The clinical features of hyper-IgM syndrome. A 4 cases report

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Abstract

The hyper-IgM (HIGM) syndromes are a group of molecular defects of immunoglobulins class switch during B cell maturation. In HIGMs the level of IgM is elevated in majority of cases but also can by in normal range or even decreased. The other class of immunoglobulins are decreased or absent. The five types of HIGM are known: one X-linked (T lymphocyte defect) and four (including B cell defects) transmitted in the autosomal recessive pattern.

The 4 cases of HIGM are shown: 3 boys diagnosed at age of 1, 6 and 15 years and one girl with DiGeorge syndrome and HIGM developed at age 4. In 2 cases the haematological symptoms (thrombocytopenia and neutropenia) were observed. The expression of CD40L on activated T lymphocytes was present in all patients but the level of expression was different. The low level of CD40L was associated with early onset and severe course of infections. All patients are treated with intravenous IgG substitution what resulted in decrease the frequency and severity of infections.

Key words: *hyper-IgM syndrome, CD40-CD40L, clinical course, IVIG therapy.*

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Introduction

The hyper-IgM syndrome (HIGM) is a heterogeneous group of antibody production disorders comprising 5 types. The first X-linked form (HIGM1) is caused by mutation in the gene encoding of CD40 ligand (CD40L). The others transmitted in autosomal recessive pattern are concerned with mutations in the genes encoding the activation-induced cytidine deaminase (HIGM2), CD40 (HIGM3) or uracil-N glycosylase (UNG deficiency – HIGM5). The most frequent autosomal recessive HIGM (HIGM4) has no defined molecular basis but the defect probably affects the DNA repair mechanism [1-10].

The CD40L (CD154) is a transmembrane protein type II belonging to TNF (tumour necrosis factor) superfamily. CD40L is predominantly expressed on mature, activated T lymphocytes, monocytes and NK cells. CD40 belongs to the same superfamily of TNF proteins and constitutively expressed on precursors and mature B-cells, macrophages/monocytes, dendritic cells, vascular endothelial cells and epithelial cells. CD40L binding to extracellular domains of CD40 induces interaction of TNF receptor associated proteins (TRAF) with the intracellular domains of CD40. The activation of this pathway leads to switch of the immunoglobulins isotype. Moreover, the interaction of CD40L/CD40 on the surface of B cell provides an essential signal for antibody production, affinity maturation and germinal centre formation in lymph nodes and rescues of B cells from apoptosis at some stages of differentiation [2, 3, 5, 7, 11, 12].

The patients with HIGM1 are unable to develop the effective T cell-dependent antibody response what results in high susceptibility to bacterial infections. These patients are also susceptible to infections caused by intracellular opportunistic pathogens such as *Pneumocystis carini*, *Cryptosporidium parvum* and many other. Defective CD40L/CD40 interaction also leads to defective T cell/monocytes co-operation and an abnormal cellular response. Ineffective interaction between T cell and antigen-presenting cells (APC) expressing CD40 resulted in low or absent of stimulation of the production of Interleukin-12 (IL-12) [7, 13].

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Bacterial infections are the main clinical symptoms observed in all types of HIGM. The majority of HIGM patients demonstrate bacterial infections of lungs and the infections of upper respiratory tract including sinusitis and recurrent otitis. In severe clinical form of HIGM the infections including viral (cytomegalovirus, adenovirus), mycobacterial pathogens and *Pneumocystis carini* pneumonia are observed early, in first year of life. The chronic diarrhea following the infection with *Cryptosporidium species*, *Gardia lamblia*, *Salmonella*, *Entamoeba histolytica* and others pathogens occurs in more than half of HIGM patients. The reasonable number of them requires total parenteral nutrition because of malnutrition syndrome. The life threatening infections of the central nervous system, chronic infections of liver or sepsis are less frequent. The cholangitis sclerotisans caused by different pathogens including Cryptosporidium leads to liver cirrhosis or malignancy what is the most serious complications of HIGM1 [5-7]. Patients with HIGM, particularly HIGM1 type, develop the haematological abnormalities such as persistent or cyclic neutropenia [5, 7]. Anaemia is observed in about quarter of HIGM patients and is associated with chronic infections, autoimmune mechanisms and bone marrow insufficiency. The lymphoid hyperplasia and splenomegaly are associated with infections particularly with persistent or recurrent forms. These symptoms are frequently noted in HIGM patients during severe infections. The persistent lymph nodes enlargement requires investigation including possibility of malignancy as HIGM patients have high risk of lymphoproliferation [6, 7].

