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Striatal Involvement in Neurodegenerative Langerhans Cell Histiocytosis

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Neurodegenerative Langerhans cell histiocytosis (LCH-ND) is rare, occurring in approximately 1% to 3% of patients diagnosed with Langerhans cell histiocytosis (LCH).¹ Thus far, it is assumed that this neurodegeneration results from paraneoplastic inflammation. However, recent data have shown that LCH-ND may result from direct brain infiltration by myeloid/monocytic cells, harboring the BRAF mutation, that cause an active demyelinating process.² LCH-ND can clinically express itself in various ways, ranging from movement disorders to cognitive and behavioral problems, depending on the brain structures involved. MRI is often used to diagnose central nervous system involvement in LCH. Moreover, it can be used to evaluate treatment effectiveness by looking at the evolution or progression of T2 hyperintensity. We present a case of a patient with LCH-ND where a new radiological feature with unknown origin was observed on one follow-up MRI.

Case Report

A currently 24 year old male presented with progressive ataxia and dysarthria that gradually developed over a period of 2 years. He had no prior medical history and his family history was unremarkable. On physical examination wide base ataxic gait was observed and the patient was unable to perform tandem gait. In addition, appendicular ataxia was present with hyper- and dysmetria on both sides, most prominent on the left. There was a bilateral intention tremor, but no resting tremor. Eye movement tests revealed saccadic intrusions and ocular dysmetria during quick saccades. Muscle strength and sensory function were intact. Reflexes were symmetrically absent.

Brain MRI showed multiple skull lesions as well as bilateral white matter abnormalities in the cerebellar white matter (Fig. 1), suspect for LCH-ND. Laboratory investigations and endocrine assessments showed no abnormalities. Subsequently performed chest x-ray revealed pulmonary lesions, which were confirmed by

additional PET-CT (images not shown). PET-CT also showed multiple bone lesions and eventually an x-ray-guided bone biopsy of a skull lesion revealed the diagnosis to be LCH with presence of the BRAF mutation V600E and complicated by LCH-ND.

Initially, our patient was treated with cytarabine, prednisolone and intravenous immunoglobulins, but the LCH proved refractory after 4 courses. Therefore, treatment was started with vinblastine and prednisolone with later addition of 6-mercaptopurine during the maintenance phase. A partial remission of the bone and pulmonary lesions was achieved, but neurological symptoms did not improve and white matter abnormalities on MRI persisted.

Over the next years, he received treatment with several courses of cladribine and later empirical anakinra. This resulted in complete remissions of the systemic lesions, but the MRI brain lesions remained unchanged with clinically slightly progressive ataxia and dysarthria.

Based on new insights on the pathophysiology of LCH-ND, in 2018 treatment with vemurafenib was started, despite the fact there was no active systemic disease. Five months after vemurafenib initiation, follow-up MRI showed an increase in susceptibility of the striatum of unknown origin (Fig. 2). Eventually vemurafenib treatment had to be stopped six months after initiation due to lack of efficacy and increasing side effects, mostly skin toxicity.

Discussion

LCH-ND is rare and related MRI features that can be observed, include T2 hyperintensity of the cerebellar white matter and pons, cerebellar atrophy and T1 hyperintensity of the basal ganglia, the globus pallidus in particular.³ Moreover, susceptibility of the globus pallidus and the SN has been demonstrated in LCH-ND.⁴ We now describe an increase in striatal susceptibility on MRI in a patient with LCH-ND, which, to our knowledge, has not been described before.

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Relevant disclosures and conflicts of interest are listed at the end of this article.

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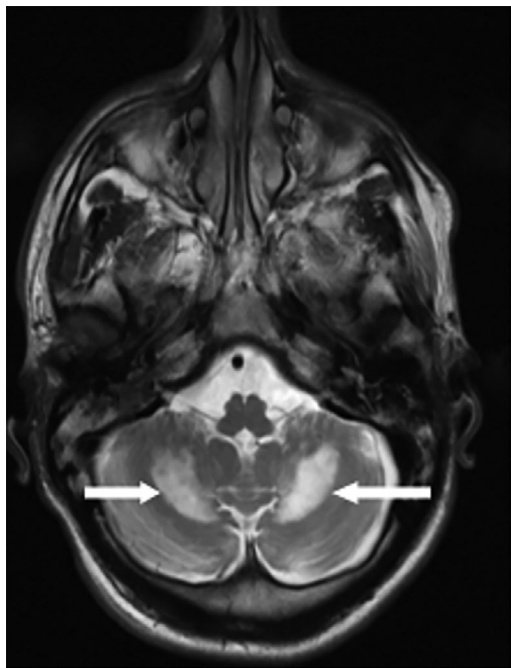


FIG. 1. Bilateral symmetrical T₂ hyperintensity of the cerebellar white matter (thick arrows).

