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Decreased IgM, IgA, and IgG response to pneumococcal vaccine in children with transient hypogammaglobulinemia of infancy

To the Editor:

Transient hypogammaglobulinemia of infancy (THI) is a primary antibody deficiency occurring in the first years of life and is characterized by a delay in the immunoglobulin production that spontaneously recovers in early infancy. In the young symptomatic child with low IgG levels and more than 2% B cells, there are no peculiar clinical and immunologic features that allow discrimination between self-limiting THI, common variable immunodeficiency, or other dysgammaglobulinemias. Only those patients whose IgG levels have normalized after age 4 years have a definitive THI diagnosis made *a posteriori*.[1,2]

In a previous study, we demonstrated that a subgroup of children with putative THI shares abnormalities of B-cell memory subsets with other defined immune deficiencies, and cautiously suggested the term "hypogammaglobulinemia during infancy" to define conditions in which it is not yet possible to discriminate THI from other primary antibody defects.[3] Recently, according to the new European Society for Immunodeficiencies diagnostic criteria, a working definition of "unclassified hypogammaglobulinemia" (UH) has been introduced to register patients with IgG values below age-related normal values detected in the first 3 years of life that will be moved to THI diagnosis if there is spontaneous resolution before age 4 years (http://esid.org/Working-Parties/Registry/Diagnosis-criteria).

Measurement of pneumococcal antibodies is an important tool in the immunologic assessment of patients with suspected immune deficiencies.[4]

The aim of this study was to analyze prospectively IgM-, IgA-, and IgG-antibody responses to pneumococcus vaccine (PV) in children with UH until THI or other immune deficiencies criteria were met.

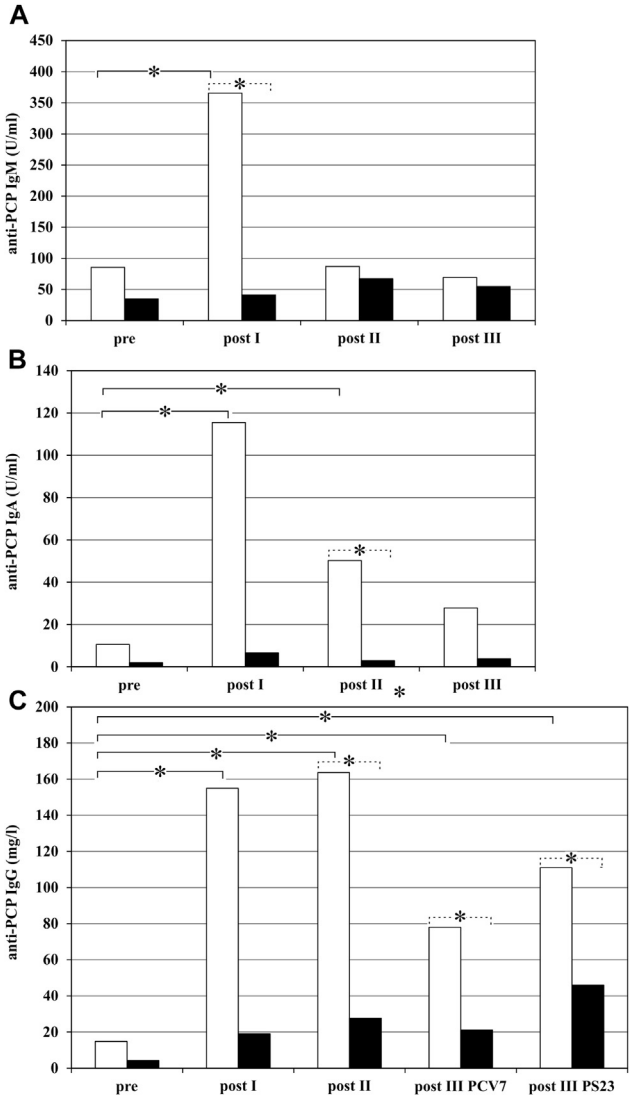

FIG 1. Median IgM **(A)**, IgA **(B)**, and IgG **(C)** anti-PCP antibodies in HC *(white bars)* and children with UH *(black bars)* before (pre) and 4 weeks after each PV dose (post-I, post-II, and post-III). **P* values <.05. The *continuous line* compares pre- and postvaccination titers within the same cohort. The *dotted line* compares postvaccination titers between HC and children with UH.

