International Journal of Infectious Diseases 19 (2014) 79–84

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Immunoglobulin deficiency in patients with *Streptococcus pneumoniae* or *Haemophilus influenzae* invasive infections

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ARTICLE INFO

Article history:
Received 25 June 2013
Received in revised form 30 October 2013
Accepted 31 October 2013

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Immunoglobulin deficiency
Streptococcus pneumoniae
Haemophilus influenzae
Invasive infections
Clinical study

SUMMARY

Objectives: Immunoglobulin (Ig) deficiency is a well-known risk factor for *Streptococcus pneumoniae* or *Haemophilus influenzae* infections and noteworthy invasive diseases. However, the proportion of these deficiencies in cases of invasive disease is unknown. The objective of this study was to evaluate the rate of Ig deficiency in cases of invasive disease.
Methods: A prospective study was conducted from January 2008 to October 2010 in two French hospitals. Measurement of Ig levels was carried out in patients hospitalized for invasive diseases.
Results: A total of 119 patients were enrolled in the study, with nine cases of *H. influenzae* and 110 cases of *S. pneumoniae* invasive disease. There were 18 cases of meningitis, 79 of invasive pneumonia, and 22 other invasive diseases. Forty-five patients (37.8%) had an Ig abnormality, 37 of whom had an Ig deficiency (20 IgG <6 g/l, four isolated IgA <0.7 g/l, and 13 isolated IgM <0.5 g/l), while eight had an elevated monoclonal paraprotein. Nineteen of these 45 patients had a clearly defined Ig abnormality, with five primary deficiencies (three common variable immunodeficiencies and two complete IgA deficiencies) and 14 secondary deficiencies, mainly lymphoproliferative disorders. All these deficiencies were either not known or not substituted.

1. Introduction

Streptococcus pneumoniae and *Haemophilus influenzae* infections are classically divided into noninvasive forms (sinusitis, acute otitis media, and pneumonia) and invasive disease, i.e., infections with isolation of the organism from a normally sterile site, especially bacteremic pneumonia and meningitis.[1] Invasive diseases are less frequent than pneumonia, although their mortality rates and sequelae are higher. In the USA, there were 43 500 cases of *S. pneumoniae* invasive disease and 5000 attributable deaths in 2009.[1] In France, before the introduction of the heptavalent vaccine, there were approximately 6700 pneumococcal invasive diseases each year, with an incidence rate of 11.4/100 000 inhabitants, and meningitis accounted for about 10% of these invasive diseases.[2] With the introduction of the heptavalent pneumococcal vaccine and routine immunization for *H. influenzae*, France, like other countries, experienced a decrease in invasive diseases in children younger than 2 years of age, while the incidence rates in older patients increased.[2,3]

The mortality rates and incidence of *S. pneumoniae* and *H. influenzae* infections are related to bacterial virulence factors, the serotypes of *S. pneumoniae*, and also, most importantly, to host factors.[4] Numerous co-morbidities such as chronic bronchitis, heart disease, hypertension, diabetes mellitus, asthma, chronic liver disease, chronic renal failure, autoimmune disease, extreme age, malignancies, immunosuppression, and modifiable risk factors such as regular cigarette smoking, alcohol consumption,

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http://dx.doi.org/10.1016/j.ijid.2013.10.020

and elevated body mass index, have been reported for *S. pneumoniae* and *H. influenzae* invasive diseases.[4–6] Immunosuppression, splenectomy, HIV infection, and particularly humoral or combined immune deficiencies are also important risk factors.[7,8] Recommendations vary according to the country, although immunoglobulin (Ig) determination is advised as a first-line test to evaluate humoral deficiency in cases of meningitis[9] or repeated *H. influenzae* or *S. pneumoniae* infections.[10] However, very few studies have focused on the rates of this deficiency in cases of *S. pneumoniae* and *H. influenzae* infection. In an earlier study in 1994, Ekdahl et al. reported that Ig deficiency was frequently observed in cases of pneumococcal bacteremia.[11] In this study we examined Ig levels in patients hospitalized for *S. pneumoniae* and *H. influenzae* invasive diseases, with the aim of evaluating the rate of Ig deficiency in cases of invasive disease.

