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BRIEF REPORT

Interest of immunodeficiency screening in adult after admission in medical intensive care unit for severe infection, a retrospective and a prospective study: the Intensive Care Unit and Primary and Secondary Immunodeficiency (ICUSPID) study

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Abstract

Background Primary immunodeficiency (PID) in adults is rare and mostly revealed by infections.

Material and Methods Adults without predisposing factors who were admitted to an intensive care unit (ICU) for infection were screened for PID.

Results Six PID cases were diagnosed, mostly revealed by encapsulated bacterial infections.

Conclusion Investigation of PID after ICU discharge should be considered to improve early detection.

Keywords Primary immunodeficiency · Secondary immunodeficiency · Infection · Adult · Intensive care unit

Introduction

Primary immune deficiencies (PID) are characterized by a failure of the immune system that is not explained by any infectious, neoplastic, or iatrogenic causes [1]. By 2017, more than 350 different inherited rare PID disorders had been described [2]. The occurrence of PID is rare in adults, with a prevalence of approximately 6.7 per 100,000 inhabitants in France [1]. Infections are the most common manifestations of PID [1, 3]. Diagnosis of PID in adulthood may be supported by six warning signs from the European Society of Immunodeficiencies (ESID) [4]. However, their guidelines do not comprehensively describe symptoms of PID, even for patients with infections. The guidelines recommend screening adults for PID after at least two severe bacterial infections [4]. Infections in patients with PID are usually recurrent and/or invasive, lead to hospitalization and have high rates of morbidity and mortality. Indeed, severe sepsis represents 37% of all admissions in some intensive care units, and immunocompromised patients represent at least 20% of these admissions [5]. The aim of this study was to evaluate the proportion of PID or secondary immunodeficiency (SID) diagnosed after a severe or opportunistic infection in patients hospitalized in a medical intensive care unit (MICU).

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Materials and methods

We first conducted a single-center retrospective study from January 2011 to December 2012. For this retrospective part, eligible patients were contacted by phone, and a consultation in either the Internal Medicine or Infectious Disease Department was scheduled for a few weeks later. We then conducted a prospective study, the "Intensive Care Unit Primary and Secondary Immunodeficiency" (ICUSPID) study. The ICUSPID study was conducted between January 2015 and December 2016 among patients admitted to the MICU of the University Hospital in Caen, France. Patients aged 18–65 who were admitted to the MICU for (1) an invasive bacterial infection, (2) an opportunistic infection or (3) sepsis without any identified organism were included. Patients were excluded if they had a medical history of (1) PID, (2) SID (3) a local–regional factor that could predispose them to infection or (4) a hospital-acquired infection. For the prospective study, a consultation with the patient was scheduled for 8 weeks after he or she was discharged from the MICU. PID screening included the following: complete blood count, blood smear, immunoglobulin (Ig) isotype (IgA, M, G) and IgG subclass levels, total hemolytic complement and complement fractions (C) 3 and 4, alternative complement pathway (AP50) in case of *Neisseria meningitidis* (NM) infection, quantitative immunophenotyping of T, B and natural killer cells, specific antibody response to diphtheria, tetanus and pneumococcal vaccine and HIV serology. The clinical and laboratory diagnostic criteria used to identify PID were based on guidelines from the ESID and the Pan-American Group for Immunodeficiency (PAGID) [6]. The research ethics committee at Caen University Hospital approved the study protocol. The study is registered at ClinicalTrials.gov, no. NCT02888535.

