

Health Policy for Common Variable Immunodeficiency: Burden of the Disease

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■ Abstract

Background: Common variable immunodeficiency (CVID) is a primary immunodeficiency disease characterized by recurrent infections and increased susceptibility to autoimmunity and malignancy.

Objectives: This study was performed to estimate the burden of CVID in Iran during 1985-2008 based on incidence, mortality, and disability-adjusted life-years (DALY).

Methods: The methods developed by the World Health Organization for national burden of disease studies were applied to estimate the incidence of disease and thus calculate the years of life lost due to premature mortality (YLL), years living with disability (YLD), and DALYs.

Results: The average age-adjusted incidence of CVID was 1 case per 200 000 per year; the average age-adjusted prevalence was 1 case per 91 000 per year. The burden of CVID (DALYs) was 25.21 years per 100 000 individuals (17.86 for YLL and 7.35 for YLD). DALYs increased significantly in patients aged 5-14 years and in those with polyclonal lymphocytic infiltration phenotypes ($P < .001$).

Conclusions: Based on the measurement of DALY in patients with CVID, reducing the rate of premature death in the polyclonal lymphocytic infiltration phenotype and the rate of infectious episodes in patients with the infectious only phenotype and appropriate management with regular intravenous immunoglobulin represent the best approach to decreasing the burden of CVID.

Key words: Common variable immunodeficiency. Disability-adjusted life-years. Years of life lost. Years living with disability.

■ Resumen

Antecedentes: La inmunodeficiencia común variable (IDCV) es un trastorno de inmunodeficiencia primaria caracterizado por infecciones recurrentes y una mayor predisposición a autoinmunidad y neoplasias malignas.

Objetivos: Este estudio se realizó para estimar la carga de la IDCV en Irán durante el período 1985-2008 sobre la base de la incidencia, la mortalidad y los años de vida ajustados por discapacidad (AVAD).

Métodos: Se aplicaron los métodos establecidos por la Organización Mundial de la Salud para estudios de carga nacional de enfermedad con el objeto de estimar la incidencia de enfermedad y calcular, de este modo, los años de vida perdidos por muerte prematura (AVPP), los años vividos con discapacidad (AVD) y los AVAD.

Resultados: La incidencia media ajustada por edad de la IDCV fue de 1 caso al año por cada 200.000; la prevalencia media ajustada por edad fue de 1 caso al año por cada 91.000. La carga de la IDCV (AVAD) fue de 25,21 años por cada 100.000 individuos (17,86 por AVPP y 7,35 por AVD). Los AVAD aumentaron de forma significativa en pacientes con edades comprendidas entre 5 y 14 años y en aquellos con fenotipo de infiltración linfocítica policlonal ($p < 0,001$).

Conclusiones: De acuerdo con el cálculo de los AVAD en pacientes con IDCV, la mejor estrategia para disminuir la carga de la IDCV es reducir la tasa de muerte prematura en pacientes con fenotipo de infiltración linfocítica policlonal y la tasa de episodios infecciosos en pacientes con solo fenotipo infeccioso, así como instaurar un tratamiento adecuado con perfusiones periódicas de inmunoglobulina intravenosa.

Palabras clave: Inmunodeficiencia común variable. Años de vida ajustados por discapacidad. Años de vida perdidos. Años vividos con discapacidad.

Introduction

Primary immunodeficiency diseases (PIDs) are a group of inherited disorders in which components of the immune system are missing or do not function properly. Patients usually experience their first symptoms during childhood, although some types may not be recognized until adulthood. Common variable immunodeficiency (CVID) is the most common symptomatic PID and has been recognized as a clinical entity for more than 5 decades; however, our understanding of the disease is incomplete [1].

Although PIDs were believed to be quite rare, the incidence of CVID can range from 1 case per 50 000 per year to 1 case per 200 000 per year in the general population; the prevalence of disease is estimated to be about 1 in 10 000 to 1 in 200 000 individuals, depending on the diagnostic skills and medical resources available in different countries [2-10].

