

Child Neurology: Treatable bilateral striatal lesions related to anti-dopamine 2 receptor autoimmunity

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Neurology® 2018;91:98-101. doi:10.1212/WNL.0000000000005774

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The symptoms of autoimmune encephalitis with antibodies directed against neuronal cell surface antigens are generally reversible by removing the antibodies or the antibody-producing B cells.¹

Although phenotypically pleomorphic, autoimmune encephalitis usually presents as a rapidly progressive encephalopathy but may present with neurologic and psychiatric manifestations without an inflammatory CSF profile² or abnormalities on brain MRI.

Antibodies directed against dopamine 2 receptor (D2R) have been described in 14 children^{3,4} presenting with encephalitis and prominent movement features. While it is debated whether D2R antibodies are pathogenic or bystanders in human disease,^{5,6} the response to immunotherapy reported for most patients⁷ helps to build the case in favor of their pathogenicity.

Clinical case

A 16-month-old healthy boy was admitted to the emergency department due to sudden onset of altered mental status and abnormal posturing of his limbs. He showed marked irritability, poor eye contact, sustained flexion of his left limbs, and extension of his right limbs alternating with mixed choreic–dystonic movements of the 4 limbs and mandible. Neurologic examination revealed considerable axial hypotonia, with the patient being unable to sit unassisted, and the patient ceased to communicate verbally, despite having prior typical language development.

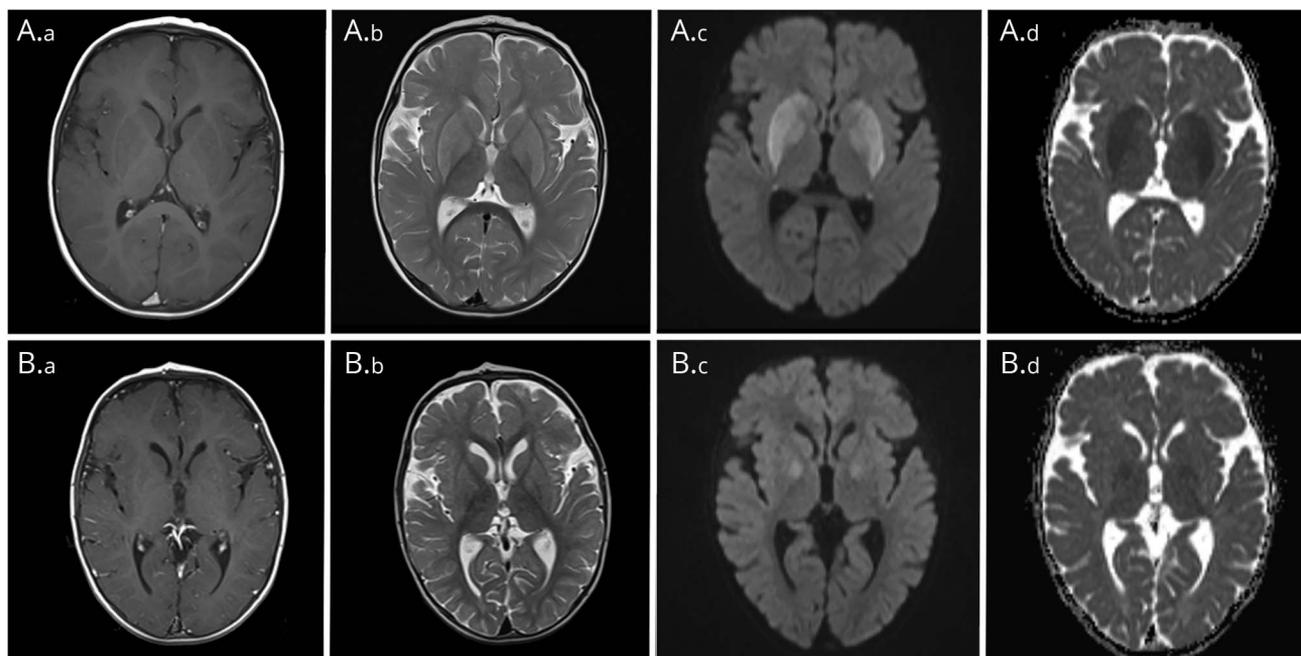
A recent history of vomiting for the last 2 days was elicited but there was no evidence of fever and bloodwork including ammonia levels had normal results.

