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**Investigation of primary immune deficiency after severe bacterial infection in children:
A population-based study in western France**

Short title: Immune investigation after bacterial infection

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Abstract

Background: Infectious diseases are still an important cause of morbidity and mortality in high-income countries and may preferentially affect predisposed children, especially immunocompromised children. We aimed to evaluate the frequency of recommended immunological tests in children with community-onset severe bacterial infection (COSBI) admitted to a pediatric intensive care unit. We also assessed the frequency and described the typology of diagnosed primary immune deficiency (PID).

Methods: We conducted a retrospective observational epidemiological study in six university hospitals in western France. All children from 1 month to 16 years of age admitted to hospital for bacterial meningitis, purpura fulminans, or meningococcal disease between August 2009 and January 2014 were included. We analyzed the frequency, type, and results of the immunological tests performed on children with meningitis, purpura fulminans, or a meningococemia episode.

Results: Among the 143 children included (144 episodes), 84 (59%) and 60 (41%) had bacterial meningitis and purpura fulminans or meningococemia, respectively: 72 (50%) had immunological tests and 8% had a complete immunological investigation as recommended. Among the 72 children examined for PID, 11 (15%) had at least one anomaly in the immunological test results. Two children had a diagnosis of PID (one with C2 deficit and the other with C8 deficit) and seven other children had possible PID. Thus, the prevalence of a definite or possible diagnosis of PID was 12% among the children examined.

Conclusion: PID is rarely investigated after COSBI. We raise awareness of the need for immunological investigations after a severe infection requiring PICU admission.

Keywords: immune deficiency, meningitis, meningococcus, pneumococcus, severe bacterial infectio

1. Introduction

Infectious diseases remain an important cause of morbidity and mortality in high-income countries [1,2], even if the incidence of community-onset severe bacterial infection (COSBI) has decreased in recent decades [3,4]. The occurrence of COSBI has become a rare but life-threatening event that may be promoted by comorbidities, primary or acquired immunodeficiency, or specific genetic susceptibilities [5,6]. Indeed, the occurrence of COSBI relies on bacterial virulence but also on host factors [7,8]. Among the primary immune deficiency (PID) cases associated with increased risk of bacterial infection, conditions such as asplenia, agammaglobulinemia, or early protein deficiency in the classic complement pathway (C1q, C1r, C1s, C2, C4) are known to confer greater susceptibility to infection caused by encapsulated bacteria such as *Neisseria meningitidis*, *Streptococcus pneumoniae*, or *Haemophilus influenzae B* [1,9–11]. Defects in the classic or alternative (e.g., properdin deficiency) complement pathways are associated with recurrent and invasive meningococcal infection [1,3,7–10,12,13].

Previous studies have suggested that PID is often diagnosed after a COSBI episode. Indeed, in up to 80% of patients with complement deficiency, the deficiency was diagnosed after an episode of bacterial (mostly meningococcal) meningitis [10,14]. The results of a recent study also suggested that 19% of PID cases were diagnosed after invasive infection with encapsulated bacteria in a young adult population (18–40 years old) [9].

Prevention measures exist to avoid recurrent and potentially fatal infections in children with immune deficiency [1,3,7,9,10,12,15–21]. Early diagnosis of these diseases has a clinical impact on patients; therefore, clinicians should be attuned to a pre-existing immune deficiency in a child with severe bacterial infection.

French (*Centre de Référence Déficiences Immunitaires Héritaires* [Reference Center for Inherited Immune Deficiencies], CEREDIH) and European (European Society for

