Gender-related analysis of the clinical presentation, treatment response and outcome in patients with immune thrombocytopenia

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Résumé

Analyse en fonction du genre sexuel de la présentation clinique et de l’évolution d’une thrombopénie immune (purpura thrombopénique idiopathique)

Contexte > La thrombopénie immune anciennement dénommée « purpura thrombopénique idiopathique » (PTI) se produisait fréquemment chez les jeunes adultes, particulièrement les femmes dans leur troisième ou quatrième décennie. La prédominance féminine suggère que les hormones sexuelles pourraient jouer un rôle dans les différents aspects du PTI. Dans ce travail nous réalisons une analyse de l’impact du genre sexuel sur les manifestations cliniques du PTI et la réponse au traitement. Méthodes > L’analyse était rétrospective. Elle incluait l’impact du genre sexuel sur la présentation clinique, la réponse au traitement et les résultats chez 225 patients consécutifs.

Summary

Background > Immune thrombocytopenia (idiopathic thrombocytopenic purpura [ITP]) frequently occurs in young adults, particularly women in their third or fourth decade. The female predominance suggests that sex hormones may play a role in the different aspects of ITP. In this paper, we report a gender-related analysis of patients with ITP, specifically examining the clinical manifestations, responses to treatment and overall outcomes of the patients.

Methods > We included patients with “ITP” attending the departments of onco-hematology or internal medicine B (university hospital of Strasbourg, France) between 1990 and December 2010 The gender-related analysis was retrospective.

Results > We studied in 225 consecutive cases of established ITP with a follow-up period of 1.7 to 12 months The mean age of the patients was 44 years; 156 patients were female.
présentant un PTI documenté, et suivis sur une période de 1,7 à 112 mois, à l’hôpital universitaire de Strasbourg, France.

Résultats > L’âge moyen des patients était de 44 ans ; plus des deux tiers (n = 156) étaient des femmes. L’analyse n’a révélé aucune différence statistique significative pour les caractéristiques cliniques entre les groupes féminin et masculin, à l’exception des éléments suivants : le score de saignement, qui est modifié, par la présence plus fréquente de meno-et/ou des métrorragies et d’hématurie chez les femmes (p = 0,03), la présence d’une anémie (p = 0,04) et la détection des anticorps antinucléaires et/ou des anticorps antiphospholipides (p = 0,02). Au cours du suivi, aucune différence statistiquement significative n’a été trouvée dans le résultat ou la réponse au traitement pour les 225 patients en fonction de leur sexe (tous les p > 0,05).

Discussion > Il ne semble pas y avoir d’effet du genre sexuel sur le tableau clinique du PTI, l’évolution ou la réponse au traitement. Toutefois, d’autres grands essais randomisés sont nécessaires pour confirmer ces résultats.

What was known

- Immune thrombocytopenia idiopathic thrombocytopenic purpura (ITP) occurs mainly in young adults, particularly women in their second or third decade, with an overall female to male ratio of 2 to 1, suggesting that sex hormones play a role in the susceptibility to ITP.
- To date, no specific work has studied the impact of gender on the clinical presentation, outcome and treatment response in patients with ITP.

What this study adds

- We analysed 225 patients with ITP.
- We observed no significant differences in patient characteristics between the female and male groups, except for the ITP bleeding score, which altered in the presence of meno- and/or metrorrhagia and hematuria in female patients (p = 0.03); the presence of anemia, with a statistically significant difference in documented cases of anemia (p = 0.04); and the detection of antinuclear and/or antiphospholipid antibodies (p = 0.02).
- During follow-up, no statistically significant difference was found regarding outcomes or treatment responses in relation to patient gender (all p > 0.05).

