Zagazig University Medical Journal
www.zumj.journals.ekb.eg

ORIGINAL ARTICLE

Association between BAFF Gene Polymorphism and Clinical Course of Newly Diagnosed Immune Thrombocytopenic Purpura in Children

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Submit Date	2019-02-12
Revise Date	2019-07-11
Accept Date	2019-07-13

ABSTRACT

Background : Primary immune thrombocytopenia is an autoimmune disorder characterized by autoantibody-mediated enhanced platelet destruction. BAFF gene polymorphisms increases BAFF expression and antibody production in ITP patients, which causes platelet destruction and megakaryopoiesis suppression. The aim of the study was to study the frequency of BAFF gene polymorphisms in newly diagnosed ITP in children and their association with it's clinical features and course. **Methods**: A case control study was conducted at Hematology Unit of Pediatric Department and Medical Biochemistry &Molecular Biology department at Zagazig University Hospital during a period from Nov. 2017 until Nov. 2018.The study Included 40 patients with newly diagnosed ITP (25 males and 15 females) and 20 age and sex-matched healthy children (11males and 9 females) as a control group. All children were subjected to a detailed medical history ,thorough clinical examination and Laboratory investigations including CBC , BM aspiration and B cell activating factor gene polymorphism (-871C/T) detection by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. **Results**: There was also a highly significant difference between ITP cases and control regarding distribution of SNP of BAFF gene where CT was founded in 55% of ITP cases versus 25% in control; also, CC was founded in 75% of control versus 20% of cases. There was non-significant difference between different subtypes of BAFF gene polymorphism regarding age, gender, initial bleeding events,CBC, type of treatment and outcome of ITP cases. **Conclusion**: Significant association of BAFF gene polymorphism with newly diagnosed immune thrombocytopenic purpura in children may indicate its possible role in disease pathogenesis.

Key words: BAFF; Gene Polymorphism; Thrombocytopenic Purpura; Children.

INTRODUCTION

Primary immune thrombocytopenia is an autoimmune disorder characterized by autoantibody-mediated enhanced platelet destruction. In addition, auto antibodies bind to megakaryocytes membranes could interfere with megakaryocytes maturation and thus resulting in decrease platelets production. According to the degree of thrombocytopenia, the risk of bleeding increased [1]. The prevalence of immune thrombocytopenia is being approximately 8 per 100,000 children [2].

Immune thrombocytopenia is characterized by transient or persistent decrease of the platelet count to less than 100 × 109/liter. The term ‘newly diagnosed ITP’ is used to describe all cases at diagnosis. Persistent ITP is defined as ITP lasting between 3 and 12 months from diagnosis while chronic ITP is

defined as the presence of ITP for more than 12 months [3].

The exact mechanism of this disease is still unknown, and several factors are incriminated in the pathogenesis; Although auto reactive B cells producing auto antibodies against self-antigens are considered to play a crucial role [4].

On the other hand direct T cell mediated cytotoxicity against megakaryocytes and platelets has been established as alternative mechanism for platelets destruction in a proportion of patients [5]. Moreover, genetic changes can be a potential factor in the development of primary ITP [6].

Single nucleotide polymorphisms are among the genetic factors causing a series of changes in the human genome and leading to the development of autoimmune disease e.g immune thrombocytopenic purpura. Some of these polymorphisms may exacerbate the disease or affect therapeutic response while others do not have any effect on the disease process [7].

B cell activating factor (BAFF) (13q34) gene is a ligand belonging to the tumor necrosis factor family and has an important role in B cells development, survival, differentiation and immunoglobulin-production [8].

Moreover, BAFF gene polymorphisms expression at positions (−871C>T) of 5′ regulatory region encoding for BAFF increases BAFF expression and antibody production in ITP patients, which causes platelet destruction and megakaryopoiesis suppression was found. Thus BAFF gene polymorphisms can be considered as a diagnostic factor to monitor the progression of ITP [5].