The aim of this study is to present 4 patients with HIGM demonstrating the heterogeneous clinical features of this immunodeficiency. The results of immunological assays at diagnosis and the expression of CD40L on activated T cells and CD40 on B cells are discussed. The clinical course of disease and the results of the IVIG therapy are presented.

Patient 1

The boy was born as a full-term, healthy, fourth child in non-consanguineous couple. The siblings of patient are healthy without symptoms of immunological defects. The patient was admitted to hospital at age of 6 months for the first time with severe interstitial pneumonia and pneumothorax. The examination of fluid specimens from pulmonary drainage of right lung showed *Pneumocystis carini* infection. The therapy with antibiotics, pentamidine, sulphonamides, and steroids was only a partially effective. He was ventilated mechanically and feeded parenteraly. The blood tests showed neutropenia, anaemia. The level of IgG and IgA were decreased and the level of IgM was within normal range. The number of T lymphocytes was decreased but B lymphocytes was increased (table 1). The bone mar-

Table 1. The patients' characteristics

	Patient 1		**Patient 2**	**Patient 3**	**Patient 4**
age at diagnosis, gender	7 months, boy		5 years, boy	15 years, boy	4 years, girl
		immunological tests			
immunoglobulins					
IgG (g/L)	2.07	1.03	0.09	<1.0	4.59
IgA (g/L)	<0.05	<0.07	0.1	<0.05	0.36
IgM (g/L)	1.47	2.12	21.90	40.0	6.44
lymphocytes T					
CD3 (%)	39	83	82	71	53
CD4 (%)	29	63	34	29	41
CD8 (%)	10	20	44	37	12
T α/β (%)	20	ND	ND	60	ND
T γ/δ (%)	1	ND	ND	7	ND
CD3/HLA-DR (%)	ND	15	ND	11	ND
lymphocytes B: CD19 (%)	54	6	8	12	41
NK (%)	8	8	ND	12	ND
adhesion molecules					
CD11a (%)	77	ND	ND	ND	ND
CD18 (%)	89	ND	ND	ND	ND
CD154 (CD40L) (%)	24	ND	90	93.3	88
CD40 (%)	100	ND	98	99	98.5
mitogen response (stimulation index)					
Nil (cpm)	1174	2160	756	465	628
PHA (cpm) (IS)	40694 (34)	3422 (1)	61190 (80)	1173 (2)	40520 (64)
ConA or CD3 (cpm) (IS)	57095 (48)	27793 (12)	30511 (40)	752 (1)	34003 (54)
PWM (cpm) (IS)	40848 (34)	70303 (32)	21448 (28)	641 (1)	28064 (44)

row aspiration showed decreased percentage of precursors and mature myeloid cells. In analysis of immunophenotype the increased percentage of B cell precursors was detected within the lymphoid cell population. The substitution with intravenous immunoglobulin IgG (IVIG) and granulocyte colony stimulating factor (G-CSF) was added to symptomatic therapy including antibiotics and bronchodilatators. The symptoms of respiratory insufficiency slowly resolved upon this therapy. After 7 months the boy was discharged from hospital with following therapy: sulphonamides, IVIG, spasmolytics and G-CSF.

