Aetiological factors of Budd-Chiari syndrome in Algeria

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Prospective Study

AIM: To study the clinical presentation of Budd-Chiari syndrome (BCS) and identify the aetiologies of this disease in Algeria.

METHODS: Patients with BCS, hospitalised in our unit from January 2004 until June 2010 were included and the aetiological factors were assessed. Patients presenting a BCS in the setting of advanced-stage cirrhosis or a liver transplantation were excluded from the study. The diagnosis was established when an obstruction of hepatic venous outflow (thrombosis, stenosis or compression) was demonstrated. We diagnosed myeloproliferative disease (MPD) by bone marrow biopsy and V617F JAK2 mutation. Anti-phospholipid syndrome (APLS) was detected by the presence of anticardiolipin antibodies, anti-β2 glycoprotein antibodies and Lupus anticoagulant. We also detected paroxysmal nocturnal haemoglobinuria (PNH) by flow cytometry. Celiac disease and Behçet disease were systematically investigated in our patients. Hereditary anticoagulant protein deficiencies were also assessed. We tested our patients for the G20210A mutation at Beaujon Hospital. Imaging procedures were performed to determine a local cause of BCS, such as a hydatid cyst or a liver tumour.

RESULTS: One hundred and fifteen patients were included. Mean follow up: 32.12 mo. Mean age: 34.41 years, M/F = 0.64. Chronic presentation was frequent...
Budd-Chiari syndrome (BCS) is a rare disease, with an estimated prevalence of 2 per 100000 inhabitants and an annual incidence of approximately 0.2 cases per million inhabitants[2].

The clinical presentation of BCS depends on the extent and the acute or progressive occurrence of venous thrombosis. We distinguish asymptomatic forms of BCS, which are discovered fortuitously, and symptomatic forms, which can be acute or chronic. The acute form is characterised by abdominal pain, ascites and hepatomegaly, without evidence of portal hypertension. This form can be complicated by fulminant hepatitis. The chronic form is difficult to distinguish from cirrhosis regardless of the aetiology. The subacute form is characterised by features of acute BCS with portal hypertension. It reflects an extension of a previous occurrence of thrombosis in the HV.

Primary BCS is the clinical expression of an underlying thrombotic condition that should be identified by an exhaustive aetiological investigation. The causal mechanism of venous thrombosis, which is frequently multifactorial, often involves a myeloproliferative disorder (MPD)[1,2]. The purpose of this work was to identify causal factors of BCS in Algeria. We also sought to study the anatomic aspects and the clinical presentation of BCS in our patients.

MATERIALS AND METHODS

This was a prospective study that included consecutive patients, over the age of 16 years with BCS, who were hospitalised in our unit from January 2004 until June 2010. Patients who presented with BCS complicating advanced-stage cirrhosis and transplantation were excluded from the study. At inclusion, Doppler ultrasound exploration, triphasic computed tomography (CT) and/or magnetic resonance (MR) angiography were performed in all patients, to confirm the diagnosis.

The diagnosis was established when a thrombosis, a stenosis or a compression of hepatic venous outflow (HV and/or suprahepatic IVC) was demonstrated. We also looked for indirect signs of BCS, such as HV dilatation upstream of a stenosis, spiderweb collateral venous circulation between HV, enlarged segment I of the liver or patchy enhancement of hepatic parenchyma.

For the aetiological work-up, we looked for acquired causes of thrombosis, especially MPD, with a bone marrow biopsy (BMB) and a test for V617F JAK2 mutation by real-time polymerase chain reaction (RQ-PCR) (JAK2 MutaQuant kit, Ipsogen). In doubtful cases, a second examination of the BMB was performed in the pathology unit of Beaujon Hospital in Paris. The diagnosis of MPD was established using the World Health Organization 2008 revised criteria[3]. MPD was considered latent if BMB was abnormal and/or if a JAK2 mutation was
found while the blood count was normal.

