The Turkish Journal of Pediatrics 32: 13-20, 1990

CLINICAL AND IMMUNOLOGICAL ASPECTS OF HYPER–IgM SYNDROME*

*Fügen Ersoy MD***, *Özden Sanal MD****, *İlhan Tezcan MD*****

Summary: Ersoy F, Sanal Ö, Tezcan İ. (Immunology Unit, Hacettepe University Institute of Child Health, Ankara, Turkey). Clinical and immunological aspects of hyper–IgM syndrome. Turk J Pediatr 32: 13-20, 1990.

Eight patients with Hyper–IgM syndrome were subjected to clinical and immunological evaluation. There were seven males and one female. All the patients had recurrent pyogenic infections; one had lymphoid hyperplasia with centrally necrotic granulomas, and one had gingivitis with neutropenia. Isohemagglutinin titers were either high or normal in all the patients and five had group 0 blood. The percentage of IgM-bearing cells were normal in five patients. The percentage of T cells were normal in all the patients, helper T cells were decreased in two patients, and suppressor T cells were increased in four patients. These results suggest that at least in some patients, the imbalances of T cell subsets may play a role in the pathogenesis of the disease rather than it being attributed to an intrinsic B cell defect. *Key words: immunodeficiency, Hyper-IgM, lymphocyte subpopulations.*

Immunodeficiency with hyperimmunoglobulinemia M (hyper–IgM) is a dysgammaglobulinemia which was first described by Rosen et al[1] in 1961, and is recognized by the World Health Organization to be one of the primary immunodeficiency syndromes[2]. This syndrome is characterized by very low or absent serum IgG and IgA levels and normal or more frequently elevated IgM concentration. The clinical manifestations of this disorder are usually similar to those of agammaglobulinemia, with frequent infections and increased risk of neoplasms at an early age[1-7]. Recurrent neutropenia, hemolytic anemia or aplastic anemia have been reported in some patients[8]. Although the disorder has been reported to occur mostly in males, and inherited in an X–linked fashion, both autosomal dominant and recessive forms, a form following congenital rubella, and acquired forms have also been described[3-9]. The immunopathogenetic mecha-

* From the Immunology Unit, Hacettepe University Institute of Child Health, Ankara.

** Professor of Pediatrics and Pediatric Immunologist, Hacettepe University Institute of Child Health.

*** Professor of Pediatrics and Pediatric Immunologist, Hacettepe University Faculty of Medicine.

**** Instructor in Pediatrics and Fellow in Immunology, Hacettepe University Institute of Child Health.

Supported by the Hacettepe University Research Foundation, Ankara.

nisms of this syndrome appear to be varied. Excessive suppressor T cell activity, abnormal B cell differentiation[5,10], lack of helper T cells[11], and failure to switch from IgM to IgG[6,12,13] have been shown in various studies. In this report, we describe the clinical and immunological data of eight patients with Hyper–IgM syndrome.

Material and Methods

The clinical diagnosis of patients was based on the history of recurrent infections, the pattern of immunodeficiency with low IgG, and IgA, normal or elevated IgM in the serum, and the presence of isohemagglutinins which conformed with the criteria of the World Health Organization for immunodeficiency and Hyper–IgM[2].

Skin tests: delayed hypersensitivity reaction in vivo was evaluated by skin reactivity to several antigens: Candida (prepared at Hacettepe University Pediatric Allergy Labs) of a 1: 10 dilution, phytohemagglutinin (PHA–P, Burroughs–Wellcome Labs) 10 μg/0.1 ml, PPD (Refik Saydam Hygiene Inst., Ankara) 3 U/0.1 ml, streptokinase– streptodornase (SKSD, Lederle Labs) 50/12.5 U/0.1 ml.

E–rosette forming cells were measured by the method described by Jondal et al[14]. In vitro blastogenic response was performed according to a previously published method[15].

Serum immunoglobulins (IgG, IgM, IgA) were determined by using the Behring–Werke immunodiffusion plates.

B lymphocytes bearing membrane Ig (Smig) were identified by direct immunofluorescence using commercial antisera against Ig isotypes (polyvalent, IgG, IgM, IgA; Behring–Werke Inst)[16].

Evaluation of T lymphocyte subsets: Pan T ($CD3^+$) cells, helper T ($BD4^+$) cells and suppressor T ($CD8^+$) cells were examined by monoclonal antibodies (OKT 3, OKT 4, OKT 8; Behring–Werke Inst) according to the standard technique[17].

İsohemagglutinins were determined using standard methods.

