Dear Editor,

In a recent letter, a new form of disease has been described: new cases of chronic hepatitis of unknown etiology. There are two possible explanations for this: (1) an epidemic of hepatitis A is a progressive and unexpected finding or (2) a new disease, not previously described, is being identified. In this letter, we would like to present a further description of the new disease.

The first case concerns a 12-year-old female patient who was referred to a pediatric clinic with the diagnosis of autoimmune hepatitis (AIH). At the time of presentation, the patient had experienced symptoms of fatigue, jaundice, and liver function tests were elevated. The patient had a history of coeliac disease, but no family history of autoimmune disease. The patient was negative for all known autoantibodies, including ANA, SMA, and dsDNA.

The second case concerns a 6-year-old female patient with a history of coeliac disease. The patient had elevated transaminase levels, with a normal AST/ALT ratio. The patient was negative for all known autoantibodies, including ANA, SMA, and dsDNA.

In conclusion, the clinical features of these two patients are consistent with the description of hepatitis of unknown etiology. Further studies are needed to determine the cause of these cases.

Table 1: Clinical characteristics and histological features found in our 2 patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical Features</th>
<th>Histological Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female, 12 years</td>
<td>Liver biopsy: fibrosis, portal inflammation</td>
</tr>
<tr>
<td>2</td>
<td>Female, 6 years</td>
<td>Liver biopsy: fibrosis, portal inflammation</td>
</tr>
</tbody>
</table>

We recommend further studies to investigate the cause of these cases and to determine if they represent a new disease or are cases of AIH.

Yours sincerely,
[Author Name]
In both cases, the investigation of the elevation of serum transaminases failed to identify its aetiology: the chemistry and metabolic panels revealed normal iron metabolism, with negative serological markers of coeliac disease (in the second case, initially positive with normalisation after removal of gluten from the diet), absence of clotting abnormalities, normal thyroid function and normal immunoglobulin levels. The patients had no history of exposure to hepatotoxic drugs, and the investigation ruled out infection, classic AIH (due to negative antibody tests), alpha-1 antitrypsin deficiency, Wilson disease, lysosomal acid lipase deficiency and muscle and metabolic disorders. Both patients underwent repeated ultrasound examinations and a magnetic resonance cholangiography, the findings of which were normal. Given that all tests gave negative results while serum transaminases remained elevated, a liver biopsy sample was obtained for histopathological examination, resulting in a diagnosis of idiopathic liver fibrosis in both cases.

We contacted the anatomical pathology department and suggested the possibility of seronegative AIH, which led to performance of a targeted review of the histological features of both cases. The examination revealed cirrhosis and plasma cell infiltration, interface hepatitis in the first case, and necrosis in the second case. Rosettes were not found in either case. Based on these findings, the pathology report indicated that the cases were compatible with seronegative AIH. Table 1 summarises the anatomical pathology findings and the clinical characteristics of these 2 patients.

In light of the histopathological findings, and since other aetiologies had been ruled out previously, we proposed the diagnosis of seronegative AIH and, in agreement with the family, decided to initiate treatment in both patients with glucocorticoids at a dose of 2 mg/kg/day to be tapered to a maintenance dose of 2.5 mg every other day, with introduction of azathioprine on day 15 at a dose of 0.5 mg/kg/day, increasing the dose gradually until reaching 2 mg/kg/day.

In both patients, the serum transaminase levels (SGOT and SGPT) had normalised at 3 months of treatment, and they remained within the normal range at 6 months with the patients receiving minimum doses of glucocorticoids. Table 2 shows the evolution of serum transaminase levels in the 2 patients.

### Table 2: Evolution of serum transaminase levels in our 2 patients.

<table>
<thead>
<tr>
<th></th>
<th>Prior to liver biopsy</th>
<th>At treatment initiation</th>
<th>At 3 months of treatment</th>
<th>At 6 months of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>62–325</td>
<td>89</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>100–430</td>
<td>163</td>
<td>58</td>
<td>35</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>80–630</td>
<td>82</td>
<td>26</td>
<td>33</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>90–820</td>
<td>93</td>
<td>22</td>
<td>18</td>
</tr>
</tbody>
</table>

Conclusions

In our experience, histological examination by a pathologist with a focus on seronegative AIH in two cases of unspecified fibrosis led to a new diagnosis and allowed effective treatment in both patients.

Seronegative AIH is a newly defined disease for which little data is available in the paediatric age group. At the moment, the possibility of an autoimmune aetiology should be considered in idiopathic cases of chronic hepatitis, especially in patients with a history of other autoimmune diseases such as coeliac disease, even if antibody detection tests are negative. We recommend performance of a liver biopsy in such cases and, should the results be compatible with autoimmune disease, early initiation of immunosuppressive therapy to halt the progression of liver disease.

### References


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