After one year the boy was re-admitted with pneumonia and respiratory insufficiency. The standard therapy with antibiotics, steroid and spasmolytics was ineffective and patient developed ARDS. He required the mechanical ventilation for one month. The chest X-ray demonstrated inflammation of lungs and pneumothorax, bronchiectases and dense foci recognised as lung fibrosis. In blood tests the severe neutropenia (below 500 neutrophils per μL), anaemia, low level of IgG and IgA were noted. Despite of therapy (IVIG, G-CSF, antibiotics) the sepsis with *Staphylococcus epidermidis* developed and was successfully treated. The slow resolution of clinical symptoms was noted and the boy was discharged from hospital after 6 months with the diagnosis of hyper IgM syndrome.

The maintenance therapy included sulphonamides, substitution of IVIG (0.4 g/kg b.w. once per month) and G-CSF daily. The following episodes of pneumonia were observed 2 years later but the clinical course was less severe. In outpatient observation the neutropenia was persistent (500-800 neutrophils per μL) despite of G-CSF injections but the infections were rare and mild in the course. A longitudinal monitoring of immunoglobulins level during IVIG therapy showed Ig level within normal range for age, IgA deficiency and low or normal level of IgM. There was no increase of IgM during 4 years of follow-up observation (figure 1) but in the present year the increase of IgM was noted despite of IVIG regular substitution. Now, the boy is in a good state, slightly underweight and underheight with the substitution of IVIG in every 4 weeks, G-CSF and sulphonamides as permanent therapy. Auscultation of the lungs reveals the crepitations what corresponds to the stationary phase of pulmonary fibrosis. Patient is under physical and symptomatic therapy improving respiration.

The initial diagnosis was hypogammaglobulinemia but after analysis of clinical course and results immunological tests (decrease of IgG, low expression of CD40L) the diagnosis was described as HIGM syndrome.

Patient 2

The boy with no history of previous severe infections was admitted to hospital at age 5 years with symptoms of bronchopneumonia, hepatosplenomegaly and lymphadenopathy. In X-ray of chest the enlargement of lymph nodes in mediastinum, disseminated inflammatory infiltrations in both lungs. The laboratory tests showed high ESR, increased leukocyte count. Serological tests were negative for CMV (both IgG and IgM), negative for *Mycoplasma pneumoniae* (both IgG and IgM) and positive for Toxoplasma gondi in IgM class only. The therapy with antibiotics (biofuroxym, biodacine, rovamycin) and metronidazole was successful. A month later the patient was re-admitted to hospital because of lymphadenitis. The sulphonamides were used with improvement of clinical symptoms. He was again hospitalised after following 5 months with symptoms of severe pneumonia and pleuritis. In laboratory tests ESR, LDH and CRP were markedly increased. The assay of immunoglobulins' level showed the trace of IgG, deficiency of IgA, and the increase of IgM level (table 1). After therapy with antibiotics the clinical symptoms improved. The IVIG therapy has been applied with decrease of IgM level (figure 1). Since the last pneumonia the patient is in a good state without symptoms of infection. The lymph nodes in maxillary and neck region are enlarged. The chest X-ray showed no remaining changes after previous pneumonias (bronchiectases, fibrosis) and no mediastinal lymphadenopathy. The patient remains under regular substitution of IVIG in every 4 weeks in outpatient system. In last year the trimetoprim was installed as anti-Pneumocystis prophylaxis.

Relatively mild clinical course in this case of HIGM may be associated with inducible expression of CD154. The lymphadenopathy noted in this case is a typical symptom noted in about half of HIGM patients [2, 5, 7].

Patient 3

The boy was born as a full-term healthy child in a family without previous history of immunodeficiency. He has a healthy, younger sister.