Immunodeficiencies, ESID) PID experts have established clinical recommendations to guide clinicians in performing immunological investigations after any episode of COSBI occurring in a child without an obvious comorbidity explaining the infection [22]. According to these guidelines, the first-line immune investigation should include a full blood count (FBC), serum immunoglobulin (Ig) testing, and vaccine serology [23]. In the case of infection caused by encapsulated bacteria, a blood smear to search for Howell–Jolly bodies, abdominal ultrasonography to search for asplenia, and investigation of the complement pathway (C3, C4, CH50, AP50) are also necessary. Systematic investigation of PID after a severe infection has been found to be efficient. In a study of children over 5 years of age and presenting with pneumococcal meningitis, 18% had at least one immunological risk factor (PID or acquired immunodeficiency) [15]. Pneumococcal meningitis occurring in children over 2 years of age was associated with PID in 26% of children in a national French study [12]. A study of 163 children with invasive pneumococcal infection revealed PID in 10% [12]. However, most studies focused on a single condition or a single bacterium. Moreover, data are lacking on the adherence of clinicians to the guidelines concerning immunological tests after an episode of severe bacterial infection in routine practice.

The objective of this study was to evaluate the frequency of investigations for immune deficiency after a diagnosis of COSBI (bacterial meningitis, purpura fulminans, and meningococemia) in a large population of children hospitalized in pediatric intensive care units (PICUs) in western France. Secondary objectives were to evaluate the frequency of PID in the tested population and to characterize the diagnosed PID cases.

2. Patients and methods

2.1. General methodology and population

We conducted a multicenter, descriptive, retrospective epidemiological study including all children from the age of 1 month to 16 years admitted to a PICU or who died before admission to hospital because of community-onset bacterial meningitis (whatever the culprit bacteria), meningococemia, or purpura fulminans. Six PICUs in adjacent administrative French districts participated in the study between August 2009 and January 2014. Children were identified by their inclusion in a larger study of children admitted to a PICU with COSBI in western France [21,24]. The study was reported according to the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) recommendations for reporting observational studies. The protocol of the present study was approved in January 2018 by the local ethics committee (*Groupe Nantais d'Ethique dans le Domaine de la Santé*).

2.2. Data collection

The data collected concerned the characteristics of children (age; sex; family history of PID; vaccine status; past medical history, particularly previous infections; underlying chronic medical conditions), infection characteristics (type of infection, bacteria), and investigation for PID after the COSBI episode. The tests used to investigate a potential PID were those recommended for first-line investigations: FBC; quantitative serum Ig tests (IgA, IgG, and IgM); complement analysis, with C3, C4, and CH50 measurement for all children and properdin for children with meningococcal infection; post-vaccination serology (measurement of antibodies [IgG] against tetanus, diphtheria, polio, and pneumococcus), and abdominal ultrasonography to search for asplenia. Testing for AP50 (alternative pathway of complement) and mannose binding level (MBL; lectin pathway of complement) was not considered part of the first-line investigation. The existence of Howell–Jolly bodies was rarely reported in the medical charts of patients. Because we did not know whether Howell–Jolly bodies were not searched for or whether the search was not reported in the medical file, we did not consider

the lack of mentioning Howell–Jolly bodies as a failure in the clinical investigation. In the case of missing data in the PICU file, the ward where children were hospitalized after their stay in the PICU was contacted for access to the hospitalization and laboratory reports.

2.3. Definitions

Meningitis was defined as clinical signs associated with the identification of a pathogenic bacteria in cerebrospinal fluid (CSF) with standard culture, antigen testing, and/or polymerase chain reaction (PCR) assay. The diagnosis of meningitis was also retained in the case of positive culture in a normally sterile body site associated with CSF pleocytosis. Meningococemia was defined as the identification of *N. meningitidis* in blood with standard culture or PCR assay. Infection due to *N. meningitidis* purpura fulminans could also be documented by a positive PCR assay of a skin specimen. For children with a typical clinical presentation of purpura fulminans, the lack of documentation did not exclude the diagnosis [24,25].

The diagnosis of PID was defined by a heterogeneous group of diseases affecting acquired or innate immunity, leading to susceptibility to infection. According to the International Union of Immunological Societies Expert Committee on PID [26,27], PID was classified according to the affected cells. If an anomaly was detected in one of the first-line immunological tests, additional investigations were performed according to the advice of the local pediatrician specialized in immunology in each center. Finally, abnormal results from the immunological tests (first-line and eventually complementary tests) were all discussed with an expert from CEREDIH to retain or reject the diagnosis of PID.

