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RESEARCH REPORT

Secondary Hemophagocytic Syndrome Associated with COG6 Gene Defect: Report and Review

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Abstract Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal disease that is characterized by proliferation and infiltration of hyperactivated macrophages and T-lymphocytes. Clinically, it is characterized by prolonged fever, hepatosplenomegaly, hypertriglyceridemia, hypofibrinogenemia, pancytopenia, and hemophagocytosis in the bone marrow, spleen, or lymph nodes. It can be classified as primary if it is due to a genetic defect, or secondary if it is due to a different etiology such as severe infection, immune deficiency syndrome, rheumatological disorder, malignancy, and inborn errors of metabolism such as galactosemia, multiple sulfatase deficiency, lysinuric protein intolerance, Gaucher disease, Niemann–Pick disease, Wolman disease, propionic acidemia, methylmalonic acidemia, biotinidase deficiency, cobalamin C defect, galactosialidosis, Pearson syndrome, and long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency. For the first time in the literature, we report on a 5-year-old girl diagnosed with a *Component of Oligomeric Golgi Complex 6* (*COG6*) gene defect complicated by HLH. Finally, we review the literature on inborn errors of metabolism associated with HLH and compare the previously reported patients of *COG6* gene defect with our patient.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal disease that is characterized by proliferation and infiltration of hyperactivated macrophages and T-lymphocytes (Verbsky and Grossman 2006). It is divided into primary and secondary HLH.

Primary HLH or familial erythrophagocytic lymphohistiocytosis (FEL) is an autosomal recessive disorder that affects infants and young children and is lethal in most patients (Janka 1983). Onset is classically within the first months or years of life. However, it can occur at any age (Janka 1983). Clinically, it is characterized by prolonged fever, hepatosplenomegaly, hypertriglyceridemia, and hypofibrinogenemia associated with pancytopenia. The following neurologic manifestations may occur early or may develop later: hypotonia, hypertonia, convulsions, cranial nerve palsies, ataxia, hemiplegia, quadriplegia, increased intracranial pressure, irritability, neck stiffness, blindness, and loss of consciousness. Lymphadenopathy and skin rash are additional less common findings. The mortality rate without treatment is high; HLH progression and infection account for the majority of deaths in untreated individuals (Zhang et al. 1993).

Primary HLH is caused by biallelic mutations in one of the following genes: *PRF1*, *UNC13D*, *STX11*, *STXBP2*,

RAB27A, *LYST*, *SH2D1A*, *BIRC4*, *IL2GR*, *IL7R*, *CD3e*, *RAG-1*, *ORA1*, *CD27*, and *ITK* (Sepulveda and de Saint Basile 2017; Tang and Xu 2011). The diagnostic criteria for HLH involve homozygous or compound heterozygous mutations in one of the aforementioned genes in addition to five out of the following eight clinical characteristics: fever, splenomegaly, cytopenia affecting at least two of three lineages in the peripheral blood, hypertriglyceridemia, hypofibrinogenemia, and hemophagocytosis in the bone marrow, spleen, and/or lymph nodes. Furthermore, the following characteristics are associated with the disease: low or absent natural killer (NK) cell activity, hyperferritinemia >500 μg/L, and high levels of soluble interleukin-2 receptor (sIL-2r) (Henter et al. 2007; Sepulveda and de Saint Basile 2017).

Secondary HLH may develop due to various etiologies, and it is difficult to differentiate from primary (familial) HLH by clinical or histologic characteristics alone. Molecular genetic testing is the best way to differentiate between primary and secondary HLH (Janka 1983). The causes of secondary HLH include the following: severe infection (usually viral), malignancy (such as lymphoma), rheumatologic disorders (such as juvenile idiopathic arthritis), and immune deficiency states (such as Griscelli syndrome type 2 and Chediak–Higashi syndrome) (Henter et al. 1993; Menasche et al. 2000; Dzoljic et al. 2015; An et al. 2017).

Inborn errors of metabolism (IEMs) have also been associated with secondary HLH (Table 1): galactosemia, multiple sulfatase deficiency, lysinuric protein intolerance, Gaucher disease, Niemann–Pick disease, Wolman disease, propionic acidemia, methylmalonic acidemia, biotinidase deficiency, cobalamin C defect, galactosialidosis, Pearson syndrome, and long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency (Olcay et al. 1998; Duval et al. 1999; Wu et al. 2005; Topaloglu et al. 2008; Sharpe et al. 2009; Karaman et al. 2010; Gokce et al. 2012; Kundak et al. 2012; Taurisano et al. 2014; Erdol et al. 2016).

To our knowledge, HLH with congenital disorders of glycosylation has not previously been reported. Herein, for the first time in the literature, we report on a 5-year-old girl diagnosed with a *Component of Oligomeric Golgi Complex 6* (*COG6*) gene defect (Shaheen syndrome, which is a type IIL congenital disorder of glycosylation).

