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Anti-thyroid antibodies in children with immune thrombocytopenia

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To assess the prevalence of anti-thyroid antibodies (AB) in pediatric patients with immune thrombocytopenia (ITP). This cross-sectional study included 50 ITP cases recruited at the Hematology Unit of the Pediatric Department at Menoufia University Hospital, along with 50 healthy controls matched by age and sex. Laboratory tests included complete blood count, measurement of anti-thyroid AB (anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG)), lactate dehydrogenase (LDH) and serum fibrinogen. The study was approved by the Institutional Review Board (IRB) of the Menoufia Faculty of Medicine (approval ID number: 4/2020PEDI12). Research was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients' parents and caregivers after explaining all aspects of the study, with the right to withdraw at any time. TPO and TG antibody levels were significantly higher in the cases than in the controls (p-value = 0.001). The chronic ITP cases showed significantly higher TPO and TG AB levels than the newly diagnosed ITP patients (p-value = 0.001). There was no significant difference between males and females in terms of anti-TPO levels (p-value > 0.05). A significant negative correlation was found between anti-TPO levels and LDH levels (r = –0.0326, p-value = 0.021) and a significant positive correlation – between anti-TPO levels and TG antibody levels (r = 0.360, p-value = 0.01). TG and anti-TPO AB levels were elevated in the children with ITP, particularly in cases of chronic ITP, with the cut-off point for chronicity being > 12.8 for anti-TPO and > 11.8 for TG antibodies.

Key words: *anti-thyroid peroxidase, thyroglobulin antibody, autoimmune thyroiditis, children, immune thrombocytopenia*

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Primary immune thrombocytopenia (ITP) is an autoimmune disorder characterized by elevated risk of bleeding and a low platelet count (< 100 × 10^9/L). The cause of ITP is typically unknown; however, it may be triggered by a viral infection, vaccination, environmental or other immunologic factors [1]. Previously known as idiopathic thrombocytopenic purpura, the current term "immune thrombocytopenia", while still abbreviated as "ITP", now acknowledges the immune-mediated mechanism of the disorder and the possibility that patients may exhibit minimal or no signs of bleeding or purpura [2]. ITP is divided into three phases according to the timing and duration of symptoms. The term "newly diagnosed ITP" is defined as the disease within 3 months of diagnosis. Persistent ITP is diagnosed when thrombocytopenia persists for 3 to 12 months, while chronic ITP lasts beyond 12 months, with but a small chance of definitive resolution [3]. The standard terminology and definitions for ITP were created by the International Working Group of expert clinicians [4].

Corticosteroids are generally recommended as first-line treatment for ITP but response rates may drop during tapering or following drug discontinuation. Patients who do not achieve sustained response to corticosteroids require additional therapy. Anti-D (anti-Rh) globulin and intravenous immune globulin are also used for first-line management of the disease. The second line of treatment for chronic ITP includes splenectomy, thrombopoietin receptor agonists (e.g., eltrombopag and romiplostim) and rituximab [5].

Secondary ITP is linked to an underlying illness whereas primary ITP is considered idiopathic. Despite limited research, the incidence of secondary ITP in children is expected to be low. Secondary ITP may be caused by systemic autoimmune diseases, secondary or primary immunodeficiencies, paraneoplastic syndromes (including malignancies and lymphomas), viral diseases, and drug-dependent antibodies (AB) [6].

As previously mentioned, autoimmunity may be induced by infectious diseases and vaccination. This holds true for primary ITP in children, as it can also be triggered by infections such as HIV, Helicobacter pylori, varicella-zoster and hepatitis C viruses, as well as by a combined measles, mumps, rubella vaccine [7].

In the study by P. Giordano et al., significantly higher prevalence of anti-thyroid AB, including anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG), was registered in the pediatric patients with chronic ITP than in the healthy controls. Despite this finding, there is a lack of conclusive data regarding the prognostic role of autoimmune thyroiditis in chronic ITP patients. There have been reports of ITP concurrent with positive anti-platelet AB, combined with decreased serum thyroid-stimulating hormone (TSH) concentrations and the presence of anti-TSH receptor AB [8].

