Child Neurology: Initial Presentation of PCDH19-Related Epilepsy with New Onset Refractory Status Epilepticus and Treatment with Anakinra

Author(s):
Robin T. Varughese, MD¹; Shefali Karkare, MD¹; Annapurna Poduri, MD²; Sanjeev V. Kothare, MD¹

Corresponding Author:
Sanjeev V. Kothare, sanjeevkothare@hotmail.com

Affiliation Information for All Authors: 1 Division of Pediatric Neurology, Department of Pediatrics, Cohen Children’s Medical Center, New Hyde Park, NY, USA 2 Departments of Neurology, Boston Children’s Hospital and Harvard Medical School, Boston, MA, USA

Equal Author Contribution:

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Contributions:
Robin T. Varughese: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Shefali Karlare: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Annapurna Poduri: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Sanjeev V. Kothare: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Figure Count:
1

Table Count:
1

Search Terms:
[ 61 ] Antiepileptic drugs, [ 297 ] Status epilepticus, Child Neurology, NORSE, PCDH19

Acknowledgment:

Study Funding:
No targeted funding reported.

Disclosures:
The authors report no disclosures relevant to the manuscript.

Preprint DOI:

Received Date:
2022-01-06

Accepted Date:
2022-04-29

Handling Editor Statement:
Note 1. Submitted and externally peer reviewed. The handling editor was Whitley Aamodt, MD, MPH.

Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
Abstract

PCDH19-related epilepsy is a developmental and epileptic encephalopathy typically presenting with epilepsy and varying degrees of intellectual disability. Seizures typically present in clusters of focal or generalized seizures, sometimes in the setting of fever. We present the case of a 7-month-old girl presenting with new-onset refractory status epilepticus (NORSE) that followed routine vaccine administration and ensuing cytokine storm. She was diagnosed with a pathogenic variant in PCDH19. The patient required five anti-seizure medications and pentobarbital-induced burst suppression for control of seizures. She was noted to have elevated serum cytokine levels (IL-2, IL-4, IL-10, IL-13, IL-17, IL-1β, and IL-8) and CSF cytokine levels (IL-6 and IL-13). Anakinra was initiated and titrated based on serial cytokine levels, with doses ranging from 5-20 mg/kg/day resulting in reduction in cytokine levels and seizure reduction. By 14 months of age, she was able to be maintained on three active anti-seizure medications and with ketogenic diet for seizure control.

Introduction

PCDH19-related epilepsy, also called Girls Clustering Epilepsy, is an X-linked, female-predominant, developmental epileptic encephalopathy (DEE) that presents with multiple seizure semiologies and is associated with varying degrees of intellectual disability; patients initially present with difficult-to-control seizures that are often triggered by fever and occur in clusters of multiple seizures in a day.1, 2 While clusters of
seizures are frequently reported with PCDH19-related epilepsy, initial presentation as a new-onset refractory status epilepticus (NORSE) in infancy has not been well reported, and the current evolving literature regarding NORSE related to PCDH19 gene has been investigated, but not confirmed.\textsuperscript{3, 4} We present a clinically challenging case of NORSE with documented cytokine storm in a female infant found to have a pathogenic variant in PCDH19 and in whom we highlight successful treatment of seizures with Anakinra.

Case Report

A 7-month-old girl with no previous medical history presented to the hospital for frequent clusters of seizures for one day. The day prior to seizure onset, the child had received the third dose of the pneumococcal vaccine and the second influenza booster, without documented fever. The patient was noted to have multiple episodes of seizures consisting of behavioral arrest, cyanosis, and with generalized tonic-clonic and tonic activity. In the Emergency Department, seizures evolved into refractory status epilepticus (SE) despite use of multiple anti-seizure medications (ASMs) (Figure), necessitating pentobarbital-induced coma to achieve burst suppression twice after seizures were refractory to midazolam and ketamine infusions. She was additionally started on a 3:1 ketogenic diet due to the refractory nature of her SE, which escalated to 4:1 ketogenic ratio at the peak of her seizure frequency. Extensive initial evaluation for infectious, metabolic, and structural causes of epilepsy was unrevealing.

