Common variable immunodeficiency (CVID) is the most common symptomatic antibody deficiency and is characterized by hypogammaglobulinemia in the absence of any recognized genetic abnormality (8, 13, 21). CVID patients are susceptible to recurrent pyogenic infections (1, 8), as well as autoimmune and neoplastic diseases (6, 17). Although infections of the respiratory and gastrointestinal tracts are common, some patients may present with meningitis (1, 8). Encapsulated organisms such as Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis are the most prominent pathogens in CVID patients (13, 26). Despite attempts during recent decades to identify the underlying immune system defects in CVID, the pathogenesis of CVID remains unknown (26). Thus, the diagnosis of CVID is based on the genetic exclusion of other hypogammaglobulinemias that are well defined at the molecular level (11). Although the underlying pathophysiology of CVID is not clearly understood, a few general defects that lead to alteration of serum immunoglobulin concentrations have been described. Patients with CVID have a defect in B-cell differentiation that leads to impaired secretion of immunoglobulins. Additionally, several abnormalities of T cells have been reported in some patients (26).

It has recently been shown that patients with CVID with loss of immunoglobulin M (IgM) memory B cells are susceptible to earlier onset of recurrent infections and more severe complications (5) than those with mild to moderate clinical manifestations. A number of other investigators have also demonstrated clinical subgroups of CVID that can be differentiated according to laboratory markers of immune function (4, 18, 20, 24, 25, 27).

The antibody response to polysaccharide vaccines among CVID patients is variable and unpredictable (5, 22). Although antibody responses to polysaccharide vaccines in CVID patients have been evaluated in a number of studies (5, 15), the relationship between the response to polysaccharide vaccine and disease severity has not been investigated. We propose that vaccine response could be used to subclassify CVID patients for clinical purposes. As the underlying defect of CVID is unknown, such a study could help us to improve our understanding of the pathophysiology of the disease.

MATERIALS AND METHODS

Patients and controls. Twenty-five patients with CVID (median age, 16 years; age range, 5 to 48 years) included in the Iranian Primary Immunodeficiency Registry (3, 21) and 25 age- and sex-matched controls (median age, 18 years; age range, 6 to 48 years) recruited from among the medical personnel of the Children’s Medical Center Hospital and their families were investigated in this study. The study was approved by the local Ethics Committee of the Tehran University of Medical Sciences and Health Services. All of the CVID patients were deficient...
in at least two serum immunoglobulin levels (serum IgG, IgA, or IgM) by 2 standard deviations from normal mean values for their ages, with no evidence of any of the well-defined single gene defects (8, 11). Mutation analysis studies were performed as part of the routine investigation to exclude other causes of hypogammaglobulinemia. For patients with B-cell populations of <1% of the total lymphocyte count who exhibited agammaglobulinemia with low numbers of B cells (X linked and autosomal recessive), mutation analysis of candidate genes (e.g., BTK) was performed (2). The patients with normal B-cell populations were genotyped at SH2D1A to exclude X-linked lymphoproliferative syndrome. The CD40L, CD40, AID, and UNG genes were also analyzed when normal or elevated serum IgM levels suggested possible hyper-IgM syndrome. Patients under 2 years of age were excluded from this study because of a possible diagnosis of transient hypogammaglobulinemia.

A high-resolution computed tomography scan was performed to identify pulmonary abnormalities, especially bronchiectasis, in all patients with recurrent respiratory tract infections. All patients underwent ultrasound examination to detect splenomegaly. Serum IgG, IgM, and IgA levels were measured by nephelometry, and lymphocyte subpopulation enumeration was performed by flow cytometry.

**Vaccination and sampling.** After giving informed consent, all subjects were vaccinated with meningococcal polysaccharide vaccine A + C (Aventis Pasteur, Lyon, France) at a dose of 0.5 ml. Vaccination of the patients was performed 3 weeks after intravenous immunoglobulin substitution. Blood samples were collected from the patients and controls at the time of vaccination and 3 weeks after, just prior to the next scheduled immunoglobulin infusion in the case of CVID patients. Serum was separated, heat inactivated, and then stored at −70°C until investigators conducted the serum bactericidal antibody (SBA) assay (16, 22, 28).

