

Thrombocytopenia in common variable immunodeficiency patients – clinical course, management, and effect of immunoglobulins

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Abstract

Common variable immunodeficiency (CVID) is a primary immunodeficiency of humoral immunity with heterogeneous clinical features. Diagnosis of CVID is based on hypogammaglobulinaemia, low production of specific antibodies, and disorders of cellular immunity. The standard therapy includes replacement of specific antibodies with human immunoglobulin, prophylaxis, and symptomatic therapy of infections. High prevalence of autoimmunity is characteristic for CVID, most commonly: thrombocytopenia and neutropaenia, celiac disease, and systemic autoimmune diseases.

The study included seven children diagnosed with CVID and treated with immunoglobulin substitution from 2 to 12 years. Thrombocytopenia was diagnosed prior to CVID in four children, developed during immunoglobulin substitution in three children. In one boy with CVID and thrombocytopenia, haemolytic anaemia occurred, so a diagnosis of Evans syndrome was established. Therapy of thrombocytopenia previous to CVID included steroids and/or immunoglobulins in high dose, and azathioprine. In children with CVID on regular immunoglobulin substitution, episodes of acute thrombocytopenia were associated with infections and were treated with high doses of immunoglobulins and steroids. In two patients only chronic thrombocytopenia was noted. Splenectomy was necessary in one patient because of severe course of thrombocytopenia.

The results of the study indicated a supportive role of regular immunoglobulin substitution in patients with CVID and chronic thrombocytopenia. However, regular substitution of immunoglobulins in CVID patients did not prevent the occurrence of autoimmune thrombocytopenia episodes or exacerbations of chronic form. In episodes of acute thrombocytopenia or exacerbations of chronic thrombocytopenia, infusions of immunoglobulins in high dose are effective, despite previous regular substitution in the replacing dose.

Key words: children, CVID, thrombocytopenia, immunoglobulins substitution, steroids.

(Centr Eur J Immunol 2015; 40 (1): 83-90)

Introduction

The common variable immunodeficiency (CVID) is a primary immunodeficiency of humoral immunity with heterogeneous clinical symptoms. The clinical symptoms typical for CVID are frequent, recurrent infections with poor response to therapy. The laboratory tests showed hypogammaglobulinaemia (IgG only, IgG plus IgA and/or IgM), low production of specific antibodies in response to vaccines, and disorders of cellular immunity. The typical therapy for CVID includes the replacement of specific antibodies with human immunoglobulin substitution in intravenous (IVIG) or subcutaneous form (SCIG), standard

dose 0.4-0.6 g/kg body weight/month, prophylaxis, and symptomatic therapy of infections [1-8]. Common variable immunodeficiency is associated with autoimmunity in about 30% of patients. Most common of all autoimmune diseases in CVID are cytopenias, including thrombocytopenia. In children, gastrointestinal autoimmune diseases (e.g. celiac disease) are noted very often, while systemic autoimmune diseases, including rheumatoid arthritis, are observed in adults [3-6, 8-10]. In half of patients with CVID and autoimmune diseases, especially cytopenias, this autoimmunity occurs prior to diagnosis of immunodeficiency [6, 7, 10].

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The cause of prevalence and pathomechanisms of autoimmunity in primary humoral immune deficiency, e.g. hyper IgM syndrome, X-linked agammaglobulinaemia, IgA deficiency, and CVID, are not well understood and different hypotheses have been suggested [4, 6, 8-10]. Moreover, the differences of autoimmune disease profiles between children and adults, and the different types of autoimmune diseases in a given humoral immune deficiency, are open questions. The association between total anterior circulation infarct (TACI) deficiency and higher frequency of autoimmune disease in CVID suggest the role of this particular genetic mutation in the autoimmune process. One of the possible explanations is that the partial TACI signal in the heterogeneous state may support the survival of autoreactive B cells. However, autoimmune diseases are noted in CVID patients without TACI deficiency [4, 8]. The common observation of reduced number of switched memory B cells (CD27+) and expansion of activated CD-21^{low} B cells containing a high proportion of autoreactive B cells are connected with another mechanism leading to autoimmunity [4, 6, 8]. Moreover, the survival of autoreactive B cells is supported by B cell activating factor (BAFF) and acidic protein rich in leucine (APRIL) noted at high levels in CVID patients with autoimmunity [4, 8]. Besides the disturbances in B cell maturation and activation, T lymphocytes are also involved in the development of autoimmunity in CVID. The decrease of T regulatory number (CD4+, CD25+, Foxp3+) is indicated as factor facilitating the autoimmune process [4, 6, 8, 9]. In the subgroup of CVID patients with lymphopaenia, an increased level of interleukin-7 (IL-7) was found, and the role of this cytokine in the expansion of autoreactive T cell clones was included into the mechanisms of autoimmunity in these patients [8].

