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Congenital Disorder of Glycosylation Following ATP6AP1 Deficiency With Normal Liver Function: A Case Report

Amirreza Jabbaripour Sarmadian[1,2] | Babak Abdinia[1] | Kia Seyed Toutounchi[3] | Mohammad Saberi[4] | Shabnam Eskandarzadeh[1]

[1]Pediatric Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran | [2]Tabriz USERN Office, Universal Scientific Education and Research Network (USERN), Tabriz, Iran | [3]Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran | [4]Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Correspondence: Shabnam Eskandarzadeh (s_eskandarzadeh@yahoo.com)

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ABSTRACT

Congenital disorders of glycosylation (CDG) are a heterogeneous group of inherited metabolic diseases (IMD) characterized by defects in the synthesis and modification of glycoproteins and glycolipids. One of these disorders is ATP6AP1-CDG, a rare X-linked disease with approximately 30 cases reported so far. Symptoms associated with ATP6AP1-CDG include immunodeficiency, liver dysfunction, and neurological manifestations. This report presents the first case of ATP6AP1-CDG in Iran and the Middle East, in a 5-month-old male infant presenting with fever, vomiting, diarrhea, and poor feeding. The patient had a history of similar symptoms at three and 4 months and had been hospitalized with a diagnosis of gastrointestinal (GI) infection. In addition, he had a history of recurrent seizures, which first began at 45 days old, and was treated with phenobarbital. On physical examinations, the patient was lethargic, severely hypotonic with decreased primitive reflexes, and dehydrated with dry mucous membranes and white plaques of candidiasis. There was no tenderness, guarding, or hepatosplenomegaly in the abdominal examination. Laboratory blood tests were requested, which revealed leukocytosis and normal liver and kidney functions, with negative blood, urine, cerebrospinal fluid, and stool cultures for bacterial growth. Considering the history of recurrent infections, idiopathic seizures, suspected immunodeficiency in the patient's deceased sibling and parental consanguinity, primary immunodeficiency was suspected as a possible diagnosis for the patient. Therefore, a panel of immune function tests was requested, all of which were within the normal range. This panel consisted of IgM, IgG, IgA, B-Cell markers (CD19), T-Cell markers (CD3, CD4, and CD8), TRECs, NK-Cell markers (CD16 and CD56), LTT-PHA, LTT-BCG, and CH50. Furthermore, whole exome sequencing (WES) was requested, which revealed a novel hemizygous deletion in the ATP6AP1 gene (NM_001183.6), designated as c.111_116del; p.Ala40_Ala41del (chrX:153657133 TGGCGGC>T, hg19 assembly).

1 | Introduction

Congenital disorders of glycosylation (CDG) represent a heterogeneous group of rare inherited metabolic diseases (IMD) characterized by defects in the synthesis and modification of glycoproteins and glycolipids [1, 2]. These disorders profoundly impact cellular function by disrupting essential pathways across multiple organelles, including the cytosol, endoplasmic reticulum (ER), ER-Golgi intermediate compartment, Golgi apparatus, and sarcolemmal membrane [3, 4]. The clinical spectrum of CDG is characterized by extensive phenotypic heterogeneity, with patients presenting multisystem

Summary

- In patients with frequent infections and neurological manifestations, ATP6AP1-CDG should be suspected even without any signs or symptoms of hepatopathy.

manifestations that commonly emerge from birth [5]. These complex presentations encompass neurological, developmental, dysmorphic, musculoskeletal, ocular, hepatic, gastrointestinal, cardiovascular, dermatologic, hematologic, endocrine, immunologic, genitourinary, respiratory, psychiatric, renal, and dental manifestations. The overlapping nature of these clinical features highlights the need for a comprehensive, multidisciplinary approach to ensure accurate diagnosis and effective patient management [6, 7].