The aim of the study was to determine the frequency of BAFF gene polymorphisms in newly diagnosed immune thrombocytopenia in children and their association with its clinical features and course.

METHODS

A case control study was conducted at Hematology Unit of pediatric department and Medical Biochemistry &Molecular Biology department at Zagazig University Hospital during a period from Nov. 2017 until Nov. 2018.The study Included 40 patients with newly diagnosed ITP (25 males and 15 females) with mean age of 5.09 ±2.93 years and 20 age and sex-matched healthy children (11males and 9 females) with mean age of 4.58 ±2.74 as a control group. The present study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964, as revised in 2000, and was approved by our local ethics committee. Informed consent was obtained from the study participants.

All children were subjected to:

A. Detailed history with emphasis on disease duration, history of bleeding (skin, mucus membrane, frank bleeding).

B. Complete clinical examination including site and shape of bleeding.

C. Laboratory investigations:

1- Complete blood count with manual platelet count.

2 – Bone marrow examination.

3– Laboratory investigations to exclude secondary causes (C_3, ANA, anti DNase).

4- Specific investigations including:

5- B cell activating factor gene polymorphism (-871C/T) detection by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.

-2 ml of peripheral venous blood, were taken from each participant under complete a septic condition and were collected in K ethylene diamine tetra acetic acid (EDTA K) and stored at -20 °C for genomic DNA extraction.

-Genomic DNA was extracted from whole blood using the commercially available G-spin ™ Total DNA Extraction Kit *(iNtron bio-tehnology, Seongnam-Si, Korea)*

-The primers used for BAFF promoter amplification were 5′-GGCACAGTCAACATGG-GAGT-3′ (forward) and 5′-GCTAAGTGTTTTAGCATTGAATTG-3′(reverse). The samples were initially denatured at 95°C for 3 min, followed by 30cycles of 1 minute at 95°C, 1 minute at 54°C , and extension for 1 minute at 72°C , then a final extension for 10 minutes at 72°C.

The samples were then run in parallel on 2% agarose gel using gel electrophoresis (

electro-4, Thermal Hybaid , Promega, Seattle, WA) and visualized on a UV transilluminator (wave length 312) to detect the presence or absence of DNA bands.

Digestion of PCR product by specific restriction enzyme for detection of BAFF gene polymorphisms was done. For BAFF -871C>T polymorphism , after amplification , the PCR product (392bp) was digested with 10 U Ssi-I in the manufactures buffer at 37°C overnight (Helena Biosciences, Sunderland, United Kingdom) , generating 2 fragments of 261 and 131 bp , and it is designated homozygous CC allele , if the T allele exists at position 871, no digestion occurred and only one 392-bp band will emerge , and it is designated TT allele (i.e homozygous for the absence of the restriction site) , if the 3 bands , 392, 261 , and 131bp , were present it is designated heterozygous CT allele.

Statistical analysis

Data were expressed as mean ± SD. Statistical significance was determined by one-way analysis of variance (ANOVA) using the Statistical Package for the Social Sciences (SPSS) version 13.0. P value less than 0.05 was considered statistically significant.

RESULTS

-Table (1) showed that the mean hemoglobin value in cases group at admission, was 10.93 gm/dl, before discharge was 11.04 gm/dl, at 5 th month was 11.07gm/dl and at 1 year was 11.31 gm/dl, while the mean platelet count at admission was $17.08\times10^3/mm^3$, before discharge was $57.70\times10^3/mm^3$, at 5 th month was $87.85\times10^3/mm^3$,and 1 year was $122.02\times10^3/mm^3$.

-Regarding Bone marrow aspiration finding among ITP cases, table (2) showed that, 47.5% of patients had hypercellular bone marrow while 52.5% had normocellular bone marrow.

-Regarding treatment received in ITP cases, thirteen patients (32.5%) had received oral steroids while (17.5%) had received intravenous dexamethasone. Intravenous immunoglobulin had been received in (25%) of patients while (15%) had received combined treatment. Three patients (7.5%) had not received any kind of treatment as shown in table (3) .

