Pediatric Neurology 62 (2016) 62–65

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

Diffuse Encephalopathy Associated with Isolated Cerebral Langerhans Cell Histiocytosis

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ABSTRACT

BACKGROUND: Langerhans cell histiocytosis is a rare disease of the monocyte–macrophage system. Abnormalities of the hypothalamic–pituitary region are common in individuals with central nervous system involvement. **PATIENT DESCRIPTION:** This six-year-old boy developed rapidly progressive aggressive behavior, central diabetes insipidus, and repeated complex partial seizures. Magnetic resonance imaging revealed a diffuse leukoencephalopathy-like pattern and numerous infratentorial and supratentorial granulomatous nodules in the brain parenchyma along with infundibular and hypothalamic mass lesions. Stereotactic serial biopsies enabled histopathologic and immunohistochemical diagnosis of Langerhans cell histiocytosis. **CONCLUSIONS:** Similar MRI findings have rarely been described in the literature. These findings represent part of the broad neuroradiological spectrum of Langerhans cell histiocytosis of the nervous system in children.

Keywords: Langerhans cell histiocytosis, MRI findings, brain parenchyma, multiple granulomas, biopsy

Pediatr Neurol 2016; 62: 62-65

Introduction

Langerhans cell histiocytosis (LCH) is a rare disorder of the monocyte–macrophage system; its estimated incidence is 3 to 5 per million during childhood.[1] Pituitary enlargement represents the most common finding associated with endocrine disorders, especially diabetes insipidus (15% to 50%).[2-5] In contrast, involvement of other areas of the brain rarely occurs in children and adolescents (2% to 4%).[6,7]

The pathogenesis of central nervous system (CNS) abnormalities due to LCH has long been elusive. Attributed to a diffuse inflammatory process dominated by CD8+ T-lymphocytes, severe tissue destruction with neuronal and axonal degeneration and secondary demyelination of neural tracts is suggested based on the comprehensive neuropathologic studies.[2,6] On the other hand, circumscribed intracranial granulomas could indicate a predilection to involve the circumventricular areas that lack a protective blood–brain barrier such as the pituitary stalk.[2,8] High serum levels of the T cell–specific cytokine interleukin 17A found during the active course of disease may promote blood–brain barrier disruption.[1,9] This might be a possible explanation for the development of space-occupying granulomas within the brain parenchyma.[10]

We describe the clinical, neuropathologic, and magnetic resonance imaging (MRI) findings of a child with isolated CNS LCH and atypical imaging appearance of pronounced parenchymal involvement.

Patient Description

This 6-year-old boy with Tanner stage 1, the first child of healthy Arabian parents, was admitted for evaluation of

Article History:
Received March 16, 2016; Accepted in final form May 4, 2016

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http://dx.doi.org/10.1016/j.pediatrneurol.2016.05.006

rapidly progressive aggressive behavior. The main clinical finding was severe generalized adiposity due to hyperphagia, with a rapid 17 kg weight gain during the previous eight months and a body mass index of 28.5 kg/m^2 (greater than the 99th percentile).

In addition, he experienced polydipsia and polyuria with a usual intake of five liters of water during the daytime and about three liters during the nighttime. Repeated complex partial seizures of one to two minutes duration with initial vomiting, disturbances of vigilance, head movement, and bulbus deviation to the left side were observed. Interictal electroencephalography showed bihemispheric diffuse slowing and sporadic spike waves. Anticonvulsive treatment with levetiracetam was successful within a short period of time. Progressive psychomotor slowing was evident.

Laboratory analyses showed normal blood count, serum electrolytes, erythrocyte sedimentation rate, angiotensin-converting enzyme, and lactate dehydrogenase serum levels. Tumor markers such as beta-human chorionic gonadotropin and alpha-fetoprotein were normal. Repeated pathologic serum and plasma hormones measured between eight and nine AM supported the diagnosis of panhypopituitarism with a disturbed pituitary–adrenal axis, diabetes insipidus, secondary or tertiary hypothyroidism, and growth hormone deficiency (Table).

Brain MRI was performed using a 1.5-T machine (Aera; Siemens, Erlangen, Germany). The protocol included axial fluid-attenuated inversion recovery images together with axial, coronal, and sagittal T2-weighted images (T2WI). Furthermore, noncontrast and postgadolinium T1-weighted images (T1WI) were recorded in the axial and sagittal planes.