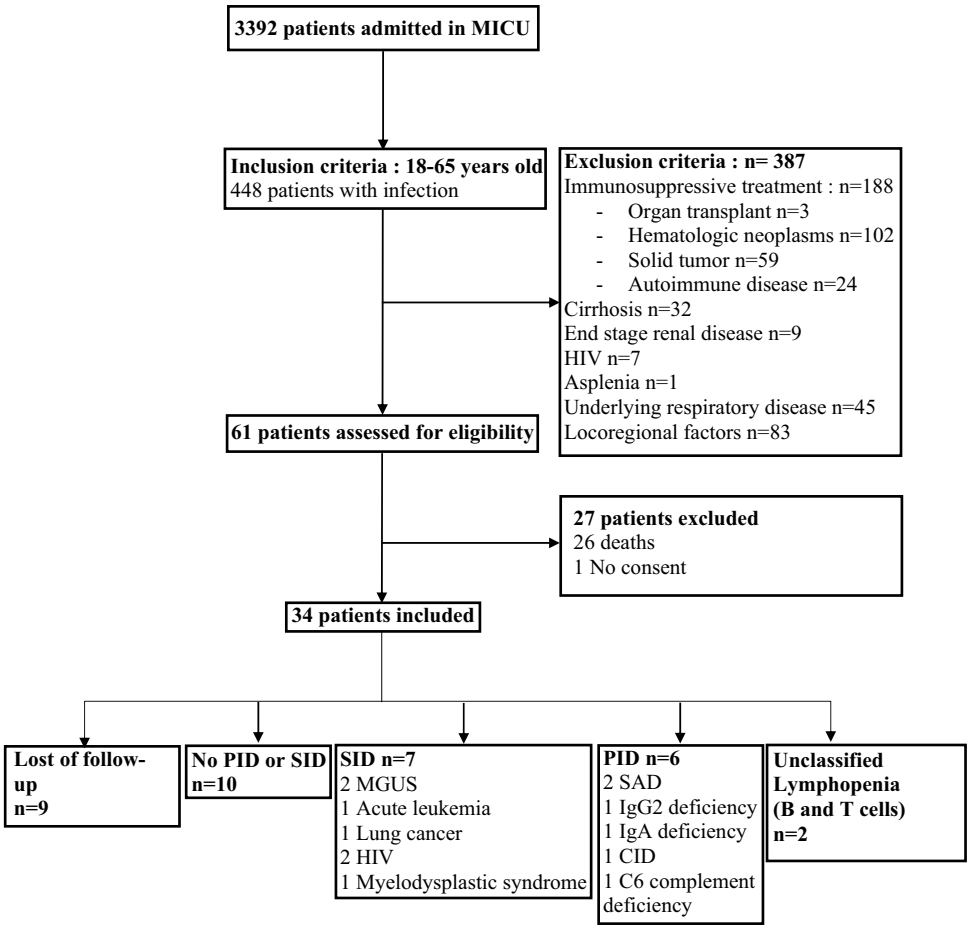
Results

During the two periods, 3392 patients were admitted to the MICU. Of these, 387 patients were excluded for pre-existing predisposing factors (including 188 on immunosuppressive treatment, 32 with cirrhosis, 9 with end-stage renal disease, 7 with HIV, 1 with asplenia, 45 with underlying respiratory disease and 83 with local–regional factors) (Fig. 1). From 61 eligible patients, 34 were included in the analysis (another 26 patients died before MICU discharge and one patient did not give consent). The retrospective study included 15 patients (patients #1–#15) and the prospective study included 19 patients (patients #16–#34) (Table 1). Demographic characteristics of the patients are summarized in Table 1.

The median age of the patients was 40.5-year [18–65], and 51% of the patients were male. The infections diagnosed were: pneumonia in 22 patients (64%), meningitis in 8 patients (24%), pneumonia associated with meningitis in one patient (3%), meningitis and arthritis in one patient (3%), arthritis in one patient (3%), skin and soft tissue infection in one patient (3%) and isolated bacteremia in one patient (3%). Thirty-one patients (91%) were admitted for a first severe infection. The most frequent pathogens involved were: NM ($n=7$, 20%), with serogroup B, C or W135 in two, four and one case(s), respectively; *Streptococcus pneumonia* (SP) ($n=6$, 17%); and *Mycoplasma pneumoniae* ($n=4$, 12%). No microorganism was detected for 9 patients (26%).

Immune deficiency was diagnosed in 13 patients (38%). Seven patients had SID (20%), including two HIV infections (patients #5 and #6) revealed by opportunistic infections (CMV and pneumocystis infection); one lung cancer (patient #7) diagnosed after a first episode of pneumonia; one myelodysplastic syndrome (patient #8) revealed by a tuberculosis infection; one acute myeloid leukemia (patient #17) who had a cellulitis; and two monoclonal gammopathies of undetermined significance (MGUS) (patients #18 and #30) revealed, respectively, by a pneumonia without pathogen identified and a meningitis due to *S. pneumoniae*. Patient #30, with MGUS disease, had recurrent infections of encapsulated bacteria (*S. pneumoniae* and *S. pyogenes*) leading to immunoglobulin replacement and vaccination against SP, *Haemophilus influenzae* and NG. After 1 year of follow-up, she had no recurrent infection.

