

# Children with chronic-refractory autoimmune cytopenias: a single center experience

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## ABSTRACT

**Background and objectives.** Autoimmune cytopenias are a group of heterogeneous disorders characterized by immune-mediated destruction of one or more hematopoietic lineage cells. The differential diagnosis of children with autoimmune cytopenias requires much time and laboratory investigations. The aim of the present study was to evaluate the clinical course and significance of autoimmune cytopenias due to immunodeficiency or autoimmune diseases in children at a single children's hospital.

**Method.** Between February 1997 and September 2015, chronic/refractory autoimmune cytopenias patient data were evaluated retrospectively. Twenty-three patients were assessed in this study.

**Results.** The median duration of following was 2.6 years (4 months-18.5 years). The median age of diagnosis was 3.1 years (6 months-16 years). A total of 13 patients (56.5%) had single-lineage and 10 (46.5%) had multi-lineage cytopenias. The most frequent single-lineage cytopenia was thrombocytopenia, followed by anemia. In 22 of the patients, cytopenias was detected before the primary diseases. All of the patients were treated with corticosteroids or intravenous immune globulin as first-line treatment. Ten patients (43.5%) needed second or further-line immunosuppressive therapies that patients diagnosed as systemic lupus erythematosus, hypogammaglobulinemia, or common variable immunodeficiency. A total of 8 patients (34.7%) recovered from autoimmune cytopenias after the treatment of primer disease. Cytopenias were continued in 14 patients.

**Conclusion.** Cytopenia may be the first finding of an immunodeficiency or autoimmune disease and primary disease may be diagnosed in the clinical course. Taking the new targeted treatment options into consideration; early diagnosis is likely to become more important in the near-future in order to begin the treatment for the underlying disease as early as possible.

**Key words:** immune cytopenia, childhood, immune deficiency, autoimmunity.

Autoimmune cytopenias are a group of heterogeneous disorders characterized by immune-mediated destruction of one or more hematopoietic lineage cells. In some instances, they are idiopathic or occur as a manifestation of other underlying disorders, such as autoimmune diseases, immunodeficiency, autoimmune lymphoproliferative syndrome

(ALPS), tumors, medications (penicillin, cephalosporins, sulphonamides, nonsteroidal anti-inflammatory drugs, etc) or infections.<sup>1-3</sup> Most children with autoimmune cytopenias have idiopathic disease. However, sometimes, the hematological manifestations precede the clinical onset of underlying immune disorders. So, the differential diagnosis of children with autoimmune cytopenias requires much time and laboratory investigations.<sup>4-6</sup>

The management of patients with chronic-refractory autoimmune cytopenias is

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heterogeneous and complex. Typically, these patients are treated with nonspecific immune suppression. Some of those patients respond to first-line immunosuppressive therapy, although many of them require second or further-line therapies. The primary goal of the therapies is directed at the underlying cause of the autoimmunity.<sup>4,7</sup> However, therapies of autoimmune cytopenias may be insufficient still more, because auto-immunity has been increasingly recognized as an important component of immune disorders.<sup>2,4,8</sup>

There have been a few reports of chronic/refractory autoimmune cytopenias in childhood.<sup>2,4,9-11</sup> Therefore, the aim of this study was to evaluate the clinical course and significance of autoimmune cytopenias due to immunodeficiency or autoimmune diseases in children followed up at our hospital.

## Material and Methods

### *Study design, selection of patients and definitions*

A total of 337 files of information belonging to patients with chronic or refractory autoimmune cytopenias except tumors were evaluated retrospectively at our hematology department between February 1997 and September 2015. Cytopenias due to medications, infections or idiopathic were excluded. Ultimately, patients with immune deficiency or autoimmune diseases (23 patients) were included in this study.

Cytopenias were the reduction of the blood cell types in the peripheral blood. Thrombocytopenia was defined as a platelet count  $<100 \times 10^9/L$  according to an International Working Group criteria.<sup>12</sup> Autoimmune hemolytic anemia (AIHA) was defined as anemia (hemoglobin  $<10$  g/dl) with evidence of hemolysis (reticulocytosis and positive direct antiglobulin test). The lower limit of the absolute number of neutrophils was accepted as  $1000/\mu L$  in infants and  $1500/\mu l$  in children over 12 months of age.<sup>13</sup> The diagnosis of autoimmune neutropenia (AIN) was accepted

a diagnosis of exclusion. When the cytopenias had persisted more than 3 months, they were accepted as chronic or refractory cytopenias.<sup>12-14</sup>