An anomaly in the first-line immunological investigation was defined by one or several of the following findings, interpreted according to reference ranges for pediatric age groups whenever applicable (FBC and quantitative serum Ig test):

- Leukopenia, neutropenia or lymphopenia on FBC [23]
- Hypogammaglobulinemia defined as decreased level of IgG, IgA, IgM classes or IgG subclass Igs [23]
- Low specific antibody level in serum after vaccination defined as
 - anti-diphtheria IgG level <0.1 kUI/L
 - anti-tetanus IgG level <0.1 kUI/L
 - anti-poliomyelitis IgG level <0.2 kUI/L for type 1 poliovirus and <0.1 kUI/L for type 2 poliovirus
 - an insufficient increase (< threefold the baseline level) in anti-pneumococcal IgG level after vaccination
- No spleen on abdominal ultrasonography
- Complement deficiency defined as a low level of one of the following complement components: C3 level < 800 mg/L, C4 level <150 mg/L, or CH50 level <70%

According to French recommendations, the first-line immunological investigation after COSBI should include FBC, measurement of Ig level in serum, post-vaccination serological tests, abdominal ultrasonography, and complement investigation. The immunological investigation was defined as complete when all the recommended tests were performed and when complementary or control tests that were indicated were performed (e.g., when post-vaccination serology showed low level of antibodies, a booster dose was usually recommended and new serology should be done after a few weeks). If one of the first-line or complementary tests was not performed, the investigation was defined as incomplete.

2.4 Primary and secondary endpoints

Our primary endpoint was the proportion of children for whom PID was properly investigated (complete investigation) after a COSBI episode, that is, the number of children for whom all the recommended tests were performed in the studied population.

Secondary outcomes were the frequency of children with partial investigation for PID and the prevalence of PID in the properly investigated population (i.e., the number of children with PID diagnosed at the time of infection to the number of children with a complete immunological investigation). We also describe the typology of PIDs diagnosed in our population.

2.5. Statistical analysis

Data are described with number (percentages) and 95% confidence intervals (CIs) or median with interquartile range (IQR; first and third quartiles) and were compared using the chi-square or Fisher exact test, as appropriate. Because the study was observational and descriptive, we did not perform any sample size calculation. Statistical tests were performed with STATA v15, with $p < 0.05$ considered statistically significant.

3. Results

3.1. Population

In all, 143 children (144 episodes of COSBI) were admitted to one of the six participating PICUs between August 2009 and January 2014 (54 in center 1, 14 in center 2, 26 in center 3, 18 in center 4, 11 in center 5, and 20 in center 6; one child had two COSBI episodes) (**Fig. 1**). Overall, 86 of the children were boys (60%, 95% CI: 52–68) and the median age was 16.2 months (IQR: 5.8–50.6) (Table 1). Seven children (5%, 95% CI: 1–9) had a previous severe bacterial infection before the COSBI episode studied. One child with meningeal breach had two episodes of pneumococcal meningitis; none of the children were under

immunosuppressive drug treatment or received chemotherapy for cancer. In total, 60 children (41%, 95% CI: 34–50) had purpura fulminans or meningococemia and 84 (59%, 95% CI: 51–67) had meningitis. Among the 74 children with documented meningococcal infection, 62% had infection due to serotype B and 19% to serotype C (**Table 1**). Overall, 18 children died in a PICU at a median age of 14.2 months (IQR: 3–37): nine with meningitis and nine purpura fulminans. The bacteria involved in the fatal infections were documented for 15 children: meningococcus for 10 (three serotype B and five serotype C), pneumococcus for three and group B streptococcus for two.

At the time of the COSBI, 100 children (available information for 142 [70%, 95% CI: 62–78]) and 19 children (available information for 141 [13%, 95% CI: 7–19]) had received at least one dose of 7- or 13-valent (depending on the age and the vaccine schedule at the time) pneumococcal conjugate vaccine and meningococcal C vaccine, respectively. None of the children who received the meningococcal C vaccine had meningococcal C infection. Two children, aged 3 and 11 months, had pneumococcal meningitis due to vaccinal serotypes despite being vaccinated. The first child had an MBL below the normal value and the second child had a partial complement deficiency in C2 (patients 3 and 5, **Table 2**).

