Case Report

Homozygous Autosomal Recessive DIAPH1 Mutation Associated with Central Nervous System Involvement and Aspergillosis: A Rare Case

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The DIAPH1 gene fulfills critical immune and neurodevelopmental roles. It encodes the mammalian Diaphanous-related formin (mDia1) protein, which acts downstream of Rho GTPases to promote F-actin polymerization and stabilize microtubules. During mitosis, this protein is expressed in human neuronal precursor cells and considerably affects spindle formation and cell division. In humans, dominant gain-of-function DIAPH1 variants cause sensorineural deafness and macrothrombocytopenia (DFNA1), while homozygous DIAPH1 loss leads to seizures, cortical blindness, and microcephaly syndrome (SCBMS). To date, only 16 patients with SCBMS have been reported, including the following variants: NM_005219: c.2332C>T; p. Q778X, c.2769delT; p.F923fs, c.3145C>T; p.R1049X; and c.68411G>A [9–11]. Only one of the previous studies highlights a clear link between SCBMS and immunodeficiency [11], though some cases with bronchiectasis or recurrent respiratory infections have also been described [9, 10]. Furthermore, aspergillosis is yet to be reported in patients with homozygous DIAPH1 loss, and the link between SCBMS and immunodeficiency remains elusive. In this study, we shed further light on this matter by reporting the clinical, genetic, and phenotypic characteristics of an Iranian boy with a long history of recurrent infections, diagnosed with SCBMS and immunodeficiency (NM_005219.5 c.3145C>T; p.R1049X variant) following aspergillosis and SARS-CoV-2 coinfection.

1. Introduction

The DIAPH1 gene fulfills critical immune and neurodevelopmental roles; it encodes the mammalian Diaphanous-related formin (mDia1) protein, which acts downstream of Rho GTPases to promote F-actin polymerization and stabilize microtubules [1–3]. Besides its role in malignancies, the DIAPH1 gene has been implicated in various Mendelian diseases [4, 5]. Dominant gain-of-function DIAPH1 variants cause sensorineural deafness and macrothrombocytopenia (DFNA1) [6–8], while homozygous DIAPH1 loss leads to seizures, cortical blindness, and microcephaly syndrome (SCBMS). In this syndrome, seizures usually develop during early infancy and are challenging to manage. Though body measurements may be normal at birth, microcephaly, cortical blindness, and intellectual disability gradually develop, sometimes with stunted growth [9–11].

To date, only 16 patients with SCBMS have been reported, including the following variants: NM_005219: c.2332C>T; p. Q778X, c.2769delT; p.F923fs, c.3145C>T; p.R1049X; and c.68411G>A [9–11]. Only one of the previous studies highlights a clear link between SCBMS and immunodeficiency [11], though some cases with bronchiectasis or recurrent respiratory infections have also been described [9, 10]. Furthermore, aspergillosis is yet to be reported in patients with homozygous DIAPH1 loss. Herein, we shed further light on this matter by reporting the case of an Iranian boy with a long history of recurrent infections, diagnosed with SCBMS and immunodeficiency (NM_005219.5 c.3145C>T; p.R1049X variant) following aspergillosis and SARS-CoV-2 coinfection.
2. Case Presentation

In February 2022, we admitted a four-year-old boy, who was a known case of CD4 deficiency, seizure, cortical blindness, and microcephaly, due to fever. On physical examination, the vital signs were stable, with the exception of a 38.7°C temperature. The skin featured a scar from a past vasculitis lesion, and both eyes had no response to light. Upon auscultation of the lungs, bilateral rales were detected. Upon admission, his weight, height, and head circumference were 12 kg (z-score: −3.37), 59 cm (z-score: −10.32), and 44 cm, respectively.

The patient had a history of seizures, blindness, and recurrent infections since birth. His birth weight was 2.98 kg, his height was 49 cm, and his head circumference was 34 cm, and the parents were distantly related. Neonatal screening for inborn errors of metabolism and endocrinopathies was normal. His seizures had commenced during early infancy in generalized tonic-clonic form; the patient was on antiseizure medications for a period of time, after which the seizures no longer occurred and the medications were tapered and discontinued. Before admission, the patient was receiving prophylactic cotrimoxazole and fluconazole. He had no family history of immunodeficiency or death of unknown cause. He had previously been hospitalized many times, and a summary of the previous five admissions is presented in Table 1. In terms of surgical history, the patient underwent a right posterior lateral thoracotomy and right upper lobectomy when he was one and a half years old due to congenital lobar emphysema. Due to the known immunodeficiency status, broad-spectrum antibiotics (intravenous vancomycin and meropenem) were initiated upon admission.

