Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Reversible hypogammaglobulinaemia

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ABSTRACT

In this report we present four patients with reversible hypogammaglobulinaemia who required immunoglobulin substitution for several years. One patient had documented systemic lupus erythematosus (SLE), the other three patients had primary hypogammaglobulinaemia without known cause. Whereas the cessation of azathioprine therapy may have contributed to the recovery in the patient with SLE, the restoration of the immunoglobulin production in the other three patients occurred spontaneously.

All four patients were IgA deficient when the hypogammaglobulinaemia was first detected and remained so after IgM and IgG production had recovered. Two of the three patients who also had anti-IgA antibodies started to produce anti-IgA again after stopping the immunoglobulin substitution. We conclude that recovery of hypogammaglobulinaemia is possible but rare.

When recovery is suspected, we recommend that immunoglobulin substitution is stopped and the antibody response to vaccination is tested.

KEYWORDS

Primary hypogammaglobulinaemia, reversibility, secondary hypogammaglobulinaemia

INTRODUCTION

Hypogammaglobulinaemia is a manifestation of various primary immunodeficiency disorders (PIDs). Common variable immunodeficiency (CVID) is the most frequently occurring PID with hypogammaglobulinaemia. Other examples of PIDs with hypogammaglobulinaemia are transient hypogammaglobulinaemia of infancy, X-linked agammaglobulinaemia (XLA), severe combined immunodeficiency (SCID), X-linked hyper IgM syndrome (XHIM), and various types of autosomal recessive gene defects with disturbed B-cell maturation.[1]

Except for transient hypogammaglobulinaemia of infancy, primary hypogammaglobulinaemia is considered to be irreversible. Still, recovery has been reported in some CVID patients after acquisition of HIV infection.[2-4] Secondary hypogammaglobulinaemia may resolve after elimination of the underlying cause. Song *et al.* reported a woman with reversible hypogammaglobulinaemia, the absence of B lymphocytes and systemic lupus erythematosus (SLE).[5] In the present study we present one child with SLE who, similar to the case of Song *et al.*, also showed a restoration of the number of B cells and immunoglobulin production. In addition, we describe three other patients, in whom the diagnosis of primary hypogammaglobulinaemia was made without identifying the underlying cause, who also manifested spontaneous recovery of gammaglobulin production.

CASE REPORTS

Case 1

The patient, a female born in 1989, presented at the age of two years with fever, walking disability and anisocoria. Viral encephalitis was suspected and treated with acyclovir. After this episode she developed muscular rigidity. Six months later, she suffered from an acute glomerulonephritis and thrombocytopenia (43 x 10^9/l). Antinuclear antibodies (ANA) and anti-dsDNA were positive. The diagnosis of SLE was made. At that time the immunoglobulin serum concentrations were IgG 12 g/l, IgM 1.83 g/l, and IgA <0.05 g/l. The glomerulonephritis was successfully treated with corticosteroids and azathioprine. In the following years, ANA and anti-dsDNA became negative. At the age of 13 years she suffered from a series of respiratory tract infections and severe hypogammaglobulinaemia was detected (IgG 1.82 g/l, IgM 0.01 g/l, IgA <0.05 g/l) with anti-IgA antibodies present (*table 1*). Circulating B cells were nearly absent, CD4 and CD8 positive T cells were normal. Bone marrow analysis revealed almost