The diagnosis of Common variable immunodeficiency (CVID) was based on 4 criteria: Age above 4 years, low serum IgG (Immunoglobulin G; reduced by more than two standard deviations below the mean for age), with or without low serum IgA (Immunoglobulin A) diminished antibody response to immunizations, and exclusion of other potential immune diseases.<sup>15</sup> Combined immune deficiency was accepted as evidence of a profound T cell defect along with evidence of a humoral defect.<sup>16</sup> Patients fulfilling the revised diagnostic criteria for ALPS were classified as ALPS patients: Chronic non-malignant lymphoproliferation, elevated double negative T cells (CD4-/CD8-, CD3+, TCR  $\alpha\beta$ +) in peripheral blood circulation and defective *in vitro* Fas-mediated associated.<sup>17</sup> Systemic lupus erythematosus (SLE) was diagnosed according to Systemic Lupus International Collaborating Clinics classification criteria.<sup>18</sup>

### *Statistical Methods and Ethical Permission*

Data were analyzed using SPSS 15.0. The results are presented as the mean, standard deviation, median, absolute number, or percentile. Comparison of median values between independent groups was carried out with the Mann Whitney test. This study was approved by local ethics committee of the Dr. Behçet Uz Children's Research and Training Hospital (number: 2018/233).

## Results

Our protocol included evaluation of the following variables for chronic- refractory cytopenias: Children were evaluated using a standard diagnostic approach, obtained thorough history, physical examination, laboratory screening tests (complete blood count, direct antiglobulin test, liver and renal function tests, measurements of immunoglobulin (IgA, IgM, IgG, and IgE), C3 and C4 complements

and antinuclear antibody levels, standard peripheral blood flow cytometry analysis (CD3<sup>+</sup>, CD4<sup>+</sup>, CD8<sup>+</sup>, CD19<sup>+</sup>, CD16<sup>+</sup>56<sup>+</sup> and if necessary double negative T cells), serology of several viral pathogens (TORCH, EBV, hepatitis, and HIV) and bone marrow aspiration evaluation (morphologic, cytogenetic).

The patients with immune thrombocytopenia (ITP) were treated with corticosteroids (30 mg/kg/d, 3 days, followed 3 days 20 mg/kg/d, then 2 days 10 mg/kg/d, pulse methylprednisolone) or a single dose of intravenous immune globulin (IVIG) at 1 g/kg as first-line treatment. Further use of IVIG was dependent on clinical response to the initial dose. The patients with AIHA were treated much like ITP as first-line treatment. The treatment of AIN was oral or intravenous antibiotics depending on the severity of bacterial infections as first line treatment. For refractory cases of ITP, AIHA, or both, second or further-line immunosuppressive therapies including rituximab, mycophenolate mofetil (MMF), cyclosporine A, azathioprine, and chloroquine have been used.

All of the patients were followed up for a maximum 18.5 years or until they recovered from cytopenia. The median duration of following was 32 months (between 4 months-18.5 years). Twenty-three of the patients with chronic or refractory autoimmune cytopenias (6.8%) had an immune deficiency or an autoimmune disease. All of the patients were younger than 18 years of age at initial application. The

**Table I.** Cytopenia detected peripheral blood cell lines.

Cell lines	Number of patients (n=23)
Platelets	9
Neutrophils	1
Erythrocytes	3
Erythrocytes + Neutrophils	2
Erythrocytes + Platelets	5
Platelets+ Neutrophils	2
Erythrocytes + Neutrophils+ Platelets	1

median age of diagnosis was 3.1 years (between 6 months-16 years) and the ratio of male/female was 1.3. A total of 13 patients (56.5%) had single-lineage cytopenias and 10 patients (46.5%) had multi-lineage cytopenias (Table I).

A total of 22 patients had cytopenia at initial application. During follow-up, it took 0-77 months to identify the underlying diseases beneath the cytopenias. Two of them were diagnosed with SLE at initial application. So, excluding these 2 patients, primary diseases were diagnosed a median 5 months after cytopenias had occurred. Only one patient was initially diagnosed as CVID, in this case cytopenia developed during the following years.

