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Delay in diagnosis affects the clinical outcome in a cohort of cvid patients with marked reduction of iga serum levels

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ABSTRACT

Common variable immunodeficiency disorders (CVID) represent a collection of diseases leading to an absent or strongly impaired antibody production. CVID presents a wide range of immunological abnormalities and clinical manifestations, including infections, inflammatory and autoimmune diseases, and malignancies. The aim of this observational study was to analyze the epidemiological and clinical features of a cohort of 75 Italian CVID patients, and evaluate the correlation with comorbidity and mortality. Clinical data were retrospectively collected: the cohort was followed-up for a maximum of 30 years (mean time of 10.24 years, median of 9 years). An higher age at the diagnosis of CVID and an higher age at onset of symptoms were significantly associated with a reduction of patients survival if stratified per median of IgA (less than or >8.00 mg/dl). Thus IgA levels at diagnosis are correlated with patients survival contributing to identify a subset with a worse prognostic outcome.

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1. Introduction

Common variable immunodeficiency disorders (CVID) represent a collection of primary immunodeficiency diseases characterized by reduced serum levels of IgG, IgA, and/or IgM, with impaired antibody production [1]. CVID is the most frequent symptomatic antibody deficiency diagnosed in adulthood [2]since selective IgA deficiency, that occurs with higher frequency overall, is often asymptomatic [3]. There are no precise data on the epidemiology of CVID. Its prevalence in Europe ranges from 0.07 to 0.98 patients per 100,000 inhabitants [4] and diagnosis is most commonly made between the ages 20 to 40 years [1]. Differently from other primary immunodeficiencies, monogenic forms count for only 2–10% of patients with CVID. Genes that have been implicated in monogenic inheritance include ICOS, TNFRSF13B (TACI), TNFRSF13C (BAFF-R), TNFSF12 (TWEAK), CD19, CD81, CR2 (CD21), MS4A1 (CD20), TNFRSF7 (CD27), IL21, IL21R, LRBA, CTLA4, PRKCD, PLCG2, NFKB1, NFKB2, PIK3CD, PIK3R1, VAV1, RAC2, BLK, IKZF1 (IKAROS) and IRF2BP2 [5]. However, polygenic inheritance is likely in most cases. According with this genetic heterogeneity, CVID presents a wide range of immunological abnormalities and clinical manifestations. Concerning immunological abnormalities, the EUROclass trial of 2008 distinguished various subgroups of patients on the basis of B cells phenotype [6]. Also various T-cell dysfunctions have been described [7–10]. Clinical manifestations of CVID include infections, inflammatory and autoimmune diseases, and malignancies (cancer and lymphoma) [11]. Frequent and severe infections, mainly of the respiratory and the gastrointestinal tract, are common at the time of diagnosis of CVID and in a large cohort of patients these are the only clinical manifestation. They do not present, in fact, complications related to immune dysregulation, though they may develop infection-related structural changes such as bronchiectasis. Conversely, the remaining part of the patients develops various non-infectious complications including autoimmunity, interstitial lung disease, granulomatous disease, gastrointestinal inflammatory disease, lymphoid hyperplasia, and/or cancer or lymphoma [12]. Because of this wide spectrum of clinical manifestations, distinct clinical phenotypes have been defined. CVID patients can be divided into four distinct phenotypes: 1 - no other disease-related complications (infections only); 2 - cytopenias (thrombocytopenia, autoimmune hemolytic anemia or neutropenia); 3 - polyclonal lymphoproliferation (granuloma, lymphocytic interstitial pneumonia, persistent unexplained lymphadenopathy); 4 - unexplained persistent enteropathy [13]. However these clinical phenotypes are not mutually exclusive, in fact a large number of patients present an overlap of at least two different clinical phenotypes. Taking into account the heterogeneity of the immunological abnormalities and of the clinical manifestations, as well as the increasing number of disease genes identified, it has become clear that CVID is not a single disease but an heterogeneous group of rare diseases characterized by a complex immune dysregulation leading to an absent or strongly impaired antibody production. The heterogeneity and the complexity of genetic, immunological and clinical features make sometimes CVID diagnosis very difficult,

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especially for the physicians that do not manage usually primary immunodeficiencies. Furthermore, not infectious diseases, such as inflammatory, autoimmune and neoplastic complications represent, sometimes, the clinical onset of the immunodeficiency making diagnosis even more challenging. For these reason, there may be a significant delay between the onset of symptoms and the establishment of the diagnosis of CVID [14–16]. The aim of this observational study is to analyze the epidemiological and clinical features of a cohort of 75 Italian CVID patients, and evaluate their possible correlation with morbidity and mortality, suggesting a possible predictive role of IgA serum levels, over 9 (median) years/patient observation period.

