Autoimmune disorders in patients with idiopathic thrombotic thrombocytopenic purpura*

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Summary

76 German patients suffering from thrombotic thrombocytopenic purpura (TTP) were interrogated about the prevalence of co-occurring autoimmune disorders. In order to analyze a possible association of TTP with the questioned diseases, a comparison of prevalence rates between the patient group and the general population has been made for each disease. Results: Compared to the estimated prevalence rates, the statistical analysis revealed an unexpected high occurrence of the following disorders within the patient group: Hashimoto’s thyroiditis (23.5% within the patients compared to 0.7% within the general population, p<0.001), systemic lupus erythematosus (SLE) (6.5% in patients to 0.025% in the general population, p<0.001), immune thrombocytopenic purpura (ITP) (6.3% in patients to 0.02% in the general population, p<0.001), psoriasis (9.4% in patients to 2.5% in the general population, p=0.005) and celiac disease (3.1% in patients to 0.2% in the general population, p=0.007). Conclusion: These findings confirm the mentioned tendency of autoimmune diseases to co-occur in one individual and argue once more for a genetic susceptibility in idiopathic TTP as well as in autoimmune disorders.

Keywords

TTP, autoimmunity, genetic susceptibility, HLA

Eli Moschcowitz firstly described thrombotic thrombocytopenic purpura in 1925. Despite new knowledge regarding diagnosis and treatment, TTP remains a life threatening diagnose even today. This rare microangiopathy is triggered by the deficiency of von Willebrand factor-cleaving protease, also known as ADAMTS13. Patients suffering from TTP normally present

- haemolytic anaemia,
- thrombocytopenia and
- microvascular thrombosis.

Nevertheless, a rapid clinical diagnosis is often impeded by a great variety of clinical symptoms, whereby, delaying the initiation of a potentially life-saving therapeutic treatment. In most patients, ADAMTS13 deficiency results from autoantibodies directed against the protease. Therefore, an autoimmune origin of the disease has been recognized. This autoimmune subtype of TTP is called idiopathic TTP. Since the discovery of an immunologic dysfunction as reason for several severe medical conditions, autoimmune diseases have been the focus of a significant amount of research. Due to numerous studies investigating the source leading to the immunologic loss of tolerance, the existence of certain genetic factors combined with a predisposing environment has been widely accepted as major causative factor in the development of autoimmune diseases. Hence, there are several studies identifying human leukocyte antigens (HLA) and other immune mediators involved in the pathogenesis of TTP.

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Untersuchungen zur Prävalenz autoimmuner Störungen bei Patienten mit thrombotischer thrombozytopenischer Purpura

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Schlüsselwörter

TTP, Autoimmunität, genetische Prädisposition, HLA

Zusammenfassung

Bei 76 deutschen Patienten mit thrombotischer thrombozytopenischer Purpura wurden anhand standardisierter Fragebögen Auftretenshäufigkeiten für weitere immunologische Störungen untersucht. Als Vergleichswerte dienten die zugehörigen Prävalenzen für die jeweilige Erkrankung in der Allgemeinbevölkerung. Die statistische Auswertung erfolgte mit dem zweiseitigen Binomialtest. Ergebnisse: Im Vergleich mit den Prävalenzen in der Allgemeinbevölkerung, zeigte sich für fünf Erkrankungen ein gehäuftes Auftreten im Patientenkollektiv: Hashimoto-Thyreoiditis (23.5% in der Patientengruppe zu 0.7% in der Allgemeinbevölkerung; p<0,001), systemischer Lupus erythematoses (SLE) (6.5% der Patienten im Gegensatz zu 0,025% in der Allgemeinbevölkerung; p<0,001), Immunthrombozytopenie (ITP) (6.3% der Patienten zu 0,02% in der Allgemeinbevölkerung; p<0,001), Psoriasis (9,4% der Patienten zu 2,5% in der Allgemeinbevölkerung; p=0,005) und Zöliakie (3,1% der Patienten zu 0,2% in der Allgemeinbevölkerung; p=0,007).

Schlussfolgerung: Diese Ergebnisse sprechen für eine Assoziation verschiedener Autoimmunkrankheiten untereinander und unterstützen die Annahme einer möglichen genetischen Prädisposition zur Ausbildung mehrerer autoimmuner Störungen innerhalb eines Individuums.
ating factors as predisposing elements to the immunological dysfunction. In the same context, it was also revealed that autoimmune diseases tend to co-occur in one individual and families (11). Therefore, even for a rare medical condition like idiopathic TTP there are several articles reporting a co-occurrence of another autoimmune disease. These case reports describe TTP in association with SLE, mixed connective tissue disease and various other autoimmune disorders (19). Nevertheless, further studies investigating the association of TTP with other autoimmune diseases had yet to be performed. To resolve this matter has been the purpose of our study.

