ORIGINAL ARTICLE

Phenotyping and follow up of forty-seven Iranian patients with common variable immunodeficiency

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Received 8 March 2015; accepted 29 April 2015
Available online 29 July 2015

KEYWORDS
Common variable immune deficiency (CVID); Follow up; Consanguinity; Age; Iran

Abstract

Background: Common variable immune deficiency (CVID) is a heterogeneous syndrome with a wide variety of signs and symptoms. This study describes the phenotyping and survival of the CVID patients in the allergy and clinical immunology department of Rasol-E-Akram Hospital of Iran University of Medical Sciences in Tehran.

Method: We retrospectively reviewed hospital files of CVID patients in our department until January 2014. All patients were diagnosed with standard diagnostic criteria of CVID, treated and visited monthly, during the follow-up period. We divided the patients into four phenotypes; infection only, cytopenia, polyclonal lymphocytic infiltration and unexplained enteropathy. The immunologic, demographic and clinical findings in different phenotypes were analysed.

Results: The study included 47 CVID patients with mean age at onset of symptoms and diagnosis of 11.2 and 20.2 years, respectively. Phenotyping of our patients was: only infection (62%), cytopenia (26%) and PLI (19%) and 94% of cases had only one phenotype. We did not find a significant relation between the clinical phenotypes and immunologic or demographic data.

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http://dx.doi.org/10.1016/j.aller.2015.04.005
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Introduction

Common variable immune deficiency (CVID) is a heterogeneous syndrome characterised by hypogammaglobulinaemia, recurrent infections, immune dysregulation and propensity to malignancies. The first case of CVID was reported in 1953 by Janeway C.A. Today it is the most common symptomatic primary immune deficiency and its prevalence is 1 in 25,000 to 50,000 in general populations. The most common infectious manifestations of CVID are sinopulmonary and gastrointestinal infections. The only available treatment for CVID is intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG) and appropriate management of its complications. The mortality rate for CVID patients has been estimated to be 6% in 11.5 years and 20% in about four decades in western countries. The purpose of this study is to classify a group of Iranian CVID patients according to the clinical phenotypes defined by Chapel et al. for European patients, and to determine the relationship between these phenotypes and morbidity, mortality, complications, age at onset of the disease and parental consanguinity.

Methods

The Allergy and Clinical Immunology department of Rasol E Akram Hospital of Iran University of Medical sciences, Tehran, Iran is a referral department for primary immune deficient patients of all ages. We retrospectively reviewed hospital files of the immunology clinic of this department until January 2014 and found 47 CVID patients who were diagnosed according to PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiency) diagnostic criteria. Patients are diagnosed as CVID when at least four years old, to exclude transient hypogammaglobulinaemia of infancy. Genetic testing to exclude autosomal recessive and X-linked agammaglobulinaemia and hyper IgM syndromes was done as a part of genetic consultation with the Research Center for Immunodeficiencies in the Children’s Medical Center of Tehran University of Medical Sciences; cases with known monogenic defect were excluded from the cohort. These patients are being visited at least monthly and treated with IVIG and antibiotics as needed. According to their Clinical and paraclinical data and based on criteria described by Chapel et al., we divided the patients into four phenotypes including; infection only (with no complication other than infections); cytopenia (thrombocytopenia, autoimmune haemolytic anaemia or neutropenia); polyclonal lymphocytic infiltration (granuloma, persistent unexplained lymphadenopathy or lymphoid interstitial pneumonitis (LIP); and unexplained enteropathy (enteropathy insensitive to gluten withdrawal). Information on overlapping phenotypes was also recorded.

Statistical analysis was carried out using STATA 10 software. Quantitative data were reported as mean and range and descriptive variables as proportion. T-test and analysis of variances (ANOVA) were used to compare means and chi-square test was used to compare proportions. P-values less than 0.05 were considered as significant.

