Common Variable Immunodeficiency (CVID) in Northern India

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Common variable immunodeficiency (CVID) is a rare condition characterised by low levels of most immunoglobulin isotypes, inability to form antibodies to antigens, absence of gross defects in cell-mediated immunity and the presence of recurrent bacterial infections. Early diagnosis, and treatment with gammaglobulin and antibiotics are essential to prevent the significant morbidity and mortality. The present work describes the spectrum of patients with CVID seen in this tertiary referral center in India.

PATIENTS AND METHODS

The case material included patients referred to the Clinical Immunology Services of the All India Institute of Medical Sciences. Detailed work-up of these patients included medical history, physical examination, appropriate immunological, microbiological and radiological investigations. The immunological investigations were: serum immunoglobulins, complement components C3, C4, lymphocyte subsets and nitroblue tetrazolium test (NBT). Cell-mediated immunity was assessed by Mantoux (Mx) tests using tuberculin, candidin, Dinitrochlorobenzene (DNCB) and during the later part of the study by using a commercially available "MULTITEST CMI" (Institut Merieux, Lyon, France) delayed-type hypersensitivity skin test kit. The normal values for various tests in this laboratory are as follows: IgG = 164.1 ± 31.1 IU/ml, IgA = 163.6 ± 51.6 IU/ml, IgM = 102.6 ± 48.1 IU/ml, C3 = 102 ± 28 mg/dl, NBT unstimulated = 10 ± 3%, stimulated = 88 ± 8%, lymphocyte subsets CD3 = 73 ± 4%, CD4 = 46 ± 5%, CD8 = 27 ± 5%, B cells 14 ± 5%. Normal healthy control had a minimum of 2 reactions with at least 6 mm combined indurations in Multitest CMI skin test, thus giving the CMI score (sum of all indurations/number of positive responses) of at least 3.

RESULTS

A total of 14 patients with CVID were studied. The age ranged from 2 to 40 years. Ten were males and 4 were females. The clinical characteristics and the results of laboratory tests are described in Table 1. All had low levels of IgG. All but one had low to undetectable IgA and IgM. All had normal CMI and normal number of B cells in lymphocyte-subset analysis. Complement (C3, C4) and NBT tests were normal. Patients 2, 3, 4, and 14 each had a sibling with similar diagnosis. They are included in the study. A brother of patient 13 had been diagnosed with panhypogammaglobulinemia elsewhere.

SUMMARY

Fourteen patients with common variable immunodeficiency (CVID) were studied. The common clinical manifestations were recurrent sore throat, sinusitis, respiratory infections, diarrhea, and malnutrition. All had low IgG, with normal cell-mediated immunity. Treatment with gammaglobulin and/or plasma was effective in most of them. There were no severe adverse events with the therapy.
and had recurrent sino-pulmonary infection.

The most common presentation was recurrent upper and lower respiratory infections, frequent diarrhea, often due to giardiasis and malnutrition. *Haemophilus influenzae* and *Streptococcus pneumoniae* were isolated from the sputa of four and three patients, respectively. Previous antibiotic use prevented the growth of any microorganisms in others. All had received multiple courses of antibiotics and amoebicidal drugs. After diagnosis of immunodeficiency, all patients received replacement therapy which consisted of intramuscular gamaglobulin (IMIG), or plasma infusion either alone or in combination in the dosage of 100 mg/kg and 10 ml/kg.

### Table 1. Clinical and Immunological features of patients with CVID (n = 14).

<table>
<thead>
<tr>
<th>S. no</th>
<th>Age/sex</th>
<th>Clinical features</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
<th>CMI</th>
<th>Mx</th>
<th>DNCB</th>
<th>MT</th>
<th>Lymphocyte-subsets</th>
<th>T3</th>
<th>T4</th>
<th>T8</th>
<th>B</th>
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<td>↓</td>
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<td>+</td>
<td>+</td>
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<td>X</td>
<td>+</td>
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<td>X</td>
<td>51 38 19 22</td>
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<td>↓</td>
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<td>X</td>
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<td>X</td>
<td>72 56 20 14</td>
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<td>92 58 32 9</td>
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</table>