2. Patients and methods

This prospective study was conducted at one general hospital and one university hospital in Alsace in northeastern France: Hôpital Civil de Colmar in Colmar and the Nouvel Hôpital Civil in Strasbourg. Patients were enrolled into the study between January 2008 and October 2010. The subjects were eligible if they had *S. pneumoniae* or *H. influenzae* invasive disease, defined as isolation of *S. pneumoniae* or *H. influenzae* in blood cultures, cerebrospinal fluid, a deep abscess, or normally sterile biological fluids (pleural, peritoneal, or synovial fluid). In the case of invasive disease, the practitioner in charge of the patient was asked to measure the Ig levels (plasma protein electrophoresis (PPE), IgG, IgA, and IgM). Patients without Ig determination were excluded. The study was approved by the local ethics committee (Strasbourg Ethics Committee "Comité de Protection des Personnes EST IV").

After enrollment into the study, data were collected from the patient's medical records: age, gender, past medical history, reason for hospitalization, date of microbiological specimen collection, date of Ig determination, and outcome during hospitalization (fatal or not). In cases with Ig abnormalities, no specific examinations were scheduled, but an etiologic diagnosis after hospitalization was sought from the patient's medical records or after contact with the practitioner in charge of the patient in order to diagnose a primary or secondary humoral deficiency.[12–15]

2.1. Immunoglobulin analysis

We carried out PPE, IgG, IgM, and IgA assays, with IgG, IgA, and IgM analyzed according to standard methods in the biochemistry departments of the two hospitals. The nephelometric dosage assay (international CRM 470) was used to measure Ig levels, while either electrophoresis on agarose gels (Hyrasis, Sebia) or capillary electrophoresis (Capillaries kit B1–B2+, Sebia) were used for PPE.

Immunoglobulin abnormalities were defined either as a measurable paraprotein peak or a low Ig level, defined as follows for adult patients >15 years of age: IgG <6 g/l, IgA <0.7 g/l, and IgM <0.5 g/l. For children <15 years of age, the reference intervals were those given by the manufacturer. Immunoglobulin values lower than the thresholds were classified as zero for the calculations. In cases of monoclonal gammopathy with a measurable paraprotein peak, an estimation of residual functional gamma-globulin was calculated using the PPE results by subtracting the value of the measured peak from the value of total gamma-globulins.

2.2. Statistical analysis

Comparisons were performed using the Wilcoxon–Mann–Whitney, Kruskal–Wallis, or Chi-square test, as appropriate. Differences were considered statistically significant at p-values ≤ 0.05. The statistical analyses were performed using StatXact 9 (Cytel Studio, Cambridge, MA, USA).

3. Results

3.1. Demographic and clinical characteristics of the study population

A total of 279 patients were hospitalized for *S. pneumoniae* or *H. influenzae* invasive disease between January 1, 2008 and October 31, 2010. One hundred and sixty of these patients were excluded from the study because of an absence of Ig determination. The remaining 119 patients were included in the study: 57 females and 62 males. The mean age of the patient cohort was 58.5 years; 10 children aged <15 years were included in the study.

The following classical risk factors were identified from the patient records: HIV infection ($n = 2$), solid organ graft ($n = 3$), chronic obstructive pulmonary disease (COPD; $n = 12$), asthma ($n = 7$), cirrhosis ($n = 7$), diabetes ($n = 18$), solid tumors ($n = 15$), renal insufficiency ($n = 6$), cardiac insufficiency ($n = 5$), ischemic cardiopathy ($n = 16$), stroke ($n = 5$), smoking ($n = 29$, eight of whom had quit), and alcoholism ($n = 16$, one of whom had stopped drinking). Two cases of bacteremic pneumonia occurred during a proven H1N1 influenza infection.

Nine patients had *H. influenzae* and 110 had *S. pneumoniae* invasive disease. Eighteen patients had meningitis, 79 patients had invasive pneumonia (74 cases of bacteremic pneumonia and five cases of pneumonia with *S. pneumoniae* isolated from pleural fluid), and 22 patients had other invasive infections. Patients with meningitis and other infections were younger than patients with invasive pneumonia: mean age 45 and 52 years vs. 63 years, respectively ($p = 0.02$).

Seventeen of the 119 patients (14.3%) with invasive disease died; the highest mortality rate occurred in patients with meningitis (33.3%), followed by patients with other invasive diseases (22.7%) and then by invasive pneumonia (7.6%). The mean age of adult patients who died was 70.3 years (range 30–95 years) vs. 62.2 years (range 18–95 years) in adults with a favorable outcome. No deaths occurred in the children. One patient with *H. influenzae* invasive disease died, while 16 patients with *S. pneumoniae* invasive disease died.