The dystonic posturing was initially interpreted as tonic seizures evolving to status epilepticus. The boy was treated with diazepam, valproic acid, and midazolam, with no clear benefit. Valproic acid was switched to levetiracetam 2 days later. Initial CSF analysis revealed no pleocytosis, normal glucose and protein levels, and tested negative for herpes simplex virus 1/2, human herpesvirus–6, and enterovirus (PCR). The patient was put on broad-spectrum antibiotics and started high-dose IV methylprednisolone (30 mg/kg/d). His brain MRI (figure), performed less than 48 hours after onset, revealed striking bilateral restricted diffusion in the basal ganglia, associated with hyperintensity on T2-weighted imaging. Magnetic resonance angiography revealed no irregularities of intracranial vessels. EEG showed moderate encephalopathy with no epileptiform activity.

Given the vast differential diagnosis of bilateral striatal lesions, a systematic approach was performed.

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Brain MRI at presentation (A) and at 6 weeks follow-up (B). (A.a) T1 with gadolinium injection: without meaningful signal alterations. (A.b) T2-fluid-attenuated inversion recovery (FLAIR): symmetrical bilateral hyperintensity restricted to the striatum. (A.c) Diffusion-weighted imaging (DWI)-weighted imaging and (A.d) apparent diffusion coefficient (ADC) map: symmetrical bilateral restricted diffusion restricted to the striatum (high signal on DWI confirmed by low ADC values). (B.a) T1 with gadolinium injection: without meaningful signal alterations. (B.b) T2-FLAIR: significant reduction of the extent of signal alteration previously described, no signs of cavitation. (B.c) DWI-weighted imaging and (B.d) ADC map: considerable resolution of the previously described restricted diffusion.

Prioritizing treatable conditions, the patient was started on biotin (10 mg/kg/d) and thiamine (100–300 mg) and completed a 5-day course of IV methylprednisolone (30 mg/kg/d) followed by a slow taper of oral prednisolone (2 mg/kg/d). Five-day courses of IV immunoglobulin (IVIg) (0.4g/kg/d) were also performed, the first course at day 5 and once monthly since then. On day 4, low-dose clonazepam was started for symptomatic relief of dystonia.

A full metabolic panel, including urinary organic acid chromatography, plasma aminoacids, CSF lactate and pyruvate, serum biotinidase activity, CSF neurotransmitter and pterins testing, acylcarnitine profile, serum and urinary copper, and serum ceruloplasmin, was negative.

On repeat CSF tap, influenza, enterovirus, and *Mycoplasma pneumoniae* PCR testing was negative. Rotavirus was identified in stool.

Five weeks after disease onset, the patient's initial CSF sample was found positive for anti-dopamine 2 receptor antibodies on a cell-based assay. The patient's serum was negative for these antibodies and both serum and CSF were negative for other antibodies (NMDA receptor, AMPA receptor, GABA-b receptor, LGI1, CASPR2, GABA-a, DPPX, mGluR5, neurexin-3, IgLON5, DNER, mGluR1, glycine receptor, and amphiphysin). Our patient samples were not tested for MOG or AQP-4 antibodies, considering there was no evidence of white matter involvement.

A diagnosis of autoimmune basal ganglia encephalitis was made. The chosen treatment strategy was to add azathioprine 1 mg/kg/d to the slow taper of oral prednisolone (8 weeks) and perform monthly 5-day IVIg courses.

The patient was discharged at 7 weeks of disease to an intensive rehabilitation facility. Clinically, he showed a gradual improvement of the initial irritability and cervical and axial hypotonia. He recovered the ability to stand with bilateral support at 5 weeks, regained the ability to speak at 6 weeks, and restarted walking unassisted at 3 months. Dystonic posturing of his right leg and choreiform mandibular movements faded progressively, being barely noticeable at discharge.

Follow-up brain MRI at 6 weeks (figure) showed considerable reversibility of the signal changes described at presentation with no suggestion of cavitation or atrophy.

Discussion

Differential diagnosis

Infectious

Clinical reasoning in the event of acute altered mental status and dystonia should prioritize common etiologies like infectious encephalitis, which is why the patient was treated initially with broad-spectrum antibiotics and antiviral therapy.