Tests were conducted to detect anticardiolipin (ACL) IgG and IgM antibodies, anti-β2 glycoprotein antibodies and lupus anticoagulant to determine the presence of anti-phospholipid syndrome (APLS). Patients were considered positive when the results from two successive tests performed within a 2 to 3 mo interval exceeded the cutoff levels of 20 U/L for ACL antibodies and 10 U/mL for AβGP antibodies. Autoantibody tests were also performed to distinguish primary and secondary APLS that may be associated with Lupus.

The classical diagnostic criteria were used to identify Behçet’s disease; genotyping for the Human Major Histocompatibility Complex (HLA) B51 was performed in doubtful cases. To identify paroxysmal nocturnal haemoglobinuria (PNH) in patients with haemolytic anemia and elevated lactate dehydrogenase (LDH) levels, flow cytometry was performed to detect CD55/CD59 deficient peripheral blood cells.

The systematic assessment for celiac disease included tests for anti-endomysium and/or anti-transglutaminase antibodies and duodenal biopsies in patients without major coagulation disorders. PCR for HLA class I and class II antigens was performed in seven patients with both celiac disease and BCS. The work-up included an examination of other acquired prothrombotic disorders including hyperhomocysteinaemia, inflammatory bowel disease and tuberculosis.

We also looked for an inherited cause of thrombosis (i.e., proteins C, S or antithrombin III deficiency). When a family survey was not available, the deficiency in anticoagulant proteins was considered to be a primary disorder in the absence of severe liver failure (prothrombin time > 60%), nephrotic syndrome, acute thrombosis or anticoagulant treatment. Activated protein C resistance was used to diagnose a factor V mutation, because genetic testing (Leiden mutation) was not available. The prothrombin gene was sequenced in 21 patients in the molecular biology unit of Beaujon Hospital, to detect the G20210A mutation.

We also looked for oral contraceptive use or the occurrence of BCS during or after pregnancy. Appropriate imaging procedures were performed to search for a local cause of BCS, notably a hydatid cyst or a liver tumour.

The statistical analysis was performed with SPSS 13.0 (SPSS Inc., Chicago, IL). Estimated variables are reported with the 95% confidence interval. P < 0.05 was considered statistically significant. Fisher’s exact test and the χ² test were used for the comparison of qualitative variables and the Fisher-Snedecor test was used for the comparison of quantitative and qualitative variables.

**RESULTS**

A total of 115 patients were included in this study. The mean time from the onset of symptoms to the diagnosis was 13.03 ± 4.5 mo (range: 4 d-10 years). The mean patient age was 34 years; the M/F sex-ratio was 0.64. The majority of patients were aged from 20 to 29 years at the time of diagnosis. The chronic form of BCS predominated, which was observed in 63.5% of the patients (n = 73). In contrast, the acute form was found in 8.7% of the patients (n = 10) and the fulminant form was observed in 3 patients.

BCS was latent and was discovered fortuitously in 9.6% of the patients (n = 11). In the majority of cases, BCS was revealed by ascites and abdominal pain, as observed in 74.8% and 42.6% of patients respectively. Revealing symptoms are reported in Table 1.

Ascites and gastrointestinal bleeding were more frequent in patients with the chronic form of BCS, however, as might be expected, pain, fever and an elevated transaminase level were predominantly observed in the acute and sub-acute forms of the disease. This difference was highly significant (P < 0.001). Demographic, clinical and laboratory features are reported in Table 2.

The Child-Pugh classification scores at admission were: B (n = 62, 53.9%); A (n = 34, 29.6%); C (n = 19, 16.5%).