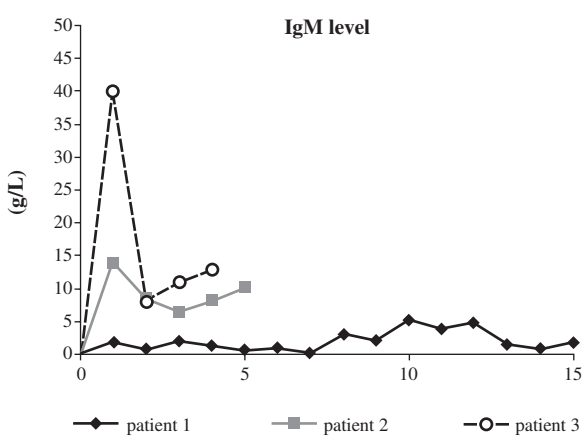

Fig. 1. The follow-up of IgM level in serum before (the first data) and during the IVIG therapy in cases 1-3 of HIGM patients. The assay was performed 3-4 times per year in a day of IgG substitution before IVIG administration

Patient did not develop any symptoms of immunodeficiency during the first 8 years of life. The bacterial pneumonia at age 9 years was the first severe infection. The chest X-ray showed involvement of right upper lobe. The antibiotic therapy was successful, but one year after the recurrent pneumonia localised within the same right lung lobe was observed. Laboratory tests revealed antibodies against *Mycoplasma pneumoniae* but only in IgM class (titre 1:100). The therapy with antibiotics (amoxicillin, amikacin, clarithromycin and cefuroxim) was effective.

The subsequent pneumonia was noted 2 years later and the inflammatory infiltrations were observed in both lungs. The clinical symptoms were severe and the patient required steroids in addition to antibiotics (tarcefoxim, roxitromycin). The symptoms resolved upon this therapy. After 4 months the patient was readmitted to hospital with the sinusitis and pyelonephritis. The therapy with antibiotics, steroids and spasmolytics was introduced with good response. Up at age of 15 years the next bronchopneumonia was diagnosed with *Staphylococcus haemolyticus* (MRSE) detected in the blood culture. The immunological tests were performed during this infection for the first time. The very high level of IgM, a trace of IgG and lack of IgA were detected (table 1). The therapy with antibiotics and intravenous immunoglobulins (IVIG – 0.4 g/kg b.w.) resulted in clinical improvement. The decrease of IgM was observed but the level remained above the normal range. From the first IVIG substitution the boy remains with no symptoms of infections. The results of laboratory tests (ESR, CRP, blood test or urine) are within normal range. The follow-up of IgM level under IVIG substitution is shown on figure 1.

In this case the proper diagnosis of HIGM was delayed because of asymptomatic course of disease during the first 8 years of life. The extremely high level of IgM, lack of IgG and IgA suggested HIGM.

Patient 4

The girl was born as third child in family without previous history of immunodeficiency. The two sisters are healthy. She was born with clinical symptoms of DiGeorge' anomaly (hypocalcemic episodes, congenital heart disease). The diagnosis of DiGeorge syndrome was genetically proved. The results of immunological test of cellular immunity are shown in table 2. The cardiac surgery for Fallot's tetralogy was successfully performed at age of 6 months. In the next 6 months of life she suffered from recurrent pneumonias (3 times). The levels of IgG and IgA were decreased but the level of IgM was within normal range. At age of 2 years the severe thrombocytopenia, neutropenia occurred. The therapy included regular IVIG (0.4 g/kg b.w.) substitution, administration of steroids and thymus-derived factor. After 6 months the side effects of steroids and the recurrence of episodes of severe thrombocytopenia (below 5000 platelets per μL) were an indication for immunosuppression (azathioprine in standard dose). The control of immunglobulins level in this time showed the increase of IgM level (table 1). The systematic increase of IgM level was observed during next 2 years of follow up (figure 2) despite of regular IVIG substitution. Till now, the chronic, therapy resistant thrombocytopenia, recurrent infections of upper respiratory tract and splenomegaly are the main problems of this patient. The maintenance therapy includes low dose of steroids, azathioprine, thymic factors, bronchodilatators and IVIG substitution. The severe haemolytic anaemia episode (January 2006) was noted during IVIG substitution so the immunoglobulins substitution was cancelled for 6 months. After high-dose steroid therapy the enlargement of spleen diminished and the suggested splenectomy was postponed. Now, the substitution was administered again because of upper respiratory tract infections. The level of IgM is still