The characteristics of the 119 patients are summarized in Table 1.

3.2. Immunoglobulin levels

Immunoglobulin levels (IgG, IgM, IgA, and PPE) were determined at a median of 4 days after bacteria isolation (range 0–214 days). Overall (adults and children) mean values were: IgG 11.27 g/l (range 1.31–44 g/l), IgA 2.59 g/l (range 0–10.1 g/l), and IgM 0.96 g/l (range 0–5.93 g/l). Adult mean values were: IgG 11.32 g/l (range 1.31–44 g/l), IgA 2.67 g/l (range 0–10.1 g/l), and IgM 0.96 g/l (range 0–5.93 g/l) (Table 1).

Patients (both adults and children) with meningitis and other infections had significantly lower serum levels of IgG and IgA than patients with invasive pneumonia: IgG 8.54 g/l and 9.3 g/l vs. 12.43 g/l ($p = 0.05$), and IgA 1.37 g/l and 2.51 g/l vs. 2.88 g/l ($p = 0.02$), respectively. These lower levels did not reach statistical significance in the adult patients. The levels of IgM were similar in the three groups. The data are summarized in Table 2 and Figure 1.

Mean Ig levels in patients who died were 11.6 g/l for IgG, 2.58 g/l for IgA, and 0.98 g/l for IgM, and were not statistically different from levels in patients with a favorable outcome (11.4 g/l, 2.68 g/l, and 0.95 g/l, respectively).

Table 1
Clinical data and immunoglobulin values (g/l) in patients with *Streptococcus pneumoniae* or *Haemophilus influenzae* invasive disease

	Total invasive disease (N = 119) 109 adults and 10 children (age < 15 years)
Age, years, mean (range)	58.5 (5 months to 95 years)
Sex ratio	62 male/57 female
Type of infection, *n* (%)	
Pneumonia	79 (66.4%)
Meningitis	18 (15.1%)
Other Infections	22 (18.5%)
Arthritis	2
Bacteremic otitis/sinusitis	3
Bacteremic endometritis	4
Primary peritonitis	2
Miscellaneous[a]	2
Primary bacteremia	9
Mortality rate, *n* (%)	17 (14.3%)
IgG, g/l, mean (range)	11.27 (1.31–44)
IgA, g/l, mean (range)	2.59 (0–10.1)
IgM, g/l, mean (range)	0.96 (0–5.93)
Immunoglobulin abnormalities, *n* (%)	45/119 (37.8%)
Low IgG[b]	20/119 (16.8%)
Isolated low IgA[b]	4/119 (3.4%)
Isolated low IgM[b]	13/119 (10.9%)
Quantified monoclonal gammopathy	8/119 (6.7%)
Defined humoral deficiencies, *n* (%)	19/119 (16%)
Primary deficiency[c]	5/119 (4.2%)
Secondary deficiency[d]	14/119 (11.8%)

[a] One endocarditis and one vascular prosthesis infection.
[b] Low adult levels: IgG <6 g/l, IgA <0.7 g/l, IgM <0.5 g/l. Low values in children are less than the reference intervals.
[c] Three cases of common variable immunodeficiency (CVID) and two cases of complete IgA deficiency.
[d] Six cases of myeloma, two unexplored monoclonal gammopathy (MGUS), four other lymphoproliferative disorders, one patient undergoing chemotherapy, and one case of severe anorexia nervosa.

