 ORIGINAL ARTICLE

Screening for celiac disease in idiopathic pulmonary hemosiderosis

Dépistage de la maladie cœliaque dans l’hémosidérose pulmonaire idiopathique

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Summary

Aim. — The aim of this report was to screen for celiac disease (CD) in patients with idiopathic pulmonary hemosiderosis (IPH).

Patients and methods. — Patients with IPH treated at the Children’s Hospital of Tunis between 1976 and 2006 were reviewed and investigated for CD, using serological and histological tests.

Results. — A total of 10 children (two boys and eight girls) had IPH. The mean age at diagnosis was 3.1 years. Three had digestive symptoms and positive CD serology, which was confirmed by histological data. Clinical and radiological findings improved markedly in all CD patients with corticosteroid treatment combined with a gluten-free diet. Symptoms of IPH and CD both returned in one patient who stopped the gluten-free diet.

Conclusion. — Three of our 10 patients with IPH also had CD. These data illustrate the close etiopathogenic link between IPH and CD, and strongly suggest that CD be looked for in IPH patients, especially in those with symptoms suggestive of CD.

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Résumé

Le but. — Le but de cette étude est de dépister la maladie cœliaque (MC) chez des patients atteints d’hémosidérose pulmonaire idiopathique (HPI).

Patients et méthodes. — Les patients atteints d’HPI, traités à l’hôpital d’Enfants de Tunis entre 1976 et 2006, ont été revus et ont eu des explorations sérologiques et histologiques à la recherche d’une MC.

Résultats. — Dix enfants (deux garçons et huit filles) avaient une HPI. L’âge moyen au moment du diagnostic était de 3.1 ans. Trois enfants, ayant des signes digestifs, avaient une sérologie

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Idiopathic pulmonary hemosiderosis (IPH) is a rare disorder in children of unknown etiopathogeny, characterized by recurrent episodes of a triad comprising diffuse alveolar hemorrhage, hemoptysis and iron-deficiency anemia. So far, few cases of celiac disease (CD) in association with IPH have been reported in the literature [1—5]. The rarity of both conditions leads some authors to consider it a coincidental association [1]. To clarify the nature of this association, we looked for CD in 10 patients with IPH treated at the Children’s Hospital of Tunis.

**Patients and methods**

**Patients**

Patients with IPH treated at the Children’s Hospital of Tunis from 1st January 1976 to 31st December 2006 were reviewed. IPH, characterized by recurrent episodes of a triad of diffuse alveolar hemorrhage, hemoptysis and iron-deficiency anemia, was confirmed by the presence of hemosiderin-laden macrophages in the bronchoalveolar lavage fluid and/or gastric washing fluid.

The patients’ records were evaluated in terms of age, gender, clinical pattern, associated diseases, diagnostic methods, treatment and outcome. Other causes of diffuse alveolar hemorrhage were excluded by specific investigations. Echocardiography showed neither mitral stenosis nor pulmonary hypertension. Laboratory investigations showed normal renal and liver function. Immunological tests were negative for antinuclear antibodies (ANA), antideoxyribonuclease antibodies (anti-DNaseA), rheumatoid factor, antineutrophil cytoplasmic antibodies (ANCA) and antigliadin antibodies (AGA) of IgG and IgA isotypes, asso-
ciated with antireticulin (ARA), antien
domysial (EmA) and antitissue transglutaminase (anti-tTGA) antibodies. Quantitative serological screening and titration of anti-tTGA became available in Tunisia only by the time that the last four patients were being screened. The diagnosis of CD was confirmed on the basis of positive serological tests, total villous atrophy on intestinal biopsy, and clinical and serologi-
cal remission with a gluten-free diet. All parents gave their consent for the serological and histological investigations.

**Methods**

All patients were investigated for CD by serological screening and intestinal biopsy, even when serological tests were negative. Laboratory investigations identified circulating antigliadin antibodies (AGA) of IgG and IgA isotypes, associated with antiendomysial (ARA), antireticulin (EmA) and antitissue transglutaminase (anti-tTGA) antibodies. Quantitative serological screening and titration of anti-tTGA became available in Tunisia only by the time that the last four patients were being screened. The diagnosis of CD was confirmed on the basis of positive serological tests, total villous atrophy on intestinal biopsy, and clinical and serological investigations.

**Conclusion.** — Parmi les dix patients atteints d’HPI, trois avaient une MC. Ces résultats illustrent le lien éthiopathogénique étroit entre l’HPI et la MC. La recherche d’une MC au cours d’une HPI se trouve justifiée, en particulier chez les patients présentant des symptômes digestifs.

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patients required azathioprine treatment because of frequent exacerbations (Observation 7) and femoral head necrosis (Observation 8) with corticosteroids. Patients with CD were started on a gluten-free diet (Cases 3, 7 and 9), and their clinical and radiological course was markedly improved. Digestive symptoms disappeared and respiratory exacerbations became infrequent with the low-dose oral corticosteroid therapy and gluten-free diet. In addition, the laboratory follow-up showed hemoglobin rates within the normal range and negative serological tests. However, no intestinal biopsies were performed to confirm CD remission histologically. Repeated dietary questioning revealed that the three CD patients were following the gluten-free diet. However, 30 months after beginning treatment, symptoms of both IPH and CD returned in Patient 7 on stopping the gluten-free diet. Frequent severe exacerbations of IPH recurred despite the fact that the patient continued to take prednisone regularly. Patients were evaluated for a mean follow-up period of seven years (range: two months to 14 years). Lung function was compromised in three patients (Cases 1, 4 and 6), and the poor respiratory prognosis in these patients was attributed to diagnostic and therapeutic delays.

