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Original Article

Predictors of Remission in Childhood Immune Thrombocytopenia

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Abstract ***Background:*** Demographic and clinical features of childhood immune thrombocytopenia (ITP) in Hong Kong were described and the clinical predictors of ITP remission were identified. ***Methods:*** We conducted a 15-year retrospective analysis of all children with newly diagnosed ITP in two regional hospitals in Hong Kong. Demographic and clinical features of childhood ITP were described. Clinical predictors of remission by 12 months were analysed by a logistic regression model. ***Results:*** One hundred and eleven cases of newly diagnosed ITP were analysed, among which 85 (77%) recovered by 12 months while 26 (23%) of them developed a chronic course. Remission was associated with the following predictors: platelet count ≤$10x10^9$/L (p=0.034), age ≤24 months (p=0.013) and acute onset of symptoms (p=0.001). ***Conclusions:*** We presented the demographic and clinical features of childhood ITP in the local population. Clinical predictors of remission were identified as a guide for disease monitoring.

Key words *Children; Chronic; ITP; Newly diagnosed; Thrombocytopenia*

Objective

Immune thrombocytopenia (ITP) is an immunological disorder characterised by unexplained thrombocytopenia. It commonly presents with unprovoked petechiae, bruises and epistaxis. In children, newly diagnosed ITP has a reported annual incidence of 1.9-6.4 cases per 100,000.[1-3] The disease remits in the majority of children. However, 20% to 25% of children with newly diagnosed ITP develop chronic disease,[1] necessitating long-term monitoring and treatment. Chronic ITP causes significant physical and psychological impact on the affected children. Studies have shown that children with the following features were more likely to have a remitted course of disease: males, younger age, acute onset of symptoms, lower platelet count at presentation, more severe bleeding symptoms, and preceding infection before ITP onset.[4-10] Our study aims to describe the demographic and clinical features of childhood ITP in this locality and to analyse the predictors associated with ITP remission.

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Methods

We retrospectively reviewed the clinical records of children with newly diagnosed ITP who were treated in United Christian Hospital and Tseung Kwan O Hospital, two regional hospitals in Hong Kong, from 2003 to 2018. Cases were identified through the Clinical Data Analysis and Reporting System (CDARS), where demographic data including date of onset, sex and age were retrieved. We included children aged 3 months to 18 years with a

diagnosis of primary ITP. The selection and definition of ITP cases were predetermined with reference from The International Work Group (IWG) criteria.[11,12] Primary ITP was defined as peripheral blood platelet count <100x10^9/L in the absence of other causes or disorders associated with thrombocytopenia. Children with recovered ITP include those having a platelet count ≥100x10^9/L by 12 months, regardless of the treatment modality given. The definition of chronic ITP was met when the condition persists or relapses beyond 12 months. Previous studies commonly used a 6-month period to define chronic ITP. Instead, we adhered to the 12-month definition of IWG, based on the observation that spontaneous remission of ITP was high between 6 to 12 months.[13]