Table 1. *Immunoglobulin levels in the patients over time*

Case 1													
Age in years	13	13.5	14	15.5	16		16.1	16.4	16.7	17	18		
Event		Start sc Ig				Stop sc Ig							
IgG g/L	1.82	1.89	*4.64*	*5.14*	*9.15*	*11.2*	9.9	13.6	27.7	16.5	13.8		
IgG 1 g/l				*3.44*	*5.94*		8.01		20.07				
IgG 2 g/l				*1.9*	*1.84*		0.76		1.56				
IgG 3 g/l				*0.14*	*0.3*		0.58		2.3				
IgG 4 g/l				*0.12*	*0.11*		<0.05		<0.05				
IgM g/L	0.01	0.01	*0.01*	*0.1*	*0.19*	*0.3*	0.26	0.6	0.23	0.29	0.3		
Case 2													
Age in years	0.3	0.5	0.7	1	2	2.5	2.75	3	4	5	6	7	8
Event		Start Ig				Stop Ig	Restart Ig	Stop Ig					
IgG g/l	5.07	3.52	*6.16*	*8.39*	*11.1*	*8.98*	11.1	*15.5*	15.2	15	18.7	15.2	17.8
IgG 1 g/l										9		9.26	
IgG 2 g/l										4.37		4.6	
IgG 3 g/l										0.67		0.82	
IgG 4 g/l										0.1		0.16	
IgM g/l	8.5	0.19	0.08	*<0.04*	*0.24*	*0.3*	0.43	*0.56*	0.8	0.61	0.79	0.65	0.77
Case 3													
Age in years	4		4.75	5	7	10	13	14	15	16	17	18	19
Event		Start sc Ig						Stop sc Ig					
IgG g/l	0.36		*6.12*	*6.02*	7.05	*8.63*	*9.34*	*9.55*	8.19	6.21	8.35	8.55	7.89
IgG 1 g/l							*5.83*			5.02	5.44	5.05	4.57
IgG 2 g/l							*2.1*			0.42	1.34	2.15	1.72
IgG 3 g/l							*0.92*			1.12	0.94	0.92	0.87
IgG 4 g/l							*0.16*			0.06	0.12	0.11	0.11
IgM g/l	0.14			*0.05*	*0.17*	*0.17*	*0.18*	*0.22*	0.18	0.15	0.18	0.17	0.16
Case 4													
Age in years	49		50	51	53	61		61.5	62	65	66	67	68
Event		Start sc Ig					Stop Ig	Gastric cancer					
IgG g/l	2.7		*3.6*	5	*4.4*	*6.9*		7.82	11.8	12.4	11.9	13.6	13.69
IgM g/l	0.26							0.46		0.95	0.75	0.72	

Normal values (6)	**IgG**	**IgM**
4-6 months	4.27 ± 1.86 g/l	0.43 ± 0.17 g/l
7-12 months	6.61 ± 2.19 g/l	0.54 ± 0.23 g/l
1-2 years	7.62 ± 2.09 g/l	0.58 ± 0.23 g/l
3-5 years	9.29 ± 2.28 g/l	0.56 ± 0.18 g/l
6-8 years	9.23 ± 2.56 g/l	0.65 ± 0.25 g/l
Adults	11.58 ± 3.05 g/l	0.99 ± 0.27 g/l

Values in italic immunoglobulin levels determined during immunoglobulin substitution.

complete absence of mature B cells with a blockade before the Cylgμ-positive-pre-B-cell stage (which means positive for cytoplasmatic μ heavy chains, a maturation defect). Subcutaneous immunoglobulin suppletion was started. Eighteen months after the start of substitution, the number of B cells in the blood returned to normal shortly after an episode of appendicitis and termination of the azathioprine. While the patient was still on stable substitution, IgG levels gradually rose to 11.20 g/l, IgM to 0.30 g/l but IgA remained absent (<0.05 g/l). There was

a normal spread of IgG subclasses. When subcutaneous immunoglobulin substitution was stopped, IgG levels remained normal and anti-IgA reappeared. Recently, our patient experienced an exacerbation of her SLE, for which she is treated with corticosteroids and methotrexate.

