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Editorial

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What Impact for Sex Difference on Immune Thrombocytopenic Purpura?

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Despite the progress in medicine the impact of gender on many diseases remains unknown or unstudied. In this context, it seemed appropriate to us, with a bit of provocation, to study the impact of gender on Immune Thrombocytopenic Purpura (ITP).

ITP, currently also known as primary immune thrombocytopenia, is an autoimmune disorder that results in acute or chronic thrombocytopenia and that may potentially lead to a life-threatening hemorrhagic event.[1]

Major advances in our understanding of the pathophysiology of ITP have been done last years (evidence of anti-platelet antibodies and the relative failure of bone marrow platelet production),[2] but the diagnosis of ITP still is based on exclusion.[1]

While ITP in childhood is usually an acute, self-limiting condition (the thrombocytopenia is transient and recovers spontaneously despite an initially severe presentation), ITP is more often a chronic disease in adults (at least 30% of cases) with an insidious onset requiring multiple therapeutic approache.[1]

ITP mainly occurs in young adults, particularly women in their third or fourth decade, with an overall female to male ratio of 3-4 to 1. These figures suggest that sex hormones, as in other immune disorders (systemic lupus, multiple sclerosis, etc.) may play a role in the susceptibility to ITP.[3] In addition to having an impact on the immune system, sex hormones may also alter the clinical picture and response to therapy.

In recent years, it has become clear that women and men may differ for drug response. There is an increasing recognition on the role of sex hormones on pharmacokinetics and pharmacodynamics as mechanism accounting for sex differences in drug effects. The available evidence suggests that sex hormones influence drug absorption, distribution, metabolism, pharmacodynamics, and adverse effects. For instance, many cardiovascular drugs are metabolized by enzymes of the cytochrome system, which is more expressed in females than in males, showing sex differences in drug response. A line of evidence also exists that posits that genetic variation among different genders may be responsible for the variability in therapeutic response.

We have previously reported such a gender-related analysis in 225 consecutive cases of established ITP followed up over a period of 1.7 to 112 in the Strasbourg University Hospital (Strasbourg, France).[4]

The analysis of the data revealed significant statistical differences between female and male for: 1) the bleeding score: 13±6.3 in females *versus* 8.4±4.1 in males (p=0.03); 2)

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the presence of a documented anemia: 7 % in females *versus* 4.3 % in males (p=0.04); and 3) the detection of antinuclear and/or antiphospholipid antibodies: 64.7 % *versus* 35.3 % (p<0.02) (Table 1). For the first 2 parameters, the difference may be related to the presence of meno- and/or metrorrhagia and hematuria in female patients.

	Female patients (n=156)	Male patients (n=69)
Mean age at initial diagnosis of ITP	45.2±24.7 years (range, 18-82)	47.8±21.4 years (range, 15-71)
Presentation of ITP: • Thrombocytopenia revealed by routine full blood count • Thrombocytopenia revealed by a bleeding diathesis	 82(52.5%) 74(47.5%)	 35(50.7%) 34(49.3%)
Mean bleeding score from Khellaf et al.	13±6.3* (range, 3-32)	8.4±4.1* (range, 3-17)
Mean platelet count	44.5±19x10^9/l (range, 1-131)	38.4±14x10^9/l (range, 1-118)
Presence of a potential life-threatening platelet count (platelet count <10x10^9/l)	28(17.9 %)	11(15.9 %)
Mean hemoglobin level	12 g/dl (range, 8.2-13.6)	12.6 g/dl (range, 9.1-14.7)
Presence of anemia (hemoglobin level <12 g/dl)	11(7%)*	3(4.3%)*
Detection of antinuclear antibodies and/or antiphospholipid antibodies (n=140)	22(64.7%)*	12(35.3%)*

*statistically significant difference.

Table 1: Gender-related analysis of clinical and biological presentations in 225 patients with idiopathic thrombocytopenic purpura (ITP).

No statistically significant difference was found regarding outcome for these 225 patients in relation to their gender (Table 2).

	Female patients (n=156)	Male patients (n=69)
Patients with CR or PR - Spontaneous response or after first-line therapy (steroids, IgIV) - After second-line therapy (splenectomy, rituximab)	 56(35.9%) 44(28.2%)	 26(37.7%) 21(30.4%)
Patients with chronic ITP requiring long-term drug use (steroids, danazol, etc.) due to recurrent and chronic bleeding and/or low platelet counts	39(25%)	19(27.5%)
Patients with chronic ITP and PR or F [7] managed with a 'wait-and-see' policy and punctual treatment	14(9%)	6(8.7%)

IgIV: intravenous immunoglobulins. CR: complete response (platelet count >150x109/l after treatment). PR: partial response (platelet count of 50 to 150x109/l or platelet levels twofold higher after treatment if the initial platelet count was <50x109/l). F: failure.

Table 2: Gender-related analysis of outcomes in 225 patients with idiopathic thrombocytopenic purpura (ITP).

An abundance of recent research indicates that there are multiple differences between males and females regarding both the normal physiological processes and the pathophysiology of disease. Studies have addressed sex-based differences in the physiology and pathophysiology of the cardiovascular, musculoskeletal, and immune systems as well as the mechanism of action of sex steroid hormone actions on nonreproductive tissues.[5]

Thus, as is the case for several other autoimmune disorders, the role of patient gender in the course and outcome of ITP should be considered.

A strikingly common feature observed in many autoimmune diseases in both humans and animal models is that females are highly susceptible to autoimmune conditions as compared with males-regardless of the differences in disease pathology.[5] This is the case in several documented studies of ITP.[1]

In several animal models, estrogens promote, whereas androgens abrogate, B-cell-mediated autoimmune diseases.[5] 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.[5] This is a potential explanation for the efficacy of danazol in ITP.[4]

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Thus to date, the impact for sex difference on immune thrombocytopenic purpura or on primary immune thrombocytopenia is not known.

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