2. Material and methods

The patients were a longitudinal cohort. In fact, from 1985 to 2015, 75 patients were diagnosed with CVID at the Division of Allergy and Clinical Immunology of the University of Naples Federico II. Written informed consent was obtained from all participants and the research protocol was in accordance with the principles of the Helsinki II Declaration [17]. All subjects enrolled fulfilled ESID diagnostic criteria of 2014 [18]. Clinical phenotypes were established in according to Chapel 2012 [13] (no other disease-related complications, cytopenias, polyclonal lymphoproliferation, unexplained persistent enteropathy), underlying, however, other significant clinical features. In particular, we distinguished: infections only; autoimmunity: cytopenias, thyroiditis, vitiligo; polyclonal lymphoproliferation: splenomegaly, lymph node hyperplasia; enteropathy; respiratory tract diseases: bronchiectasis, interstitial lung disease, lung nodules, chronic sinusitis; malignancies: lymphoma, gastrointestinal cancer, mammalian cancer, meningioma, lung cancer, rhino-pharyngeal cancer, sarcoma.

Clinical data were retrospectively collected at the data lock: December 31, 2015. All the patients included in the longitudinal cohort had available data of diagnosis. Items in the analysis were sex, IgG, IgM and IgA levels at diagnosis, date of onset of symptoms, date of diagnosis, diagnostic delay, and clinical features.

Comparisons of continuous variables between groups were performed with unpaired *t*-test for normally distributed variables and the Mann-Whitney test for variables that were not normally distributed. For categorical variables the χ^2 test was used.

The relationship between the set of variables and patient survival was examined by means of the Kaplan-Meyer life tables. The length of patient survival was defined as the time from the date of diagnosis/onset to the date of death. Patients who did not die were censored at the point of last follow-up. The effect of each variable was quantified by a survival diagram. Statistical comparisons were based on the non-parametric Wilcoxon test. If not stated otherwise, the level at which results were defined as being statistically significant was set at a P value of <0.01. All reported P values are 2 sided.

Statistical analyses were performed using IBM SPSS Statistics version 20.

3. Results

The data of diagnosis were reported by the Division of Allergy and Clinical Immunology of the University of Naples Federico II between 1985 and 2015 (30 years). We analyzed 75 patients. At the time of data lock (31 Dec 2015) 71 patients were reported to be alive, whereas 4 were deceased (5.3%). No living patient was lost to follow-up. 37 patients (49.3%) were male and 38 patients (50.7%) were female.

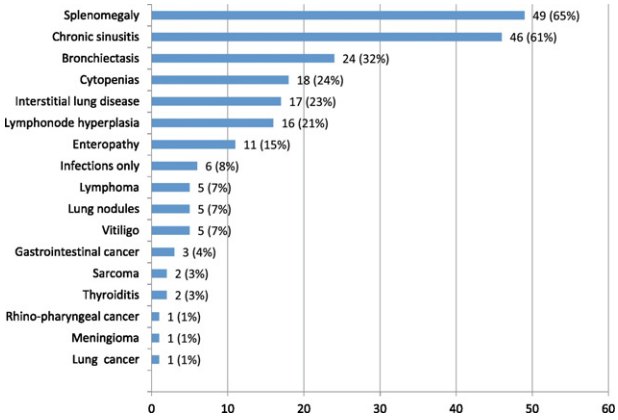


Fig. 1. Clinical features in our cohort of 75 patients (more symptoms affecting the same patient). [Absolute Count (%)].

The mean age up to date 2015, including only living patients was 50.08 years (median = 49.00 years).

All the patients had available the data of onset and the date of CVID diagnosis. The median of age at onset was 32.00 years. The median of age for the age at diagnosis was 40.00 years. The median diagnostic delay was 7.00 years (Interquartile Range (IQR) = 3.00 ÷ 13.00 years) (Table 1). Clinical features are reported in Fig. 1. The main frequencies of patients with overlapped clinical features are reported in Fig. 2.

Starting from time of diagnosis the patients were followed-up for a mean time of 10.24 years (median = 9.00 years, IQR = 4 ÷ 15 years).

The overall median of year of diagnosis was 2006. No significant difference was observed by comparing the diagnostic delay between patients diagnosed before and from 2006 (M-W $P = 0.249$).

The overall median of age at onset was 32.00 years. No significant difference was observed by comparing the diagnostic delay between patients aged before and after 32 years (M-W $P = 0.074$).

10 patients (13.3%) were asymptomatic at the time of diagnosis.