Standard therapy of acute and chronic thrombocytopaenia in CVID patients is based on steroids in high doses, followed prolong therapy with maintenance doses and immunoglobulins. The intravenous infusion of high doses of immunoglobulins (1.0-2.0 g/kg body weight) are effective in increasing platelet numbers; however, a long-lasting effect is noted only in some CVID patients. This therapy with high doses of immunoglobulins in acute thrombocytopaenia episodes is more effective in patients without CVID [7, 11]. Moreover, in the clinical course of thrombocytopaenia in CVID patients, resistance to therapy is noted, suggesting active autoimmune process, despite regular immunoglobulin substitutions in replacement doses. This amount of immunoglobulins seemed to be too low to show anti-autoimmune mechanisms active when high dose was used. However, this low dose of immunoglobulins was able to stimulate dendritic cell maturation, which was shown in agammaglobulinaemia patients with defective dendritic cell phenotypes [5]. A similar defective phenotype of dendritic cells was found in CVID patients. This observation is important

for the autoimmune process because dendritic cells play a critical role in predisposition to several pathological conditions, including autoimmunity. Stimulation of dendritic cell maturation might prevent the autoimmunity predisposition associated with the defective function of these cells in immunodeficient patients. It is believed that regular substitution of immunoglobulins, even in a replacing dose, restores phenotypes and normal function of dendritic cells in immunodeficiency [5]. In CVID patients with refractory thrombocytopaenia, recurrent episodes of exacerbations, or chronic thrombocytopaenia, second-line therapy with immunosuppressive drugs like azathioprine, vincristine, cyclophosphamide, and splenectomy is used [7, 10, 11]. Splenectomy is effective in these patients, similarly to patients without immunodeficiency, and safe without higher risk of severe infections in immunodeficiency [11]. The use of rituximab in CVID patients with a normal number of B cells and severe autoimmunity symptoms seemed to be another therapeutic proposition [11, 13], but regular substitution of immunoglobulins is indicated because of increased risk of severe infections [4, 7, 11, 13].

Aim of the study

Observations of thrombocytopaenia in patients with CVID and the effect of regular substitution of immunoglobulins in replacing dose.

Material and methods

Patients

The study included 7 patients (six boys, one girl) diagnosed as CVID (Table 1) based on hypogammaglobulinaemia (IgG, IgG/IgA, IgG/IgM), low level of specific antibodies and disturbances of cellular immunity (reverse CD4 : CD8 ratio), and poor response of lymphocytes to stimulation with mitogens (PHA, PWM) and antigens (CD3, PPD and Candida).

The clinical symptoms included recurrent infections (mainly in the respiratory tract), pneumonias, otitis, and sinusitis in older children. Following diagnosis of CVID, all patients were treated with regular immunoglobulin substitution (every month, intravenously) in a replacing dose (0.4-0.6 g/kg body weight). The thrombocytopaenia was diagnosed before diagnosis of CVID in four patients, and after CVID diagnosis in the remaining three patients (Table 2).

Thrombocytopaenia prior to diagnosis of CVID was treated with high doses of IVIG and/or steroids (high dose pulses) when the IVIG effect was short lasting. One patient underwent splenectomy followed by a high and stable number of platelets, which excluded this patient from further observation.