Results

Characteristics of patients

Our study included 47 CVID patients with a mean age of 27 years (range: 4–63) and mean follow-up time of 6.8 years (range: 0.5–23). The mean age of onset of CVID symptoms was 11.2 years (range: 1–32). Table 1 includes demographic and immunologic data, phenotypes and complications of the patients. Phenotyping of our patients was: only infection (62%), cytopenia (26%) and PLI (19%) with no case in the unexplained enteropathy group. 94% of our cases had only one phenotype. We compared immunologic and demographic data between the patients with the infection only phenotype and other phenotypes all together and found no significant difference, except the rate of splenomegaly which was significantly lower in the infection only phenotype (10% vs. 71%, P value = 0.00001). In 85% of patients the first sign of immunodeficiency was infections, while autoimmune or auto-inflammatory manifestations were the first sign in the other 15%. Sino pulmonary infections were the most common infection of our CVID patients (98%) (Table 2). Twenty patients (43%) complained from chronic/recurrent diarrhoea; among them, eight cases were diagnosed to have inflammatory bowel disease (IBD), five had recurrent bacterial gastroenteritis, two had cytomegalovirus enterocolitis, one had chronic resistant giardiasis, while in four patients, recurrent diarrhoea without endoscopic and pathologic signs of IBD or enteropathy persists with no identifiable germ that responds partially to antibiotic therapy.

Four patients with a mean age at onset of 17 years had history of chronic wart; among them two had IBD, one had recurrent diarrhoea and none of them had neutropenia. Three patients with a mean age at onset of nine years and no lymphopenia had history of oral thrush; among them one
Table 1  Demographic and immunologic data of 47 Iranian CVID patients.

<table>
<thead>
<tr>
<th>Total</th>
<th>CVID phenotypes</th>
<th>CVID complications</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only infection</td>
<td>Cytopenia/PLI</td>
<td>Autoimmunity</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Patients number (%)</td>
<td>47</td>
<td>29</td>
<td>18</td>
</tr>
<tr>
<td>Male (%)</td>
<td>47</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>27</td>
<td>24.8</td>
<td>30.6</td>
</tr>
<tr>
<td>Mean age at onset (years)</td>
<td>11.2</td>
<td>9.2</td>
<td>14.5</td>
</tr>
<tr>
<td>Mean age at diagnosis (years)</td>
<td>20.2</td>
<td>16.6*</td>
<td>26</td>
</tr>
<tr>
<td>Mean follow up time (years)</td>
<td>6.9</td>
<td>8.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Mean diagnostic delay (years)</td>
<td>9</td>
<td>7.4</td>
<td>11.5</td>
</tr>
<tr>
<td>Parental consanguinity rate (%)</td>
<td>47</td>
<td>52</td>
<td>39</td>
</tr>
<tr>
<td>IgG mg/dl, (mean)</td>
<td>198</td>
<td>206.8</td>
<td>183.9</td>
</tr>
<tr>
<td>IgM mg/dl, (mean)</td>
<td>41</td>
<td>34</td>
<td>52</td>
</tr>
<tr>
<td>IgA mg/dl, (mean)</td>
<td>20</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>CD3 (%)</td>
<td>77</td>
<td>77</td>
<td>78</td>
</tr>
<tr>
<td>CD4 (%)</td>
<td>36</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>CD4/CD8 ratio</td>
<td>1.15</td>
<td>1.1</td>
<td>1.22</td>
</tr>
<tr>
<td>CD19 (%)</td>
<td>7.0</td>
<td>6.6</td>
<td>7.6</td>
</tr>
</tbody>
</table>

* P value <0.05.
developed leukaemia, one had history of CMV pneumonia and LIP and one had history of recurrent pneumonia and warts since 20 years of age who died because of progressive multifocal leuкоencephalopathy with John Cunningham virus at 30 years old.

Parental consanguinity

Patients with parental consanguinity had significantly lower age of onset of CVID symptoms (7.5 vs. 14.6 yrs, \( P \) value = 0.01), lower age of diagnosis (14.5 vs. 25.2 yrs, \( P \) value = 0.002) and higher baseline IgG level (266 vs. 141 mg/dl \( P \) value = 0.01). Other clinical and immunological data were not significantly different.

