CASE REPORT

Case Report: Genetic analysis and anesthetic management of a child with Niemann-Pick disease Type A [version 1; peer review: 2 approved]

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Abstract

A 14-month-old child, recently diagnosed with Niemann-Pick disease type A, presented for a laparoscopic placement of a gastrostomy tube under general anesthesia. The disease was confirmed and further characterized by genetic testing, which revealed evidence of the presence of two known pathogenic mutations in the SMPD1 gene, and enzyme studies showed a corresponding very low level of enzymatic activity of acidic sphingomyelinase. The anesthetic management involved strategies to manage an anticipated difficult intubation and avoid post-operative ventilation.

Keywords

Anesthesia, Niemann-Pick disease, genomic and biochemical analysis

Open Peer Review

Approval Status

1

2

version 1

10 Dec 2015

1. James J. Fehr, Washington University in St. Louis, St Louis, USA

2. Rakesh Garg, All India Institute of Medical Sciences, New Delhi, India

Any reports and responses or comments on the article can be found at the end of the article.
Introduction
Niemann-Pick disease (NPD) is a rare inherited autosomal recessive lysosomal storage disorder (incidence about 1:40,000 in general population) caused by pathogenic mutations in the SMPD1 gene and characterised by enzyme studies showing a corresponding very low level of enzymatic activity of acidic sphingomyelinase (ASM), associated with intracellular accumulation of lipids\(^1\). People with NPD type A (NPA; generally a very rare presentation of NPD) have little or no ASM production (less than 1% of normal) while those with NPD type B (the most frequent presentation of NPD) have approximately 10% of the normal level of ASM. There is no information on the anesthetic management of a patient with fully genetically characterized and biochemically confirmed NPA, and only one previous report describing a pediatric patient with presumably diagnosed NPA\(^1\). In this case report, we describe the genetic background, pathophysiology and anesthetic-related problems in a patient with NPA who presented for surgery.

Case report
A 14-month-old Caucasian child (residing in the United States, diagnosed with NPA, presented to our hospital pre-anesthesia assessment clinic for laparoscopic placement of a gastrostomy tube. There was no known family member or relatives diagnosed with NPD; mother reported a distant relative of Jewish origin. On physical exam, he was a well-proportioned child, weight was 8.32 kg (10\(^{th}\) percentile) and height was 77 cm (50–75\(^{th}\) percentile), head circumference was 48.3 cm (90–95\(^{th}\) percentile). Craniofacial features included frontal bossing, protuberant tongue and mild bilateral ptosis. Generalized hypotonia with head lag and weakness in upper girdle and lower leg muscles, decreased deep tendon reflexes and hepatosplenomegaly (3 cm below the costal margin) were noted. Liver function tests revealed elevation of alanine transaminase (ALT) levels - 90 u/L (normal range 13–69), aspartate transaminase (AST) levels - 271 u/L (normal range 9–80), alkaline phosphatase levels - 252 u/L (normal range 8–240) and creatine phosphokinase (CPK) - 318 (normal range 55–170).

The child had G-tube feeds commenced following surgery and subsequently discharged to home the following day and made an uneventful clinical recovery. Subsequently over the course of next few months, the child had episodes of intractable seizures which were medically managed. The patient was referred to home hospice care and expired at home at the age of 2 years.

Biochemical evaluation
The results of enzymatic evaluation of patient blood and leukocytes by an outside laboratory are presented in Table 1.

Genetic evaluation
Extracted DNA was PCR-amplified for analysis of the coding exons 1 to 6 of the SMPD1 gene and their flanking splice sites, using a standard Sanger sequencing approach. Bi-directional sequence was obtained and the DNA sequence was analyzed and compared to the published gene sequence. Reportable variants were confirmed by repeat sequence analysis. Based on the genetic diagnostic laboratory (Proprietary information from GeneDx, Gaithersburg, MD) 99% sensitivity is expected in detecting mutations identifiable by sequencing. Please refer to Table 2.

Figure 1. Laryngeal view at intubation with the videolaryngoscope.

Table 1. Biochemical enzymatic pattern of investigated patient (by Lysosomal Diseases Testing Laboratory, Philadelphia, PA).

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Tissue source</th>
<th>Results (nmol/hr/mg protein)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-galactosidase</td>
<td>L/P</td>
<td>62.5/17.7</td>
<td>Normal range</td>
</tr>
<tr>
<td>Beta-mannosidase</td>
<td>L</td>
<td>100.9</td>
<td>Normal range</td>
</tr>
<tr>
<td>Alpha-L-fucosidase</td>
<td>L</td>
<td>52.3</td>
<td>Normal range</td>
</tr>
<tr>
<td>Alpha-mannosidase</td>
<td>L</td>
<td>207.1</td>
<td>Normal range</td>
</tr>
<tr>
<td>Beta-glucuronidase</td>
<td>L</td>
<td>313.6</td>
<td>Normal range</td>
</tr>
<tr>
<td>Beta-hexaminidase A</td>
<td>L</td>
<td>284.0</td>
<td>Normal range</td>
</tr>
<tr>
<td>Sphingomyelinase</td>
<td>L</td>
<td>0.06</td>
<td>Abnormally low</td>
</tr>
<tr>
<td>Glucocerebrosidase</td>
<td>L</td>
<td>19.5</td>
<td>Normal range</td>
</tr>
<tr>
<td>Alpha-L-idorinidase</td>
<td>L</td>
<td>31.8</td>
<td>Normal range</td>
</tr>
<tr>
<td>Alpha-glucosaminidase</td>
<td>P</td>
<td>71.1</td>
<td>Normal range</td>
</tr>
<tr>
<td>Mucolipidoses II/III</td>
<td>P</td>
<td>N/A</td>
<td>Ruled out</td>
</tr>
</tbody>
</table>

