



FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS TYPE 3 - UNC13D MUTATION: A RARE CASE REPORT WITH COMPREHENSIVE MANAGEMENT AND OUTCOME

By

Sarah Mohamed Alfaqaih

Department of Pediatrics, Faculty of Medicine, Misurata University, Misurata, Libya

ABSTRACT

Background: Familial hemophagocytic lymphohistiocytosis (FHL) is a rare autosomal recessive disease, resulting in an often-fatal presentation with persistent pyrexia, splenomegaly and cytopenia. The familial type of hemophagocytic lymphohistiocytosis caused by mutations in several genes, including PRF1, STX11, STXBP2, Munc13-4, HPLH1, and UNC13D. We aimed to identify the genetically confirmed case of FHL and the pattern of presentation and outcome.

Case presentation: We report a 4-month-old female patient who presented with typical signs and symptoms that fulfil HLH-2004 criteria. The UNC13D gene by whole exome sequences confirms a homozygous likely variant detected "*c. 1828_1839 del p(Arg610_Gln613del)*". The HLH-2004 protocol was administered with excellent response. As a reason for delayed allogeneic hematopoietic stem cell transplantation (HSCT) after the protocol completion of 52 weeks, the patient has disease reactivation, which required re-induction of the protocol that ended successfully with HSCT.

Conclusions: Our case aimed for a multifaceted presentation and clinical pattern in FHLH; remission can be achieved with immunosuppressive therapy and chemotherapy, but allo-HSCT is required for cure.

Keywords: Hemophagocytic Lymphohistiocytosis, FHLH type 3, UNC13D

Introduction

Familial hemophagocytic lymphohistiocytosis (F-HLH) is an uncommon hyperinflammatory disorder, characterized by activation and excess proliferation of T-lymphocytes and histocytes with hemophagocytic activity⁽¹⁾. The causative genes including (PRF1, STX11, STXBP2, Munc13-4, HPLH1, UNC13D) are related for autosomal recessive disorder of F-HLH⁽²⁻⁴⁾. Mutations in the UNC13D gene disrupt production of the Munc13-4 protein, which is essential for immune cell

function, thereby impairing cytotoxic granule release⁽⁵⁾.

F-HLH is characterized by persistent, prolonged fever, cytopenia, splenomegaly and uncommon presentation with rash and lymphadenopathy. Other biochemical results have been associated with HLH, including hypertriglyceridemia, hypofibrinogenemia and raised levels of various cytokines and soluble interleukin-2 receptor, which are considered biological markers for HLH⁽⁶⁾. Histologic features of HLH include infiltration by hemophagocytic cells, with involvement of the

reticuloendothelial system (spleen and lymph nodes), the central nervous system, and the marrow⁽⁷⁾.

Familial HLH is considered primary HLH, while non-genetic causes of FHL are called secondary HLH(S-HLH). Epstein-Barr virus infection is regarded as the most common association with S-HLH, although various viral and fungal infections have also been reported. Malignancy and genetic syndromes (Chediak-Higashi syndrome 1, Griscelli syndrome 2 and X-linked proliferative syndrome) and autoimmune disorders have also been related to S-HLH^(2,8).

The Histiocyte Society established diagnostic criteria and a treatment protocol for HLH to minimize overlapped presentation with other differential diagnoses and delayed initiation of therapy⁽⁹⁾. The untreated cases of HLH have a median survival rate of around two months. The overwhelming progression of organ dysfunctions, uncontrolled infection and bleeding accounts for the common cause of dismal outcomes^(2,9,10).

We aimed to report the genetic findings and the clinical presentation of F-HLH in a Libyan patient.

CASE PRESENTATION

A four-month-old female infant who was referred to the pediatric oncology department of the National Cancer Institute of Misurata in February 2020 with a history of prolonged pyrexia of a week reaching up to 40°C, not responding to antimicrobial therapy, was reported to have hepatosplenomegaly and cytopenia for evaluation. She had an uneventful perinatal history and ended up with a full-term smooth delivery, and she was discharged with her mother. The family history was significant for consanguineous marriage and for a

sibling who died at 2 months of age (Figure 1).

