ORIGINAL ARTICLE

Association of Budd-Chiari syndrome and celiac disease

Association syndrome de Budd Chiari et maladie cœliaque


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Available online 8 October 2010

Summary

Background and aims. — An association between Budd-Chiari syndrome (BCS) and celiac disease (CD) is uncommon. The aims of our study were to investigate the etiology of BCS and to search for a particular HLA Ag pattern among patients.

Patients and methods. — BCS diagnosis was based on Doppler ultrasound and CD diagnosis on duodenal biopsy, transglutaminase (TGAb) and gliadin antibodies (GAb). Patients were screened for prothrombotic disorders and seven had a PCR-SSO test for HLA genotypes. Patients were treated with anticoagulants and gluten-free diet.

Results. — Nine patients were included; mean age 27 years (20—42); sex ratio (F/M) 2; mean follow-up duration 31 months (6—54). All patients had endoscopic and histological features of CD. GAb/TGAb were found in 78% (n = 7). Ag HLA found were HLA DQ-A9251*02 (n = 6) and DQ-A9251*03 (n = 3). Prothrombotic conditions identified were latent myeloproliferative disorder (n = 1), protein C deficiency (n = 1), probable factor V Leiden (n = 1) and oral contraceptive use (n = 1). No prothrombotic state could be identified in the five other patients.

Conclusion. — The BCS—CD association is relatively frequent in our country. Underlying prothrombotic conditions were absent in more than 50% of cases, suggesting CD plays a role in the occurrence of thrombosis. HLA alleles found are strongly associated with CD, without any particular pattern for the BCS—CD association.

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Budd-Chiari syndrome (BCS) is a relatively rare condition characterized by an obstruction of the hepatic venous outflow tract and/or suprahepatic portion of the inferior vena cava (IVC), in the absence of sinusoidal obstruction syndrome, right heart failure or constrictive pericarditis [1]. Its prevalence is estimated at approximately one case per 100,000 inhabitants [2]. The thrombotic obstruction can be due to hereditary deficiency of coagulation factors or acquired prothrombotic condition.

A myeloproliferative disorder is implicated in about 50% of cases [3] and a combination of at least two thrombophilic disorders is found in 25% of cases [4].

Celiac disease (CD) may be implicated in deep venous thrombosis [5–7], but it is rarely responsible for hepatic veins thrombosis. Fifteen cases of CD—BCS association have been reported in the literature [8–15, 17–19]. We report the largest series reported on this pathological association.

The etiological work-up for the prothrombotic condition included: bone-marrow biopsy (BMB) and search for JAK2 mutation (in 7/9 patients) for the diagnosis of myeloproliferative disorder, search for G20210A mutation of the prothrombin gene, a review of autoimmunity (anti-nuclear, anti-smooth muscle, anti-LKM and anti-mitochondrial antibodies) and serology for celiac disease (anti-endomysium (AAE), anti-gliadin (AGA) and/or anti-transglutaminase antibodies (AATG)). We also looked for coagulation protein deficiencies (C, S, anti-thrombin III) (5/9 patients), activated protein C resistance (APCR), anti-cardiolipin antibodies, anti-β2 glycoprotein antibodies (IgM and IgG) and homocysteine levels among patients having a normal prothrombin time. Paroxysmal nocturnal hemoglobinuria was investigated in five patients.

Hepatitis B and C virological markers were searched for systematically. The diagnosis of celiac disease was established based on histological data (subtotal to total villous atrophy, crypt hyperplasia with inversion of the crypt/villi ratio and increased intraepithelial lymphocytes) and serological data (AAG, AAE, AATG). An immunogenetic study was performed in seven patients, assessing for HLA antigens (Ag) class I (A, B) and II (DQ-DR), using molecular biology technique PCR-SSO. All patients were treated by gluten-free diet (GFD), oral anticoagulants (anti-vitamin K) and diuretics in case of ascites.

### Results

The mean age of patients was 27 years, ranging from 20 to 42 years. Female gender predominated (6F/3 M) with a sex ratio of 0.5. CD was diagnosed before the liver disease in three patients, who were under a poorly monitored gluten-free diet (GFD).

The first patient had digestive symptoms including chronic diarrhea at diagnosis of the liver disease. She also had short stature, skin appendages disorders, secondary amenorrhea, ascites and signs of portal hypertension (PHT).

On investigation, this patient had a family history of CD (two brothers carrying the disease). The two other patients had episodic diarrhea.

In the six other cases, the diagnosis of both diseases was simultaneous. The CD was diagnosed during the etiological assessment of BCS.

The liver disease was revealed by ascites in 84% of patients (n = 5) and abdominal pain in 16% (n = 1). On physical examination, short stature was present in 45% of patients (n = 4) and a clinical and/or biological deficiency syndrome in 55% (n = 5). B and C viral serological markers were negative in all patients. The clinical presentation was suggestive of BCS, with hepatomegaly, refractory ascites, splenomegaly and superficial thoraco-abdominal cirrhosis in six patients.

