EDITORIAL

Hemophagocytic lymphohistiocytosis as a possible cause of prolonged fever, splenomegaly, and cytopenia

Linfohistiocitosis hemofagocitica como posible cause de fiebre prolongada, espelomegalia y citopenia

Hyperinflammatory response may be one of the causes for a long-lasting unexplained fever in children and adults. Although HLH is an aggressive and potentially life-threatening disorder, it is hardly known among many physicians.

It has been proposed that the clinical manifestation of HLH is caused by an uncontrolled activation and proliferation of immune cells in response to variety of congenital and acquired factors. Macrophages and cytotoxic CD8+ lymphocytes massively release various inflammatory mediators (e.g., INF-γ, TNF-α, IL-6, IL-8, IL-10, IL-12, IL-18, MIP 1-α), and hematopoietic growth factors (e.g., GM-CSF). Aforementioned phenomena together with an impaired cytotoxic function of natural killer (NK) cells and CD8+ lymphocytes, result in the hyperinflammatory phenotype.

Depending on the etiology, HLH can be divided into genetic (primary) and acquired (secondary) forms. Inherited familial forms of HLH (FHL) usually present in infancy or early childhood (80% of cases). However, the first episode of FHL can occur at any point in a patient's life (i.e., both fetuses and adults). Therefore, the possibility of late-onset FHL in adults with HLH cannot be univocally excluded before tests of NK/T cell degranulation and activity, as well as genetic testing, is performed.

Perforin gene mutation as a cause of HLH was first described in 1999. Over the next few years, mutations in genes PRF1 (FHL-2), UNC13D (FHL-3), STX11 (FHL-4) and STXB2 (FHL-5) were identified as responsible for the development of genetic HLH. Their common feature is impairment in the production of proteins necessary for the proper functioning of granule cytotoxicity. HLH may occur in very rare immune deficiency syndromes associated with albinism (i.e., Griscelli syndrome 2, Chédiak–Higashi syndrome, and Hermansky–Pudlak syndrome type II, which are caused by mutations in genes RAB27A, LYST, and AP3B1, respectively) and lymphoproliferative syndromes associated with chromosome X (XLP1 and XLP2, which are caused by mutations in genes SH2D1A and BIRC4, respectively). Other inherited conditions that can present with HLH are some known immunodeficiency syndromes such as X-linked SCID, X-linked hypogammaglobulinemia, Wiskott–Aldrich syndrome, and DiGeorge syndrome del (22q11.2). Recently, mutations in IL-2-inducible T cell kinase (ITK), CD27 and magnesium transporter gene (MAGT1) have been reported to be associated with EBV-associated lymphoproliferation, lymphoma and HLH.

In FHL, the only manifestation of the disease is HLH. In other cases of genetic HLH, hemophagocytic syndrome is only one of the disease manifestations and does not need necessarily be present.

An acquired HLH develops as a consequence of intense immune activation caused by infection, autoimmunity disorder or malignancy (i.e., infection-associated HLH, I-HLH; autoimmune-associated HLH, A-HLH; malignancy-associated HLH, M-HLH).

Besides persistent fever, the most common symptoms of HLH are splenomegaly and peripheral blood cytopenia. Hepatomegaly, lymphadenopathy, neurological symptoms, edema or skin rush could also be present.

Laboratory hallmarks of HLH include hyperferritinemia, increased level of the alpha chain of the soluble receptor for interleukin-2 (sIL-2Rα; sCD25), hypertriglyceridemia, hypofibrinogenemia, coagulopathy, hyponatremia, and elevated liver transaminases and bilirubin. Low/absent NK cell activity is typical of FHL. High levels of the sIL-2Rα in serum are seen in all forms of HLH. Although sIL-2Rα together with hyperferritinemia are markers of generalized inflammation, but very high levels of sIL-2Rα are almost never seen outside HLH. Similarly, ferritin levels >3000 μg/L are concerning for HLH, and levels >10,000 μg/L are highly suspicious.
However, Noteworthy, Early I-HLH Therapy Many patients had elevated hemophagocytosis in bone marrow aspirate smear showing three macrophages displaying hemophagocytic activity (May–Grünewald–Giemsa stain; magnification 400×).

Cytohistological examination of bone marrow, spleen, liver, lymph nodes or cerebrospinal fluid may reveal accumulation of lymphocytes and macrophages, sometimes with hemophagocytic activity (Fig. 1). However, hemophagocytosis is a rather late sign of HLH, occurring in an advanced stage of this syndrome. Many patients lack hemophagocytic cells (HPCs) on their initial bone marrow examination. Noteworthy, the presence of HPCs in tissue specimens is only one of the HLH diagnostic criteria, and it is not privileged in any way as compared with the other criteria.

Our experience based on bone marrow assessment of 29 consecutive adults with HLH associated with hematological malignancies (8 patients with T/NK-cell lymphoma, 11 patients with B-cell lymphoma, and 10 patients with myeloid malignancy), revealed that 28 patients (97%) in the entire group had detectable HPCs. Interestingly, at the time of initial evaluation, HPCs in bone marrow had been detected in only 17 patients (58%).

According to the current guidelines (HLH-2004), at least five of eight diagnostic criteria must be fulfilled for HLH diagnosis:

1. fever,
2. splenomegaly,
3. cytopenia affecting ≥2 cell lines (hemoglobin <90 g/L, and in infants <100 g/L; platelet count <100 × 10⁹/L; neutrophils <1.0 × 10⁹/L),
4. hyperferritinemia (>500 µg/L),
5. hypertriglyceridemia (fasting triglycerides >3.0 mmol/L) and/or hypofibrinogenemia (<1.5 g/L),
6. hemophagocytosis in bone marrow, spleen, liver, or lymph nodes,
7. elevated level of sIL-2Rα >2400 U/mL,
8. low/absent NK cell activity.

Of note, the presence of typical FHL gene mutations, detected with molecular genetics modalities, is sufficient to establish a diagnosis, regardless of the number of fulfilled criteria according to the HLH-2004.

The literature on the topic of HLH in adults is limited. A retrospective study from Japan revealed that the frequency of different forms of HLH in adults varied depending on the age bracket. I-HLH was the most common (68%) among patients aged 15–29 years, but M-HLH was the most frequent (68%) in the group of patients aged ≥60 years. Noteworthy, M-HLH in East Asia is most often associated with NK/T-cell lymphomas, but in Europe M-HLH tends to more frequently develop in the course of the other hematological malignancies.

HLH is a potentially reversible condition; however, without proper treatment it usually results in death of the patient. Therapy of HLH is difficult, long-lasting and often associated with a high morbidity. Early diagnosis and immediate introduction of adequate HLH therapy are crucial for the successful treatment of HLH.

Since HLH can be encountered by various medical specialists, basic knowledge of HLH and its diagnostic criteria should be familiar to all physicians. Helping to spread the knowledge about HLH, I would warmly recommend to the readers of the Revista Clínica Española a paper by Mostaza-Fernández and colleagues, published in this issue of the journal.

Conflict of interest

The author reports no conflict of interest regarding this article.

References


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