UNC13D Deficiency Associated With Epileptic Seizures and Antibody Deficiency: The First Case from the Iranian National Registry

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J Investig Allergol Clin Immunol 2019; Vol. 29(2): 160-162
doi: 10.18176/jiaci.0362

Key words: Hemophagocytic lymphohistiocytosis (HLH). FHL-3. UNC13D.

Palabras clave: Linfohistiocitosis hemofagocítica (HLH). FHL-3. UNC13D.

Familial hemophagocytic lymphohistiocytosis (FHL) is a heterogeneous autosomal recessive disorder caused by mutations in *PRF1* (FHL2), *UNC13D* (FHL3), *STX11* (FHL4), and *STXBP2* (FHL5). All of these genes are related to formation and function of secretory lysosomes within cytotoxic T lymphocytes and NK cells [1]. Here, we describe the first *UNC13D*-deficient case of FHL from the Iranian national registry of primary immunodeficiency disorders (PIDs) presenting with a unique phenotype of antibody deficiency and epileptic seizures.

A 1-month-old boy was admitted for 120 days with high fever and diarrhea associated with anemia and organomegaly. The patient was the first child of consanguineous parents, and analysis of the family history revealed that the paternal grandfather had had cancer and the grandmother had had chronic asthma. In addition, his maternal uncle had died of unknown causes several months after birth (Figure S1). At the age of 6 months, the patient was admitted to the intensive care unit because of pneumonia and recurrent diarrhea. He was diagnosed with hypogammaglobulinemia (low Ig levels and B-cell count, Table) and referred to our center for further assessment and treatment. Given the low B-cell count, subset analysis and functional tests were not conducted. The patient received monthly intravenous immunoglobulin (IVIG) replacement therapy for hypogammaglobulinemia. A chest x-ray indicated a consolidation in the upper right lobe and confirmed pneumonia. A computed tomography (CT) scan revealed no significant manifestations in the brain.

At the age of 8 months and despite regular IVIG replacement therapy, the patient presented severe complications including high fever, epileptic seizures (involving the hands and head), respiratory distress, and fidgeting. Subsequently, he received oxygen (for respiratory distress) and phenytoin (for the epileptic seizures). In addition to IVIG replacement therapy, the patient received a broad range of antibiotics because of prolonged fever. To further evaluate the etiology of his lymphoproliferative and neurologic symptoms, additional laboratory tests were performed (Table). Based on additional

Table. Laboratory and Immunologic Data of the Patient With UNC13D Deficiency

Parameter	Result	Reference Value
WBCs, $\times 10^6/\mu L$	4.13	4.00-12.00
Neutrophils, %	41.7	50.0-70.0
RBCs, $\times 10^6/\mu L$	3.86	3.50-5.20
Platelets, $10^3/\mu L$	34	150-450
Hemoglobin, g/dL	8.7	12.0-16.0
ESR, 1 h	13	0-20
CRP, mg/L	78	Up to 6.0
Lymphocytes, %	41.2	20.0-60.0
$CD3^+$, %	92	51-77
$CD4^+$, %	57	35-56
$CD8^+$, %	25	12-23
$CD16^+$, %	3	3-14
$CD56^+$, %	3	2-10
$CD19^+$, %	0.5	11-41
$CD20^+$, %	0.5	5.1-42
IgM, mg/dL	35	40-230
IgG, mg/dL	450	700-1600
IgA, mg/dL	36	41–297
BUN, mg/dL	4	5-20
Creatinine, mg/dL	0.3	0.3-0.7
Cholesterol, mg/dL	122	130-200
Triglycerides, mg/dL	252	40-160
AST, U/L	140	Up to 37
ALT, U/L	84	Up to 41
ALP, U/L	1802	180-1200
Ferritin ng/mL	6171	10-400
Fibrinogen, mg/dL	129	150-350
Albumin g/dL	2.9	3.5-5.2
Herpes simplex virus	Negative	–
Cytomegalovirus	Negative	–
Epstein-Barr virus	Negative	–
Human immunodeficiency virus	Negative	–

Abbreviations: ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RBC, red blood cell; WBC, white blood cells.

clinical and laboratory findings including an increase in ferritin, triglyceride, and C-reactive protein levels and a decrease in cholesterol and fibrinogen levels, the possibility of hemophagocytic lymphohistiocytosis syndrome was suggested.

