Concurrent Autoimmune Diseases in Patients With Autoimmune Hepatitis

Andreas Teufel, MD, PhD,* Arndt Weinmann, MD,* George J. Kahaly, MD,* Catherine Centner, MD,* Anja Piendl, MD,* Marcus Wöns, MD,* Ansgar W. Lohse, MD,† Peter R. Galle, MD,* and Stephan Kanzler, MD*‡

Background: Although the pathomechanisms of autoimmune diseases in various organs remain unresolved, an accumulation of autoimmune diseases in individual patients has been observed. An overlap of autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC) or primary sclerosing cirrhosis has been well documented. However, the overlap of autoimmune diseases other than PBC or PSC has not yet been investigated in a large cohort.

Goal: The goal of our analysis was to investigate the incidence of concurrent autoimmune diseases in patients with AIH.

Study: We analyzed our cohort of 278 patients with AIH for concurrent autoimmune diseases.

Results: A total of 111 patients (40%) were diagnosed with additional autoimmune diseases. Besides overlap syndromes for PBC and PSC, autoimmune thyroiditis was the most common concurrent disease (26 patients, 10%). Other concurrent autoimmune diseases comprised vitiligo (5 patients), rheumatoid arthritis (5 patients), Sjogren syndrome (4 patients), ulcerative colitis (4 patients), con-junctivitis (4 patients), celiac disease (3 patients), systemic lupus erythematoses (2 patients), type 1 diabetes (2 patients), multiple sclerosis (2 patients), polymyalgia rheumatica (2 patients), and urticaria (2 patients). One patient each was diagnosed with Crohn’s disease, autoimmune gastritis, collagenous colitis, hypophysitis, and sarcoidosis. Investigating 100 patients with polyglandular syndrome and autoimmune thyroid disease for the occurrence of auto-antibodies associated with AIH, we identified AIH-associated antibodies only in 1 patient.

Conclusions: Concurrent autoimmune diseases are common in patients with AIH and mirror the full range of known autoimmune diseases. Therefore, an extended diagnostic screening for accumulating autoimmune diseases, especially autoimmune thyroiditis, seems reasonable in patients with AIH.

Key Words: AIH, overlap, thyroiditis, autoimmune disease

(J Clin Gastroenterol 2010;44:208–213)

The observation of a concurrence of diverse autoimmune diseases has been frequently reported. Acknowledging these concurrencies, a concept or hypothesis of shared autoimmunity has been proposed, although molecular or genetic proof is still lacking. In the context of this concept, diverse forms of occurrence of autoimmune diseases have been discussed for developing because of a shared autoimmunity mechanism. This idea was substantiated on the one hand, by the occurrence of not only a single autoimmune disease in several members of the same family, which have also been referred to as multiplex families,

We and other investigators have earlier reported on overlap syndromes of AIH with primary biliary cirrhosis (PBC) or primary sclerosing cirrhosis (PSC) and the epidemiologic details on these overlap syndromes as well as their clinical course.6-9 These AIH/PBC and AIH/PSC overlap syndromes are frequent and it was estimated that AIH/PBC overlap diseases may occur in their full manifestations in about 10% to 20% of cases and AIH/PSC overlap with a frequency of 2% to 8% of patients.6

In contrast, only very limited data exist on the frequency of concurrent autoimmune diseases other than PBC or PSC in larger collectives. The largest reported collective to be investigated for the wide variety of associated autoimmune diseases so far contained 38 patients.10 Furthermore, most reports on simultaneously occurring autoimmune diseases in patients with AIH have mainly been focussing on individual diseases simultaneously occurring with AIH, mostly as single case reports (Table 1).

At present, an analysis of a large cohort of patients with AIH has not yet been reported. Thus, the aim of our study was to investigate our large collective of 278 patients with AIH (including patients with overlap syndromes of PBC and PSC) to further elucidate the incidence of diverse individual autoimmune diseases in patients with AIH. Results of this study may be of significant value with respect to the diagnosis of associated autoimmune diseases as frequently associated autoimmune diseases may become part of the initial screening in patients with newly diagnosed AIH.

MATERIALS AND METHODS

Study Cohort

Two hundred and seventy-eight patients satisfied the international criteria for the diagnosis of AIH.7,8 All patients...
that matched these criteria were included. All patient records were manually searched for indications of concurrent autoimmune diseases. Primary care physicians were not contacted. Of these 278 patients, 229 (82%) were women and 49 (18%) were men. Median age at diagnosis was 46 years, ranging between 10 and 82 years. Most of these patients were white. Further demographic data were not available for all patients. They had been enrolled in our chronic liver disease program from 1970 until present. All patients had been followed in a uniform manner up to 34 years. On the basis of immunoserologic assessment for autoantibodies, 206 patients were assessable for a subtype of AIH. Of these, 194 patients (94%) were classified as type-1 AIH because of positive anti nuclear antibodies (ANA), or anti-SLA/LP autoantibodies.55,79 Twelve (6%) patients had elevated liver kidney microsome (LKM) autoantibodies, characteristic of type-2 AIH.80 Seventy-two patients had no detectable autoantibodies, but nevertheless fulfilled the AIH criteria.