All the patients had available the data of IgA at diagnosis. The median IgA was 8.00 mg/dl (IQR = 6 ÷ 25 mg/dl).We found that both the age at diagnosis (estimate at 75% percentile = 50.00 years) and the age at onset of symptoms (estimate at 75% percentile = 39.00 years) were significantly associated with patient survival (Wilcoxon Test, $P = 0.009$ and $P = 0.003$ respectively) stratified per median of IgA (less than or >8.00 mg/dl) (Figs. 3 and 4).

4. Discussion

As mentioned above, CVID is a collection of rare diseases characterized by primary antibody production failure and unknown etiology [19–20]. Because of the genetic, immunological and clinical heterogeneity, CVID diagnosis may be sometimes very challenging [21–24].

Our cohort of CVID patients presented with a large spectrum of clinical manifestations (Fig.1). Splenomegaly (65%) and infection-related structural changes (chronic sinusitis - 61%, and bronchiectasis - 32%) were the most prevalent features. An overlap of different clinical phenotypes was observed: 29,3% of patients had polyclonal lymphoproliferation + respiratory tract diseases; 12% had autoimmunity + polyclonal lymphoproliferation + respiratory tract diseases; 5,3% had even an overlap of enteropathy + autoimmunity + polyclonal lymphoproliferation + respiratory tract diseases (Fig. 2).

Table 1
Demographic characteristics in our cohort.

Demographic characteristics					
Males (number)	Females (number)	Mean age (years) [SD]	Median age at onset (years) [SD]	Median age at diagnosis (years) [SD]	Median diagnostic delay (years) [SD]
37 (49.3%)	38 (50.7%)	50.08 [15.81]	32 [17.82]	40 [16.01]	7 [8.06]

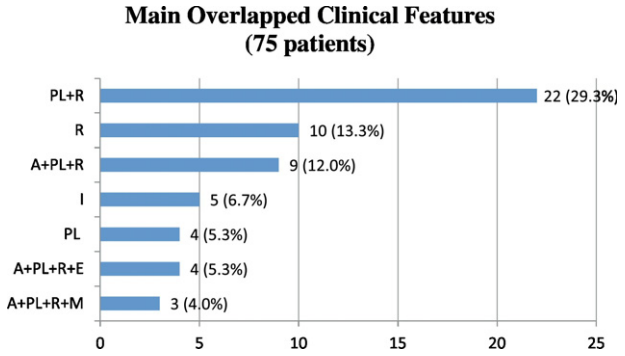


Fig. 2. Frequencies of main overlapped clinical features per patient. Legend [Absolute count patient, %], n = 75 patients: PL + R [22, 29.3%] = Polyclonal lymphoproliferation + Respiratory tract diseases. R [10, 13.3%] = Respiratory tract diseases. A + PL + R [9, 12.0%] = Autoimmunity + Polyclonal lymphoproliferation + Respiratory tract diseases. PL [4, 5.3%] = Autoimmunity + Polyclonal lymphoproliferation + Enteropathy + Respiratory tract diseases. I [5, 6.7%] = Infections only. A + PL + R + E [4, 5.3%] = Polyclonal lymphoproliferation. A + PL + R + M [3, 4.0%] = Autoimmunity + Polyclonal lymphoproliferation + Respiratory tract diseases + Malignancies.

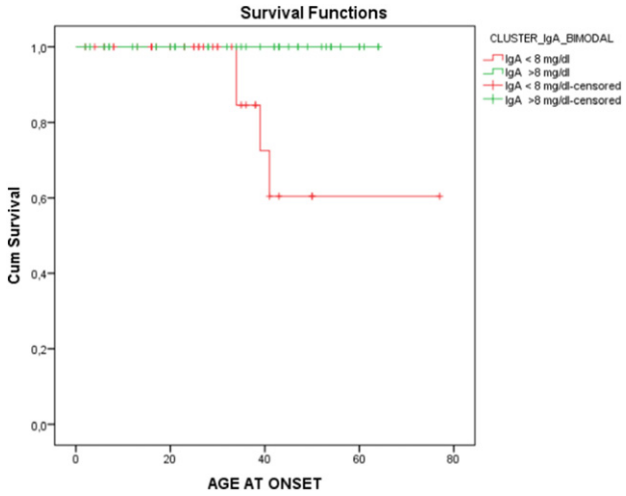


Fig. 4. Age at onset (estimate at 75% percentile = 39.00 years, SE = 4.08) and patient survival (Wilcoxon Test, $P = 0.003$) stratified per median of IgA (less than or >8.00 mg/dl).