Patient Report

We report on a 5-year-old girl, born preterm at 34 weeks of gestation after a complicated pregnancy with intrauterine growth restriction (IUGR). Her birth weight was 1,500 g (−4.0 SD), birth length was 50 cm (0.5 SD), and head circumference was 28 cm (−3.5 SD). She is the child of healthy consanguineous Saudi parents. She stayed in the neonatal intensive care unit for 6 days due to respiratory distress, and urinary tract infection, which was treated successfully with antibiotics.

The first concern noted was poor feeding and lethargy at the age of 2 months. However, no specific diagnosis was made at the time. At the age of 3 years, she presented at our center with a 2-day history of fever (up to 40°C, which was decreased by antipyretic treatment) and vomiting associated with decreased oral intake and activity. She had motor and speech disability. She required support to stand and spoke only two words (functioning at the level of a 10-month-old). Additionally, she had a history of hypohydrosis.

On examination, her height was 86 cm (−2.5 SD), weight was 10.5 kg (−2.1 SD), and head circumference was 45 cm (−2.2 SD). She had dysmorphic features, including microcephaly, broad palpebral fissures, retrognathia, wide mouth with thin lips, prominent nose, and bilateral epicanthal fold. She had strabismus, enamel hypoplasia with dental caries and dark discoloration of the teeth, and axial hypotonia. Multiple lymph nodes were bilaterally detected in the anterior cervical, supraclavicular, and inguinal region. They varied in size (the largest was 1 cm) and were mobile, not tender, and not attached to the skin. There was no erythema or skin changes. The clinical examination was otherwise normal.

Radiological investigations revealed generalized osteopenia by skeletal survey, and magnetic resonance imaging (MRI) of the brain showed brain atrophy, a thin corpus callosum, and a tiny subdural hemorrhage in the right occipital lobe. Abdominal ultrasound showed normal liver and spleen. Biochemical investigations revealed elevated serum transaminases (aspartate transaminase [AST] 779 (5–34) U/L, alanine transaminase [ALT] 113 (5–55) U/L), and a slightly increased gamma-glutamyltransferase (γ-GT) level. Lactic acid concentrations ranged between 2.2 and 4.5 mmol/L (normal: <2.2 mmol/L), and there was generalized hyperaminoaciduria. Serum transferrin isoelectric focusing (TIF) showed a type 2 pattern. Whole-exome sequencing revealed a previously reported homozygous pathogenic variant of the *COG6* gene, c.1167-24A>G (Shaheen et al. 2013). The following investigations showed normal results: acylcarnitine profile, plasma amino acids, urine organic acids, ammonia, total homocysteine, creatine kinase level, abdominal ultrasound, hearing tests, respiratory chain enzymology in skin fibroblasts and muscle, partial thromboplastin time, and activated partial thromboplastin time.

At the age of 4 years, the patient exhibited episodic epistaxis and gum bleeding, no bruises, persistent fever, and decreased activity. Lab results showed low hemoglobin at 80 (110–145) g/L, low platelets at 27 (150–450) × 10^9/L, low fibrinogen at 0.61 (1.5–4.1) g/L, high ferritin at 1,744.8 (4.6–204) μg/L, hypertriglyceridemia at 7.01 (≤0.84) mmol/L, prolonged coagulation profile (PT: 13.4

Table 1 Summary of published patients of inborn errors of metabolism (IEM) associated with HLH

No.	References	Number of cases	Inborn error of metabolism (IEM)	Country	Gender	Age of onset	Fulfilled diagnostic criteria for HLH	Treated according to HLH protocol	Prognosis
1	Ikeda et al. (1998)	1	Multiple sulfatase deficiency	Japan	M	10 months	Yes	No	Improved dramatically
2	Olcay et al. (1998)	1	Galactosialidosis	Turkey	M	7 months	Yes	No	Improved dramatically
3	Duval et al. (1999)	4	Lysinuric protein intolerance	France	4 M	3 months	Yes	Yes	NA
4	Wu et al. (2005)	1	Cobalamin C disease	USA	F	4 months	Yes	No	Improved dramatically
5	Topaloglu et al. (2008)	1	Pearson syndrome	France	M	7 months	Yes	No	Died
6	Sharpe et al. (2009)	1	Gaucher disease	Turkey	F	5.5 months	Yes	Yes	Died
7	Karaman et al. (2010)	1	Niemann–Pick disease	Turkey	F	3 months	Yes	No	Died
8	Gokce et al. (2012)	3	Propionic acidemia	Turkey	2 M, 1 F	Mean 4 years	Yes	Yes	One died Two improved dramatically
9	Kardas et al. (2012)	1	Biotinidase deficiency	Turkey	M	4 months	Yes	No	Improved dramatically
10	Taurisano et al. (2014)	1	Wolman disease	Italy	F	4 months	Yes	No	Died
11	Kundak et al. (2012)	1	Galactosemia	Turkey	F	12 days	Yes	Yes	Improved dramatically
12	Erdol et al. (2016)	1	LCHAD deficiency	Turkey	F	4 months	Yes	Yes	Died
13	This chapter	1	*COG6* gene defect	Saudi Arabia	F	4 years	Yes	Yes	Improved dramatically