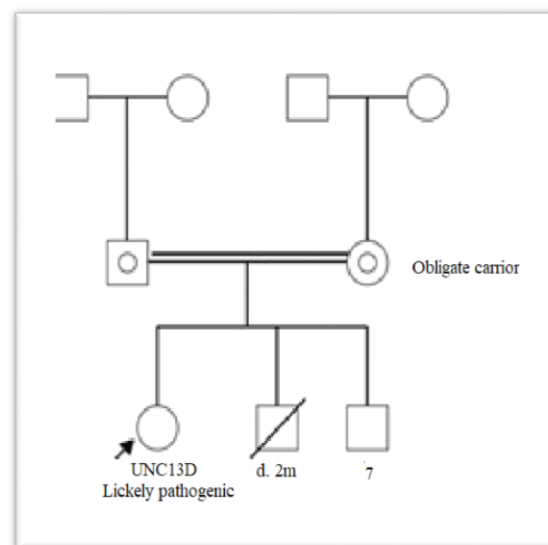


Figure 1: Family pedigree

On physical examination, the patient had a temperature of 39 °C, a heart rate of 150 bpm, a blood pressure of 60/40 mmHg, a respiratory rate of 35 cpm, and an oxygen saturation of 99% on room air. Her weight is 6.5kg (50-75th percentile), height is 60cm (25th percentile), and head circumference is 40cm (50th percentile). She was lethargic, pale, jaundiced, with generalized oedema. She has no noticeable facial dysmorphic features, aside from full cheeks and a low hairline. Heart, chest, and lung fields were normal. The abdominal examination showed hepatosplenomegaly.

Initial laboratory results revealed bicytopenia (anemia and thrombocytopenia), elevated ferritin levels, hypertriglyceridemia, low fibrinogen levels, elevated liver enzymes, hyperbilirubinemia (direct), and elevated immunoglobulin levels.

Further evaluation of bone marrow aspiration and lumbar puncture was conducted. Bone marrow study

revealed a normocellular aspirate with regular cellular morphology, whereas cerebrospinal fluid showed numerous monocytes and large macrophages exhibiting hemophagocytosis of small lymphocytes and erythrocytes. Because seven of eight HLH-2004 guideline criteria were met, HLH was established on February 2020, and a genetic test via whole-exome sequencing (WES) was

ordered. Genetic diagnosis of autosomal recessive F-HLH type 3 were confirmed. The homozygous likely

pathogenic variant was identified in the UNC13D gene mutation "c. 1828_1839del p(Arg610_Gln613del)". HLH-2004 protocol was conducted (corticosteroids, etoposide (VP16), cyclosporine, IV immunoglobulin) (Figure 2)^(9,11).

