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Hypogammaglobulinaemia associated with normal or increased IgM (the hyper IgM syndrome): a case series review

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Abstract

The clinical and immunological aspects of 16 children with the syndrome of hypogammaglobulinaemia associated with normal or increased IgM (the hyper IgM syndrome) and their responses to treatment are reviewed. Increased concentrations of IgM, neutropenia, and recurrent infections could usually be controlled by antimicrobial and intravenous immunoglobulin treatment. Together with the bacterial infections characteristic of hypogammaglobulinaemia, these patients often developed opportunistic infections, including *Pneumocystis carinii* pneumonia, often presenting in the first year of life. The occurrence of sclerosing cholangitis, neurological complications, and neutropenia may be a result of an underlying cell mediated immune deficiency, autoimmunity, or infection. Despite a high incidence of opportunistic infections, immunological investigations did not show any abnormality of T cell function. These findings are discussed in the light of the recent demonstration that the lack of expression of a T lymphocyte activation antigen is the molecular basis of the X linked form of the disorder.

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Primary hypogammaglobulinaemia associated with normal or increased IgM (the hyper IgM syndrome) was first described in 1961.[1] A literature review from 1992 documents only 67 cases and describes considerable genetic heterogeneity within this group.[2] Inheritance is usually X linked[3] but in addition may be autosomal dominant[4] and autosomal recessive.[1] The gene for the X linked form has been cloned by several groups and encodes a T cell activation molecule which is the ligand for the CD40 molecule.[5 6] X linked hyper IgM is distinguished from the more common X linked agammaglobulinaemia (Bruton's disease) by the presence of circulating B lymphocytes and polyclonal IgM in X linked hyper IgM syndrome, which are absent in X linked agammaglobulinaemia. Like X linked agammaglobulinaemia, hyper IgM syndrome is regarded as a primary humoral defect, but there are prominent features that suggest a T lymphocyte deficiency. We describe the clinical and laboratory features of 16 children with hyper IgM syndrome and discuss the pathogenetic mechanisms implied by these observations.

Methods

Sixteen children who presented to the Hospital for Sick Children, London and the 'Aghia Sophia' Children's Hospital between 1977 and 1991 with this syndrome are reviewed. Clinical, genetic, and immunological features and their response to treatment have been retrospectively studied. Four of these patients have been partially described previously: patients 1 and 2[7] and patients 12 and 13.[8]

Results

FAMILY HISTORIES

Fourteen of the 16 patients were boys and a family history of immunodeficiency or unexplained death in childhood was suggested in seven (table 1). Of the 16 patients, two sets of children were siblings (patients 1 and 2 and 12 and 13) and the parents of patients 1 and 2 were first cousins.

CLINICAL FINDINGS

The age of presentation was between 1 month and 10 years (mean 2 years) (table 1). Table 1 gives the medical histories before diagnosis. Most patients had symptoms consistent with immunoglobulin deficiency, which included recurrent diarrhoea and vomiting, recurrent upper respiratory tract infections, otitis media, and failure to thrive. Seven children developed *Pneumocystis carinii* pneumonia; in six *P carinii* pneumonia was the presenting feature in the first year of life and two of these children went on to have a second episode. In addition, there was one case of cytomegalovirus pneumonitis.

Additional features more consistent with cell mediated immunodeficiency were seen in most patients. Severe neurological disease occurred in five children, one (patient 14) had cryptococcal meningitis which responded to antifungal treatment. Two siblings had acute encephalitis. One (patient 1) recovered with high doses of intravenous immunoglobulin and intraventricular immunoglobulin, but the other (patient 2) died from encephalitis associated with the isolation of papovavirus from urine and adenovirus from stool samples. Two children (patients 9 and 13) died from idiopathic progressive neurological disorders. Three patients developed sclerosing cholangitis. Two died, one (patient 4) during liver transplantation, the second (patient 16) from hepatic failure. The disease is static in the third (patient 15).

Table 1 Age, sex, ethnicity, family history, and medical histories in the hyper IgM syndrome