Results

Clinical findings of the patients with Hyper–IgM syndrome are shown in Table I. Only one out of eight patients was a girl (RS), whose family history did not suggest any immunodeficiency diseases. She had pneumonia at six months of age followed by recurrent infections and chronic suppurative otitis. She had developed bronchiectasia. There were no signs of congenital rubella. The parents were first cousins and healthy. She had a healthy brother.

Two of our patients were siblings (ER, EK) from one family and three were siblings (OF, AF, FF) from another family. The parents in each family were unrelated. While a pattern of X–linked inheritance was determined in six patients (three families), there was no evidence of familial occurrence in two (Table I). Five

TABLE I: Characteristics of Patients With Hyper–IgM Syndrome

Family No	Patient No	Name	Age/Sex (yrs)	Consanguinity of Parents	Familial Occurrence	Clinical Findings
1	1	RS	4.5/F	First cousins	–	Growth retardation, chronic otits recurrent pneumonia, bronchiectasia
2	2	DH	4/M	First cousins	+	Growth retardation, chronic diarrhea, chronic otitis
3	3	EK	12/M	–	+	Recurrent pneumonia, cervical and mediastinal lymphadenopathy
3	4	EK	14/M	–	+	Sinopulmonary infections
4	5	OF	4/M	–	+	Gingivitis, aphthous stomatitis, growth retardation, neutropenia
4	6	AF	6 mo/M	–	+	Chronic diarrhea, malnutrition, bronchopneumonia, hepatomegaly,
4	7	FF	10 mo/M	–	+	Diarrhea
5	8	HK	8/ mo/M	First cousins	–	Malnutrition, sinopulmonary infection

patients had recurrent respiratory infections, two had chronic suppurative otitis, two developed hepatomegaly, and one had aphthous stomatitis with neutropenia prior to gammaglobulin therapy (OF). One patient (EK) was admitted to our hospital presenting with fever, dyspnea, and bilateral neck and mediastinal masses. The lymph node biopsy from the supraclavicular region revealed centrally necrotic granulomas. There were lymphocytes and neutrophils in the centers. Scattered follicles and plasma cells were also noted. These enlarged lymph nodes disappeared after the beginning of gammaglobulin therapy.

One of the patients (AF), who had hepatomegaly and icterus, died at home. His brother (OF) developed malabsorption due to intractable giardiasis and hepatomegaly at six years of age. There are also twin siblings in this family, a boy and a girl. The male twin was diagnosed as having Hyper-IgM syndrome at 10 months of age. The girl is healthy.

Immunological findings of the patients are shown in Table II. Total lymphocyte counts of all the patients were within normal limits. Only one patient (OF) had neutropenia. The percentages of E-rosette forming cells were found to be within normal limits in all patients. Delayed hypersensitivity skin tests were negative and the in vitro PHA response was low in three patients.

TABLE II: Immunological Findings of the Patients With Hyper-IgM Syndrome

No	Patient	Total lymphocyte count/ mm^3	Skin Tests	E-rosettes (%)	In vitro PHA response	Immunoglobulins (mg/dl) Serum IgG	IgM	IgA	Blood group	Isohemagglutinins
1	RS	2600	–	64	Low	22	290	0	B	Anti A:1/32
2	DH	4800	–	59	Low	160	392	0	Nd	
3	EK	2600	+	65	Normal	22	345	0	0	Anti A:1/156 Anti B:1/512
EK	EK	6000	+	71	Normal	22	483	0	A	Anti B:1/256
5	OF	7200	+	69	Normal	120	215	0	0	Anti A:1/512 Anti B:1/64
6	AF	4000	–	66	Low	102	58	0	0	Anti A:1/4 Anti B:1/2
7	FF	7200	+	68	Nd	103	59	0	0	Anti A:1/64 Anti B:1/32
8	HK	6160	+	64	Nd	55	483	0	0	Anti A:1/128 Anti B:1/512

Nd: not done.

The serum IgG and IgA levels were either very low or absent in all the patients. The IgM levels were found to be increased in six patients and within normal limits in two.

Isohemagglutinin titers were either normal or increased in all the patients; five patients had blood group 0.

Subpopulations of T cells and surface immunoglobulin bearing B cells were studied in seven of the patients and the results are shown in Table III. The percentage of $CD3^+$ cells (pan T cells) was found to be within normal limits in all patients. $CD4^+$ cell (helper T cells) percentages were below two standard deviations of normal values in two patients (DH, EK). There was a slight increase in the percentages of $CD8^+$ (suppressor T cells) in four patients (DH, EK, EK, HK), and the $CD4^+$ / $CD8^+$ cell ratio was found to be reversed in two (DH, EK). While the percentages of total immunoglobulin and IgM bearing cells were normal, IgG and IgA bearing cells were either absent or low in all the patients studied.