M male, *F* female, *NA* not available

(9.38–12.3 s) seconds, INR: 1.23 (0.8–1.2) and PTT: 41 (24.8–34.9 s) seconds). Bone marrow biopsy showed hemophagocytosis in addition to low NK cells by flow cytometry. Spleen enlargement was detected by abdominal ultrasound. PCR-based tests for Epstein-Barr virus and cytomegalovirus in serum samples were negative. She had 7/8 HLH diagnostic criteria: fever, splenomegaly, cytopenia, hypertriglyceridemia, hemophagocytosis in bone marrow, low NK cells and high ferritin. Secondary HLH was confirmed after the negative result of sequencing the familial HLH gene panel covering the most common genes (Otrock et al. 2017); *PRF1*, *UNC13D*, *STX11*, and *STXBP2*, in addition to deletion/duplication analysis.

The patient was started on intravenous immunoglobulin, dexamethasone, and platelet transfusion (Zhang et al. 2013). Her lab results markedly improved in terms of liver function tests, and her hemoglobin, platelets, fibrinogen, ferritin, triglycerides, and coagulation results were almost normalized.

Currently, the patient is 5 years old with a global developmental disability, microcephaly, hypohydrosis, enamel hypoplasia, strabismus, splenomegaly, and hypotonia. Additionally, she has elevated transaminases, but otherwise normal lab results.

Discussion

The conserved oligomeric Golgi (COG) complex is a family of eight protein subunits that have a major role in regulating transport in the Golgi apparatus (Shaheen et al. 2013). Pathogenic variants of the *COG6* gene are a cause of Shaheen syndrome, an autosomal recessive disorder of glycosylation first described by Lubbehusen et al. (2010). Shaheen et al. reported on the largest cohort of patients with this disorder, consisting of 12 individuals from three consanguineous Saudi families. All these patients exhibited intellectual disability, global developmental disability, anhidrosis, palmoplantar keratosis, and progressive microcephaly (Shaheen et al. 2013). This is an autosomal recessive *N*- and *O*-linked glycosylation disorder (Sparks and Krasnewich 1993; Peanne et al. 2017; Foulquier et al. 2007).

CDG-COG6 is multisystem disorder, with at least 28 reported patients including detailed phenotypes in 17 (Table 2) (Lubbehusen et al. 2010; Huybrechts et al. 2012; Shaheen et al. 2013; Rymen et al. 2015; Alsubhi et al. 2017).

One of the distinctive features of *COG6* gene defect is hypohydrosis. This finding, in association with intellectual disability, could be a clue for diagnosis, to differentiate CDG-COG6 from other CDG.

Interestingly, the patient discussed in this case report had enamel hypoplasia with dental caries and black teeth discoloration, and this was reported in three other patients. Additionally, the present patient had intracranial bleeding in the form of subdural hemorrhage, similar to the first case reported in the literature (Lubbehusen et al. 2010). However, this bleeding ceased and had no consequences. Immunological manifestations include recurrent infections (41%). Rarely, patients have B-cell, T-cell, and neutrophil dysfunction, monocytosis, deficient polysaccharide antibody response, and combined immune deficiency (Rymen et al. 2015).

CDG-COG6 should be suspected in patients with a type 2 TIF pattern, which was found in 94% of the reported patients (but a normal pattern does not exclude it). Additional common laboratory findings include high transaminase levels (59%), pancytopenia (35%), prolonged coagulation profile (30%), high creatine kinase levels (24%), and high lactic acid levels (12%). Occasionally, patients have high lipase, high cholesterol, ferritin, and glucose, and low insulin growth factor-1 (IGF-1) (Alsubhi et al. 2017).

The mechanism underlying HLH associated with IEM remains unclear. However, it is hypothesized that increased metabolites decrease NK cell activity and increase cell activation and expansion. Furthermore, macrophage activation and tissue infiltration could be involved. This type of inflammatory response can cause extensive tissue damage and associated symptoms (Taurisano et al. 2014). Other potential pathomechanisms, similar to what is seen in lysosomal storage disorders like Gaucher disease, Niemann–Pick disease, and Wolman disease defects, affect the cellular secretory pathway due to the Golgi apparatus dysfunction and could lead to HLH based on a common pathomechanism.