3.3. Humoral deficiencies

Forty-five patients (37.8%) had an immunoglobulin abnormality; 37 had Ig deficiencies and eight had normal or elevated immunoglobulin rates but with an elevated paraprotein level (quantified monoclonal gammopathy peak). One 14-month-old girl had an Ig deficiency that was an isolated partial IgA deficiency. All other deficiencies occurred in adults: 20 of the 109 adults (18.3%) had an IgG value <6 g/l, isolated or associated with a low IgA or IgM; three (2.75%) had an isolated IgA value <0.7 g/l; and 13 (11.9%) had an isolated low IgM <0.5 g/l. Twenty-six Ig deficiencies did not have a determined etiology. Only 19 patients had a clearly defined Ig abnormality: five cases of primary deficiency (three cases of common variable immunodeficiency (CVID) and two complete IgA deficiencies) and 14 cases of secondary deficiency (six myeloma, two unexplored monoclonal gammopathy (MGUS), four other lymphoproliferative disorders (chronic lymphocytic leukemia/low-grade lymphoma), one patient undergoing chemotherapy, and one patient with severe anorexia nervosa). Of the 12 secondary hematological deficiencies, eight diseases were known previously but had not been treated with Ig replacement, while four diseases were discovered during the study. Of the two patients with a secondary non-hematological deficiency, the causative disease was known but not the humoral deficiency. For the eight patients with normal or high Ig values and a gammopathy peak, the gamma-globulin levels were either normal or elevated in relation to the monoclonal Ig, although the estimated residual functional Ig showed a pronounced gamma-globulin deficiency with a mean residual total Ig functional level of 3.7 g/l (range 1.1–7.9 g/l). These data are summarized in Table 1. A small number of patients had experienced invasive disease before 2008 or recurrent infections consistent with *S. pneumoniae* or *H. influenzae* infection (pneumonia, sinusitis, or otitis). Of the 74 patients with normal Ig values, three developed recurrent infections, while among the 45 patients with abnormal Ig values, two had developed *S. pneumoniae* or *H. influenzae* invasive disease previously (one CVID and one idiopathic low IgG) and four patients had recurrent infections (one CVID, two myeloma, and one idiopathic low IgM).

4. Discussion

Immunoglobulins play a crucial role during *S. pneumoniae* or *H. influenzae* infection via opsonization or inhibition of toxins. An Ig deficiency exposes patients to numerous infections, particularly those caused by *S. pneumoniae* or *H. influenzae*,[8] although there are only limited data on the frequency of Ig deficiencies in *S. pneumoniae* and *H. influenzae* invasive diseases. This study showed a high rate of Ig abnormalities in patients with invasive *S. pneumoniae* or *H. influenzae* infection hospitalized in the Colmar and Strasbourg hospitals from January 2008 to October 2010.

4.1. Immunoglobulin levels according to invasive diseases and outcome

Invasive diseases occurred mainly in adults (91.6%) and were mostly due to *S. pneumoniae* (91.6%). Patients with meningitis or other invasive diseases were younger and had lower IgG and IgA levels than patients with invasive pneumonia. These lower Ig levels may reflect the role played by Ig in meningitis and eventually other invasive diseases; in cases with a low rate this may participate in inadequate lowering of bacteremia or bacterial load, which experimentally appears to correlate with meningitis.[16] Mortality in invasive disease patients in the present study was high (14.3%) and similar to that reported by the US Centers for Disease Control and Prevention (CDC) in 2010.[1] These findings reflect the severity of these invasive diseases, with meningitis and other invasive diseases having a higher mortality than invasive pneumonia. However, Ig levels did not differ between survivors and non-survivors.

Table 2
Comparison of age and immunoglobulin levels in patients with *Streptococcus pneumoniae* or *Haemophilus influenzae* meningitis, invasive pneumonia, and other invasive infections[a]

	Meningitis (n = 18) 14 adults 4 children (age 1 month to 1 year)	Pneumonia (n = 79) 74 adults 5 children (age 1–14 years)	Other (n = 22) 21 adults 1 child (age 7 years)	p-Value
Age, years	45 (5 m–89 y)	63 (1–95 y)	52 (9 m–94 y)	0.02
IgG, g/l	8.54 (1.31–20.6)	12.43 (1.36–44)	9.30 (2.25–22.9)	0.05
IgG, g/l, adults >15 years	9.58 (1.31–20.6)	12.31 (1.36–44)	9.45 (2.25–22.9)	NS
IgA, g/l	1.37 (0–3.57)	2.88 (0–10.1)	2.51 (0–6.36)	0.02
IgA, g/l, adults >15 years	1.60 (0–3.57)	2.88 (0–10.1)	2.60 (0–6.36)	NS
IgM, g/l	0.86 (0–2.43)	0.97 (0–5.93)	1.01 (0–3.24)	NS
IgM, g/l, adults >15 years	0.85 (0–2.43)	0.96 (0–5.93)	1.02 (0–3.24)	NS

NS, not significant.
[a] Results are given as the mean (range).