The following information was retrieved from the database: platelet count at presentation, platelet count at 3, 6 and 12 months after diagnosis, duration of bleeding symptoms, bleeding severity, presence of preceding infection, antinuclear antibody (ANA) status, treatment modalities given and comorbid physical conditions. Bleeding severity is classified into two groups: cutaneous bleeding (Grade I to II) and mucosal bleeding (Grade III to IV), referencing from the classification of bleeding severity by the international consensus report.[11] The duration of symptoms was classified into acute onset (less than 2 weeks) and insidious onset (more than 2 weeks) respectively. Presence of infection within 4 weeks of diagnosis was ascertained from the clinical history. ANA was considered positive if the serum titre was ≥1:80. All cases with a diagnostic coding of ITP (ICD-9: 287.30-31) were retrieved. As our study focused on primary ITP, cases of secondary ITP attributed to autoimmune disorders, malignancies, congenital thrombocytopenia, bone marrow failure and platelet-depleting medication were excluded. Infants younger than 3 months were excluded from the study in order to avoid diagnostic confusion with thrombocytopenia caused by congenital infection and neonatal alloimmune thrombocytopenia. Patients with incomplete clinical information and those who were not initially managed within the participating units were not included in the final analysis. The process of cases retrieval and outcomes are shown in Figure 1.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 23.0 statistical programme. Continuous variables were analysed by Mann-Whitney U or independent *t*-tests. Chi-square test was used to determine the bivariate relationship between the remission group and the chronic group with regards to age, sex, platelet count at diagnosis, bleeding severity, duration of symptoms, presence of preceding infection, ANA positivity and the modality of treatment given respectively. Age was further classified into two groups: ≤24 months and >24 months, as a multisite cohort study found that children ≤2 years of age had the least risk of developing chronic ITP.[14] Platelet count at presentation was dichotomised using 10x10^9/L as a cut-off value, because a level below this value signifies chances of more severe bleeding according to previous research findings.[4,15] A logistic regression model was used to analyse statistically significant variables at disease presentation. P-value <0.05 was considered statistically significant.

Results

A total of 111 cases of newly diagnosed ITP were analysed. There were 54 males (49%) and 57 females (51%) with a median age of 38 months. Eighty-five children (77%) attained remission by 12 months while 26 children (23%) developed chronic ITP. The median platelet count at presentation was 8x10^9/L. The seasonal distribution of all newly diagnosed ITP cases is shown in Figure 2. More than a quarter of cases presented in April and May. Sixty-eight percent of children received at least one type of treatments at presentation (e.g. IVIG, corticosteroids), while 32% were managed expectantly. Sixty percent of children presented with cutaneous bleeding while 40% of children presented with mucosal bleeding.

The median onset age was 30 months for the remission group and 66.5 months for the chronic group (p=0.012). The median platelet count was 6x10^9/L for the remission group and 16x10^9/L for the chronic group (p=0.007). Subgroup analysis shows that mucosal bleeding is associated with a platelet count ≤10x10^9/L at presentation (p=0.029). The demographic and clinical features of both groups are shown in Table 1. Two children (1.8%) had spontaneous intracranial haemorrhage and their clinical presentations are summarised in Table 2.

Statistically significant variables at disease presentation were analysed by a logistic regression model. This model included statistically significant variables on univariate analysis: age, platelet count and duration of symptoms. ITP remission by 12 months is associated with the following factors: age ≤24 months (adjusted OR 4.47, 95% CI 1.12-17.86), platelet count ≤10x10^9/L (adjusted OR

4.19, 95% CI 1.35-13.02) and acute onset of symptoms (adjusted OR 8.50, 95% CI 2.83-25.81) (Table 3).

Discussion

Our study summarised the data of childhood ITP of the local community in recent years. To our knowledge, this is the first study in Hong Kong describing the general clinical pattern of childhood ITP. The epidemiological data in our study is largely consistent with published data in other countries. There is an almost equal occurrence among boys and girls. The majority of children with newly diagnosed ITP (77%) attained remission by 12 months.

Seasonality

Cases of newly diagnosed ITP were observed to present with a seasonal pattern. There is a peak occurrence in April and May, following a higher level of influenza activity in winter and spring in Hong Kong. Authors in other countries

