MAJOR ARTICLE

Invasive Pneumococcal Disease in Children Can Reveal a Primary Immunodeficiency

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Background. About 10% of pediatric patients with invasive pneumococcal disease (IPD) die from the disease. Some primary immunodeficiencies (PIDs) are known to confer predisposition to IPD. However, a systematic search for these PIDs has never been carried out in children presenting with IPD.

Methods. We prospectively identified pediatric cases of IPD requiring hospitalization between 2005 and 2011 in 28 pediatric wards throughout France. IPD was defined as a positive pneumococcal culture, polymerase chain reaction result, and/or soluble antigen detection at a normally sterile site. The immunological assessment included abdominal ultrasound, whole-blood counts and smears, determinations of plasma immunoglobulin and complement levels, and the evaluation of proinflammatory cytokines.

Results. We included 163 children with IPD (male-to-female ratio, 1.3; median age, 13 months). Seventeen children had recurrent IPD. Meningitis was the most frequent type of infection (87%); other infections included pleuropneumonitis, isolated bloodstream infection, osteomyelitis, endocarditis, and mastoiditis. One patient with recurrent meningitis had a congenital cerebrospinal fluid fistula. The results of immunological explorations were abnormal in 26 children (16%), and a PID was identified in 17 patients (10%), including 1 case of MyD88 deficiency, 3 of complement fraction C2 or C3 deficiencies, 1 of isolated congenital asplenia, and 2 of Bruton disease (X-linked agammaglobulinemia). The proportion of PIDs was much higher in children aged >2 years than in younger children (26% vs 3%; $P < .001$).

Conclusions. Children with IPD should undergo immunological investigations, particularly those aged >2 years, as PIDs may be discovered in up to 26% of cases.

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Keywords. *Streptococcus pneumonia*; primary immunodeficiency; primary antibody deficiency; innate deficiency; complement deficiency.

Streptococcus pneumoniae is an almost ubiquitous gram-positive encapsulated bacterium. Cross-sectional studies have shown that, at any given time, 20%–50% of healthy children harbor at least 1 serotype of this bacterium in the rhinopharynx, whereas longitudinal studies have shown that almost all children can be shown to carry this bacterial species [1, 2]. *Streptococcus pneumoniae* is a leading cause of benign conditions, such as otitis media [3], but may also cause more serious illnesses, such as pneumonitis [4]. Therefore, it constitutes a public health burden worldwide for young children [5]. In rare cases, *S. pneumoniae* may even cause severe, life-threatening diseases, such as arthritis [6], peritonitis [7], septicemia, and meningitis [8], collectively known as invasive pneumococcal disease (IPD) [9]. The greatest risk factor for IPD in children, apart from young age, is IPD itself, as this condition has a recurrence rate of 2%–4% [10]. The rarity of IPD, despite the asymptomatic carriage of *S. pneumoniae*, strongly suggests that host factors play a key role in the pathogenesis of this disease [11–14]. Indeed, a number of acquired and inherited host factors that confer predisposition to IPD have been identified. The best-known acquired factors that determine susceptibility to recurrent IPD are coinfection with human immunodeficiency virus (HIV) [9, 15] and splenectomy [16]. Other acquired factors include certain cancers [17] and traumatic cerebrospinal fluid fistulas [18–20]. Host genetic factors have also long been known to confer predisposition to IPD, as in sickle cell disease [21] and certain primary immunodeficiencies (PIDs) [22].