In the context of the Italian Primary Immunodeficiency Network, we enrolled 21 patients (age range, 12-36 months) with a history of recurrent infections who had an initial diagnosis of UH in accordance with our national protocol for THI (http://www.aieop.org/stdoc/prot/rec_thi_en_06.pdf) and monitored them until age 4 years with regular clinical and immunologic evaluations. Eighteen healthy age-matched children (HC) (age range, 15-40 months) were used as controls. Informed consent was obtained from the patient's parents. The Institutional Ethical Committee approved the study. All patients and HC received 3 doses of 7-valent conjugated pneumococcus vaccine (PCV 7, Prevnar, Pfizer), with the exception of 5 children with UH and 6 HC who received the third PV dose with unconjugated pneumococcus polyvalent vaccine (Pneumo23; Aventis, Milan, Italy) because they were older than 2 years. Serum samples were collected from children with UH and HC before and 4 weeks after each

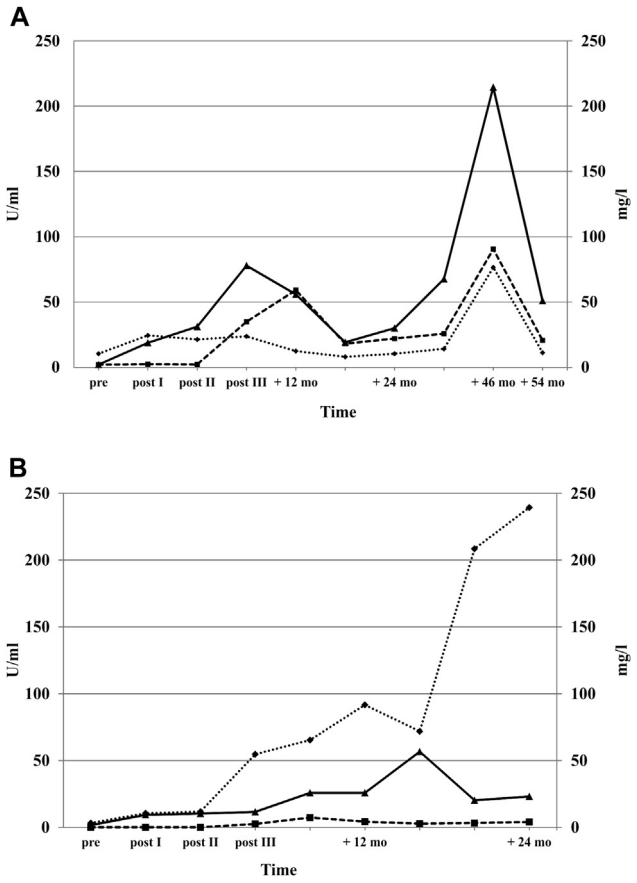

FIG 2. Pneumococcal IgM, IgA, and IgG kinetics at time of pre, post-I, post-II, post-III and months after the completion of the primary immunization series in patient 1 with UH **(A)** and in patient 2 with common variable immunodeficiency **(B)**. The *left axis* refers to IgA and IgM values (U/mL), and the *right axis* refers to IgG values (mg/L). Pneumococcal polysaccharide IgM *(dotted line with black diamond)*, IgA *(dashed line with black squares)*, and IgG *(continuous line with black triangles)* are shown.

dose of vaccine (post-I, post-II, and post-III). We measured anti–pneumococcal capsular polysaccharide (PCP) antibodies, anti–polyribosyl-ribitol phosphate antibodies (specific to Hib), and anti–tetanus toxoid by ELISA (The Binding Site, Birmingham, United Kingdom: VaccZyme Anti-PCP IgG Enzyme Immunoassay; Anti-PCP IgA and Anti-PCP IgM EIA kit; VaccZyme Human Anti-Hib Enzyme Immunoassay; VaccZyme Tetanus toxoid IgG).[5] Group comparisons were performed using the Mann-Whitney test. Data are presented as median. *P* values of less than .05 were considered statistically significant. Statistical analysis was performed using Statistical Analysis Software.