Immunoserologic Assessments

SMA, ANA, and LKM were analyzed by indirect immunofluorescence on murine tissue sections as described earlier. Anti-SLA/LP was analyzed by inhibition enzyme-linked immunosorbent assay.79 A serum titer of 1:80 or higher was considered positive for ANA. 55 A titer of 1:40 or higher was considered positive for SMA and anti-LKM-1. All patients were tested for SMA and ANA and 193 patients (91%) were tested for anti-LKM-1. Patients with SMA and/or ANA in the absence of anti-LKM-1 were classified as type-1 AIH. Patients with anti-LKM1 were classified as type-2 AIH. These immunologic assessments for the above antibodies associated with AIH were made the same way in patients with autoimmune thyroid disease as a screening test for AIH in these patients.

Screen for Concurrent Autoimmune Diseases in Patients With AIH

All available medical records from the archive of the Department of Medicine I of the University of Mainz have been manually searched for evidence/notes of concurrent autoimmune diseases.

Screening for AIH in Patients With Autoimmune Thyroiditis

Since 1988, more than 15,000 patients with endocrine diseases have been screened for polyglandular autoimmune syndromes (PAS) at our institution. A total of 360 patients

### TABLE 1. Summary on Concurrent Disease in Patients With Autoimmune Hepatitis Reported in Individual Case Reports

<table>
<thead>
<tr>
<th>Disease</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison disease</td>
<td>Bergwitz et al11; Tauchmanova et al12</td>
</tr>
<tr>
<td>Anticardiolipin antibody syndrome</td>
<td>Gurudu et al13</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>Dourakis et al14; Hadjigogos and Marinaki15; Hueber et al16; Linares et al17; Pathmakanthan et al18; Sema et al19</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>Bergwitz et al21</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Gurudu et al3</td>
</tr>
<tr>
<td>Autoimmune hyperlipidemia</td>
<td>Rumbo et al30</td>
</tr>
<tr>
<td>Autoimmune pancreatitis</td>
<td>Gaburri et al32</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Arvola22; Biecker et al31; Bridoux-Henno et al24; Caïulo et al25; Csak et al26; Maggiore and Capraï27</td>
</tr>
<tr>
<td>Colitis ulcerosa</td>
<td>Cronin et al29; Linares et al17</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Biecker et al3</td>
</tr>
<tr>
<td>Erythema annulare</td>
<td>Gulati et al29</td>
</tr>
<tr>
<td>Felty syndrome</td>
<td>Inaba et al10; Sema et al19</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Takahashi et al31</td>
</tr>
<tr>
<td>Grave disease</td>
<td>Cui et al32; Inoue et al33; Nagai et al34</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Seibold et al35</td>
</tr>
<tr>
<td>Lupus erythematoses</td>
<td>Angulo et al36; Fujiwara et al37; Iwai et al38; Kaw et al39; Kooy et al40; Moriwaki et al41; Satoh et al42; Shoenfeld et al43; Suzuki et al44; Takahashi et al45; Tojo et al46; Usta et al47</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>Maeda et al48</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Luth et al49</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>de Seze et al50</td>
</tr>
<tr>
<td>Panniculitis</td>
<td>Allen-Mersh52</td>
</tr>
<tr>
<td>Polyglandular autoimmune syndrome</td>
<td>Oki et al53; Smith et al54</td>
</tr>
<tr>
<td>Rheumatic diseases</td>
<td>Czaja et al37; Nobili et al56</td>
</tr>
<tr>
<td>Sjogren syndrome</td>
<td>Biasi et al57; Hoshino et al58; Katayama et al59; Lee et al60; Matsumoto et al61; Ramos-Casals et al62; Wada et al63; Wanchu et al64</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Marie et al65; Lis-Swiety et al66; Ishikawa et al67</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>Shibuya et al68; Yamaike et al69</td>
</tr>
<tr>
<td>Thymoma</td>
<td>Asakawa et al8; Han et al51</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>Bergwitz et al41; Nagai et al30; Nobili et al71; Salvi et al72; Tomsic et al73; Soy et al74</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>Arvola et al22</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Bloom et al75; Kamal et al76; Romanelli et al77</td>
</tr>
</tbody>
</table>
were positive for PAS II and have been followed regularly since 1990. In these patients, quantitative enzyme immunoassay (Immunoradiometric assay method; Brahms, Berlin, Germany) was used to test for the presence of autoantibodies against thyroid-stimulating hormone receptor. Enzyme-linked immunosorbent assay (Pharma/Upjohn GmbH, Freiburg, Germany) was applied for autoantibodies against thyroid peroxidase, thyroglobulin (positive, > 100 IU/mL), and glutamic acid decarboxylase (positive, > 1500 U/mL). Analysis of clinical data showed that, taken together, both autoimmune thyroid diseases had the highest prevalence (n = 99; 65.6%), with equal numbers of Graves disease (n = 50; 33.1%) and autoimmune thyroiditis (n = 49; 32.5%),81,82 Sera of these patients were chosen for further evaluation of antibodies associated with AIH. Antibody screening was done as described above.