**SBA assay.** *N. meningitidis* serogroup C strain CSBP1 G-244 (Collection Standard Bacterial Pasteur Institute, Tehran, Iran) was used in the SBA assay (22).

The subjects' sera were heat inactivated for 30 min at 56°C before the test was begun. Pooled sterile baby rabbit (3 to 4 weeks old; Pasteur Institute of Iran) serum with no bactericidal activity against the strains was used as a source of complement. The serum bactericidal antibody (SBA) assay (16, 22, 28, 29) is conducted in 96-well flat-bottomed plates. The wells contained a bacterial suspension, heat-inactivated serum, and complement. Plates were incubated for 15 min at room temperature before the addition of 12.5 µl of pooled rabbit complement per well. Thus, the total volume in each well of the plate was 50 µl, i.e., 25 µl of serum, 12.5 µl of bacterial suspension, and 12.5 µl of complement. Control samples were (i) serum and bacteria (complement-dependent control) and (ii) buffer, bacteria, and complement (complement-dependent control). Moreover, a known positive sample was included in each assay. After all of the components were added to each well of the plate, a 7-µl aliquot of each control sample (n = 2) was spotted onto a GC agar plate containing 1% IsoVitaXe. The cell culture plates were incubated for 60 min at 37°C. The GC agar plate with 1% IsoVitaXe was incubated overnight (for 18 h) at 37°C in a 5% CO₂ atmosphere. Following incubation, a 7-µl aliquot was taken from each well and spotted onto a GC agar plate containing 1% IsoVitaXe. After 18 h of incubation at 37°C in 5% CO₂, the colonies on plates at baseline and after 60 min of incubation were counted. The actual number of CFU per well added at baseline was obtained by multiplying by two the average colony count after overnight incubation. The serum bactericidal titer was recorded as the reciprocal of the highest serum dilution yielding more than 50% bacterial killing compared to the number of CFU present before incubation with serum and complement at time zero (16, 22, 28).

**Statistical analysis.** Data analysis was done with the SPSS statistical software package (version 11.0). Geometric mean titers (GMTs) were calculated, and an SBA titer of ≥8 following vaccination was considered protective for each patient. The numbers of positive samples in the patient and control groups were compared by using the chi-square test. The patients were subclassified into two groups, i.e., responders (an SBA titer of ≥8 postvaccination and a fourfold or greater rise from pre- to postvaccination) and nonresponders (an SBA titer of <8 postvaccination and a less-than-fourfold rise from pre- to postvaccination). The clinical and laboratory parameters of the two groups were compared. The odds ratios (OR) and 95% confidence intervals (CI) for disease and laboratory parameters among nonresponders were calculated.

**RESULTS**

**Characteristics of CVID patients.** Twenty-five patients with CVID (18 male and 7 female; mean age, 19.2 ± 12.1 years) were investigated in this study (Table 1). The serum IgG, IgM, and IgA levels of all of the patients enrolled were reduced more than 2 standard deviations from the normal mean values for their ages. The median serum IgG level was 270 mg/dl (range, 50 to 480 mg/dl). The median serum IgM and IgA levels were 20 mg/dl (range, 10 to 241 mg/dl) and 5 mg/dl (range, 0 to 70 mg/dl), respectively. Although the CD4/CD8 ratio in 60% of the patients (n = 15) was >1, T-lymphocyte subset analysis showed a reversed CD4/CD8 ratio in 40% of the patients (n = 10).

**Clinical features of CVID patients.** Recurrent infections were a feature of almost all of our patients, particularly involving the respiratory and gastrointestinal systems; all of the patients developed upper or lower respiratory tract infections, and 20 patients had gastrointestinal manifestations (Table 2). In 10 patients, the course of disease was complicated by

**TABLE 1. Characteristics of responders and nonresponders among CVID patients**

| Group                  | No. of males | No. of females | Current age (yr) | Onset age (mo) | Diagnosis age (mo) | Diagnosis lag (mo) | Follow-up age (mo) |
|------------------------|--------------|----------------|------------------|---------------|-------------------|-------------------|-------------------|
| All patients (n = 25)  | 18           | 7              | 16               | 5–48          | 1–480             | 97                | 18–513            |
| Responders* (n = 16)  | 10           | 6              | 15               | 5–48          | 103.5             | 45                | 2–452             |
| Nonresponders* (n = 9)| 8            | 1              | 17               | 9–26          | 81                | 45                | 2–204             |

* Responders had a postvaccination titer of ≥8 and a rise of fourfold or greater from pre- to postvaccination.