Doppler ultrasound allowed the diagnosis of BCS in all patients, showing an isolated involvement of the HV (thrombosis and/or ostial stricture) in six patients and combined impairment of the HV and IVC in three patients (Table 1).

### Patients and methods

The diagnosis of BCS was based on non-invasive imaging methods: Doppler ultrasound and triphasic CT scan. The diagnosis criteria were the demonstration of direct signs such as an obstruction of the hepatic veins (HV) and/or the IVC and hepatic venous collaterals. Indirect signs such as hypertension of the caudate lobe and "pseudo-HNF" parenchymal nodules were sometimes found.

The etiological work-up for the prothrombotic condition included: bone-marrow biopsy (BMB) and search for JAK2 mutation (in 7/9 patients) for the diagnosis of myeloproliferative disorder, search for G20210A mutation of the prothrombin gene, a review of autoimmunity (anti-nuclear, anti-smooth muscle, anti-LKM and anti-mitochondrial antibodies) and serology for celiac disease (anti-endomysium (AAE), anti-gliadin (AGA) and/or anti-transglutaminase antibodies (AATG)). We also looked for coagulation protein deficiencies (C, S, anti-thrombin III) (5/9 patients), activated protein C resistance (APCR), anti-cardiolipin antibodies, anti-β2 glycoprotein antibodies (IgM and IgG) and homocysteine levels among patients having a normal prothrombin time. Paroxysmal nocturnal hemoglobinuria was investigated in five patients.

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### Patients and methods

The aims of this study were to highlight the clinical characteristics of these patients, to search for other causal factors responsible for the BCS apart from celiac disease and to search for specific HLA antigens, which could explain the frequency of the association of these two affections.

### Table 1: Patient characteristics.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>CD diagnosis</th>
<th>Thrombosis site</th>
<th>Etiology</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>F</td>
<td>Before BCS</td>
<td>HV</td>
<td>-</td>
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<tr>
<td>2</td>
<td>24</td>
<td>M</td>
<td>Before BCS</td>
<td>HV</td>
<td>APCR*</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>F</td>
<td>Simultaneous</td>
<td>HV</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>M</td>
<td>Simultaneous</td>
<td>IVC + HV</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>F</td>
<td>Simultaneous</td>
<td>HV</td>
<td>Oral contraceptives during 3 years</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>F</td>
<td>Simultaneous</td>
<td>HV</td>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>F</td>
<td>Simultaneous</td>
<td>IVC + HV</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>F</td>
<td>Before BCS</td>
<td>HV</td>
<td>Latent MPDb</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>M</td>
<td>Simultaneous</td>
<td>IVC + HV</td>
<td>-</td>
</tr>
</tbody>
</table>

* Activated protein C resistance.
* Myeloproliferative disorder.
Association of Budd-Chiari syndrome and celiac disease

The association of CD and BCS appears to be rather frequent in our country. Indeed, among the 14 published cases, 11 were from North Africa \([8,10,13–15,17,19]\). From 2002–2007, 55 patients with BCS were hospitalized in our unit.

CD was associated with liver disease in 11% of these patients \((n=6)\).

Genetic or environmental factors (geophagia) have been suggested by some authors \([14,15]\) without being formally demonstrated. Others have suspected the passage into the portal circulation of substances present in North African food via an atrophied intestinal mucosa at the occurrence of liver disease \([20]\). Geophagia, intake of toxic substances or special diet, was not found in any of our patients.

The frequency of CD in North Africa could also explain the high prevalence of the BCS–CD association. An epidemiological study conducted in Oran, western Algeria has estimated the incidence of CD at 2.37 ± 1.3 per 1000 live births \([21]\).

Various mechanisms have been suggested: (1) malabsorption of vitamin K causing protein C, S and antithrombin III deficiency, (2) hyperhomocysteinemia secondary to folic acid deficiency, (3) thrombocytosis and (4) association with serum lupus anticoagulant \([9]\). In our series, none of the patients had hyperhomocysteinemia or antiphospholipid syndrome. Thrombocytosis \((422,000\text{ and }581,000/\text{mm}^3)\) was present in only two patients, without any abnormal cell proliferation on the BMB.

Serum titration of coagulation inhibitor proteins has unfortunately not been performed in all patients. It revealed a protein C deficiency 54% in only one patient, who had a low prothrombin time. This deficiency could therefore be secondary to liver failure. Complete family screening for coagulation disorders was impossible.

In summary, only two patients had an obvious cause of thrombosis \((\text{SMP, use of oral contraceptives associated with thrombocytosis})\) and two others had a probable thrombotic condition \((\text{factor V Leiden and protein C deficiency})\). In five other patients, search for a thrombophilic condition was negative, apart from CD.