Doppler ultrasound was performed in 90% of patients (n = 104) and established the diagnosis in 87%. For the remaining cases, the diagnosis was based on the CT-scan. MR-angiography completed the work-up in 46% of patients (n = 53). According to the radiological investigations, BCS was secondary in 5.3% (n = 6) and primary in 94.7% (n = 109). Secondary BCS was caused by a hydatic liver cyst (n = 5) or hepatocellular carcinoma (n = 1). Isolated involvement of the HV was observed in 72% of patients and both the HV and IVC were involved in 25.2%. Involvement of the IVC alone was observed in 3 patients. Thrombosis in other venous areas was observed in 32.7% of the cases (Table 3). Thoraco-abdominal collateral venous circulation (CVC) was predominant in patients with an isolated HV thrombosis (P = 0.05), whereas lumbar CVC was prevalent in patients with combined HV and IVC thrombosis (P = 0.007). A dysmorphic liver was found in 64.3% of patients (n = 74). Hypertrophy of the caudate lobe was noted in 86.1% of the cases (n = 99). Intrahepatic collateral veins typical of BCS were found in 81.7% (n = 94) and hypervascular regenerative macronodules were observed in 27.8% of the patients (n = 32).

The aetiologies of BCS are reported in Table 4. At least one cause of BCS was found in 77.4% of the cases (n = 89) and a combination of several prothrombotic

| Table 1  Revealing symptoms |
|-----------------------------|
| Symptoms                     | n   | %   |
| Ascites                     | 86  | 74.8|
| Abdominal pain              | 49  | 42.6|
| Jaundice                    | 16  | 13.9|
| Bleeding                    | 14  | 12.2|
| Hepatic encephalopathy      | 6   | 5.2 |
| Fever                       | 18  | 15.7|
| Lower limb edema            | 15  | 13  |
was observed in 34% (\(n = 31\)). The most common aetiologic association was MPD and APLS. Secondary BCS was often associated with an underlying thrombophilia.

MPD was the predominant causal factor of BCS and was observed in 34% (\(n = 36\)) of the tested patients. A BMB was performed in 95 cases (83%) and testing for the JAK2 mutation was performed in 53 patients (46%). The MPD was patent in 19 cases (polyglobulia \(n = 9\); myelofibrosis \(n = 1\)) and latent in 17 cases. Fourteen patients were positive for the JAK2 mutation and 30 patients had signs of MPD on BMB. Among patients with JAK2 mutation, 8 had histological features of MPD. The BMB was not contributive otherwise (\(n = 6\)). Patients with and without MPD were comparable; no statistically significant differences were observed between the groups with respect to the mean age, sex ratio, disease onset or site of thrombosis.

ACL antibodies were detected in 21% of the tested patients (\(n = 20\)), and were associated with systemic lupus in one patient. A second cause of thrombophilia was associated with APLS in 79% of these patients.

Celiac disease was found in 10 patients and was diagnosed during the work-up for BCS in most cases (\(n = 6\)). In these patients, an underlying thrombophilia, apart from celiac disease was noted in only 40% of cases. The immunogenetic study failed to disclose any HLA class I specificity. With respect to the HLA class II antigens, the patients were positive for DQ\(\beta\)1*03 and DQ\(\beta\)1*07.

PNH was found in 4 patients and had been undetected prior to the BCS work-up in 3 of them. Severe anaemia with an elevated LDH level was found in 3 patients; the flow cytometry results were positive in all of these patients (\(n = 4\)). An associated splanchnic vein thrombosis was noted in 27% (\(n = 31\)). The most common aetiologic association was MPD and APLS. Secondary BCS was often associated with an underlying thrombophilia.

### Table 2 Clinical and laboratory characteristics at diagnosis

| Demographic parameters |   |   |
|------------------------|---|---|
| Age (yr)               | 34 (16-72) |   |
| M/F (\(n\))            | 45/70 |   |

| Distribution by age, \(n (\%)\) |   |   |
|---------------------------------|---|---|
| < 20 yr                         | 8 (9) |   |
| 20-40 yr                        | 63 (72) |   |
| > 40 yr                         | 20 (24) |   |