Several COG-CDG show apparently an effect on the immune system, in the form of recurrent infections and unexplained high fever. These included COG4, COG6, COG7, and COG8 defects (Foulquier et al. 2007; Morava et al. 2007; Reynders et al. 2009; Huybrechts et al. 2012).

COG complex mutations are known to affect the morphology and function of Golgi apparatus, in addition to the cellular membrane trafficking (Ungar et al. 2002). Glycosylation involves a huge number of proteins carrying out variable functions, which may explain the multisystem involvement of the CDG including the perturbation of the immune system. Golgi apparatus is essential in regulating the immune system in variable mechanisms including the Major Histocompatibility Complex (MHC) proteins glycosylation (Ryan and Cobb 2012), Natural Killer (NK) cells cytotoxicity (Mace et al. 2014), and antibody glycosylation process. (Jennewein and Alter 2017) All these and other examples corroborate the role of the Golgi apparatus in general and the COG complex in maintaining immunological homeostasis mainly through the glycosylation process. However, as long as there is only one patient reported

Table 2 Most common clinical features of the previously reported patients of COG6 gene defect compared to the present patient

Characteristic	Previously reported cases	Present case	All cases
Number[a]	16	1	17
Gender	8 M, 8 F	F	8 M, 9 F
Country	8 (Saudi Arabia), 4 (Turkey), 4 (Morocco), 1 (Bulgaria)	Saudi Arabia	53% from Saudi Arabia
Consanguinity	11	Yes	71%
Clinical features			
Global developmental disability	17	Yes	100%
Dysmorphic features[b]	14	Yes	88%
Progressive microcephaly	14	Yes	88%
Failure to thrive	12	Yes	71%
Hypohydrosis	9	Yes	59%
Hypotonia	9	Yes	59%
Hepatosplenomegaly	7	Yes (only splenomegaly)	47%
Death	6	No	35%
Radiological findings (10/17)			
Thin corpus callosum	3	Yes	40%
Brain atrophy	3	Yes	40%
Laboratory findings			
Type 2 TIF pattern	15	Yes	94% (15/17, 1 patient not assessed and 1 normal)
Increased liver transaminase levels	9	Yes	59%
Pancytopenia	5	Yes	35%
Decreased coagulation factors	4	Yes	30%

M male, *F* female, *IUGR* intrauterine growth retardation, *TIF* transferrin isoelectric focusing

[a] 11 patients (4 males, 3 females, and 4 of unreported gender) reported by Shaheen et al. (2013) were excluded because of incomplete clinical profiles. The authors reported that all presented with similar clinical features to the index case

[b] Broad palpebral fissures, retrognathia, wide mouth with thin lips, prominent nose, slight epicanthus, short neck, asymmetric thorax, and post-axial polydactyly, anal anteposition

with this association, it is premature to speculate about a pathogenic link between COG6-CDG and HLH.

The diagnosis of HLH based on the reported criteria could be challenging particularly in vulnerable patients with metabolic diseases, which could affect variable body systems and present with signs and symptoms mimicking those of HLH (Otrock et al. 2017). Special precautions and a high index of suspicion should be considered as delaying the diagnosis and management could have serious consequences on the patient's outcome. In our patient, the management was started immediately once the criteria of HLH were fulfilled, while the diagnosis was confirmed only after the complete recovery of the patient by following her hematological and biochemical markers going back to the baseline, in addition to the negative familial HLH gene panel.

Conclusion

The present report is what we believe to be the first on a patient with COG6-CDG and HLH. Before concluding that this is not a fortuitous association, we have to wait for more patients with this combination. We recommend that clinicians consider HLH in any patient with a congenital glycosylation disorder presenting with prolonged fever, splenomegaly, hypertriglyceridemia, and hypofibrinogenemia associated with pancytopenia. A high index of suspicion and prompt management might improve the patients' outcome.

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Take-Home Message

Hemophagocytosis could be the presenting clinical feature in several inborn errors, including lysosomal storage disorders associated with hepatosplenomegaly. In the present report, we describe the first Golgi secretory pathway-related patient with HLH and review the literature on reported GOG6-CDG patients with our patient.

General Rules

Author Contributions

NAT: write the first draft and prepare Tables 1 and 2, AAS: diagnose and manage the hematological manifestations and edit the manuscript, EM: review, edit the manuscript and contributed to the clinical diagnosis and management of the patients. MAF: supervise, coordinate the whole work associated with preparing, writing and submitting the manuscript and contributed to the clinical diagnosis and management of the patients.

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Competing Interests

None declared.

Informed Consent

Informed consent was obtained from parents of the patients included in the study. Proof that informed consent was obtained is available upon request.

Ethic Approval

The study was approved by the ethics committee at King Abdullah International Medical Research Centre (RC/16/113/R).

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