P – Plasma, L – Leukocytes – Bold face denotes abnormal results
This result therefore permits mutation-specific carrier testing for lesions (in trans), i.e., each mutation coming from a different parent. The observed c.573delT mutation in the SMPD1 gene in our case has been reported previously in association with NPD type A. The deletion causes a frame shift starting with codon Serine 192, changes this amino acid to an Alanine residue and creates a premature Stop codon at position 65 in the new reading frame denoted p.Ser192AlafsX65. This mutation is predicted to cause abnormal protein function either through protein truncation or nonsense-mediated mRNA decay. The c1783_1784delCT deletion causes a frame shift starting with codon Alanine 597, changes this amino acid to a Proline residue, and creates a premature stop codon at position 7 of the new reading frame denoted p.Ala597ProfsX7. This mutation is predicted to cause loss of normal protein function through protein truncation. Specifically, the last 35 correct residues are replaced by six incorrect residues. Therefore, the presence of these mutations is consistent with the diagnosis of an SMPD1-related disorder, if the mutations were inherited on different alleles (in trans), i.e., each mutation coming from a different parent. This result therefore permits mutation-specific carrier testing for family members and prenatal diagnosis for the parents of this child, if desired. However, targeted carrier testing of both parents is necessary prior to or concurrently with any carrier testing or predictive testing in this family.

Patients with NPA and NPB have significantly different clinical course. While NPA is associated with severe neurological deficits leading to early death, patients with NPB have minimal neurological involvement and may survive to adulthood, although hepatosplenomegaly and cardiorespiratory problems may occur. We believe therefore that it is important to distinguish these form of NPD preoperatively, because NPA requires much more strict anesthetic management (avoidance of muscle relaxants and opioids, if at all possible) and it could associated more frequently with step-up level of postoperative care.

Consent
Written informed consent for publication of clinical details and/or images was obtained from the parent of the patient.

Author contributions
PD and PJ prepared the initial draft of the manuscript. MC, MH, RL and DR did further literature review and modifications of the manuscript. RL gave considerable input on the genetic concepts in the manuscript. All authors have seen and agreed to the final content of the manuscript. RL and DR did further literature review and modifications of the manuscript.

Competing interests
The authors declared no competing interests.

Grant information
The author(s) declared that no grants were involved in supporting this work.

References

Table 2. The sequencing analysis provided evidence of the presence of two pathogenic mutations in the SMPD1 gene.

<table>
<thead>
<tr>
<th>Gene</th>
<th>cDNA</th>
<th>Variant</th>
<th>Zygosity</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPMD1</td>
<td>*c.573delT</td>
<td>p.Ser192AlafsX65</td>
<td>heterozygous</td>
<td>Disease-causing mutation</td>
</tr>
<tr>
<td>SPMD1</td>
<td>**c.1783_1784delCT</td>
<td>p.Ala597ProfsX7</td>
<td>heterozygous</td>
<td>Disease-causing mutation</td>
</tr>
</tbody>
</table>

*The normal sequence with the base that is deleted in braces is: ACCCCC(T)AGCC. **The normal sequence with the bases that are deleted in braces is: TAC(T)TTGT.
Open Peer Review

Current Peer Review Status:  ✔  ✔

Version 1

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Please provide more details of airway management i.e. difficulty level. Was it predicted and preparation done before inducing anaesthesia?

Please provide detail (positive or negative ) for any other additional comorbidities - structural or functional.

Please mention duration of surgery, need of any NMB drugs, other analgesia, hemodynamic status intraoperatively.

Since the title says anaesthetic management as well, It would be good if authors could add an table for various perioperative concerns in such child and their suggestions for the management.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 01 February 2016

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James J. Fehr
St Louis Children’s Hospital, Washington University in St. Louis, St Louis, MO, USA

This is novel case report of a 14 month old with NPA who is undergoing an anesthetic. The manuscript is generally written, a few missing articles were noted, but the substance of the article is sound. The report is supported by appropriate references from the literature and the case description is succinct but complete. A modest improvement might be made by including the clinical presentation of NPA (what to be concerned about) in the introduction which would serve to focus the reader on the subsequent anesthetic management.

**Competing Interests:** No competing interests were disclosed.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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