost everywhere except the cerebellum. This discrepancy in reporting is difficult to understand but may be related to the fact that imaging findings may precede the clinical findings by several years; that cerebellar dysfunction is a later manifestation of multifocal disease, such that complications of therapy and primary disease may have confused the issue; and that most cerebellar disease reported in the autopsy literature is leptomeningeal in nature, which may go clinically and radiographically undetected if small. Our four patients probably represent a specific subset of patients with CNS disease. It is important not only to be aware of the cerebellum as a focus of disease but to realize that demyelination, gliosis, and cellular loss may all contribute to the abnormalities we have described in our patients, leading to a similar pattern of symmetric hypodensities on CT and hyperintensities on long-TR/long-TE MR in the dentate nuclei regions and adjacent white matter. We believe that the specific cerebellar findings are related to the primary disease process and are not iatrogenic. Greater experience is needed to draw more certain conclusions about its pathophysiology and relationship to the clinical cerebellar dysfunction.

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