| Clinical parameters, \(n (\%)\) |   |   |
|----------------------------------|---|---|
| Disease onset                    |   |   |
| Acute                            | 8.7 (10) |   |
| Chronic                          | 63.5 (73) |   |
| Subacute                         | 27.8 (32) |   |
| Ascites                          | 62.6 (72) |   |
| Hepatomegaly                     | 62.6 (72) |   |
| Splenomegaly                     | 42.6 (49) |   |

| Biological parameters |   |   |
|-----------------------|---|---|
| ALT (ULN)             | 2.5 (1.6-6.0) |   |
| Bilirubin (mg/dL)     | 20.38 (3-265) |   |
| Prothrombin time (%)  | 57 (14-98) |   |
| Haemoglobin (g/dL)    | 11.7 (3-17) |   |
| RBC (10\(^6\)/mm\(^3\)) | 4.5 (1.7-7.9) |   |
| WBC (10\(^3\)/mm\(^3\)) | 7.7 (1.3-21.5) |   |
| Platelet count (\(10^9/mm^3\)) | 263212 (29000-695000) |   |

| Albumin (g/L) | 29.4 (16.7-45) |
| Thrombocytosis (\%) | 20 (23) |
| Erythrocytosis (\%) | 11.3 (13) |
| Hyperleucocytosis (\%) | 25.2 (29) |
| Cholestasis (\%) | 73.9 (85) |
| Hyperbilirubinaemia (\%) | 41.7 (48) |
| Elevated liver enzymes (\%) | 49.5 (57) |
| Liver failure (\%) | 61.7 (71) |
| Renal failure (\%) | 9.5 (11) |

### Table 3 Radiological features

| Thrombosis site |   |   |
|-----------------|---|---|
| Hepatic veins   | 83 | 72.2 |
| IVC             | 3  | 2.6 |
| IVC and HV      | 29 | 25.2 |
| Associated thrombosis | 37/113 | 32.2 |
| Retrohepatic IVC | 7  | 6.0 |
| Portal vein     | 26 | 22.6 |
| Mesenteric vein/splenic vein | 4  | 3.4 |
| Renal veins     | 4  | 3.4 |
| Iliac veins     | 3  | 2.6 |

| IVC: Inferior vena cava; HV: Hepatic veins. |

### Table 4 Budd-Chiari syndrome aetiologies

| Aetiologies          | Tested patients |   | % (\(n/\text{tested} n\)) |
|----------------------|----------------|---|--------------------------|
| MPD                  | 104            | 36 | 34.6                     |
| Patent               | 19             |   |                          |
| Latent               | 17             |   |                          |
| APL syndrome         | 92             | 20 | 21.7                     |
| Protein C deficiency | 67             | 13 | 19.4                     |
| Protein S deficiency | 59             | 5  | 8.5                      |
| Antithrombin deficiency | 68           | 0  | 0                        |
| APCR                 | 68             | 7  | 10.3                     |
| Celiac disease       | 88             | 10 | 11.4                     |
| Hyperhomocysteinemia | 42             | 5  | 11.9                     |
| PNH                  | 11             | 4  |                          |
| Systemic disease\(^1\) | 106           | 6  | 5.6                      |
| Inflammatory bowel disease\(^1\) | 60 | 5  | 8.3                      |
| Gene II mutation     | 21             | 1  | 4.7                      |
| Liver hydatic cyst   | 115            | 5  | 4.3                      |
| Hepatocellular carcinoma | 115         | 1  | 0.8                      |
| Hormonal factors     | 70             | 25 | 35.7                     |
| Oral contraception   | 70             | 24 | 34.3                     |
| Pregnancy            | 70             | 3  | 4.3                      |
| Hormonal treatment   | 70             | 1  | 1.4                      |
| Unknown aetiology    | 24             | 20 | 20.9                     |

\(^1\)Systemic lupus erythematosus (\(n = 1\)), granulomatosis (\(n = 1\)), sarcoidosis (\(n = 1\)), Behçet disease (\(n = 3\)), \(^1\)Ulcerative colitis (\(n = 1\)), Crohn’s disease (\(n = 4\)). PNH: Paroxysmal nocturnal haemoglobinuria; APL: Anti-phospholipid syndrome; APCR: Activated protein C resistance; MPD: Myeloproliferative disease.