Table 2. Case 4 – the results of immunological tests for cellular immunity

Date	02.01.2003	18.03.2003	25.11.2003	26.02.2004	21.09.2004	27.07.2006	29.06.2006
T cell subpopulations							
CD3 – % (/μL)	53(ND)	60 (ND)	64 (ND)	82 (1804)	78 (2262)	86 (1118)	80 (1600)
CD4 – % (/μL)	41 (ND)	46 (ND)	52 (ND)	70 (1540)	61 (1769)	70 (910)	61 (1220)
CD8 – % (/μL)	12 (ND)	15 (ND)	14 (ND)	11 (242)	16 (464)	15 (195)	19 (380)
CD3/HLA-DR	ND	17 (ND)	ND	ND	ND	ND	ND
B cell number							
% (/μL)	11 (ND)	15 (ND)	14 (ND)	7 (156)	5 (145)	4 (52)	4 (80)
stimulation response							
Nil cpm	628	3006	568	1972	634	354	516
PHA cpm (S.I.)	40520 (64)	15865 (5)	21452 (37)	42883 (22)	561 (1)	602 (1)	469 (1)
CD3	34003 (54)	14272 (4)	7051 (12)	37924 (19)	733 (1)	360 (1)	447 (1)
PWM	28064 (44)	9622 (3)	4392 (7)	11935 (6)	677 (1)	362 (1)	384 (1)
Nil	ND	ND	ND	ND		ND	220
PPD	ND	ND	ND	ND		ND	264 (1)
Candida albicans	ND	ND	ND	ND		ND	224 (1)

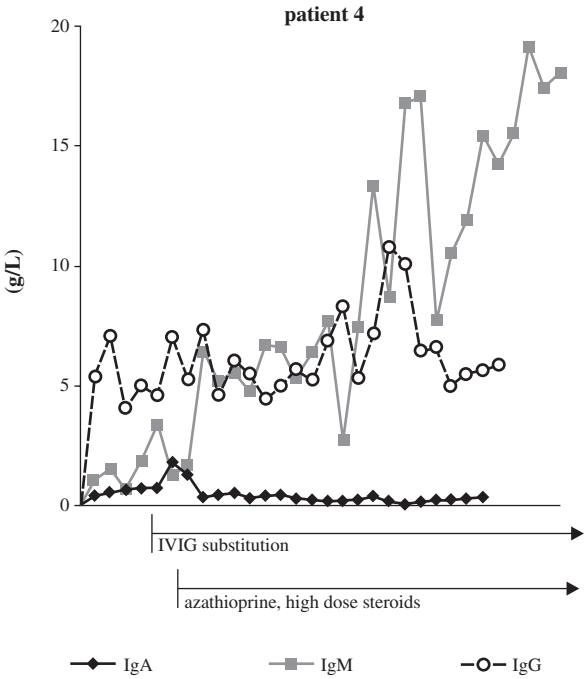

Fig. 2. The follow-up of IgG, IgA and IgM level in case 4. The assay was performed in every 3 months in a day of IgG substitution before IVIG administration

high (range 15 g/l – 30 g/l) with no association with clinical state or symptomatic and steroid therapy. The electrophoresis of IgM showed polyclonal IgM. The elevated IgM or secondary HIGM was diagnosed based on immunological results. The level of IgM in this patient is "resistant" to changes of IgG level (substitution) and there is no feed--back phenomenon observed in majority of HIGM.

Immunological tests

The immunoglobulins level in patients' serum was measured with nephelometry (Dade-Behring Corporation Germany).