3.2. Frequency of immunological investigations

Among the 143 children included, 72 (50%, 95% CI: 42–59) were examined for PID with first-line tests, 12 (8%, 95% CI: 3–13) with complete and 60 (42%, 95% CI: 34–50) incomplete immunological investigations (**Table 3**). Post-vaccination serology testing and abdominal ultrasonography were performed for less than 50% of the 72 children. In total, 46 of 72 children (64%, 95% CI: 53–75) examined had lymphocyte subset analysis, which is not recommended among the first-line tests.

Three of the children not investigated for PID were born prematurely: two had a cardiac congenital malformation and one had an anatomic predisposition to meningitis (meningeal breach), with two episodes of pneumococcal meningitis. The seven children with a severe infectious episode before the COSBI episode under study had not previously been examined for immune deficiency: One died and one had severe sequelae at PICU discharge. An immunological investigation was rarely performed for children who died (4/18, 22%, 95% CI: 0–44).

The proportion of children with an immunological investigation varied significantly among centers, from 16% to 76% ($p=0.002$). The probability of undergoing an immunological investigation also significantly differed between children depending on the documented bacteria, with the highest probability for children with pneumococcal meningitis (67%) and those with documented bacteria other than *N. meningitidis*, *S. pneumoniae* or Group B streptococcus (100%) (**Table S1**). Children who were investigated tended to be younger than those not investigated (median age 1 year and 2.3 years, respectively, $p=0.07$). The diagnosis (purpura or meningococemia versus meningitis) did not change the probability of undergoing an immunological investigation.

3.3. Prevalence of PID and description of diagnosed PIDs

Among the 72 complete and incomplete investigations, 11 yielded one or more abnormal results. The prevalence of anomaly in the immunological investigations was 15% (95% CI: 7–23). Of the 72 children investigated for PID, the diagnosis of PID could be confirmed in two (3%, 95% CI: 0–7), was suspected in seven (10%, 95% CI: 2–18), and was ruled out for two patients (3%, 95% CI: 0–8) (**Table 3**). The prevalence of definite or possible PID among the examined children was thus 12% (95% CI: 4–20).

Among the two children with confirmed PID diagnosis, one had homozygote deficiency in C2 complement with normal C3 and C4 levels and undetectable (0%) CH50 (total hemolytic complement). Genetic analysis revealed a 28-bp deletion on exon 6 of the C2 gene. The second child had C8 deficiency with normal C3 and C4 levels, undetectable CH40, and low serum C8 antigen level (36%). The diagnosis was confirmed by genetic analysis, finding a rare variant, c.1105+1G>A, in *C8B*.

Among the seven children with possible PID, one had athymia and lymphopenia, in the context of cardiac surgery and investigations were incomplete; two had incomplete investigations and had died; and three had hypogammaglobulinemia without control of the immunoglobulin level. One child had a partial deficit in C2. There was no available genetic analysis for this child to confirm this deficit (**Table 2**).

Among the two children with abnormal results without PID, one had moderate hypogammaglobulinemia and meningeal breach considered responsible for the infection. One had MBL deficiency. After discussion with the CEREDIH, this anomaly was not considered to be PID because it is present in 15–30% of healthy and asymptomatic individuals.

4. Discussion

In this population-based study in western France, PID was rarely investigated after an episode of COSBI requiring admission to a PICU, with only 50% of children investigated. When PID was investigated, the investigation was rarely complete: Only 8% of the immunological investigations performed were in accordance with national recommendations (CEREDIH) [23]. However, when immunological tests were performed, anomalies were detected in 11 of 72 (15%) children admitted with meningitis, meningococemia, or purpura fulminans, and a possible or definite diagnosis of PID was made in 12%. Among the children showing anomalies in immunological test results, two (3%) had a diagnosis of PID, one had

homozygote deficiency of C2 complement, and one had a C8 complement deficiency. The diagnosis of PID could not be confirmed owing to incomplete investigations in seven (10%) children; the diagnosis was ruled out in the two other children (3%).