TABLE III: Lymphocyte Subpopulations of the Patients With Hyper–IgM Syndrome (%)

No.	Patient	$CD3^+$	$CD4^+$	$CD8^+$	CD4/CD8 Ratio	Polyvalent	$SigG^+$	$SigM^+$	$SigA^+$
1	RS	73	35	25	1.4	14	4	7	1
2	DH	78	27	41	0.7	15	0	8	0
3	EK	69	37	38	1	17	0	11	0
4	EK	64	31	42	0.7	22	Nd	Nd	Nd
5	OF	75	52	18	2.9	19	1	10	1
6	AF	63	38	32	1.2	26	Nd	Nd	Nd
7	FF	Nd	Nd	Nd	Nd	Nd	Nd	Nd	Nd
8	HK	82	40	40	1	8	1	8	1
Normal values		66.9±13.3	45.6±5.2	27±6.9	1.8±0.5	22.2±5	9.1±3.6	8.2±4.2	4.5±3.1

Discussion

A variety of clinical features have been described in Hyper–IgM syndrome; the most consistent being recurrent pyogenic infections. Although the initial description of this disorder reported a pattern of X–linked inheritance, other genetic and nongenetic forms have been described[3-9]. Our study population consisted of eight patients from five families. There were seven males and only one female. Six of the eight patients exhibited X–linked inheritance. In three out of five families the parents were first–degree relatives. All our patients had recurrent pyogenic infections including otitis media, bronchopneumonia, and chronic diarrhea, usually beginning during the first year of life. Stomatitis and mouth ulcers

with neutropenia have been reported in some patients[4,8,18]. One of our patients (OF) had gingivitis and aphthous stomatitis with neutropenia which disappeared after intramuscular gammaglobulin therapy.

Marked enlargement of the tonsils, cervical lymph nodes, spleen and liver are common manifestations of this syndrome. The presence of lymphoid hyperplasia in this condition often diverts the physician from a diagnosis of immunodeficiency[2,18,19]. One patient (EK) was admitted to our hospital with dyspnea caused by cervical and mediastinal masses. Histopathology of the lymph node biopsy revealed centrally necrotic granulomas. Goldstein et al[7] have reported a patient with the acquired form of Hyper–IgM syndrome who presented striking cervical lymphadenopathy which contained necrotizing granulomas. They suggested that this histopathologic picture may represent either an unusual inflammatory response in a patient with impaired humoral immunity or may be secondary to some unknown agent capable of impairing the patient's humoral immune system and affecting the reticuloendothelial system in such a way as to stimulate production of nonspecific necrotizing granulomas. Since our patient had the X–linked form of Hyper–IgM syndrome, lymphoid hyperplasia containing necrotizing granulomas was suggested to be secondary to the humoral immunodeficiency disease.

Hyper–IgM syndrome is characterized by elevated or normal serum IgM levels and very low or undetectable quantities of IgG and IgA. Although thymic dependent lymphoid tissues, T cell subpopulations and their functions are usually normal in most of the patients. Some impairment of cellular immunity as shown by abnormal results in skin tests, in the in vitro blastogenic response to PHA, increased T cell suppression or lack of helper T cells have been reported[4,10,11,19,20]. The findings of this study reflect the heterogeneity in this respect. While total lymphocyte counts, percentages of E–rosette forming cells and $CD3^+$ cells were normal in all patients, skin tests were found to be negative and the in vitro PHA response was low in three patients. The percentage of helper T cells was low in two patients, and suppressor T cells were increased in four. The helper/suppressor T cell ratio was found to be low in four of seven patients and reversed in two. Although most of the previous studies in patients with this syndrome have suggested that the defect is intrinsic to the B cell, the imbalances of T cell subsets detected in the present study may play a role in the pathogenesis of the disease. In fact, Mayer et al[13] described a type of T cell, derived from a patient with a Sezary–like syndrome which can induce IgG and IgA secretion in B cells from patients with Hyper–IgM syndrome regardless of the pattern of inheritance or acquisition. This data has suggested that the defect, at least in some patients with this syndrome, may be exogenous to the B cell and may reflect a defect in switch T cells.

The total number of immunoglobulin bearing cells and IgM bearing cells was found to be normal in our study and conformed with the findings of previous studies[5,12,19].