Last diagnoses of the patients are given in Table II. Two of the patients were diagnosed as ALPS, 3 of the patients were diagnosed as CVID, 8 of the patients were diagnosed as hypogammaglobulinemia, 5 of the patients were diagnosed as SLE, 2 of the patients were diagnosed as Wiskott–Aldrich syndrome (WAS), one was diagnosed as combined immunodeficiency, one was diagnosed as DiGeorge syndrome, and one was diagnosed as celiac disease. DiGeorge syndrome and Wiskott-Aldrich syndrome were diagnosed by genetic mutation analysis.

All of the patients were treated with corticosteroids or IVIG as first-line treatment. Ten patients (43.5%) needed second or further-line immunosuppressive therapies. These patients were diagnosed as SLE, hypogammaglobulinemia, or CVID. Rituximab was used on 6, MMF was used on 5, cyclosporine A was used on 3, and azathioprine was used on 3 patients. Two patients had undergone splenectomy. Only one patient with neutropenia needed granulocyte-colony stimulating factor treatment. He was diagnosed with combine immune deficiency (Table II).

A total of 8 patients (34.7%) recovered from autoimmune cytopenias after the treatment of primer disease. Of these 8

**Table II.** The clinical features of patients.

Patients	Age at Application (Year)	Sex	Cytopenia(s) at Application	Hb (g/dl)	ANC (µL)	PLT (x10 <sup>9</sup> /L)	Immune Disorder	Time* (month)	Treatment	Current Status of Cytopenia(s)
1	4.3	F	AIHA+ITP	9.1	1815	54	DiGeorge syndrome	77	First-line	CwR
2	7	M	AIHA+ITP	11.4	3320	13	SLE	0	Chloroquine	Recovered
3	2	M	ITP	11.5	2200	55	CVID	66	First-line	Continue
4	8	M	AIHA+ITP	8.6	2910	4	HG	6	First-line	CwR
5	13	F	AIHA+ITP	9.9	3250	7	SLE	0	Azathioprine	Recovered
6	7	F	AIHA	7.4	6140	340	ALPS	27	Rituximab, MMF	CwR
7	2.3	M	AIHA+ITP	8.3	2680	67	HG	4	MMF, Rituximab, cSA, splenectomy	CwR
8	0.7	M	ITP	11.5	3210	34	HG	12	MMF, Rituximab, cSA Azathioprine, splenectomy	CwR
9	11	F	AIHA+AIN	9.6	240	158	ALPS	23	First-line	CwR
10	3	M	ITP	11.6	7930	10	Celiac disease	9	First-line	Recovered
11	1.5	F	ITP	11.2	16000	11	HG	5	First-line	Recovered
12	3	M	AIHA	7.9	2000	569	CVID	32	Rituximab, MMF, cSA	Exitus
13	11	F	ITP	11.8	4390	17	SLE	2	Chloroquine, Azathioprine	Recovered
14	1.3	F	AIHA+AIN	8.4	10	432	HG	6	First-line	Recovered
15	2	M	AIN	11.1	690	714	CID	2	First-line, G-CSF	CwR
16	0.5	F	ITP+AIN	11.7	830	26	HG	5	First-line	CwR
17	1.5	M	ITP	12.9	1940	3	HG	2	First-line	Recovered
18	1	F	AIHA	3.7	5650	465	HG	1	Rituximab	CwR
19	8.5	F	ITP	14.4	3580	13	SLE	3	First-line	CwR
20	13.5	F	ITP+AIN	13.0	1070	98	CVID	36**	Rituximab	CwR
21	16	M	ITP	13.9	6790	130	SLE	4	MMF	Recovered
22	7	M	Pancytopenia	9.0	1190	8	WAS	3	First-line	Continue
23	1	M	ITP	12.4	13070	34	WAS	8	First-line	Continue

\*: Diagnosis time of between cytopenias and underlying diseases, \*\*: Cytopenia was occurred after diagnosis of CVID  
 Hb: hemoglobin, ANC: absolute number of neutrophils, PLT: platelet, M: male, F: female, AIHA: autoimmune hemolytic anemia, ITP: immune thrombocytopenia, AIN: autoimmune neutropenia, SLE: systemic lupus erythematosus, HG: hypogammaglobulinemia, CVID: common variable immunodeficiency, ALPS: autoimmune lymphoproliferative syndrome, CID: combined immune deficiency, WAS: Wiskott-Aldrich syndrome, G-CSF: granulocyte-colony stimulating factor, CwR: Continue with recurrences, MMF: mycophenolate mofetil, cSA: cyclosporine A.

patients; 4 were diagnosed with SLE, 3 with hypogammaglobulinemia and 1 with celiac disease. The patient with celiac disease recovered from autoimmune cytopenia after starting gluten-free diet. Cytopenias had continued in 14 of the patients, 11 of them had a least one recurrence. The Clinical Features of Patients are given in Table II. None of these patients had received bone marrow transplantation. No malignancy was detected. One patient with CVID died.