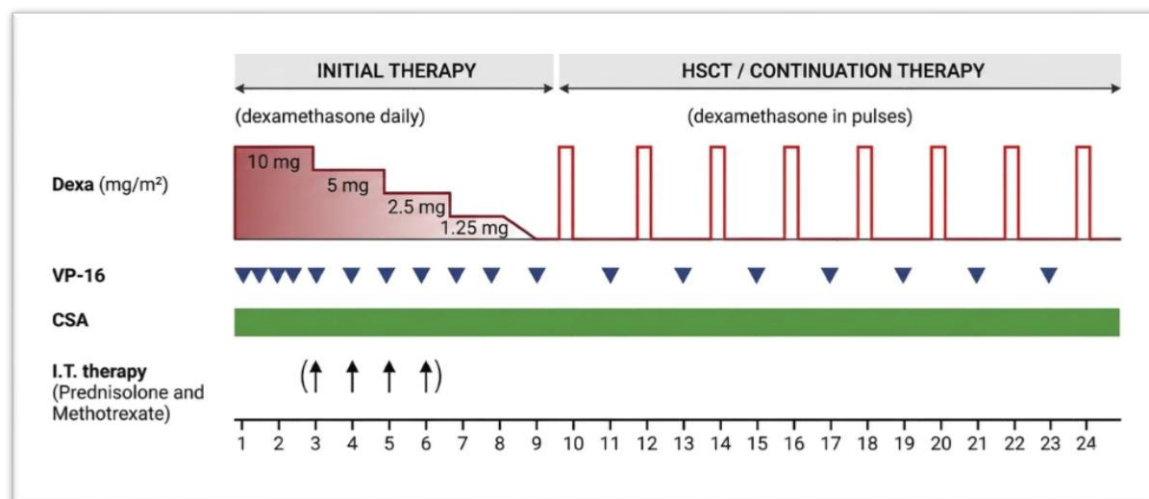


Figure 2: Overview of the treatment protocols

HLH-2004⁽⁹⁾ consists of an initial 8-week course of immunosuppressive and cytotoxic agents, followed by continuation therapy, for patients with familial, relapsing, or severe and persistent disease, with the aim of achieving an HSCT as soon as an acceptable donor becomes available. Daily dexamethasone (Dexa) (10 mg/m² per day weeks 1-2; 5 mg/m² per day weeks 3-4; 2.5 mg/m² per day weeks 5-6; 1.25 mg/m² per day week 7, and tapering during week 8), and etoposide (VP-16) (150 mg/m², twice weekly weeks 1-2, then once weekly) is administered during the initial therapy. The continuation therapy consists of Dexa every second week (10 mg/m² per day for 3 days), VP-16 (150 mg/m²) every second week, and CSA (aiming at

200 µg/L trough value). For patients with progressive neurological symptoms during the first 2 weeks, or if an abnormal cerebrospinal fluid value at onset has not improved after 2 weeks, intrathecal (I.T.) treatment is recommended (up to 4 doses, weeks 3, 4, 5, 6 to I.T. MTX, I.T. prednisolone (doses by age: <1 year, 4 mg; 1-2 years, 6 mg; 2-3 years, 8 mg; >3 years, 10 mg each dose) is recommended.

We observe a dramatic clinical and biochemical response after initiation of the recommended protocol. At 21 weeks of treatment in July 2020, the patient had an event of an enlarged solitary right axillary lymph node. Although the normality of biochemical markers, the histopathology report of the biopsied lymph node showed

involvement with hemophagocytic lymphohistocytosis, the patient continued on the protocol of treatment without modification. In February 2021, a total of 52 weeks had been delivered. Because HSCT was unavailable, the HLH-2004 protocol was extended from 40 weeks to 52 weeks, as in the HLH-94 protocol⁽¹¹⁾. Two weeks after the termination of treatment, she presented with

reactivation of HLH with almost a similar biochemical imbalance. Re-

induction of the HLH-2004 protocol was conducted in March 2021, and the disease burden was controlled. She received another 12 weeks and was transferred for HSCT abroad in July 2021. The patient underwent successful allogeneic SCT in May 2022. She is in contact with the clinic and doing well on regular follow-up. She has standard developmental parameters; her most recent contact was in January 2026 (Figure 3).