In the laboratory workup, the following findings were significant: WBC 13,700/μl (62% lymphocytes), Hb 11.1 g/dL, Plt 475,000/μl, ESR 65 mm/hr, CRP 38 mg/l, D-dimer 4,360 ng/mL, ferritin 506.4 ng/ml (high), procalcitonin 0.69 ng/ml (equivocal), SARS-CoV-2 IgG 0.2 (negative), SARS-CoV-2 IgM <0.01 (negative), negative serum aspergillus galactomannan Ag, and normal total IgE and HIV Ab/IgM (equivocal), SARS-CoV-2 IgG 0.2 (negative), SARS-CoV-2 IgM <0.01 (negative), negative serum aspergillus galactomannan Ag, and normal total IgE and HIV Ab/IgM (equivocal). The other three were Omani siblings (two females; one male) who had the c.3145C>T variant of homozygous DIAPH1 loss. The first reported instance of such a mutation affected five siblings in a Saudi Arabian family, who had developmental delay, intellectual disability, blindness, microcephaly, seizures, and stunted growth caused by the c.2332C>T variant (p.Gln778†, RefSeq NM_005219.4) variant. In that report, immunodeficiency was not mentioned, though one patient succumbed to a chest infection at the age of 18 [10]. In the second report on this issue, the variants were detected in four individuals with SCBMS from two unrelated consanguineous families. The first was a boy from the United Arab Emirates who had SCBMS as well as recurrent sino-pulmonary infections (causing chronic cough and secretions), though sweat testing and immunological function screenings were normal. He also suffered from wheezing early on and needed supplemental oxygen for seven months. Notably, he had the same variant (c.3145C>T; p.R1049X) as our patient. The other three were Omani siblings (two females; one male) who had the c.2769delT; p.F923fs variant of homozygous DIAPH1 loss. Again, immunodeficiency was not detected, though one female had severe bronchiectasis and died of pneumonia at age 13 [9].

In the only report to have linked homozygous DIAPH1 loss with SCBMS and immunodeficiency, Kaustio et al. described five Finnish patients homozygous for the NM_005219:c.6841G>C splice-variant and two Omani patients with the NM_005219:c.2769delT; p.F923fs frame-shift-variant. In addition to SCBMS, these patients were susceptible to infections due to defective lymphocyte maturation, with three of them developing B-cell lymphoma. Immunophenotyping revealed poor lymphocyte activation and proliferation, defective B-cell maturation, and a lack of naïve T cells. The recurrent infections in the patients included otitis media, respiratory infections, candida, mycobacteria, VZV, HSV, EBV, CMV, RSV, MRSA, molluscum contagiosum, recurrent watery diarrhea, rubella vaccine strain skin infection, JCV encephalitis, Staphylococcus haemolyticus, Elizabethkingia meningoseptica, and Streptococcus pneumoniae [11]. Similarly, our patient also had recurrent pulmonary infections and a CMV urinary tract
<table>
<thead>
<tr>
<th>Admission</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
<th>Fifth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years and months)</td>
<td>1 y 4 m</td>
<td>1 y 6 m</td>
<td>2 y 5 m</td>
<td>2 y 7 m</td>
<td>3 y 7 m</td>
</tr>
<tr>
<td>Chief complaint</td>
<td>Productive cough, vomiting</td>
<td>Cough</td>
<td>Fever, cough</td>
<td>Fever</td>
<td>Fever</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Pneumonia</td>
<td>Congenital lobar emphysema</td>
<td>Sepsis vs. pneumonia, CD4 deficiency</td>
<td>COVID-19, sepsis</td>
<td>Suspected sepsis</td>
</tr>
<tr>
<td>Duration of admission (days)</td>
<td>7</td>
<td>5</td>
<td>10</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

