Introduction

Immune thrombocytopenia (ITP) of childhood is a bleeding disorder with an estimated incidence of 0.46-12.5 cases/100,000/yr with a male predominance in younger ages [1,2]. ITP could be either primary or secondary. Primary as well as secondary ITP are characterized by low platelet count (PLT) (< 100,000 c/μL) but in cases of primary ITP the absence of any other known identifiable cause establishes the diagnosis. It occurs more often between 2-7 years of age and a preceding viral illness of the upper respiratory system is usually recorded 2-4 weeks earlier. Secondary ITP is due to either other medical conditions such as autoimmune disorders, primary/secondary immunodeficiencies or to drug treatment.

The spectrum of the clinical manifestations of the disease varies from several petechiae and ecchymoses to severe bleeding from gastrointestinal tract or intracranial hemorrhage. Fortunately, intracranial bleeding is very rare accounting for 0.1-1% of newly diagnosed pediatric ITP cases. The terminology of ITP was changed recently. According to new nomenclature the lower normal cutoff of platelet count is 100,000 c/μL. Additionally, the terms acute and chronic ITP were replaced by the terms newly diagnosed, persistent and chronic when the thrombocytopenia lasts for < 3 months, 3-12 months and > 12 months respectively.

Another significant change in disease approach is the fact that the “watch and wait” practice has gained attention. According to this, treatment may be omitted in cases of low bleeding risk (PLT >20,000 c/μL in the absence of bleeding, or...
other identified comorbidities known to cause bleeding dia-
thesis). It is agreed that the treatment should be tailored to
the patient and the platelet count is not the only thing that
counts in terms of treatment decisions. It must be taken into
account along with other parameters, such as the bleeding
phenomena, the age of the patient and the other possible
co-morbidities. Nevertheless, ITP treatment options are
based not only on the above parameters but also on treat-
ing physician’s determination to face family’s anxiety and re-
spond effectively to their concerns. The unpredictable course
duration of the disease impose significant concerns to
the treating physician and augments the anxiety of patient’s
family.

Even though peripheral destruction of antibody-coated platelets
still remains the main mechanism of thrombocyto-
penia, reports revealed that the same antibodies could target
not only the platelets but also the megakaryocytes as well
[3]. The later mechanism gave rise to new therapeutic agents,
the so-called thrombopoietin (TPO) receptor agonists (romi-
plostim, eltrombopag). Nowadays the therapeutic approach
of ITP in children is challenging and includes the “watch and
wait” option as well as immunomodulatory treatments such
as intravenous immunoglobulin G (IVIG), corticosteroids, rit-
uximab and TPO agonists. A few retrospective studies tried
to shed light as far as the duration and respond to treatment
are concerned [4-6]. Most of them did not take into consider-
ation the new terminology of the disease. Our goal is to apply
the new criteria of duration of the disease and prospective-
ly evaluate the clinical course and characteristics of the dis-
ease along with the compliance of treating physicians to the
‘watch and wait’ practice.

Patient and Methods

We prospectively evaluated children with newly diag-
osed ITP from January 2015 to December 2017. The children
were admitted to the pediatric ward of a tertiary pediatric
hospital, which is one of the two referral pediatric centers
in central and south Greece. Hospitalization criteria includ-
ed PLT < 10000 c/μL, severe mucosal bleeding or living far
away from the hospital. Demographic, clinical and laboratory
data were collected from all patients along with medical and
family history. The patient underwent thorough clinical and
laboratory evaluation with full blood count, immunological
and biochemistry markers. We divided the study group in
two subgroups: The newly diagnosed/persistent (0-3 and 3-12
months from diagnosis respectively) and the chronic group
(ITP lasting > 12 months).

The diagnosis of primary ITP was established by the pres-
ence of isolated thrombocytopenia (PLT < 100000/μL) in an
otherwise healthy child without any other possible cause of
secondary thrombocytopenia. All children were followed for
at least one year. The ‘watch and wait’ approach was applied
in a few cases. For the rest of the cases, treatment with IVIG
or corticosteroids was administered.