Given the patient’s fulminant onset of refractory SE, she was diagnosed with NORSE. Given presumed immunological factors that lead to NORSE in general, she was
treated symptomatically with intravenous methylprednisolone and intravenous immunoglobulin (IVIg). Initial serum cytokine panels revealed elevated serum IL-1, IL-1β, IL-2, IL-4, IL-8, IL-10, IL-13, and IL-17 levels (Table) and CSF IL-6 and IL-13 levels. Given the elevated cytokine levels, an evaluation for secondary hemophagocytic lymphohistiocytosis was performed and was negative. A rapid epilepsy gene panel revealed the pathogenic PCDH19 variant c.1211 C>T, resulting in the p.T404I amino acid substitution.

At the peak, the patient presented with greater than 25 seizures in a day, requiring clobazam 20mg nightly (2mg/kg/day), brivaracetam 50mg twice a day (10mg/kg/day), phenobarbital 97mg three times a day (30mg/kg/day), cannabidiol 100mg nightly (10mg/kg/day). Given the elevated cytokine levels, anakinra was started with dose escalation (5-20mg/kg/day) and slowly weaned off, guided by repeat cytokine panels. She was successfully weaned off pentobarbital with subsequent cytokine panels showed continued improvement. Following an attempt to reduce the anakinra dose, seizures recurred and cytokine levels were re-checked showing residual cytokine elevation notably in markers of adaptive immunity, such as IL-4, IL-5, and pro-inflammatory IL-17, which led to re-titration of anakinra (Figure). Eventually, seizures abated and Anakinra was weaned off successfully with no recurrence of seizures. Given the similarities in presentation between our case and some patients with Dravet Syndrome (DS), fenfluramine was included as part of the final anti-seizure regimen in preparation for discharge using doses employed for patients with DS.5

After 52 days, the patient was discharged home on five ASMs: clobazam, cannabidiol, and fenfluramine and the ketogenic diet that were maintained and
phenobarbital and brivaracetam that were actively being weaned. She remained seizure-free at 6-month follow-up. She has progressed from nasogastric tube feeding to oral intake of pureed feeds, has shown improved strength, and is achieving some developmental milestones, such as sitting up with support, with speech, physical, occupational and feeding therapies in place.

Discussion:

We report the case of an infant girl with PCDH19-related epilepsy who presented with NORSE one day after administration of routine vaccinations without concurrent febrile illness or vaccine-associated febrile response. Vaccination-induced seizures have been well documented in genetically predisposed epilepsy patients, such as those with Dravet Syndrome (DS)\(^1,6\) and anecdotally with PCDH19-related epilepsy\(^7\). While fever is reported as a trigger for seizures in girls with PCDH19-related epilepsy, as with DS, initial presentation of NORSE in a previously healthy child has not been previously reported in the context of PCDH19-related epilepsy.

Our case report demonstrates the presence of an immune-mediated process in the form of an unrelenting “cytokine storm” that we posit contributed to the sudden presentation and refractoriness of our patient’s epilepsy presentation as NORSE. Serum cytokine panels demonstrated a robust cytokine reaction, and CSF findings demonstrated IL-6 elevation, a pro-inflammatory marker, that may have contributed to the severity of NORSE in this child. Given that fever and presumably associated inflammation is known to trigger seizures in patients with pathogenic variants in PCDH19, we posit that this patient’s cytokine-mediated response to vaccination in the setting of PCDH19
dysfunction led to her severe NORSE presentation. Although the pathogenesis of PCDH19-related epilepsy remains unclear, case studies focused on courses of corticosteroids have demonstrated efficacy in prophylaxis and abortion of repetitive seizure clusters. This further underscores the possible involvement of an underlying neuroinflammatory mechanism for PCDH19 epilepsy.

Anakinra was added to this patient’s regimen because of observed increased cytokine levels, resulting in elimination of seizures. While Tocilizumab has been reported as treatment for super-refractory status epilepticus (not specific to a genetic etiology), Tocilizumab was not administered in the patient in this report due to its side effect profile, including immunosuppression, which would impact the vaccination schedule in this age group. A limitation of this case report is the difficulty in determining whether anakinra acutely helped to reduce seizures directly or helped slow progression of disease or whether the seizures reduced in frequency over time, as has been reported in the natural history of NORSE. Another potential confound is that the frequent adjustments of the patient’s ASMs may also have contributed to seizure reduction and elimination. However, it appeared at one period during this patient’s hospitalization that anakinra was required to be increased to a higher dose for seizure control after an attempt to taper the dose (Figure).