Case 2

A boy, born in 1998, presented at the age of four months with a progressive cough, tachypnoea, dyspnoea and failure to thrive. The diagnosis of *Pneumocystis jirovecii* infection was made after chest X-ray and bronchoalveolar lavage. This finding prompted analysis for an immunodeficiency. At presentation, serum IgG was 5.07 g/l, IgM 8.50 g/l, and IgA 0.08 g/l, with a rapid decrease within two months to IgG 3.52 g/l, IgM 0.19 g/l, and IgA undetectable (*table 1*). No anti-IgA-antibodies were found. Immunoglobulin substitution was started successfully. From this point onwards, no major infections occurred. B cells identified by flow cytometry on CD19 and CD20, at the start of substitution, were absent. Bone marrow analysis at this time showed a relative accumulation of pre-B-I cells, normal pre-B-II cells and a decreased number of immature and mature B cells. T-cell analysis showed CD3+ cells 1.30 x 10^9/l, CD4+ cells 1.06 x 10^9/l, and CD8+ cells 0.15 x 10^9/l. CD40 ligand was normally expressed and T cells were also normal. No mutations in the *BTK* gene were found.

At the age of 2 years, the serum IgG concentrations had increased gradually to 11.1 g/l (*table 1*) and mature B cells became detectable in peripheral blood. Based on these findings it was decided to stop the subcutaneous immunoglobulin suppletion under cover of prophylactic antibiotics that later had to be withdrawn because of allergic reactions to various antibiotics. Six weeks after withdrawal of the subcutaneous immunoglobulin substitution, the patient was vaccinated with the combined unconjugated diphtheria, tetanus and poliomyelitis vaccine (DTP) and with conjugated *Haemophilus influenzae* type-b (Hib) polysaccharide vaccine. The antibody response (IgG) to DTP was normal (diphtheria 0.66 IU/ml, tetanus 0.24 IU/ml, pneumococcal serotype 3: 9 U/ml, serotype 4: 4 U/ml, serogroup 9V: 2 U/ml) but to Hib no response (Hib IgM <1 U/ml, Hib IgG 3 U/ml) developed. This latter poor response to polysaccharide antigens and the problems with the antibiotic prophylaxis led to the decision to restart IgG substitution. When, at the age of three years, the serum IgG concentration had reached 15.5 g/l and IgM had increased to 0.56 g/l, suppletion of immunoglobulin was definitively stopped. Repeated DTP and Hib vaccination at this time resulted in a good response (diphtheria 2.45 IU/ml, tetanus 2.79 IU/ml, Hib IgM 47 U/ml, Hib IgG 131 U/ml). During follow-up to the age of eight years, serum IgG and IgM concentrations remained normal although IgA deficiency persisted. Major infections have not occurred.

Case 3

The patient is male, born in 1988, with mild mental retardation who presented with frequent upper respiratory tract infections and otitis media at the age of 4 years. Blood analysis showed concentrations for IgG of 0.36 g/l, IgM of 0.14 g/l and IgA <0.05 g/l (*table 1*). Antibodies against IgA were present. The number of B cells was normal (CD19 0.9 x 10^9/l), peripheral blood T cells were increased (CD3+ 6.0 x 10^9/l, CD4+ 2.86 x 10^9/l, and CD8+ 2.5 x 10^9/l). The patient was treated with weekly subcutaneous immunoglobulin suppletion, resulting in virtually complete disappearance of infections. At the age of 14 years, IgG levels (under substitution) were found to be 9.5 g/l. (Re)vaccination with DTP and Hib resulted in a good antibody response (diphtheria 2.61 IU/ml, tetanus 2.23 IU/ml, pneumococcal serotype 3: 32 U/ml, serotype 4: 9 U/ml, serogroup 9V: 11 U/ml, Hib IgM 13 U/ml, Hib IgG 107 U/ml). IgG suppletion was stopped at the age of 15 years. Infections did not recur and the IgG levels have remained normal. Anti-IgA antibodies reappeared.