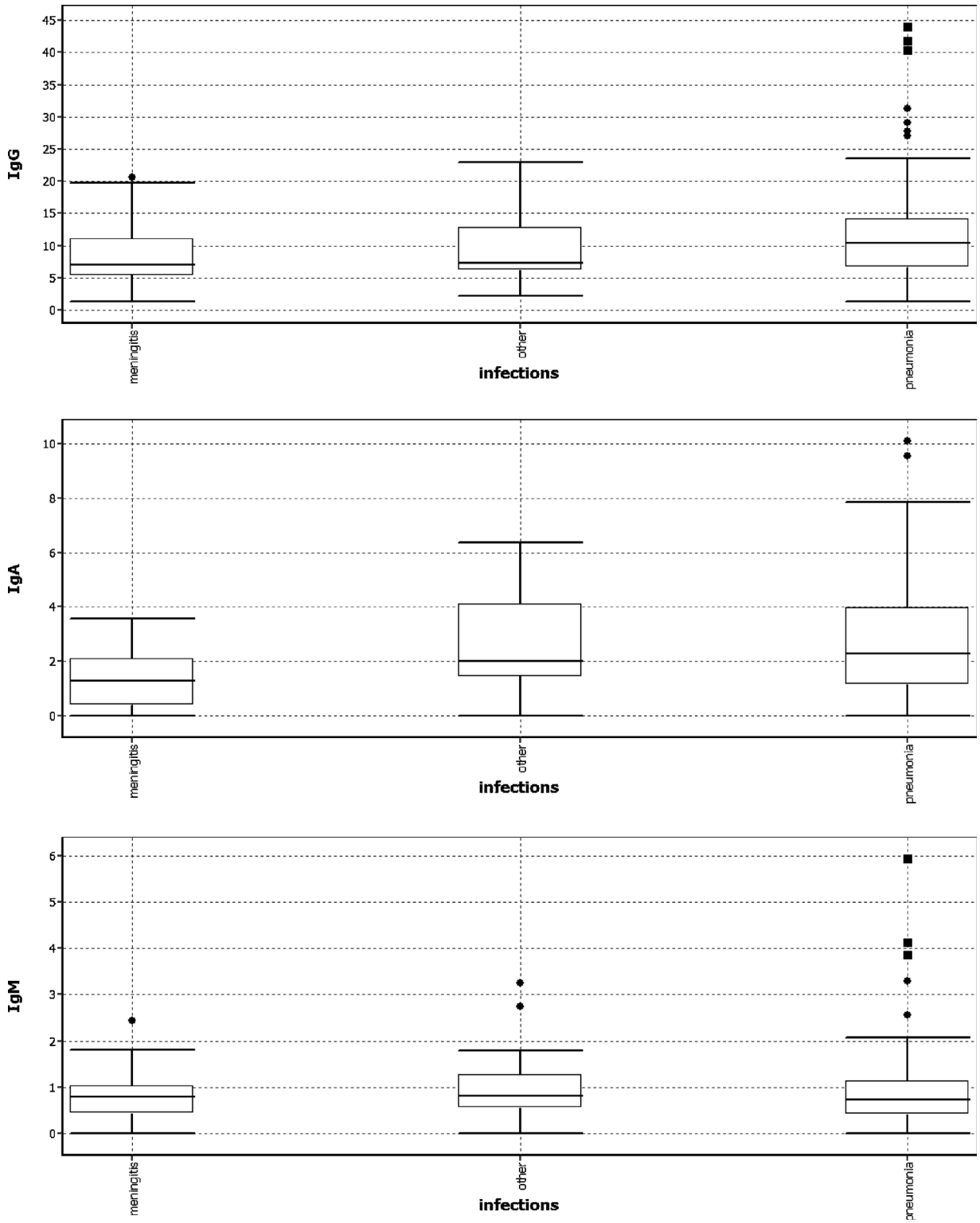

Figure 1. Immunoglobulin values (IgG, IgA, and IgM; g/l) among patients with *Streptococcus pneumoniae* or *Haemophilus influenzae* meningitis (left box), other infections (middle box), and invasive pneumonia (right box). Each box is bisected by a line representing the median value. The vertical lines (whiskers) represent the ranges of the values. Whiskers extend to the most extreme values within 1.5 interquartile range (IQR). Mild outliers (within 3 IQR) are shown with points, and extreme outliers with squares.