URTI = upper respiratory tract infection, LRTI = lower respiratory tract infection, D = diarrhea, M = malnutrition, Bo = boils, G = giardiasis, E = eczema, F = fever, B = bronchiectasis, OT = oral thrush, MT = Multitest CMI, X = not done, (-) = negative, (+) = positive, N = normal.
Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus and Pseudomonas aeruginosa are the common microorganisms CVID patients have normal CMI Combined Immunodeficiency (SCID), although mild CMI abnormality are present in normal number. Most of the patients had difficulty, on some occasions, in receiving gammaglobulin and/or plasma therapy due to availability and financial reasons which led to the significant morbidity.

**DISCUSSION**

The present study is the second in the series from this center on primary immunodeficiency diseases in India. Worldwide CVID is rare and an incidence of 6–12 cases per 1 × 106 live births has been suggested. Patients with CVID can manifest as late as the second decade of life or even later. Unlike X-linked Bruton’s agammaglobulinemia, CVID is equally represented in both genders. Patients with CVID have an intrinsic B cell defect with a block in their normal differentiation into plasma cells after antigenic stimulation. Helper T cells (CD4+ve cells) and B cells are present in normal number. Defects in either B cell receptors for interleukins or IL–2 synthesis have been reported. Unlike Severe Combined Immunodeficiency (SCID), CVID patients have normal CMI although mild CMI abnormality may be found.

As this study documents, CVID is a heterogenous syndrome, characterised by hypogammaglobulinemia and recurrent bacterial infections. Streplococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus and Pseudomonas aeruginosa are the common microorganisms manifesting as sinusitis, otitis media, bronchitis, pneumonia and bronchiectasis. Giardia infestation leading to diarrhea and malnutrition is common. There is also an increased incidence of autoimmune and malignant diseases.

Along with antibiotics, gammaglobulin therapy, either intra-muscularly or intravenously, is essential for the treatment of these patients. The usual dose is 400 mg/kg intravenous gammaglobulin (IVGG) once each 4 weeks. The dose and frequency can be adjusted based on the trough level of IgG and control of recurrence of infections. The optimum trough level should be 500 mg/dl IgG 4 weeks after last infusion. The dose for IMIG is 0.2 ml/kg monthly with readjustment depending on clinical response. As only a limited amount can be given at one site, the dose can be given in two or more sites. Since IVIG can be given in larger amounts with higher serum levels, it has replaced IMIG in the developed world. Gammaglobulin therapy is safe to administer in hypogammaglobulinemic patients. The typical symptoms that may occur are minor and usually occur during the first 30 minutes. Slowing the infusion and premedication with aspirin or corticosteroids usually control these symptoms. More severe adverse events including anaphylaxis may rarely occur if anti IgA antibodies are present in the recipient. Cohn fractionation in manufacturing process prevents the risk of hepatitis B and HIV infection although hepatitis C infection has been documented to occur with IVIG.

If IMIG/IVIG is unavailable, patients with CVID may be given monthly fresh-frozen plasma (10 mg/kg) infusions in developing countries. The donor of the plasma is a heterogenous group of healthy adults in the USA. As only a limited amount can be given at one site, the dose can be given in two or more sites. Since IVIG can be given in larger amounts with higher serum levels, it has replaced IMIG in the developed world. Since IVIG can be given in larger amounts with higher serum levels, it has replaced IMIG in the developed world. Gammaglobulin therapy is safe to administer in hypogammaglobulinemic patients. The typical symptoms that may occur are minor and usually occur during the first 30 minutes. Slowing the infusion and premedication with aspirin or corticosteroids usually control these symptoms. More severe adverse events including anaphylaxis may rarely occur if anti IgA antibodies are present in the recipient. Cohn fractionation in manufacturing process prevents the risk of hepatitis B and HIV infection although hepatitis C infection has been documented to occur with IVIG.

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**REFERENCES**


