Cerebral Venous Thrombosis in an Adolescent with Celiac Disease
Sara Sabiry, Salma Louzi, Zainab Abdulhakeem, Hicham EL Otmani, Mohamed Abdoh Rafai, Bouchra EL Moutawakil

Hassan II University of Casablanca, Department of neurology and Clinical neurophysiology, IBN ROCHD University Hospital of Casablanca, Morocco

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*Corresponding author: Sara Sabiry, MD

Abstract

Celiac disease (CD) is a gluten-induced or gluten-sensitive enteropathy. It is considered as a chronic autoimmune disease affecting the gastrointestinal tract leading to malabsorption. CD may also affect other systems and it has been described as a disease associated with both arterial and venous thrombotic events. In this presentation, we report a case of a 16-year-old girl who had CD and cerebral venous thrombosis (CVT). We emphasized that CD can be investigated in patients with CVT and it is essential to search for risk factors.

Keywords: Celiac disease, cerebral venous thrombosis, deep venous thrombosis.

Introduction

Celiac disease (CD) is a gluten-induced or gluten-sensitive enteropathy. It is considered as a chronic autoimmune disease affecting the gastrointestinal tract, mainly small intestines, of genetically susceptible individuals, causing malabsorption.

CD may also affect other systems leading to extra intestinal manifestations. Thus; neurological, psychiatric, cutaneous, endocrine, hepatic, skeletal and dental, hematological, oncological, infertility as well as gynecological disorders are continually reported [1, 2].

The incidence of CD-related neurological manifestations has been estimated at 6-10% [1]. Including epilepsy, cerebellar ataxia, central nervous system degenerative disorders and dementia. As for peripheral neuropathy, myopathy, and stroke, they have been rarely reported.

CD has been described as a disease associated with both arterial and venous thrombotic events. Portal vein or Budd-Chiari syndrome caused by abdominal venous thrombosis is the frequently observed condition. CD-related cerebral venous thrombosis (CVT) has been scarcely reported in the literature, especially in adolescents [3, 4]. Pathogenesis is multifactorial and not well known. We report a case of a 16-year-old girl who had CD and CVT.

Case Report

A 16-year-old girl, with a history of recurrent untreated diarrhea since the age of 6, was admitted to our department with a two-week’ history of an acute headache, visual blurring, photophobia without vomiting, associated with confirmed deep venous thrombosis of the left common iliac vein.

The patient reported that, five months earlier, her gastrointestinal symptoms exacerbated leading to dehydration and secondary amenorrhea.

Physical examination revealed normal vital signs, conjunctival and skin pallor with a severely low body mass index at 13.6. Ophthalmic examination noted a stage 1 papilledema and normal visual acuity. Both the neurological and somatic examination was unremarkable.

Brain MRI showed left transverse sinus thrombosis (Figure 1). Lumbar puncture revealed elevated CSF pressure (28 cm H2O) with normal CSF analysis.

Blood testing found a malabsorption syndrome with iron deficiency (microcytic hypochromic anemia at 10.8g/dl), normal vitamin B12 and homocysteine levels, hypocalcemia at 77 mg/L (normal: 90-105 mg/L), hypoalbuninemia at 18.1 g/L (normal: 39-49 g/L) and hypoprothrombinemia (58%). Serum glucose, liver and renal function tests, cholesterol and triglyceride levels, erythrocyte sedimentation rate and thyroid hormone...
values were within normal range. C-reactive protein was negative. Feces analysis and abdominal ultrasound were normal.

Checking for a factor V Leiden, MTHFR and prothrombin 20210 gene mutations, lupus anticoagulant, anticardiolipin, antinuclear and antiDNA antibodies were negative. But low levels of antithrombin III, protein C and S were noted. Anti-tissue transglutaminase and anti-endomysium antibodies were positive. Gastroesophageal endoscopy and duodenal biopsy revealed villous atrophy. The diagnosis of CD was confirmed, and gluten free diet was started. The patient received adequate anticoagulant therapy (heparin then lifelong vitamin K antagonists (VKA) and symptomatic treatments. A favorable long-term outcome was noted. The patient gained weight and remained symptom free.

Fig-1: Brain MRI: a) Axial T1-weighted MRI with contrast and b) MR angiography; showed CVT of the left transverse sinus

**DISCUSSION**

CD is no longer considered a childhood malabsorption syndrome, this autoimmune disease can affect individuals at any time across their lifespan. The disorder is frequently unrecognized by physicians, in part because of its variable clinical presentations and symptoms. CD is easily diagnosed in children with symptomatic malabsorption syndrome but most of them lack this symptom and the clinical picture varies widely at presentation. Genetic, immunological and environmental factors are necessary for the expression of the disease [5].

Classical forms revealed by the triad malabsorption, diarrhea and abdominal pain represent only 10–20 % of cases and clinical presentation is often polymorphic [6]. Neurological presentations are rare in children. Whereas, as many as 36% of adult patients present with neurological changes [7].

The occurrence of thrombosis in cerebral veins during CD remains poorly described. Ungprasert et al, concluded to a significant increase in the risk of encountering thromboembolic events in patients with CD [8]. The pathogenesis of this association is not well defined. It seems, however, that it is related to a hypercoagulability state. Multiple pathogenic pathways [3] and various hypothesis have been proposed: hyperhomocysteinemia secondary to folic acid deficiency due to the malabsorption syndrome was the primary risk factor for venous thromboembolism, protein C and S deficiency secondary to vitamin K malabsorption and thrombocytosis leading to blood's hyperviscosity [9].

Further on, several autoimmune disorders are associated with thromboembolic phenomenon during CD but the antiphospholipid syndrome (APS) is the most known one. In fact, autoimmune disorders (lupus erythematosus and APS) associated with CD, increase the hypercoagulability state as a result of high levels of circulating antibodies [10, 2].

Other mechanisms are still debated, and controversial. Another widely incriminated factor is autoimmune central nervous system vasculitis, in which tissue transglutaminase, the main auto-antigen contributing to maintaining the integrity of endothelium tissue, plays a major role [11].

The initially reported risk factors for stoke and CVT in the pediatric population are: Dehydration, local head and neck or systemic infections, congenital heart disease, and anemia. Whereas, genetic and acquired prothrombotic disorders have, later, been highlighted [12, 13].

Etiologic investigation, in our case, revealed double protein C and S deficit. This latter could be explained by vitamin K deficiency secondary to malabsorption, leading to a thrombophilic status [14]. Other prothrombotic risk factors and predisposing conditions are high level factor VIII, low factor XII, factor V Leiden, prothrombin 20210 and homozygote
MTHFR mutations, as well as high levels anticardiolipin IgG antibodies.

The majority of reported cases, in the literature, were treated with anticoagulation and all with Gluten free diet (GFD) including our patient, but no guidelines exist concerning the VKA’s duration to be considered in these cases. In some patients with recurrent thrombosis, lifelong anticoagulation was decided. Lee et al, showed that the intestinal mucosa does not recover completely and inflammation does not quiet resolve despite strict GFD up to 2 years following diagnosis [9]. Thus, we decided to maintain a lifelong VKA in our patient.

CONCLUSION

In the light of this knowledge, it is established that there is a tendency toward thromboembolic events in patients with CD, especially during acute exacerbation periods. Further studies should focus on the overall relative risk of thromboembolic episodes in patients with celiac disease and identify those patients who need thrombo-prophylaxis.

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