PIDs known to underlie clinical disease caused by encapsulated bacteria, such as *S. pneumoniae,* include congenital asplenia [23, 24], complement deficiency [22, 25], and antibody deficiency [22]. Fourteen years ago, hypomorphic mutations of *NEMO* were identified in patients with anhidrotic ectodermal dysplasia with immunodeficiency [26, 27]. In these patients, impaired nuclear factor κ-B signaling results in susceptibility to multiple pathogens, including *S. pneumoniae* in particular [28, 29]. The molecular genetic basis of a more selective predisposition to IPD remained elusive until the identification of children with mutations of *IRAK4* or *MYD88* genes [30, 31]. These 2 genes encode proteins specifically involved in the Toll-like and interleukin receptors (TIRs) superfamily signaling pathway. However, the pathogenesis of IPD in most children remains unknown. Sporadic, isolated childhood IPD, which is generally described as "idiopathic," may be favored by undetected, underlying PIDs that confer a selective predisposition to IPD. The proportion of children presenting with IPD with known inherited susceptibility factors, including conventional PIDs in particular, has never been precisely evaluated. In 2005, we set up a collaboration with GPIP/ACTIV (Saint-Maur-des-Fossés, France) to address this question by creating an observatory comprising French pediatric hospitals. These hospitals were asked to collect blood samples prospectively from children who had recovered from IPD. In this study, we aimed to carry out systematic explorations of the immunity of hospitalized children with IPD by looking for both known and unknown PIDs.

METHODS

Definitions and Data Collection

The National Observatory for IPD was created by the GPIP/ACTIV network and brings together 28 pediatric units across France that included all children hospitalized for IPD. Children with sickle cell disease and HIV-positive children were excluded. Children who died were included whenever immunological explorations had been performed before death. IPD was defined as an infection requiring hospitalization confirmed by the isolation of *S. pneumoniae* from a normally sterile site (blood, cerebrospinal fluid, synovial fluid, pleural fluid, but not sputum). If pneumococcus was isolated from blood, signs of hemodynamic shock were required for inclusion.

The following data were collected: family and patient history, pneumococcal vaccination status, clinical signs, microbiological data, abdominal ultrasound results, whole-blood cell (WBC) counts with smears, and determinations of immunoglobulins (Ig) and complement. Most children also underwent interleukin (IL)-6 determinations after stimulation. All children with recurrent meningitis underwent brain magnetic resonance imaging (MRI) to rule out the possibility of cerebrospinal fistula. Children with normal results for abdominal ultrasound, WBC counts, smears, plasma Ig levels, classic and alternative complement studies, and evaluations of IL-6 production by WBC were considered not to have a PID. If any of these examinations had not been carried out or the results were missing, the patient was classified in the "incomplete exploration" category. We considered 2 time periods: 2005–2009 (before introduction of the 13-valent pneumococcal vaccine, PCV13) and 2010–2011 (after PCV13 implementation), 2010 being the year in which French national authorities recommended switching from PCV7 to PCV13 for antipneumococcal immunization.

Microbiology

Streptococcus pneumoniae was identified by standard methods in the microbiology laboratories of the various participating hospitals. Serotyping was performed with latex particles sensitized with

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antisera purchased from the Statens Serum Institut (Copenhagen, Denmark), most at the national reference center.

Immunological Explorations and Whole-Blood Activation

Classic and alternative complement tests were carried out with standard techniques using enzyme-linked immunosorbent assay (ELISA; Wielisa-kit, Lund, Sweden) or nephelometry (Dade Behring, Paris La Defense, France). Whenever complete lack of CH50 or AP50 was identified, genetic tests were carried out to determine which component was missing. The IgG subclasses were assessed by ELISA methods [32]. Total IgG antibody levels against multiple pneumococcal serotypes (23 serotypes) were assessed by multiplexed bead assay or standard ELISA techniques (The Binding Site Inc, Birmingham, United Kingdom) [33]. Children with a persisting defect in the production of antibodies specific for pneumococcal capsular antigens with normal Ig after age 2 years were considered to have "specific polysaccharide antibody deficiency" (SPAD). Patients' blood samples were diluted 1:2 in RPMI 1640 medium (Gibco-BRL, Invitrogen, USA) and incubated at 37°C in the following sets of conditions for 48 hours: with medium alone; with 20 ng/mL IL-1β (R&D Systems); with 1 ng/mL lipopolysaccharide (Sigma, USA); with 100 μg/m PAM2CSK4 (InvivoGen, USA); with 10^7 particles/mL SAC (InvivoGen); with 5×10^6 particles/mL heat-killed pneumococcal strains; or with 10^{-7}M phorbol myristate acetate (Sigma) plus 10^{-5}M ionomycin (Sigma). Supernatants were collected and IL-6 levels were assessed using ELISA (Sanquin kit) according to the manufacturer's instructions and read with an MRX microplate reader (Thermo Lab Systems, USA).