The examination demonstrated enlargement of the pituitary stalk together with circumscribed hypothalamic and pineal gland mass lesions. Moreover, there was a lack of the physiologic hyperintense signal of the posterior pituitary on sagittal T1WI (Fig 1). Fluid-attenuated inversion recovery and T2WI revealed extensive hyperintense signal alterations in the cerebellar and cerebral white matter (Fig 2A). In addition, multiple nodular lesions were found in the dentate nuclei, cerebellar vermis, brainstem, pontomesencephalic region, amygdalae, hippocampi, and basal ganglia, as well as in the corticosubcortical region of the cerebellar and cerebral hemispheres. On contrast-enhanced T1WI (gadoteric acid, 0.5 mmol/mL; Guerbet, Villepinte, France) almost all the lesions showed sharp demarcation and intense enhancement (Fig 2B-D). Of interest, osseous lesions of the skull or

TABLE.
Hormonal Data of the Patient at the Time of Admission (Blood was Drawn at 9 am)

Parameters	Level	Reference Values
Serum cortisol (ng/mL)	9	50-180
Plasma adrenocorticotropic hormone (pg/mL)	4.5	7-28
Serum insulin-like growth factor 1 (ng/mL)	26	32-258
Serum insulin-like growth factor binding protein 3 (μg/mL)	1.8	2.0-5.5
Serum thyroid stimulating hormone (μU/mL)	2.93	<4
Serum free thyroxine 4 (pg/mL)	4.6	9-15

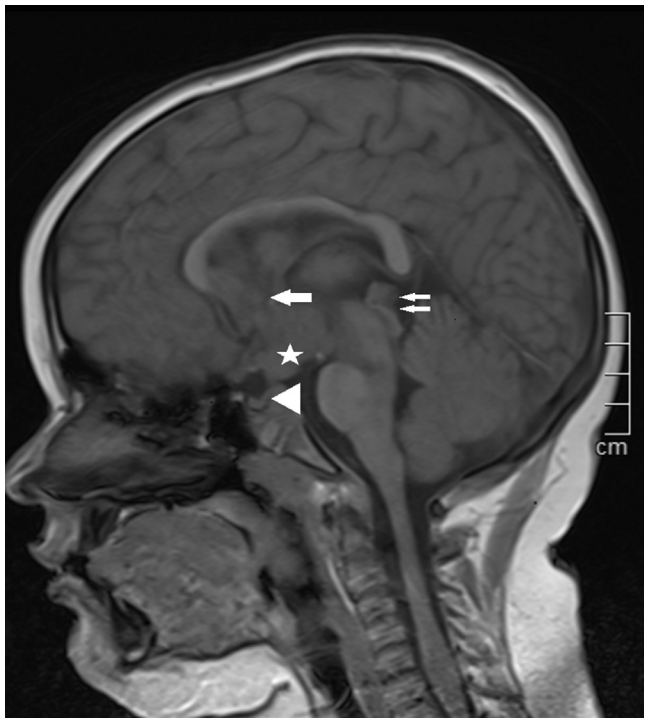

FIGURE 1.
Brain MRI at age 6 years. Sagittal T1-weighted unenhanced image demonstrates a lack of the physiologic hyperintense signal of the posterior pituitary (arrowhead) together with enlargement of the pituitary stalk and hypothalamic (asterisks), subcallosal (arrow), and pineal gland (double arrows) mass lesions.

craniofacial bones were not found. Moreover, abdominal ultrasonography and the whole-body MRI were able to permit exclusion of the involvement of extracranial organ systems.

Because of progressive encephalopathy, ambiguous MRI findings, and foreign ancestry, a broad spectrum of infectious viral and bacterial causes were excluded, including serum and cerebrospinal fluid investigations for cytomegalovirus, Epstein–Barr virus, herpes simplex virus-1/2, human immunodeficiency virus-1/2, hepatitis B, Aspergillus, Echinococcus, Toxoplasma, *Cryptococcus neoformans*, and tuberculosis.

Successfully performed stereotactic serial biopsies enabled histopathologic investigations, showing brain tissue with reactive changes in the form of Rosenthal fibers and activated astrocytes, as well as inflammatory cell infiltrations consisting of lymphomonocytic and histiocytic cells (Fig 3A). Immunohistochemistry confirmed the suspected diagnosis of LCH based on the finding of cell clusters showing distinct expression of CD68, CD1a, and S100 protein (Fig 3B-D). Polymerase chain reaction testing for John Cunningham and BK virus in biopsy specimens was negative.

Immunomodulatory chemotherapy was initiated with vinblastine and prednisone. As this regimen did not achieve significant improvement of the cerebral lesions, cladribin therapy has been initiated according to the international guidelines. Clinically, his encephalopathy recovered partially and temporarily, but he died at age nine years because of intractable infectious complications.