The immunogenetic study showed no association with particular HLA antigens. The patients had in most cases DQB1*02 and/or DQB1*03 alleles, which are frequently associated with celiac disease \([22]\). Indeed, 95% of patients are either DQ2 (HLA DQA1*05-DQB1*02) or DQ8 (HLA DQA1*03-DQB1*03), compared with 35% in the general population \([16,23,24]\). DQ2 homozygous patients have higher risk of developing the disease than heterozygous patients.

A comparative study with other groups of patients with CD or BCS alone would be useful.

Regarding the clinical course of these patients under treatment, the two with persistent ascites did not abide by

<table>
<thead>
<tr>
<th>Patients</th>
<th>HLA-A</th>
<th>HLA-B</th>
<th>HLA-DR</th>
<th>HLA-DQ</th>
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<tbody>
<tr>
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<td>A*01</td>
<td>B*08</td>
<td>DRB1*03</td>
<td>DQB1*02</td>
</tr>
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<td>B*49</td>
<td>DRB1*07</td>
<td>DQB1*02</td>
</tr>
<tr>
<td>3</td>
<td>A*24</td>
<td>B*13</td>
<td>DRB1*04</td>
<td>DQB1*03</td>
</tr>
<tr>
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<td>A*30</td>
<td>B*40</td>
<td>DRB1*16</td>
<td>DQB1*05</td>
</tr>
<tr>
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<td>B*18</td>
<td>DRB1*03</td>
<td>DQB1*02</td>
</tr>
<tr>
<td>6</td>
<td>A*68</td>
<td>B*53</td>
<td>DRB1*04</td>
<td>DQB1*03</td>
</tr>
<tr>
<td>7</td>
<td>A*01</td>
<td>B*35</td>
<td>DRB1*04</td>
<td>DQB1*02</td>
</tr>
</tbody>
</table>

In seven patients with a good clinical course, the Doppler ultrasound showed persistent thrombosis of the HV and/or the IVC, but with the development of a major portosystemic venous circulation. By contrast in patients with refractory ascites, we noted the persistence of HV thrombosis, complicated by an extension of the thrombosis into the IVC above and below the liver in one patient.

**Table 2** Results of HLA typing.

IVC impairment was seen as a short stricture \((22–25\text{ mm})\) next to the HV ostium, except in one case where thrombosis of the IVC extended above and below the liver reaching the renal veins.

Beside signs of PHT, all patients exhibited a typical endoscopic picture of CD. The diagnosis was confirmed by histological examination of duodenal biopsies. Serological markers of celiac disease were positive in seven patients; two patients were already under gluten-free diet at the time of exploration. No specific HLA class I features were noted (Table 2). Regarding Class II antigens, the patients carried allele DQB1*02 and/or DQB1*03, both alleles known to be strongly associated with celiac disease and alleles DRB1*04 and/or DRB1*07 known for their linkage imbalance with DQB1*03 and *02 DQB1 respectively.

Thrombotic disease assessment revealed a latent myeloproliferative disorder in one patient who had a normal platelet count \((288,000/\text{mm}^3)\) despite significant splenomegaly. BMB found hyperplasia of the three hematopoietic cell lines with megakaryocytic dystrophy. Unfortunately search for the JAK2 mutation was not undertaken to confirm this result. For the six other patients, JAK2 mutation was absent. A lowered resistance to activated hematopoietic cell lines with megakaryocytic dystrophy.

Serum titration of coagulation inhibitor proteins has unfortunately not been performed in all patients. It revealed a protein C deficiency 54% in only one patient, who had a low prothrombin time. This deficiency could therefore be secondary to liver failure. Complete family screening for coagulation disorders was impossible.

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A comparative study with other groups of patients with CD or BCS alone would be useful.

Regarding the clinical course of these patients under treatment, the two with persistent ascites did not abide by
their GFD, while those who maintained an adequate diet were asymptomatic. It is not known whether diet alone is sufficient to explain the clinical outcome.

Patients with refractory ascites ($n=2$) are candidates for a trans-jugular intrahepatic portosystemic shunt (TIPS). One of them has an extensive thrombosis of the IVC associated with HV thrombosis, which is considered as a limiting factor for both TIPS and other therapeutic options such as angioplasty or liver transplantation.

While waiting for a specific treatment, these two patients are being treated by iterative paracentesis with blood volume expansion.

**Conclusion**

The association of CD and BCS appears to be relatively common in our country. An underlying prothrombotic condition was found in less than 50% of the patients in our series, suggesting the role of CD. Factors usually implicated in the occurrence of HV thrombosis in CD, including hyperhomocysteinemia, geophagia, special diet, deficit in protein C and S and thrombocytosis were not always found in our patients. The HLA Ag identified are those frequently associated with CD, with no specific pattern for the BCS–CD association. Other genetic abnormalities other than those of the HLA system should be searched for in these patients.

**Conflict of interest statement**

No conflict of interest.

**References**


