Burden of Poor Health Conditions and Quality of Life in 656 Children with Primary Immunodeficiency

Vincent Barlogis, MD, PhD[1,2,3], Nizar Mahlaoui, MD[2,4,5], Pascal Auquier, MD, PhD[3], Fanny Fouyssac, MD[2,6], Isabelle Pellier, MD, PhD[2,7], Camille Vercasson, MS[3], Maya Allouche, PhD[1], Carolina Brito De Azevedo, PhD[2], Despina Moshous, MD, PhD[2,4,5], Bénédicte Neven, MD, PhD[2,4,5], Marlène Pasquet, MD, PhD[2,8], Eric Jeziorski, MD, PhD[2,9], Nathalie Aladjidi, MD[2,10], Caroline Thomas, MD[2,11], Virginie Gandemer, MD, PhD[2,12], Françoise Mazingue, MD[2,13], Capucine Picard, MD, PhD[2,4,5], Stéphane Blanche, MD[2,4,5], Gérard Michel, MD[1,2,3], and Alain Fischer, MD, PhD[2,4,5,14]

Objective To gain insight into how primary immunodeficiencies (PIDs) affect children's health status and quality of life.

Study design The French Reference Center for PIDs conducted a prospective multicenter cohort that enrolled participants who met all criteria: patients included in the French Reference Center for PIDs registry, children younger than18 years, and living in France. Participants were asked to complete both a health questionnaire and a health-related quality of life (HR-QoL) questionnaire. A severity score was assigned to each health condition: grade 1 (mild) to grade 4 (life-threatening). HR-QoL in children was compared with age- and sex-matched French norms.

Results Among 1047 eligible children, 656 were included in the study, and 117 had undergone hematopoietic stem cell transplantation; 40% experienced at least one grade 4 condition, and 83% experienced at least one grade 3 or 4 condition. Compared with the French norms, children with PID scored significantly lower for most HR-QoL domains. Low HR-QoL scores were associated strongly with burden of poor conditions.

Conclusions Our results quantify the magnitude of conditions in children with PID and demonstrate that the deleterious health effects borne by patients already are evident in childhood. These results emphasize the need to closely monitor this vulnerable population and establish multidisciplinary healthcare teams from childhood. *(J Pediatr 2017;■■:■■-■■).*

Trial registration ClinicalTrials.gov: NCT02868333 and EudraCT 2012-A0033-35.

Primary immunodeficiencies (PIDs) represent a growing group of more than 330 single-gene inborn immune defects that result in increased susceptibility to recurrent infections, autoimmune disorders, inflammation, allergy, and malignant diseases.[1] Although some PIDs may appear during adulthood, the disease most often is diagnosed during childhood, especially severe forms. All forms of PIDs require life-long antibiotic or antifungal prophylaxis or immunoglobulin-replacement therapy and appropriate management of complications.[2-4] Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only definitive cure for severe PID, although gene therapy also has become an effective option for a selected number of patients.[5-7]

PIDs represent a vast group of conditions that are chronic and likely to affect life expectancy. With advances in the quality of healthcare, overall patient survival has improved steadily. As a result, assessment of the long-term health status of patients with PID is now a major challenge. A few long-term studies have been published, which focused on either specific diseases[8] or specific complications of transplanted severe combined immunodeficiency survivors.[9-11]

CEREDIH	French Reference Center for PIDs
CTCAE	Common Terminology Criteria for Adverse Events
ENT	Ear, nose, and throat
F-CILC	French Childhood Immune Deficiency Long-Term Cohort
HR-QoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
PAD	Predominantly antibody deficiency
PID	Primary immunodeficiency
VSP-A	Vécu et Santé Perçue de l'Adolescent
VSP-Ae	Vécu et Santé Perçue de l'Enfant
VSP-Ap	Vécu et Santé Perçue par les Parents

From the [1]Department of Pediatric Hematology-Oncology, Assistance Publique-Hôpitaux de Marseille, Marseille; [2]French National Reference Center for Primary Immune Deficiency (CEREDIH), Necker Enfants Malades University Hospital, Assistance Publique-Hôpitaux de Paris, Paris; [3]Department of Public Health—EA 3279 Research Unit, Aix-Marseille University, Provence; [4]Pediatric Immuno-Haematology and Rheumatology Unit, Necker Enfants Malades University Hospital, Assistance Publique-Hôpitaux de Paris; [5]INSERM UMR1163, Imagine Institute, Sorbonne Paris Cité, University Paris Descartes, Paris; [6]Department of Pediatric Hematology-Oncology, University Hospital of Nancy, Nancy; [7]Department of Pediatric Oncohematology, University Hospital of Angers, Angers; [8]Department of Pediatric Hematology, University Hospital of Toulouse, IUCT-Oncopole, INSERM, Toulouse; [9]Department of Pediatrics, Hôpital Arnaud de Villeneuve, Montpellier University Hospital, Montpellier; [10]Department of Pediatric Hematology, CIC 0005, INSERM CICP, University Hospital of Bordeaux, Bordeaux; [11]Pediatric Hematology-Oncology Unit, University Hospital of Nantes, Nantes; [12]Department of Pediatric Hematology/Oncology, University Hospital of Rennes, Rennes; [13]Department of Pediatrics, Hôpital Jeanne de Flandre, University Hospital of Lille, Lille; and [14]Division of Médecine Expérimentale, Collège de France, Paris, France

Supported by the French National Program for Clinical Research (Programme Hospitalier de Recherche Clinique, Ministry of Health). The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.10.029

To better understand the determinants of the health status and quality of life (HR-QoL) of patients with PID, the French PID Reference Center (CEREDIH) has a national prospective cohort (the French Childhood Immune Deficiency Long-Term Cohort [F-CILC]). To our knowledge, the F-CILC is the first national program addressing long-term outcomes of patients diagnosed with PID during childhood. We recently have reported the health status of 329 adults diagnosed during childhood and included in the F-CILC. We showed that PID had a significant impact on all dimensions of patient HR-QoL, regardless of the diagnosis, prophylactic treatment, or duration of the disease.[12] Here, we describe the health status and HR-QoL of 656 children with PID enrolled in our national cohort and investigate the impact that PID had on patient HR-QoL.

