Retrospective study on clinical manifestation, treatment and outcome in FHL2 and FHL3

Familial hemophagocytic lymphohistiocytoses (FHL) are a group of genetic disorders of cytotoxicity, which predispose to the life-threatening syndrome of HLH. FHL2 (Perforin deficiency) and FHL3 (MUNC13-4 deficiency) are the most frequent forms of the disease. Current therapies include control of the aberrant immune activation by immune-/chemotherapy followed by HSCT still show about 20 **to 40**% overall mortality.

It is our vision that major advances in FHL therapy will depend on early patient identification, ideally by newborn screening, followed by patient-tailored curative therapy. Due to their frequency and severity, FHL2 and FHL3 are attractive target diseases for gene therapy approaches. However, data on natural history, treatment and outcome of FHL have so far mostly been reported in collective studies on genetic diseases predisposing to HLH, usually also including XLP and albinism syndromes and a limited number of FHL2/3 patients. **Detailed disease-specific information focussed on FHL2 and FHL3** would help to specifically define the clinical needs for these diseases with respect to their natural history, treatment and outcome using current standard of care. Such data are essential when approaching regulatory authorities with concepts of newborn screening and gene therapy.

Several groups with advanced pre-clinical programs in gene therapy for FHL2 (Claire Booth, London, Sujal Ghosh, Düsseldorf) and FHL3 (Despina Moshous/Marina Cavazzana, Paris and Stephan Ehl/Toni Cathomen, Freiburg) have therefore joined forces to develop new diagnostic and therapeutic strategies. To achieve this aim, **detailed disease-specific data will be collected in** a **retrospective analysis of patients diagnosed with FHL2 and FHL3, respectively, within the time period 2010-2020**. The study has been approved by the Inborn Errors Working Party of the EBMT and will cover both transplanted as well as non-transplanted patients. Patients will mainly be captured in Europe, since the data are intended to reflect the current situation in those countries, where gene therapy trials will be initiated. If individual countries or centers with similar HLH treatment standards outside Europe wish to contribute, participation will be discussed individually.

The study will have two steps: The first step aims at simple patient identification at the contributing centers while avoiding double registrations. The second step will be the actual data collection, for which the framework is currently being created. The backbone for data collection will be the PROMISE database of the EBMT, where HSCT data are captured and a small additional pre-SCT dataset for FHL will be implemented. Data on non-transplanted patients will be captured by the common HLH registry of ESID and the Histiocyte Society, through extension of the currently available core dataset. Data collection is planned to be initiated in the second quarter of 2022.

We invite you to participate in this joint effort on FHL2 and FHL3, helping us as a community to pave the way for newborn screening and gene therapy for these life-threatening diseases. Two separate publications are planned based on this data collection and all physicians contributing data will be considered as authors. For study participation, please contact Stephan.ehl@uniklinik-freiburg.de, c.booth@ucl.ac.uk, despina.mosohus@inserm.fr or sujal.ghosh@med.uni-duesseldorf.de).

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