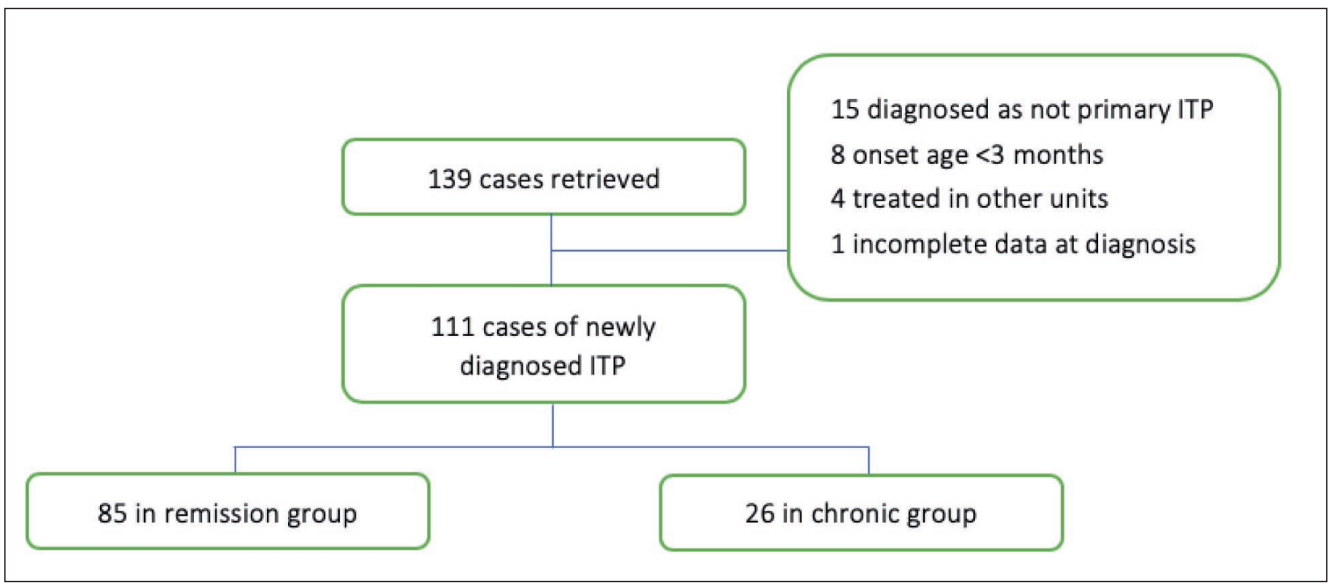

Figure 1 Cases retrieval and outcome.