-As regards to clinical course of ITP cases, 62.5% had acute course while 35% had persistent course and chronic course was 2.5% of studied patients as shown in table (4)

-Table (5) showed that there was also a highly significant difference between ITP cases and control regarding distribution of SNP of BAFF gene where CT was founded in 55% of ITP cases versus 25% in control; also, CC was founded in 75% of control versus 20% of cases.

-Table (6) showed that there non-significant difference between different subtypes of BAFF gene polymorphism regarding age, gender, initial bleeding events and type of treatment of ITP cases.

Also, There was also non-significant association between SNP of BAFF gene and outcome where acute ITP was common in TT subtype (90%) followed by CC and CT subtypes (62.5%, 50% respectively) while persistent ITP was common in CT subtype (45.5%).

- There was non-significant difference between different subtypes of BAFF gene polymorphism regarding hemoglobin level and platelet count of ITP cases at admission, before discharge, at 5^{th} month and at 1 year of diagnosis. Although CC subtype was associated with increased levels of hemoglobin and platelet at different duration compared to CT and TT subtypes, platelets count was higher at 1 year of diagnosis in TT subtype. There was also non-significant association between SNP of BAFF gene polymorphism and bone marrow cellularity where

37.5%, 63.6% and 20% of CC, CT and TT patients respectively had hypercellular bone marrow (p-value=0.059) as shown in table (S1).

Table 1. Hemoglobin and platelet values in cases group:

	Mean±SD	Range
Values at admission		
Hb (g/dl)	10.93±1.48	7.3-14
PLT (x10^3/mm^3)	17.08±16.1	1-60
Values Before discharge		
Hb (g/dl)	11.04±1.27	7.6-14.2
PLT (x10^3/mm^3)	57.70±81.62	2-350
Values at 5th month		
Hb (g/dl)	11.07±1.25	8-13
PLT (x10^3/mm^3)	87.85±79.64	5-333
values at 1 year		
Hb (g/dl)	11.31±1.1	9-13.7
PLT (x10^3/mm^3)	122.02±100.23	5-391

Hb: Haemoglobin, PLT: platelet, SD: standard deviation

Table 2. Bone marrow aspiration status in cases group:

Bone marrow	Number	Percent
Hyper-cellular	19	47.5%
Normo-cellular	21	52.5%

Table 3. Distribution of cases according to the type of Treatment:

Type of treatmentt	Number	Percent
Oral Steroids	13	32.5%
IV Dexamethasone	7	17.5%
IV immunoglobulin	10	25%
Combined Treatment	6	15%
Other Treatment	1	2.5%
No treatment	3	7.5%

Other treatment: rituximab and dexamethasone , Combined Treatment: Oral Steroids and IV immunoglobulin

Table 4. Outcome of cases group

Outcome	Number	Percent
Acute	25	62.5%
Persistent	14	35%
Chronic	1	2.5%

Table 5. Distribution of studied groups according to BAFF genes expression:

Parameter		Cases group N=40	Control group N=20	Test value	P value
BAFF gene	***CT***	22 (55%)	5 (25%)	18.188x2	<0.001 (HS)
	CC	8 (20%)	15 (75%)		
	TT	10 (25%)	0 (0%)		

X2: chisquare test, S: significant, HS: Highly significant

Table 6. Relation between epidemiological, clinical, and outcomes of studied cases and different subtypes of BAFF gene expression:

