The first Polish cohort of adult patients with common variable immunodeficiency from four specialized centers: do we provide standards of care?

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The first Polish cohort of adult patients with common variable immunodeficiency from four specialized centers: do we provide standards of care?

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Short title: Adult cohort of CVID in Poland

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Introduction

Common variable immunodeficiency (CVID) is the most clinically significant primary antibody deficiency (PAD) diagnosed in adulthood. However, the disease is rarely included in the diagnostic protocol for adults in Poland. Moreover, an analysis of Polish adult patients with CVID is lacking. CVID prevalence ranges from 2/100 000 to the highest 6.9/100 000 [1, 2]. The number of CVID cases reported in European registry was strikingly lower in Poland compared to other countries: minimum prevalence for Poland was 0.073 compared to 0.524 in Germany and to 0.977 in France [3].

Lifelong immunoglobulin (Ig) replacement therapy is essential in the treatment of CVID patients. Therapeutic, polyclonal Ig can be administered intravenously (IVIG), subcutaneously (SCIG) and subcutaneously facilitated by recombinant human hyaluronidase (fSCIG). Reimbursement for home SCIG treatment was introduced in 2014, and for fSCIG in 2016. There are limited real life data on the modes of administration in adult Polish CVID patients.

Objectives

The aims of this study were to describe demographic, clinical and serological features, and mode of Ig replacement in Polish adult patients with CVID.

Patients and methods

The records of 77 adult (age ≥ 18) patients diagnosed with CVID from four specialist PID centers were reviewed. We used modified ESID criteria [4] presented in supplementary materials (Table 1S). All patients had documented marked decrease of IgG and IgA. If neither hemagglutinin results nor vaccine response was available, patients had to have absence of class 3 Ig or low memory B cells or typical clinical features. The subjects’ data were gathered in an internet database. We analyzed their history of clinical infections and the 5 clinical
phenotyping categories defined in literature: autoimmunity (including organ-specific autoimmune conditions and cytopenias); polyclonal lymphocytic infiltration (including unexplained granuloma, unexplained hepatomegaly, persistent lymphadenopathy, and lymphoid interstitial pneumonia); lymphoid malignancy (proven and treated); unexplained enteropathy (biopsy-proven and gluten-insensitive); and no disease-related complications [5]. Further items were sex; Ig isotype levels at diagnosis, median IgG trough level; age at onset and at diagnosis; and diagnostic delay. If applicable, data are presented as mean (SD) values. Statistical analysis was performed using U Manna-Whitneya test or exact Fisher test. A P value of less than 0.05 was considered significant.

We recorded the present mode of Ig administration, and prior changes. The data lock occurred on 30 Sep 2017.

Results

The mean age of the 77 included patients was 39.19 (13.61) years, 46 were male (59.77%). The patients’ mean follow-up was 4.26 (4.26) years. The mean age at diagnosis was 32.29 (14.94) years, for men 33.39 (15.12), for women 30.65 (14.77) years. In 59 patients (76.6%) diagnosis was established after the age of 18. The mean age at onset was 22.16 (14.32) years. Mean diagnostic delay was 10.13 (10.53) years in the cohort, 11.63 (11.35) in patients diagnosed in adulthood (age ≥ 18) and 5.22 (4.82) in patients diagnosed before 18 years of age (P = 0.02). Patients were diagnosed between 1990 and 2017. Five patients (6.49%) were diagnosed between 1990 and 1999; 22 (28.7%) between 2000 and 2009; and 50 (64.94%) between 2010 and the database lock in Sep 2017.

Infections
Seventy six out of 77 patients reported increased susceptibility to infection due to common pathogens. The location and percentage of infections taking into account the change after immunoglobulin treatment introduction are presented in supplementary materials (Table 2S).

Five patients were diagnosed with the following atypical pathogens: Achromobacter denitrificans (blood culture), Ureaplasma urealyticum (knee joint), Aspergillus (lungs), Campylobacter pylori and Aeromonas hydrophila (both in the gastrointestinal tract).

