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Hemophagocytic lymphohistiocytosis in newborn and infants

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Familial hemophagocytic lymphohistiocytosis (FHL or HLH) is a rare disorder of early infancy with autosomal recessive inheritance and usually fatal outcome. Its frequency has been estimated around 1 in 50.000 children/year in Sweden. The disease was initially reported in 1952 by a pediatrician who already described most of its prominent features, i.e. propensity to fatal outcome following an infectious disease, a lymphoma-like picture, peculiar observation of hypertriglyceridemia and hemophagocytosis. The familial recurrence of this disease clearly pointed to a genetic defect.

The age at onset of the disease is usually within the first two years, with some patients presenting as newborn and some as older children or adolescents. The clinical picture is characterized by fever, hepatosplenomegaly, cytopenia, liver and central nervous system damage. The natural course of the disease is rapidly fatal due to lymphohistiocytic organ infiltration: about one half of the patients die within 6 months from the diagnosis of infection or of multiorgan failure.

The diagnosis of FHL may be a difficult one. The clinical picture may recall leukemia or lymphoma, and once these have been ruled out, the diagnostic work-up may be not easy, especially if FHL is not suspected. Familial recurrence or parental consanguinity may address to an inherited, constitutional defect. Yet, a genetic marker for the disease was not available for over 40 years.

One big step forward was represented by the identification of the immune defect in FHL patients: T and NK cells cellular cytotoxicity was recognized to be deeply impaired, leading to uncontrolled proliferation of macrophages and lymphocytes, overproduction of inflammatory cytokines and extensive tissue damage.

In 1999 in two simultaneous reports Oha-di et al and Duforq-Lagelouse et al. described a linkage of FHL with two different regions on chromosomes 9 and 10. While the region on chromosome 9q21.3-22 was never followed by identification of the involved FHL-1 gene, in 1999 Stepp *et al.* identified the genetic defect in the chromosome 10q22 as

due to PRF1 mutations. Following initial screening of the two proposed loci and PRF1 mutations, it was soon clear that FHL is a heterogenous disorder. Recently, genetic defects in the genes Munc13-4, and syntaxin 11 have been associated with additional subsets of FHL patients, defined as FHL-3, and FHL-4, respectively.

Recently, chemo-immunotherapy has been identified as appropriate to achieve rapid disease control, with reduction of cell proliferation and inflammatory burden. Given a constitutional defect of lymphocyte cellular cytotoxicity is at the basis of the disease, hematopoietic stem cell transplant (HSCT) remains the only available curative procedure so far.

A clinical picture of HLH, overlapping that of the familial form (FHL), was described already during the 80s by a panel of clinical and pathologists who described patients with a completely overlapping clinical picture, which resolved when the associated immune depressive therapy could be omitted. This was defined as virus-associated hemophagocytic syndrome (VAHS). Clearly for these patients treatment of the associated viral (or parasitic, as documented later) infection was sufficient to induce resolution of HLH. Thus, the clinicians had the dilemma of how to define the indication to HSCT for a patient with the clinical diagnosis of HLH especially in non-familial cases.

Based on the above data, differential diagnosis between the genetic form of HLH (FHL) and these similar "secondary" cases — including the so-called VAHS — must be exploited with great caution. Currently identified genetic defects account for no more than two thirds of the families with FHL. Thus a significant proportion of patients still await for identification of their familial marker. Availability of a genetic marker is pivotal in order to provide a complete assistance to families with FHL, since it allows to confirm the diagnosis, support indication to HSCT, screen the familial carriers, identify the HLA-matched and genetically unaffected siblings as possible donors, and to perform prenatal diagnosis.