Statistical Analysis

We used standard statistical tests implemented in R v2.15.1 software to compare categorical variables and means. P values < .05 were considered statistically significant.

Ethics

This study was conducted in accordance with the Helsinki Declaration, with informed consent obtained from each patient's family. The local ethics committee of Necker-Enfants Malades Hospital, Paris, France, approved the study.

RESULTS

Epidemiology

Between January 2005 and December 2011, 163 pediatric cases of IPD were identified. Seven hospitals reported 10 or more cases and 4 hospitals included between 5 and 9 children. The male-to-female ratio was 1.3 (91 males and 72 females; $P = .14$). Median age was 13 months (range, 1 month–15 years), with a peak in the number of cases at age 3 months to 6 months. There was seasonal variation in the number of cases, with a peak in February. Meningitis occurred most frequently in this cohort (n = 142; 87%), followed by pleuropneumonitis (n = 11; 7%), bloodstream infection (n = 6; 4%), osteomyelitis (n = 1), arthritis (n = 1), endocarditis (n = 1), and mastoiditis (n = 1). Seventeen patients (10%) had recurrent IPD. The proportion of patients with meningitis seemed to be higher in children aged <2 years (n = 98/109, 90%) than in older children (n = 44/54, 81%; $P = .21$). Overall vaccination coverage with the conjugate vaccine against *S. pneumoniae* was 71% for the children included in the study (n = 114/160; data missing for 3 cases). Vaccination coverage increased from 69% (n = 81/118) during the 2005–2009 period to 79% (n = 33/42) during the 2010–2011 period ($P = .31$, ns). This trend was observed in both children aged <2 years and in children aged >2 years, 81% and 41%, respectively, in 2005–2009; this increased to 88% and 65%, respectively, in 2010–2011 (ns; Table 1).

Ten patients were from families known to be consanguineous. No underlying conditions (including PIDs) had previously been identified in these children. However, 17 patients had already been hospitalized for IPD: 11 for meningitis, 4 for pleuro/pneumonitis, 1 for osteoarthritis, and 1 for septicemia. In addition, 4 children had previously presented with another severe infectious disease: 1 with regional bacille Calmette-Guérin–itis, 1 with encephalopathy due to *Mycoplasma pneumonia*, and 2 with ethmoiditis for which the causal microbe was not identified but was probably bacterial, given the response to antibiotic treatment observed. Nine children (6%) aged 3 months to 9 years died, all secondary to pneumococcal meningitis (recurrent in 1 case). We identified a cerebrospinal fluid fistula in an 8-year-old girl hospitalized for her third episode of meningitis due to *S. pneumoniae*, on brain MRI, despite the normal results obtained for a brain scan after the second meningitis.

Bacteriology

Infection was documented by culture (154 cases), polymerase chain reaction (2 cases), or the presence of soluble antigens (7 cases); *S. pneumoniae* serotype was available for 130 isolates (Table 1). Nine children correctly vaccinated for age developed infection due to a serotype included in the vaccine (5 for PCV7 and 4 for PCV13). The proportion of infections due to a serotype included in the PCV7 vaccine decreased between the 2005–2009 and 2010–2011 periods (n = 12/100 vs n = 1/30; ns), as did the proportion of infections due to serotype 19A after the introduction of PCV13 (n = 30/100 vs n = 5/30; ns). Overall, the serotypes included in the PCV7 vaccine accounted for 10% (n = 13/130) of infections, and those included in the PCV13 vaccine accounted for 63% of infections (n = 82/130). The distribution of serotypes differed between children aged <2 years and those aged >2 years, with a higher proportion of children aged >2 years presenting infections with serotypes

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Table 1. Epidemiology of the Cases