Methods

We conducted a multicenter prospective follow-up program enrolling participants who met the following criteria: (1) patient with a PID included in the CEREDIH registry,[13] (2) children younger than 18 years of age, (3) alive and living in France, and (4) who gave their written informed consent to participate in the study. Contact and recruitment of eligible children began in June 2013 via a unique procedure previously described.[12] Children were considered to be "participant" when the questionnaire was completed and returned along with the written informed consent document signed by both patients and parents. Patients were considered as "lost to follow-up" when extensive efforts failed to locate them. Patients were considered as "nonparticipant" when either their parents declined to participate verbally via telephone or in writing or they indicated their willingness to participate but failed to return the completed questionnaire and signed informed consent document. The study (ClinicalTrials.gov: NCT02868333) was part of the French National Program for Clinical Research (Programme Hospitalier de Recherche Clinique, Ministry of Health, EudraCT.ema.europa.eu: 2012-A0033-35) and has been approved by the review board Comité National Informatique et Libertés, the local ethics committee (Comité de Protection des Personnes Sud-Méditerranée: trial number 12.024), and the Comité Consultatif sur le Traitement de l'Information de Recherche dans la Santé (trial number 12.681).

Information concerning demographic data, clinical and genetic PID diagnosis, onset of PID symptoms, date of clinical diagnosis of PID, therapy history (particularly immunoglobulin replacement and HSCT), and clinical laboratory results were obtained from the CEREDIH registry, which was updated on an annual basis.[13] According to the criteria of the International Union of Immunological Society, PID was classified into the following subgroups: predominantly T-cell deficiencies, predominantly antibody deficiencies (PADs), phagocytic disorders, defects of innate immunity, immune dysregulation (ie, familial hemophagocytic lymphohistiocytosis, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome), complement deficiencies, and other well-defined PIDs.[1]

Parents of participants completed the French Childhood Immune Deficiency Long-Term Study Group questionnaire. This self-administered questionnaire included 638 items covering the following topics: sociodemographic characteristics, PID diagnosis, medical care practices (eg, immunoglobulin replacement, HSCT), and physical health condition (eg, cardiac; respiratory; ear, nose, and throat [ENT]; gastrointestinal; dermatologic; genitourinary; musculoskeletal; neurologic; endocrinopathy; surgery; and malignancy). The 320 items concerning physical health conditions were based on the questionnaire previously published for the Childhood Cancer Survivor Study and then adapted to the PID context.[14,15]

Each health condition was self-rated by the patient according to the 4-grade scale: grade 1 = mild, grade 2 = moderate, grade 3 = severe, and grade 4 = life-threatening/disabling. To avoid under-grading, each self-reported condition was then reviewed and graded by a dedicated medical team, who applied the Common Terminology Criteria for Adverse Events (CTCAE) v4.0: grade 1 = mild, grade 2 = moderate, grade 3 = severe, and grade 4 = life-threatening/disabling ("grade 5 = death" was not applicable in this study).[16] Then, the higher of the 2 grades (from both the self-report and medical evaluation) was selected for the final evaluation. Conditions not listed in the CTCAE (eg, aspergillosis, pneumocystosis) were assessed in severity on the 4-grade scale by the same dedicated medical team. In situations in which we were unable to distinguish between the 4 grades because of a lack of information, the lower score was selected.

The HR-QoL of children and adolescents was assessed with the Vécu et Santé Perçue de l'Adolescent et de l'Enfant (VSP-A and VSP-Ae) questionnaires.[17] Two pediatric versions were available: the VSP-Ae, designed to be answered by children from 8 to 10 years of age, and the VSP-A, designed to be answered by adolescents from 11 to 17 years of age. One parent version also was available, the VSP-Ap, which is designed to assess the parental point of view of their child's or adolescent's HR-QoL. The VSP-Ae described 7 dimensions and a summary score. Both VSP-A and VSP-Ap questionnaire responses consider 9 dimensions and a summary score: relationships with parents, body image, vitality, relationships with friends, psychological well-being, physical well-being, leisure activities, school work, and relationships with teachers[17,18]; it also described a complementary dimension, relationships with medical staff. All scores ranged from 0 to 100, with greater scores indicating better HR-QoL. The general French population reference values for parents[19] as well as children and adolescents aged 8-17 years[20] were available for sex- and age-matched comparison purposes. No reference values for parents of children younger than 8 years of age were available.

Statistical Analyses

We determined the prevalence and severity of physical health conditions by using 2 endpoints, which were used throughout the analysis: life-threatening/disabling (grade 4), reported either by the patient or via medical assessment (according to CTCAE score), and severe or life-threatening/disabling (grade 3-4), reported either by the patient or via

FLA 5.5.0 DTD ■ YMPD9537_proof ■ November 30, 2017