Patient No	*Age at diagnosis (months)*	*Sex*	*Ethnic origin*	*Family history and probable inheritance pattern*	*Medical history before diagnosis*	*Status after diagnosis*
1	40	M	Indian	Parents first cousins, brother of patient 2, autosomal recessive	Cryptosporidiosis, combined adenovirus and echovirus meningoencephalitis, recurrent candidiasis, recurrent URTI	Well
2	72	F	Indian	Parents first cousins, sister of patient 1, autosomal recessive	Recurrent URTI, encephalitis, aspergillus pneumonia	Died from encephalitis
3	3	M	English	Sporadic	*P carinii* pneumonia, CMV pneumonitis, recurrent URTI, recurrent diarrhoea and vomiting	Well
4	9	M	English	Sporadic	*P carinii* pneumonia	Cryptosporidiosis, cirrhosis secondary to sclerosing cholangitis, second attack of *P carinii* pneumonia, died during liver transplantation
5	19	M	English	Sporadic	Recurrent chest infections, osteomyelitis, recurrent cutaneous abscesses	Recurrent chest infections, suspected tuberculous osteomyelitis
6	10	M	English	Maternal uncle died at 6 months, X linked	Recurrent otitis media, red cell aplasia	Neutropenia that responded to high doses of intravenous immunoglobulin
7	7	M	Pakistani	Two brothers died at 1 year (pneumonia) and 2 years (gastroenteritis), immunology uncertain, X linked	*P carinii* pneumonia, recurrent URTI, candidiasis	Ventilated for laryngotracheobronchitis, associated soft tissue pseudomonas infection
8	6	M	English	Sporadic	*P carinii* pneumonia	Pneumococcal pneumonia when not receiving treatment
9	30	F	Indian	Sporadic	Recurrent cutaneous abscesses	Died from progressive idiopathic neurological deterioration
10	6	M	English	Six male deaths over two generations: X linked	*P carinii* pneumonia	Well
11	120	M	Iraqi	Sporadic	Recurrent URTI, recurrent otitis media	Well
12	48	M	English	Brother of patient 13, X linked or autosomal recessive	Recurrent mouth ulcers, pericentric inversion of chromosome 7	Well
13	5	M	English	Brother of patient 12, X linked or autosomal recessive	*P carinii* pneumonia, giardiasis, developmental delay with pericentric inversion of chromosome 7	Recurrent *P carinii* pneumonia, progressive idiopathic neurological deterioration, died aged 12 years
14	30	M	Greek	Sporadic	Recurrent gastroenteritis, recurrent otitis media and URTI, eczema	Cryptococcal meningitis, erysipelas, neutropenia responsive to granulocyte colony stimulating factor and high dose intravenous immunoglobulin
15	28	M	Irish	Sporadic	Recurrent bacterial infections, sclerosing cholangitis	Well
16	17	M	Greek	Sporadic	*P carinii* pneumonia, recurrent chest infections and hepatosplenomegaly	Death from sclerosing cholangitis

URTI=upper respiratory tract infection: CMV=cytomegalovirus.

HAEMATOLOGY AND IMMUNOLOGY

Tables 2 and 3 give the haematological and immunological indices. IgG and IgA were low in all 16 patients, but were rarely undetectable. IgM was increased in seven patients and normal in nine. Six patients were neutropenic at presentation with neutrophil counts less than 1×10^9/l. T lymphocyte enumeration showed a low CD4 count ($0{\cdot}5\times10^9$/l, patient 11; table 3) in one patient and a low CD3 count ($1{\cdot}1\times10^9$/l, patient 12, table 3) in another. Phytohaemagglutinin stimulation was normal in all patients. No autoantibody was detected in the six patients screened.

RESPONSE TO TREATMENT

All patients received immunoglobulin replacement treatment, with a decrease in the frequency and severity of bacterial and viral infections. Opportunist infections, including cryptococcal, *P carinii* pneumonia, and chronic cryptosporidial infections, have occurred, however, although with no relation with either intravenous immunoglobulin treatment or immunosuppression. Neutropenia resolved in all six patients once adequate doses of immunoglobulin treatment had been given. Granulocyte colony stimulating factor was used in combination with intravenous immunoglobulin in one patient. High doses of intravenous immunoglobulin were required to prevent infection (up to 1 g/kg, every three weeks). All but one child (who developed red cell aplasia while receiving co-trimoxazole) are being treated with prophylactic co-trimoxazole because of their susceptibility to *P carinii* pneumonia.

Discussion

This report significantly increases the documented number of patients with this rare disorder and highlights the underlying T cell immunodeficiency with the occurrence of opportunistic infections. Twelve of the 16 patients have not previously been described. The clinical descriptions of our patients add to the spectrum of diseases found in this disorder[2] and emphasise the clinical evidence for a

Table 2 Haematological indices in children with hyper IgM syndrome

	Patient No															
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*
Haemoglobin (g/l)	105	94	105	134	133	47	100	120	97	120	119	106	124	N/A	109	103
Platelet count ($\times10^9$/l)	274	300	726	N/A	500	435	N/A	830	697	N/A	315	268	335	200	132	N/A
White cell count ($\times10^9$/l)	6·9	5·0	17·8	18·6	5·1	12·6	10·2	33·5	11·8	18·3	17·4	3·5	16·8	8·6	2·1	2·0
Lymphocyte count ($\times10^9$/l)	4·2	1·4	9·4	12·9	3·5	9·6	9·5	15·1	1·8	7·1	5·7	2·5	12·0	4·8	1·9	1·6
Neutrophil count ($\times10^9$/l)	2·4	3·4	7·7	6·1	0·7	0·3	0·2	18·4	9·7	7·5	10·6	0·4	2·5	3·8	0·1	0·2
Monocyte count ($\times10^9$/l)	0·2	0·1	0·5	0·2	0·9	0·9	0·2	0·0	0·2	0·0	1·0	0·5	0·7	0·0	0·0	0·2

N/A=not available.