RESULTS

In our cohort of 278 patients with AIH, a total of 111 patients (40%) were diagnosed with additional autoimmune diseases. Besides overlap syndromes for PBC and PSC, autoimmune thyroiditis was the most common concurrent disease, diagnosed in 28 patients (10%). Other concurrent autoimmune diseases comprised vitiligo (5 patients, 1.8%), rheumatoid arthritis (5 patients, 1.8%), Sjogren syndrome (4 patients, 1.4%), ulcerative colitis (4 patients, 1.4%), conjunctivitis (4 patients, 1.4%), celiac disease (3 patients, 1.1%), systemic lupus erythematoses (2 patients, 0.7%), type I diabetes (2 patients, 0.7%), multiple sclerosis (2 patients, 0.7%), polymyalgia rheumatica (2 patients, 0.7%), and urticaria (2 patients, 0.7%). One patient each was diagnosed with Crohn’s disease, autoimmune gastritis, collagenous colitis, hypophysitis, and sarcoidosis (0.4% each) (Table 2).

Besides the incidence of concurrent autoimmune diseases in patients with AIH, we further investigated whether simultaneous occurrence of other autoimmune diseases in these patients was correlated with a more aggressive course of the disease. Thus, as a measure of aggressiveness of the disease we examined the rates of relapses of AIH in these patients and compared the group of patients with concurrent other autoimmune diseases with those not showing any concurrent autoimmune diseases.

However, no significant differences in the number of relapses were observed between these 2 groups. Of the 167 patients suffering from AIH but not from other autoimmune diseases, 62 (35%) suffered at least 1 relapse of the disease. Of the 111 AIH patients with additional autoimmune diseases, 52 (47%) suffered at least 1 relapse (P = 0.25, 2-tailed Fisher test).

Furthermore, recurrences in patients with AIH/PBC or AIH/PSC overlap syndromes were also shown not to differ significantly, depending on additional autoimmune diseases. In 56 patients with AIH/PBC or AIH/PSC overlap syndromes without further autoimmune diseases, 25 (44%) showed at least 1 recurrence of the disease. Similarly, 11 (61%) of 18 patients with AIH/PBC or AIH/PSC overlap syndromes and additional autoimmune diseases suffered from recurrent AIH (P = 0.5, 2-tailed Fisher’s test, Table 3). However, our data showed a trend toward higher recurrence in patients with additional autoimmune diseases, which may need to be further addressed in the future (47% vs. 35% for AIH and 61% vs. 44% for overlap syndromes AIH/PBC or AIH/PSC only). Also comparing the rate of cirrhosis in patients with or without concurrent autoimmune diseases did not reveal any significant differences (Fisher test, P = 0.1).

As autoimmune thyroiditis was found to be by far the most prevalent concurrent autoimmune disease other than PBC or PSC in patients with AIH, we investigated the prevalence of AIH in patients with autoimmune thyroiditis. To assess the prevalence of autoimmune liver infection in patients with immunothyroiditis, autoantibodies associated with autoimmune liver disease (ANA, SMA, LKM, anti-SLA/LP) were investigated in 100 patients with PAS and autoimmune thyroiditis. Some of these patients suffered from additional endocrine diseases. However, of these only in 1 patient were ANA autoantibodies shown to be elevated in the serum. Thus, in contrast to our patients with AIH, in patients with PAS and autoimmune thyroiditis no significant concurrent liver infection, and therefore no correlation to AIH, was observed.