Table 1. Characteristics and course of common variable immunodeficiency (CVID) in the studied patients

Patient number	1	2	3	4	5	6	7
Age of diagnosis: CVID	6 years	8 years	3 years 6 months	12 years	10 years	8 years	5 years
Main symptoms of CVID	infections of respiratory tract, lymphadenopathy splenomegaly	thrombocytopenia splenomegaly	severe thrombocytopenia lymphadenopathy splenomegaly	thrombocytopenia leukopaenia	thrombocytopenia	thrombocytopenia	pneumonias lymphadenopathy, splenomegaly
Laboratory data at diagnosis of CVID	low level of IgG, IgA, low number of T cells, reverse CD4:CD8 ratio, weak response to vaccines	low level of IgG, IgA, IgM, low number of T, B, and NK cells	low number of T cells, lack of response T cells to stimulation, low level of IgG	low level of IgG, IgA and IgM, low number of T, B and NK cells	low level of IgG	low level of IgG, IgA	low level of IgG, IgM, lack of IgA, leukopaenia, weak response to vaccines
Other symptoms	mild leukopaenia	leukopaenia	severe haemolytic anaemia	severe leukopaenia	no	no	agenesis of kidney, LJP, lung fibrosis (progression), bronchiectases
Response to IgG	good, no infections	good	good	weak (increase of platelets 2-3 days)	good	good	weak (low level of IgG)
Complications	adverse reaction to IVIG, shift to SCIG						severe osteoporosis, overweight, delay of puberty
Other therapies	steroids before IVIG						steroids, azathioprine prolonged because of lung fibrosis progression
Present status	SCIG	IVIG, LJP diagnosis	no substitution, hematologic care	IVIG, hematologic care	no substitution, no symptoms	no substitution, no symptoms	SCIG, lungs and kidney insufficiency, splenomegaly

LJP – lymphocyte infiltrating pneumonia, IVIG – intravenous substitution of IgG, SCIG – subcutaneous form of substitution

Table 2. Characteristics and course of chronic thrombocytopaenia in common variable immunodeficiency (CVID) patients

Patient number	1	2	3	4	5	6	7
Gender	boy	boy	boy	girl	boy	boy	boy
Age of diagnosis: thrombocytopaenia	14 years	4 years	4 years 10 months	8 years	11 years	7 years	13 years
Therapy of thrombocytopaenia	steroids (pulses)	IVIg 1.0 g/kg b.w. steroids, azathioprine	steroids, azathioprine, IVIG 1.0 g/kg b.w.	steroids	steroids, IVIG 1.0 g/kg b.w.	steroids	steroids
Complications, other symptoms	no	no	severe haemolytic anaemia (Evans syndrome)	diabetes, severe overweight	no	no	
Lowest number of platelets (/μl)	28 000	0	0	0	27 000	20 000	37 000
Number of platelets at beginning of IVIG (/μl)	253 000	156 000	133 000	15 000	27 000	87 000	126 000
Mean dose of IVIG (g/kg b.w./month)	0.43-0.38	0.36-0.45	0.35-0.42	0.35-0.45	0.38-0.3	0.4-0.35	0.42-0.50
Mean number of platelets during IVIG (/μl) (range)	149 100 (120 000-196 000)	123 000 (57 000-198 000)	131 000 (97 000-154 000)	51 460 (18 000-68 000)	113 500 (56 000-154 000)	172 400 (99 000-264 000)	112 700 (86 000-133 000)
Episodes of exacerbations of thrombocytopaenia during IVIG	1	0	3 (1 severe)	4	1 severe	0	0
Therapy of thrombocytopaenia exacerbations	IVIg 1.0 g/kg b.w. steroids		steroids, platelets, erythrocytes and plasma transfusions, plasmapheresis	IVIg 1.0 g/kg b.w.	steroids, splenectomy		
Time of observation	12 years	2 years	7 years	4 years	5 years	4 years	11 years