In recent years, significant advancements in genomics and metabolomics have expanded the spectrum of CDGs to approximately 200 phenotypes, associated with 189 distinct genetic defects, further complicating their diagnosis [5, 6]. One of the recently identified CDGs is associated with mutations in the ATP6AP1 gene, known as ATP6AP1-CDG (OMIM #300972). This extremely rare X-linked multisystem disorder has been reported in approximately 30 cases worldwide to date [8]. ATP6AP1-CDG was initially characterized in patients exhibiting a distinctive triad of clinical features: (1) immunodeficiency, marked by recurrent bacterial infections and hypogammaglobulinemia; (2) neurological manifestations, including intellectual disability, seizures, hypotonia, delays in psychomotor and speech development, learning difficulties, and behavioral disturbances; and (3) liver involvement, such as hepatomegaly, elevated liver enzymes, cholestasis, and fibrosis [9]. Although this triad remains the most prominent and frequently reported clinical presentation, both the phenotypic and genotypic spectrum of this disorder continue to expand [8, 10]. Here, we report the first documented case of ATP6AP1-CDG in Iran and the Middle East, featuring a novel genomic mutation and an atypical clinical presentation characterized by recurrent gastrointestinal (GI) infections and seizures, notably in the absence of liver involvement, deviating from the classical features commonly described in earlier cases.

2 | Case History/Examination

A 5-month-old Iranian male infant was brought to the emergency department by his parents with a 2-day history of worsening fever, vomiting, diarrhea, and poor feeding. The mother reported that the infant had experienced similar episodes at 3 and 4 months of age, during which he was hospitalized elsewhere with a diagnosis of gastrointestinal infection and subsequently discharged after symptom improvement. Additionally, the patient had been suffering from recurrent seizures since 45 days of age, for which he was on phenobarbital treatment. He also had a history of neonatal jaundice that resolved spontaneously without hospitalization. The infant had been vaccinated according to the national immunization schedule. Notably, the parents were consanguineous and had previously lost a child at 23 months of age who had not undergone medical evaluation.

On physical examination, the patient was lethargic and severely hypotonic, with diminished primitive reflexes. Vital signs revealed a blood pressure of 100/65 mmHg, a heart rate of 150 bpm, an axial body temperature of 38.4°C, a respiratory rate of 56 breaths per minute, and an oxygen saturation of 94% on room air, decreasing to 90% when using an oxygen hood. Signs of dehydration were evident, including dry mucous membranes and white candidiasis plaques. Cardiac and pulmonary exams showed tachycardia without murmurs or additional sounds, and clear lung fields. Abdominal examination revealed no tenderness, guarding, or hepatosplenomegaly.

3 | Methods (Differential Diagnosis, Investigations, and Treatment)

Due to the patient's unstable condition, he was admitted with an initial diagnosis of sepsis. Blood, urine, cerebrospinal fluid (CSF), and stool cultures were obtained prior to the initiation of antibiotic therapy to evaluate for possible bacterial infection. Subsequently, intravenous fluids, along with empirical antibiotic and antifungal therapy, were promptly administered while the patient's condition was closely monitored. This approach was considered appropriate given the severity of his symptoms and the unavailability of culture results at the time.

Laboratory tests were requested to further evaluate the patient's condition. The complete blood count (CBC) was largely unremarkable except for leukocytosis, predominantly lymphocytic. Additional investigations showed a normal coagulation profile, including prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR). Liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, and total and direct bilirubin, were within normal limits. Renal function tests, such as serum creatinine and blood urea nitrogen (BUN) were also normal for the patient's age. Despite the history of diarrhea and dehydration, serum electrolytes, including sodium, potassium, calcium, and magnesium, remained within normal ranges. All cultures, which were finalized after several days, yielded negative results.

To investigate the underlying cause of the patient's syndromic features, including recurrent GI infections and idiopathic seizures, despite normal laboratory test results, primary immunodeficiency was suspected due to the combination of other puzzle pieces such as consanguineous parents and the early death of the patient's brother from an unknown cause. Given the high prevalence of such disorders in our region, this diagnosis was actively pursued. Therefore, a comprehensive panel of immune function tests, along with whole exome sequencing (WES), was conducted, and intravenous immunoglobulin (IVIG) therapy was initiated as part of the patient's treatment regimen.