ALT: Alanine aminotransferase; ULN: Upper limit of normal; M/F: Male/female; RBC: Red blood cells; WBC: White blood cells.
thrombosis was also found in 100% of cases (n = 4).

Other acquired causes of thrombosis were: systemic disease (n = 6) and inflammatory bowel disease (n = 5).

Anticoagulant protein deficiency was observed in 28% of patients (n = 18), dominated by protein C deficiency (n = 13). Only 5 patients demonstrated a protein S deficiency, one had a mutation in the prothrombin gene and no patient demonstrated an antithrombin deficiency.

In 3 cases, BCS occurred during pregnancy or during the post-partum period. Nevertheless, a general cause of thrombosis was found in the majority of these patients.

DISCUSSION

This series collected 115 cases of BCS over a period of seven years in a single centre, which corresponds to approximately 18 cases annually. This is comparable with the data provided by the French national BCS observatory (20 new cases/year)[13]. The present series is the largest reported to date in North Africa.

Except for a few series in Asia, where the mean age was less than 30 years[6,7] and the M/F sex-ratio > 1[8], BCS has generally been observed in young female patients[9-11]. This was the case in our series where the M/F ratio was 0.6, and the mean age was 34 years.

The diagnosis of BCS depends on the results of non-invasive imaging techniques. Though the results of Doppler-ultrasound are operator-dependent, its estimated diagnostic yield is 90%, according to recent studies[12-14], or even greater with advanced technical devices such as contrast ultrasound[15]. The diagnostic yield was estimated to be 87% in our series. MR-angiography should be proposed if the diagnosis by Doppler ultrasound is doubtful, because it avoids the radiation exposure associated with CT-angiography. In our work, MR-angiography was performed in only 46.1% of the patients because it was not available before October 2007.

Isolated HV involvement occurred in 72% of our patients. This same pattern is generally reported in the European series[11,16], but not in Asian series, particularly those from Japan, where the M/F sex-ratio > 1[8]. Splanchnic thrombosis, which worsens the prognosis of patients with BCS, was observed in 23% in our series, which contrast with the literature, where this association is noted in less than 14%[8,11]. The number of aetiological factors has been significantly related to the extension of the thrombosis into the splanchnic territory[18]. Indeed, in our patients, multifactorial thrombophilia was more frequently observed among patients with combined BCS and portal vein involvement (34% vs 24% for isolated BCS). An earlier and well-conducted anticoagulant regimen would most likely reduce the rate of this complication which compromises the efficacy of the therapeutic options for BCS.

Our work-up, although incomplete, enabled an etiological diagnosis in 77.4% of cases.

In the literature, the cause of thrombophilia was found in 87%, 72% and 84% of the cases presented in recent studies from India[8], Turkey[19] and Europe[20] respectively. The causes encountered in our work were similar to those observed in Europe, with a clear predominance of MPD. In Southeast Asian countries, bacterial and parasitic infections have been suggested to be risk factors for IVC thrombosis[20,21]. In recent studies from India, the aetiological profile of SBC has changed. Prothrombotic states are now found in more than 60% of the cases in those series[22,23], which is similar to the rates reported in Western series. This could be linked to the widespread availability of diagnostic tests, including the essays to detect the JAK2 mutation.

In our series, the rate of MPD-related BCS did not reach 50% as reported in the Western literature, but was most likely underestimated because only 46% of our patients were tested for JAK2 mutation. The concordance of the JAK2 mutation with BMB was not strong in our study: among the 14 patients with a positive mutation, only 8 (57%) had histological features of MPD on BMB. This finding is most likely related to the poor sample quality of the BMB.

