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SHORT COMMUNICATION

Common Variable Immunodeficiency (CVID) in Northern India

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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 immunoglobulin and/or plasma was effective in most of them. There were no severe adverse events with the therapy.**

Common variable immunodeficiency (CVID) is a rare[1] 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 desribes the spectrum of patients with CVID seen in this tertiary referral center in India.

PATIETNS 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,[2] complement components C3, C4,[2] lymphocyte subsets[3] and nitroblue tetrazolium test (NBT).[4] Cell-mediated immunity was assessed by Mantoux (Mx) tests using tuberculin,[5] candidin,[5] Dinitrochlorobenzene (DNCB)[6] 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.[7] 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

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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 gammaglobulin (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).

S. no	Age/ sex	Clinical features	IgG	IgA	IgM	CMI			Lymphocyte-subsets			
						Mx	DNCB	MT	T3	T4	T8	B
1	40/F	LRTI, D, G, F	↓	↓	↓	+	+ + +	X	68	30	43	17
2	17/M	LRTI, D,G, E, F	↓	↓	↓	-	+ +	X	36	X	X	59
3	15/F	URTI, D,G, M	↓	↓	↓	X	+ + ±	X	59	31	24	21
4	14/M	URTI, LRTI, D, M	↓	↓	↓	X	+ + +	X	51	38	19	22
5	4/M	LRTI, Bo, M	↓	↓	N	±	X	X	62	42	26	18
6	2/M	LRTI, D, E, F, G, B	↓	Nil	↓	+	+ +	X	61	X	X	12
7	12/M	LRTI, D,G, M, F	↓	↑	↓	-	+ +	4 +	69	38	26	20
8	5/M	LRTI, D,G	↓	↓	↓	-	X	3 +	71	45	X	10
9	4/M	URTI, LRTI, D	↓	↓	↓	-	X	3 +	60	40	20	28
10	26/M	URTI, D,G, M	↓	↓	↓	+	X	X	83	42	29	19
11	5/M	URTI, LRTI, D, M	↓	↓	↓	X	X	4 +	86	50	45	21
12	16/F	LRTI, D, Bo	↓	↓	↓	+	X	X	72	56	20	14
13	5/F	LRTI, D, G, M, OT	↓	↓	↓	X	X	2 +	73	44	30	18
14	5/M	URTI, LRTI, D, G, M	↓	↓	↓	X	X	3 +	92	58	32	9

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.

respectively, in the interval which was sufficient to prevent diarrhea and chest infections.

All but two tolerated the infusion well. Two patients had minor adverse events of nausea, arthralgia and chills. There was no anaphylactic reaction in any of the patients.

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.[8] Worldwide CVID is rare and an incidence of 6–12 cases per 1×10^6 live births has been suggested.[1] Patients with CVID can manifest as late as the second decade of life or even later.[9] Unlike X-linked Bruton's agammaglobulinemia,[10] 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.[9] Helper T cells (CD4+ve cells) and B cells are present in normal number.[9] Defects in either B cell receptors for interleukins[11] or IL-2 synthesis have been reported.[12] 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. *Streptococcus 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.[9]

Along with antibiotics, gammaglobulin therapy, either intramuscularly or intravenously, is essential for the treatment of these patients. The usual dose is 400 mg/kg intravenous gammaglobulin (IVGG) once each 4 weeks.[9,13,14] The dose and frequency can be adjusted based on the trough level of 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 repalced IMIG in the developed world. Gammaglobulin therapy is safe to administer in hypogammaglobulinemic patients.[13,14] 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.[13] More severe adverse events including anaphylaxis may rarely occur if anti IgA antibodies are present in the recipient.[13,14] Cohn fractionation in manufacturing process prevents the risk of hepatitis B and HIV infection[14] although hepatitis C infection[15] has been documented to occur with IVIG.

If IMIG/IVIG is unavailable, patients with CVID may be given monthly fresh-frozen plasma (10 ml/kg) infusions in developing countries.[16] The donor of the plasma should, however, be negative for hepatitis B, C and HIV infections. IVIG is presently being imported from overseas and is expensive in our country. Once it is manufactured in India it will help these patients.

REFERENCES

1. Ryser O, Morell A, Hitzig WH: Primary immunodeficiencies in Switzerland: first report of the national registry in adults and children. J Clin Immunol 1988; 8 : 479-485.
2. Mancini G, Carbonara AO, Heremans JF. Immunochemical quantitation of antigens by single radial immunodiffusion. Int J Immunochem 1965; 2 : 235-8.
3. Erber WN, Pinching AJ, Manson DY. Immunocytochemical detection of T and B cell population in routine blood smears. Lancet 1984; i : 1042-5.
4. Wilkinson PC. Neutrophil leukocyte function tests. In Thompson RA Ed. Techniques in clinical immunology. Blackwell Scientific Publications, Oxford 1981; pp 276-7.
5. Rocklin RE, Meyers OL, David JR. An *in vitro* assay for cellular hypersensitivity in man. J Immunol 1970; 104 : 95-102.
6. Catalona WJ, Taylor PR, Robson AS, Chretain PB. A method of DNCB contact sensitisation: a clinicopathological study. N Engl J Med 1972; 286 : 399-402.
7. Kniker W, Anderson C, McBryde J, Roumiantzeff M, Lesourd B. Multitest CMI for standardised measurement of delayed cutaneous hypersensitivity and cell-mediated immunity. Normal values and proposed scoring system for healthy adults in the USA. Ann Allergy 1984; 52 : 75-8.
8. Malaviya AN, Rajagopalan P, Taneja RL. Pattern of primary immunodeficiencies seen in India. J Assoc Physicians India 1977; 25 : 465-74.
9. Sneller MC. Clinical spectrum of common variable immunodeficiency, pp 720-722. In: Sneller MC, ed. New insights into common variable immunodeficiency. Ann Intern Med 1993; 118 : 720-7.
10. Bruton OC. Agammaglobulinemia. Paediatrics 1952; 9 : 722-7.
11. Bonagura VR, Cunningham-Rundles S, Edwards BL, Ilowite NT, Wedgwood JF, Valacer DJ. Common variable hypogammaglobulinemia, recurrent *Pneumocystis carinii* pneumonia on intravenous γ-globulin therapy, and natural killer deficiency. Clin Immunol Immunopathol 1989; 51 : 216-31.

12. Rump JA, Jahreis A, Schlesier M, Drager R, Melchers I, Peter HH. Possible role of IL-2 deficiency for hypogammaglobulinaemia in patients with common variable immunodeficiency. Clin Exp Immunol 1992; 89 : 204-10.

13. Buckley RH, Schiff RI. The use of intravenous immune globulin in immunodeficiency diseases. N Engl J Med 1991; 325 : 110-17.

14. Berkman SA, Lee ML, Gale RP. Clinical uses of intravenous immunoglobulins. Ann Intern Med 1990; 112 : 278-92.

15. Williams PE, Yap PL, Gillon J, Crawford RJ, Urbaniak SJ, Galea G. Transmissions of non A, non B, hepatitis by pH 4 treated intravenous immunoglobulin. Vox Sang 1989; 57 15-18.

16. Ammann AJ, Fudenberg HH. Immunodeficiency diseases. In: Fudenberg HH, Stites DP, Caldwell JL, Wells JV (eds). Basic and clinical immunology, Lange Medical Publications, Los Altos 1980 : 413-4.