BAFF		CC N=8	CT N=22	TT N=10	Test value	P value
Age (years)		5.75±3.01 4(3-10)	4.8±2.9 4.5(1.2-10)	5.15±3.15 5(1.5-10)	0.402KW	0.818 (NS)
Gender	***Female***	2 (25)	10 (45.5%)	3 (30%)	1.367 X2	0.505 (NS)
	Male	6 (75%)	12 (54.5%)	7 (70%)		
Initial bleeding event	***Purpura***	7 (87.5%)	16 (72.7%)	8 (80%)	5.752 X2	0.452 (NS)
	Ecchymosis	1 (12.5%)	4 (18.2%)	0 (0%)		
	Purpura with Gum bleeding and epistaxis	0 (0%)	2 (9.1%)	2 (20%)		
Treatment received	***Oral steroids***	1 (12.5%)	10 (45.5%)	2 (20%)	3.854 X2	0.146 (NS)
	IV dexamethasone	3 (37.5%)	1 (4.5%)	3 (30%)	5.856 X2	0.054 (NS)
	IV immunoglobulin	3 (37.5%)	3 (13.6%)	4 (40%)	3.382 X2	0.184 (NS)
	Combined treatment*	1(12.5%)	4(18.2%)	1(10%)	0.410 X2	0.815(NS)
	Other treatment*	0 (0%)	1 (4.5%)	0 (0%)	0.839 X2	0.657 (NS)
	No Treatment	0 (0%)	3 (13.6%)	0 (0%)	2.654 X2	0.265 (NS)
Outcome	***Acute***	5 (62.5%)	11 (50%)	9 (90%)	5.065 X2	0.281 (NS)
	Chronic	0 (0%)	1 (4.5%)	0 (0%)		
	persistent	3 (37.5%)	10 (45.5%)	1 (10%)		

**Other treatment: rituximab and dexamethazone, Combined treatment: oral steroids and IV immunoglo*bulin, KW: Kruscal wallis test, X2: chisquare test, S: significant , NS: Non significant

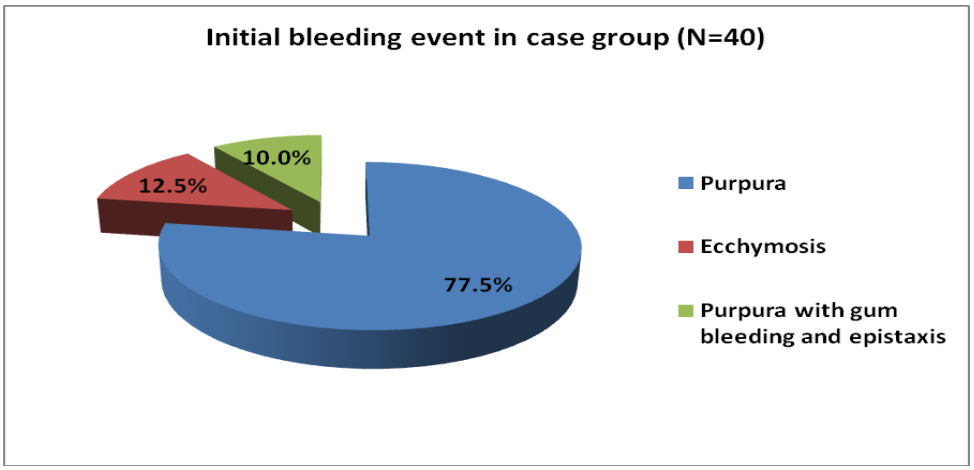

Figure1. *Initial bleeding events in cases group*

DISCUSSION

Autoimmune disorders always have a complex genetic background. there has been great advancement of knowledge about genetic risk factors for human autoimmunity. Also, genetic changes can be a potential factor in the development of primary ITP [6].

Single nucleotide polymorphisms are among the genetic factors causing a series of changes in the human genome and leading to the development of autoimmune disease e.g. immune thrombocytopenic purpura. Some of these polymorphisms may exacerbate the disease or affect therapeutic response while others do not have any effect on the disease process [7].

This study was designed to evaluate the frequency of BAFF gene polymorphism in newly diagnosed immune thrombocytopenic purpura in children and their association with its clinical features and course.

To achieve our aim we conducted this study on 60 subjects, 40 patients with newly diagnosed ITP and 20 age, sex matched healthy children as control group the mean age of our patients was 5.09 ±2.93 year with 62.5% were males and 37.5% were females.