Of the six patients with PID (17%), four were diagnosed during the retrospective study and two during the prospective study, most of whom had humoral immune defects (66%). The median age of these patients was 34.5-year-old [19–65], and 83% were female ($n=5$). For 83% of these patients ($n=5$), it was the first episode of severe infection. Two patients (#1 and #2) had specific antibody deficiency (SAD) with decreased levels of IgG2 subclass revealed by pneumococcal pneumonia. According to Lopez et al. a defective response to the pneumococcal vaccine was found [7]. Both patients had recurrent pulmonary infections within 1 year after diagnosis that led to antibioprophylaxis with trimethoprim–sulfamethoxazole. No recurrent infection was noted after 5 years of follow-up. One patient (patient #3) had an IgG2 subclass deficiency revealed after a pneumococcal pneumonia. She was vaccinated against SP. However, this patient was lost to follow-up, so her response to the SP vaccine could not be evaluated. Patient #4 had a selective IgA deficiency revealed by NM meningitis, and no recurrence after 5 years of follow-up. Patient #16 had a combined immunodeficiency disease (CID) revealed by invasive pneumonia with a medical history of recurrent bacterial and fungal infections. His immune



CID : Combined immunodeficiency; HIV : Human immunodeficiency virus; MGUS : Monoclonal gammopathy of undetermined significance; PID : Primary immunodeficiency ; SAD : specific antibody deficiency; SID : Secondary immunodeficiency.

Fig. 1 Flow chart. *CID* combined immunodeficiency, *HIV* human immunodeficiency virus, *MGUS* monoclonal gammopathy of undetermined significance, *PID* primary immunodeficiency, *SAD* specific antibody deficiency, *SID* secondary immunodeficiency

tests showed the following: quantitative T cell deficiency (CD4 + 178/mm^3 (N 530–1300/mm^3), CD8 + 179/mm^3 (N 330–920/ mm^3)), no total B cells (141/mm^3 (N 110–150/ mm^3)) or NK cells (104/mm^3 (N 70–480/mm^3)) deficiency. Specific tests revealed decreased level of memory B cells, naïve T cells (CD4+ and CD8+) and IgG2 (0.42 g/l N 2.4–7 g/l), IgA (0.62 g/l N 0.7–3.12 g/l). No complement deficiency was noted, and whole exome sequencing showed no abnormality. He was vaccinated against SP without response, NM and *H. influenzae*, and he received antibioprophylaxis with trimethoprim–sulfamethoxazole. He had no infectious recurrences during the 3 years of follow-up. Patient #34 had an NM meningitis infection and was diagnosed with homozygous C6 complement deficiency. She was vaccinated against NM, and familial screening was proposed. Two patients had isolated B and T cell lymphopenia without ESID/PAGID-defined PID. Immune tests were normal for ten patients (29%), and nine patients (26%) were lost to follow-up.

Discussion

This study offers a novel dataset that highlights the necessity of investigating primary and secondary immunodeficiencies among adult patients hospitalized in the MICU due to severe infection, which has previously been demonstrated only in childhood [8]. In the retrospective study by Suavinho et al. of 53 patients who were hospitalized for severe infections, only 7 children had PID investigations. PID was diagnosed for 5 patients (71.4%), mainly antibody deficiency with 3 IgG deficiency, as well as one cyclic neutropenia and one Wiskott–Aldrich syndrome. In our study, the estimated prevalence of immunodeficiencies was 38%. Of these, 17% ($n = 6$) were PID, mostly antibody deficiencies diagnosed after invasive infections due to encapsulated bacteria. PID in adults is rare compared to the occurrence of PID during childhood; this could explain the small number of patients included in both the