Case 4

A woman, born in 1939, was referred in 1988 at the age of 49 years by a peripheral hospital with the diagnosis of CVID established two years earlier. She suffered from recurrent upper and lower respiratory tract infections. At that time, IgG was 2.7 g/l, IgM 0.26 g/l and IgA was undetectable with anti-IgA antibodies present. Two of the patient's children were known to have selective IgA deficiency. Immunoglobulin supplementation was started in a dosage of 2.4 g IgG per week, subcutaneously because of the presence of anti-IgA antibodies. After initiation of immunoglobulin substitution the patient remained free of respiratory tract infections. At the age of 61 years, a remarkably high serum IgG concentration (7.82 g/l) was found, while she had not had the subcutaneous γ-globulin during the previous month. Vaccination with the 23-valent pneumococcal polysaccharide vaccine, two months after withdrawal of supplementation, showed a clear response (IgG antibody titre against serotype 3 increased in three weeks from 5 to 53 U/ml, the titre against serotype 4 increased from 12 to 264 U/ml) but the response to Hib vaccination was poor. A few months later she complained of progressive abdominal discomfort. Gastroscopy showed atrophic gastritis with metaplasia without evidence of *Helicobacter pylori* infection. A control endoscopy two months later revealed a poorly differentiated adenocarcinoma of the antrum stage $pT_2N_0M_x$. The carcinoma could be completely removed surgically. In the years after surgery, IgG and IgM concentrations remained normal without further supplementation. IgA remained deficient, but anti-IgA antibodies did not reappear. After more than five years of follow-up, the patient remained free of infections and the gastric cancer did not recur.

DISCUSSION

In the current study we report four patients with reversible hypogammaglobulinaemia. One of them had SLE, in the other three patients the cause of the hypogammaglobulinaemia was unknown. These four patients belong to a population of approximately 200 patients with hypogammaglobulinaemia known in our combined paediatric and general internal clinical practice in a university hospital. Thus, recovery from hypogammaglobulinaemia can occur but is rare.

Hypogammaglobulinaemia may be found in patients with SLE;[5-8] recovery has been described in one SLE patient.[5] The pathogenesis of the development of hypogammaglobulinaemia in SLE is probably multicausal. In our patient (case 1), bone marrow analysis showed almost complete absence of mature B cells. Regarding the pathogenesis, a number of possibilities come to mind. First, autoantibodies against B lymphocytes (or relevant T lymphocytes) could play a role.[9] This possibility was not checked in our patient. A second possibility is a defect in the intercellular signalling molecules, such as Fas or Fas-ligand (CD95). In MRL/lpr mice this defect leads to the development of SLE and hypogammaglobulinaemia.[10] Autoimmune lymphoproliferative syndrome (ALPS) is also based on such a deficiency and can present with similar symptoms as SLE, such as glomerulonephritis or arthritis. However, a diagnostic criterion of ALPS is the presence of CD3+, CD4-, and CD8- lymphocytes, which was not the case in our patient. Fas was not measured in our patient. The spontaneous recovery of hypogammaglobulinaemia also argues against such a congenital defect. A third explanation may be the immunosuppressive treatment with azathioprine. When azathioprine was withdrawn in our patient, the B cells rapidly returned and the IgG recurred thereafter. Remarkably, during the period of hypogammaglobulinaemia, the SLE was in remission. This phenomenon, i.e. recovery of SLE during disappearance of autoantibodies, has been reported before.[5,11] This is corroborated by our observation that the patient had a resurgence of her SLE, requiring resumption of therapy, during reappearance of B cells and IgG.

Normalisation of antibody production in primary hypogammaglobulinaemia has been described in some patients with CVID after the acquisition of HIV infection.[2-4] These patients had low T cell counts. We had no suspicion of HIV infection in our patients with hypogammaglobulinaemia because of normal T-cell counts and absence of signs even after a long period of follow-up.