Data of IgM, IgA, and IgG anti-PCP in HC are reported in Fig 1, *A-C*. The median level of IgM anti-PCP increased from 85 U/mL before vaccination to 366 U/mL ($P = .028$) after the first dose. This 4-fold increase was followed by a titer decline to prevaccination values after the second and third doses (87 and 69 U/mL, respectively). The median level of IgA anti-PCP prevaccination titer reached a more than 10-fold increase after the first dose (from 10 U/mL to 115 U/mL; $P = .018$) and then decreased to 50 and 27 U/mL after the second ($P = .015$) and third dose, respectively. The median level of IgG anti-PCP showed a more than 10-fold increase after the first dose (from 14 mg/L to 154 mg/L; $P = .018$). The post-I titer was stable at the post-II evaluation (164 mg/L; $P = .008$) and approximately halved at the post-III evaluation (78 mg/L in children who received 3 doses of PCV 7 and 111 mg/L in children who received the third PV dose with unconjugated PV vaccine because they were older than 2 years). The post-III titer maintained a more than 4-fold concentration in comparison to prevaccination titers independently of the type of vaccine used for the third immunization (pre vs post-III: $P = .01$ for PCV7; $P = .006$ for unconjugated PV). Thus, HC showed a transient IgM response and a persistent IgG response. Of interest was the finding of a strong initial specific IgA response followed by a rapid decline, suggesting an impaired capacity in the first years of life to maintain IgA-mediated memory responses.

IgM, IgA, and IgG anti-PCP in children with UH showed a completely different pattern. As shown in Fig 1, *A-C*, poor specific anti-PCP responses were generally observed. The median IgM anti-PCP levels after each PV dose did not show any significant increase in children with UH (from a prevaccination titer of 35 U/mL to 41 U/mL [post-I], 67 U/mL [post-II], and 54 U/mL [post-III]). The IgA anti-PCP response was generally very low (from a prevaccination median titer of 2 U/mL to 7 U/mL [post-I], 3 U/mL [post-II], and 4 U/mL [post-III]). The IgG anti-PCP response was low (from a median prevaccination titer of 4 mg/L to 19 mg/L [post-I], 28 mg/L [post-II], and 21 mg/L in children who received 3 doses of PCV 7 and 46 mg/L in children who received unconjugated pneumococcus polyvalent as the third dose because they were older than 3 years [post-III]).

All except 1 child with UH responded to tetanus toxoid vaccination (median, 1 IU/mL). All children with UH responded to Hib vaccine (median, 1.75 mg/L). B-cell subsets were similar to those already reported in THI children[3]—$CD27^-IgM^+IgD^+$: 84.6% ± 5.7%; $CD27^+IgM^+IgD^+$: 8.8% ± 3%; $CD27^+IgM^-IgD^-$: 4.8% ± 3.1%; $CD38^{++}IgM^{++}$: 11.5% ± 5.3%.

About 90% (19 of 21) of the children with UH normalized their serum total IgG values, within age 22 months, allowing the diagnosis of THI. Conversely, 2 of 21 continued to suffer from recurrent respiratory infections and showed a persistent condition of hypogammaglobulinemia after the fourth year of life. One patient (no. 1) maintained the diagnosis of UH, owing to a marked decrease in IgG level with normal antibody responses. One patient (no. 2) met the criteria for common variable immunodeficiency diagnosis, owing to a marked decrease in IgG (495 mg/dL; age-matched healthy donors, 528-1312 mg/dL) and IgA (23 mg/dL) levels, poor antibody response to vaccines, and low switched memory B cells (2.7%). In this patient, we identified a heterozygous C104R variant in the TNFRSF13B gene encoding the transmembrane activator and calcium modulator and cyclophilin ligand interactor.

In the 2 patients who did not normalize total IgG levels at age more than 4 years, we prospectively monitored IgM, IgA, and IgG anti-PCP after the completion of the primary vaccination series for a period of 54 months in patient 1 and for a period of 24 months in patient 2. As shown in Fig 2, *A*, in patient 1, anti-PCP IgM, IgA, and IgG levels declined over time from the completion of the cycle of immunization and then increased, with a peak at 46 months, when an acute infection, caused by *Streptococcus pneumoniae*, occurred. In patient 2, anti-PCP IgG and IgA responses were almost undetectable over time whereas only specific IgM antibodies were evident (Fig 2, *B*).