In our study, thirty-one patients (77.5%) presented with purpura while five patients (12.5%) presented with ecchymosis and only three patients (10%) presented with purpura in addition to mucous membrane bleeding.

Our results came similar to Abdel-Hamid and Al-Lithy [8], who reported that, purpura and petechiae were reported in 77.5% of patients with ITP but ecchymosis occurred less frequently in those patients. Similarly, Gozmen et al, [9] reported in their study that petechiae and purpura were prevalent in 70% of patients with acute ITP.

Our results showed that the mean platelet count at admission was $17.08\times10^3/mm^3$, with range of $(1\text{-}60\times10^3/mm^3)$ and before discharge was $57.70\times10^3/mm^3$, at 5month was $87.85\times10^3/mm^3$ and at 1 year was $122.02\times10^3/mm^3$, Also, the mean hemoglobin level at admission was 10.93 gm/dl, before discharge was 11.04 mg/dl, at 5^{th} month was 11.07gm/dl and at 1 year was 11.31 gm/dl.

Close to our results, Elhoseny et al, [10] reported in their study the mean platelet count at admission was $31.0\times10^3/mm^3$ with range of $6\text{-}67\times10^3/mm^3$ and mean hemoglobin level at admission was 12.9 gm/dl. Also, Eiada et al [11] reported in their study mean platelet count at admission was $36.0\times10^3/mm^3$ and $36.0\times10^3/mm^3$ at follow up. also, hemoglobin level at admission was 11.0 gm/dl. Moreover, Jing et al [12] found that the mean platelets count at admission was $25\times10^3/mm^3$.

Regarding bone marrow cellularity among our cases, we found that, 47.5% of patients had hypercellular bone marrow while 52.5% had normocellular bone marrow.

Regarding treatment received in ITP cases, thirteen patients (32.5%) had received oral steroids while (17.5%) had received intravenous dexamethasone. Intravenous immunoglobulin had been received in (25%) of patients while (15%) had received combined treatment. Three patients (7.5%) had not received any kind of treatment.

Moreover, Eiada et al, [11] found in their study that 48 patients (61%) received steroid, 2 patients (2.5%) received immunoglobines, 12 patients (15.2%) received immunosuppressive drugs, and 2 patients (2.5%) did splenectomy while 31 patients (39%) received no treatment.

Also, Abdel-Hamid and Al-Lithy [8] reported that 32 patients (80%) were steroid sensitive and 8 patients (20%) received immunosuppressive treatment.

Regarding patient's outcome, our results revealed that 62.5% of patients achieved complete response, 35% of patients achieved partial response and 2.5% showed no response. Similarly, Eiada et al [11] reported that 45 patients (72.5%) achieved complete response, 10 patients (16.5%) achieved partial response and 7 patients (11%) showed no response.

Defects in the production of BAFF and/or expression of its receptors have now been recognized to be involved in the pathogenesis and maintenance of various hematological disorders including autoimmunity (SLE, RA, SS, myasthenia gravis and ITP), malignancy (non-Hodgkin lymphoma [NHL], B-CLL and immunodeficiency [13].

Elevated BAFF levels in inflamed tissues could have several consequences such as B-cell survival and increased B- and T-cell activation, a situation that can prolong autoantibody production and lymphocyte-mediated tissue damage [14].

In this study, the frequency of BAFF gene polymorphism genotypes-871 C>T were studied in newly diagnosed ITP versus control group and there was a highly significant difference between ITP cases and control (P<0.001). where 22 patients (55%) express heterozygous C/T genotype, 8 patients (20%) express homozygous CC genotype and 10 patients (25%) express homozygous TT genotype. while in control group 5 (25%) express heterozygous C/T genotype, 15 (75%) express homozygous CC genotype and no one express TT genotype.