Methods

The following assays were used for patients at least twice, before the establishing the diagnosis and during the substitution of immunoglobulins. The level of immunoglobulins (IgG, IgA, IgM) in serum were assayed with nephelometry using the paediatric level of sensitivity. The percentage of T, B lymphocytes and NK cells within lymphocytes were assayed with flow cytometry followed by recalculation of the number per μl based on total white blood cells count from the same sample. The flow cytometry assay included the T cell subpopulations ratio (CD4:CD8, TCR α/β : TCR γ/δ), and the percentage and number of activated T cells (CD3/HLA-DR). The response of lymphocytes to stimulation was tested in three-day culture (PHA, CD3, and PWM) and seven-day culture (PPD, Candida) ending with H^3 -thymidine uptake. The borderline value of the stimulation index was 20. The response to vaccines was assayed with anti-HBs, anti-rubeola, anti-tetanus, anti-bordetella, and anti- *Streptococcus pneumoniae* antibodies (if the child was vaccinated for this antigen). Moreover, the antibodies for CMV and EBV antigens were tested as common viral antigens.

The number and mean volume of platelets, and other parameters of morphology were checked on every visit associated with infusion of immunoglobulins, and in meantime if necessary. In all patients with thrombocytopenia, the presence of autoantibodies (antinuclear standard panel with fluorescent microscopy) was assayed. The volume of platelets was normal in all of our patients (WAS syndrome exclusion). Other tests (biochemistry, microbiology, virusology, Coomb's test) and analyses were performed according to individual symptoms in patients [e.g. ultrasonography (USG), computed tomography (CT), magnetic resonance imaging (MRI), high-resolution computed tomography (HRCT) of lungs, spirometry].

Results

The onset of thrombocytopenia in patients 1 to 6 was acute, mainly associated with infections, and the last patient (number 7) developed thrombocytopenia in chronic form without acute episodes (Tables 1, 2).

In patient 1 thrombocytopenia occurred after a short, mild viral infection during regular substitution of IVIG because of diagnosis of CVID [lymphadenopathy, splenomegaly, low number of T lymphocytes (348/ μl), low number of B lymphocytes (124/ μl)]. This patient was additionally diagnosed for ALPS (autoimmune lymphoproliferative disease), but the apoptosis was normal, so ALPS was excluded. The most probable explanation for leukopenia and lymphopenia despite thrombocytopenia was spleen hyperactivity. On regular substitution in the replacing dose, the level of IgG was from 5.36 g/l to 7.7 g/l, which was within the normal range for the patient's

age. However, the patient developed an adverse reaction to immunoglobulin preparation. Changing the product was enough to prevent this reaction in the following infusions. The number of T and B lymphocytes was still below the lower limit of normal value for age. The episode of acute thrombocytopenia occurred during a mild viral infection (lowest platelets number – 28 000/ μl). The effect of IVIG used in high dose ($2 \times 1.0 \text{ g/kg b.w.}$) in this episode of thrombocytopenia was transient, and steroids (dexamethasone pulses followed by regular oral steroid therapy) were used for four months. After this therapy the number of platelets was within the normal range. During the following four years of continued regular substitution (subcutaneous form) the number of platelets was between 120 000/ μl and 196 000/ μl without decrease, despite infections (mainly viral with mild clinical course).