The panel included immunoglobulin levels (IgM, IgG, and IgA) to assess humoral immunity; B-cell (CD19), T-cell (CD3, CD4, CD8), and NK-cell (CD16, CD56) markers to evaluate lymphocyte populations; T-cell receptor excision circles (TRECs) to indicate new T-cell production; lymphocyte transformation tests with phytohemagglutinin (LTT-PHA) and Bacillus Calmette-Guérin (LTT-BCG) to assess T-cell function; and total hemolytic complement

activity (CH50) to evaluate complement system integrity. All tests were within normal ranges, effectively ruling out major immune defects. The only minor findings were a slightly low IgG level and CD56 counts near the lower limit of normal, neither of which was considered clinically significant. Based on the immune function tests, the patient did not exhibit hypogammaglobulinemia.

WES was performed using the Twist Exome Target Enrichment Kit, and sequencing was carried out on the NovaSeq platform with a mean coverage depth of 356× by CeGaT, Germany. Genetic analysis identified a novel hemizygous deletion in the *ATP6AP1* gene (NM_001183.6), designated as c.111_116del; p.Ala40_Ala41del (chrX:153657133 TGGCGGC>T, hg19 assembly). This deletion occurs in exon 1 within a stretch of nine consecutive alanine residues, resulting in the loss of two alanines from the amino acid chain. Given the strong correlation of both the patient's clinical presentation and supporting evidence with ATP6AP1-CDG (OMIM #300972), despite the absence of remarkable findings in other laboratory tests, the identified variant is classified as likely pathogenic in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines. Therefore, a diagnosis of ATP6AP1-CDG was established for the patient. The parents were also invited to undergo WES testing for segregation analysis; however, they declined to give consent.

Further systematic evaluations were undertaken to explore other potential manifestations of the disease, with no additional abnormalities identified. Particular attention was given to neurological assessment, which revealed no specific abnormal findings. During hospitalization, despite the continued administration of phenobarbital as prescribed by the attending physician, the patient experienced one seizure episode. Consequently, an electroencephalogram (EEG) was performed, which showed no abnormalities at that time; however, previous EEG records were unavailable. Developmental screening using the Ages and Stages Questionnaires (ASQ), appropriate for the patient's age, was also conducted and showed results within normal limits for a 5-month-old infant. Given the known liver involvement in ATP6AP1-CDG, liver evaluation was prioritized. Liver and biliary tract ultrasonography was performed and found to be normal. In addition, serial liver function tests, including ALT, AST, ALP, albumin, and total and direct bilirubin, remained within normal limits throughout the hospitalization.

Despite normal immune function tests, due to the patient's history of multiple hospitalizations for relatively severe infections, IVIG therapy was continued at a dose of 400 mg/kg monthly to provide immunological support and reduce the risk of further infections. In addition, prophylactic antibiotic and antifungal therapies were continued, along with ongoing phenobarbital treatment for seizure control.

4 | Conclusion and Results (Outcome and Follow-Up)

During regular follow-up visits over a 2-year period, the patient was closely monitored for the emergence of additional