MATERIALS AND METHODS

This cross-sectional study included 50 cases with ITP (23 females and 27 males, aged 2.5 to 13 years old) who had been recruited at the Hematology Unit of the Pediatric Department at Menoufia University Hospital, along with 50 healthy controls matched by age and gender. The study was approved by the Institutional Review Board (IRB) of the Menoufia Faculty of Medicine (approval ID number: 4/2020PEDI12). Research was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients' parents and caregivers after explaining all aspects of the study, with the right to withdraw at any time.

Inclusion criteria: pediatric patients with ITP with a platelet count of < 100×10^9/L and an increased risk of bleeding as defined by the American Society of Hematology. ITP was classified as newly diagnosed, persistent and chronic.

Exclusion criteria: ITP due to other factors such as sepsis, infection, drugs, ITP secondary to other conditions (systemic lupus erythematosus, Evans syndrome), post-vaccination ITP, ITP following treatment of autoimmune lymphoproliferative syndrome, active life-threatening bleeding at the time of recruitment.

All the participants underwent a clinical examination, detailed history-taking and laboratory tests including measurements of anti-thyroid AB (TPO and TG), serum fibrinogen and lactate dehydrogenase (LDH), as well as complete blood count (CBC).

Samples were collected using aseptic venipuncture technique and divided into four parts. One part was placed in a tube with dipotassium ethylenediaminetetraacetic acid (K2-EDTA) for a CBC. A second portion of the sample was added into a tube with sodium citrate and used to measure plasma fibrinogen levels. A third portion was put in a plain vacutainer tube, allowed to clot, and then centrifuged to obtain serum for LDH measurement. The remaining portion was also placed in a plain vacutainer tube, allowed to clot, and then centrifuged at 3000 rpm for 10 minutes. The separated sera were stored at –20°C until testing (an evaluation of TPO and TG AB).

In our study, we used the following systems and equipment: 1. The automated Sysmex XN-1000 hematology analyzer (Sysmex Corporation, Kobe, Japan) for CBC. 2. The STA compact coagulation analyzer (Diagnostica Stago, Asnières, France) for plasma fibrinogen measurement using the Clauss method. 3. The AU680 chemistry analyzer (Beckman Coulter Inc, Brea, California, USA) for serum LDH measurement. 4. Electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany) for the determination of TPO-TG AB.

Statistical analysis

The data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS) version 22 (SPSS, Inc., Chicago, Illinois, USA) on an IBM personal computer. Quantitative data were analyzed using mean, standard deviation (SD), range, and percentages, while for qualitative data we employed numbers and percentages. The chi-square test was used to investigate the correlation between two qualitative variables. The non-normally distributed quantitative variables were compared using the t-test. The Mann-Whitney test was used to compare the two groups with non-normal distribution and quantitative variables. Spearman's correlation (r) was used to determine the correlation between two quantitative variables. We also plotted ROC curves which are a graphical representation of the relationship between specificity and sensitivity of a diagnostic test at various cut-off points. A p-value of < 0.05 was set as the significance level.

RESULTS

Hemoglobin levels, serum fibrinogen, reticulocyte count, platelet count, and plateletcrit were considerably lower in the cases than in the controls. MPV and PDW were significantly higher in the cases than in the controls, as shown in *table 1*. In the studied groups, anti-thyroid AB, namely, AB to TG and anti-TPO AB, were significantly higher in the cases than in the controls, as displayed in *table 2*. There was a significant negative correlation between anti-TPO and LDH levels and a significant positive correlation between anti-TPO and TG AB levels in the studied cases, as demonstrated in *figure 1*. At a cutoff point of > 12.8 IU/ml, anti-TPO AB test had a sensitivity of 91% and a specificity of 78% in detecting children with chronic ITP. Additionally, at a cutoff point of > 11.8 ng/ml, TG antibody test had a sensitivity of 82% and a specificity of 68%, as displayed in *table 3* and *figures 2A, B*.

DISCUSSION

Autoimmune hemolytic anemia, antiphospholipid syndrome, systemic lupus erythematosus, Hashimoto's thyroiditis, and Graves' disease can all be associated with ITP [9]. Anti-thyroid AB (anti-TPO and anti-TG) have been reported to be positive in 18% to 36% of patients with ITP. The relationship between subsequent development of autoimmune thyroiditis such as Hashimoto's thyroiditis and the positivity for anti-thyroid AB,

as well as the potential impact on the outcome of ITP remain unclear [10, 11].

