

## Correspondence

**“A bad wound may heal, but a bad name can kill”—lessons learned from “hyper-IgM syndrome”**

To the Editor:

Today, the database Online Mendelian Inheritance in Men includes information on diseases related to more than 12,000 genes, and novel techniques such as next-generation sequencing will further increase our knowledge especially on rare diseases. For primary immunodeficiencies, a prototype class of rare diseases, the existing classification of primary immunodeficiencies is therefore constantly growing.<sup>1</sup> In order to structure this knowledge for diagnostic purposes, clinicians need both appropriate names for specific diseases and “umbrella terms” to group clinical entities. So far, these 2 categories are often confused, which may have serious consequences for individual patients. A striking example is the inappropriate name “hyper-IgM (HIGM) syndrome”<sup>2</sup> for a certain group of primary antibody deficiencies.

The term “hyper-IgM syndrome” suggests that an elevated serum IgM level is both indicative and typical for the disease. We revisited 136 published cases of the HIGM syndrome, all defined by mutations in *CD40LG*, *CD40*, activation-induced cytidine deaminase, or uracil DNA glycosidase (Table I). In fact, only 62.5% of these patients actually had elevated IgM levels at the time point of initial immunological evaluation (Fig 1). Moreover, only 32% of toddlers—an age when therapy most effectively reduces morbidity and health care costs—had presented with elevated IgM levels.

On the other hand, we reviewed 25 published cases of a more-prevalent primary immunodeficiency disease, ataxia telangiectasia (AT),<sup>3</sup> ascertained by either AT mutated (*ATM*) gene mutations or the absence of ATM protein in Western blot analysis. *ATM* mutations lead to a profound defect in cellular DNA repair and defective immunoglobulin class switch. Remarkably, in 64% of *ATM* patients, IgM values also surpassed the age-specific reference at the initial immunological evaluation (Fig 2). Seventy-six percent of these patients either were initially misdiagnosed as suffering from the HIGM syndrome or had presented with key features suggestive of this phenotype. In these cases, the correct diagnosis was established after a mean duration of 20 months (range, 1-60 months). Such diagnostic delay may cause fatal therapeutic errors. For example, a 7-year-old girl with the HIGM syndrome recently died following radiotherapy for an abdominal malignancy. Postmortem studies showed that the correct diagnosis was AT.<sup>4</sup>

Taken together, an elevated serum IgM level possesses both low sensitivity and specificity as a screening marker for the HIGM syndrome; hence, it can be misleading and lead to serious consequences for the patient. According to the registry of the European Society for Immunodeficiencies,<sup>5</sup> the prevalence of “true” HIGM syndrome is 0.66/1,000,000, whereas AT presenting with immunodeficiency shows a prevalence of 2.12/1,000,000. Hence, in a group of patients with typical signs of the HIGM syndrome, the likelihood of having AT is 3 times higher than that of having “true” HIGM syndrome.

In order to prevent such cases of misdiagnosis, we propose to avoid the misleading, although catchy label “hyper-IgM syndrome.” However, which alternatives could be recommended to avoid diagnostic delays and misdiagnosis?

Alternative 1: Would renaming “hyper-IgM syndrome” to just another umbrella term improve the situation in regard to the time point of initial diagnosis? In fact, at initial immunological evaluation, no other clinical feature in the case histories we reviewed (such as hypogammaglobulinemia, neutrophil count, T- and B-cell counts, marker-infections, autoimmunity, or cancer) had sufficient sensitivity and specificity to distinguish the 2 diseases. To alternatively subsume HIGM syndromes under the term “B-cell class-switch defect” yields, although scientifically correct and better confining, no diagnostic hint for clinicians at the time point of initial evaluation.

Alternative 2: To generate a new classification and subsume all diseases that might present with elevated IgM (such as “hyper-IgM sign”) levels is also not helpful. Although hyper-IgM sign does not carry the inherent confidence associated with the term “syndrome,” it offers only low sensitivity and specificity for a certain disease. Hyper-IgM sign could indicate manifold diseases such as ATM, common variable immunodeficiency, the “HIGM syndrome” as listed in Online Mendelian Inheritance in Men, or the elevation of serum IgM level during an infection. Hence, this term would probably fail to improve diagnostic success in rare diseases.