Clinical phenotypes and complications

Twenty six patients (33.77%) had an exclusively infectious phenotype. Almost half of the subjects (48%) had autoimmune features, which were mostly hematological: thrombocytopenia, AIHA or both. Thirty four (44.16%) patients had polyclonal lymphocytic infiltration. Twelve percent of patients had granulomatous inflammation mainly in lungs and gastrointestinal tract but also unusual locations were identified, such as the gingiva or retina. A more common finding were polyclonal lymphadenopathies affecting 20 patients. Unexplained enteropathy was seen in 2 cases with proven diffuse nodular lymphoid hyperplasia of the small intestine and large intestine. Lymphoid malignancy (follicular lymphoma) occurred in one patient with childhood onset and previous polyclonal lymphoproliferation. Seven other malignancies were diagnosed. Clinical phenotypes and organ complications in a cohort are presented in table 1. The clinical presentation was similar for the population diagnosed under 18 years of age compared to diagnosed as adults (presented in supplementary material, table 2S).

Laboratory abnormalities

At the time of diagnosis 74 patients had low IgG: mean 184.44 (171.41) mg/dl, 32 had IgG < 100 mg/dl. Three results from the time of diagnosis were missing but low IgG was confirmed later on. Only 4 patients had IgG levels exceeding 500 mg/dl at diagnosis. Mean IgA was 11.46 (13.64) mg/dl, 22 patients had IgA < 7 mg/dl. Mean IgM was 21.42 (28.19) mg/dl and
31 patients had IgM < 10 mg/dl. Fifteen of 74 patients (20.27%) had undetectable IgG, IgA and IgM at diagnosis.

Forty nine (63.64%) patients had isohegamaglutinin assayed, which were absent in 20 cases, present in 12 cases. Seven results were not available for analysis. Response to vaccination was tested in 15 cases (19.8%), for pneumococcal polysaccharide vaccine (Pneumo 23) in 7 cases, and for tetanus in 8 cases. The tests were negative respectively in 1 and in 3 cases, but for 6 cases results were pending.

Forty one (53.25%) patients had performed flow cytometric B cell phenotyping and 27 of them had low switched memory B cells below 2%.

Immunoglobulin replacement

At the time of database lock, 74 of the 77 patients (96.1%) were treated with immunoglobulin, 53 (71.62%) received SCIG (40 patients by conventional SCIG and 13 fSCIG).

The mean monthly dose of immunoglobulins in grams per kilogram body weight per month was 0.4 (0.18). The mean monthly dose for respective modalities were: 0.52 (0.14) for IVIG, 0.35 (0.17) for SCIG, and 0.35 (0.19) for fSCIG.

Mean IgG trough levels in patients treated with immunoglobulins were 760.53 (221.49) mg/dl and by modality were: 658.68 (236.97) mg/dl on IVIG, 841 (209.57) mg/dl on SCIG, and 661.77 (121.27) mg/dl on fSCIG.

In the study group 55/74 (74.32%) changed the mode of immunoglobulin administration. The rate of variation was as follows: IVIG->SCIG 39 patients (70.91%), IVIG->SCIG->fSCIG 11 patients (20.00%), IVIG->SCIG->IVIG 3 patients (5.45%) and IVIG->fSCIG 2 patients (3.64%). Eighteen patients (24.32%) started and continued intravenous therapy.

Discussion

To the best of our knowledge, this is the first reported Polish cohort of CVID adult patients. The diagnostic delay was 10 years although our cohort is demographically similar to other
reported adult European [5]. Infections were the cardinal feature with respiratory tract infection being the most common. Almost half of the subjects had autoimmune features. Only a minority of patients had been assessed for response to vaccination.

Diagnostic delay in our study is one of the longest reported in Europe. This is in contrast with a previously reported delay in the ESID cohort estimated for Polish patients to be 1.8 years – the shortest in Europe [3]. Probably this was due to the small number of reported Polish CVID patients and their selective reporting by pediatric centers. Despite similar clinical phenotype it was significantly shorter in patients diagnosed before 18 years and correlated with longer disease duration and older age, which suggests that patients are seldom suspected of having hereditary PID at a later age. We found that over time there was a significant increase in the number of diagnosed cases with a peak of 50 new cases identified from 2010 to 2017, when specialized adult centers were established. It seems that we are currently closing the gap from the time when long-standing CVID cases were missed or misdiagnosed due to lack of tertiary PID adult centers. Our estimated diagnosis delay is similar to that in Spanish patients diagnosed before 2000 [1]. Delay in CVID diagnosis is still a frequent finding in Europe. Recent reports on a Danish and Italian cohort estimated it to be 7 years and 8.9 years, respectively [6,7,8].