We conducted this study to assess the prevalence of anti-thyroid AB in pediatric ITP patients and their correlation with disease progression. The studied patients were matched by age and gender, with a slight male predominance (54%) that was consistent with the study by Mohammed et al. (2022) [12] who had discovered that the majority of the cases under investigation were male. Badrawy et al. (2013) [13] also discovered male predominance in newly diagnosed ITP patients, while Makis et al. (2017) [14] found that ITP affected both genders equally. In contrast to our study, Eyada et al. (2012) [15] discovered female predominance among the children diagnosed with ITP. At the same time, Donato et al. (2009) [16] observed that patients under two years old were mostly male.

The median age in our study was five years, consistent with the findings of Ahmed et al. (2004) [17], and Makis et al. (2017) [14].

In our study, 30% of the patients experienced mucosal bleeding, which coincided with the findings of Al-Zuhairy (2013) [18] who had reported that petechiae and/or bruising were the most common clinical signs among the ITP patients (92%), followed by epistaxis (44%) and oral hemorrhage (32%).

As for bleeding grades, 21 (42%) patients experienced grade II bleeding and 29 (58%) patients – grade III bleeding. This is consistent with the results of Mohammed et al. (2022) [12], who had found that all the cases had cutaneous bleeding, with 47.4% exhibiting epistaxis and 57.9% – gingival bleeding. Grade I bleeding was experienced only by three (6%) patients, grade II – by 25 (52%) cases, and grade III – by 20 (43%) cases. Makis et al. (2017) [14] reported that 70% of the sample population of 43 children experienced mucosal bleeding, 2 patients had conjunctival bleeding, and 1 struggled with menorrhagia; however, no hepatosplenomegaly was observed.

In terms of ITP classification, 28 patients had newly diagnosed disease, while 22 patients (44%) had chronic ITP. Consistent with Mohammed et al. (2022) [12], about 40% of the cases had acute disease, 37.5% had chronic and 22.9% had persistent ITP. Similarly, Bay et al. (2013) [19] discovered that 51.7% of the

Table 1
A comparison of demographic data and laboratory findings in the studied groups

Variable	The cases (*n* = 50)	The controls (*n* = 50)	Test of sig.	*p*-value
Age, years: mean ± SD median (range)	5.76 ± 2.71 5 (2.50–13.0)	6.31 ± 2.76 6 (3.00–13.0)	U 1.17	0.242
Sex, *n* (%): male female	27 (54.0) 23 (46.0)	26 (52.0) 24 (48.0)	χ^2 0.040	0.841
Hb, gm/dl: mean ± SD median (range)	10.8 ± 0.64 10.7 (10.0–13.0)	12.6 ± 0.85 12.7 (11.0–13.8)	U 7.73	**0.001***
TLC, × 10^3: mean ± SD median (range)	7.18 ± 0.81 7.05 (5.90–9.10)	6.94 ± 1.77 6.75 (4.00–10.8)	U 1.57	0.116
Reticulocyte, %: mean ± SD median (range)	1.31 ± 0.37 1.3 (0.70–2.10)	1.65 ± 0.36 1.6 (1.00–2.50)	U 3.98	**0.001***
MPV, fl: mean ± SD median (range)	13.4 ± 0.83 13.5 (11.8–16.1)	9.27 ± 0.88 9.30 (7.50–10.9)	t-test 24.3	**0.001***
PDW, %: mean ± SD median (range)	18.2 ± 2.09 18 (14.2–25.1)	12.3 ± 1.30 12 (10.5–14.7)	U 8.57	**0.001***
Platelet count, × 10^3: mean ± SD median (range)	31.0 ± 7.11 30 (20.0–60.0)	258.5 ± 73.5 255 (160–452)	U 8.62	**0.001***
Plateletcrit, %: mean ± SD median (range)	0.03 ± 0.03 0.02 (0.02–0.25)	0.23 ± 0.04 0.23 (0.17–0.31)	U 8.38	**0.001***
LDH, mg/L: mean ± SD median (range)	274.5 ± 103.0 273 (110.0–537.0)	160.8 ± 49.2 122 (115.0–234.0)	U 5.57	**0.012**
Fibrinogen, mg/dl: mean ± SD median (range)	73.7 ± 57.0 50 (15.0–215.0)	273.6 ± 56.9 270 (200.0–380.0)	U 8.49	**0.001***
Anti-TPO, IU/ml: mean ± SD median (range)	17.0 ± 12.9 13.5 (1.80–41.1)	5.40 ± 2.23 5.5 (1.80–8.90)	U 4.95	**0.001***
TG AB, ng/ml: mean ± SD median (range)	15.1 ± 11.8 11.8 (1.50–46.0)	7.56 ± 3.09 7.2 (3.90–13.2)	U 3.87	**0.001***

