Hemophagocytic lymphohistiocytosis
A challenge for the pediatric hematologist-oncologist

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Hemophagocytic lymphohistiocytosis (HLH) is a genetically heterogeneous disorder characterized by an hyper-inflammatory syndrome with fever, hepatosplenomegaly, cytopenia and, less frequently, central nervous system involvement. Frequent alterations include low levels of fibrinogen, high levels of ferritin, triglycerides, and the α-chain of the soluble interleukin-2 receptor (sCD25). Since symptoms may resemble those of leukemia or lymphoma, patients will be referred to pediatric haematology-oncology units, and bone marrow aspiration is usually performed early during the diagnostic work-up, showing — at first or at repeated evaluations during the disease course — hemophagocytosis by activated macrophages.

The natural course of HLH is rapidly fatal within a few weeks in the majority of cases unless appropriate treatment, including corticosteroids, cyclosporine, and etoposide result in transient disease control. So far, only patients who underwent hematopoietic stem cell transplant have been cured.

Differential diagnosis of HLH may be difficult. When HLH is diagnosed according to current criteria, the main duty of the pediatric haematologist-oncologist is to try to put the patient in a more stable condition, since this disease still has a relatively high risk of rapid fatal progression within a few weeks when unrecognized, occasionally even despite chemo-immunotherapy. Once initial disease control has been achieved, the main target is to try to understand why the patient developed HLH, a clinical syndrome characterized by macrophage hyperactivation. This may occur due to several reasons: concurrent acquired immune deficiency (chemotherapy, immunosupression following organ transplant) or infection (EBV, Leishmania, bacteria..) or autoimmune systemic disease (juvenile arthritis, lupus) which may be even heralded by HLH. Otherwise, a previously healthy infant may present with HLH as the initial manifestation of a constitutional immune defect. In such cases, report of consanguinity or undiagnosed fatalities in siblings may direct the diagnostic work-up toward a congenital immune deficiency.

Demonstration of frequent association with common pathogens and evidence of impaired natural killer cytotoxic activity provided the rational for considering HLH as a selective immune deficiency.

Linkage analysis led to identification of an association between FHL and the genomic region 9q21.3-22 (FHL1, MIM 603552), where the gene responsible for the disease was not yet identified. A simultaneous report established a linkage with another region, 10q21-22, in which the perforin (PRF1) gene was identified as responsible for a wide proportion of cases of FHL (FHL2, MIM 603553). In patients with FHL2, PRF1 mutations induce a complete or partial reduction of the synthesis of the perforin protein. As a result, the cytotoxic machinery of NK cells is markedly impaired. Since a formal genotype-phenotype study is not yet available, the exact contribution of the different mutations reported in the literature is not yet clear, although some linkage between a few individual mutations and particular ethnic groups appear to be preliminarily defined. In 2003 a third locus, 17q25, was reported in linkage with FHL (FHL3, MIM 608898). The product of the involved gene, the Munc13-4 protein, is thought to contribute to the priming of the secretory granules before they fuse into the plasma cell membrane. Mutations in this gene impair the delivery of the effector proteins, perforin and granzymes, into the target cells resulting in defective cellular cytotoxicity and a clinical picture which appears identical to that associated with PRF1 mutations.
Very recently, on the basis of a genome-wide screening, a fourth chromosomal region (6q24) has been reported in linkage with FHL in a subset of Kurdish patients (FHL4). Mutations of the syntaxin 11 gene, mapped in this region, are thought to alter intracellular vesicle trafficking of the phagocytic system.

Based on the current knowledge, PRF1 mutations account for about 40% of cases of FHL (type 2), and mutations of the Munc13-4 gene for an additional 30% (type 3). This last subtype may present at any age including young adult, often with major CNS involvement, and is usually associated with a marked defect of NK activity.

At present the clinical approach to patients diagnosed with HLH includes evaluation of NK activity and flowcytometric analysis of intracytoplasmic perforin. Most of patients who lack perforin expression will show PRF1 mutations. Oculo-cutaneous albinism will address to one of the few syndromes with immune deficiency. For the remaining patients mutation analysis of the Munc13-4 gene will be the next step, since about 30% of patients will be linked to this gene.

Current research in this field is aimed at identification of the genetic defect hopefully in far most of FHL families. Although expensive and time consuming, it is mandatory to confirm the diagnosis, to refine the therapeutic choice including indication to hematopoietic stem cell transplant, to identify the carriers and thus select familial donors. Information on the familial genetic marker may allow also prenatal diagnosis. Identification of pre-symptomatic affected siblings may represent another challenge for the medical team, which will provide a tailored clinical and functional monitoring to determine if and when treatment may be indicated. In the minority of families in which none of the available markers is helpful, analysis of putative genes and linkage analysis of consanguineous families may provide novel insights.

References