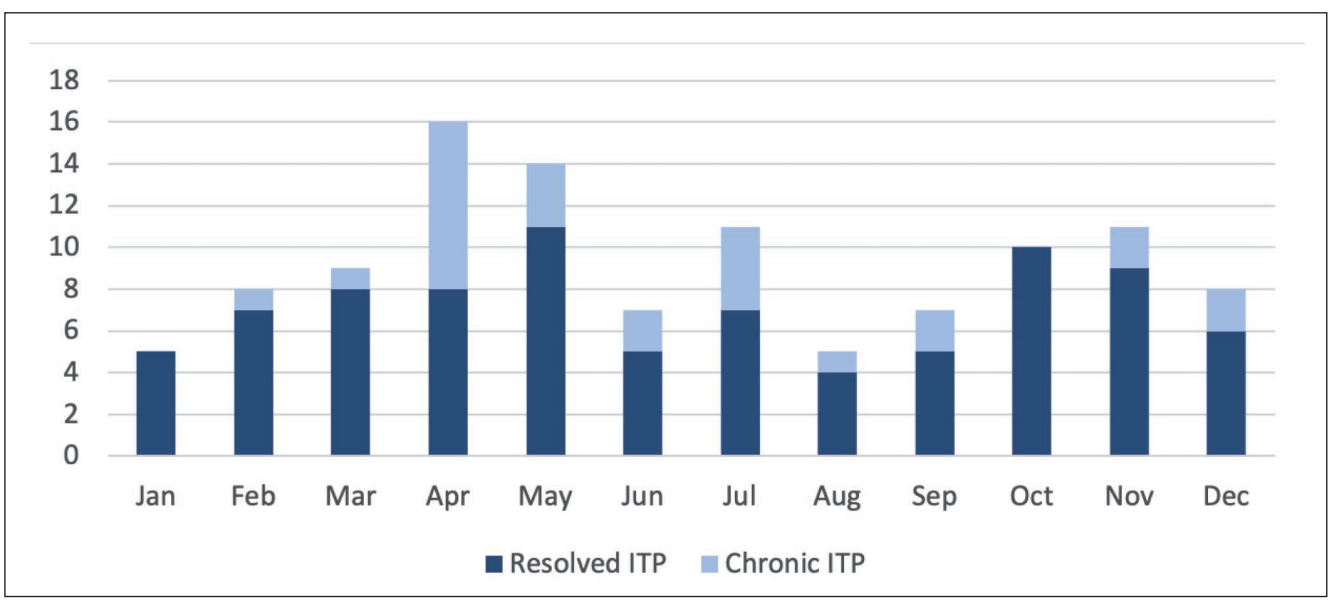

Figure 2 Seasonal distribution of newly diagnosed ITP cases.

Table 1 Demographic and clinical features of children with newly diagnosed ITP

	Remission (n=85)	Chronic (n=26)	p-value
Age at diagnosis [median (range)] (months)	30 [3-201]	66.5 [10-187]	**0.012**
≤24 months, n (%)	33/85 (39%)	4/26 (15%)	**0.021**
>24 months, n (%)	52/85 (61%)	24/26 (85%)	
Platelet count at diagnosis [median (range)] (x10^9/L)	6 [1-56]	16 [2-79]	**0.007**
≤10x10^9/L, n (%)	54/85 (64%)	9/26 (35%)	**0.013**
>10x10^9/L, n (%)	31/85 (36%)	17/26 (65%)	
Sex, n (%)			0.246
Male	38/85 (45%)	15/26 (58%)	
Female	47/85 (55%)	11/26 (42%)	
Duration of symptoms, n (%)			**<0.001**
Acute	70/81 (86%)	10/24 (42%)	
Insidious	11/81 (14%)	14/24 (58%)	
Bleeding severity, n (%)			0.491
Cutaneous bleeding	51/85 (60%)	18/26 (69%)	
Mucosal bleeding	34/85 (40%)	8/26 (31%)	
Preceding infection within 4 weeks, n (%)	54/82 (66%)	12/24 (50%)	0.156
Anti-nuclear antibody (Titre ≥1:80), n (%)	2/49 (4%)	4/23 (17%)	0.057
IVIG treated, n (%)	52/84 (62%)	13/26 (50%)	0.281
Corticosteroids treated, n (%)	20/83 (24%)	14/25 (56%)	**0.003**

Table 2 Clinical presentations of the two cases complicated by intracranial haemorrhage (ICH)

	Sex	Age	Platelet count on discovery of ICH	Symptoms associated with ICH	Extent of ICH	Duration of bleeding symptoms before onset of ICH	Other bleeding symptoms	Course of ITP
Patient 1	M	8	4x10^9/L	Headache	Bilateral parietal parenchymal haematoma with mass effect	2 days	Epistaxis, gum bleeding, gross haematuria	Remission
Patient 2	F	10	2x10^9/L	Headache	Left parietal subdural haematoma with mass effect and cerebral oedema	4 months	Epistaxis, gum bleeding	Chronic

Table 3 Predictors of remission by 12 months by a logistic regression model

	Adjusted odds ratio (95% confidence interval)	p-value
Age ≤24 months	4.47 (1.12-17.86)	**0.034**
Platelet count ≤10x10^9/L	4.19 (1.35-13.02)	**0.013**
Acute onset of symptoms	8.54 (2.83-25.81)	**<0.001**

have also reported seasonal predilection for childhood ITP, but their findings had not been entirely consistent. The International Childhood ITP Registry of 38 countries reported a peak occurrence of ITP in spring and a nadir in autumn.[16] A Nordic study found a winter bulk of post-infectious ITP occurrence.[15] Some other studies found no seasonal fluctuations at all.[17,18] The seasonal difference could be related to different local climates and viral activities.

