CLINICAL/SCIENTIFIC NOTES OPEN ACCESS

Childhood choreoathetosis secondary to hyper-IgM syndrome (CD40 ligand deficiency)

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CD40 ligand (CD40L) deficiency is an uncommon primary immune deficiency disorder caused by X-linked mutations in the CD40L gene and resulting in hyper-IgM syndrome, clinically characterized by sinopulmonary and gastrointestinal opportunistic infections, whereas neurologic symptoms are rare.[1] Herein, we present a case of CD40L deficiency in childhood associated with the development of a generalized chorea, successfully treated with deep brain stimulation (DBS) of the globus pallidus interna (GPi).

MORE ONLINE

Video

Clinical case

Our patient presented with recurrent fever in the context of low immunoglobulin G (IgG) and immunoglobulin A (IgA). He was diagnosed with hyper-IgM syndrome at seven months of age secondary to a 1.5kb sub-genic deletion encompassing exon 3 of the CD40L gene. By age 3, he began receiving regular IV immune globulin. At the age of 13 years, he developed rapidly progressive visual deterioration due to optic atrophy, a new onset choreoathetoid movement disorder, cognitive deterioration, and generalized epilepsy. The deterioration occurred over a 2-year period. Hyperkinetic movements were bilateral, with choreoathetosis predominantly afflicting the head, neck, and limbs, which resolved during sleep.

MRI findings included supratentorial volume loss, subtle fluid-attenuation inversion recovery hyperintensity involving the insular regions, posterior periventricular and deep white matter, and mild symmetric T2 hypointensity bilaterally involving the globus pallidus (figure, A and B). Serial MRIs demonstrated progressive supratentorial volume loss over 2 years. The CSF analysis was unremarkable.

The patient was treated empirically for a suspected neuroinflammatory process with steroids, plasma exchange and rituximab as well as symptomatically for hyperkinetic movements with tetrabenazine and clonidine. Chorea remained severe and intractable such that he became bound to bed (video 1, segment 1) and required bilateral GPi DBS (figure, C). A simultaneous cortical biopsy revealed lymphocytosis (T cells) of the leptomeninges and parenchyma with activated microglia (figure, D). Microbiological analysis of the specimen was negative.

DBS was programmed on the fifth postoperative day with 2V and double monopolar settings bilaterally. An immediate decrease of choreiform movements was observed (video 1, segment 2). The patient's Movement Disorder Childhood Rating Scale from 4 to 18 years score improved from 22/28 preoperatively to 15/28 postoperatively.

After an excellent initial response, within 6 weeks, the patient experienced a recurrence of choreiform movements predominantly affecting the head and neck, prompting sequential adjustments

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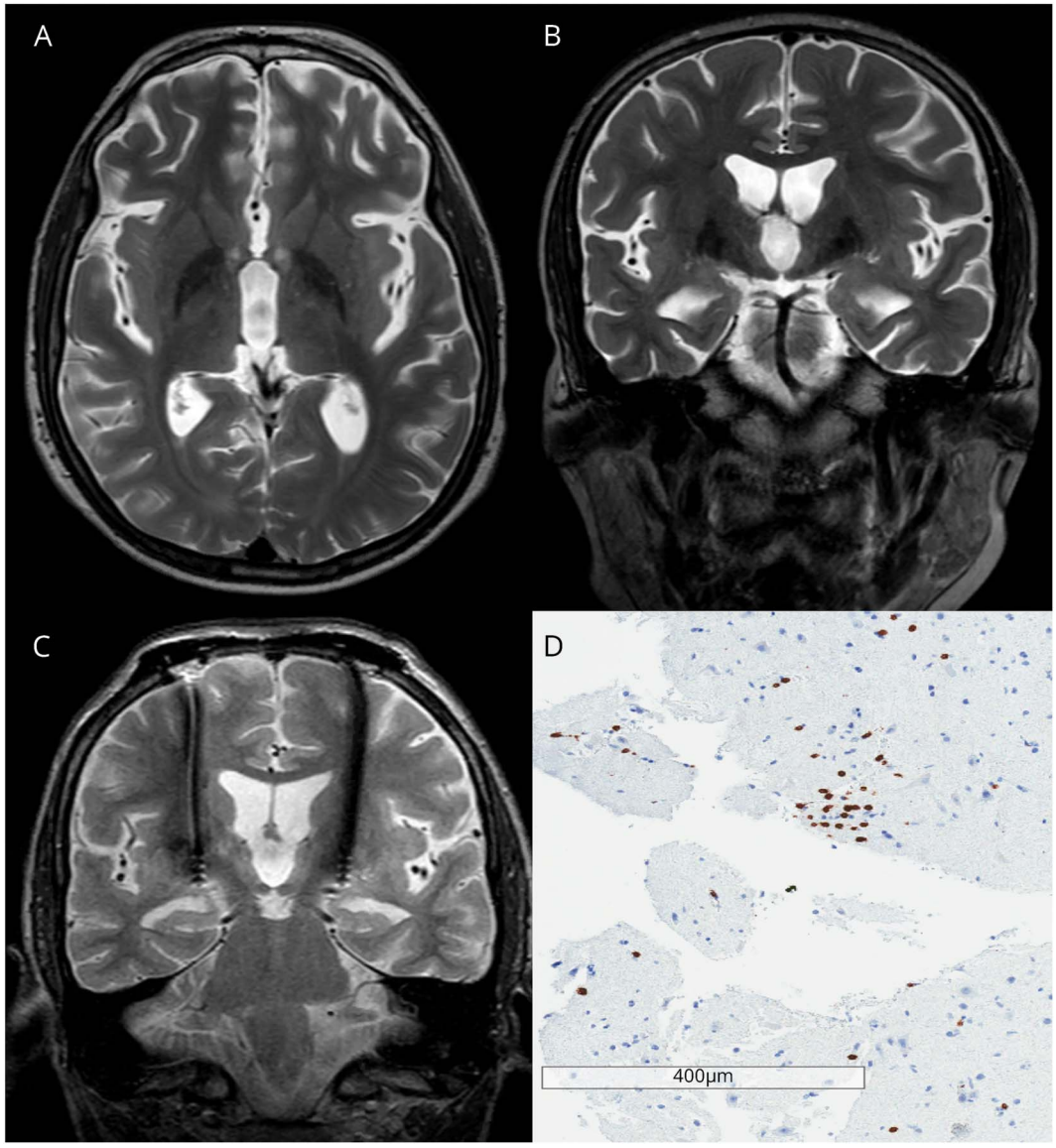
Written consent was obtained from the patient's legal guardian including permission to include images and a video as part of the study.

