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Case Report

Neonatal infectious hemophagocytic lymphohistiocytosis

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Abstract. Hemophagocytic lymphohistiocytosis (HLH) is a disorder of the mononuclear phagocytic system and a severe, life-threatening syndrome due to an excessive immune activation. This hyperinflammatory condition is often triggered by a variety of agents or events, mostly genetic or infectious; and its scarcity in the neonatal period often delay diagnosis and adequate management. We report a peculiar neonatal case with multivisceral involvement, managed promptly and aggressively. Discussing the most important relevant points in both diagnosis and therapy of this peculiar disorder is highlighted in purpose of increasing awareness and enhancing early determinant recognition.

Keywords: Hemophagocytic lymphohistiocytosis, neonatal period, life-threatening, diagnosis, therapy

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe, life-threatening syndrome due to an excessive immune activation and inflammation, most frequently affecting infants less than 18 months of age. It can be triggered by a variety of events that disrupt immune homeostasis [1]. The rarity of this syndrome, its scarcity in the neonatal period, combined to the lack of specificity of the clinical and laboratory findings often delay diagnosis and adequate management [2].

Case presentation

A male, term newborn initially admitted for perinatal asphyxia, presented at day 3 an acute, severe combination of multivisceral deficiency (hepatic, renal and cardiac) associated to a myriad of clinical and biological signs including anemia, thrombocytopenia and febrile spleno-megaly. The balance sheets show a marked inflammation (serum ferritin > 1500 ng/ml); hyponatremia (117 mEq/L) and hypertriglyceridemia (> 3 g/L). A probable infectious neonatal HLH was then highly considered.

A holistic approach, with antibiotics (Ceftriaxone: 100 mg/kg/day, and Amikacin: 15 mg/kg/day, twice), antiviral (Acyclovir*: 1 g/m²), and steroids (methyl prednisolone: 04mg/kg/day, every 6h) is ordered.

A close monitoring and supportive care with transfusion and glucose 10% perfusion were also conducted. The newborn recovered within 5 days. Total duration of treatment was of 15 days of antibiotics (Ceftriaxone) and antiviral. Steroids were tapered from the 7th day. One month after discharge, the infant did well and was free of symptoms.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a disorder of the mononuclear phagocytic system [3]. It represents a severe hyperinflammatory condition with the cardinal symptoms: prolonged fever, cytopenias, hepato-splenmegaly, and hemophagocytosis by activated, morpho-logically benign macrophages. Biochemical markers include elevation of ferritin and triglycerides, and low fibrinogen [4] (Table 1).

This syndrome, first described in 1939 by Scott and Robb-Smith, is classically divided into primary (genetic) hemophagocytic syndrome and secondary (reactive) hemophagocytic syndrome [5] (Table 2).

According to the last International Classification of Primary Immune Deficiency, HLH ought to be considered first among the “Diseases of Immune Dysregulation” [4].
In fact, impaired function of natural killer (NK) cells and cytotoxic T-cells (CTL) is characteristic for both genetic and acquired forms of HLH [5]. However, both primary

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TABLE 1
DIAGNOSTIC CRITERIA FOR HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (REF. 4)

1. Familial disease or known genetic defect
2. Clinical and laboratory criteria (5/8 criteria)
1. Fever
2. Splenomegaly
3. Cytopenia , at least 2 cell lines
A. Hemoglobin < 9.0 g/dl (below 4 weeks < 120 g/l)
B. Platelets < 100 · 000/ml
C. Neutrophils < 1000/ml
4. Hypertriglyceridemia and/or hypofibrinogenemia
A. Fasting triglycerides ≥ 3 mmol/l
B. Fibrinogen < 1.5 g/l
5. Ferritinemia > 500 mg/l
6. sCD25 ≥ 2400 U/ml
7. Decreased or absent NK-cell activity
8. Hemophagocytosis in bone marrow, CSF or lymph nodes
Supportive evidence :
- cerebral symptoms with moderate pleocytosis and/or elevated protein
- elevated transaminases, bilirubin, LDH.

TABLE 2
HEMOPHAGOCYTIC SYNDROME CLASSIFICATION (REF. 5)

1. Primary or genetic hemophagocytic syndrome
Familial hemophagocytic lymphohistiocytosis
Immune deficiency syndromes
Chediak-Higashi syndrome
Griscelli syndrome
X-linked lymphoproliferative syndrome
Wiskott-Aldrich syndrome
Severe combined immunodeficiency
Lysinuric protein intolerance
Hermansky-Pudlak syndrome
2. Secondary or reactive hemophagocytic syndrome
Infection associated hemophagocytic syndrome
Viral
Herpes viruses (herpes simplex virus, varicella zoster virus, cyto-megalovirus, Epstein-Barr virus, human herpesvirus 6 and 8)
HIV
Other viruses (adenovirus, hepatitis viruses, parvovirus, influenza)
Other infections
Bacteria including mycobacteria and spirochetes
Parasites
Fungi
Malignancy-associated hemophagocytic lymphohistiocytosis (mainly lymphoma)
Macrophage activation syndrome (in autoimmune diseases)

and secondary syndromes can be precipitated by an infection, and the latter can lead to severe HLH [6], even in the newborn.