The study protocol was in accordance with the Helsinki
declaration and was approved by the Ethics Committee of the
hospital. Informed consent was given in advance from pa-
tients’ parents or legal guardians.

| Table 1: Demographic and clinical characteristics of the study population. |
|--------------------------|-------------------------------|
| Characteristic           | No (%), median(range)        |
| Age (months)             | 54 (1.4-180)                  |
| Sex                      |                               |
| Boys                     | 24 (53.33%)                  |
| Girls                    | 21 (46.67%)                  |
| Type of ITP              |                               |
| Acute ITP                | 39 (86.67%)                  |
| Chronic ITP              | 6 (13.33%)                   |
| Transient ITP            |                               |
| ITP remission            | 33 (73.33%)                  |
| ITP relapse              | 12 (26.66%)                  |

Statistical Analysis

Stata for windows (StataCorp. 2009. Stata Statistical
Software: Release 11. College Station, TX: StataCorp LP) was
used for statistical computation. Data are presented as actual
numbers (proportions) for categorical variables and median
(interquartile range) for continuous variables. Comparisons
between groups were assessed with Fisher’s exact test for
categorical variables and the Mann-Whitney U test for con-
tinuous variables. In order to preserve the familywise error-rate
p < 0.004 was considered statistically significant.

Results

The study group consisted of 45 children (24 boys) with
median age 54 (1.4-180) months. According to new nomen-
clature 39/45 (86.7%) children were characterized as newly
diagnosed/persistent cases and 6/45 (13.3%) children exhib-
ted thrombocytopenia for > 12 months (chronic ITP) (cITP)
(Table 1). In the newly diagnosed/persistent subgroup 19 pa-
tients (49%) were boys and 20 (51%) patients were girls while
in the chronic subgroup 5 patients (83%) were boys and 1 pa-
tient (17%) was a girl.

The patients’ median age was 54 (1.4-180) months distrib-
uted as 35 below 10 years of age and the remaining 10 being
exact 10-year-old or older. The median age of the subgroup
of newly diagnosed/persistent disease was 54 (1.4-180) months.
The median age of the subgroup of chronic disease was 75
(36-168) months. Comparison of the two subgroups revealed
that first manifestation of thrombocytopenia at an older age
was linked to development of chronic disease but these re-
results lacked statistical significance (Table 2). There was a ten-
dency for greater proportion of eosinophils in patients with
cITP compared to those with newly diagnosed/persistent ITP
at the first presentation of the disease (Table 2).

Recent previous vaccination was recorded in 6 out of 45
patients (13%) and infection in 26 out of 45 patients (58%)
respectively. Most of the post-infection cases of ITP belonged
to the newly diagnosed/persistent ITP group (23/39, 59%).
The majority of cases occurred during spring. For the types of
hemorrhagic manifestations we found that 26 among 45
(26/45) (58%) exhibited only ecchymoses while 19/45 (42%)
patients had mucosal bleeding. The majority of patients with minor bleeding phenomena belonged to the newly diagnosed/persistent subgroup (24/39, 61.5%) (Table 2). The patients with severe mucosal bleeding belonging to the newly diagnosed/persistent group were 15/39 (38.5%) and those of the chronic ITP group were 4/6 (67%). No patients manifested life-threatening hemorrhage. Initial baseline immunological profile and fundoscopy were negative for all patients in both study subgroups. None of the patients received a diagnosis of malignancy while one patient received a diagnosis of systemic lupus erythematosus within 2 years from the first manifestation of ITP. After parents’ information of the therapeutic options, the ‘watch and wait’ approach was applied in 9/45 (20%) of the patients while the rest 36/45 (80%) had been treated with either IVIG or corticosteroids at the time of diagnosis. The latter percentage was much higher than expected according to guidelines. No one of the patients (9/45) included in the ‘watch and wait’ practice needed any kind of treatment during follow up.

**Discussion**

The aim of the present study was to evaluate the clinical course and characteristics of the disease along with initial laboratory evaluation and the compliance of treating physicians to the ‘watch and wait’ practice based on the new guidelines [2].