Calculation of disease burden is necessary for health planning, research, resource allocation, and generation of policies and practices. Moreover, baseline burden facilitates the analysis of the cost-effectiveness of new interventions and programs [11].

The overall national burden of diseases (NBD) in Iran was calculated to be about 21 500 disability-adjusted life-years (DALYs) for all diseases and injuries per 100 000 citizens [1]. However, the exact burden of PIDs has not yet been estimated, as these diseases could be distributed in different categories—mainly infectious diseases, diseases of the blood-forming organs, and neoplasms—because of inaccurate diagnosis, multiple organ involvement, and different phenotypes [12].

Therefore, individualized measurement of the burden of PID is necessary. As CVID is the most common symptomatic PID, it can be considered the primary candidate when calculating disease burden. The objective of this study was to estimate the burden of CVID in Iran during 1985-2008 based on incidence, mortality, and DALYs.

Materials and Methods

The diagnostic criteria of CVID include reduced levels of at least 2 serum immunoglobulin (Ig) isotypes (IgG, IgA, or IgM) by 2 standard deviations from normal mean values for age in patients older than 4 years and exclusion of other well-defined primary antibody deficiencies. Patients were classified according to 5 clinical phenotypes: autoimmune disorders, polyclonal lymphocytic infiltration, malignancy, enteropathy, and infections only. This division is consistent with the classification criteria used in Europe [1].

All epidemiological indexes in Iran, including incidence, prevalence, case fatality rate, and duration of CVID, were estimated based on data from the Iranian Primary Immunodeficiency Registry at the Children's Medical Center [13,14], a pediatric center of excellence in Iran that is affiliated to Tehran University of Medical Sciences and is the referral center for both pediatric and adult patients with PIDs [15]. These data are assumed to be a good approximation of all cases in Iran. They were taken from the national census (1985 and 2008) and extrapolated.

The population denominator data were obtained according to the country profile of the environmental burden of disease of the World Health Organization (WHO; <http://www.who.int/countries/irn/en/>). In this report, gross national income per capita was US\$10 800 and life expectancy was 71 years. The average size of the population in Iran during the study period was approximately 74 million inhabitants. Refugees from other countries were not counted as part of the population for calculation of incidence, prevalence, and mortality rates. Age-standardized incidence and mortality rates were calculated using the direct method, with the WHO world population as a standard [10]. Linear regression was performed in the analysis of incidence and mortality trends using Dismod II (<http://www.hsph.harvard.edu/Organisations/bdu/dismod/index.html>) [16].

The estimated burden of CVID is expressed in terms of a summary health-outcome measure, DALYs, which combines measurement of premature mortality and disability. This indicator is the aggregation of years of life lost (YLL) and years living with disability (YLD) at the population level and thus reflects the burden of disease in the population. The method used in this study to estimate DALYs was largely based on that developed for the global burden of disease study by Murray et al [11]. YLL and YLD were measured by modifying the counts of life expectancy based on a discount rate ($r=3\%$) and age weighting constant ($C=0.1658$).

For YLD, the duration of CVID was taken as the total time of diagnostic delay and follow-up, as no patients are completely cured from this genetic disease. Length of follow-up, overall mortality and time since diagnosis were calculated for each patient.

Moreover, the disability weight of CVID as a PID was assumed to be that of AIDS. The disability weight for recurrent infections, minor symptoms, and highly active antiretroviral therapy in AIDS was 0.55 according to mean visual analog scale values in 5 Western European countries and professional category [17]. Furthermore, we rechecked this count with analog scale values, time trade off, person trade off, and standard gamble methods in a selected number of CVID patients and clinical immunologists.

DALYs were compared between different phenotypes using an analysis of variance, and statistical significance was set at $P<.05$.

