RESEARCH LETTER

The first Polish cohort of adult patients with common variable immunodeficiency from 4 specialized centers: do we provide standards of care?

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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. The prevalence of CVID ranges from 2/100 000 to as high as 6.9/100 000.[1,2]

Lifelong immunoglobulin (Ig) replacement therapy is essential in the treatment of CVID. 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 patients with CVID.

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

Patients and methods We reviewed the records of 77 adult patients (age ≥18 years) diagnosed with CVID from 4 treatment centers specializing in primary immunodeficiency (PID). We used the modified European Society for Immunodeficiencies (ESID) criteria[3] presented in Supplementary material (*Table S1*). All patients had a documented marked decrease of IgG and IgA levels. 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. Patient data were gathered in an internet database. We analyzed history of clinical infections and the 5 clinical phenotyping categories defined in literature.[4] The remaining data were sex, Ig isotype levels at diagnosis, median IgG trough level, age at onset and at diagnosis, and diagnostic delay. If applicable, data were presented as mean (SD) values. Statistical analysis was performed using the Mann–Whitney 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 were locked on September 30, 2017.

Results The mean (SD) age of the 77 included patients was 39.19 (13.61) years; there were 46 male patients (59.77%). The mean (SD) follow-up duration was 4.26 (4.26) years, and the mean (SD) age at diagnosis was 32.29 (14.94) years: 33.39 (15.12) for men and 30.65 (14.77) years for women. In 59 patients (76.6%), the diagnosis was established after the age of 18. The mean (SD) age at onset was 22.16 (14.32) years. The mean (SD) diagnostic delay was 10.13 (10.53) years in the whole cohort: 11.63 (11.35) in patients diagnosed in adulthood (age ≥18) and 5.22 (4.82) in those 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;

TABLE 1 Clinical phenotypes and organ complications in a cohort of adult Polish patients with primary immunodeficiency (n = 77)

Clinical phenotypes and organ complications		No. (%) of patients
Increased susceptibility to infections		76 (98)
No disease-related complications		27 (35)
Bronchiectases		15 (19)
Unexplained enteropathy		2 (2)
Autoimmunity		
Any		37 (48)
Thrombocytopenia		17 (22)
Hemolytic anemia		7 (9)
Leukopenia		7 (9)
Addison–Biermer disease		1 (1)
Celiac disease		4 (5)
Vitiligo		3 (3)
Chronic seronegative polyarthritis		2 (2)
Sjögren syndrome		1 (1)
Myasthenia gravis		1 (1)
Alopecia areata		1 (1)
Nonspecific inflammatory bowel disease		1 (1)
Polyclonal lymphocytic infiltration		
Any		34 (44)
Generalized lymphadenopathy		20 (25)
Granulomatous lesions	Any	12 (15)
	Lungs	8 (10)
	Lymph nodes	3 (3)
	Others	4 (5) (gingiva, spleen, liver, retina)
Malignancy		
Lymphoid malignancy		1 (1)
Other malignancies		7 (9) (pituitary gland adenoma, colon tubular adenocarcinoma, squamous cell carcinoma [lungs], basal cell carcinoma, intestinal tubular adenoma [low grade], breast adenocarcinoma, cervical metaplasia)

22 (28.7%), between 2000 and 2009; and 50 (64.94%), between 2010 and the database lock in September 2017.

Infections Of the 77 patients, 76 reported increased susceptibility to infection due to common pathogens. The location and percentage of infections taking into account the change after Ig treatment introduction are presented in Supplementary material (*Table S2*).

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 An exclusively infectious phenotype was observed in 26 patients (33.77%). Almost half of the subjects (48%) had autoimmune features, which were mostly hematological: thrombocytopenia, autoimmune hemolytic anemia, or both. Polyclonal lymphocytic infiltration was observed in 34 patients (44.16%). Twelve percent of patients had granulomatous inflammation mainly in the lungs and gastrointestinal tract, but also unusual locations were identified, such as the gingiva or retina. A more common finding was 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 1 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 patients diagnosed under 18 years of age compared with those diagnosed as adults (Supplementary material, *Table S3*).