Genetic evaluation based on targeted PID-associated gene sequencing was performed to investigate the genes associated with FHL and humoral and syndromic immunodeficiency. Mutations in genes involved in early B-cell development (eg, *BTK, BLNK, CD79A, CD79B, IGLL1*, and *IGHM*), diseases of immune dysregulation (eg, *XIAP* and *SH2D1A*), and syndromic combined immunodeficiency (eg, *TBX1, PNP, ADA, LYST, NBS1, ATM, BLM, MRE11, DNMT3B, ZBTB24, CHD7, EPG5*, and *TAZ*) were ruled out using a standard published targeted sequencing gene panel and pipeline analysis [2]. However, the molecular diagnosis of FHL3 due to a homozygous c.1208T>C missense mutation in the *UNC13D* gene in exon 14 was confirmed in this proband. This variant substituted leucine into a proline at amino acid 403 (p.Leu403Pro; combined annotation dependent depletion score, 17.440; mutation significance cut-off, 0.001). The patient was again hospitalized at 12 months of age owing to fever, cough, skin rash, and fatigue. Based on the confirmed diagnosis, the subject became a candidate for hematopoietic stem cell transplantation. After several days, his level of consciousness decreased, manifested epileptic gaze deviation, and he eventually died at the age of 13 months owing to a substantial reduction in oxygen, respiratory failure, and bradycardia.

We report the first case of FHL3 with an atypical presentation of humoral immunodeficiency from our national registry. FHL3 accounts for nearly 30%-40% of cases of FHL. Its underlying cause is a mutation in the *UNC13D* gene located on 17q25. The gene encodes the Munc13-4 protein [3]. Compound heterozygous mutations in FHL patients are prevalent, as such mutations have previously been reported in *UNC13D* [4]. Nevertheless, homozygous mutations are common in populations with a high prevalence of consanguineous marriage [5]. Zur Stadt et al [6] previously reported this mutation in a Turkish patient. Most mutations in previously reported cases were located in deep intronic regions within intron 1 and with inversion in intron 30, suggesting that not only should the coding sequences of *UNC13D* be evaluated, but introns and noncoding regions should also be sequenced.

According to the HLH-2004 guideline, the presence of 5 out of 8 criteria is sufficient for diagnosis of the disease. However, our patient fulfilled 6 of these criteria. The least common symptoms of the disease are neurological symptoms, skin rash, and jaundice [7]. Although clinical manifestations of FHL3 are indistinguishable from other types of FHL, central nervous system involvement seems to be more common in FHL3 (10%-30%) [8] and includes seizures, decreased consciousness, facial palsy, dysphagia, and dysarthria. Neurological damage was not observed in our patient, although he did experience epileptic seizures. In addition, his vision was impaired and he died of bradycardia. These observations have not been reported to date in FHL.

We also observed a substantial reduction in $CD19^+$ and $CD20^+$ counts; no B-cell disorders have previously been reported in FLH3. However, immune dysregulation and antibody deficiency have been reported in patients with defects in regulatory T cells (eg, LRBA and CTLA4 deficiencies, and STAT3 gain-of-function disease) and higher susceptibility to herpesvirus family infections (eg, X-linked lymphoproliferative disease, CD27 and CD70 deficiencies) [9]. In the only targeted study that evaluated B cells in HLH patients, B-cell abnormalities were not observed in a patient with *UNC13D* deficiency [10]. Furthermore, based on the International Union of Immunological Societies (IUIS) classification, B cells are normal in FHL3 disease. This immunological finding represents an unusual clinical symptom in our case; however, further studies are required to confirm the possibility of other genetic or environmental modifying factors for antibody deficiency in the context of FHL3.

We present the first report of *UNC13D* deficiency with unusual signs including epileptic seizures, visual impairment, cardiac disorders, and B-cells abnormalities. Therefore, unusual signs and B-cell abnormalities should be evaluated in cases of suspected FHL3 to ensure that this disease does not go undiagnosed and that patients receive appropriate treatment and management.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Manuscript received July 25, 2018; accepted for publication December 11, 2018.

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