The clinical characteristics of our cohort are in line with previously reported cohorts [5]. However in our study the age at onset formed a continuum from the first to the fifth decade, which is in contrast with previously published data [3,6].

Infections are the cardinal feature of CVID with respiratory tract infection being the most common. However almost half of the subjects have autoimmune features, granulomatous inflammation or polyclonal lymphadenopathies thus CVID should be considered in all patients with unexplained general lymphadenopathy or autoimmunity [1,4].
Lymphomas are the most frequently reported malignancies in CVID [9, 10]. The childhood onset, previous polyclonal lymphoproliferation are predictors identified in other studies [5]. Other single, solid malignancies are reported in patients diagnosed in adulthood, and according to published data, they are more likely to develop in the fifth and sixth decade [11]. According to diagnostic criteria, all patients with CVID have low IgG and IgA. As normal Ig and IgA levels exclude CVID, quantification of serum Ig levels is a useful initial laboratory test. The low switched memory B cells reduced below 2%, strongly supports CVID diagnosis. The flow cytometric B cell phenotyping should be routine immunological work-up but is not available in all centers. Also minority of patients (15 cases) had been assessed for response to vaccination. Similar gaps in laboratory testing were identified by Westh et al in a Danish cohort study [6]. Of all reported patients 21% had isohemagglutinin titers measured, 29% were assessed for response to pneumococcal vaccine and only 17.9% were characterized by flow cytometric B cell phenotyping [6]. Lifelong immunoglobulin replacement therapy is essential in the treatment of CVID patients. It prevents bacterial infections and helps to avoid organ damage related to infections and all patients should have access to all modes Ig replacement. In contrast to data published in 2014, when the IVIG:SCIG ratio for Polish adult patients was 70:30 [12] in present study the IVIG:SCIG ratio was 28:72. This illustrates the increased availability of SCIG for adults in the last 3 years. On follow up, over 70% patients changed the mode of therapy, mainly from IVIG to SCIG or fSCIG.

The main advantage of this study is multicenter approach, inclusion exclusively patients with CVID and results which reflect current routine practice in PID adult centers.

The major limitation of our study was a relatively small sample size. However, we analyzed all eligible patients who had a firm diagnosis established in centers experienced in PID management and avoided inclusion of patients with other types of PAD. We could not
precisely analyze all lymphocytes sub-phenotypes, as different protocols were used in each center.

To conclude, in the present paper we report the first Polish cohort of CVID adult patients. We confirm that currently patients have access to a wide spectrum of Ig products and the possibility to individualize their modes of Ig administration. Our analysis points to a long diagnosis delay, which should be improved and point out the need to implement immunologic diagnostic procedures, especially vaccine response.
References


Table 1 Clinical phenotypes and organ complications in a cohort of 77 Polish adult PID patients

<table>
<thead>
<tr>
<th>Clinical phenotypes and organ complications (n = 77)</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Increased susceptibility to infections</td>
<td>76</td>
</tr>
<tr>
<td>No disease-related complications</td>
<td>27</td>
</tr>
<tr>
<td>Bronchiectases</td>
<td>15</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>37</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>17</td>
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<tr>
<td>Hemolytic anemia</td>
<td>7</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>7</td>
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<tr>
<td>Addison-Biermer disease</td>
<td>1</td>
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<tr>
<td>Celiac disease</td>
<td>4</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>3</td>
</tr>
<tr>
<td>Chronic seronegative polyarthritis</td>
<td>2</td>
</tr>
<tr>
<td>Sjoegren syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>1</td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>1</td>
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<tr>
<td>Non-specific inflammatory bowel disease</td>
<td>1</td>
</tr>
<tr>
<td>Polyclonal lymphocytic infiltration</td>
<td>34</td>
</tr>
<tr>
<td>Generalized lymphadenopathy</td>
<td>20</td>
</tr>
<tr>
<td>Granulomatous lesions</td>
<td>12</td>
</tr>
<tr>
<td>Lungs</td>
<td>8</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>4 (gingiva, spleen, liver, retina)</td>
</tr>
<tr>
<td>Unexplained enteropathy</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoid malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Other malignancies</td>
<td>7</td>
</tr>
<tr>
<td>Pituitary gland adenoma, colon tubular adenocarcinoma, squamous cell carcinoma (lungs), basal cell</td>
<td></td>
</tr>
</tbody>
</table>


carcinoma, intestinal tubular adenoma (low grade), breast adenocarcinoma, cervical metaplasia of the cervix