According to a recent Jeffrey Modell Foundation survey, THI is generally listed within the top 10 more prevalent primary immunodeficiency disorders worldwide and as the most frequently reported in Eastern Europe.[6] Although its outcome is considered benign, the psychological impact of this condition, due to patient's age and frustrating uncertainty on the long-term outlook, is greater than expected.[7]

In this study, although preliminary for the cohort size and the potential bias of age and vaccination schedule, we demonstrated that children with THI showed an abnormal anti-PCP response. Consistent with our previous report, a further tile is added to B-cell memory defect and immunoglobulin defect.

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Extrapulmonary tuberculosis mimicking Mendelian susceptibility to mycobacterial disease in a patient with signal transducer and activator of transcription 1 (*STAT1*) gain-of-function mutation

To the Editor:

Signal transducer and activator of transcription 1 (*STAT1*) mutations cause several rare primary immunodeficiencies.[1] Chronic mucocutaneous candidiasis disease (CMCD) is characterized by persistent or recurrent skin, nail, and mucosal membrane infections caused by *Candida albicans*. Patients with Mendelian susceptibility to mycobacterial disease (MSMD) suffer from atypical mycobacterial infections or severe tuberculosis infections. The gain-of-function *STAT1* mutations cause an autosomal-dominant form of CMCD,[2] whereas the loss-of-function *STAT1* alleles cause MSMD.[3] Furthermore, *STAT1* mutations are associated with severe-lethal clinical phenotypes[4] or even autoimmune/immune dysregulation phenotypes.[5]

Here we report the case of an 18-year-old man with the gain-of-function *STAT1* mutation who presented severe tuberculosis infection mimicking MSMD. The identical gain-of-function *STAT1* mutation was found in his mother, who developed gingival squamous cell carcinoma.

The proband was admitted to a general hospital because of high fever and a 1-month history of worsening left-sided abdominal pain. His medical history was unremarkable apart from recurrent cutaneous candidiasis on the sole of his right foot (Fig 1, *A*). He had received a BCG vaccination without any complication. A contrast-enhanced computed tomography scan identified an infiltration in the left lower lobe of his lung and multiple enlarged intestinal lymph nodes with calcification in the abdomen (Fig 1, *B*). No pathogenic bacterium was detected in his sputum, whereas *Mycobacterium tuberculosis* was detected on the culture of gastric aspirate specimens and was confirmed by PCR. The pathological examination of his duodenal mucosa revealed histiocyte aggregation (Fig 1, *C*), and subsequent Ziehl-Neelsen staining detected acid-fast bacilli. His tuberculous lymphadenitis responded well to triple therapy (rifampicin, isoniazid, and ethambutol). However, before and during the treatment, repeated QuantiFERON-TB test results (Cellestis Limited, Carnegie, Victoria, Australia) were negative. Tuberculin skin test results (2.5 TU) were also negative even after the completion of therapy. Therefore, congenital cellular immune defects were suspected and he was referred to our hospital.

His total lymphocyte (0.9×10^9/L) and $CD4^+$ lymphocyte (0.3×10^9/L) counts were decreased, but the proliferative responses for concavalin A and phytohemagglutinin were normal. With patient's written informed consent, we sequenced 6 genes associated with MSMD. Unexpectedly, we identified a heterozygous gain-of-function *STAT1* mutation that was associated with CMCD (c.821G>A, p.Arg274Gln) (Fig 2, *A* and *B*). Subsequent analysis revealed enhanced STAT1 phosphorylation in response to IFN-γ and resistance to staurosporine-driven dephosphorylation, which is a characteristic of CMCD (Fig 2, *C*; see Fig E1 in this article's Online Repository at www.jacionline.org).[6] We confirmed that the antimicrobial activity of the patient's macrophages against *Mycobacterium avium* was decreased compared with that in healthy volunteers (Fig 2, *D*).

A familial genetic study identified the identical gain-of-function *STAT1* mutation in his mother (c.821G>A, p.Arg274Gln) (Fig 2, *A* and *B*). She had no history of heavy drinking or smoking. She had suffered from chronic bronchiectasis and oral candidiasis (Fig 1, *D*) for several decades. At the age of 44 years, she developed esophageal intraepithelial neoplasia and lower gingival squamous cell carcinoma (Fig 1, *D-F*). She underwent surgical tumor resection, subtotal esophagectomy, and esophagogastric anastomosis.

A few cases of patients with CMCD with a mycobacterium infection are reported. Sampaio et al[7] reported a patient who