Similarly, Abdel-Hamid and Al-Lithy [8] found in in their comparative case control study that -871 C>T homozygous (CC) and T allele (T/C and T/T) genotypes were highly expressed in chronic ITP patients than control with highly statistically significant difference (P<0.001). where 17.5% had a homozygous (CC) genotype and 82.5% had T allele genotype (57.5% were heterozygous C/T and 25% were homozygous T/T), while among the control group, 80% had a homozygous (CC) genotype and 20% had heterozygous C/T genotype.

In contrast to our results Emmerich et al [15] studied BAFF -871 C>T promoter polymorphism genotypes expression in 17 patients with ITP and 10 control subjects and reported that CC, CT and TT genotypes frequencies were 35.5%, 35.5% and 29%, respectively, for their patients and 50%, 40% and 10%, respectively, for control group subjects. This apparent difference in frequency of -871 C>T polymorphism expression is a consequence of variation in procedures used: the number of amplification cycles of performed RFLP-PCR assays and the differences in chosen primers, which may influence the sensitivity and the specificity of the detection method.

Also, Liu et al[16] identified -871 C>T polymorphism of BAFF promotor in 133 ITP patients and 117 healthy controls and reported that CC, CT and TT genotypes frequencies were 33.1%, 42.1% and 24.8%, respectively, for their patients and 55.6%, 33.3% and 11.1%, respectively, for control group subjects. There was significant difference in the BAFF -871 C>T genotypic frequency between the ITP patients and healthy controls (P < 0.05). In this study, we noticed that there was no significant difference between different types of BAFF gene polymorphism (C/C, C/T, T/T) and each of age , gender , initial bleeding events and different types of treatment in ITP cases .

Similarly, Abdel-Hamid and Al-Lithy [8] found no statistical significant correlation between BAFF gene polymorphism at position (-871C>T) and age, sex, duration of disease, clinical data of patients with ITP.

Regarding relation between different types of BAFF gene polymorphism (CC, CT, TT) genotypes and patients' outcome, we found that 90% of patient with BAFF gene (TT genotype) followed by 62.5% and 50 % of

patients with BAFF gene (CC and CT genotypes) respectively behaves like acute ITP. On the other hand, 45.5% of patients BAFF gene (CT genotype) behaves like persistent ITP and chronic ITP was reported in only one patient with BAFF gene (CT genotype_ with no significant difference (P=0.281) and as we mentioned before Abdel-Hamid and Al-Lithy [8] found BAFF gene (T/C and T/T) genotypes were highly expressed in chronic ITP patients (P<0.001). In this study, we found no relation between different types of BAFF gene polymorphism (CC, CT, TT) genotypes and patients' laboratory data, regarding hemoglobin level and platelet count (at admission, before discharge, at 5th month and at 1 year of diagnosis) p>0.05.

Although BAFF gene (CC genotype) was associated with increased levels of hemoglobin and platelet at different disease duration compared to BAFF gene (CT and TT genotypes) also, platelets count was higher at 1 year of diagnosis in BAFF gene (TT genotype) but with no statically significant difference (p>0.05). Also, we didn't find statistical significant correlation between BAFF gene polymorphism and bone marrow cellularity p= 0.059.

Close to our finding, Abdel-Hamid and Al-Lithy [8] reported that no statistical significant correlation between BAFF gene polymorphism and different hematological laboratory data in patients with ITP.

CONCLUSION

We can conclude that significant association of BAFF gene polymorphism with newly diagnosed immune thrombocytopenic purpura in children may indicate its possible role in disease pathogenesis.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding information: None declared