DISCUSSION

Accumulation of autoimmune diseases in individual patients has been observed earlier and the association of AIH with PBC or PSC repeatedly has been well documented.6-9 However, the association of AIH with autoimmune diseases other than PBC or PSC has only rarely been described, mostly as single case reports. Summarizing these case reports, AIH may be observed to overlap with the full variety of known autoimmune diseases from localized autoimmune diseases, such as uveitis, to systemic autoimmune disorders such as lupus erythematoses or systemic autoimmune diseases.
sclerosis. Thus, we investigated the incidence of concurrent autoimmune diseases in our large cohort of 278 patients with AIH. In our cohort of 278 patients with AIH a total of 111 patients (40%) were diagnosed with additional autoimmune diseases. This frequency of associated autoimmune diseases was approximately in range with the frequency observed by Choudhuri et al. who had reported on associated autoimmune diseases in 39% from a much smaller cohort. From these analyses it became clear that, in general, association of AIH with other autoimmune diseases is common. It must be acknowledged, however, that many diagnoses were made by general practitioners regularly treating these patients, as we see most of them on a consultant basis. Thus, many of the concurrent autoimmune diseases were reported to us on subsequent visits through documents from other hospitals. As these patients did not undergo a systematic search for concurrent autoimmune diseases, there may be an additional number of undetected cases and thus the real number of concurrent autoimmune diseases may even be higher.

Extracting overlap syndromes of AIH to PBC or PSC from the analysis, we still observed 68 additional autoimmune diseases in these patients. By far the most common of these autoimmune diseases other than PBC or PSC in patients with AIH was autoimmune thyroiditis. This finding was again shared by Choudhuri et al. who found thyroiditis in approximately 8% of patients with respect to a smaller number of their cohort. The higher incidence of associated type I diabetes (4 patients, 11%) was not met by our patient cohort, which may be attributed to the low overall number and resulting sampling error of patients in the study by Choudhuri et al. As approximately 10% of the patients with AIH exhibit autoimmune thyroid disease it seems reasonable to recommend routine screening for autoimmune thyroid disease in patients with AIH. Interestingly, all patients suffering from AIH and autoimmune thyroiditis were women. It remains to be investigated further whether this condition of both autoimmune diseases develops in women only. The pathophysiological reasons for this high rate of patients showing an overlap to immunothyroiditis remain to be investigated further. As one may speculate on a potential cross-reactivity of the respective antibodies to cause other autoimmune diseases, and especially immunothyroiditis, we investigated the occurrence of these antibodies in patients suffering from PAS and immunothyroiditis. However, despite the high association of autoimmune thyroid disease in patients with AIH screening did not reveal any commonly associated liver disease in these patients.

However, the most common overlap syndromes with other autoimmune diseases were overlap of PBC or PSC, with a total of 72 (26%) patients suffering from overlapping autoimmune liver disease. These figures were absolutely in the range reported earlier by Dienes et al. who had estimated that AIH/PBC overlap diseases may occur simultaneously in their full manifestations in about 10% to 20% of cases and AIH/PSC overlap, with a frequency of 2% to 8% in patients with PSC.

Besides autoimmune thyroid diseases, concurrent autoimmune diseases in these patients exhibited the full range of diversity of autoimmunity from localized autoimmune diseases such as Sjogren syndrome to generalized autoimmune diseases such as systemic lupus erythematoses. These findings again mirror the reported assembly of individual case reports describing the association of individual autoimmune diseases with AIH.

With autoimmune diseases affecting more than a single organ, the liver in particular, one may think of a more aggressive susceptibility toward autoimmune diseases. Such a rather aggressive clinical course of (some) overlap syndromes, despite a response of clinical manifestations to standard treatment, had been suggested earlier in the context of autoimmune rheumatic disease. Thus, we further investigated whether concurrence of additional autoimmune diseases in these patients was correlated with a more aggressive course of the disease. As a measure of aggressiveness of the disease, we examined the rates of relapse of AIH in these patients. However, compared with patients without other associated autoimmune diseases, we were not able to show a significantly higher rate of recurrence. Therefore, it must be concluded from our present data that the concurrence of additional autoimmune diseases in patients with AIH does not alter the clinical course or severity of AIH. However, in all subsets a trend toward a higher recurrence in patients with additional autoimmune diseases was observed. Thus, this issue may need further evaluation in larger multicenter studies.

CONCLUSIONS

We conclude that association of additional autoimmune diseases other than PBC or PSC in patients with AIH is common. Association of further autoimmune disease was not significantly correlated with a more severe course or increased recurrence of disease. However, as a trend toward higher recurrence was observed, this may need further investigation. The most commonly associated syndromes besides PBC or PSC was AIH/Thyroiditis. Thus, it must be regarded mandatory to recommend routine screening for immunothyroiditis in patients with AIH.

REFERENCES