**TABLE 2. Clinical manifestations of responders and nonresponders among patients with CVID**

| Clinical manifestation                      | No. (%) of patients | P value | Total no. (%) of patients |
|--------------------------------------------|---------------------|---------|--------------------------|
| Responders (n = 16)*                       |                     |         |                          |
| Pneumonia                                  | 15 (93.75)          | 0.640   | 24 (96)                  |
| Diarrhea                                   | 13 (81.25)          | 0.609   | 20 (80)                  |
| Sinusitis                                  | 10 (62.50)          | 0.057   | 19 (76)                  |
| Otitis media                               | 10 (62.50)          | 0.661   | 17 (68)                  |
| Eczema                                     | 7 (43.75)           | 0.691   | 10 (40)                  |
| Conjunctivitis                             | 7 (43.75)           | 0.401   | 9 (36)                   |
| Septic arthritis                          | 5 (31.25)           | 0.364   | 6 (24)                   |
| Musocutaneous candididiasis                | 2 (12.05)           | 0.142   | 6 (24)                   |
| Superficial abscesses                      | 4 (25.00)           | 0.636   | 5 (20)                   |
| Pyelonephritis                             | 3 (18.75)           | 0.542   | 4 (16)                   |
| Bacterial meningitis                       | 0 (0)               | 0.360   | 1 (4)                    |

* Responders had a postvaccination titer of ≥8 and a rise of fourfold or greater from pre- to postvaccination.
brachiectasis (Table 3). Autoimmune diseases, including psoriasis, autoimmune thyroiditis, alopecia areata, and celiac disease, were seen in seven patients. Three patients developed malignancies, including Hodgkin’s lymphoma, lymphoma of mucosa-associated lymphoid tissue, and gastric adenocarcinoma.

**Antibody response to vaccine.** The serum bactericidal GMT postvaccination was significantly increased in both the CVID and control groups in comparison with the GMT prevaccination ($P < 0.001$). Although the GMT rise in the control group was much higher than in the patient group, the difference was not statistically significant ($P = 0.097$) (Fig. 1).

Twenty-four (96%) of the 25 controls had a protective SBA titer (≥8 postvaccination), while only 16 (64%) of the 25 patients with CVID had such a titer. This difference was significant ($P = 0.013$). All of the subjects with an SBA titer between 8 and 32 postvaccination had at least a fourfold rise in SBA titer from pre- to postvaccination. We have previously reported (22) the SBA results of 16 of the 25 CVID patients included in the present study.

**Comparison of clinical and laboratory findings of the two CVID groups.** There were important clinical differences between responders and nonresponders to the vaccine. The patients who did not respond to meningococcal vaccine (titer of <8 postvaccination and a less-than-fourfold rise from pre- to postvaccination) had presented with their first symptoms at a significantly younger age than the patients who responded to the vaccine (mean of 16.8 versus 75.4 months; $P = 0.04$). Additionally, a formal clinical diagnosis of CVID for members of the nonresponder group was made earlier than for those in the responder group but the difference was not significant (mean of 92.44 versus 159.63 months; $P = 0.53$) (Table 1).

Upper and lower respiratory tract infections and mucocutaneous candidiasis were more common in the nonresponder group, whereas superficial abscesses and septic arthritis were more common in the responder group; however, the differences were not statistically significant. All patients with mucocutaneous candidiasis in the nonresponder group had a reversed CD4/CD8 T-cell ratio.

Splenomegaly was significantly more common in the patients who did not respond to meningococcal vaccine (77.8% in the nonresponder group versus 25% in the responder group; $P = 0.016$). Additionally, 77.8% of the CVID patients in the nonresponder group had bronchiectasis, compared with 18.75% in the responder group ($P = 0.008$). Five patients exhibited both splenomegaly and bronchiectasis. All of these patients belonged to the nonresponder group. The presence of autoimmune disorders was also significantly more common in the nonresponders than in the responders (55.6% versus 12.5%; $P = 0.034$) (Table 3).