**Significant laboratory data**

- (i) WBC 11,100/μl
- (ii) Hb 11.6 g/dl
- (iii) Plt 285,000/μl
- (iv) Brain MRI: Thin corpus calosum splenium suggestive of mid-central cortical atrophy
- (v) Spiral chest CT: Multiple cystic structures measuring about 60x55x40 mm in mid-zone of right lung contains multiple air-containing cysts with variable size and septation suggestive of type 1 Congenital pulmonary airway malformation. Diffuse patchy air space opacities in both upper and lower lobes with multiple air space nodules suggestive of bronchopneumonia

- (i) WBC 3000/μl (32% lymph.)
- (ii) Hb 6.6 g/dl
- (iii) Plt 488,000/μl
- (iv) Flow cytometry: CD3 71%, CD4 12%, CD8 55%, CD16 23%, CD19 6%, CD56 23%, CD14 16%, CD4/CD8 0.22
- (v) Karyotype study on bone marrow culture: normal (46,XY)
- (vi) Bone marrow aspiration biopsy/immunohistochemistry: erythroid hypoplasia with parvovirus B19 infection; 4-5% immature myeloid cells; about 30% hematogones
- (vii) Left leg lesion skin biopsy: lymphocytic vasculitis
- (viii) ANA 3.9 U/ml†
- (ix) dsDNA (IgG) 26.0 IU/ml²
- (x) dsDNA (IgM) 32.7 IU/ml²
- (xi) ACLA IgM 5.1 U/ml²
- (xii) Anti Ri (SSA) IU/ml 83.2
- (xiii) IgG 16.34 g/l
- (xiv) IgM 19.77 g/l
- (xv) IgA 1.21 mg/dl
- (xvi) IgE 15.8 IU/ml (normal)
- (xvii) ASMA neg.
- (xviii) P-ANCA (Anti MPO) neg.
- (xix) C-ANCA (Anti PR3) 132.0 U/ml†

† High/positive,‡ Borderline/equivocal,§ Low.
infection, though he also developed COVID-19 and aspergillosis, which were yet to be reported in patients with homozygous DIAPH1 loss.

Aspergillosis is an opportunistic fungal infection that can be life-threatening in those who are immunocompromised. Factors that render an individual susceptible include neutropenia, corticosteroid use, hematologic malignancies, diabetes, underlying lung disease, and AIDS [16–19], with low CD4 counts being associated with a higher incidence of this condition [20]. In our patient, hematologic malignancies were ruled out and corticosteroids were not routinely used, though underlying lung disease was present in addition to a low CD4 count (920/µL).

According to the Kaustio et al. study, patients with SCBMS can have combined immune deficiency as cytoskeletal organization disorganization and mitochondrial dysfunction are implicated in the pathogenesis of the syndrome [11]. In that study, T cells derived from the patients had impaired adhesion and inefficient microtubule-organizing center translocation to the immune synapse, which is essential for T-cell function. Such a defect has previously been shown in animal models, so immunodeficiency can be expected in such patients given the functions of DIAPH1 loss, indicating that this DIAPH1 variant was responsible for the observed phenotype.

An incidental finding reported in our genetic workup was the heterozygous c.1129 C>T variant in the DNAJC3 gene. While homozygous mutations in DNAJC3 on chromosome 13q32 cause combined cerebellar and peripheral ataxia with hearing loss and diabetes mellitus (ACPHD) [24], there is no evidence to suggest a link between the homozygous variant found incidentally in our patient and his specific phenotype. Rather, the phenotypic features seen in our case are generally well-aligned with the prior reports on homozygous DIAPH1 loss, indicating that this DIAPH1 variant was responsible for the observed phenotype.

The strengths of this study include the characterization of the phenotype related to a very rare form of immunodeficiency for the first time in an Iranian patient. The main limitation is the cross-sectional nature of this report, though the patient remains under our follow-up and longitudinal data can be collected in the future. Our results add evidence in support of the link between homozygous DIAPH1 loss and T-cell deficiency. Hence, physicians who manage SCBMS patients must be prepared to prevent or treat severe or recurrent infections, and corticosteroid use may need to be limited in these patients to prevent aspergillosis. Further investigations should be conducted into the exact mechanism behind the defective T-cell responses in patients with homozygous DIAPH1 loss.

**Ethical Approval**

A written informed consent was obtained from the patient’s guardian for performing and publishing this study.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest.

**References**