Autoimmunity

Autoimmunity was detected in 23 cases (49%) and 12 of them had more than one autoimmune disorder. Autoimmunity was the first manifestation of CVID in seven patients, but in six cases it was occurring during five years, in four cases in a period of 5–10 years and in six cases 10 years after CVID onset. Fifty seven percent of patients with autoimmunity have parental consanguinity vs. 37% in the others, which was not significant (\( P \) value = 0.19). The most common autoimmunity was idiopathic thrombocytopenic purpura (ITP) which was detected in 12 (26%) cases (Table 3). Three cases underwent splenectomy to treat ITP; two of them had this procedure before CVID diagnosis. IVIG replacement in routine doses for treatment of hypogammaglobulinaemia in CVID did not modify the pattern or recurrence of autoimmune disorders significantly.

The mean age of onset of CVID symptoms in cases with autoimmune manifestations was 14.2 years vs. 8.4 years in others (\( P \) value = 0.03) and 48% of them had an age of onset of >16 years vs. 21% of cases without autoimmunity (\( P \) value = 0.05).

IBD was diagnosed in eight (17%) cases, from which 62% also had other autoimmune disorders. The diagnosis of IBD was made according to clinical manifestations, endoscopic view, and pathological findings. In all these cases, IBD was diagnosed prior to the CVID. All the patients were treated with local and systemic anti-inflammatory and immunosuppressive drugs successfully. Of IBD cases one died because of severe hepatic failure and two cases developed malignancy in the course of disease.

Table 2  Infective disorders in 47 Iranian CVID patients.

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Infective disorder</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Infections</td>
<td>Sino pulmonary infections</td>
<td>46 (98)</td>
</tr>
<tr>
<td></td>
<td>Chronic/recurrent diarrhoea</td>
<td>12 (25)</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal infections (arthritis, osteomyelitis)</td>
<td>10 (21)</td>
</tr>
<tr>
<td></td>
<td>Skin abscess, cellulitis</td>
<td>9 (19)</td>
</tr>
<tr>
<td></td>
<td>Central nervous system infection (meningitis, brain abscess)</td>
<td>6 (13)</td>
</tr>
<tr>
<td></td>
<td>Visceral abscess</td>
<td>3 (6)</td>
</tr>
<tr>
<td></td>
<td>Skin warts</td>
<td>4 (9)</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus (pneumonia, colitis, gastroenteritis)</td>
<td>4 (9)</td>
</tr>
<tr>
<td></td>
<td>Varicella (recurrent or severe zona, pneumonia)</td>
<td>4 (9)</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex virus (sever skin infection or gingivostomatitis)</td>
<td>3 (6)</td>
</tr>
<tr>
<td></td>
<td>Progressive multifocal leuкоencephalopathy with John Cunningham virus</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Viral infections</td>
<td>Oral thrush</td>
<td>3 (6)</td>
</tr>
<tr>
<td></td>
<td>Pneumocystis jirovecii pneumonia</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fungal infections</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3  Autoimmune and auto-inflammatory disorders in 47 Iranian CVID patients.

<table>
<thead>
<tr>
<th>Autoimmune – Auto-inflammatory disorders</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune – idiopathic thrombocytopenic purpura (ITP)</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Autoimmune haemolytic anaemia (AHA)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Aphthous lesions</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Pernicious anaemia</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diabetes mellitus type 1</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Malignancies

Malignancy occurred in the follow up of six patients (13%). One patient had two different malignancies; breast cancer at 55 years old and gastrointestinal adenocarcinoma at 63 years old. Malignancy risk per case was 15%. Malignancies occurred in a period of 3–33 years after onset of CVID (mean of 17.4 years). Hodgkin’s lymphoma was the most common malignancy (three cases, 6%). Other malignancies included: breast cancer, gastrointestinal cancer, leukaemia, and brain cancer. The mean age at onset and age at diagnosis of CVID in patients with malignancy was significantly higher than CVID cases without malignancy (18.5 and 38.8 vs. 10.2 and 18.7 years).
years, respectively) (P values = 0.04 and 0.03, respectively). Splenomegaly (years before the onset of malignancy) was more common in CVID cases with malignancy than the others (83% vs. 25%) (P value = 0.004) (Table 1).