Although the serum immunoglobulin levels in the responders were much higher than those in the nonresponder group, the differences were not statistically significant (310.2 versus 232.2 mg/dl for IgG, 41.9 versus 27.4 mg/dl for IgM, and 14.6 versus 5.8 mg/dl for IgA). A reversed CD4/CD8 ratio was observed in 6 (66.7%) of 9 nonresponder patients, compared to 4 (25%) of 16 responder patients ($P = 0.053$; OR, 0.17; 95% CI, 0.02 to 1.32).

**DISCUSSION**

The wide variety of clinical and immunological manifestations in CVID patients is likely due to the heterogeneity of the underlying mechanisms (1, 7–9, 13). CVID is the most frequent primary immunodeficiency disease in Iran (3, 21), which may be a consequence of the genetic backgrounds in the region and the high consanguinity rate in the Iranian population (23). As the genetic defects leading to CVID remain largely undiscovered, there have been several attempts to subclassify the patients according to various functional and quantitative B- and T-lymphocyte abnormalities (4, 25, 26). In this study, we sought to identify subgroups of CVID patients on the basis of bactericidal antibody responses to a polysaccharide meningococcal vaccine.

Patients with CVID are prone to recurrent bacterial infections, including meningitis (1, 19). Although only 1 of 25 CVID

![FIG. 1. Serum bactericidal GMTs before and after vaccination and GMT rises in CVID and control groups.](http://cvi.asm.org/)
patients in this study had a previous history of bacterial meningitis, approximately 10% of the CVID patients in Iran have had meningococcal disease to date (1, 21). Therefore, vaccination against N. meningitidis should be recommended for these patients. However, the polysaccharide vaccines may not induce protective levels of antibodies in all individuals with CVID (5). In our study, the serum bactericidal GMTs after vaccination were significantly increased in both groups of CVID patients and controls. However, only 64% of the CVID patients had protective titers. The antibody response to polysaccharide vaccines could be an indicator of a T-cell-independent immune response in these patients.

Comparison of clinical manifestations and complications between the two patient groups of responders and nonresponders revealed that nonresponders present to medical services with features of disease much earlier than responders. Regarding specific disease manifestations, mucocutaneous candidiasis was seen in 44% of the nonresponders, in comparison with 12% of the responders. The presence of such opportunistic infections in CVID patients could indicate some defects in T cells, as well as B cells (10). In our study, a reversed ratio of CD3+ CD4+ T cells to CD3+ CD8+ T cells was significantly more common in the nonresponders than in the responders.

The presence of autoimmunity, bronchiectasis, and splenomegaly was significantly more common in the nonresponder group of patients. The development of bronchiectasis in the nonresponder group is likely to reflect the severity of the immune defect. Splenomegaly and autoimmune disorders seem to be more frequent in a subgroup of CVID patients with recurrent and chronic infection or a fundamental defect in T-cell function.

Response to meningococcal polysaccharide vaccination could routinely be monitored by SBA assay and therefore used as a prognostic tool in CVID. The responder patients may have a good prognosis, while nonresponder patients may have undefined immune abnormalities leading to several complications, such as bronchiectasis, opportunistic infections, splenomegaly, and autoimmunity. This practical classification, which could easily be performed for each CVID patient, could help physicians identify high-risk patients at the time of diagnosis.

This study indicates that some CVID patients can produce protective postvaccination titers similar to those of the normal population, in contrast to the general notion that patients with CVID respond poorly to vaccination. Considering the fact that polysaccharide vaccines are safe and induce protective levels of antibodies in a group of CVID patients, vaccination of CVID patients against encapsulated organisms (S. pneumoniae, H. influenzae, and N. meningitidis) should be recommended in addition to immunoglobulin replacement therapy. Further studies on this group of patients should be performed to evaluate the long-term efficacy of this vaccine. Moreover, further studies on the efficacy of conjugate vaccines in patients with CVID should be undertaken, as these may induce enhanced responses.

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