Immune-mediated

Given the potential reversibility of symptoms with immunotherapy and the relevance of early treatment to minimize neuropsychological and motor sequelae,⁷ basal ganglia encephalitis should nonetheless come high on the differential diagnosis list. According to the revised criteria of autoimmune encephalitis,² a provisional diagnosis can be made in the presence of subacute altered mental status associated with a new focal CNS sign, even in the absence of preliminary CSF or MRI abnormalities, as long as there is reasonable exclusion of alternative diagnosis. It is therefore supported that immunotherapy can and should be started in those instances while awaiting antibodies results. Interestingly, CSF neopterin levels that have been described to be more sensitive markers of active CNS inflammation⁸ were also normal in our patient.

It is interesting that the clinical movement disorder phenotype was asymmetric, given the apparent symmetry of the MRI findings.

Metabolic/mitochondrial

Sudden neurologic deterioration in the setting of systemic illness in a child is the clinical hallmark presentation of inborn errors of metabolism and mitochondrial disorders. An acute insult to the basal ganglia on brain MRI also fits these 2 major groups of disorders. Preliminary negative results of the metabolic panel obtained during the crisis, as well as blood and CSF lactate and pyruvate, however, reduced our level of suspicion of a metabolic disorder. This, together with the progressive improvement of symptoms, made Leigh disease less likely. Therapy with biotin and thiamine has been recommended in the setting of MRI evidence of bilateral neostriatal lesions,⁹ until the diagnosis of biotin–thiamine-responsive basal ganglia disease can be excluded by genetic testing (SLC19A3), which is why our patient received this therapy. Considering this hypothesis, it might have been prudent to avoid valproic acid on the preliminary approach.

Pathophysiology

Proving or excluding an etiologic link between the rotavirus infection and the clinical phenotype is difficult. There has been a description of basal ganglia involvement and positive rotavirus PCR in the CSF¹⁰ but that case was not tested for antineuronal surface antibodies and did not respond to immunotherapy. Rotavirus has also been described to underlie acute necrotizing encephalitis, which is an immune-mediated process.¹¹ In this context, we are convinced that this was not a case of rotavirus encephalitis given the lack of CSF pleocytosis, although rotavirus PCR was not performed in the CSF. The fact that the patient improved on immunotherapy is considered to be a strong indicator that an autoantibody-mediated mechanism must be involved in the pathophysiology of the disease, even if it was indeed triggered by rotavirus infection.

Contrary to previously described cases, D2R antibodies were only detected in the CSF of our patient. Although this serum/

CSF dissociation is not unusual in centers where serum and CSF are systematically examined, this finding highlights the need to test both CSF and serum when CNS inflammation is suspected. We hypothesize that failure to meet these standards might partially explain the paucity of described D2R antibody disease cases.

Imaging features

Striatal lesions on brain MRI classically begin with T2 and fluid-attenuated inversion recovery hyperintensity of swollen neostriata and progress with atrophy and hypointensity on T1-weighted images suggesting cavitation. Some cases, however, like in our patient, do not progress with cavitation⁹ and show reversibility of the initial abnormalities.¹² What is interesting is that restricted diffusion on acute imaging is believed to represent a more destructive process,¹² which was not the case. Furthermore, MRI abnormalities may be absent in approximately 50% of patients with D2R encephalitis.³ It has not yet been established which factors determine the imaging and clinical evolution of striatal lesions.

Management and prognosis

Little is known about which therapeutic strategy provides the best results, which outcome goals should guide therapy, and when to escalate therapy. The protocols described by experts, largely based on small series and case reports, use a combination of first-line therapies (steroids plus IVIg or plasmapheresis) eventually escalating to rituximab or cyclophosphamide.^{3,5,13} The question of chronic immunosuppression and the role of steroid-sparing agents is a sensitive one when dealing with children, considering the potential influence of long-term therapy on fertility and the risk of future cancer.⁵

There are not enough data to estimate a relapse rate or a tumor association in this subtype of autoimmune encephalitis but overall, it remains a treatable disease with good response to early immunotherapy and functional outcome.

Author contributions

Cláudia Marques-Matos: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision. Cláudia Melo: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Mafalda Sampaio: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision. Esmeralda Rodrigues: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Raquel Sousa: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision. Dílio Alves: drafting/revising the manuscript, study concept or design,

accepts responsibility for conduct of research and final approval, study supervision.

Acknowledgment

The authors thank Professor Josep Dalmau and coworkers at Hospital Clínic, University of Barcelona, for performing the antibody analysis.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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This information is current as of July 9, 2018

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