4.2. Immunoglobulin deficiencies

We found a high rate of Ig abnormalities, with 45 of the 119 (37.8%) patients having an abnormal Ig and 20 of the 109 adult patients having a low IgG level (18.3%). These proportions, although high, are lower than those reported by Ekdahl et al.[11] All but one of these deficiencies occurred in adults, although children were under-represented in our study, probably because of vaccination protection in developed countries. The only deficiency we observed in children was a partial IgA deficiency in a 1-year-old girl with *H. influenzae* meningitis. However, it is probable that her IgA level may subsequently have risen to a normal level.[17] Of the 19 patients with a defined etiology, there were only five cases of primary deficiency, with three of these cases (2.52%) having CVID,

which is considerably higher than expected in the general population (1/3400 to 1/30 000). One patient was known to have CVID but had no Ig replacement, while two were new cases confirmed by further investigations.[12] Although we only selected undetectable IgA as primary IgA deficiency, we diagnosed two cases of complete IgA deficiency, that is 1.68% of the invasive disease population in comparison to an expected IgA deficiency rate of 1/333 to 1/2000.[7,8,18] Similar to CVID, IgA deficiency is a heterogeneous syndrome with some patients having no infection. It is often recognized that other humoral deficiencies, such as IgG2 and IgG4 subclasses, or pneumococcal polysaccharide antibody deficiency, combine with IgA deficiency to cause severe infections, although these abnormalities are not systematically associated.[18,19] We found a high level of selective IgM deficiency (13/109), primarily in the oldest patients. A selective IgM deficiency is rare and is defined as a low IgM value with normal IgG and IgA levels.[20] The literature describes IgM deficiency as a heterogeneous disorder that may occur as a primary or secondary disorder (after celiac disease for example) that can be asymptomatic or associated with infections including those caused by encapsulated bacteria.[20,21]

Twelve of the Ig abnormalities we observed were secondary to lymphoproliferative diseases,[13–15] mainly myeloma and chronic lymphocytic leukemia. These diseases are known to increase the risk of invasive disease, especially that caused by *S. pneumoniae* by more than 35-fold.[22] These lymphoproliferative disorders were either not known (four cases) or did not receive Ig replacement.

4.3. Study limitations

Our study had several limitations that may have affected the results and analysis. Firstly, there was only a small number of children in the study and also a considerably lower number of *H. influenzae* infections than pneumococcal infections. Secondly, some data were only recorded in the medical charts as recurrent infections, which may have led to an underestimation of their actual rate. Thirdly, early and late determination of the Ig levels may have affected the Ig values as discussed below. The cut-off levels we used to define the Ig abnormality are a matter of debate. No data exist to certify a threshold under which an infectious risk exists. Therefore most authors have used laboratory values to assess normality, with 'abnormal' values less than 6 g/l for IgG, 0.7 g/l for IgA, and 0.5 g/l for IgM. We used artificial cut-off levels similar or lower to those provided by our laboratory or the literature. Immunoglobulin determination is a simple and broadly available test. The quality of the immune response as determined by the pneumococcal polysaccharide antibody measurement would be of interest to explore, as an adapted immune response may compensate for an inadequate Ig level. However, these techniques can be difficult to perform and therefore are considered as second-line tests for exploring humoral deficiencies.[10] We did not include IgG subclasses in our study as their interpretation and management are difficult and, similar to pneumococcal polysaccharide antibody determination, are regarded as second-line examinations.[10] Half of the Ig measurements were carried out within 4 days of invasive disease, although a few patients had considerably later measurements (0–214 days) due to long hospitalizations, with a change of ward allowing new Ig assays when the data were missing. These late measurements, although rare, were included in the statistical analyses. The infections may have artificially modified IgG levels as a result of consumption or hemodilutions caused by fluid resuscitation. No recommendations for Ig determination have been published and the results of previous studies are confusing. Herer et al. found no variation in Ig levels during community-acquired pneumonia at admission, at recovery, or after discharge,[23] although Ekdahl et al. found lower IgG levels during acute infections.[11] Another study performed by Venet et al. during septic shock found lower IgG and IgM, but not IgA levels during the first 4 days, with normalization thereafter.[24] In the present study, Ig deficiency was unknown or unexplained in 26 cases, and therefore a second analysis should always be performed in such cases to confirm the deficiency, as the infection may have caused the lower Ig levels. The high rate of explained abnormalities (19 primary or secondary deficiencies) confirmed the need for immediate Ig determination as a first screening test to detect humoral deficiencies.[10] The precise timing of the Ig dosage during hospitalization should be determined accurately (probably after several days), but this was not within the scope of the current study and therefore was not required. Immunoglobulin determination during acute infections allows prompt immunological diagnosis and avoids losing patients to follow-up, although a second Ig test should always be carried out at a later time.