The prevalence of immunological disorders we found was lower than that previously described: from 10% to 20% depending on the deficit [9,10,12,15]. The non-systematic and often incomplete immunological investigations in the present study may have led to under-diagnosis. Failure to perform splenic ultrasonography in more than half of the reports could have impeded the diagnosis of asplenia. Moreover, the ultrasonography performed did not always include Doppler analysis, which allows functional asplenia to be evaluated. The search for Howell–Jolly bodies was rarely reported, but it is a simple and discriminating test used to diagnose or rule out asplenia, particularly when abdominal ultrasonography does not reveal an ectopic spleen. The complement analysis performed in only 68% of cases may also have led to underestimating the prevalence of complement deficits found in up to 80% of children after type Y meningococcal sepsis [10].

In addition, PID was rarely investigated for children who died, but these children may be more likely to have PID. In fact, death due to bacterial infection is more frequent in children with PID than in immunocompetent children [5]. Immune test results can be affected by infection. For example, complement analysis and blood cell counts may be low owing to consumption related to the immune response. When the child dies, these tests cannot be controlled and may lead to an uncertain diagnosis.

Mahlaoui et al.[28] also assumed an underestimation of the prevalence of PID in France, in part because patients are not systematically referred to an immunology specialist after a COSBI episode. We observed a significant variation in the frequency of immune investigations among centers. This finding could reflect differences in care pathways and care supply (some centers may not be able to offer consultation with an immunology specialist,

and the organization of consultations in another center may complicate the care pathway). However, these differences among centers may also reflect differences in the level of awareness among clinicians of the importance of a timely diagnosis of PID. In France, recommendations concerning the search for PID indicate investigating PID with warning signs such as recurrent infection or severe bacterial infection. A recent US study proposed a statistical model to generate data on risk management and probability of PID [20] by using the 10 warning signs (including two or more severe infections such as septicemia) and neonatal screening for severe combined immune deficiency (SCID). An integration of screening for SCID with the Guthrie test in France is under study [29], but this test detects only SCID and not all PIDs, and thus vigilance regarding COSBI in children is still needed.

Our results suggest that the documented bacteria may affect the decision for immunological investigation. Overall, 67% of children with pneumococcal meningitis were tested as compared with only 14% of children with Group B streptococcus. This situation may be due to the Group B streptococcus infections concerning neonates, who, because of the immaturity of their immune system, are considered more susceptible to infection than are older children. Nevertheless, Group B streptococcal infection does not affect all colonized neonates, which supports the hypothesis of individual immunological or environmental factors conferring increased risk of infection in these children [30]. By contrast, children who were not examined tended to be older than examined children, and thus clinicians may consider that the probability of diagnosing PID might be lower in older than in younger children. However, studies of adults have shown that PID could be diagnosed even after childhood [6].

This study has some limitations. First, its retrospective nature may have led to missing data. For example, vaccination dates were not available, which may have limited the interpretation of post-vaccination serological testing. Moreover, we have little information on

the search for Howell–Jolly bodies in the results of immunological tests, but we were not able to determine whether this search was not done or was simply not mentioned in the results. Furthermore, the children were hospitalized in a PICU at the time of infection but were then transferred to another ward in the same center or in another hospital. When data were not available in the PICU chart and children were transferred to another hospital, we contacted the wards where children were transferred to collect data concerning immunological tests, but some children may have been examined later out of the hospital. Second, the prevalence of PID may have been underestimated because immunological testing was not systematically performed and not complete. Third, we focused on children with meningitis and meningococemia and not all children admitted to a PICU with COSBI. This situation may have led to underestimating the prevalence of PID diagnosed after any COSBI. Nevertheless, some of the children admitted to a PICU with COSBI could have pyelonephritis or intra-abdominal infections that may be associated with anatomical rather than immunological predisposition. Children with meningitis and meningococemia may be more likely to have PID than children with pyelonephritis, which would have justified systematic immunological tests. Finally, we do not have long-term follow-up data for the included children to determine whether the severe infections recurred.