Table 3 Immunological indices in children with hyper IgM syndrome (reference ranges in brackets)

	Patient No															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
IgG (g/l)	1·7 (4·7–14·8)	3·6 (5·5–14·0)	1·1 (3·0–13·0)	0·2 (2·6–9·6)	1·0 (4·2–12·0)	0·8 (2·6–9·6)	0·5 (3·0–9·0)	0·1 (2·0–11·2)	1·7 (4·2–12·0)	<0·6 (2·6–9·6)	<0·9 (6·0–16·0)	0·5 (5·5–14·0)	0·7 (2·6–9·6)	2·5 (6·0–11·0)	3·8 (4·2–12·0)	<0·6 (5·0–10·0)
IgA (g/l)	0·2 (0·4–1·9)	0·03 (0·4–1·9)	0·1 (0·4–1·5)	0·03 (0·2–1·0)	0·09 (0·2–1·3)	<0·02 (0·2–1·0)	0·2 (0·2–1·1)	0·08 (0·1–0·9)	<0·1 (0·24–1·3)	0·03 (0·2–1·0)	<0·20 (0·6–2·8)	0·4 (0·4–1·9)	0·05 (0·2–1·0)	0·2 (0·4–1·2)	0·03 (0·24–1·3)	<0·02 (0·4–1·2)
IgM (g/l)	0·7 (0·3–1·5)	0·6 (0·4–1·9)	1·59 (0·4–2·0)	3·3 (0·3–1·5)	4·9 (0·4–1·8)	0·5 (0·3–1·5)	1·3 (0·4–1·6)	1·0 (0·1–0·8)	1·3 (0·4–1·8)	0·4 (0·3–1·5)	31·0 (0·5–2·1)	1·5 (0·4–1·8)	0·8 (0·3–1·5)	4·8 (0·8–1·6)	8·26 (0·4–1·8)	8·0 (0·6–1·4)
CD count (×10⁹/l)	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	CD4 low (0·5)	CD3 low (1·1)	Normal	Normal	Normal	Normal

T lymphocyte deficiency which may underlie the hypogammaglobulinaemia. The molecular basis of the X linked form of hyper IgM has been shown to be due to abnormalities of a T lymphocyte activation molecule.[5 6]

Most patients presented with respiratory symptoms in the first year of life and later had bacterial and viral infections which were well controlled with intravenous immunoglobulin. Relatively high doses of intravenous immunoglobulin were often required to control symptoms, particularly the neutropenia commonly associated with the syndrome. The mechanism for an improvement in the neutrophil count may have been the modulation of an autoimmune process, but may also have been the result of preventing infections causing secondary neutropenia. This emphasises the importance of considering secondary phenomena when describing the immunophenotype of an immunodeficiency disorder, particularly those due to single gene defects. This is well illustrated in this disorder where the high concentrations of IgM can be shown to be secondary by the return of the IgM to normal or subnormal levels once infection has been controlled and prevented.

Infections such as *P carinii*, *Cryptococcus neoformans*, cryptosporidia, cytomegalovirus, and other viruses which are more characteristic of T lymphocyte deficiency were more prominent in this series than in previous reviews.[2 9] As in other series, however, the outstanding laboratory abnormality in these patients was very low concentrations of IgG and IgA with apparently normal T cell function. In contrast with the other more common form of X linked hypogammaglobulinaemia, there were normal or increased numbers of circulating B lymphocytes capable of producing normal or increased amounts of IgM but not IgG or IgA. This implies disturbance of the normal mechanism whereby B lymphocytes producing IgM mature to produce cells able to produce other immunoglobulin isotypes.[10] This mechanism has been shown to be intrinsically intact in B lymphocytes from affected subjects,[10 11] and is controlled by T lymphocytes. Thus, both the clinical spectrum and laboratory findings suggest that X linked hyper IgM syndrome is a primary T lymphocyte abnormality. This would explain the failure to detect non-random X chromosome inactivation in the B lymphocytes of obligate carriers.[11 12]

In addition to the overall high frequency of opportunistic infections, certain other clinically important findings deserve emphasis. Features not previously described in association with this syndrome include sclerosing cholangitis (two deaths) and severe neurological disease, which was fatal in three patients.

The aetiology of hepatic and neurological disease may have been due to infection or an autoimmune process. The clinical feature which particularly emphasises the T lymphocyte deficiency in this disorder is *P carinii* pneumonia. *P carinii* pneumonia was a prominent finding with seven of 16 patients affected, six of whom had *P carinii* pneumonia on presentation. This point is particularly important in the differential diagnosis of infants presenting with interstitial pneumonia, most of whom are assumed to have congenital HIV infection or, less commonly considered, severe combined immunodeficiency. In two patients *P carinii* pneumonia recurred while receiving immunoglobulin replacement treatment, and all patients should receive long term *P carinii* pneumonia prophylaxis. Only seven other cases of hyper IgM have had documented *P carinii* pneumonia,[2] all occurring in boys, suggesting that this is a feature of the X linked form of the disorder.

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