Patient 2 was treated with immunoglobulins in high dose because of acute thrombocytopenia and leukopenia (lack of platelets and 2800/ μl of leukocytes) prior to diagnosis of CVID. The effect of steroids was short (2-3 days) despite a high dose (pulses of dexamethasone), and therapy with azathioprine was introduced. The thrombocytopenia slowly resolved during three months. The therapy with steroid and azathioprine was stopped. After two following years without episodes of thrombocytopenia, during a prolonged infection of the respiratory tract hypogammaglobulinaemia was noted with low number of T lymphocytes (997/ μl) and NK cells (65/ μl), and a lack of B lymphocytes (20/ μl). The splenomegaly, leukopenia and lymphadenopathy (localised in lungs hilus), and decrease of platelet number to 57 000/ μl developed in the last year of observation, despite regular substitution of immunoglobulins in a dose of 0.45-0.6 g/kg b.w. every month. Regular substitution resulted in a decreased number of infections, milder course, and better response to therapy with antibiotics. The IgG level was below 5.0 g/l despite higher doses of immunoglobulins in infusions, which suggested another process of loss or process of tissue binding immunoglobulins. The additional tests for ALPS were performed because of progressing splenomegaly, lymphadenopathy, thrombocytopenia, and leukopenia. The number of DNT α/β lymphocytes was below 2%, which excluded this diagnosis. There were no symptoms or laboratory data suggesting protein loss enteropathy. In the last month, a lung biopsy was performed due to disseminated non-inflammatory consolidations of lung tissue, implying lymphocyte interstitial pneumonia (LIP) with typical infiltrates. After high-dose steroid therapy for two weeks, followed by maintenance dose of steroids, the LIP symptoms resolved and the mean level of IgG increased to above 6.0 g/l.

In patient 3 low levels of IgG and IgA, low number of T lymphocytes, and recurrent infections were observed since 3.5 years of life, but the substitution of IgG was delayed until the 4th year of life (overlapping THI and CVID symptoms). The response of lymphocytes to stimulation

was poor (indexes 1-5), which suggested a diagnosis of CVID. After the episode of acute thrombocytopenia treated with steroids, the stabilisation of platelets was obtained with azathioprine use for a prolonged period (nine months) concurrent with IVIG introduced due to established diagnosis of CVID. The number of platelets in this time was between 95 000/ μ l and 147 000/ μ l, and the dose of immunoglobulins was 0.6 g/kg b.w. because of persistent leukopenia (2100-3500/ μ l). Two months after cessation of azathioprine therapy, severe, life-threatening thrombocytopenia (platelets nadir – 16 000/ μ l) and haemolytic anaemia (erythrocytes – 1.7 mln/ μ l) with anti-erythrocyte antibodies (direct Coomb's positive test) was seen. The patient was treated with steroids (high-dose pulses), platelet and erythrocyte transfusions, and immunoglobulins in high dose (2.0 g/kg b.w./3 days infusion) with transient improvement of clinical symptoms. The plasmapheresis was followed by a high dose of immunoglobulins and steroids for a prolonged period (six months), which was effective. The regular substitution of immunoglobulins in a replacing dose was continued in the patient with leukopenia, stable number of platelets (86 000-168 000/ μ l), and splenomegaly. The diagnosis was changed to Evans syndrome in CVID. Now, three years later, the patient is without substitution of immunoglobulins but under haematological control without episodes of thrombocytopenia (platelet count 120 000-183 000/ μ l).

The first episode of thrombocytopenia occurred in a 10-year-old girl (patient 4) after viral infection. Therapy with steroids (pulses of dexamethasone) was effective, but the number of platelets was steroid dependent, so the dose of steroids was high and used for a prolonged time. After two years of such therapy the number of platelets was within normal range, but diabetes and overweight were noted as side effects of prolonged steroid therapy. The diagnosis of CVID was made two years after the first episode of thrombocytopenia. Hypogammaglobulinaemia (IgG and IgM), low number of T and B lymphocytes (820/ μ l and 138/ μ l, respectively), few NK cells (16/ μ l), leukopenia (2600/ μ l), and mainly neutropenia were indications for regular substitution of immunoglobulins in a replacing dose. The number of platelets was checked every two weeks, and the next episode of thrombocytopenia was noted two months after the beginning of immunoglobulin substitution. This episode of severe thrombocytopenia (8000/ μ l platelets) and the next three episodes were treated only with high doses of immunoglobulins (2.0 g/kg b.w./3 days infusion), but the effect was transient and unsatisfactory. Steroids were not used due to severe side effects after the previous therapy. The leukopenia (number of leukocytes was from 1200 to 3800/ μ l), low number of lymphocytes T (490/ μ l), B (105/ μ l), and NK cells (98/ μ l), and chronic thrombocytopenia (mean number of platelets was about 50 000/ μ l) were noted during the next four years of regular substitution of immunoglobulins, despite

a single episode of mild infection. Last year a high level of antibodies to thyroid peroxidase was detected followed by thyroid hormone supplementation due to subclinical hypothyroidism. The number of platelets is still below normal value without diathesis, with present obesity and normal glucose level.