Characteristics	Pre PCV13 2005–2009		Post PCV13 2010–2011		Total 2005–2011		Total
Age, y	<2	>2	<2	>2	<2	>2	
Demographics							
Total number	82	37	27	17	109	54	163
Sex = F	38	17	13	4	51	20	72
Sex = M	44	20	14	13	58	33	91
Median age (mo)	7	48	6	72	7	55	13
Range (mo)	[1–22]	[24–162]	[2–23]	[37–185]	[1–23]	[24–185]	[1–185]
Type of infection							
Meningitis	73	29	25	15	98	43	142
Pneumonia	3	7	0	1	3	8	11
Bloodstream infection	4	1	0	1	4	2	6
Osteomyelitis/arthritis	1	0	1	0	2	0	2
Mastoiditis	0	0	1	0	1	0	1
Endocarditis	1	0	0	0	1	0	1
Vaccination							
Yes	66	15	22	11	88	26	114
No	15	22	3	6	18	28	46
NA	1	0	2	0	3	0	3
Pneumococcal serotypes							
PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F)	4	8	0	1	4	9	13
1	3	3	0	0	3	3	6
3	3	2	0	0	3	2	5
5	1	0	0	0	1	0	1
6A	2	0	1	0	3	0	3
7F	12	2	4	1	16	3	19
19A	25	5	4	1	29	6	35
Other[a]	18	11	13	5	32	16	48
NA	13	6	5	9	18	15	33
Abnormal results for immunological explorations (N = 162)							
Yea	10	10	1	5	11	15	26
No	55	20	19	7	74	27	101
Incomplete explorations[b]	17	6	7	5	24	11	35

Abbreviations: NA, not analyzed; PCV7, 7-valent pneumococcal vaccine; PCV13, 13-valent pneumococcal vaccine.

[a] Other: three 8, one 9N, two 10A, one 11A, five 12F, three 15B, one 22F, and four 33F (total of 20 included in the 23-valent nonconjugated pneumococcal vaccine); one 6C, one 9F, three 15A, one 15C, four 16F, two 17F, two 21, one 23A, one 23B, five 24F, two 25A, one 31, and four 35B (total of 28 not included in the 23-valent vaccine).

[b] Determinations of immunoglobulin (Ig) G, -A, and -M were missing for 14 patients and IgG subclass data for 8 children aged >2 years; CH50 and AP50 data were missing for 8 patients, AP50 data alone were missing for 2 patients, and IL-6 production data were missing for 5 patients.

included in the PCV7 vaccine (n = 4/91 vs 9/39; $P < .01$). Patients with and without PID were infected equally frequently with nonvaccine serotypes (8/20 vs 39/110; $P = .89$; serotype data were missing for 5 children in the PID group and 28 children in the non-PID group).

Immunology

All immunological explorations were carried out for 127 patients, whereas these explorations were incomplete for 35 patients (Table 1). The patient with the cerebrospinal fluid fistula was excluded from the immunological analysis. Abnormal immunological responses were discovered in 26 children (16%; Table 2). These patients included 17 (11%) displaying a persistent immunodeficiency after age 2 years. One patient displayed impaired IL-6 production in response to TIR agonists. This led to the identification of the first case of MyD88 deficiency in this 11-month-old boy [31]. This patient had previously had ethmoiditis at age 8 months. Low complement levels led to the identification of 3 genetically confirmed complement deficiencies (2 C2 and 1 C3) in children aged 1, 3, and

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Table 2. Primary Immunodeficiencies Identified