## Discussion

Cytopenia is one of the most common autoimmune manifestations in immune disorders. The clinical course and significance of autoimmune cytopenias due to immunodeficiency or autoimmune diseases in children were evaluated in current study. Twenty-three of the patients with chronic or refractory autoimmune cytopenia (6.8%) had an immunodeficiency or an autoimmune disease. Currently, there are a few reports examining the autoimmune cytopenias in childhood. In their large series with 326 CVID patients, Wang et al.<sup>10</sup> reported that 11% of patients had a history of autoimmune hematologic disease and 19 of patients (5.8%) had the first episode of thrombocytopenia or AIHA prior to the diagnosis of immunodeficiency. A slight male predominance was observed. The ratio of male/female (M/F) was found 1.3. While this ratio has reported as <1 in adults, it has reported as variable in childhood (M/F=0.7-2.7) in previously studies. Also a tendency for male predominance in younger children was mentioned, similar to our finding.<sup>11,19</sup>

The median age of detection of cytopenia was 3.1 years (between 6 months-15.9 years). The median age at initial cytopenia was reported approximately median 5 years in children with chronic or refractory autoimmune cytopenia in previous studies (5-5.7 years).<sup>7,9,11</sup> We found that the diagnosis of primary disease was delayed up to 77 months (median 5 months) after cytopenias had occurred. There are currently

a few reports examining the delay between the occurrence of cytopenia and diagnosis of immune disorders. Savaşan et al.<sup>20</sup> reported that the delay of diagnosis in patients with CVID was approximately 8 years. Wang et al.<sup>10</sup> reported that 5.8% of patients had the autoimmune cytopenia prior to the diagnosis of immunodeficiency and they reported that ITP occurs a median of 2 years before a diagnosis of CVID can be made. In a French Cohort, onset of Evans syndrome (ES) was concurrent with diagnosis of SLE in 3/13 patients, but was later within a 1- to 10 year period in 10/13 patients.<sup>11</sup>

A total of 13 patients (56.5%) had single-lineage cytopenia and 10 patients (46.5%) had multi-lineage cytopenia in our study. The most frequent single-lineage cytopenia was thrombocytopenia, followed by anemia, in accordance with reports in the literature.<sup>5,21-24</sup> The percentage of multi-lineage cytopenia has been given different ratios in previous studies: Some of studies have given its ratio as 52-60.9% in their series.<sup>5,22-25</sup> Also, Bride et al.<sup>7</sup> reported that 24/30 patients had multi-lineage cytopenia in patients with relapsed/refractory autoimmune cytopenia. However, Resnick et al.<sup>23</sup> have reported that 4.2% percentage of CVID patients have multi-lineage cytopenia.

Different definitions for ES have been made in the previous studies. Some of them defined it as a multi-lineage cytopenia due to autoimmune destruction of the cells, others defined it as AIHA and ITP with or without AIN.<sup>4,5,11,26-29</sup> Recently, in a French National cohort study, they observed that ES is associated with immune manifestations including hypogammaglobulinemia.<sup>11</sup> As a result, it is suggested that patients with ES (defined as an autoimmune multi-lineage cytopenias) should be screened for ALPS, CVID, and SLE.<sup>4</sup>

Three of the patients were diagnosed with CVID and 2 of the patients were diagnosed with ALPS. Approximately 20% percentage of patients with CVID can be diagnosed at less than 20 years of age.<sup>23</sup> Also, it was reported that, ALPS did not have a high incidence in children

with Evans syndrome.<sup>4</sup> So, the scantiness of patients with CVID and ALPS may be due to the study being made with a pediatric population. Eight of the patients (34.7%) were diagnosed with hypogammaglobulinemia (deficiency of IgA and/or IgG). Immune thrombocytopenia has been reported to occur in approximately 1/200 of patients with selective IgA deficiency. Also, ITP and AIHA were seen in selective IgA deficiency which has been reported in previous studies.<sup>21,30</sup> It is reported that various associated immune clinical or laboratory manifestations (lymphoproliferation, other autoimmune disease, and hypogammaglobulinemia) were observed in 93 children (60%) with ES.<sup>11</sup> As a possibility, maybe some of our patients with hypogammaglobulinemia will fulfill the criteria for ALPS, CVID or SLE in the future.