Patient 5 was diagnosed with CVID before the onset of thrombocytopenia. The first episode of thrombocytopenia occurred despite regular immunoglobulin substitution (intravenous 0.42 g/kg b.w.). Therapy included only steroids, and a slow increase of platelet count was observed within two months (from 27 000/ μ l to 44 000/ μ l). In next one and a half years, the numbers of platelets (about 120 000/ μ l) and leukocytes (3500-4100/ μ l) were stable, and the regular substitution of immunoglobulins in a replacing dose was continued. The mild viral infection induced severe exacerbation of thrombocytopenia and was treated with steroids (dexamethasone in pulses). The platelet number was unstable, and after eight months of therapy with steroids and immunoglobulins in high dose (1.0-2.0 g/kg b.w.), the decision to perform splenectomy was made by a haematologist. After this surgery the platelet count was 409 000/ μ l and the boy was excluded from further observation. Due to CVID diagnosis the substitution of immunoglobulins is continued in subcutaneous form.

Patient 6 was diagnosed with CVID after the first episode of thrombocytopenia treated with steroids. Hypogammaglobulinaemia (IgG and IgA) and infections of the respiratory tract were noted as symptoms of immunodeficiency. The number of leukocytes, lymphocytes, subpopulations of T lymphocytes, B lymphocytes, and NK cells were within normal range for age. The number of platelets was 87 000/ μ l at the beginning of regular substitution because of CVID. In the following three years of regular substitution of immunoglobulins, the number of platelets was stable, slowly increasing to 264 000/ μ l, without exacerbations, despite respiratory tract infections. Stable level of immunoglobulins, few infections with mild clinical course, and good response to therapy led us to finish the regular substitution. The patient was offered immunoglobulin infusion as supportive therapy during severe infection but until now (six more years of observation) he has not required it.

Patient 7 was diagnosed with CVID in the fifth year of life after hypogammaglobulinaemia during first four years of life, diagnosed as transient hypogammaglobulinaemia of infancy (THI). Infusions of immunoglobulins were indicated as supportive therapy for episodes of pneumonia, but there were no indications for regular substitution due to THI. The clinical symptoms of CVID at diagnosis included lymphadenopathy, splenomegaly ("megaspleen"), hypogammaglobulinaemia (IgG, lack of IgA), and leukopenia with low number of T and B lymphocytes in this patient. Moreover, this boy was born with one kidney. The regular substitution of immunoglobulins introduced after CVID diagnosis helped decrease the number of respira-

tory tract infections. In the following years bronchiectases and progressing fibrosis with lymphocyte infiltration (lymphocytic interstitial pneumonia – LIP) developed. After two years of immunosuppressive therapy with steroids to inhibit the progress of lung fibrosis and lymphocytic infiltrates, severe adverse reactions to steroids (osteoporosis, overweight, inhibition of growth) were observed without any visible inhibitory effect on the fibrotic process. The positive effect of steroid therapy was resolving of LIP symptoms (checked with lung biopsy). The number of platelets and leukocytes were stable, close to the lower limit of normal value. The next therapy with azathioprine was administered in the hope of inhibiting the progress of lung fibrosis, but the response to this therapy was poor. Moreover, as a side effect of this immunosuppression, the number of platelets dropped below 100 000/ μ l and leukopenia with low number of T and B lymphocytes, and lack of NK cells were noted within one year. The fibrosis of lungs is progressing slowly, but kidney insufficiency is now a clinical problem. The therapy with azathioprine was stopped. The number of platelets is still below 100 000/ μ l, leukocytes below 3000/ μ l, but the bone marrow is normal with rich cellularity and proper representation of myeloid and lymphoid ontogeny. The persistent leukopenia, mild thrombocytopenia, megaspleen, and lung fibrosis are still indications for suppression, but the kidney insufficiency (progressing) and severe side effect are limitations for such therapy. Now, the patient is under careful clinical control with symptomatic and supportive therapy for lung function and regular substitution of immunoglobulins (up to 0.5 g/kg b.w. subcutaneously). The prognosis for this patient is poor due to clinical symptoms and increasing laboratory parameters of lung and kidney insufficiency.