According to age and chronicity, younger children exhibited shorter duration of the disease after the first manifestation of thrombocytopenia. The median age of the patients belonging to newly diagnosed/persistent subgroup was 54 (1.4-180) months and in patients with chronic ITP the median age was 75 (36-168) months. This is in accordance with previous reports from the Intercontinental Childhood ITP Study Group where children above 10 years of age were more likely to suffer from chronic ITP [7,8]. Male gender predominated in chronic cases of ITP. A meta-analysis from Heitink-Pollé, et al. reported that the female gender predominated in cITP stud-

| Characteristic                  | Newly diagnosed/persistent ITP (n = 39) | chronic ITP (n = 6) | p value |
|--------------------------------|----------------------------------------|--------------------|---------|
| Age (months)                   | 54 (1.4, 180)                          | 75 (36, 168)       | 0.28*   |
| Sex (boys),                    | 19 (48.72%)                            | 5 (83.33%)         | 0.126** |
| WBC (c/μL)                     | 10000 (4730, 18200)                    | 8250 (2600, 16200) | 0.5*    |
| EO (c/μL)/%                    | 2.15 (0, 11)                           | 4 (3, 8)           | 0.025*  |
| PLT (c/μL)                     | 7000 (200, 86000)                      | 5500 (2000, 41000) | 0.87    |
| PLT < 10000 c/μL               | 25/(64.1%)                             | 4 (66.67%)         | 0.642** |
| Hgb (gr/dL)                    | 12.4 (8.7, 15.1)                       | 12.7 (10.6, 13)    | 0.76    |
| Hct (%)                        | 37.2 (26.2, 46.9)                      | 38.1 (31.9, 39.5)  | 0.77    |
| Mucosal bleeding               | 15 (38.5%)                             | 4 (66.67%)         | 0.195** |
| Vaccination                    | 5 (12.8%)                              | 1 (16.67%)         | 0.609** |
| Infection                      | 23 (59%)                               | 3 (50%)            | 0.476** |
| Spring season                  | 14 (35.9%)                             | 3 (50%)            | 0.407** |

*Mann-Whitney U-test; **Fisher’s exact test.

**Table 2: Characteristics of children with newly diagnosed/persistent ITP vs children with chronic ITP on initial assessment.**

An increase of the initial percentage of eosinophils in cases which have been evolved to cITP was noted (Table 2). Noteworthy is that no patient with eosinophilia had a history of atopy or recent use of any medication. It seems that the degree of eosinophilia at first presentation might be related with chronicity. A possible explanation could be an ongoing antibody dependent cell-mediated cytotoxicity which through IL-9, IL-13 and IL-15 indirectly induces eosinophilia.

An extended initial immunological evaluation did not have a significant prognostic role for the duration of the disease, as we did not find differences between the two subgroups of patients. We recommend against extended immunological testing at the time of diagnosis. This is in line with previous reports and emphasizes the need for further immunological evaluation only in chronic or atypical cases of ITP [9].

No one patient had clinical findings suggestive of malignancy during the study period and the need for bone marrow aspiration is doubted even in cases where treatment with corticosteroids must be started. This is in accordance with previous reports [10-12].

We found that the majority of cases occurred during spring. We do not have an explanation of this seasonal variation. Larger studies are necessary to clarify this observation. A preceding viral illness was reported in 26/45 (58%), mostly in the subgroup of newly diagnosed/persistent cases (23/39-59%). The most common preceding infection was influenza infection. All patients of the study group had been tested for influenza with PCR and 22 got a positive result (20 from the newly/persistent group and 2 from the chronic group). Eighteen patients received treatment with oseltamivir. Our findings are in line with previous reports where a viral infection is more often linked to newly diagnosed/persistent ITP with a short duration and quick resolution of thrombocytopenia without severe bleeding [2,5,6,8]. Additionally, there was a
tendency of relapse in cases presented during spring. A preceding influenza infection was reported in 5/12 relapsed cases. To our knowledge this is the first time to report a possible seasonal correlation with the recurrence of the disease.

A previous vaccination history was reported in 6/45 (13.3%) of our patients. As in other reports, thrombocytopenia occurred 2-3 weeks after the first dose of vaccination (MMR - 5 cases, Hepatitis A 1 case) and resolved spontaneously within a few weeks [13]. All subjects’ immunization schedules had been checked and only 6 of them had a vaccination 2-3 weeks before overt manifestation of thrombocytopenia and no one of them reported any hematological problem in the past. We emphasize the need of vaccination since the risk of complications especially from measles is much higher than the risk of post-vaccination thrombocytopenia.