Patients, methods

Using standardized questionnaires, 76 German adult patients suffering from acquired TTP were interrogated about the prevalence of co-occurring immunologic disorders. 66 patients were female, 10 were male. The questioned disorders included Hashimoto’s thyroiditis, systemic lupus erythematosus (SLE), immune thrombocytopenic purpura (ITP), psoriasis vulgaris, celiac disease, multiple sclerosis, Sjögren’s syndrome, ankylosing spondylitis, atopic dermatitis, rheumatoid arthritis, chronic inflammatory bowel disease (IBD) and allergies.

In order to analyze a possible association of TTP with the mentioned diseases, a comparison of prevalence rates between the patient group and the general population has been made for each disease. The results were evaluated employing the two-sided binomial test.

As not every patient answered all the questions, the sample size may vary for the different analyzed diseases. A detailed list of the given sample sizes, the calculated frequencies within the patient group, the estimated prevalence rates in the general population and the corresponding p-values for each disease can be found in the Table.

Results

The results have been summarized in the Table. Compared to the estimated prevalence rates, the statistical analysis revealed an unexpected high occurrence of five autoimmune disorders within the patient group.

Particularly notable was the high occurrence of Hashimoto’s thyroiditis: 23.5% of patients suffered from this autoimmune disorder.

In the general population, the estimated prevalence is 0.7% (21), (p < 0.001). 6.5% of patients affirmed the positive diagnosis of SLE. The prevalence of this autoimmune connective tissue disease is generally found to be moderately low (0.025% in the general population (14), p < 0.001). For ITP, a similar situation was found: Despite an estimated prevalence of 0.02% in the general population (5), 6.3% of patients suffered from this hematologic disorder (p < 0.001). 9.4% of patients, contrary to 2.5% of the general population (20), had been positively diagnosed for psoriasis (p = 0.005). In 3.1% of patients, a co-occurrence of celiac disease and TTP had been detected. The estimated prevalence of celiac disease in the general population is 0.2% (16) (p = 0.007). For the remaining autoimmune disorders the comparison of frequencies did not produce any striking results: Only 3.1% of patients, compared to a prevalence rate of 1% in the general population (6), suffered from rheumatoid arthritis (p = 0.135). The same percentage of patients suffered from atopic dermatitis. This autoimmune dermatologic disorder occurs in 2% of the general population (22) (p = 0.367). One patient (1.6%) had a chronic inflammatory bowel disease, namely an ulcerative colitis. Chronic inflammatory bowel diseases tend to occur in Europe with an average prevalence rate of 0.8% (18) (p = 1). Almost matching prevalence rates between the patient group and the general population had been found for Sjögren’s syndrome: 1.5% of patients had been positively diagnosed for this systemic autoimmune disease of the exocrine glands. In general, the estimated prevalence rate is 1.75% (7) (p = 1). 1.7% of patients, compared to an estimated prevalence rate of 0.86% in the general population (4), suffered from ankylosing

### Table

<table>
<thead>
<tr>
<th>Autoimmune Disease</th>
<th>Sample Size</th>
<th>Prevalence (%)</th>
<th>Patient Group</th>
<th>General Population</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>68</td>
<td>23.5 (16)</td>
<td>0.7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>62</td>
<td>6.5 (4)</td>
<td>0.025</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ITP</td>
<td>64</td>
<td>6.3 (4)</td>
<td>0.02</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td>64</td>
<td>9.4 (6)</td>
<td>2.5</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Celiac disease</td>
<td>64</td>
<td>3.1 (2)</td>
<td>0.2</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>64</td>
<td>3.1 (2)</td>
<td>1</td>
<td>0.135</td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>65</td>
<td>46.3 (39)</td>
<td>40</td>
<td>0.314</td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>64</td>
<td>3.1 (2)</td>
<td>2</td>
<td>0.367</td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>64</td>
<td>1.6 (1)</td>
<td>0.8</td>
<td>0.402</td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>60</td>
<td>1.7 (1)</td>
<td>0.86</td>
<td>0.404</td>
<td></td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>65</td>
<td>1.5 (1)</td>
<td>1.75</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>63</td>
<td>0</td>
<td>0.15</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

1As not every patient answered all the questions, the sample size may vary for the different analyzed diseases. 2For each percentage, citations displaying the corresponding reference data can be found in the text.
spondylitis (p = 0.404). Almost half of the patient group (46.3%) stated to be affected by an allergy. Although this percentage seems quite high, the estimated prevalence rate of allergies in Germany did not display a significant deviation (40% (10), p = 0.314). Multiple sclerosis did not occur within the patient group. In the general population, this neurological disease is fairly rare. The prevalence rate is approximately 0.15% (9) (p = 1).

Discussion

Our research revealed a significantly high occurrence of five autoimmune conditions within patients suffering from idiopathic TTP. The high prevalence rate of Hashimoto’s thyroiditis within the patient group argues for a strong association between idiopathic TTP and the autoimmune thyroiditis. Even though, Hashimoto’s thyroiditis has not yet been described in association with TTP, the appearance of autoimmune thyroid diseases in patients with several autoimmune disorders is a well-recognized condition and has been described in association with ITP and celiac disease amongst others (1). In this case, the severity of the haemostatic disorder appears to depend on the degree of thyroid dysfunction.