5. Conclusion and perspectives

This study reveals a lack of systematic investigation for PID after a COSBI. The results of this study should sensitize physicians and pediatricians caring for children with COSBI to the importance of immunological tests after an episode of severe infection whatever the bacteria and the age of the child. Early diagnosis of PID may lead to specific prevention and avoid further infection. When children die, diagnosing PID may be important for siblings. The first-line test can be prescribed by any pediatrician and should include FBC, quantitative testing

for serum Ig (IgA, IgG and IgM), analysis of the complement pathway (C3, C4, CH50), post-vaccination serological tests, blood smear to search for Howell–Jolly bodies, and abdominal ultrasonography to search for asplenia. Moreover, a complete analysis of complement with an alternative (AP50, properdin) and lectin (MBL) should also be performed in the case of COSBI due to encapsulated bacteria. The results of these first-line tests as well as the relevance of complementary tests should be discussed with an immunology specialist. Moreover, in children who died due to COSBI, blood samples should be systematically collected for genetic analysis because results of immunological tests are difficult to interpret at the very acute stage of infection and cannot be controlled afterwards.

Declaration of Conflict of Interest

The authors declare no conflicts of interest.

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Table 1. Characteristics of the 143 children (144 episodes) with bacterial meningitis, purpura fulminans, or meningococemia admitted to a pediatric intensive care unit in western France from August 2009 to January 2014.

	Effective (N=143) ^a
Sex, n (%) [95% CI]	
Male	86 (60) [52–68]
Female	58 (40) [32–48]
Age (months), median (IQR)	16.2 (5.8–50.6)
Comorbidities, n (%) [95% CI]	
Congenital malformation	5 (3) [0–6]
Prematurity	6 (4) [1–7]
Warning signs compatible with potential immune deficiency, n (%) [95% CI]	
Previous severe infection ^b , n (%) [95% CI]	7 (5) [1–9]
Delayed separation of the umbilical cord	5 (3) [1–7]
Severe atopic dermatitis	2 (1) [0–3]
Recurrent otitis	14 (10) [5–15]
Growth retardation, n (%) [95% CI]	3 (2) [0–4]
Diagnosis, n (%) [95% CI]	
Purpura fulminans or meningococemia ^c	60 (41) [34–50]
Meningitis	84 (59) [51–67]
Bacteria, n (%) [95% CI] (N=144)^a	
<i>Neisseria meningitidis</i>	74 (51) [43–59]
B	46 (62) [51–73]
C	14 (19) [10–28]
W135	1 (1) [0–3]
A	1 (1) [0–3]
X	1 (1) [0–3]
Y	1 (1) [0–3]
<i>Streptococcus pneumoniae</i>	30 (21) [14–28]
Group B streptococcus	7 (5) [1–9]
<i>Escherichia coli</i>	2 (1) [0–3]
<i>Haemophilus influenzae</i> (non-B serotype)	1 (1) [0–3]
Group A streptococcus	1 (1) [0–3]
Not identified ^d	29 (20) [13–27]
Health outcome, n (%) [95% CI]	
Survival without sequelae	110 (77) [70–84]
Survival with sequelae	16 (11) [6–16]
Death	18 (13) [7–19]

95% CI, 95% confidence interval, IQR: interquartile range

a One child had two episodes of pneumococcal meningitis

b Meningitis (n=2), pneumonia (n=2), pyelonephritis (n=1), septicemia (n=1), abscess (n=1)

c Eight children had both purpura and meningitis

d Nine cases of purpura fulminans and 17 meningitis

Table 2. Description of children with abnormal result(s) for the immunological investigations performed after community-onset severe bacterial infection (SBI) (*n*=11)