Table 1 Characteristics of the included patients

#/Gender/age/study	History of infection	Diagnosis on admission	Pathogen	Immune deficiency	Follow-up (10 months–5 years) and management
Patient #1 F/36 Retrospective	No	Pneumonia	*S. pneumoniae*	Specific antibody deficiency	Recurrent infection SP, HI, NM vaccine Antibioprophylaxis Follow-up: 5 years
Patient #2 F/65 Retrospective	Yes Pneumonia	Pneumonia	*S. pneumoniae*	Specific antibody deficiency	Recurrent infection SP, HI, NM vaccine Antibioprophylaxis Follow-up: 5 years
Patient #3 F/45 Retrospective	No	Pneumonia	*S. pneumoniae*	IgG2 deficiency	Lost to follow-up SP, HI, NM vaccine
Patient #4 F/19 Retrospective	No	Meningitis	*N. meningitidis* B	IgA deficiency	No recurrent infection Follow-up: 5 years
Patient #5 M/53 Retrospective	No	Pneumonia	*P. jirovecii* CMV	HIV	No recurrent infection HAART Follow-up: 5 years
Patient #6 M/42 Retrospective	No	Pneumonia Bacteremia	*P. jirovecii* CMV *S. typhimurium*	HIV	No recurrent infection HAART Follow-up: 5 years
Patient #7 M/51 Retrospective	No	Pneumonia	No pathogen identified	Lung cancer	No recurrent infection Chemotherapy Follow-up: 4 years
Patient #8 M/65 Retrospective	No	Pneumonia Meningitis	*M. tuberculosis*	Myelodysplastic syndrome	No recurrent infection Chemotherapy Follow-up: 4 years
Patient #9 M/31 Retrospective	No	Pneumonia	*M. pneumoniae*	No immunodeficiency	No recurrent infection Follow-up: 5 years
Patient #10 M/43 Retrospective	Yes Otitis	Pneumonia	No pathogen identified	No immunodeficiency	No recurrent infection Follow-up: 4 years
Patient #11 F/23 Retrospective	No	Pneumonia	*M. pneumoniae*	Lost to follow-up	Lost to follow-up
Patient #12 F/60 Retrospective	No	Meningitis	*S. pneumoniae*	Lost to follow-up	Lost to follow-up
Patient #13 F/33 Retrospective	Yes Pneumonia	Pneumonia	*M. szulgai*	Incomplete PID screening	Death
Patient #14 M/51 Retrospective	No	Pneumonia	*S. pyogenes*	Lost to follow-up	Lost to follow-up
Patient #15 M/23 Retrospective	No	Meningitis	*N. meningitidis* B	Lost to follow-up	Lost to follow-up
Patient # 16 M/33 Prospective	Yes Fungal infection Meningitidis Pneumonia	Pneumonia	No pathogen identified	CID	No recurrent infection SP, HI, NM vaccine Antibioprophylaxis Follow-up: 3 years
Patient #17 M/18 Prospective	No	Cellulitis with abscess	No pathogen identified	Acute myeloid leukemia	Chemotherapy

Table 1 (continued)

#/Gender/age/study	History of infection	Diagnosis on admission	Pathogen	Immune deficiency	Follow-up (10 months–5 years) and management
Patient #18 40/F Prospective	No	Pneumonia	No pathogen identified	MGUS	No recurrent infection Follow-up: 3 years
Patient #19 M/65 Prospective	No	Meningitis	*N. meningitidis* C	Lymphopenia Neutropenia Thrombopenia	No recurrent infection Follow-up: 1 year
Patient #20 M/20 Prospective	No	Meningitis	*M. pneumoniae*	Lost to follow-up	Lost to follow-up
Patient #21 F/65 Prospective	No	Pneumonia	No pathogen identified	Lost to follow-up	Lost to follow-up
Patient #22 M/49 Prospective	No	Pneumonia	No pathogen identified	Lost to follow-up	Lost to follow-up
Patient #23 F/40 Prospective	No	Pneumonia	*S. pyogenes*	Lost to follow-up	Lost to follow-up
Patient #24 F/20 Prospective	No	Meningitis	*N. meningitidis* C	No immunodeficiency	No recurrent infection Follow-up: 2 years
Patient #25 M/33 Prospective	No	Pneumonia	No pathogen identified	No immunodeficiency	No recurrent infection Follow-up: 2 years
Patient #26 F/24 Prospective	No	Meningitis Bacteremia Arthritis	*N. meningitidis* W	Incomplete PID screening (No APH50 test)	Lost to follow-up
Patient #27 F/44 Prospective	No	Pneumonia	*M. pneumoniae*	No immunodeficiency	No recurrent infection Follow-up: 2 years
Patient #28 F/35 Prospective	No	Pneumonia	*S. pyogenes*	No immunodeficiency	No recurrent infection Follow-up: 2 years
Patient #29 F/41 Prospective	No	Pneumonia	No pathogen identified	Lymphopenia	No recurrent infection Follow-up: 1 year
Patient #30 F/53 Prospective	No	Meningitis	*S. pneumoniae*	MGUS	Recurrent infection due to *S. pyogenes* SP, HI, NG vaccine Immunoglobulin replacement Follow-up: 1 year
Patient #31 M/41 Prospective	No	Pneumonia	*Legionella pneumophila*	No immunodeficiency	No recurrent infection Follow-up: 10 months
Patient #32 M/54 Prospective	No	Pneumonia	*S. pneumoniae*	No immunodeficiency	No recurrent infection Follow-up: 10 months
Patient #33 M/22 Prospective	No	Meningitis	*N. meningitidis* C	No immunodeficiency	No recurrent infection Follow-up: 10 months
Patient #34 F/19 Prospective	No	Meningitis	*N. meningitidis* C	Homozygous C6 complement deficiency	No recurrent infection NM vaccine Follow-up: 10 months