Age at onset of CVID symptoms

According to the age of onset, patients were divided into two groups; 31 cases below and 16 cases above 16 years. Patients with age of onset of less than 16 years had higher baseline IgG level (236 vs. 120 mg/dl, P value = 0.027) and higher consanguinity prevalence (58% vs. 25%, P value = 0.03). Other differences in clinical and immunologic data were not significant.

Mortality

During the follow up period, three cases (6%) died. Causes of death were malignancy, hepatic failure and progressive multifocal leukoencephalopathy. Mean age of onset, follow up time and age at death in these cases were 24, 4, and 36 years, respectively.

Discussion

This study showed that the mean age of onset of CVID symptoms is about 11.2 years, while this was reported to be lower than three years in most previous reports from other centres in Iran.6,18-21 In Western countries the CVID symptoms usually begin in the second and third decades of life.3,5,17 It was hypothesized that this difference may be due to the high rate of parental consanguinity in Iranian CVID cases (72%),21 compared to Western countries. In the French DEFI (deficits immunitaires) study the rate of parental consanguinity in CVID patients was 5.5% and there was no relationship between age of onset and parental consanguinity.22 In this study, age at onset and age at diagnosis of CVID were significantly lower in cases with parental consanguinity. Our department is built in a general hospital that is a referral centre for children and adult CVID patients and in addition to lower rate of parental consanguinity (47% vs. 72%), this can be another explanation of the higher age of onset compared to other centres that are in children’s hospitals.

Clinical phenotypes and the severity of CVID has been shown to be related to parental consanguinity in some registries,21,22 but in our study there is no relationship between CVID phenotypes or complications such as autoimmunity or malignancy and parental consanguinity.

This study showed that higher age of onset of CVID is significantly associated with the higher risk of malignancy, which has been shown in previous studies.23 We also found significant association between these variable and autoimmune disorders.

As in other studies,11,24,25 infections are the first manifestation in most (85%) of our CVID cases and autoimmune or auto-inflammatory manifestations are the first sign in the rest of the cases. Sino pulmonary and gastrointestinal infections were the most common infections in our study, but 25% of patients had problematic viral infections which can be due to associated abnormalities in T cell and innate immunity.26-28

Autoimmunity has been reported in about 20–25% of CVID patients.11,29 In an Iranian report in a children’s medical centre, 11% of CVID patients had autoimmunity21 and the autoimmunity rate was not associated with parental consanguinity and age at onset. In this study, 49% of CVID cases had autoimmunity, and ITP was the most common type. The age at onset was significantly higher in CVID cases with autoimmunity, with no significant difference in parental consanguinity rate.

Malignancies has been reported in 2.5–8% of CVID patients21 and non-Hodgkin’s lymphoma is the most common type in most reports.1,21,30 In our study, 13% of patients are complicated with malignancy and Hodgkin’s lymphoma was the most common. In another study from Tehran Children Medical Center, the malignancy rate in CVID patients was 10% after 5.2 years follow up and Hodgkin’s lymphoma was the most common.2 Age at onset of CVID symptoms was significantly higher in cases with malignancy with no significant difference in consanguinity rate.

We found no association between parental consanguinity, IgG, IgM, IgA, CD4 and CD8 levels with clinical phenotypes while previous studies have shown significant associations.14,17,21,12

An Iranian study in 2007 reported 35% mortality during 6.5 years post diagnosis,31 while in our study 6% of patients died in 6.8 years follow up period. The lower mortality rate in our study can be related to greater availability of IVIG drugs, supportive care and early diagnosis of disease due to increased overall awareness of physicians and patients.

Higher age at onset and probable genotypic differences in our population of CVID in comparison to the Children’s Medical Center can be another reason for the difference in the mortality rate.

Conclusions

Age at onset of CVID symptoms and parental consanguinity may have an important role in CVID manifestations. The survival rate of CVID patients has been improved in recent years due to socioeconomic improvements.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in this study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients mentioned in the article. The author for correspondence is in possession of this document.
Conflict of interest

The authors have no conflict of interest to declare.