In the patient from case 2, the occurrence of a *Pneumocystis jirovecii* pneumonia in combination with high serum IgM levels, low IgG and IgA deficiency at presentation, raised the suspicion of hyper-IgM syndrome. However, this diagnosis was ruled out because B cells were absent and CD40 ligand was normally expressed. In addition, the diagnosis of SCID was ruled out because normal numbers of CD3+, CD4+ and CD8+ cells were found. We did not look for other types of hyper-IgM syndromes, such as uracil-N-glycosylase (UNG), activation-induced cytidine deaminase (AID) and nuclear factor-kappaB essential modulator (NEMO) because in these diseases B cells are normally present, these diseases are not associated with bone marrow maturation defects and there is a difference in clinical presentation. Very rarely, *Pneumocystis jirovecii* pneumonia has been diagnosed in a patient with transient hypogammaglobulinaemia of infancy.[12] However, in contrast to our patient, children with this disease also have B cells. Bone marrow analysis in our patient showed a maturation defect of the B-cell lineage of unknown origin. However, the patient must have had – at least during a certain period after birth – functional B cells given the high IgM levels (the IgG levels at that age could have been of maternal origin). As seen in the follow-up, the B-cell deficiency was reversible. We can only speculate about the cause of this transient disappearance of B cells in early life. Several mechanisms, such as autoimmunity or a postinfectious complication, may have played a role.

In the patient from case 3, we also considered the diagnosis of transient hypogammaglobulinaemia of infancy but rejected this diagnosis. In our patient the hypogammaglobulinaemia was very profound even at the age of 4 years and persisted for years, whereas in transient hypogammaglobulinaemia of infancy the decrease of immunoglobulins is less extreme and recovery is expected between 9 and 15 months of age, with a range of up to a maximum of 5 years of age. In the patients from case 3 and 4, we also considered the diagnosis CVID. Recovery from CVID is rare. Eisenstein and co-workers[13] showed that culturing CVID B cells for several days in co-culture with activated normal allogenic T-cells with anti-CD40 and IL10 added, results in IgM and IgG secretion *in vitro*. Based on these experiments they suggested that the defect of CVID B cells to secrete antibodies might be reversible. In 1991, Seligmann *et al*. described several CVID patients with changes in serum immunoglobulin patterns.[14] One of these patients had an almost complete IgG deficiency at presentation, except for IgG3, with IgA and IgM deficiency. During IgG therapy, IgG1 and IgG3 as well as IgM became normal and substitution was stopped. In the subsequent two years, IgG1 and IgG3 stayed normal, but eventually decreased to values similar to those at presentation. The course in our patient from case 3 may be comparable. After cessation of substitution his IgG level is gradually decreasing.

In the patient from case 4, recovery of the endogenous immunoglobulin production was suspected when relatively high IgG levels were measured under minimal immunoglobulin substitution. It is intriguing that at the same time, gastric cancer was diagnosed. The adequate responses to Hib and pneumococcal vaccines were found

just before resection of the gastric cancer. One hypothesis is that the tumour played a causative role, for instance by producing a humoral factor counteracting the defect. Although we did not analyse the tumour tissue for such factors, this possibility is ruled out as the patient had a curative resection of the tumour with a follow-up of more then five years and persisting normal immunoglobulin levels. The reverse hypothesis that the hypogammaglobulinaemia was caused by the tumour is highly unlikely given the long history of CVID in this patient and the positive vaccination responses before surgery.

It is of interest to note that all our four patients were IgA deficient at presentation and remained so after recovery. In two of the three patients with anti-IgA antibodies at the moment of diagnosis, these antibodies became detectable again when immunoglobulin substitution was withdrawn. Therefore, it is unknown whether the absence of anti-IgA antibodies was explained by the masking effect of donor IgA or by the transient disappearance of the anti-IgA producing plasma cells.

In brief, as shown in the four patients described above, reversibility of hypogammaglobulinaemia can occur. When suspected, it is recommended to measure IgA and IgM, components that are not part of the immunoglobulin substitution. The next step would be to stop immunoglobulin substitution and to measure immunoglobulin concentrations after at least six weeks, followed by the measurement of the antibody response to vaccination with a protein and with a polysaccharide vaccine. When in doubt, one could test the response to vaccination with a neo-antigen (e.g. rabies vaccine), even during immunoglobulin substitution. Based on these findings a decision can be made to stop the substitution permanently.

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