The immunophenotype assay of mononuclear was performed on venous blood after staining with monoclonal antibody in double staining method. There were two methods of staining the mononuclear cells: one performed on whole blood followed with lysis of erythrocytes and the second performed on the mononuclear cells population (PBMC) isolated based on density gradient (Ficoll/Isopaque, Elkabe, Sweden). The set of fluorochrome conjugated monoclonal antibodies (IMK kit – Becton-Dickinson, Belgium) – anti CD3, CD4, CD8, CD45, CD14, CD19 was used for routine immunophenotype assay with whole blood method. The additional antibodies – anti-HLA-DR, TCR α/β, TCR γ/δ, NK cells, CD11a, CD18, CD40, CD154 (PharMingen/Becton-Dickinson, Belgium) FITC or PE or PerCP conjugated were used for immunophenotype assay on PBMC. These antibodies are used for patients with immunodeficiency. The inducible expression of CD154, CD40 was assayed on PBMC cultured for 4 hours in medium or in the presence of stimulators: PMA (50 ng/ml) (Sigma, Germany) and ionomycin (3 μg/ml) (Sigma). The mononuclear cells from healthy person were cultured in parallel and use as control [4].

Flow cytometry assay

The cells stained with monoclonal antibodies according to manufacturer procedure, washed, suspended in PBS were assayed in flow cytometer (FACS Calibur, Becton-Dickinson, Palo Alto, CA) after acquisition of 10 000 events from each tube. The isotype control was run in parallel. The analysis was performed on mononuclear cells (after lysis of erythrocytes from the whole blood) and on lymphocytes (PBMC and cultured cells) gated on FSC and SSC dot plot. The dot plot and histograms overlay were use for visualization of results with the quadrant and histograms statistics.

There no molecular tests for CD40L gene performed.

Mitogen/antigen response of lymphocytes

Isolated PBMC were cultured in medium (RPMI1640) supplemented with 10% of foetal calf serum (FCS, Biochrom, Germany), antibiotics in the presence of medium only, phytohaemagglutinin (PHA – 2.5 μg/ml) (Murex), monoclonal antibody against CD3 (CD3 – 1 μg/ml) (Immunotech, Germany) and pokeweed mitogen (PWM – stock dilution 1:1000) (Gibco, Germany) for 72 hrs in humid, 5% CO_2 atmosphere in 37°C temperature. For the last 6 hrs the ^{3}H-thymidine (NEN, England) was added than the cells were harvested. Incorporation of ^{3}H-Thymidine was measured in a liquid scintillation beta counter (Beckman Instruments). Stimulation index is a ratio between proliferation (assayed as cpm) of stimulated cells and non-stimulated cells.

Discussion

In HIGM syndrome the serum level of IgG, IgA and IgE immunoglobulins are markedly decreased or even absent. It is known that at diagnosis the serum level of IgM may be increased, normal or decreased [5-7]. The typical clinical features of HIGM patients represent infections, mainly upper respiratory tract with different clinical course from severe, life threatening to mild. The presented 4 patients with diagnosis of HIGM syndrome reveal variety of clinical symptoms observed in HIGM. The 3 boys (case 1-3) represent the primary probable cases of HIGM whereas the girl (case 4) with late onset of HIGM represents probably the "secondary" form of HIGM.

The HIGM diagnosis of case 1 was difficult because of normal level of serum IgM. Moreover, the clinical course including early onset, overlapped the diagnosis of HIGM with common variable immunodeficiency (CVID). The

persistent neutropenia resistant to G-CSF correction and the results of immunological tests (CD154 assay) were indicating the HIGM diagnosis (figure 3). However, in some cases of CVID the clinical course is severe and the expression of CD154 may be low [5] what possibly lead to misdiagnosis of HIGM. In our case the study of CD154 expression were performed at age 7 years what helped us to avoid the decrease of CD154 observed in neonatal period or in transient hy-