In accordance with the data from the literature[2,9], the second leading cause of BCS in our patients after MPD was APLS. ACL antibodies were detected in 21.7% of the tested patients. An associated thrombophilia was observed in 75% of these patients. This result is comparable with data published by Espinoza from a series of 43 patients with APLS-associated BCS, where ACL antibodies were often associated with another thrombophilic disorder[24].

The rate of factor V Leiden mutation, the most common inherited cause of thrombophilia, was unusually low in our study. However, the only test available for the diagnosis of this condition at our centre was the activated protein C resistance test, which lacks diagnostic reliability, and most likely underestimates the frequency of this condition.

A high rate of celiac disease was also noted in our patients with BCS. This association seems to be frequent in North Africa. We found 16 published cases in the literature until 2012[25-35], and noted that 12 of them were originated from Algeria or Tunisia. Environmental factors, particularly geophagia or special diets might be involved, although they were not demonstrated. These factors were excluded in our patients. The immunogenetic study that was performed did not show any association with a specific major histocompatibility complex antigen in these patients[36]. Further information from a broader genetic study might be useful.

The frequency of celiac disease in Maghreb might also explain the high number of the association of celiac disease with BCS. An epidemiological study conducted in Oran (west Algeria) gave an estimated rate of 2.34 ± 1.3 celiac disease cases per 1000 live births[37]. In our setting, we thus propose a systematic search for celiac disease in the aetiological work-up for BCS.

All of patients with PNH died. The management of these patients was challenging in our setting because
oral anticoagulants were often discontinued when haemolytic events occurred. This led to an extension of the thrombosis to the splanchic veins. It should be noted, however, that Eculizumab was not yet available when this study was conducted. This treatment has significantly improved the prognosis of patients with PNH by reducing the rate of thromboembolic events[38]. Furthermore, in specialised centres, patients with PNH–BCS currently have the same prognosis as other patients with BCS[39].

As mentioned above, the aetiological workup was not exhaustive. The lack of molecular biology techniques constitutes the main limitation of our work. Tests for mutations in JAK2 and prothrombin genes were not performed in all patients, whereas tests for factor V Leiden mutation were simply unavailables. We used indirect methods for the diagnosis of this last condition, which may be insufficient. An improvement in the diagnostic tools should most likely enhance the results of the aetiological investigation in our patients.

In conclusion, this study demonstrates that BCS is not rare in Algeria and that the predominant cause of thrombophilia is MPD, as reported in Western countries. There is however one particular aspect that concerns the presence of celiac disease and hydatid cysts of the liver that should be systematically included in the aetiological work-up of BCS in our geographic location.

**COMMENTS**

**Background**

The relevance of this article is that Budd-Chiari syndrome (BCS) has never been explored in the authors’ region. Practitioners often associated BCS with Behçet’s disease; the authors provided an update on this pathology, imperfectly known, and they proved that the predominant etiology was not Behçet’s disease but the myeloproliferative syndrome.

**Research frontiers**

This is a research work because the authors identified the etiologies of this disease in Algeria, which were not previously known. The results can serve as reference for future works on this field. The authors achieved an aetiological assessment including molecular biology, like JAK2 mutation and prothrombin gene mutation. Some of these tests have required moving abroad to achieve them. For all this, they can consider that this is research work.

**Innovations and breakthroughs**

Some studies have been made in the same field in other Maghreb countries but it was a low sample studies or case reports. The authors work will allow a breakthrough in understanding the etiologies of BCS in their region.

**Applications**

The work has practical applications. Thus, in any patient with Budd-Chiari originated from Algeria or even from Maghreb, practitioners must first search for a myeloproliferative syndrome or systemic autoimmune disease. Celiac disease should also be sought systematically, given the frequency of the association of these two diseases in their study.

**Terminology**

The authors ensured that the words used in the text are easily understood by all scientists’ readers. Abbreviations are always enclosed in parentheses, next to the full name at the first appearance in the text.

**Peer-review**

The authors have performed a good study, the manuscript is interesting.

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