Immune thrombocytopenia, also known as ITP, is an autoimmune disorder that results in acute or chronic thrombocytopenia and that may potentially lead to a life-threatening hemorrhagic event [1,2]. Despite major advances in our understanding of the pathophysiology of ITP (evidence of anti-platelet antibodies and the relative failure of bone marrow platelet production) [1–3], the diagnosis of ITP still is based on exclusion [1,2]. While ITP in childhood is usually an acute, self-limiting condition (the thrombocytopenia is transient and recovers spontaneously despite an initially severe presentation) [1,4], ITP is more often a chronic disease in adults with an insidious onset requiring multiple therapeutic approaches [5,6]. ITP frequently occurs in young adults, particularly women in their third or fourth decade, with an overall female to male ratio of 2 to 1. These figures suggest that sex hormones may play a role in the susceptibility to ITP [7]. In addition to having an impact on the immune system, sex hormones may also alter the clinical picture and response to therapy. However, to date, no studies are available to confirm these theories. We report a gender-related analysis of the clinical manifestations, treatment responses and outcomes in patients with ITP.

Methods

Patient selection

We searched the Strasbourg university hospital database for all patients attending the departments of onco-hematology or
internal medicine B with ITP between 1990 and December 2010. Some of these data have previously been reported [8]. All patients with established ITP were included. The diagnosis of ITP was based on the existence of a peripheral thrombocytopenia with a normal bone marrow examination (normal or increased numbers of megakaryocytes); all other potential causes of thrombocytopenia were excluded [9,10]. Each patient had a platelet count of $<150 \times 10^9/L$ on at least two consecutive blood counts in the absence of other clinical or biological findings to explain the thrombocytopenia. We excluded cases of non-idiopathic immune thrombocytopenia [8–10], such as thrombocytopenia induced by drugs, infectious agents, or related to other diseases (e.g., systemic lupus erythematosus, antiphospholipid syndrome and/or lymphoma or myelodysplasia). Children less than 15 years of age were also excluded.

Study procedure
The study was a retrospective gender-related analysis. The data analyzed were collected from the patient’s notes. Information was also obtained from family members and general practitioners. For each patient, the following data were verified independently by two members of the monitoring committee: age, gender, clinical characteristics, bleeding score [11], full blood count and bone marrow examination, antinuclear and antiphospholipid antibody status, response to therapy, outcome and mortality rate.

The patients were retrospectively divided to two groups (male or female), and the data analysis was carried out according to gender.

Response criteria
The criteria defining the response to treatment were:

- a complete response (CR) was defined as a platelet count that rose to a normal level (platelet count $>150 \times 10^9/L$) after treatment;
- a partial response (PR) was defined as a platelet count of 50 to 150 $\times 10^9/L$;
- treatment failure (F) was defined as a platelet count below 50 $\times 10^9/L$ [12].

Patients whose initial platelet count was $<50 \times 10^9/L$ were considered to have a PR if the number of platelets was two fold higher after treatment. We did not use the response criteria according to the current guidelines because of the retrospective nature of the present work.

Statistical analysis
Data were expressed as the mean and standard deviation (±SD) and were analyzed using the Pearson’s Chi² test and Fisher’s exact test. A $P$ value $<0.05$ was considered to be statistically significant.

Results

Patient characteristics
Two hundred and fifty patients had an ITP. We excluded 25 patients: 18 cases of non-idiopathic immune thrombocytopenia, and 17 children. We analyzed 225 consecutive cases of established ITP followed up over a period of 1.7 to 112 months. All patients except for one were Caucasian; their mean age was 44 ± 18.2 years (range, 15–82); 156 were female (table 1).

Our analysis revealed statistically significant differences regarding the patient characteristics between the female and male groups with two exceptions: the bleeding score (which was altered in the presence of meno- and/or metrorrhagia and hematuria in female patients) and the detection of antinuclear and/or antiphospholipid antibodies ($P = 0.03$ and $P = 0.02$, respectively).

The initial presentation included bleeding diathesis in 108 patients (48%) and thrombocytopenia, which was detected on a routine full blood count in the remaining 117 subjects (52%). Bleeding was limited to the skin in 48 patients (21.3%), while in 51 patients (22.7%), cutaneous hemorrhages were accompanied by bleeding at one or more other sites. Only nine patients (4%) presented with bleeding solely in non-cutaneous sites. Bleeding sites other than the skin included epistaxis ($n = 28$), meno- and/or metrorrhagia ($n = 28$), hematuria ($n = 8$), rectorrhagia ($n = 3$), conjunctival hemorrhage ($n = 3$), mild hemoptysis ($n = 2$) and hematemesis ($n = 2$).