**Discussion**

IPH is an unusual disorder in children. Only about one new case of IPH every three years is diagnosed in our single-

**Table 2  Diagnostic methods.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Chest X-ray</th>
<th>Hb (g/dL)</th>
<th>Siderophages</th>
<th>Intestinal biopsy</th>
<th>CD serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bilateral infiltrates</td>
<td>3</td>
<td>GWF</td>
<td>Normal</td>
<td>AGA++</td>
</tr>
<tr>
<td>2</td>
<td>Pulmonary edema</td>
<td>2.8</td>
<td>GWF</td>
<td>Normal</td>
<td>AGA+++</td>
</tr>
<tr>
<td>3</td>
<td>Bilateral infiltrates</td>
<td>7</td>
<td>GWF</td>
<td>Total villous atrophy</td>
<td>AGA++, EmA+++</td>
</tr>
<tr>
<td>4</td>
<td>Bilateral infiltrates, cardiomegaly</td>
<td>5</td>
<td>GWF</td>
<td>Normal</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>Bilateral infiltrates</td>
<td>4</td>
<td>GWF, BALF</td>
<td>Normal</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Basal bilateral infiltrates</td>
<td>9</td>
<td>GWF, BALF</td>
<td>Normal</td>
<td>AGA+++</td>
</tr>
<tr>
<td>7</td>
<td>Pulmonary edema, pneumomediastinum</td>
<td>4.8</td>
<td>BALF</td>
<td>Total villous atrophy</td>
<td>AGA: 4.5 IU/L&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Bilateral infiltrates</td>
<td>7</td>
<td>GWF, BALF</td>
<td>Normal</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>Pulmonary edema</td>
<td>2</td>
<td>BALF</td>
<td>Total villous atrophy</td>
<td>AGA: 3.2 IU/L, anti-tTG: 28 IU/L</td>
</tr>
<tr>
<td>10</td>
<td>Bilateral infiltrates</td>
<td>8.1</td>
<td>BALF, GWF</td>
<td>Normal</td>
<td>AGA: 0.2 IU/L, anti-tTG: 1 IU/L</td>
</tr>
</tbody>
</table>

Hb: hemoglobin; GWF: gastric washing fluid; BALF: bronchoalveolar lavage fluid; AGA: antigliadin antibodies; ARA: antireticulin antibodies; EmA: antiendomysial antibodies; anti-tTGA: antitissue transglutaminase antibodies.

<sup>a</sup> Normal levels 0.28−2.22 IU/L.
<sup>b</sup> Normal levels ≤ 10 IU/L.
center institution. IPH is more frequent in females than males (gender ratio: 5:1). Although the association of IPH and CD has been rarely reported in the literature, it occurs in nearly three out of 10 patients. The first report of an association between IPH and CD was by Lane et al. in 1971 [6]. The high-frequency of CD in our series may be attributed to the high prevalence of CD in children in Tunisia, which has been evaluated to reach 1/157 to 1/170 among schoolchildren aged 8—10 years [7]. Yet, screening for CD in IPH patients remains controversial. Reading et al. [3] advocate routine intestinal biopsy for all IPH patients, even in the absence of clinical symptoms, whereas Pacheco et al. [5] recommend intestinal biopsy only for patients with positive AGA or ARA of IgG and IgA isotypes. Perelman et al. suggest an intestinal patency test with lactulose—mannitol for all patients with IPH [4]. In our series, only symptomatic patients showed positive CD serology and intestinal villous atrophy on biopsy. In fact, villous atrophy was not consistently observed, and was never seen when serology was negative or digestive symptoms were absent. Thus, CD should be looked for specifically in IPH patients who have digestive symptoms. Furthermore, even in the absence of gastrointestinal symptoms, Malhotra et al. [8] suggest that CD be sought in patients with IPH when the severity of anemia is disproportionate to radiological findings. Screening for CD should be performed with the use of EmA and anti-tTGA, whereas AGA may still be useful in young children. Nevertheless, although positive serology is an important biochemical basis for a diagnosis of CD, intestinal biopsy remains the gold standard [9].

Many previous studies suggest that treatment of CD could lead to remission of IPH [3—5,7,9]. However, the clinical and serological remission of both IPH and CD achieved with a gluten free-diet in CD patients (Cases 3, 7 and 9) are confounded, as the patients also received concomitant corticosteroids. Nevertheless, although CD remission was not confirmed by histology, the return of symptoms of both IPH and CD in the patient who stopped the gluten-free diet—despite continuing corticotherapy—favours an immunological gluten-dependent mechanism. The immunoallergic pathogenesis of IPH has been previously suggested with Heiner syndrome [10]. Also, three pathogenic hypotheses to explain the association of IPH and CD are discussed in the literature: deposition of circulating immune complexes involving food allergens on the basement membrane of alveolar capillaries; reaction between ARA and alveolar basement membrane antigen; and an effect of adenovirus 12, a potential causative factor for CD [11].

In conclusion, although the association of IPH and CD has been rarely reported, it was seen in three out of 10 patients in our series. Investigation of CD in IPH was positive only in patients with digestive symptoms. The relapse of both IPH and CD symptoms in the patient who stopped the gluten-free diet supports a gluten-dependent mechanism for IPH. These data illustrate a close etiopathogenic link between IPH and CD, and strongly suggest that CD be looked for in IPH patients.

References