In summary, we add NORSE to the PCDH19 disease spectrum. While the presence of SE per se in the setting of PCDH19 is not surprising and PCDH19 has been hypothesized as a possible cause of NORSE, PCDH19-related epilepsy presenting as NORSE has not been appreciated. Attention to cytokine levels in a child with NORSE led
to treatment of our patient with an immunomodulatory medication that appeared to have a favorable acute response. Rapid genetic testing allowed for a precise explanation for the child’s predisposition to epilepsy. As there is no specific treatment for PCDH19-related epilepsy to date, a regimen including fenfluramine because of similarities between this condition and DS could be considered in addition to immunomodulatory therapy. Future studies with more patients will be needed to determine whether the use of either of these strategies—anakinra and/or fenfluramine—can be generalized to all patients with PCDH19-related epilepsy.

References


10.1542/peds.2014-0690


10. Schoonjans, AS, Lagae L, and Ceulemans B; “Low-Dose Fenfluramine in the Treatment of Neurologic Disorders: Experience in Dravet Syndrome.” *Therapeutic...*
**Legends:**

**Table: Serum Cytokine Panel Results**
Serum cytokine panels collected during hospital course. Bolded values reflect elevated interleukin markers based on laboratory reference ranges.

**Figure: Relationship Between Immunomodulatory and Anti-Seizure Medications and Seizure Frequency**
Relationship of seizure frequency and medication interventions, most notably with the start and modulation of Anakinra with respect to elevated cytokine levels and recurring seizures. We note the increase in seizures when anakinra was first decreased as well as down-trending cytokine levels correlating with successful reduction of seizure frequency in this patient. BS= Burst Suppression. IVIG= Intravenous Immune Globulin.
### Table: Serum Cytokine Panel

<table>
<thead>
<tr>
<th>Serum Cytokine Panel</th>
<th>Hospital Day 12</th>
<th>Hospital Day 29</th>
<th>Hospital Day 34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin 1 beta [&lt;=6.7pg/mL]</td>
<td>14.9</td>
<td>&lt;6.5</td>
<td>&lt;6.5</td>
</tr>
<tr>
<td>Interleukin 2 [&lt;=2.1pg/mL]</td>
<td>&lt;2.1</td>
<td>&lt;2.1</td>
<td>&lt;2.1</td>
</tr>
<tr>
<td>Interleukin 2 Receptor, Soluble [175.3-858.2pg/mL]</td>
<td>1868.2</td>
<td>3488.5</td>
<td>4921.6</td>
</tr>
<tr>
<td>Interleukin 4 [&lt;=2.2pg/mL]</td>
<td>5.2</td>
<td>2.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Interleukin 5 [&lt;=2.1pg/mL]</td>
<td>&lt;2.1</td>
<td>2.2</td>
<td>&lt;2.1</td>
</tr>
<tr>
<td>Interleukin 6 [&lt;=2.0pg/mL]</td>
<td>5.7</td>
<td>&lt;2.0</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>Interleukin 8 [&lt;=3.0pg/mL]</td>
<td>538.1</td>
<td>&lt;3.0</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Interleukin 10 [&lt;=2.8pg/mL]</td>
<td>13.6</td>
<td>11.6</td>
<td>10.5</td>
</tr>
<tr>
<td>Interleukin 12 [&lt;=1.9pg/mL]</td>
<td>&lt;1.9</td>
<td>&lt;1.9</td>
<td>&lt;1.9</td>
</tr>
<tr>
<td>Interleukin 13 [&lt;=2.3pg/mL]</td>
<td>58.1</td>
<td>&lt;1.7</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td><strong>Interleukin 17</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[&lt;=1.4pg/mL]</td>
<td>8.0</td>
<td>3.9</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Tumor Necrosis Factor Alpha</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[&lt;=7.2pg/mL]</td>
<td>22.3</td>
<td>13.7</td>
<td>20.3</td>
</tr>
<tr>
<td><strong>Interferon Gamma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[&lt;=4.2pg/mL]</td>
<td>8.3</td>
<td>&lt;4.2</td>
<td>&lt;4.2</td>
</tr>
</tbody>
</table>
Child Neurology: Initial Presentation of PCDH19-Related Epilepsy with New Onset Refractory Status Epilepticus and Treatment with Anakinra
Neurology published online June 3, 2022
DOI 10.1212/WNL.00000000000200855

This information is current as of June 3, 2022

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/early/2022/06/03/WNL.00000000000200855.full

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Antiepileptic drugs
http://n.neurology.org/cgi/collection/antiepileptic_drugs
Status epilepticus
http://n.neurology.org/cgi/collection/status_epilepticus

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

Reprints
Information about ordering reprints can be found online:
http://n.neurology.org/subscribers/advertise