The presence of a potentially life-threatening platelet count was detected in 39 patients, with no statistically significant difference between the groups.

The mean hemoglobin level among these 225 patients was $12.2 \pm 2.5$ g/dL (range, 8.2–14.7), with a statistically significant difference in documented cases of anemia: 11 patients (7%) in the female group versus three patients (4.3%) in the male group ($P = 0.04$).

Antinuclear and antiphospholipid antibodies were analyzed in 140 patients and were positive in 34 (24.3%) patients. These antibodies were found significantly more frequently in females: in 22 (64.7%) females versus 12 (35.3%) males ($P < 0.02$).

Follow-up and outcome
The follow-up period for all patients ranged between 1.7 and 112 months. During this period, 82 patients (36.5%) were cured definitively (CR or complete response), either spontaneously or after first-line therapy, including steroids or intravenous immunoglobulins. Moreover, 62 patients (27.5%) were also cured definitively (CR group) with second-line therapy – either a splenectomy ($n = 62$) and/or rituximab administration ($n = 5$).

Conversely, 58 patients (25.8%) required long-term therapy (regular, chronic treatment including steroids, danazol) because of chronic ITP with recurrent bleeding episodes
TABLE I
Gender-related analysis of clinical and biological presentations in 225 patients with idiopathic thrombocytopenic purpura (ITP)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 225)</th>
<th>Females (n = 156)</th>
<th>Males (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age at initial diagnosis of ITP (years)</strong></td>
<td>46 ± 18.2</td>
<td>45.2 ± 24.7</td>
<td>47.8 ± 21.4</td>
</tr>
<tr>
<td><strong>Presentation of ITP</strong></td>
<td></td>
<td></td>
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<tr>
<td>Thrombocytopenia revealed by routine full blood count</td>
<td>117 (52%)</td>
<td>82 (52.5%)</td>
<td>35 (50.7%)</td>
</tr>
<tr>
<td>Thrombocytopenia revealed by a bleeding diathesis</td>
<td>108 (48%)</td>
<td>74 (47.5%)</td>
<td>34 (49.3%)</td>
</tr>
<tr>
<td><strong>Mean bleeding score from Khellaf et al. [11]</strong></td>
<td>11.6 ± 4.2</td>
<td>13 ± 6.3</td>
<td>8.4 ± 4.1</td>
</tr>
<tr>
<td><strong>Mean platelet count (× 10^9/L)</strong></td>
<td>42.6 ± 15 (range: 1–131)</td>
<td>44.5 ± 19 (range: 1–131)</td>
<td>38.4 ± 14 (range: 1–131)</td>
</tr>
<tr>
<td><strong>Presence of a potential life-threatening platelet count (platelet count &lt; 10 × 10^9/L)</strong></td>
<td>39 (17.3%)</td>
<td>28 (17.9%)</td>
<td>11 (15.9%)</td>
</tr>
<tr>
<td><strong>Presence of anemia (hemoglobin level &lt; 12 g/dL)</strong></td>
<td>14 (6.2%)</td>
<td>11 (7%)</td>
<td>3 (4.3%)</td>
</tr>
<tr>
<td><strong>Detection of antinuclear antibodies and/or antiphospholipid antibodies (immunofluorescence &gt; 1/80, IgG anticardiolipin antibodies &gt; 10 UGPL) (n = 140)</strong></td>
<td>34 (24.3%)</td>
<td>22 (64.7%)</td>
<td>12 (35.3%)</td>
</tr>
</tbody>
</table>

1Statistically significant difference.