Results

All CVID patients with Persian origin during 1984-2008 were included in the study (54.2% males and 45.8% females). Median age was 12.4 years (range, 4-56); median age at onset was 2 (range, 0.6-46) years with a median diagnostic delay of 4 years (range, 0.25-39). Age at onset of CVID had a bimodal distribution. Most patients presented in mid-childhood (5-15 years); few presented in early to mid-adulthood (20-30 years). The average annual age-adjusted CVID incidence rate was 1 case per 200 000 persons for both sexes. The corresponding prevalence rate was previously estimated at 1 in 91 000 persons [14]. In both sexes, the highest incidence rates were registered

Table 1. YLD, YLL, and DALY per 100 000 Persons due to CVID by Age and Sex in Iran: Average Values for the Period 1984-2008

Sex	Age, y	No. of Cases	Duration of Disease (Onset to Follow-up)	YLD (Without Severity)	YLD (0.5)	No. of Deaths	Life Expectancy	YLL	DALY
Both		1.09		14.7	7.35	0.42		17.86	25.21
Male	<4	0.19	5.6	1.06	0.53	0.11	33.26	3.65	4.18
	5-14	0.24	7.8	1.87	0.93	0.14	36.71	5.13	6.06
	15-24	0.1	14.3	1.43	0.71	0.06	34.31	2.05	2.76
	25-34	0.09	22.4	2.01	1.00	0.05	29.02	1.45	2.45
	>35	0.07	23.9	1.67	0.83	0	22.85	0	0.83
	Total	0.69		8.61	4.30	0.26		12.30	16.6
Female	<4	0.13	5.5	0.72	0.36	0.04	33.37	1.33	1.69
	5-14	0.17	8.4	1.42	0.71	0.08	36.86	2.94	3.65
	15-24	0.08	14.7	1.17	0.58	0.02	34.52	0.69	1.27
	25-34	0.06	25.3	1.52	0.76	0.02	29.31	0.58	1.34
	>35	0.06	22.6	1.35	0.67	0	23.26	0	0.67
	Total	0.5		6.18	3.09	0.16		5.56	8.65

Abbreviations: CVID, common variable immunodeficiency; DALY, disability-adjusted life-years; YLD, years living with disability; YLL, years of life lost.

in patients aged 5 to 14 years. The median duration of follow-up was 4.4 years (range, 0.5-18); therefore, the median total duration of disease (from onset to end of follow-up) was 8.5 (1-24) years.

For calculation of YLL, the average annual age-adjusted mortality rate due to CVID was 0.42 per 100 000 for the whole population. The highest mortality rates were present in patients aged 5-14 years (0.14 per 100 000 in males and 0.08 per 100 000 in females). Moreover, the average case fatality rate in each year was 0.018.

Table 1 shows complete measurement of DALYs due to CVID in 100 000 individuals. Based on this data, overall DALY was 25.21 (YLL, 17.86; YLD, 14.7) years

per 100 000 individuals, which is equal to a total of 2063.1 years (YLL=363.4+1699.7) lost due to CVID for the whole population.

The burden of CVID, expressed as YLD, YLL, and DALY, was greater for males than for females ($P<.001$). The highest average DALY rates for males and females were recorded in patients aged 5 to 14 years ($P=.02$) (Table 1).

The effects of different phenotypes of CVID are shown in Table 2. Infectious only phenotypes had the highest YLD (2.09; 28% of total YLD), which entailed significantly greater disability for CVID patients than for other phenotypes. YLD and DALY were higher in patients with polyclonal lymphocytic infiltration than in other patients ($P<.001$).