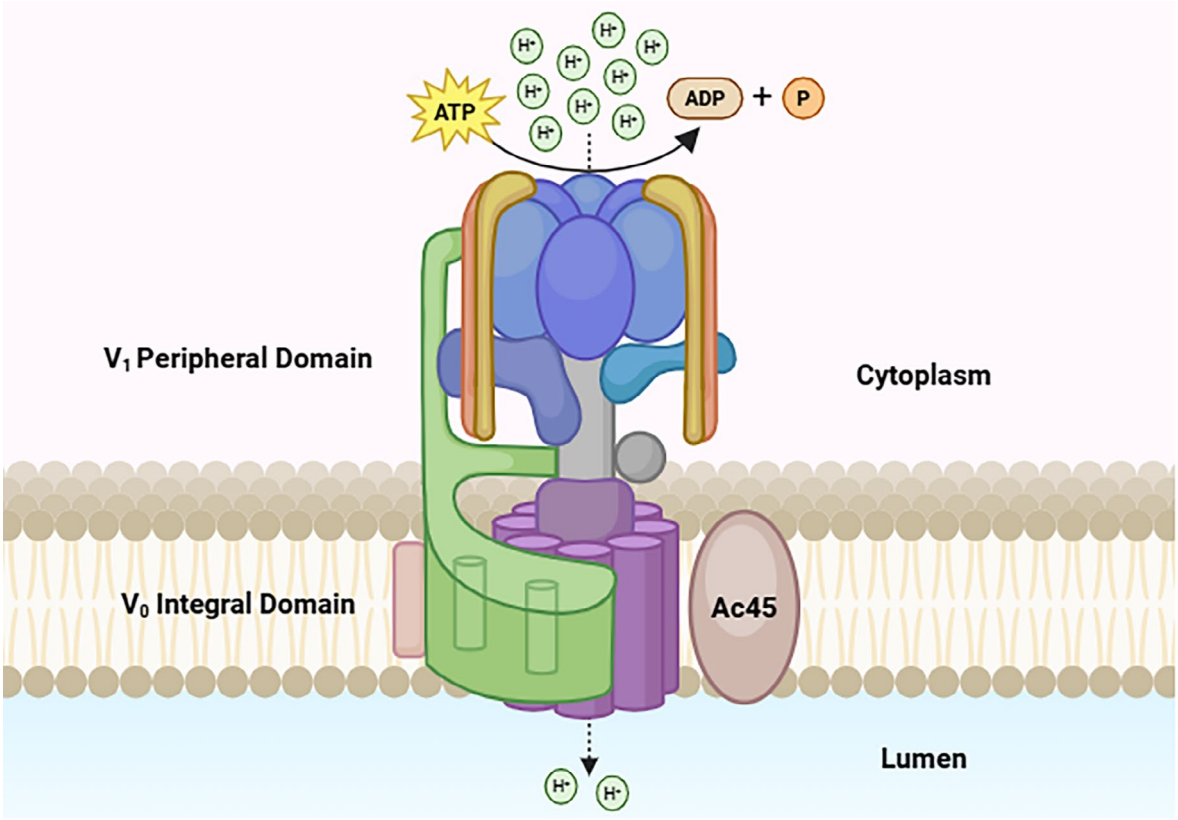

FIGURE 1 | Schematic representation of the V-ATPase complex. The V-ATPase is a multi-subunit enzyme consisting of a peripheral V1 domain, responsible for ATP hydrolysis, and a transmembrane V0 domain, which mediates proton translocation across membranes. ATP6AP1 (Ac45) functions as an accessory subunit involved in the assembly and trafficking of the complex. Created with BioRender.com.

symptoms. Periodic systemic, neurological, developmental, and hepatic evaluations, including physical examinations, laboratory tests, EEG, ASQ, and ultrasonography, consistently yielded normal findings. IVIG therapy was maintained throughout this period. However, the patient required multiple hospitalizations due to recurrent infections. According to the parents, despite continued treatment with phenobarbital, he occasionally experienced breakthrough seizures.

5 | Discussion

Primary immunodeficiency disorders warrant consideration in patients presenting with recurrent infections, familial history, and associated syndromic features [11, 12]. In this case, the constellation of recurrent GI infections and idiopathic seizures, combined with a suspected immunodeficiency in the patient's deceased sibling and parental consanguinity, heightened clinical suspicion for an underlying genetic immunodeficiency. This suspicion was subsequently validated through WES, which identified ATP6AP1-CDG as the underlying etiology.

ATP6AP1, also known as Ac45, serves as an accessory subunit of the vacuolar proton (H^+)-ATPase (V-ATPase) complex, a large multi-subunit enzyme comprising two major functional domains: the peripheral V1 domain responsible for ATP hydrolysis and the transmembrane V0 domain that mediates proton transport (Figure 1) [13, 14]. This complex is essential for the acidification of intracellular compartments such as endosomes, lysosomes, and the Golgi apparatus, a process critical for protein degradation, receptor recycling, and vesicular trafficking in eukaryotic cells. Beyond its housekeeping roles, V-ATPase is involved in cell type-specific functions across a wide range of tissues, including neurons, retinal pigment epithelial cells, inner ear supporting cells, olfactory epithelial cells, pulmonary ionocytes, pancreatic β-cells, renal intercalated cells, osteoclasts, keratinocytes, eccrine sweat gland clear cells, epididymal clear cells, spermatozoa, neutrophils, and macrophages. Consequently, pathogenic variants in genes encoding V-ATPase subunits, such as Ac45, can lead to a broad spectrum of syndromic disorders, often with multisystem involvement [15, 16].

