

Correspondence

Reply

To the Editor:

In their correspondence, Hennig et al¹ propose to abandon the term “hyper-IgM (HIGM) syndrome” that has been widely used in the medical literature because of low sensitivity and specificity of IgM serum levels in defining the disease. Indeed, only a proportion of patients with the HIGM syndrome have elevated IgM levels at the time of diagnosis, and even fewer present with high IgM levels early in childhood, when correct recognition of the disease and prompt treatment would be most needed. Furthermore, elevated serum IgM levels are not unique to the HIGM syndrome but can also be found in other conditions such as ataxia-telangiectasia.

Medicine is not an exact science. Progress in medicine is often based on careful observation of clinical phenotype, accurate recording of laboratory data, and critical assessment of previously established standards (and definitions). The history of the HIGM syndrome is no exception to this rule. The first cases, reported in 1961, were not given the “catchy” label of the HIGM syndrome but the more neutral term “dysgammaglobulinemia.”² It did not take long to recognize that the HIGM syndrome is heterogeneous, including congenital as well as acquired forms. Nonetheless, the use of serum IgM level as a biomarker was essential to recognize the existence of the X-chromosome-linked form of the disease, ultimately allowing identification of CD40 ligand gene (*CD40LG*) mutations.³ On the other hand, analysis of families with autosomal recessive HIGM syndrome allowed identification of disease-causing mutations in the *AICDA* gene, encoding for activation-induced cytidine deaminase (AID).⁴ A comparison of the clinical phenotype between these 2 major groups of the HIGM syndrome showed that males with the *CD40LG* defect are at high risk of opportunistic infections and liver/biliary tract disease and show reduced survival⁵ whereas AID-deficient patients suffer from recurrent bacterial infections, lymphadenopathy, and autoimmunity.⁴ Hematopoietic cell transplantation has been proposed as the treatment of choice for *CD40LG* deficiency⁶ but has no role in AID deficiency.

Because of these significant clinical and prognostic differences, the International Union of Immunological Society Committee on Primary Immunodeficiencies decided in 2005 to abandon the term “HIGM syndrome” and to refer to the specific gene defect. This decision has been maintained in all classifications of primary immune deficiencies that have been published since 2006.⁷ In this regard, the proposal by Hennig et al to avoid the misleading, although catchy, label “hyper-IgM syndrome” is not new.

Nonetheless, the importance of biomarkers that may reliably help identify a primary immune deficiency cannot be overlooked.

In spite of its low sensitivity and specificity, the presence of elevated serum IgM level in the patient or in other family members—especially if associated with low levels of other immunoglobulin isotypes—should capture physicians’ attention and prompt consultation with immunologists. In most cases, a combination of clinical, laboratory, and genetic tests will permit to define the real nature of the disease, with no mention of the “HIGM syndrome.”

However, it is becoming increasingly clear that even accurate definition of the disease (with identification of a specific gene defect) may not be sufficient to predict clinical course and outcome. Many, but not all, males with *CD40LG* defect experience severe infections and liver disease, and regional differences in clinical phenotype seem to exist. There is no consensus to consider hematopoietic cell transplantation as soon as the diagnosis of *CD40LG* deficiency is made.

Phenotypic heterogeneity of genetic diseases often represents a challenge for the treating physician. Understanding its molecular and cellular basis, and what role is possibly played by environment, represents another frontier of the progress in medicine.

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Disclosure of potential conflict of interest: The author has declared that he has no conflict of interest.

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doi:10.1016/j.jaci.2011.07.040