4.4. Immunoglobulin deficiency treatment

Supportive care for patients with these humoral deficiencies is based on vaccination against *S. pneumoniae* and *H. influenzae*, and for certain patients Ig replacement and oral antibiotic therapy is necessary. Vaccination is probably the simplest prevention, even though its efficacy is not guaranteed.[8,25–27] The 13-valent pneumococcal polysaccharide conjugate vaccine, followed by the 23-valent vaccine is now recommended in non-immunized immunocompromised patients.[27] Immunoglobulin substitution is indicated in primary hypogammaglobulinemia, using different guidelines.[28,29] Treatment of secondary hypogammaglobulinemia mainly involves treating the underlying cause or discontinuing medications that may result in hypogammaglobulinemia. Supportive treatment in the form of replacement Ig and antibiotics may be considered for hypogammaglobulinemia secondary to a hematological malignancy (B-cell chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, and other B-cell tumors).[25,27–30] In secondary deficiency most recommendations are for repeated infections, although it has been suggested that patients with IgG levels <4 g/l should receive intravenous Ig therapy.[7] For myeloma, assessing humoral deficiency is problematic because of pathologically high or normal Ig levels due to the presence of paraprotein. However, in the present study, the estimated residual Ig level was low, around 4 g/l. Immunoglobulin replacement can be difficult in cases of high paraprotein levels with the associated risk of hypercoagulability due to hyperviscosity,[31] and it is therefore necessary to consider Ig substitution during the steady state.

5. Conclusions

Immunoglobulin determination during invasive disease appears to improve the diagnosis of primary immunodeficiencies, especially CVID, which are otherwise frequently diagnosed after recurrent infections, with a delay of 6–8 years after the onset of the first characteristic symptoms.[32] Immunoglobulin determination during invasive disease also diagnoses a high rate of secondary immunodeficiency, particularly hematological malignancies not known or not adequately substituted. Measurement of immunoglobulins during invasive diseases allows an early immunological diagnosis and preventive therapy and is indicated as a first-line test to detect humoral deficiencies. Although this study did not demonstrate a significant improvement in the outcome of infection, it is our view that patients with frequent and potentially fatal infections of *S. pneumoniae* or *H. influenzae* invasive disease should have Ig levels measured. This approach would allow the diagnosis of most immunoglobulin abnormalities and therefore allow implementation of preventive strategies when necessary.

Conflict of interest: No conflict of interest to declare.