Table 2. YLD, YLL, and DALY per 100 000 People From Different Phenotypes of Patients With CVID

Sex	Age, y	New Incident Cases, %	Duration of Disease (Onset to Follow-up)	Disability Weight	YLD	Mortality Rate	YLL	DALY
All	15 (3-59)	1.09	14 (3-42)	0.5	7.35	0.42	17.86	25.21
Polyclonal lymphocytic infiltration	11 (3-34)	37%	10 (5-18)	0.55	1.89	0.21	8.53	10.42
Infections only	13 (4-19)	45%	7 (3-22)	0.6	2.09	0.07	5.36	7.45
Autoimmunity	19 (14-44)	10%	15 (6-30)	0.4	0.93	0.03	0.21	1.14
Enteropathy	17 (10-37)	10%	15 (5-23)	0.45	1.12	0.03	0.23	1.35
Lymphoid malignancy	16 (12-59)	10%	16 (5-42)	0.5	1.32	0.06	3.53	4.85
<i>P</i> value	<.001	.23	.011	.43	.04	.01	<.001	<.001

Abbreviations: CVID, common variable immunodeficiency; DALY, disability-adjusted life-years; YLD, years living with disability; YLL, years of life lost.

Discussion

The *International Classification of Diseases, Ninth Revision (ICD-9)* code for CVID was 279.06; the *ICD 10* code was D83. The disease has 5 subgroups (D83.0, CVID with predominant abnormalities of B-cell numbers and function; D83.1, CVID with predominant immunoregulatory T-cell disorders; D83.2, CVID with autoantibodies to B cells or T cells; D83.8, other CVID; D83.9, unspecified CVID) [18-20]. ICD codes were adopted on the advice of the World Health Assembly and the WHO Nomenclature Regulations for use in most current revisions for mortality and morbidity statistics by all WHO Member States. Moreover, the *ICD* codes facilitated analysis of general health status, monitoring of the incidence and prevalence of diseases, and other general epidemiological variables. To enable the storage and retrieval of diagnostic information for clinical, epidemiological, and quality analysis, *ICD* records also provide the basis for the compilation of national mortality and morbidity statistics, which may be presented as DALYs.

Therefore, although calculation of the burden of CVID as a representative of PIDs is necessary, no studies have been performed in this field. Furthermore, distribution of DALYs in different categories, particularly in infectious diseases, diseases of blood-forming organs, and neoplasms, forced us to tailor our measurement of the burden of CVIDs.

The overall NBD in Iran was calculated at more than 21 500 DALYs based on all diseases and injuries per 100 000 inhabitants of all ages and both sexes. Of this total number of DALYs, 62% were due to YLD and 38% were due to YLL; 58% were due to noncommunicable diseases, 28% to injuries, and 14% to communicable, maternal, prenatal, and nutritional conditions [1]. According to the results of this study, the value for DALYs of CVID was 2063.1 (YLL=363.4+1699.7), which may represent about 0.5% of all DALYs due to blood-forming organ disease (500 000 years) reported in the NBD in Iran [12].

The incidence of new CVID cases was 1 case per 200 000 per year, which was very near to the minimum incidence reported by the WHO for this disease [10]. In our calculation of DALYs, the incidence of CVID was underestimated because of a lack of knowledge among pediatricians and long diagnostic delays. Therefore, DALYs of CVID in our region could be higher, given the incidence rates reported in previous studies (1 case per 10000 per year [2,21], 1 case per 25000 per year [2], 1 case per 30000 per year [5], 1 case per 50000 per year [7,22], 1 case per 66000 per year [3,4], and 1 case per 75000 per year [8,9]).

In this study, the greatest percentage of DALYs in Iranian CVID patients is for YLL, probably as a result of premature death and a high incidence in children, especially in those aged 5 to 14 years. The highest percentages of generation of YLD and YLL were in the infectious only and polyclonal lymphocytic infiltration phenotypes, respectively. Therefore, every attempt should be made to reduce premature death in the polyclonal lymphocytic infiltration phenotype with severe acute manifestations and multiple organ failure. Moreover, a reduction in the number of episodes of infection in patients with the infectious only phenotype and appropriate management with regular intravenous immunoglobulin could decrease DALY and the burden of CVID.

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