TABLE II
Gender-related analysis of outcomes in 225 patients with idiopathic thrombocytopenic purpura (ITP)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 225)</th>
<th>Females (n = 156)</th>
<th>Males (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with CR or PR [7]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous response or after first-line therapy (steroids, IgIV)</td>
<td>82 (36%)</td>
<td>57 (37%)</td>
<td>24 (35%)</td>
</tr>
<tr>
<td>After second-line therapy (splenectomy, rituximab)</td>
<td>65 (29%)</td>
<td>44 (28%)</td>
<td>21 (30%)</td>
</tr>
<tr>
<td><strong>Patients with chronic ITP requiring long-term drug use (steroids, danazol, etc.) due to recurrent and chronic bleeding and/or low platelet counts</strong></td>
<td>58 (26%)</td>
<td>41 (26%)</td>
<td>19 (28%)</td>
</tr>
<tr>
<td><strong>Patients with chronic ITP and PR or F [7] managed with a “wait-and-see” policy and intermittent treatment</strong></td>
<td>20 (9%)</td>
<td>14 (9%)</td>
<td>5 (7%)</td>
</tr>
</tbody>
</table>

IgIV: intravenous immunoglobulin; CR: complete response (platelet count > 150 × 10^9/L after treatment); PR: partial response (platelet count of 50 to 150 × 10^9/L or platelet levels twofold higher after treatment if the initial platelet count was < 50 × 10^9/L); F: failure.

and/or low platelet counts. These patients were in either the PR or F group.
As shown in Table II, no statistically significant difference was found regarding outcome for these 225 patients in relation to their gender (all P > 0.05). During this period, two females with chronic ITP died (not as a direct result of the ITP) (0.9%).

Discussion
Our study, which includes 225 patients with documented ITP, is the first to evaluate the influence of gender on the clinical characteristics, presentation and outcomes of patients with ITP. Diagnosis of immune thrombocytopenia is solely based on platelet count < 100 × 10^9/L and doesn’t require...
systematic bone marrow examination (if patient are under 60 years). For the bleeding, ITP score and documented anemia, there were significant statistical differences that may be related to the presence of menno- or metrorrhagia and hematuria in female patients.

It’s important to keep in mind (potential bias) that the ITP bleeding score was primarily designed to assess the severity of the hemorrhagic syndrome on clinical examination and situation of severe thrombocytopenia (platelets < 20 × 10^9/L) and to judge whether or not the use of IVIG. It is not designed to be calculated on the basis of historical data recorded as in the present work.

In our study, anemia was reported to be more frequent in women, exclusively in relation with gynecologic bleeding. However as a potential bias, it’s to note that we have use a cut for anemia definition of hemoglobin < 12 g/L/dl but normal range of hemoglobin is generally accepted as lower in women than man.

The patients reviewed in the study displayed, unsurprisingly, the same demographics as those regularly found in adult patients with ITP: three quarter of the patients were female, most of the patients were relatively young (mean age at initial ITP diagnosis: 40 years), half of the patients had bleeding diathesis, and the mean platelet count was approximately 40 × 10^9/L [13–19]. As in other studies, one quarter of our patients were antinuclear or antiphospholipid antibody-positive at the time of diagnosis [20]. Finally, more than 60% of our patients were cured with therapy, as has also been reported by several other authors [13–19].

A strikingly common feature observed in many auto-immune diseases in both humans and animal models is that females are highly susceptible to auto-immune conditions as compared with males – regardless of the differences in disease pathology [21]. This is the case in several documented studies of ITP [1]. In several animal models, estrogens promote, whereas androgens abrogate, B-cell-mediated auto-immune diseases [22]. Estrogens are able to influence the immune response via several mechanisms, but recently, they have been shown (along with other sex hormones) to largely exert their effects on immune effector cells, modulating the expression and production of several cytokines [23]. These effects potentially explain the efficacy of danazol in ITP [24].

This study demonstrates the potential role of gender in the presentation of ITP. The ITP bleeding score is most influenced by gender, but clinical manifestations, treatment response and outcome appear to be unaffected. Further large-scale randomized trials are needed to confirm the influence of gender on the presentation, treatment response and outcome in cases of ITP.

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References