*Notes. U – Mann–Whitney test; χ^2 – a chi-square test; HB – hemoglobin; TLC – total leukocyte count; MPV – mean platelet volume; PDW – platelet distribution width; * – significant.*

Table 2
A comparison of anti-TPO and TG AB between the newly diagnosed and chronic ITP cases

Studied variables	Cases (*n* = 50)		Test of sig.	*p*-value
	Newly diagnosed (*n* = 28)	Chronic (*n* = 22)		
Anti-TPO, IU/ml: mean ± SD median (range)	8.25 ± 5.36 7.10 (1.80–19.0)	28.2 ± 10.8 33.5 (9.10–41.1)	U 5.18	0.001*
TG AB, ng/ml: mean ± SD median (range)	9.07 ± 4.19 8.75 (1.50–21.5)	22.9 ± 13.9 19.3 (5.50–46.0)	U 3.97	0.001*

*Notes. U – Mann–Whitney test; * – significant.*

Table 3
Sensitivity and specificity of TPO and TG antibody tests in detecting children with chronic ITP

Studied variable	AUC	*p*-value	Cut-off point	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
Anti-TPO	0.930	0.001	> 12.8	91	78	77	91.6	84
TG AB	0.830	0.001	> 11.8	82	68	67	83	74

Notes. AUC – area under the curve; PPV – positive predictive value NPV – negative predictive value.

151 ITP patients were newly diagnosed with acute ITP, while 48.3% were chronic.

Eltrombopag was administered in 22 (46%) patients, high-dose dexamethasone – in 15 (30%) patients, and oral prednisolone – in 13 (24%) patients.

We discovered that platelet count and hemoglobin levels were significantly lower in the cases compared to the controls. In view of the subclinical bleeding observed in the ITP patients, particularly those with chronic disease, MPV and PDW levels were significantly higher in the cases than in the controls. This is in line with the results of Tantawy et al. (2010) [20] who discovered that the total white blood cell and platelet counts and mean hemoglobin levels were significantly lower in all the ITP groups than in the healthy controls. These data are inconsistent with the findings of Mohammed et al. (2022) [12] who reported that mean platelet count at diagnosis was 12.42 × 10^9/L and that there was no statistically significant difference in hemoglobin levels between the cases and controls.. Similarly, Al-Zuhairy (2013) [18] reported the mean platelet count of 13.2 × 10^9/L. Conversely, Makis et al. (2017) [14] demonstrated that the mean platelet count in recently diagnosed ITP patients was 5.5 × 10^9/L.

This finding was consistent with the fact that plateletcrit was substantially lower in the cases than in the controls. Arshad et al. (2021) [21] observed that the cases had a lower platelet count than the controls.

LDH levels were not significantly higher in the cases compared to the controls but fibrinogen levels were significantly lower in the cases. This is in line with the findings of Velik-Salchner et al. (2007) [23] who demonstrated that the functional consequences of thrombocytopenia can be mitigated by administering fibrinogen concentrate. Since fibrinogen is essential for coagulation activity and the binding of FXIII required for clot stabilization, the cases with higher fibrinogen levels were less prone to hemorrhagic complications. Furthermore, fibrinogen plays a vital role in platelet activation and aggregation by binding to the platelet glycoprotein GPIIb/IIIa receptor. In contrast, Álvarez-Román et al. (2016) [24] found fibrinogen levels to be normal in both the healthy adults and the cases with ITP.