Laboratory abnormalities At diagnosis, 74 patients had low IgG levels: mean (SD) 184.44 (171.41) mg/dl; 32 patients had IgG levels below 100 mg/dl. Three results from the time of diagnosis were missing but low IgG levels were confirmed later on. Only 4 patients had IgG levels exceeding 500 mg/dl at diagnosis. Mean (SD) IgA levels were 11.46 (13.64) mg/dl; 22 patients had IgA below 7 mg/dl. Mean (SD) IgM levels were 21.42 (28.19) mg/dl; 31 patients had IgM below 10 mg/dl. Of the 74 patients, 15 (20.27%) had undetectable IgG, IgA, and IgM at diagnosis.

Isohemagglutinins were assayed in 49 patients (63.64%), of whom 20 showed negative results. 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 in 1 and 3 cases, respectively, but for 6 cases the results were pending.

Flow cytometric B cell phenotyping was performed in 41 patients (53.25%), of whom 27 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 Ig, 53 (71.62%) received SCIG (40 patients by conventional SCIG, and 13, by fSCIG).

The mean (SD) monthly dose of Igs was 0.4 (0.18) g/kg bw/month. The mean (SD) monthly dose for the different modalities were: 0.52 (0.14), 0.35 (0.17), 0.35 (0.19) g/kg bw/month for IVIG, SCIG, and fSCIG, respectively.

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

Of the 74 patients (74.32%), 55 changed the mode of Ig 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 our knowledge, this is the first reported Polish cohort of adult patients with CVID. The diagnostic delay was 10 years although our cohort is demographically similar to other reported adult European cohorts.[4,5] Infections were the cardinal feature, with respiratory tract infection being the most common. Almost half of the patients had autoimmune features, and only a minority 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, which is the shortest in Europe.[1] Probably this was due to the small number of reported Polish CVID patients and their selective reporting by pediatric centers. Despite a 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 rarely suspected of having hereditary PID at a later age. 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.[6-8]

The clinical characteristics of our cohort are in line with previously reported cohorts.[4,5] 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.[1,6]

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.[1,3]

Lymphomas are the most frequently reported malignancies in CVID.[9,10] The onset at childhood and previous polyclonal lymphoproliferation were predictors identified in other studies.[4] 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 decades of life.[11]

According to diagnostic criteria, all patients with CVID have low IgG and IgA levels. As normal IgG and IgA levels exclude CVID, quantification of serum Ig levels is a useful initial laboratory test. The levels of low switched memory B cells below 2% strongly supports CVID diagnosis. The flow cytometric B cell phenotyping should be routine immunological workup but is not available in all centers. Also, a minority of patients (15 cases) had been assessed for response to vaccination. Similar gaps in laboratory testing were identified by Westh et al[6] in a Danish cohort study. Of all 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 Ig replacement therapy is essential in the treatment of CVID patients. All patients should have access to all modes of Ig replacement. In contrast to data published in 2014, when the IVIG to SCIG ratio for Polish adult patients was 70:30,[12] in the present study the ratio was 28:72. This illustrates the increased availability of SCIG for adults in the last 3 years. On follow-up, over 70% of patients changed the mode of therapy, mainly from IVIG to SCIG or fSCIG.

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

The major limitation was a relatively small sample size. However, we analyzed all eligible patients and avoided inclusion of patients with other types of PAD.

To conclude, we report the first Polish cohort of adult CVID patients. We confirm that currently patients have access to a wide spectrum of Ig products. Our analysis emphasizes a long diagnosis delay and points out to the need for implementing immunologic diagnostic procedures, especially vaccine response.

SUPPLEMENTARY MATERIAL Supplementary material is available with the article at www.pamw.pl.

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