The differential diagnosis of striatal susceptibility is broad and can be divided into unilateral and bilateral striatal susceptibility. In this case symmetrical bilateral susceptibility of the striatum was observed, of which the etiology is not specific, but can be observed in the following conditions: age-related mineralization, metabolic disorders (e.g., iron accumulation disorders), and neurodegenerative diseases (e.g., Huntington's disease or parkinsonism), though considered unlikely based on the clinical evaluation.⁵

Given that this patient is known to have LCH-ND it could be possible that the increase in striatal susceptibility is related to this disorder. However, he also received multiple lines of chemotherapy and any or a combination of these treatments can for that reason not be excluded as a cause of the increased striatal susceptibility. The treatments for LCH-ND that this patient received were tested in small research cohorts.^{2,6,7} Therefore, little is known about their exact effects and side effects. As far as we know, increased striatal susceptibility has not been described as a side-effect of any of the received treatments, but more research on the treatments for LCH-ND is necessary to validate this.

In conclusion, on MRI we observed increased bilateral symmetrical striatal susceptibility in a patient with LCH-ND, something that might be related to LCH-ND. Further observation in patients with LCH-ND, either receiving treatment or not, is warranted to determine its etiology and clinical significance.

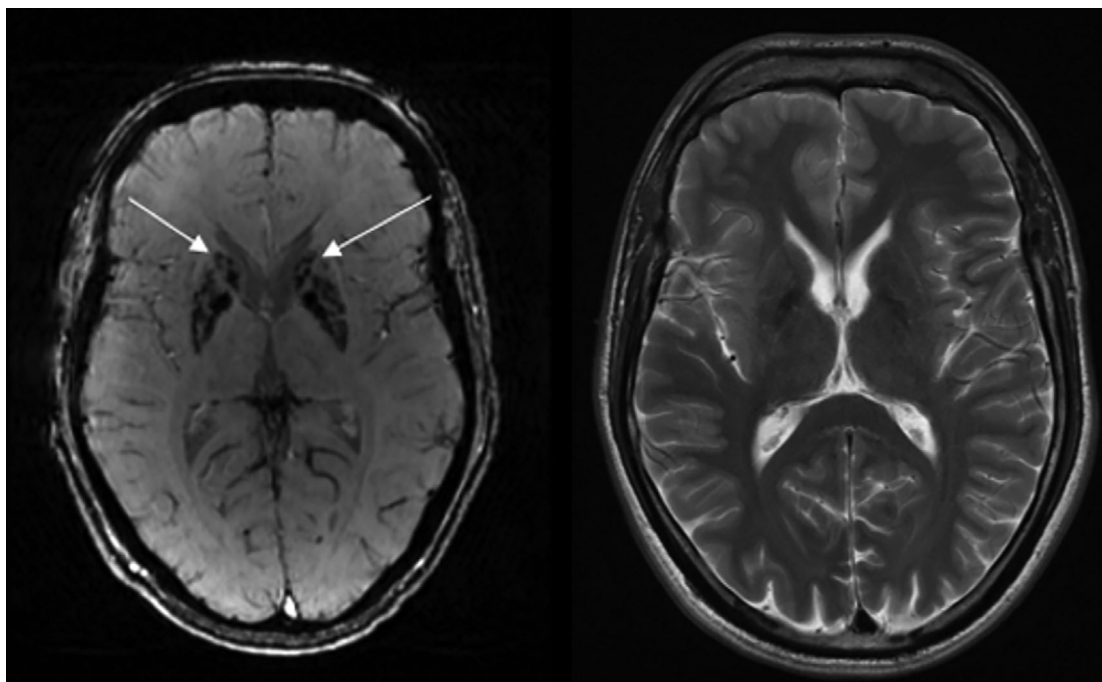


FIG. 2. Left: bilateral symmetrical susceptibility of the striatum (thin arrows). Right: corresponding T₂-weighted sequence showing a striatum with normal signal intensity.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

S.d.H.: 3A and 3B

W.v.d.V.: 3B

F.M.: 3B

Disclosures

Ethical Compliance Statement: Approval of an ethics committee was not necessary for this manuscript. Informed patient consent was not necessary for this work. We confirm that we have

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