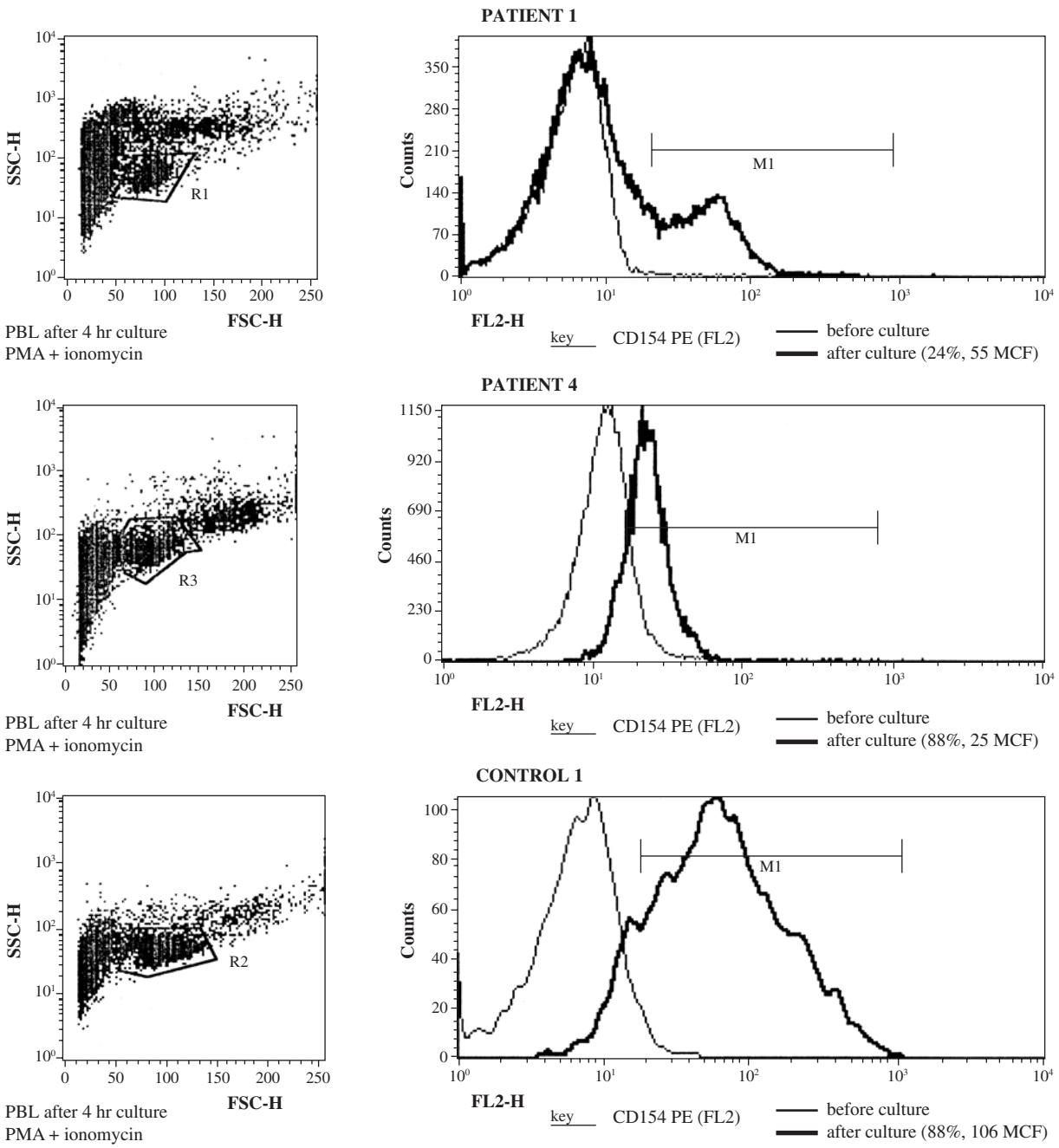

Fig. 3. The flow cytometry assay of CD154 expression on CD3+ (T lymphocytes) cells. The peripheral blood mononuclear cells (PBMC) were activated with PMA and ionomycin for 4 hrs. The cells isolated from healthy person were run in parallel and used as control. The expression of CD154 was shown as histogram of gated population of CD3+ cells. The overlay of histogram unstimulated and stimulated cells show the increase of fluorescence mean as expression of CD154. The comparison to control cells showed the lower expression in case 1 (only 24% of cells) and case 4 (whole population with lower MCF). The expression of stimulated cells from case 2 and case 3 was comparable to control cells (data not shown)

pogammaglobulinemia of infants [5]. Taking into the consideration the early onset, severe clinical course, neutropenia, results of CD154 tests and the response to IVIG therapy the diagnosis of HIGM seemed most probable in this case.