Alternative 3: All aforementioned efforts to rename syndromes or to establish new classifications are very difficult to implement in reality. The most logical solution would be to avoid all kinds of umbrella terms during diagnostic procedures. In this case, to correctly diagnose an affected patient, only a broad presumptive diagnosis (such as “primary immunodeficiency disease related to B-cell function”) should be made by an experienced clinician, followed by a case-specific diagnostic workup in a specialized center for immunodeficiencies. That workup might include in the case of the HIGM syndrome genetic studies, radiosensitivity

**TABLE I.** PubMed IDs of papers reviewed that contain clinical data about patients with HIGM syndrome and patients with AT

PubMed IDs of references for patients with the HIGM syndrome: 6605368, 7539026, 7690328, 7717401, 8094231, 8669967, 9030857, 9344700, 9710455, 9894727, 10228294, 10373076, 10867853, 11007475, 11112359, 11237554, 11850600, 11885719, 12105778, 12584544, 12715918, 12823286, 12910268, 12952351, 12958596, 14754981, 14962793, 15114594, 15358621, 15661021, 15893695, 15997875, 16169277, 17146684, 17553565, 18030213, 18056008, 18594157, 18805740, 19575287, 19707993, 19931163, 20591076, 20981468

PubMed IDs of references for patients with AT: 10463295, 10575419, 11037863, 12911515, 17591387, 17632790, 18193295, 18504682, 19224889, 20051774, 20380744, 20945614

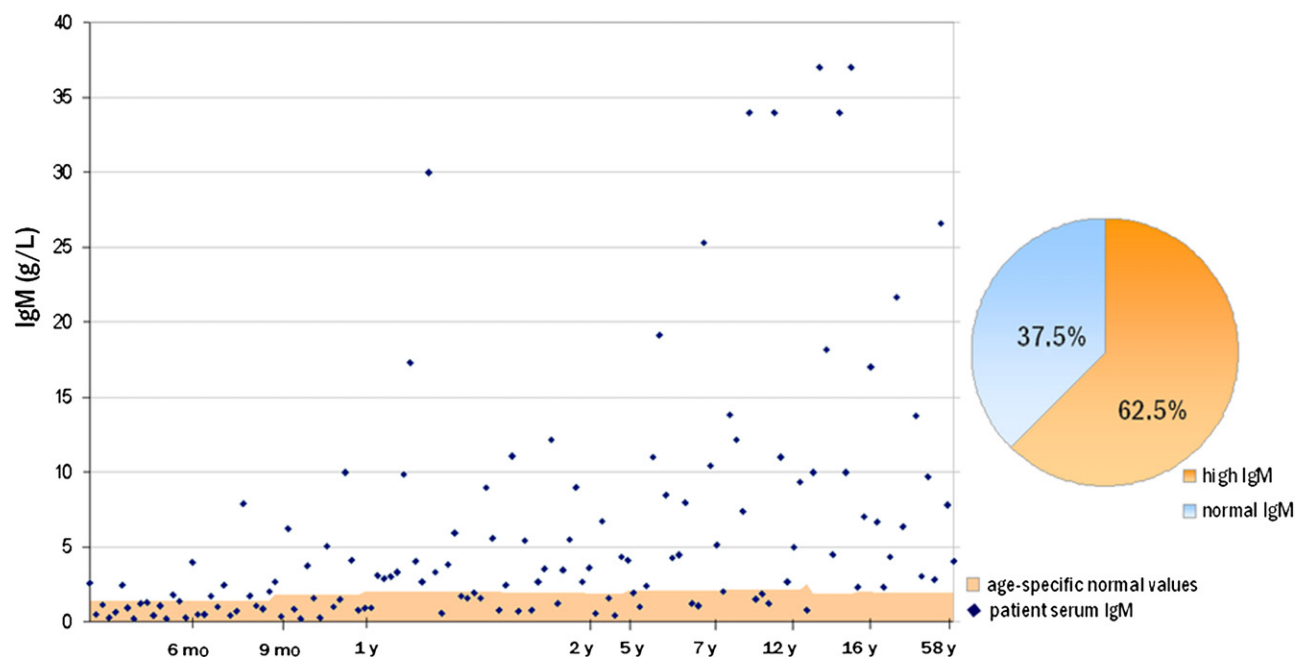


**FIG 1.** Serum IgM values at initial immunological evaluation of patients diagnosed with the HIGM syndrome ( $n = 136$ ). Each dot represents 1 patient. Age-dependent normal values are taken from PubMed IDs 7550761 and 15661021. Note that age is not depicted in a linear fashion for better visualization.