ATP6AP1-CDG is a type II CDG characterized by abnormal protein N- and O-glycosylation [17]. It was first introduced by Jansen et al. [9] in 11 male patients with impaired protein glycosylation, 9 patients with N- and O-glycosylation, and 2 patients with only N-glycosylation defects, where pathogenic variants in the encoding gene were identified through exome sequencing. The predominant clinical presentation among the initially reported patients was recurrent bacterial infections associated with hypogammaglobulinemia, including plantar abscesses, GI infections, pneumonia, and purulent otitis media. Our patient was also referred due to frequent GI infections; however, hypogammaglobulinemia was not present. Additionally, varying degrees of liver damage were reported, with hepatomegaly observed in 8 patients during clinical examination, an abnormality not seen in our case. Reported liver involvement ranged from neonatal jaundice and mildly elevated transaminase levels to abnormal liver histology, cirrhosis, and liver failure. In contrast, our patient only had a history of neonatal jaundice, which resolved

TABLE 1 | Summary of clinical and genetic findings in our patient.

Gender	Age	Ethnicity	Family history	cDNA mutation	Infections	Hypogammaglobulinemia	Neurological symptoms	Abnormal liver function	Hepatomegaly	Splenomegaly	Death
Male	5 M	Iranian	Unknown (Possible)	c.111_116del; p.Ala40_Ala41del	+	–	+	–	–	–	–

spontaneously without hospitalization, and no evidence of liver damage was found in laboratory tests or ultrasound imaging. Splenomegaly was reported in 5 patients but was also absent in our case. Neurological manifestations were another predominant feature, observed in 7 patients, including seizures, mild intellectual disabilities, and behavioral abnormalities. Similarly, our patient exhibited neurological symptoms in the form of recurrent idiopathic seizures. Other reported findings included GI issues, muscle weakness with mildly elevated serum creatine kinase, B-cell differentiation defects, sensorineural hearing loss, and hyperopia. Laboratory abnormalities included leukopenia, elevated serum transaminases, low copper and ceruloplasmin levels, and elevated ALP. In contrast, our patient presented with leukocytosis, normal liver function (ALT, AST, ALP, albumin, bilirubin, and coagulation profile), and normal kidney function (creatinine and BUN).

It should be noted that various symptoms may also be reported in these patients, which may be due to concomitant genetic disorders [9]. However, other reports have shown more diverse manifestations in addition to immunodeficiency, liver dysfunction, and neurological manifestations, including the need for liver transplantation, cutis laxa, cardiac malformations, pancreatic insufficiency, umbilical hernias, inguinal hernias, congenital diaphragmatic hernias, pectus carinatum, micropenis, and hypospadias [10, 17–24]. These manifestations were not seen in our patient, and a summary of our patient's findings is presented in Table 1. To the best of our knowledge, this is the first case of ATP6AP1-CDG in Iran and the Middle East, presenting with recurrent GI infections and seizures without hepatopathy. However, Khoodoruth et al. [25] reported a case of type II CDG due to a homozygous pathogenic variant (c.1167-24A>G) in the COG6 gene on chromosome 13 at position 40,273,614, which differs from the variant identified in our patient.

Author Contributions

Amirreza Jabbaripour Sarmadian: investigation, writing – original draft, writing – review and editing. **Babak Abdinia:** conceptualization, supervision, validation. **Kia Seyed Toutounchi:** data curation, investigation. **Mohammad Saberi:** supervision, validation, writing – review and editing. **Shabnam Eskandarzadeh:** methodology, project administration, supervision, validation.

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Ethics Statement

This study was conducted in accordance with the principles of the World Medical Association's Declaration of Helsinki, revised in 2000, concerning research involving human subjects. Ethical approval was obtained from the Tabriz University of Medical Sciences Ethics Committee, with Approval No. IR.TBZMED.REC.1402.755, dated 2024/01/01.

Consent

The patient's parents were informed regarding publishing this case report, and written informed consent was obtained to publish this report under the journal's patient consent policy.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available from the corresponding author on reasonable request.

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