Table S1 is shown in online supplement

REFERENCES

1. Yang L, Wang L, Zhao CH, Zhu XJ, Hou Y, Jun P, et al. Contributions of TRAIL mediated megakaryocyte apoptosis to impaired megakatyocytes and platelet production in immune thrombocytopenia. Blood, 2010;116: 4307-416.
2. Terrell DR, Beebe LA, Neas BR, Vesely SK, Segal JB, George JN, et al. Prevalence of primary immune thrombocytopenia in Oklahoma .[Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't], 2012; 87: 848-852.
3. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Clinical Standardization of terminology, definitions and outcome criteria in immune thrombocytopenia purpura of adult and children: report from an international working group. Blood, 2009;113(11): 2386-2393.
4. McMillan R. The pathogenesis of chronic immune thrombocytopenic purpura. Semin Hematol, 2007;44: 3-6.
5. Zhang F, Chu X, Wang L, Zhu Y, Li L, Ma D, et al. Cell-mediated lysis of autologous platelets in chronic idiopathic thrombocytopenic purpura. Eur J Haematol, 2006; 76: 427–431.
6. Satoh T, Pandey JP, Okazaki Y, Asahi A, Kawakami Y, Ikeda Y, et al. Single nucleotide polymorphism of interleukin-1b associated with Helicobacter pylori infection in immune thrombocytopenic purpura. Tissue Antigens, 2009;73(3): 353–357.
7. Aref S, El-Ghonemy MS, El-Aziz SA, Abouzeid T, Talaab M, El-Sabbagh A. Impact of serum immunoglobulins level and IL-18 promoter gene polymorphism among Egyptian patients with idiopathic thrombocytopenic purpura. Hematology, 2017; 22: 99–104.
8. Abdel-Hamid SM, Al-Lithy HN. B cell activating factor gene polymorphisms in patients with risk of idiopathic thrombocytopenic purpura. Am J Med Sci, 2011; 342(1): 9–14.
9. Gozmen S, Karapnar TH, Tufekci O, Vergin C, Yuksel F, Irken G, et al. B-cell-activating factor, a proliferation inducing ligand and co-stimulatory molecules in the pathogenesis of immune thrombocytopenia in childhood. Blood Coagul Fibrinolysis, 2016;27(5): 494-499.
10. Elhoseiny SM, Morgan DS, Elhadidy KES. The association of lymphoid protein tyrosine phosphatase non-receptor 22 (PTPN22) gene polymorphism with Egyptian immune thrombocytopenic purpura. Comp Clin Pathol, 2013;22(3): 395-402.

11. Eiada TK, Amin DG, Amin ES, Morgan DS, Gad Elkareem ME. Expression of B-cell activating factor and its receptor in idiopathic thrombocytopenic purpura. EJH, 2012;37(3): 166-171.
12. Jing Ge, Huiyuan Li, Dongsheng Gu, Weiting Du, Freng Xue,Jianhui Xu, et al. PTPN22-1123G4C polymorphism is associated with susceptibility to primary immune thrombocytopenia in Chinese population. Platelets, 2013;24(6): 448-453.
13. Tangye SG, Bryant VL, Cuss AK, Good KL. BAFF, APRIL and human B cell disorders. Semin Immunol, 2006;18(5): 305-317.
14. Mackay F, Tangye SG. The role of the BAFF/APRIL system in B cell homeostasis and lymphoid cancers. Curr Opin Pharmacol, 2004;4(4): 347-354.
15. Emmerich F, Bal G, Barakat A, Milz J, Muhle C, Dorner T, et al. High-level serum B-cell activating factor and promoter polymorphisms in patients with idiopathic thrombocytopenic purpura. Br J Haematol, 2007;136(2): 309-314.
16. Liu XG, Ma SH, Sun JZ, Ren J, Shi Y, Sun L, et al. High-dose dexamethasone shifts the balance of simulatory and inhibitory Fc gamma receptors on monocytes in patients with primary immune thrombocytopenia. Blood, 2011;117(6): 2061-2109.

To Cite This Article: Mervat AH, Marwa ZM, Amal FA and Ebtihaj AA. Association between BAFF Gene Polymorphism and Clinical Course of Newly Diagnosed Immune Thrombocytopenic Purpura in Children.ZUMJ 2020;26(1);165-173.DOi: 10.21608/zumj.2019.7944.1043