There are only a few studies proposing certain HLA as predisposing factors in the development of Hashimoto’s thyroiditis. HLA-DRS has been identified as possible susceptibility gene triggering the autoimmune hypothyroidism (17). These results correspond with the findings for idiopathic TTP. Here, the high occurrence of DRB1*11 (DR11) and DQB1*02:02 suggests a predisposing role of these two alleles in disease development (13). Therefore, a HLA-based connection of the two diseases seems possible.

On the opposite, it is a well-known fact that TTP can co-occur in other multi-systemic diseases like SLE. The significantly elevated prevalence rate of SLE in our study group confirms the reported association of TTP and SLE. As both disorders share many characteristics with each other, a difficult clinical distinction may hinder the fast initiation of a matching therapy. Together with other factors, this explains the higher mortality rate in patients suffering from both diseases (15). Even though, ADAMTS13-activity and autoantibodies against the protease have been reported in patients with SLE (15), the exact reason causing both diseases to co-occur within each other remains to be explained. Regarding a genetic susceptibility for SLE, an association seems possible (8) with
- HLA-DR2 (DRB1*1501/DQB1*0602) and
- HLA-DR3 (DRB1*0301/DQB1*0201).

The mentioned alleles have also been found in some patients with idiopathic TTP, but the evaluation of a possible role for disease susceptibility did not reach any significant level (13). Therefore, an HLA-based association seems unlikely and the existence of other, yet unknown factors connecting both diseases remains to be explained.

Even though the results of our study propose a significant association of TTP with ITP, there are few case reports describing a co-occurrence of these two autoimmune haemostatic disorders. Despite the normally easily distinguishable diseases, Baron et al. (3) propose the existence of a distinct clinical syndrome, a mixed immune thrombocytopenia, in patients with underlying immunologic dysfunction (e.g. HIV). As there have not been any studies investigating a genetic susceptibility to ITP, an HLA-based association of the two diseases cannot yet be excluded. On the other hand, ITP is well known to be associated with several other autoimmune disorders, such as autoimmune thyroid diseases (1). Furthermore, it has also been described in patients with celiac disease (1). As both of these autoimmune disorders demonstrated a significant accumulation in our study group, the high prevalence of ITP may also have been due to the association with these two diseases. However, even in this context, a causative factor explaining the association has yet to be determined.

Psoriasis vulgaris, an autoimmune skin disease, has not yet been described in association with idiopathic TTP. Adding the fact that psoriasis normally does not present haemostatic dysfunction, the factors combining possible disease susceptibility to psoriasis as well as to TTP remain undetected. On the other hand, the small sample size combined with the high prevalence rate of psoriasis in the general population argues rather for a random accumulation than for a real association.

A similar effect regarding the significant accumulation of celiac disease in patients with idiopathic TTP has to be considered possible. As a common life-long food sensitive enteropathy in humans, celiac disease appears with an estimated prevalence rate of 0.2% (16). Therefore, it is possible that the high co-occurrence within the patient group displays a random event. On the other hand, there are several articles describing celiac disease in association with other autoimmune diseases, such as ITP and autoimmune thyroid disorders (1). As these diseases have also been significantly accumulated within the patient group, the association with ITP may also have caused the observed prevalence of celiac disease. An HLA-based analysis showed an accumulation of HLA-DQ2 (DQA1*0501/ DQB1*0201) and HLA-DQ8 (DQA1*0301/ DQB1*0302) in patients with celiac disease (2). As the DQB1*02:02 allele, which encodes the serologic antigen DQ2, has also been significantly accumulated in patients with idiopathic TTP (13), an HLA-based association between celiac disease and TTP seems possible.

There are several articles describing TTP in association with other autoimmune disorders, such as Sjogren’s syndrome, ulcerative colitis, rheumatoid arthritis and ankylosing spondylitis amongst others. Nevertheless, our study could not confirm a relevant association.

Conclusion

Our findings confirm the well-known association of TTP with SLE. We also suggest a strong association of TTP with Hashimoto’s thyroiditis. Regarding Hashimoto’s thyroiditis and celiac disease, an HLA-
based association seems unlikely. The reported association of ITP and celiac disease may have been a major factor influencing the high prevalence of these two diseases. However, this fact does not explain the occurrence of these diseases in idiopathic TTP. It is most likely that the significant accumulation of psoriasis in our patient group is a misleading effect caused by the small sample size. Nevertheless, a yet unknown association cannot be excluded.

Our findings confirm the mentioned tendency of autoimmune diseases to co-occur in one individual and argue once more for a genetic susceptibility in idiopathic TTP as well as in autoimmune disorders.

Conflict of interest
The authors declare, that there is no conflict of interest.

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