Child Neurology Open
Volume 3: 1-3

DOI: 10.1177/2329048X16668970
cno.sagepub.com
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Pediatric Hereditary Neuralgic Amyotrophy: Successful Treatment With Intravenous Immunoglobulin and Insights Into *SEPT9* Pathogenesis

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Abstract

Hereditary neuralgic amyotrophy is a rare disorder characterized by the sudden onset of recurrent episodes of painful brachial plexus neuropathies, followed by atrophy within a few weeks. The authors present the case of a 5-year-old boy who developed hereditary neuralgic amyotrophy in the right upper limb after a gastroenteritis illness. He made a full and rapid recovery with the use of intravenous immunoglobulin. A subsequent episode in the left upper limb during the course of intravenous immunoglobulin was significantly attenuated. A de novo c.262C>T mutation in exon 2 of the *SEPT9* gene was identified. To our knowledge, he is the first pediatric patient with *SEPT9* hereditary neuralgic amyotrophy to be treated with intravenous immunoglobulin. The authors hypothesize that the c.262C>T mutation in exon 2 of the *SEPT9* gene generates pathology via the numerous isoforms under specific conditions and that intravenous immunoglobulin can play a role at the epigenetic level of improving dysfunctional *SEPT9* expression.

Keywords

hereditary neuralgic amyotrophy, intravenous immunoglobulin, *SEPT9*

Received March 13, 2016. Received revised July 20, 2016. Accepted for publication August 18, 2016.

Hereditary neuralgic amyotrophy is a peripheral nervous system disease associated with the sudden onset of neuropathic pain followed by muscular atrophy in the upper limbs. Patients with hereditary neuralgic amyotrophy can have minor dysmorphic features such as short stature, partial syndactyly, cleft uvula or cleft palate, ocular hypotelorism, and excessive partial circumferential skin folds on the neck and arms.[1-3] Hereditary neuralgic amyotrophy is associated with pathogenic mutations in the *SEPT9* gene (OMIM 604061) on chromosome 17q25 in 55% of the affected families.[4,5]

Few studies provide evidence for any specific treatment modality in hereditary neuralgic amyotrophy in children. Herein, the authors report a child with first presentation of hereditary neuralgic amyotrophy due to a pathogenic mutation in *SEPT9* and describe his successful response to intravenous immunoglobulin treatment. The authors report a full and rapid recovery and postulate the role of intravenous immunoglobulin can be epigenetic in this disease process rather than a primary immune modulatory effect.

Case Report

A 5-year-old boy presented with 4-week history of increasing right shoulder and elbow pain, paresthesia, and had demonstrated limited right shoulder adduction above the horizontal plane, following an episode of gastroenteritis. Subsequently, he

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developed wasting of the supraspinatus and infraspinatus muscles, causing significant functional impairment. He had no sensory abnormalities. Biceps reflex was absent and triceps reflex was reduced.

The child had attained normal neurodevelopmental milestones. He had subtle dysmorphic features of hypotelorism, epicanthic, and mild midface hypoplasia, simple helix with small ears, pectus excavatum, and unusual skin folds on the forearms (which were more prominent during infancy). There was no significant family history, and his parents were morphologically normal.

Magnetic resonance imaging of the brachial plexus showed patchy decreased signal within the right supraspinatus and infraspinatus muscles indicative of denervation. A diagnosis of hereditary neuralgic amyotrophy secondary to a de novo *SEPT9* mutation was confirmed with the identification of a pathogenic de novo heterozygous mutation, c.262C>T [p.Arg88Trp] (performed in Diagenom GmbH, Medical Genetics Laboratory Germany http://www.diagenom.de/).

The child was administered a single infusion of 50 g (2 g/kg) intravenous immunoglobulin as induction treatment and showed an improvement in his right shoulder function and a reduction in pain within 6 hours of treatment. He continued to receive monthly maintenance intravenous immunoglobulin infusion (dose 0.4 g/kg) over 12-month period. Five months into treatment, he evolved to have left-sided brachial neuritis features, although were significantly attenuated to the pain and the muscle bulk wasting compared to the initial presentation. He remained on the same maintenance dose of infusion monthly without further induction dose. Twelve months into treatment, patient regained full functions of both right and left shoulders with recovery of scapular muscle bulk.

Discussion

The septin family of guanosine triphosphate-binding proteins serve as scaffolds and diffusion barriers that control the cellular localization of numerous proteins.[6,7] There are 13 known mammalian septin genes, with >30 protein isoforms because of alternate splicing.

SEPT9 is involved in T-cell development and proliferation,[8] as well as being highly expressed in Schwann cells in the peripheral nerve.[3,9] Under hypoxic conditions, the c.262C>T mutation reduces the translation of the *SEPT9_v4* isoform, which encodes the *SEPT9* protein isoform e (GenBank NM_001113494.1 and NP_001106966.1).[10] An altered response to stress and the inherent role of *SEPT9* in myelin maintenance and T-cell development can account for the episodic nature of hereditary neuralgic amyotrophy. Similarly, alternate *SEPT9* isoforms, for example, could play differential roles during embryonic development, thus accounting for the dysmorphic features associated with the condition.

There is no clear consensus regarding the treatment of neuralgic amyotrophy. Cochrane review of the treatment of neuralgic amyotrophy provided some evidence, suggesting early corticosteroid therapy with or without intravenous immunoglobulin might have a positive effect on pain and recovery in a few patients.[11] Adult patients with hereditary neuralgic amyotrophy have demonstrated favorable outcomes from intravenous immunoglobulin after failure to response to corticosteroid.[12-14]

Intravenous immunoglobulin has been used to treat autoimmune disorders. The mechanistic effects of intravenous immunoglobulin in autoimmune diseases include (1) antibodies, (2) complement, (3) degenerative proinflammatory molecules, (4) gene expression,[15] and (5) stimulating Schwann cell maturation.[16] Gene expression profiles in patients with inflammatory myopathies treated by intravenous immunoglobulin have demonstrated significant dysregulation across a number of systems.[17] Most notably, downregulated genes included the cell adhesion genes such as *ICAM-1* and *KAL1*.[17] Intravenous immunoglobulin-induced dysregulation of gene expression in key inflammatory, cellular migration, and cell survival pathways has been demonstrated in autoimmune diseases such as dermatomyositis and inclusion body myositis.[15-17] The multimodal effects of intravenous immunoglobulin, including altered gene expression, may be relevant to our case in the context of his relapse. This relapse occurred in the absence of any infectious or traumatic triggers and was clinically attenuated by the ongoing maintenance of monthly intravenous immunoglobulin dosing, postulating an epigenetic modification of the disease process.

How this myriad of clinicopathological mechanisms promotes such a successful modulation of hereditary neuralgic amyotrophy in our patient remains unclear. While the initial hereditary neuralgic amyotrophy episode in our patient appeared to have been triggered after an episode of viral gastroenteritis, the second episode occurred during intravenous immunoglobulin treatment without any infective triggers, although the clinical course and severity were significantly attenuated by the ongoing administration of intravenous immunoglobulin. Thus, the authors hypothesize that the c.262C>T mutation in exon 2 of the *SEPT9* gene generated pathology via the numerous isoforms under specific conditions and that intravenous immunoglobulin can play a role at the epigenetic level of improving dysfunctional *SEPT9* expression. Our case also demonstrated that intravenous immunoglobulin is a safe and effective form of therapy for children with hereditary neuralgic amyotrophy.

Author Contributions

RC and MS contributed equally as co-first authors.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

Ethical approval was obtained by the UnitingCare Human Ethics and Research Committee.

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