Figure Illustrative radiological and immunohistological imaging



(A and B) show axial and coronal T2 preoperative images demonstrating supratentorial volume loss and bilateral T2 globus pallidus hypointensity. (C) Coronal T2 sequence illustrating deep brain stimulation electrodes. (D) Immunohistological image demonstrating CD3 positivity (brown) indicative of lymphocytosis.

of the DBS settings (table e-1, links.lww.com/NXI/A331). The patient continues to experience substantial symptomatic relief 6 months after surgery.

Discussion

More than 200 variants of the CD40L gene have been identified, including a subset of mutations which encompass exon 3, as in our case.[1,2] All variants result in phenotypes of CD40L deficiency, which is the most common form of hyper-IgM syndrome.[1] CD40L mediates interactions between T cells and other cells via contact with its receptor, CD40. Deficiency of the CD40/CD40L axis deleteriously affects biologic pathways of different cell lineages which manifests as defective cellular and humoral immunity. Patients are particularly vulnerable to opportunistic infections.[3]

The evolution of symptoms and supratentorial volume loss we observed on sequential imaging is consistent with progressive neurodegeneration. Iron accumulation within the globi pallidi may explain the hypointense MRI appearance, though we believe this to be a secondary, rather than primary phenomenon. Although CNS infections are known to occur in cases of CD40L deficiency (incidence >10%), neurodegeneration is rare. Nevertheless, it is a recognized, though poorly understood phenomenon and thought to occur in the setting of primary immunodeficiency disorders secondary to chronic meningoencephalitis and/or an autoimmune

process.[4,5] Autoimmune complications manifest in 20% of patients with CD40L deficiency due to an improper maintenance of tolerance.[5] A favorable initial response to steroids, together with the brain biopsy results support the possibility of an inflammatory process in this case, however the underlying pathogenesis is unclear.

Movement disorders can rarely occur as sequelae to disorders of immunity such as AIDS.[6] A choreiform movement disorder evolving in the context of CD40L deficiency reported herein, is an unusual association. Although the GPi has proved to be a successful stimulation target in other hyperkinetic disorders of childhood, the effect in this case was uncertain prior to implantation.[7] DBS, rather than lesioning effect, is the most likely cause of improvement as the immediate and significant reduction of choreiform movements occurred following commencement of stimulation on the fifth postoperative day and has continued during 6 months of follow-up.

We have described a rare intractable movement disorder of childhood related to primary immunodeficiency, which was resistant to medical therapy. GPi DBS has returned some quality of life. We advocate early consideration of the treatment in medically resistant hyperkinetic movement disorders.

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Han Yan, MD	Hospital for Sick Children, Toronto, Canada	Prepared radiologic images and revised manuscript for intellectual content
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