Both TPO and TG AB levels were significantly higher in the cases than in the controls, with the chronic cases also having much higher AB levels than the newly diagnosed ones. This finding is in line with the results of Bay et al. (2013) [19] who discovered a higher prevalence of these autoantibodies in the ITP cases. However, the prevalence of anti-thyroid AB did not differ significantly between the chronic and the recently diagnosed ITP cases.

A number of mechanisms that link thyroid diseases and thrombocytopenia have been identified. Hyperthyroidism is associated with genetic predisposition, increased expression of T-lymphocyte-associated antigen 4 (a T-cell surface molecule involved in the control of T cell proliferation), immune dysregulation, and elevated reticuloendothelial phagocytic activity. Additionally, the platelet lifespan is reduced [25].

Contrary to our results, Giordano et al. (2019) [8] found positive anti-thyroid AB in 11.6% of the study patients with chronic ITP and did not observe any correlation between the prevalence of positive anti-thyroid AB and platelet count. Mohammed et al. (2022) [12] reported that none of the patients had abnormal thyroid

Figure 1
A correlation between anti-TPO and LDH levels and between anti-TPO and TG AB levels in the studied cases

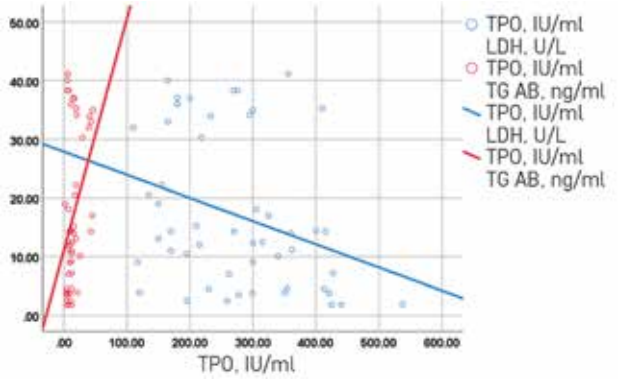
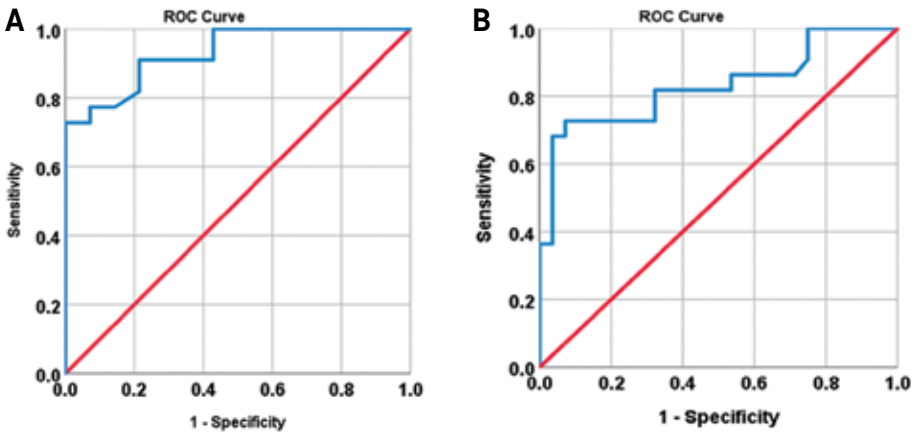


Figure 2
A – an ROC curve: sensitivity and specificity of anti-TPO testing in detecting children with chronic ITP; B – an ROC curve: sensitivity and specificity of TG AB testing in detecting children with chronic ITP



function or abnormal anti-thyroid AB levels during their study.

We demonstrated a significant negative correlation between TPO and LDH levels. A significant positive correlation was observed between TPO and TG antibody levels. In the cases, no significant correlations were found either between TPO levels and other laboratory findings or between TG antibody levels and other laboratory results.

We found that anti-TPO test had a sensitivity of 91% and a specificity of 78% in detecting children with chronic ITP at a cut-off point of > 12.8.

Our study was the first one to investigate the possibility of using thyroid AB to predict ITP in children. We discovered that TG antibody test had 82% sensitivity and 68% specificity at a cut-off of > 11.8.

CONCLUSION

Elevated TPO and TG antibody levels were observed in children with ITP, especially in those with chronic ITP. A cut-off point of > 12.8 for anti-TPO and > 11.8 for TG AB were used to determine chronicity.

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CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

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