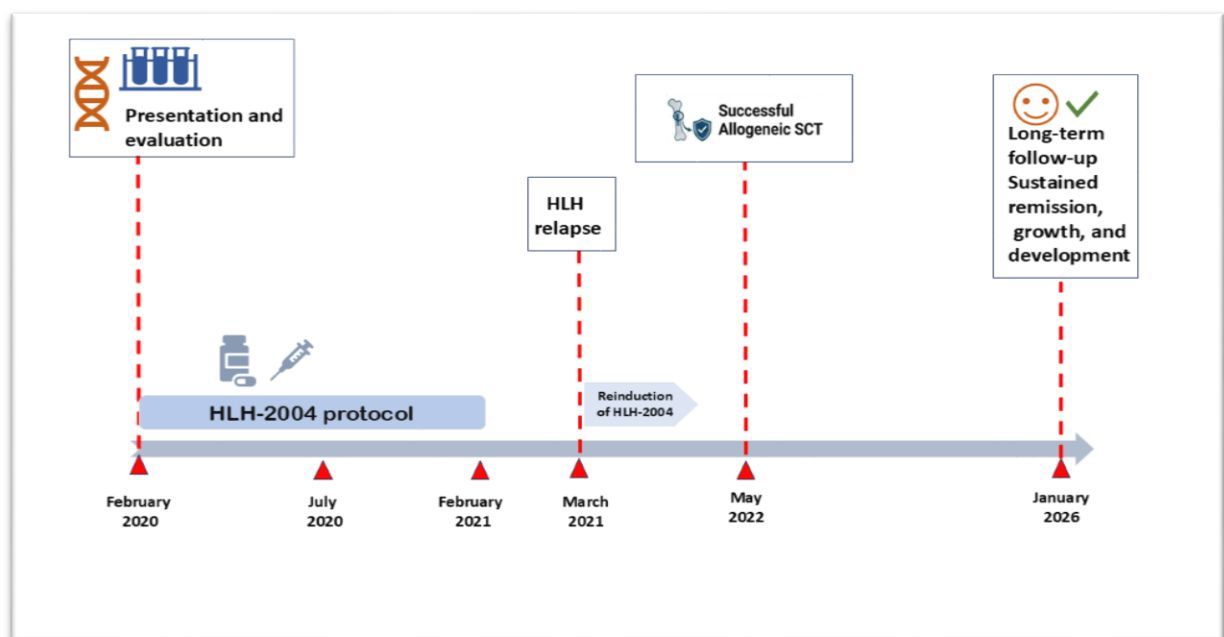


Figure 3: Clinical course of F-HLH Type 3 in a 4-month-Old female infant

DISCUSSION

HLH is a heterogeneous condition and a potentially life-threatening syndrome⁽³⁾. HLH is caused by the over-activation of macrophages, triggered by either genetics or acquired conditions^(9,12,13). HLH presents with a range of signs and symptoms that overlap with those of other clinical conditions. The prolonged fever, splenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia are the most frequent clinical and laboratory findings, as has already been reported in

the literature^(4,8,10,13-15). Because institutional access to molecular genetics studies, NK cell activity assessment, and IL-2 (sCD25) assessment has been limited, the Histocyte Society developed eight diagnostic criteria, with clinical and laboratory findings reported most often. Only five out of eight criteria are needed to establish a HLH diagnosis⁽⁹⁾. The UNC13D gene mutation is responsible for FHL type 3 (FHL3), which accounts for nearly 30-40% of FHL⁽⁴⁾. According to reports in the literature, FHL 3 was a commonly subtyped form of FHL in Turkey (17-

19%), South Korea (89%), and Japan (20-25%)^(1,15). Amirifar et al.⁽⁴⁾, an extensive systematic review of 32 patients with FHL3 was conducted, showed a severe phenotype presentation account for 12% of affected individuals. Fever was the most frequent presentation (87.1%). Pancytopenia was more frequent in the severe form than in the mild phenotype (60% vs 27.6%; $p=0.016$).

Hepatosplenomegaly was observed in 76.3% of all UNC13D-affected individuals. The zygosity pattern of all 322 patients with UNC13D has been reported: homozygous in 36.3%, heterozygous in 15.6%, and compound heterozygous in 47.6% (53.4% in exons and 46.6% in introns). Our patient had a likely homozygous UNC13D in-frame deletion in exon 13, as previously reported by Feldmann et al⁽¹⁶⁾.

Since FHL is a rapidly fatal disease, a median survival of two months has been reported^(17,18). Prompt diagnosis and treatment are crucial for a favourable outcome. The success rate of chemotherapy was 52% ($n=26$), and the transplant success rate was 82% ($n=23$), the median post-transplant survival was estimated at 14 months based on the collected data⁽⁴⁾. Moreover, Henter et al.⁽¹⁹⁾, reported that the overall survival of patients post-HSCT was 62% ($N=65$), with a median follow-up of 30 months. The patient was treated in accordance with the HLH-2004 guidelines and achieved a successful outcome.

CONCLUSION

FHL3 patients present with a broad spectrum of phenotypes, and genetic sequencing is required to identify the FHL subtypes. We emphasize early initiation of treatment and HSCT to achieve a favorable outcome.

INFORMED CONSENT

Informed consent was obtained from the patient's legal guardians for the publication of this case report.

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