The cases 2 and 3 represent mild course of disease what resulted in late diagnosis. The expression of CD154 was comparable to inducible expression of CD154 observed on lymphocytes from healthy person and the results of IVIG therapy were spectacular. The IVIG substitution was associated with a sharp and immediate decrease of IgM level. However, the follow-up of immunoglobulins' level showed IgM still above the normal value but below the high value observed at diagnosis, before the IVIG administration. The expected effect of IVIG in decrease of severity and frequency of infections was also noted.

The girl with DiGeorge' syndrome (case 4), therapy--resistant thrombocytopenia, splenomegaly and episodes of neutropenia, showed the elevated IgM level at age 4 years despite of IVIG substitution. It suggested the diagnosis of the secondary or acquired form of HIGM. The induction of CD154 expression on T lymphocytes was lower than in control (figure 3). The immunosuppressants and steroids used for thrombocytopenia, thymic-growth factor used in DiGeorge' syndrome supplementary therapy were considered as the factors inducing increase of IgM production (HIGM). There is no relation between the IgM level and IVIG substitution supported the hypothesis of secondary/acquired form of HIGM.

The low expression of CD154 observed as low percentage of CD154 positive cells (case 1), low expression on stimulated cells (case 4) were associated with early symptoms and severe course of disease. The similar observations of severe course of infections in patients with present but low CD154 expression were noted [5, 7, 11]. These clinical features and low expression of CD154 are very difficult to discriminate between the severe form of CVID and HIGM. In these cases the molecular studies of CD154 gene mutations are the only method to prove the clinical diagnosis of HIGM, in particular HIGM1 type [5]. The association of low or absent expression of CD154 with the increase of IgM is not so obvious and the high level of IgM was noted only in part of HIGM cases [11]. The lack of CD154 expression (HIGM1 type) is associated with mechanisms different than in other types of HIGM, includes the intrinsic T cell defect, lack of efficient delivery of activation signal from T to B lymphocytes. In patients with HIGM1 the persistent or cyclic neutropenia, resistant to G-CSF is frequent what facilitates the occurrence of severe and prolonged infections [7]. The therapy with IVIG and sulphonamides diminished the effect of persistent neutropenia, however, in some cases the neutropenia was clinically silent [7].

The coexistence of DiGeorge' anomaly and HIGM syndrome is extremely rare or even described for the first time. The low expression of CD154 was observed when the level of IgM was high but this assay was performed for the first time. The explanation of elevated IgM level (HIGM) in this case is difficult and might include the different factors. There is some data indicating that high level of IgM might reflect chronic antigenic stimulation and normalised after appropriate therapy of infections [11]. In our case the level of IgM became high after the long period of severe, recurrent infections. However, the therapy with IVIG and steroids did not normalise IgM level. It suggests another mechanism involved in the regulation of IgM production in this case and the diagnosis of secondary/acquired form of HIGM was proposed.

Presented cases of HIGM showed that screening for primary immunodeficiency including CD154 expression should be performed in patients presenting infections with severe clinical course, particularly recurrent pneumonias. Moreover, the screening for primary immunodeficiency should include patients in older age than infants and small children what may help to diagnose HIGM syndrome with mild clinical course. The therapy with IVIG resulted in normalisation of IgM level and decrease of the frequency and severity of infections. The early diagnosis followed with IVIG therapy might be beneficial for patients in prophylaxis against infections and complications of these infections as a factor improving the general condition and life comfort of patients.

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