References

En el paciente polisensibilizado

Crecemos en concentración  Crecemos en beneficios

POSIBLES COMBINACIONES
- Gránumes + Olea
- Gránumes + Cupressus
- Gránumes + Parietaria
- Cupressus + Olea
- Olea + Parietaria
- Cupressus + Parietaria
- Salsola + Gránumes
- Salsola + Olea
- Salsola + Parietaria
- Platanus + Gránumes

Prosima combinación

Dos tratamientos en uno

- Máxima concentración de cada fuente alérgica sin dilución en la mezcla
- FUENTE ALÉRGICA 1
- FUENTE ALÉRGICA 2
- 100% de la concentración de cada una de las fuentes alérgicas

Con cuantificación de alérgenos mayores1-9

- Comodidad para el paciente polisensibilizado
- Ahorro para el paciente frente a vacunas individuales

Alérgenos polimerizados y adsorbidos en hidróxido de aluminio que reducen su capacidad de unión a IgE. El tratamiento consiste en una preparación retard en la que los alérgenos previamente polimerizados son liberados de manera gradual. Los alérgenos son activados de manera individual, a la vez que se produce una concentración 2B16MPE08 02/16

1. NOMBRE DEL MEDICAMENTO: ALLERGOVAC POLIPLUS. 2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA: Extraitos alérgenos estándarizados biológicamente en unidades TPU/mg, molinizado con glatiradex y analizado por técnicas inmunocromatográficas. Se presentan adosados en hidratos de aluminio y suspendidos en solución salina isotónica. El escrutinio con efecto conocido. Este medicamento contiene menos de 1 ng/ml de ados por alérgeno, por lo que se considera exentamente "esóedo de ados". Para consultar la lista completa de reactivos ver sección 6.1. FORMA FARMACÉUTICA: Suspensión estéril para inyección por vía subcutánea. 4. DATOS CLÍNICOS. 4.1 Indicaciones terapéuticas: Enfermedades alérgicas respiratorias mediadas por IgE y causadas por alérgenos, que incluyen: foto, miconjarina y asma bronquial. 4.2 Posología y forma de administración: Posología: La relación consignada en el escala progresiva de la dosis hasta alcanzar la dosis de mantenimiento. ALLERGOVAC POLIPLUS se puede administrar dosándose dosis diarias, la Pauta 1 día, en la que se logra a la dosis de mantenimiento al cabo de un año, y la Pauta rápida, en la que se logra a la dosis de mantenimiento a cabo de 11 meses. 6.4 Fenol, hidróxido de aluminio, cloruro de sodio, hidróxido de sodio y agua para inyección. 6.3 Periodo de validez: 24 meses. 6.2 Incompatibilidades: 3. V01A. Grupo farmacoterapéutico: Alergenos. Código ATC: 5.4 Interacción con otros medicamentos y otras formas de interacción: Se produce cuando el tratamiento ha llegado a la dosis de mantenimiento, no habiéndose presentado reacciones adversas de importancia, podrá continuarse. La inmunoterapia con alérgenos alimenticios puede ser utilizada en centros de salud acreditados. 4.9 En caso de una sobredosis accidental o de una aplicación incorrecta del tratamiento, pueden presentarse cuadros de reacciones adversas, algunas de ellas severas, como la desviación en el aparato digestivo, con posibilidad de hipotensión arterial y disminución de la presión arterial sistémica. Archivos de la FPMF. - 6.5. Número de viales y contenido del envase: En un tubo contienen 1-2 viales de 2,5 ml cada uno. 4.6 Fertilidad, embarazo y lactancia: Por tanto si la administración de éstos se interrumpe, debe valorarse la posibilidad de modificación de la pauta terapéutica. En el apartado 4.3 Contraindicaciones se hace referencia a los medicamentos que no deben ser administrados durante un posible tratamiento con POLIPLUS. 4.7 Efectos sobre la capacidad de conducir y utilizar máquinas: Se produce con frecuencia en pacientes que se presentan en nefritis aguda o crónica, infecciones oportunistas, como alergia intestinal, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópica, dermatitis atópe...