A total of 5 patients had been diagnosed as SLE. None of them had neutropenia. Hematologic manifestations have been reported as a percentage of 34-38% in childhood SLE.<sup>26</sup> Also, it was reported that, autoimmune cytopenias were significantly more frequent in the childhood SLE group.<sup>31</sup> Hematologic abnormalities associated with SLE can include lymphopenia, hemolytic anemia and thrombocytopenia. However, neutropenia is uncommon in SLE.<sup>32-34</sup> Our results are compatible with previous studies for SLE patients. Moreover, it is reported that the absence of neutropenia in children with SLE suggests that AIN is not a relevant mechanism in this disease.<sup>26</sup>

Two of the patients were with diagnosis of WAS. Thrombocytopenia is one of the major component of WAS. Pathophysiology of thrombocytopenia in patients with WAS is not clear but generally anomaly in actin cytoskeleton has been accused.<sup>35</sup> Beside this, immune mediated clearance of platelets may have a role in thrombocytopenia of patients with WAS.<sup>36</sup> Recently, it was shown that WAS is linked to defective regulatory T (Treg) cells and impaired T cell development.<sup>8</sup> Therefore we included these patients in our study.

Five of the patients with multi-lineage cytopenias required second-line treatments. In a large series, Aladjidi et al.<sup>11</sup> reported that 69% of their patients had needed several second-line treatments in children with ES. It is known that the management of patients with chronic-refractory autoimmune cytopenias is complex. Corticosteroids and IVIG are recommended as first-line therapy in a newly diagnosed patient. Second-line therapies are varied depending on the cell lineages affected and underlying disease. For example, patients with autoimmune cytopenias due to SLE are typically treated with medications for SLE, patients with ALPS are often treated with corticosteroids or MMF, whereas patients with CVID are often treated with IVIG per month.<sup>3,4,7,12</sup>

In the current study, none of the patient treated with rituximab had recovered from cytopenia. A number of studies have shown remarkable efficacy with rituximab in autoimmune cytopenias because it targets B cells.<sup>3,4,22</sup> It is suggested that when a patient does not respond to rituximab, a calcineurin inhibitor may be used because the underlying autoimmune disease can be caused by a T-cell disorder. Also, it is reported that a patient with partial response to rituximab may benefit from a drug that suppresses both B and T cells, such as MMF.<sup>4</sup> However, therapies for autoimmune cytopenias may still be insufficient since we still do not know much about the biology of autoimmune cytopenias. As a result, often times these patients are treated similarly to patients with primary disease.<sup>3,4,22</sup> As we improve our understanding about the underlying biological mechanisms, new treatment options including bortezomib, belimumab, tocilizumab and epratuzumab will be used for autoimmune cytopenias.<sup>11</sup> Recently, sirolimus has been recommended as a first or second line agent for patients with chronic-refractory autoimmune cytopenias 2016.<sup>7</sup> During our study, none of our patients were treated with those agents.

Two patients who failed to respond to medical treatment had to undergo splenectomy. Both of

them had hypogammaglobulinemia. If a patient has an immune deficiency, splenectomy should have been avoided. However, sometimes splenectomy may be opted for patients who have persistent diseases.<sup>4,12,27</sup>

In the current study, a total of 8 patients (34.7%) recovered from cytopenia. The rate of recovery from autoimmune cytopenia in this study is similar to that in previous childhood studies.<sup>6,26</sup> Cytopenias had continued in 14 patients and 11 of them had a least one recurrence. Recurrent episodes were treated in a similar manner. In a long-term outcome of a French study, 74% of those patients (67/90) had experienced a relapse.<sup>11</sup>

No malignancy was detected in our patients. Various malignancies (including lymphoma, Hodgkin's disease, or breast cancer) have been reported in patients with immunodeficiency or autoimmune disease.<sup>11</sup> However, it has been reported that none were diagnosed with malignancy.<sup>11</sup>

One patient with CVID died. No patient death has been reported for autoimmune cytopenias due to SLE, whereas 7-36% mortality rates have been reported for autoimmune cytopenias due to other immune disorders.<sup>11,26</sup>

Cytopenia may be the first finding of an immunodeficiency or autoimmune disease and primary disease may be diagnosed during the clinical course. Taking the new targeted treatment options into consideration; early diagnosis is likely to become more important in the near-future in order to begin treatment for the underlying disease as early as possible.

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