Primary Immunodeficiency	Sex	Year	Age	Consan-guinity	History	Infection	Serotype	Vaccinated (Number of Injections)
Innate immunity deficiency								
Asplenia	M	2011	3 y	No	No	Meningitis	12F	No
C2 deficiency	M	2011	11 mo	No	No	Meningitis	24F	No
C2 deficiency	F	2008	3 y	No	No	Meningitis	24F	PCV7 (4)
C3 deficiency	M	2008	7 y	Yes	No	Meningitis	15B	No
MyD88 deficiency	M	2005	11 mo	Yes	Ethmoiditis	Meningitis	19A	No
Antibody deficiency								
XLA	M	2006	4 y	No	Osteoarthritis (*Sp*)	Meningitis	6B	No
XLA	M	2011	7 y	No	Pleuropneumonitis (*Sp*)	Meningitis	NA	No
Hypogammaglobulinemia	M	2008	5 y	Yes	Ethmoiditis	Meningitis	Ag	No
Hypogammaglobulinemia	M	2010	4 y	No	No	Meningitis	NA	PCV13 (1)
Hypogammaglobulinemia	M	2006	9 y	No	No	Meningitis	18C	No
Hypogammaglobulinemia	M	2011	3 y	No	No	Meningitis	NA	PCV13 (NA)
Subclass IgG2 deficiency	F	2005	2 y	Yes	No	Meningitis	19F	PCV7 (3)
Subclass IgG2 deficiency	M	2005	2 y	No	No	Meningitis	17F	No
SPAD	M	2009	22 mo	No	No	Meningitis	7F	PCV7 (4)
SPAD	M	2005	3 y	No	No	Meningitis	14	No
SPAD	M	2005	3 y	No	No	Pleuropneumonitis	1	No
SPAD	M	2008	6 y	No	No	Pleuropneumonitis	1	No
Transient immunoglobulin deficiency								
Hypogammaglobulinemia	F	2007	2 mo	No	No	Meningitis	19A	No
Hypogammaglobulinemia	M	2011	8 mo	No	No	Meningitis	33F	No
Hypogammaglobulinemia	F	2009	14 mo	No	No	Meningitis	12F	PCV7 (4)
Hypogammaglobulinemia	M	2008	14 mo	No	No	Meningitis	23F	No
Hypo IgG2 and IgG4	F	2005	12 mo	Yes	No	Meningitis	19A	No
Hypo IgG2 and IgG4	F	2005	18 mo	Yes	No	Meningitis	6A	PCV7 (2)
Hypo IgG2	M	2005	2 y	No	No	Meningitis	17F	PCV7 (2)
Hypo IgG3	M	2005	20 mo	No	No	Pleuropneumonitis	Ag	PCV7 (3)
Pneumococcal antibody deficiency	F	2005	3 mo	No	No	Meningitis	18C	PCV7 (3)

Abbreviations: Ag, pneumococcal antigen; IgG, immunoglobulin-G; NA, not analyzed; PCV7, 7-valent pneumococcal vaccine; PCV13, 13-valent pneumococcal vaccine; *Sp*, *Streptococcus pneumoniae*; SPAD, specific polysaccharide antibody deficiency; XLA, X-linked agammaglobulinemia.

7 years. Blood smears revealed the presence of Howell–Jolly bodies in a 3-year-old boy with meningitis; isolated congenital asplenia in this patient was confirmed by an abdominal ultrasound scan and splenic scintigraphy.

Twelve children had a primary antibody deficiency: 1 boy aged 7 years and 1 boy aged 4 years had Bruton disease (X-linked agammaglobulinemia [XLA]) with a hemizygous *BTK* mutation; 4 children had hypogammaglobulinemia; 2 had an IgG2 production deficiency; and 4 had a SPAD, established after confirmation of the deficiency following immunization with pneumococcal polysaccharide vaccine. Isolated IgG deficiency was identified in 9 children aged <2 years considered to have "transient IgG deficiency," either because spontaneous correction of the deficiency was observed after age 2 years during follow-up or because these children had not yet been checked. The cases of transient deficiency included 4 children with impaired total Ig production, 1 with impaired IgG2 production, 1 with IgG3 deficiency, 1 child aged 12 months and 1 child aged 18 months with combined IgG2 and IgG4 subclass deficiencies, and a 14-month-old child with both IgG and IgA deficiencies. Finally, 8 children had isolated low levels of IgA production (below the third percentile for age); 6 were aged <1 year and the 2 remaining were aged 2 years and 5 years. These patients were not included in the "abnormal immunological responses" group.