Patient no.; age	Comorbidity	SBI type	Anomaly of the investigation	Diagnostic of PID	Evolution
1; 15 y	Tympanic-vestibular meningeal breach	Pneumococcal meningitis (3 episodes)	Hypogammaglobulinemia (IgG: 5.6 g/L)	No	Survival without sequelae, IgG level normalized
2; 18 m	Cleft palate, aortic valve stenosis	Meningitis with unidentified bacteria	Lymphopenia T CD8 (350/ μ L) and athymia	Possible, incomplete investigation	Survival without sequelae, antibiotic prophylaxis with cotrimoxazole
3; 11 m	None	Pneumococcal meningitis	Heterozygous deficit in mannose-binding lectin	No	Survival without sequelae
4; 3 y	None	Pneumococcal meningitis	Hypogammaglobulinemia (IgG: 0.29 g/L)	Possible, incomplete investigation	Death
5; 3 m	None	Pneumococcal meningitis with bifrontal empyema	Partial deficit in C2 (10 mg/L then 8 mg/L), normal C3, C4 and CH50	Possible, no genetic analysis	Survival without sequelae
6; 2 y	Juvenile arthritis, chronic cough, respiratory allergy	Pneumococcal meningitis	Homozygous deficit in C2, reduced CH50, C3 and C4 normal	Confirmed, homozygous deficit in C2	Perception deafness, placement of cochlear implant
7; 13 m	Recurrent rhinopharyngitis	Meningococcal B meningitis	Hypogammaglobulinemia (IgG2: 0.42 g/L), no tetanus, poliovirus and diphtheria immunity	Possible, incomplete investigation	Survival without sequelae
8; 4 y	Suspected Bart syndrome with dilated cardiomyopathy	<i>Haemophilus influenzae</i> type B meningitis	Hypogammaglobulinemia (IgG: 5 g/L and IgA to 0.41 g/L)	Possible, IgG level control not available	Survival without sequelae
9; 4 m	None	Pneumococcal meningitis	Hypogammaglobulinemia (IgG: 2.0 g/L, normal IgA, IgM: 0.71 g/L) and lymphopenia (LT CD4: 500/mm ³ , LT CD8: 133/mm ³)	Possible, incomplete investigation	Death
10; 7 y	No	Purpura and meningitis, unidentified germ	C8 deficiency, C3 and C4 normal and CH50 low level	Confirmed, C8 deficiency	Survival without sequelae
11; 2 y	No	Pneumococcal meningitis	Hypogammaglobulinemia (IgG4: 0.004 g/L)	Possible, incomplete investigation	Survival without sequelae

Ig: immunoglobulin; LT: T lymphocytes, m: months, PID: primary immunodeficiency; y: years

Table 3. Immunological investigations performed

Explorations	Immune explorations performed, (%) [95% CI], N=72	Abnormal explorations, n (%), [95% CI]
Full blood count	72/72(96) [91–100]	1/72 (1) [0–3]
Post-vaccination serology	35/72(49) [37–61]	3/35 (9) [0–18]
Complement exploration*	48/72(67) [56–78]	2/48 (4) [0–10]
Properdin	1/72(1) [0–3]	0/1
Lymphocyte sub-population	46/72(64) [53–75]	2/46 (4) [0–10]
Immunoglobulin exploration	58/72(81) [72–90]	10/58 (17) [7–27]
Splenic ultrasonography	29/72(40) [29–51]	0/29

*C3 complement fraction, C4 complement fraction, CH50, hemolytic complement 50

Figure

Figure 1: Flowchart of study participants.

PICU: pediatric intensive care unit; SBI: severe bacterial infection; PID: primary immunodeficiency

Children with a community SBI admitted to a PICU
in western France between 2009 and 2014
N=261 (262 episodes of infection)

Children with an SBI other than meningitis,
purpura fulminans, meningococemia N=119

Children with meningitis, purpura fulminans or
meningococemia N=143 (144 episodes of
infection)

Immune investigation not performed
N=72 with 14 deceased children

Immunological investigation performed
N=72

Incomplete investigation
N=60

Complete investigation
N=12

No anomalies
N= 49

Anomalies but no PID
N= 2

Possible PID
N= 7

PID
N=2

No PID
N=12