Intracranial Haemorrhage

Intracranial haemorrhage (ICH) occurred in 1.8% of our children. This percentage is slightly higher than large-scale epidemiological studies reported in western communities. The rate of ICH in the ICIS registry and Nordic registry were 0.6% and 0% respectively.[16,19] Among the Chinese population, the rate of ICH was 1.7% in a study of 663 children and 2.9% in a Hong Kong case series of 276 patients.[20,21] A territory-wide study would be needed to assess if the relatively higher incidence of ICH amongst children reflects the true incidence in the local population. Concerning the relationship between platelet count and the severity of bleeding, we noted an association between mucosal bleeding and a presenting platelet count ≤10x10^9/L. The two cases of ICH presented at a platelet count below this level and both developed mucosal bleeding. Based on this observation, we suggest clinicians consider active treatments when the platelet count drops below 10x10^9/L or when there is the presence of mucosal bleeding (Figure 3). Clinicians should also be aware that clinical conditions can change rapidly; platelet reading at a single time point cannot be the only determinant in management. The decision to treat or to observe entails a thorough consideration of the health condition of a child, health-related quality of life, medication side effects and efficacy and anticipatory follow-up plans.[22]

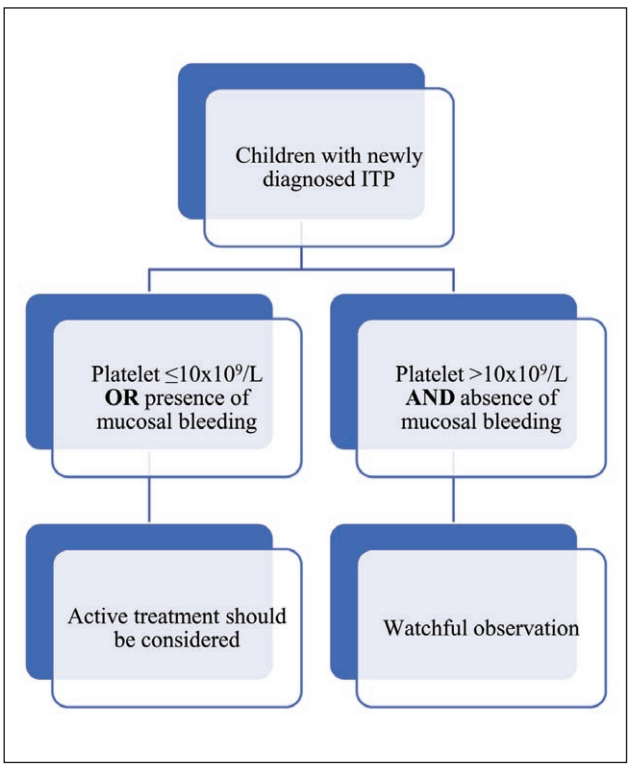

Figure 3 Initiating active treatment in children with newly diagnosed ITP.

Couse of Disease

What concerns children and their parents most about ITP is the likelihood of recovery. Given the fact that about a quarter of children persists to have low platelet count 12 months after newly diagnosed ITP, it is useful to delineate the factors associated with remission and chronicity, to guide the frequency and duration of disease monitoring. The observed differences between the two groups could be explained by the fact that ITP is a highly heterogeneous condition. Its underlying pathophysiology is complex and not yet fully understood. The remitted and chronic forms of ITP in children might have developed through different immune pathways.

Demographically speaking, recent studies reported that children with chronic ITP were more likely to be older.[5,7,15] Similarly, our study demonstrated that children with disease remission had a lower median age. Onset age ≤24 months was independently associated with ITP remission. In terms of sex difference, a recent meta-analysis concluded that chronic ITP is more likely to occur in girls than in boys.[4] However, we observed a similar occurrence of chronic ITP in both sexes.