PIDs were more frequently detected in children aged >2 years (14/53, 26%) than in those who were younger (3/109, 3%; $P < .001$). Immunological deficiencies other than those affecting antibodies were rare among children aged >2 years. PIDs were detected more frequently in boys than in girls (15/91 vs 2/71;

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Table 3. Description of Patients With Recurrent Invasive Pneumococcal Disease (N = 17)

Age	Sex	Prior Pneumococcal Infections (Serotype)	Infection Upon Inclusion (Serotype)	Vaccinated (Number of Injections)	Identified Primary Immunodeficiency	Outcome
4 mo	F	Meningitis and cerebral abscess	Meningitis (Ag)	Yes (3)	No	Alive
4 mo	M	Meningitis	Meningitis (6A)	Yes (2)	No	Alive
8 mo	F	Meningitis × 2	Meningitis (14)	Yes (3)	No	Dead
9 mo	M	Meningitis	Meningitis (NA)	Yes	No	Alive
14 mo	F	Maternofetal infection	Sepsis (NA)	Yes (3)	No	Alive
19 mo	M	Meningitis	Meningitis (19A)	Yes	No	Alive
3 y	M	Meningitis (19A)	Meningitis (6B)	Yes (3)	No	Alive
3 y	F	Pneumonitis	Sepsis (7F)	Yes (4)	No	Alive
4 y	F	Pleuropneumonitis	Pleuropneumonitis (Ag)	No	No	Alive
4 y	F	Meningitis	Meningitis (NA)	Yes	No	Alive
4 y	M	Osteoarthritis and maxillary abscess	Meningitis (6B)	No	XLA	Alive
6 y	F	Pleuropneumonitis	Pleuropneumonitis (NA)	Yes	No	Alive
7 y	M	Meningitis (15B)	Meningitis (22F)	Yes (3)	No	Alive
7 y	M	Pleuropneumonitis	Meningitis (NA)	No	XLA	Alive
8 y	*F*	Meningitis *×2(22 F and 9)*	Meningitis *(11A)*	No	No*	*Alive*
10 y	M	Meningitis and arthritis	Meningitis (23A)	No	No	Dead
15 y	M	Meningitis	Meningitis (17F)	No	No	Alive

Abbreviations: Ag, pneumococcal antigen; NA, not analyzed; XLA, X-linked agammaglobulinemia.

* *Cerebrospinal fistula.*

$P < .01$), even when X-linked defects were retrieved. This trend persisted when both transient and permanent deficiencies were considered (20/91 for boys vs 6/71 for girls; $P = .03$). Patients from consanguineous families were more likely to have a PID than patients from nonconsanguineous families (4/10 vs 13/152; $P = .01$). The proportion of patients with detectable PIDs did not differ significantly between the pleuropneumonitis group (2/11) and the meningitis group (15/141; $P = .35$). Finally, the proportion of patients found to have a PID was similar in children hospitalized for their first episode of IPD (15/146) and in children hospitalized for recurrent IPD (2/16; $P = .68$; Table 3).

Follow-up

All children with PIDs underwent rigorous clinical follow-up, every six months, until 2013. Most children with no identified PID (120/145) were followed up for at least one year (108 were followed up for two years). None of the patients died during the follow-up period, and no invasive infection occurred during follow-up in any of the patients from our cohort. Nonetheless, two boys (one with hypogammaglobulinemia and one with hypoIgG1) had more than two episodes of pneumonitis, and one girl with no identified PID had a cutaneous infection complicating chicken pox. In addition, one girl had monthly bouts of fever, requiring antibiotics six times per year, until the age of five years, another had idiopathic thrombocytopenic purpura and a 22-month-old boy developed acute lymphoblastic leukemia revealed by macrophage activation syndrome secondary to pneumococcal sepsis.