Initially, and more specifically in the very young infants (i.e. < 3 months), HLH may masquerade as any infection. Awareness of the clinical symptoms and of the diagnostic criteria of HLH is important to start life-saving therapy with immunosuppressive/immunomodulatory agents in time [3, 5, 6].

Systemic infections and/or sepsis share many features with HLH, such as fever, cytopenias, and hepatic involvement, disseminated intravascular coagulation and cytokine abnormalities. However, ferritin levels tend to be static in patients with infections, but are prone to dramatic increases in case of HLH [1]. Fever is, however, less common in newborns and therefore is not essential for the diagnosis of HLH [7].

The clinical dilemma for the physician then is to distinguish between this systemic hyperinflammatory condition and other hyperferritinemia causes like sepsis or perinatal hemochromatosis, so that sharp and timely therapy could be initiated [8].

A review of ferritin levels in pediatric patients found a cut off of 10 000μg/l to be 90% sensitive and 96% specific for the diagnosis of HLH [9]. A rapid and reliable pathway would also evaluate serum triglycerides and blood cells: Mahlaoui et al. [10] reported high triglyceride levels in 89% and decreased blood counts in 95%of the HLH population.

Among infectious triggering agents in this period of age, mostly are viral (Herpes viruses) and bacterial. In Japan, up to 36% of neonatal HLH were found in association with herpes simplex virus infection [2]. A polymerase chain reaction, PCR-search for infectious agents (including herpes simplex virus (HSV), Epstein Barr virus (EBV), cytomegalovirus (CMV) has been recommended by some authors [11]. Moderate/mild cases of infectious HLH tend to be self-limiting, requiring chiefly a prompt supportive (*i.e.* antibiotic/antiviral) management.

Immunomodulation (i.e. steroids, immunosuppressive agents or polyvalent immunoglobulins) are the cornerstone of lifesaving therapies for severe cases / late recognition. Better responses have been reported with high dose steroids (2 to 4 mg/kg/day of prednisolone) [12]. Lack of specific therapy or even late management may be fatal. Whatever the treatment is based on, it has to be continued until all clinical (fever and visceromegaly) biochemical and hematological abnormalities subside. Outcome depends largely on the infectious trigger and the delay of diagnosis [1, 5, 6].

In conclusion, HLH is a rare, life-threatening condition characterized by clinical (fever, visceromegaly, multi-organic deficiency) and biological features (cytopenias, low fibrinogen, high plasma triglycerids, and hyper-ferritinaemia), associated to pictures of hemophagocytosis. Infection, most frequently by viruses, is an important driver of acquired HLH; genetic causes of HLH being the most renowned source of neonatal HLH [1, 13]. The potential infectious agents must, therefore, be actively searched and promptly treated. Organ failures must be supported and immunomodulation (*i.e.* corticosteroids) therapy is also crucial [13].

Conflict of Interest

The authors declare no conflicts of interest.

References

1. McClain K. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date: Topic. 87499, 2014.

2. Suzuki N, Morimoto A, Ohga S, Kudo K, Ishida Y, Ishii E, HLH/LCH Committee of the Japanese Society of Pediatric Hematology. Characteristics of hemophagocytic

lymphohistiocytosis in neonates: a nationwide survey in Japan. J Pediatr 155:235-238, 2009.

3. Bousfiha A et al. The 2015 IUIS phenotypic classification for primary immunodeficiencies. J Clin Immunol 35:727-738, 2015.

4. Tanoshima R, Takahashi H, Hokosaki T, Yamaguchi K, Goto S, Kai S. Hemophagocytic lymphohistiocytosis in very young infants. Pediat Blood Cancer 52:137-139, 2009.

5. Janka GE. Hemophagocytic syndromes. Blood Rev 21:245-253, 2007.

6. Rouphael NG et al. Infections associated with haemophagocytic syndrome. Lancet Infect Dis 7:814-22, 2007.

7. Freeman HR, Ramanan AV. Review of haemophagocytic lymphohistiocytosis. Arch Dis Child 96:688-693, 2011.

8. Kapoor S. Distinguishing hemophagocytic lymphohistiocytosis from hemochromatosis in patients with hyperferritinemia. Pediatr Blood Cancer. 50:1287-1288, 2008.

9. Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 50:1227-1235, 2008.

10. Mahlaoui N, Ouachée-Chardin M, deSaint Basile G et al. Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins: a single-center retrospective report of 38 patients. Pediatrics 120:e622-628, 2007.

11. Ansuini V, Rigante D, Esposito S. Debate around infection-dependent hemophagocytic syndrome in paediatrics. BMC Infect Dis 13:15, 2013.

12. Pramanik S, Pal P, Das PK, Chakrabarty S, Bhattacharya A, Banerjee S. Reactive haemophagocytic lymphohistiocytosis. Indian J Pediatr. 76: 643-645, 2009.

13. Gonzalez F, Vincent F, Cohen Y. Syndrome d'activation macrophagique d'origine infectieuse: étiologies et prise en charge. (Article in French). Réanimation 18:284-290, 2009.