In respect of clinical features, we observed that an acute onset of symptoms was associated with ITP remission, similar to other published reports.[8-10,15] Also, our results were consistent with other reports that a platelet count ≤10x10^9/L was associated with a favourable recovery from ITP.[7,10,15,23,24] While other studies have reported ITP remission being associated with the presence of preceding infection and higher-grade bleeding,[15,25,26] such associations were not significant in our study.

As the risk of developing chronic disease is low in the subset of young children presenting with acute symptoms, we suggest that routine platelet count surveillance for these children is unnecessary when platelet count shows signs

of recovery. Blood tests should be ordered only when clinical symptoms recur. On the other hand, for older children with insidious symptoms, regular platelet count monitoring should continue until at least 12 months after the initial presentation.

Limitations of the Study

Our study is limited in certain aspects. Firstly, the study was carried out retrospectively with missing data in a few subjects. Secondly, our study could have overestimated the true number of children with primary ITP, because a small number of children with chronic ITP might eventually be diagnosed with other disease entities. For example, it has been reported 4% of children with ITP ultimately developed Systemic Lupus Erythematosus (SLE)[27] while the rate of SLE development in adult ITP patients was 1-5%.[27-29] In our study, six children (5%) had a positive ANA titre (≥1:80) without other distinctive clinical manifestations of SLE. Finally, the association of treatment modalities was not analysed in the regression model as we found significant heterogeneity in the treatment timing and dosage. Future studies with standardised protocols could help better study their association with the course of ITP.

Summary

In summary, our study described the demographics of newly diagnosed ITP in children and identified predictors associated with ITP remission, consistent with previous findings. Devising an objective clinical score for the Chinese population could be the next area of research. A clinical score has been proposed by the NOPHO ITP Working Group to predict the course of ITP, based on data from the Nordic countries.[5] Being able to predict the course of ITP can alleviate anxiety among parents and minimise unnecessary follow-up and blood taking. Further prospective studies performed in multi-centre settings and data registry analyses would help provide a more comprehensive clinical picture to the condition.

Ethics Approval

This study was approved by the Hospital Authority Kowloon East Cluster Research Ethics Committee (Reference No.: KE/KC-18-0260/ER-4). The requirement for patient informed consent was waived.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Declaration of Interest

None

References

1. Kühne T, Buchanan GR, Zimmerman S, et al. A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from the Intercontinental Childhood ITP Study Group. J Pediatr 2003;143: 605-8.
2. D'Orazio JA, Neely J, Farhoudi N. ITP in children: pathophysiology and current treatment approaches. J Pediatr Hematol Oncol 2013; 35:1-13.
3. Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports. Am J Hematol 2010;85:174-80.
4. Heitink-Polle KM, Nijsten J, Boonacker CW, de Haas M, Bruin MC. Clinical and laboratory predictors of chronic immune thrombocytopenia in children: a systematic review and meta-analysis. Blood 2014;124:3295-307.
5. Edslev PW, Rosthøj S, Treutiger I, et al. A clinical score predicting a brief and uneventful course of newly diagnosed idiopathic thrombocytopenic purpura in children. Br J Haematol 2007;138: 513-6.
6. Bolton-Maggs PH, Moon I. Assessment of UK practice for management of acute childhood idiopathic thrombocytopenic purpura against published guidelines. Lancet 1997;350:620-3.
7. Bruin M, Bierings M, Uiterwaal C, et al. Platelet count, previous infection and FCGR2B genotype predict development of chronic disease in newly diagnosed idiopathic thrombocytopenia in childhood: results of a prospective study. Br J Haematol 2004; 127:561-7.
8. ElAlfy M, Farid S, Abdel Maksoud A. Predictors of chronic idiopathic thrombocytopenic purpura. Pediatr Blood Cancer 2010; 54:959-62.
9. Robb LG, Tiedeman K. Idiopathic thrombocytopenic purpura: predictors of chronic disease. Arch Dis Child 1990;65:502-6.