DISCUSSION

We provide the first detailed description of the immunological features of children presenting with IPD. All but 17 of the patients were included after an initial episode of pneumococcal infection, meningitis in most cases. Between 2005 and 2008, the incidence of IPD in France was 23/100 000 in children aged <2 years and 5/100 000 in children aged >2 years [35]. During this period, we included 94 children (59 aged <2 years and 35 aged >2 years). These figures are similar to those reported in other developed countries, such as the United States [36], Scotland [37], and Australia [38]. The introduction of conjugated pneumococcal vaccines has reduced the burden of IPD in developed countries, in both vaccinated and unvaccinated populations (due to herd immunity) [39–41]. Routine infant immunization with PCV7 was introduced in France in 2006 [42], and there was a switch to PCV13 in 2010. Vaccination coverage in children aged 2–3 years had reached almost 93% by 2011 [43]. Although not designed for this purpose, our study highlighted a clear impact of pneumococcal vaccination on serotype distribution, with the serotypes included in the PCV7 vaccine accounting for only 10% of the cases of IPD included in this report. This study was, nevertheless, subject to several limitations. First, the noninclusion of some of the children who died made it

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impossible to determine the true proportion of children suffering from IPD with a PID. This proportion may exceed 10%, as the prognosis of IPD might be more severe in children with PIDs. Second, mortality in our cohort (n = 9/162, 6%) was below the 12% overall death rate following IPD in the most active hospitals (those including more than 5 patients; $n = 23/194$; $P = .04$; data not shown) and below the 11% fatality rate after pneumococcal meningitis observed in France between 2001 and 2008 [44]. Third, there was probably an overrepresentation of meningitis and an underrepresentation of sepsis in our cohort because most of the patients were included during/after a stay in a pediatric intensive care unit.

In our study, 10% of children with IPD were found to have a PID, and this proportion reached 26% in children aged >2 years. The main deficiency identified was primary antibody deficiency (12 patients, including 2 XLA patients), followed by innate immunity deficiencies (5 cases, including 2 patients with C2 deficiency, 1 with C3 deficiency, 1 with MyD88 deficiency, and 1 asplenic patient). The C3 and MyD88 deficiencies were identified in patients from consanguineous kindreds. Two other children with primary antibody deficiency and 2 with normal immunological findings were from consanguineous kindreds and are currently the subject of genetic studies based on whole-exome sequencing (WES). PID could have been suspected in 4 patients before the episode of IPD: the 2 patients with XLA had suffered previous episodes of IPD and the patient with MyD88 deficiency had previously had ethmoiditis. For the other 16 children with a history of severe bacterial infection, complete immunological explorations were carried out and the results were normal. WES will be performed for these patients in order to identify new genetic disorders, as in the discovery of many other novel PIDs [45–47, 34]. Eight children from our cohort were found to have low levels of IgA; this proportion (5%, 8/162) is greater than would be expected from findings for the general population (1/600) [48], but the clinical impact of these low levels of IgA on infection status has yet to be determined.

The identification of new genetic etiologies of IPD by WES would provide further evidence that IPD results from a group of single-gene inborn errors of immunity, at least in some children [49, 50]. It would also make it possible to determine the proportion of pediatric IPD cases attributable to human monogenic variants in this cohort of patients. It would, thus, provide fundamental new insight into the genetic basis of childhood IPD at the patient and population levels. This information would enable physicians to provide patients with a molecular diagnosis and their families with genetic counseling. It would also provide a basis for new avenues of treatment. Going beyond IPD, our findings should lead to a paradigm shift in the field of PIDs by providing proof-of-principle that a life-threatening infectious disease striking otherwise healthy patients may actually result from a new group of PIDs, specifically impairing immunity to *S. pneumoniae*. Finally, this new information should pave the way for investigations of the molecular genetic basis of other pediatric infections. In conclusion, we advocate systematic immunological exploration for all children hospitalized for IPD. These explorations should include abdominal ultrasound scans, WBC counts with blood smears, the determination of plasma Ig levels (and IgG subclasses for patients aged >2 years), classic (and alternative) complement pathway analysis, and checking for a traumatic cerebrospinal fistula if the patient has been diagnosed with meningitis, particularly in cases of recurrent meningitis. This would make it possible to detect a nonnegligible number of PIDs and to provide the affected patients with the best preventive treatment available. However, we are fully aware that WES and, in the near future, whole-genome sequencing will prove to be more powerful for both the diagnosis of known genetic etiologies and the discovery of new ones.

Notes

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