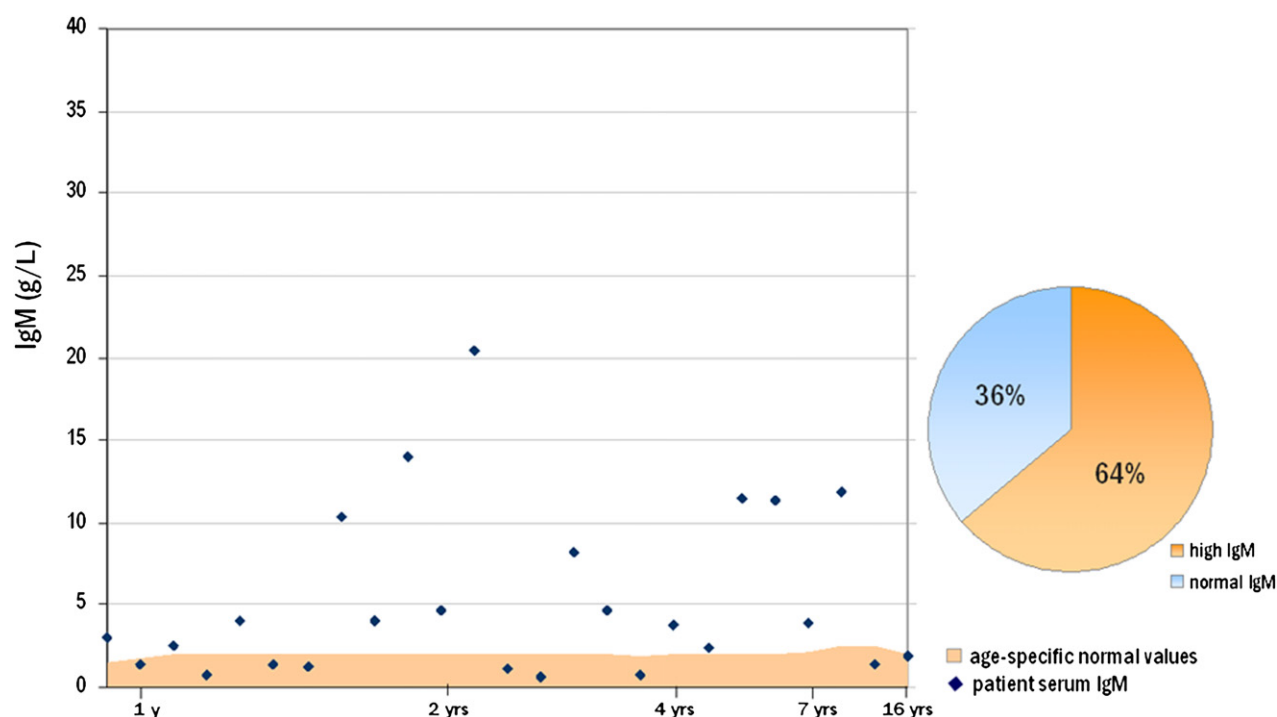


**FIG 2.** Serum IgM values at initial immunological evaluation of patients diagnosed with AT ( $n = 25$ ). Each dot represents 1 patient. Age-dependent normal values are taken from PubMed IDs 7550761 and 15661021. Note that age is not depicted in a linear fashion for better visualization.

assays, or *in vitro* class-switch tests<sup>6</sup>—a process that would additionally benefit from novel computerized diagnostic support systems.<sup>7</sup>

Finally, in our opinion, the most effective way to prevent morbidity and health care costs in the field of rare diseases is

promoting easy and direct communication between outpatient clinicians and specialized centers of expertise at the time point of presumptive diagnosis. This contact, leading to an ideal, patient-tailored, and computer-supported diagnostic workup, should not be delayed by a misleading nomenclature.

As a Scottish proverb says, “A bad wound may heal, but a bad name can kill.”

*Christian Hennig, MD  
Christine Happle, MD  
Gesine Hansen, MD*

From the Department of Paediatric Pneumology, Allergology and Neonatology, Hannover Medical School, Hannover, Germany. E-mail: [hennig.christian@mh-hannover.de](mailto:hennig.christian@mh-hannover.de).

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

## REFERENCES

1. International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies, Notarangelo LD, Fischer A, Geha RS, Casanova JL, Chapel H, Conley ME, et al. Primary immunodeficiencies: 2009 update. *J Allergy Clin Immunol* 2009;124:1161-78.
2. Davies EG, Thrasher AJ. Update on the hyper immunoglobulin M syndromes. *Br J Haematol* 2010;149:167-80.
3. Lavin MF. Ataxia-telangiectasia: from a rare disorder to a paradigm for cell signaling and cancer. *Nat Rev Mol Cell Biol* 2008;9:759-69.
4. Pietrucha BM, Heropolitańska-Pliszka E, Wakulińska A, Skopczyńska H, Gatti RA, Bernatowska E. Ataxia-telangiectasia with hyper-IgM and Wilms tumor: fatal reaction to irradiation. *J Pediatr Hematol Oncol* 2010;32:e28-30.
5. Gathmann B, Grimbacher B, Beauté J, Dudoit Y, Mahlaoui N, Fischer A, et al, ESID Registry Working Party. The European internet-based patient and research database for primary immunodeficiencies: results 2006-2008. *Clin Exp Immunol* 2009;157:3-11.
6. Hennig C, Baumann U, Ilginus C, Horneff G, Foell J, Hansen G. Successful treatment of autoimmune and lymphoproliferative complications of patients with intrinsic B-cell immunodeficiencies with Rituximab. *Br J Haematol* 2010;148:445-8.
7. Adams N, Hennig C, Hoehndorf R, Oellrich A, Rebholz-Schuhmann D, Hansen G. The ontology of primary immunodeficiency diseases (PIDs): using PIDs to rethink the ontology of phenotypes. *Proceedings of the 2nd Workshop for Ontologies in Biomedicine and Life sciences (OBML)*. 2010:51-4.

doi:10.1016/j.jaci.2011.07.041