The bleeding phenomena were more severe in the subgroup of chronic ITP according to our results. Patients with chronic ITP were more likely to exhibit mucosal bleeding at the time of diagnosis in contrast to newly diagnosed/persistent patients that exhibited mainly petechiae and ecchymoses. Some previous papers reported that the more severe the bleeding the shorter the duration of the disease [5,6,8]. The difference in our results could be explained by the small size of the study group. We did not have life-threatening hemorrhages even in children with extremely low platelet counts (< 10000 c/μL). Our results are in line with previous reports highlighting the fact that the severity of thrombocytopenia is not the only thing that matters in terms of bleeding risk stratification and medical intervention [14]. The latter is well established from large studies and in the last decade there was a significant shift towards the “watch and wait” approach especially in the UK [10,15,16].

Unfortunately the “watch and wait” approach is difficult to apply, as there are main issues such as parental stress and medical liability. Our results are in accordance with reports from the United States as far as treatment is concerned. In details, a much higher percentage 36/45 (80%) than expected according to guidelines, received treatment at the time of diagnosis. No one of the patients (9/45) included in the ‘watch and wait’ practice needed any kind of treatment during follow up. According to UK treatment criteria based not only on the platelet count but also on the severity of bleeding, a significant percentage of our study group could have been remained untreated as only 19/45 (42.2%) displayed mucosal bleeding and 29/45 (64.4%) firstly presented with extremely low number of platelets (< 10000 c/μL). In accordance with our study a previous study from Kühne, et al. reported the same percentage (20%) of newly diagnosed children being observed without treatment [17]. In favor of the above “watch and wait” practice is the report from Heitink-Polle, et al. which demonstrated no significant difference in the rate of cITP development between the untreated and the IVIG-treated patients [18]. The fact that we did not reach the desirable percentage of “watch and wait” cases could be attributed mainly to the lack of expert education of the medical staff on this topic. We came across doctors who were unwilling to recognize the need for the aforementioned practice. In those cases, it seems that the fear of legal problems overcomes any rational thought. When it comes to patients’ families, a thorough and detailed discussion with a well-educated practitioner on the treatment options, in most cases resulted in acceptance of the “watch and wait” practice. We need adequately prepared doctors, to discuss in a relaxed way with the families and try to persuade them for the value of the “watch and wait” strategy underscoring the possible side effects and the cost of an unnecessary treatment.

According to our institutional protocol initial baseline fundoscopy was performed and it was negative in all subjects. Even though the need for ophthalmological examination is very weak, it is difficult to avoid it in patients receiving IVIG and complaining of headache. In a study by Capua, et al. it was stated that routine fundoscopy is not obligatory in ITP patients without vision impairment. We absolutely agree, and we no longer perform fundoscopy during initial assessment [19].

Our study has several strengths and limitations as well. The strengths are the prospective design of the study along with the lack of loss of individuals to follow up. On the other hand the small size of the sample and the relatively short duration of the study are considered its main limitations.

Conclusions

In conclusion, ITP in children is a rather benign self-limiting disease. In the majority of cases thrombocytopenia lasts < 12 months especially in younger children with short duration of bleeding phenomena. Severe hemorrhage is very rare. Post-infection ITP seems to have a short duration and occur mainly during spring. An increased initial percentage of eosinophils might determine a higher chance of developing chronic ITP. Extended immunological work up, fundoscopy and bone marrow aspiration are not necessary for typical cases. The avoidance of unnecessary treatment was difficult task due to parental anxiety and to fear for legal issues from the practitioners. A further detailed discussion with the family could alleviate their concerns and increase the rate of acceptance of the ‘watch and wait’ practice in eligible cases. For this purpose, practitioners should be trained to answer family’s reasonable questions in a rather relaxed and not anxious way. Further larger and long-lasting studies are necessary to clarify our results. Overall ITP in children is still a diagnosis of exclusion with good outcome that needs individualized evaluation and approach.

Declarations

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Conflict of interest

Authors declare no conflict of interest.

Contribution of each co-author

Kosivis Lydia: Main investigator, responsible for the design of the study and the writing of the paper.

Tsentidis Charalambos: Responsible person for the statistical analysis.
Marinaki Maria: Responsible person for the collection of the specimens, demographic data and informed consent forms.

Douna Varvara: Hematologist responsible for the evaluation of the complete blood counts and peripheral blood and bone marrow aspirates aspirates hematologically.

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