Five out of seven patients were blood group 0 and all the patients had normal levels of isohemagglutinins. Similarly, since most of the cases reported previously have been blood group 0 and positive for isohemagglutinins A and B of the IgM type, investigators have suggested that this disorder might be genetically linked to the 0 blood group[4].

REFERENCES

1. Rosen FS, Kevy SV, Janeway CA, Merler E. Recurrent bacterial infections and dysgammaglobulinemia: deficiency of 7S gammaglobulins in the presence of elevated 19S gamma-globulins. *Pediatrics* 28:182, 1961.
2. Meeting Report. Primary Immunodeficiency Diseases Report prepared for the WHO by a scientific group on immunology. *Clin Immunol Immunopathol* 28:450, 1983.
3. Stiehm ER, Fudenberg HH. Clinical and immunologic features of dysgammaglobulinemia type I. Report of a case diagnosed in the first year of life. *Am J Med* 40:805, 1966.
4. Kyong CU, Virella G, Fudenberg HH, Darby CP. X-linked immunodeficiency with increased IgM: clinical, ethnic and immunologic heterogeneity. *Pediatr Res* 12:1024, 1978.
5. Brahmi Z, Lazarus KH, Hodes ME, Baehner RL. Immunologic studies of three family members with the immunodeficiency with hyper-IgM syndrome. *J Clin Immunol* 3:127, 1983.
6. Levitt D, Haber P, Rich K, Cooper MD. Hyper-IgM immunodeficiency. A primary dysfunction of B lymphocyte isotype switching. *J Clin Invest* 72:1650, 1983.
7. Goldstein MF, Kornstein MJ, Talbot S, Levinson AI. Acquired hyper-IgM syndrome with necrotizing granuloma. *J Allergy Clin Immunol* 75:472, 1985.
8. Amman AJ. Immunodeficiency diseases. In Stites DS, Stobo JD, Wells JV (eds). *Basic and Clinical Immunology.* Los Altos: Lange, 1987, pp. 317-355.
9. Hinz CF JR, Boyer JT. Dysgammaglobulinemia in the adult manifested as auto-immune hemolytic anemia. Serologic and immunochemical characterization of an antibody of unusual specificity. *N Engl J Med* 296:1329, 1963.
10. Herrod HG, Perlman DB, Buckley RH. Evidence of excessive T suppressor cell activity in X-linked immunodeficiency with Hyper-IgM. *Pediatr Res* 12:480, 1978.
11. Mitsuya H, Tomino S, Hisamitsu S, Kishimoto S. Evidence for the failure of IgA specific T helper activity in a patient with immunodeficiency with hyper IgM. *J Clin Lab Immunol* 2:337, 1979.
12. Geha RS, Hyslop N, Alami S, et al. Hyper-immunoglobulinemia M in immunodeficiency (dysgammaglobulinemia). Presence of immunoglobin M-secreting plasmacytoid cells in peripheral blood and failure of immunoglobin M-immunoglobin G switch in B-cell differentiation. *Clin Invest* 64:385, 1979.
13. Mayer L, Kwan SP, Thompson C, et al. Evidence for a defect in "switch" T cells in patients with immunodeficiency and hyper-immunoglobulinemia M. *N Engl J Med* 314:409, 1986.
14. Jondal M, Holm G, Wigzell H. Surface markers on human T and B lymphocytes. I.A large population of lymphocytes forming non-immune rosettes with sheep red blood cells. *J Exp Med* 136:207, 1972.

15. August CS, Berkel Aİ, Levey RH, et al. Establishment of immunological competence in a child with congenital thymic aplasia by a graft of fetal thymus. *Lancet* 1:1080, 1970.

16. Aiuti F. Identification, enumeration and isolation of B and T lymphocytes from peripheral blood. *Clin Immunol Immunopathol* 3:584, 1985.

17. Reinherz EL, King PC, Goldstein G, et al. Separation of functional subsets of human T cells by a monoclonal antibody. *Proc Natl Acad Sci USA* 76:4061, 1979.

18. Ochs HD, Wedgwood RJ. Disorders of the B cell system. In Stiehm ER (ed). *Immunologic Disorders in Infants and Children.* Philadephia: WB Saunders, 1989, pp. 226-256.

19. Buckley RH. Humoral immunodeficiency. *Clin Immunol Immunopathol* 40:13, 1986.

20. Krantman HJ, Stiehm ER, Stevens DH, et al. Abnormal B cell differentiation and variable increased T cell suppression in immunodeficiency with hyper-IgM. *Clin Exp Immunol* 40:147, 1980.