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

Ian C. Coulter, FRCS(SN), Han Yan, MD, Carolina Gorodetsky, MD, Melika Akhbari, MBBS, MSc, Sara Breitbart, MSc, Suneil K. Kalia, MD, PhD, Alfonso Fasano, MD, PhD, and George M. Ibrahim, MD, PhD

Neurol Neuroimmunol Neuroinflamm 2020;7:e899. doi:10.1212/NXI.0000000000000899

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).

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 affecting 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...
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. All variants result in phenotypes of CD40L deficiency, which is the most common form of hyper-IgM syndrome. 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.

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.
Autoimmune complications manifest in 20% of patients with CD40L deficiency due to an improper maintenance of tolerance. Movement disorders can rarely occur as sequelae to disorders of immunity such as AIDS. 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. 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.

Acknowledgment
The authors are grateful for the assistance provided by Cynthia Hawkins and Famida Spatare from the Division of Neuropathology at the Hospital for Sick Children, Toronto, for preparing the histological image.

Study funding
No targeted funding reported.

Disclosure
The authors did not receive any funding/sponsorship in relation to the above clinical case report. The authors do not have any relevant funding disclosures to make. Go to Neurology.org/NN for full disclosures.

Publication history
Received by Neurology: Neuroimmunology & Neuroinflammation May 27, 2020. Accepted in final form August 31, 2020.

Appendix Authors

| Name                  | Location                              | Contribution                                      |
|-----------------------|---------------------------------------|--------------------------------------------------|
| Ian C. Coulter, FRCS(SN) | Hospital for Sick Children, Toronto, Canada | Drafted and revised the manuscript for intellectual content |
| Han Yan, MD           | Hospital for Sick Children, Toronto, Canada | Prepared radiologic images and revised manuscript for intellectual content |
| Carolina Gorodetsky, MD | Hospital for Sick Children, Toronto, Canada | Revised the manuscript for intellectual content |
| Melika Akhbari, MBBS, MSc | Hospital for Sick Children, Toronto, Canada | Revised the manuscript for intellectual content |
| Sara Breitbart, MSc    | Hospital for Sick Children, Toronto, Canada | Prepared the video and revised the manuscript for intellectual content |
| Suneil K. Kalia MD, PhD | Toronto Western Hospital, Toronto, Canada | Contributed to the study concept and revised the manuscript for intellectual content |
| Alfonso Fasano, MD, PhD | Toronto Western Hospital, Toronto, Canada | Contributed to the study concept and revised the manuscript for intellectual content |
| George M. Ibrahim, MD, PhD | Hospital for Sick Children, Toronto, Canada | Designed and conceptualized the study and revised the manuscript for intellectual content |

References
1. Du X, Tang W, Chen X, et al. Clinical, genetic and immunological characteristics of 40 Chinese patients with CD40 ligand deficiency. Scand J Immunol 2019;90:e12798.
2. Leven EA, Maffucci P, Ochs HD, et al. Hyper IgM syndrome: a report from the USIDNET registry. J Clin Immunol 2016;36:490–501.
3. França TT, Barreiros LA, al-Ramadi BK, Ochs HD, Cabral-Marques O, Condino-Neto A. CD40 ligand deficiency: treatment strategies and novel therapeutic perspectives. Expert Rev Clin Immunol 2019;15:529–540.
4. Bishu S, Madhavan D, Perez P, et al. CD40 ligand deficiency: neurologic sequelae with radiographic correlation. Pediatr Neurol 2009;41:419–427.
5. Yazdani R, Fekravand S, Shahkarami S, et al. The hyper IgM syndromes: epidemiology, pathogenesis, clinical manifestations, diagnosis and management. Clin Immunol 2019;198:19–30.
6. Sevigny JJ, Chin SS, Milewski Y, Albers MW, Gordon ML, Marder K. HIV encephalitis simulating Huntington’s disease. Mov Disord 2005;20:610–613.
7. Elkaim LM, Aloitaib N, Sigal A, et al. Deep brain stimulation for pediatric dystonia: a meta-analysis with individual participant data. Dev Med Child Neurol 2019;61:49–56.
Childhood choreoathetosis secondary to hyper-IgM syndrome (CD40 ligand deficiency)
Ian C. Coulter, Han Yan, Carolina Gorodetsky, et al.
*Neurol Neuroimmunol Neuroinflamm* 2020;7;
DOI 10.1212/NXI.0000000000000899

This information is current as of October 16, 2020

Updated Information & Services
including high resolution figures, can be found at:
http://nn.neurology.org/content/7/6/e899.full.html

References
This article cites 7 articles, 0 of which you can access for free at:
http://nn.neurology.org/content/7/6/e899.full.html##ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
All Immunology
http://nn.neurology.org/cgi/collection/all_immunology
All Pediatric
http://nn.neurology.org/cgi/collection/all_pediatric
Chorea
http://nn.neurology.org/cgi/collection/chorea
Surgery/Stimulation
http://nn.neurology.org/cgi/collection/surgery-stimulation

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://nn.neurology.org/misc/about.xhtml#permissions

Reprints
Information about ordering reprints can be found online:
http://nn.neurology.org/misc/addir.xhtml#reprintsus

*Neurol Neuroimmunol Neuroinflamm* is an official journal of the American Academy of Neurology. Published since April 2014, it is an open-access, online-only, continuous publication journal. Copyright Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Online ISSN: 2332-7812.