SP S. pneumoniae, HI Haemophilus influenzae, NM N. meningitidis, CMV cytomegalovirus, *HAART* highly active antiretroviral therapy, *HIV* human immunodeficiency virus, *Ig* immunoglobulin, *MGUS* monoclonal gammopathy of undetermined significance, *PID* primary immune deficiency, *CID* combined immune deficiency

retrospective and prospective parts of the study, as well as the lower prevalence of PID compared with the study by Suavinho et al. [1, 8]. Antibody deficiencies were the first PID to be diagnosed in adulthood and are mainly represented by common variable immune deficiency (CVID) [9]. In this study, 80% of PID cases were antibody deficiencies and the main PID was SAD, which is known to predispose patients to recurrent and/or severe infection, especially with encapsulated bacterial infections [10]. This type of PID can develop during adulthood [10]. In a previous work, Sanges et al. reported a 19% prevalence of PID in adults with a first encapsulated bacterial infection [11]. Moreover, Audemard-Verger et al. showed that half of patients with a complement deficiency were diagnosed at their first invasive infection [12]. Thus, PID in adults can be revealed by a first invasive infection without any ESID warning signs. Early recognition of PID in adulthood is crucial, as delayed diagnosis may lead to recurrent infections and to an increased risk of mortality that could be prevented by specific treatments, including immunoglobulin replacement, vaccination or antibioprophylaxis [9, 11]. This study had several limitations. In the design of the retrospective part, patients who were admitted for a severe infection but were not screened for PID could have been missed. Furthermore, 27% of the patients included were lost to follow-up. Regarding this result, patients' general practitioners should be more closely involved to increase patient compliance. The small number of patients included is another limitation of our study. Adult PID is a rare condition, but it is probably more frequent than is currently known, and this study highlights the necessity of new PID screening protocols.

Despite the fact that primary immunodeficiencies are still considered rare, secondary immunodeficiencies may also be predisposed and revealed after an infection. Medical practitioners should be made more aware of immunodeficiency problems in order to prevent these infections and to provide better treatment for patients once the immunodeficiency is identified.

This and previous studies suggest that an initial screening for PID and SID could be performed after (1) a first episode of severe infection, (2) recurrent infections, (3) an opportunistic infection or (4) an infection due to encapsulated bacteria, in the absence of predisposing factors. Immune tests should be conducted within a few weeks after the infection to limit the impact of immune dysfunction during a severe infection. As first-line tests we propose (1) complete blood count (lymphopenia, thrombopenia, anemia, etc.); (2) blood smear (abnormal cells, Howell–Jolly body, etc.); (3) Ig isotype (IgA, M, G); (4) total hemolytic complement, C3, C4 and alternative complement pathway (AP50) in case of infection due to encapsulated bacteria; (5) quantitative immunophenotyping of T, B and natural killer cells; (6) specific antibody response to diphtheria, tetanus and pneumococcal vaccine; and (7) HIV serology. A full-body CT scan could also be performed if a tumor is suspected.

Conclusion

This pilot study highlights that PID and SID may be revealed in adults by a first episode of invasive infection leading to a MICU admission, despite the absence of ESID warning signs. A larger, multicenter prospective study might more reliably test these results and may help to identify new PID screening protocols for adults. Early detection of PID may prevent recurrence. Medico-economic and morbidity–mortality impacts remain to be assessed by larger studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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