Discussion

Thrombocytopenia associated with immunodeficiency presented two forms – episodes of acute thrombocytopenia, alone or as a part of Evans syndrome with remission (normal number of platelets), and chronic thrombocytopenia with platelet count always below normal level [7, 11]. In our group of CVID patients with thrombocytopenia these (recurrent acute or chronic) forms of thrombocytopenia were noted without relation to time of CVID diagnosis. Regular intravenous substitution of immunoglobulins in the CVID patients for exacerbation of chronic thrombocytopenia or episodes of acute thrombocytopenia were not effective. Routine therapy with steroids and high doses of immunoglobulins was necessary and was used with success despite regular immunoglobulin substitutions before the episode. After infusion of immunoglobulins in high dose, in remission of thrombocytopenia, the regular substitution was continued. However, there are problems of thrombocytopenia in CVID – short effect of high-dose immunoglobulin therapy and indication for

maintenance e.g. steroid therapy to support the remission, or chronic thrombocytopenia after short remission with normal number of platelets. If the therapy with high-dose immunoglobulins and/or steroids is effective, the remission with normal number of platelets in some CVID patients is long lasting, similarly to children without CVID. The second group of patients demonstrated chronic thrombocytopenia with the number of platelets below 100 000/ μ l, and this level of platelets seemed to be stable during regular substitution of immunoglobulins in replacing doses. These patients did not require additional therapy with steroids or azathioprine as long as the number of platelets decreased and the clinical symptoms of thrombocytopenia occurred. A large decrease in platelet count with life-threatening clinical symptoms or refractory, severe thrombocytopenia are always indications for splenectomy without regard to CVID diagnosis [7, 10, 11]. Moreover, in CVID patients the refractory thrombocytopenia seemed to be more frequent with a higher ratio of indications for splenectomy than in otherwise healthy children. In chronic thrombocytopenia regular substitution of immunoglobulins in the replacing dose seemed to stabilise the platelets count, particularly in intravenous form of substitution. Clinical observations of our two patients with chronic thrombocytopenia showed increased platelet count only for a few days after infusion of immunoglobulins, followed by a slow decrease during the following three weeks, but the level was still higher than in acute episodes. This stable, safe level of platelets meant that the patients lived with immunoglobulin substitution without additional therapy of thrombocytopenia. Some of these patients with CVID and thrombocytopenia demonstrate persistent leukopenia. The intravenous regular immunoglobulin substitution in a replacing dose and the trough level of IgG have no effect on the white blood cell count in these patients. However, this leukopenia is mild in the majority of patients, and additional therapy is needed in singular cases only.

The autoimmunity symptoms observed in CVID patients are often overlapping, which is an indication for additional diagnosis of WAS, ALPS syndrome, or rare complications of CVID, such as GLILD (granulomatous and lymphocytes interstitial lung disease) or protein loss enteropathy due to atypical celiac or other inflammatory bowel diseases (e.g. Leśniowski-Crohn's disease). These autoimmune syndromes associated with CVID are more difficult to diagnose and require more aggressive therapy due to atypical clinical course and therapy resistance.

Conclusions

Regular infusion of immunoglobulins in replacing doses is a good supportive therapy in chronic thrombocytopenia associated with CVID.

Regular substitution of immunoglobulins in a replacing dose does not prevent the occurrence of autoimmune

thrombocytopenia and exacerbations of chronic thrombocytopenia in CVID.

In episodes of acute thrombocytopenia or exacerbations of chronic thrombocytopenia, infusions of immunoglobulins in high dose are effective, despite previous regular substitution of immunoglobulins in a replacing dose.

The authors declare no conflict of interest.

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