References

1. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs) Report: Emerging Infections Program Network. *Streptococcus pneumoniae*, provisional—2009. Atlanta, GA: US Department of Health and Human Services, CDC; 2010. Available at: http://www.cdcgov/abcs/reports-findings/survreports/spneu (accessed 12/16/2013).
2. Lepoutre A, Georges S, Varon E, Lévyl-Bruhl E; les microbiologistes du réseau Epibac. Evolution de l'incidence des infections invasives à pneumocoques. *Bull Epidemiol Hebd (Paris)* 2007;**5**:37–9.
3. Surveillance des infections invasives à Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus pneumoniae, Streptococcus agalactiae (B) et Streptococcus pyogenes (A) en France métropolitaine. Données épidémiologiques 2010. http://www.invs.sante.fr/surveillance/epibac/donnees.htm. (accessed 12/16/2013)
4. Calbo E, Garau J. Factors affecting the development of systemic inflammatory response syndrome in pneumococcal infections. *Curr Opin Infect Dis* 2011, 24:241–7.
5. Almirall J, Bolibar I, Serra-Prat M, Roig J, Hospital I, Carandell E, et al. New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Respir J* 2008;**31**:1274–84.
6. European Centre for Disease Prevention and Control. ECDC annual epidemiological report on communicable diseases in Europe: surveillance report 2010. ECDC. 2010 Available at: http://www.ecdc.europa.eu/ (accessed 12/16/2013).
7. Furst DE. Serum immunoglobulins and risk of infection: how low can you go? *Semin Arthritis Rheum* 2009;**39**:18–29.
8. Oksenhendler E, Gerard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, et al. Infections in 252 patients with common variable immunodeficiency. *Clin Infect Dis* 2008;**46**:1547–54.
9. Société de Pathologie Infectieuse de Langue Française. [17th Consensus conference. Consensus conference on bacterial meningitis. Short text]. *Med Mal Infect* 2009;**39**:175–86.
10. de Vries E. Patient-centred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists: 2011 update. *Clin Exp Immunol* 2011;**167**:108–19.
11. Ekdahl K, Rollof J, Oxelius VA, Engellau J, Braconier JH. Analysis of immunoglobulin isotype levels in acute pneumococcal bacteremia and in convalescence. *Eur J Clin Microbiol Infect Dis* 1994;**13**:374–8.
12. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). *Clin Immunol* 1999;**93**:190–7.
13. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, Melton 3rd LJ. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med* 2002;**346**:564–9.
14. Blade J, Dimopoulos M, Rosinol L, Rajkumar SV, Kyle RA. Smoldering (asymptomatic) multiple myeloma: current diagnostic criteria, new predictors of outcome, and follow-up recommendations. *J Clin Oncol* 2010; **28**:690–7.
15. Gribben JG. How I treat CLL up front. *Blood* 2010;**115**:187–97.
16. Brandt CT, Lundgren JD, Lund SP, Frimodt-Moller N, Christensen T, Benfield T, et al. Attenuation of the bacterial load in blood by pretreatment with granulocyte-colony-stimulating factor protects rats from fatal outcome and brain damage during *Streptococcus pneumoniae* meningitis. *Infect Immun* 2004;**72**:4647–53.
17. Kutukculer N, Karaca NE, Demircioglu O, Aksu G. Increases in serum immunoglobulins to age-related normal levels in children with IgA and/or IgG subclass deficiency. *Pediatr Allergy Immunol* 2007;**18**:167–73.
18. Edwards E, Razvi S, Cunningham-Rundles C. IgA deficiency: clinical correlates and responses to pneumococcal vaccine. *Clin Immunol* 2004;**111**:93–7.
19. French MA, Denis KA, Dawkins R, Peter JB. Severity of infections in IgA deficiency: correlation with decreased serum antibodies to pneumococcal polysaccharides and decreased serum IgG2 and/or IgG4. *Clin Exp Immunol* 1995;**100**:47–53.
20. Guill MF, Brown DA, Ochs HD, Pyun KH, Moffitt JE. IgM deficiency: clinical spectrum and immunologic assessment. *Ann Allergy* 1989;**62**:547–52.
21. Hong R, Gupta S. Selective immunoglobulin M deficiency in an adult with *Streptococcus pneumoniae* sepsis and invasive aspergillosis. *J Investig Allergol Clin Immunol* 2008;**18**:214–8.
22. Kyaw MH, Rose Jr CE, Fry AM, Singleton JA, Moore Z, Zell ER, Whitney CG. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. *J Infect Dis* 2005;**192**:377–86.
23. Herer B, Labrousse F, Mordelet-Dambrine M, Durandy A, Offredo-Hemmer C, Ekindjian O, et al. Selective IgG subclass deficiencies and antibody responses to pneumococcal capsular polysaccharide antigen in adult community-acquired pneumonia. *Am Rev Respir Dis* 1990;**142**:854–7.
24. Venet F, Gebeile R, Bancel J, Guignant C, Poitevin-Later F, Malcus C, et al. Assessment of plasmatic immunoglobulin G, A and M levels in septic shock patients. *Int Immunopharmacol* 2011;**11**:2086–90.
25. Snowden JA, Ahmedzai SH, Ashcroft J, D'Sa S, Littlewood T, Low E, et al. Guidelines for supportive care in multiple myeloma. *Br J Haematol* 2011; **154**:76–103.
26. Morrison VA. Infectious complications in patients with chronic lymphocytic leukemia: pathogenesis, spectrum of infection, and approaches to prophylaxis. *Clin Lymphoma Myeloma* 2009;**9**:365–70.
27. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2012;**61**:816–819.
28. Provan D, Nokes T, Agrawal S, Winer J, Wood P, Agrawal S, et al. Clinical guidelines for immunoglobulin use. 2nd ed. London, UK: Department of Health; 2008.
29. National Blood Authority. Criteria for the clinical use of intravenous immunoglobulin in Australia. Turner, Australia; National Blood Authority; 2009.
30. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. *Leuk Lymphoma* 2009;**50**:764–72.
31. Mizrahi M. The hypercoagulability of intravenous immunoglobulin. *Clin Adv Hematol Oncol* 2011;**9**:49–50.
32. Ballow M, Notarangelo L, Grimbacher B, Cunningham-Rundles C, Stein M, Helbert M, et al. Immunodeficiencies. *Clin Exp Immunol* 2009;**158**(Suppl 1): 14–22.