The cohort was followed-up for a maximum of 30 years (mean time of 10.24 years, median of 9 years) and 4 patients deceased during the period of observation. These patients died for lymphoma, lung cancer, respiratory failure and acute myocardial infarction respectively. Accordingly, in a large Italian cohort, mortality over a 4 decades observation was mainly due to not hematological malignancies, lymphomas or respiratory failure [25]. We tried to assess a correlation between any of the clinical features and patients' survival. We found that an higher age at the diagnosis of CVID was significantly associated with a reduction of patients survival if stratified per median of IgA (less than or >8.00 mg/dl) (Fig. 3). Also, we assessed the age of onset of the disease and found that the higher age at onset of symptoms was significantly associated with a reduction of patients survival when stratified per median of IgA (Fig. 4). Resnick et al., in a large cohort of CVID patients, demonstrated that mortality was significantly correlated both with earlier age at diagnosis and the age at symptoms onset [26]. However, that cohort of CVID patients was heterogeneous for demographic characteristics, including also patients with a pediatric onset. In addition the results were not stratified per IgA values. The cut-point to identify the patients with low IgA levels in our cohort was up to 8.00 mg/dl, since this value was the median of the IgA serum levels. This value may be considered equivalent to the cut-point of 7.00 mg/dl fixed by the ESID to characterize patients with absolute IgA deficiency [18]. These findings correlate IgA levels at diagnosis with patients survival and

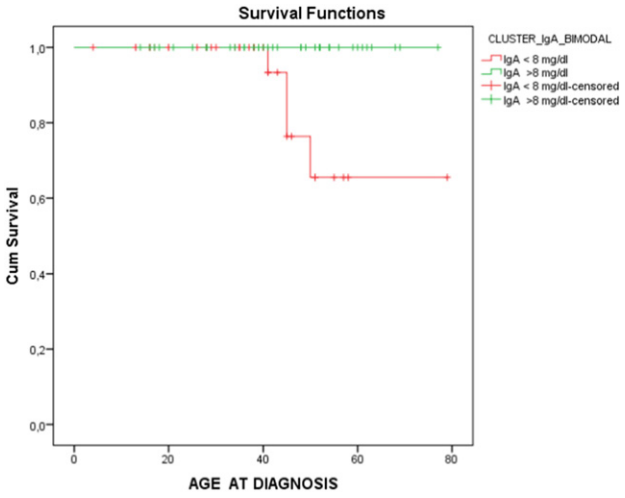


Fig. 3. Age at diagnosis (estimate at 75% percentile = 50.00 years, SE = 4.67) and patient survival (Wilcoxon Test, $P = 0.009$) stratified per median of IgA (less than or >8.00 mg/dl).

contribute to identify a subset with a worse prognostic outcome among the patients with marked reduction of serum IgA levels at diagnosis (IgA < 8.00 mg/dl). Quinti et al. demonstrated that IgA serum levels at the diagnosis lower than 7 mg/dl was an independent risk factor for pneumonia during the course of the disease (hazard risks 2.6), thus defining a sub-group of patients with a worse prognosis [27]. In our cohort, the fact that, in the subgroup of CVID patients with very low IgA serum levels, the higher age at diagnosis and the higher age at onset of symptoms were significantly associated with a reduced patient survival, can be considered an indirect markers of diagnostic delay. In fact, it is plausible that patients receiving diagnosis and/or telling the onset of symptoms at an higher age, have suffered from clinical manifestations, disease-related complications and immunological abnormalities of CVID since many years before [28–31]. We maintain that diagnostic delay can be considered a negative prognostic indicator in CVID patients with very low IgA serum levels at diagnosis (<8.00 mg/dl). Because of the heterogeneity of the disease, delay in diagnosis is a frequent occurrence in CVID and ranges widely in the various European records [12,28]. In a large Italian cohort it was estimated in 8.9 years [16]. Diagnostic delay may be due to a number of conditions: the clinical onset of the immunodeficiency may be atypical, because, in a large number of cases, the first clinical manifestation of the disease is not infectious [32–36]. Moreover, the onset of the varied clinical manifestations and laboratory abnormalities do not necessarily coincide [37]. Finally, clinical manifestations that can complicate the primary immunodeficiency, as B lymphoproliferative diseases or enteropathy, can be per se cause of a secondary hypogammaglobulinemia [38–46]. Beyond the effects on patient survival, diagnostic delay also affects the costs of the management of CVID, and more generally of primary immunodeficiency (PID). In a study on the economic impact of PID conducted by the Jeffrey Modell foundation on >60,000 U.S. patients, costs of medical care per patient before and after PID diagnosis were evaluated [47]. So they estimated that the diagnosis of PID and the initiation of Ig replacement therapy led to an annual saving per patient of $ 78,166 (including the cost of Ig replacement therapy). We conclude that early diagnosis is the first goal to achieve in order to improve the prognostic outcome of CVID. Furthermore, our results highlight the importance of IgA serum levels at diagnosis in defining a subset of CVID patients with a worse prognosis. Finally, an appropriate diagnosis reduces the economic impact of CVID.

Appendix A. Supplementary data

Supplementary tables

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