10. Roganovic J, Letica-Crepulja M. Idiopathic thrombocytopenic purpura: a 15-year natural history study at the Children's Hospital Rijeka, Croatia. Pediatr Blood Cancer 2006;47:662-4.
11. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86.
12. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113:2386-93.
13. Imbach P, Kühne T, Müller D, et al. Childhood ITP: 12 months follow-up data from the prospective registry I of the Intercontinental Childhood ITP Study Group (ICIS). Pediatr Blood Cancer 2006;46:351-6.
14. Glanz J, France E, Xu S, Hayes T, Hambidge S. A population-based, multisite cohort study of the predictors of chronic idiopathic thrombocytopenic purpura in children. Pediatrics 2008; 121:e506-12.
15. Zeller B, Rajantie J, Hedlund-Treutiger I, et al. Childhood idiopathic thrombocytopenic purpura in the Nordic countries: epidemiology and predictors of chronic disease. Acta Paediatr 2005;94:178-84.
16. Kühne T, Imbach P, Bolton-Maggs PH, et al. Newly diagnosed idiopathic thrombocytopenic purpura in childhood: an observational study. Lancet 2001;358:2122-5.
17. Paling A, Stefan DC. Idiopathic thrombocytopenic purpura in childhood: a 10-year audit. Hematology 2008;13:175-80.
18. Evim MS, Baytan B, Güneş AM. Childhood Immune Thrombocytopenia: Long-term Follow-up Data Evaluated by the Criteria of the International Working Group on Immune Thrombocytopenic Purpura. Turk J Haematol 2014;31:32-9.
19. Rosthøj S, Hedlund-Treutiger I, Rajantie J, et al. Duration and morbidity of newly diagnosed idiopathic thrombocytopenic purpura in children: A prospective Nordic study of an unselected cohort. J Pediatr 2003;143:302-7.
20. So MY, Li CH, Lee AC, Kwong NS. Intracranial haemorrhage among Chinese children with immune thrombocytopenia in a Hong Kong regional hospital. Hong Kong Med J 2013;19:129-34.
21. Zhou F, Xu Y, Zhang Z, Wu X, Jin R. Severe Hemorrhage in Chinese Children With Immune Thrombocytopenia. J Pediatr Hematol Oncol 2015;37:e158-61.
22. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190-207.
23. Ahmed S, Siddiqui AK, Shahid RK, Kimpo M, Sison CP, Hoffman MA. Prognostic variables in newly diagnosed childhood immune thrombocytopenia. Am J Hematol 2004;77:358-62.
24. Akbayram S, Dogan M, Ustyol L, et al. The clinical outcome of 260 pediatric ITP patients in one center. Clin Appl Thromb Hemost 2011;17:E30-5.
25. Bennett CM, Neunert C, Grace RF, et al. Predictors of remission in children with newly diagnosed immune thrombocytopenia: Data from the Intercontinental Cooperative ITP Study Group Registry II participants. Pediatr Blood Cancer 2018;65(1). doi: 10.1002/pbc.26736. Epub 2017 Aug 9.
26. Makis A, Gkoutsias A, Palianopoulos T, et al. Prognostic Factors for Immune Thrombocytopenia Outcome in Greek Children: A Retrospective Single-Centered Analysis. Adv Hematol 2017;2017: 7878605.
27. Hazzan R, Mukamel M, Yacobovich J, Yaniv I, Tamary H. Risk factors for future development of systemic lupus erythematosus in children with idiopathic thrombocytopenic purpura. Pediatr Blood Cancer 2006;47:657-9.
28. Altintas A, Ozel A, Okur N, Cil T, Pasa S, Ayyildiz O. Prevalence and clinical significance of elevated antinuclear antibody test in children and adult patients with idiopathic thrombocytopenic purpura. J Thromb Thrombolysis 2007; 24:163-8.
29. Zimmerman SA, Ware RE. Clinical significance of the antinuclear antibody test in selected children with idiopathic thrombocytopenic purpura. J Pediatr Hematol Oncol 1997;19:297-303.