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CASE REPORT

REVISED Case Report: Cerebral venous thrombosis revealing celiac disease [version 2; peer review: 2 approved]

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Abstract

Celiac disease (CD) is an autoimmune enteropathy resulting from intolerance of an individual genetically predisposed to gluten. It has a large clinical polymorphism ranging from a classic digestive clinical presentation due to the malabsorption syndrome to extra-intestinal symptoms. Among the hematologic abnormalities, venous thromboembolic disease (VTE) has been reported, and they are most often located in the abdomen or lower limbs, but the cerebral localization was exceptionally described. We report a case of CD revealed by cerebral thrombophlebitis.

A 44-year-old patient with no medical history and no drug intake, presented with hemiplegia followed by a status epilepticus in a context of apyrexia, initially hospitalized in intensive care. Magnetic imaging resonance displayed a cerebral venous thrombosis of the sigmoid sinus requiring anticoagulant treatment, then transferred to our department for the etiological investigation. On questioning, the patient reported chronic diarrhea and weight loss with no other associated symptoms. The examination revealed an underweight patient with pale conjunctiva, improvement of her deficit symptoms, and no other abnormalities.

Laboratory tests noted biological signs of malabsorption. The thrombophilia assessment revealed a protein C deficiency with a slight increase in anticardiolipin antibodies and anti-Beta 2 glycoprotein 1 antibodies. Immunological tests noted positives anti-transglutaminase and IgA anti-endomysium antibodies. Duodenal biopsy demonstrated villous atrophy. After ruling out the other causes of VTE, the diagnosis of cerebral venous thrombosis secondary to CD was retained. Early diagnosis and treatment of CD improves the quality-of-life for patients and may spare them various long-term or even fatal complications.

Open Peer Review**Approval Status**

	1	2
version 2		
(revision)
10 Sep 2021	view	view

version 1
28 Jul 2021	view	view

1. **Juha Taavela** , Tampere University,
 Tampere, Finland
 Central Finland Central Hospital, Jyväskylä,
 Finland

2. **Bouomrani Salem**, Military Hospital of
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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Celiac disease; venous thromboembolic disease; malabsorption syndrome; Hypercoagulability.

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REVISED Amendments from Version 1

I would like to express my sincere thanks to the reviewers for their constructive comments and suggestions for improving the manuscript.

This versions respond to the reviewer's advices and includes the rest of thrombophilia assessment which is negative factor 2 mutation and lupus anticoagulant, and immunological test which is negative antinuclear antibodies.

I mentioned that protein C deficiency has been reported in previous studies related to CD and due to vitamin K deficiency and particularly malabsorption.

I added two new paragraphs about thromboembolic and cardiovascular complications associated with CD and a proportion of CD is nowadays found while screening in-at risk groups.

Any further responses from the reviewers can be found at the end of the article

Introduction

Celiac disease (CD) is an autoimmune enteropathy resulting from intolerance of an individual genetically predisposed to gluten. It affects 0.6–1.0% of the world population.¹ It has a large clinical polymorphism ranging from a classic digestive clinical presentation due to the malabsorption syndrome; diarrhea and abdominal pain; to extra-intestinal symptoms.² It requires lifelong adherence to a gluten-free diet.

Among the hematologic abnormalities, venous thromboembolic disease (VTE) has been reported in the literature, with a 25% higher risk in patients with CD compared with the general population.³ VTE is most often located in the abdomen or lower limbs, but the cerebral localization has been exceptionally described.⁴

Here, we report a case of CD revealed by cerebral venous thrombosis discovered while exploring a status epilepticus. This clinical situation remains exceptional and unusual during CD.

Case report

A 44-year-old Tunisian female patient, housewife, with no medical history and no drug intake, presented with hemiplegia followed by a status epilepticus in a context of apyrexia, initially hospitalized in intensive care. Neuroimaging displayed a cerebral venous thrombosis of the superior sagittal sinus (Figure 1) requiring anticoagulant treatment (low-molecular-weight-heparin 100 IU/kg $\times$ 2/24 h followed by Warfarin for 6 months. After treatment, the patient was transferred to our department of Internal Medicine for the etiological investigation.

On examination, the patient reported chronic diarrhea and weight loss with no other associated symptoms. Physical examination revealed an underweight patient (BMI:16.9) with pale conjunctiva, improvement of hemiparesis, and no other abnormalities. Laboratory tests noted biological signs of malabsorption. [(Hemoglobin: 10 g/dl (normal range > 12 g/dl), Albumin: 17.9 g/L, cholesterol: 2.8 mmol/l (normal range < 5,1 mmol/l).]

Thrombophilia assessment revealed a protein C deficiency 57% (normal range: 70-120%), a slight increase in anti-cardiolipin antibodies 11 IU/ml (normal range <7 UI/ml) and anti-Beta 2 glycoprotein 1 antibodies 18 IU/ml (normal range <

Figure 1. Cerebral CT scan (A, B: axial plane, C: Sagittal plane) showing a venous thrombosis of superior sagittal sinus (A, C) and a left temporoparietal porencephalic cyst (B).

8 IU/ml) in two tests with 12 weeks apart, normal levels of protein S, antithrombin III and homocysteinemia, and negative factor II mutation, factor V Leiden and lupus anticoagulant. Immunological tests noted positive anti-transglutaminase >50 IU/ml (normal range < 8 U/ml) and anti-endomysium antibodies at 0.6 g/L (normal range < 0.2 g/L) with negative antinuclear antibodies.

From examination and laboratory results, VTE was diagnosed and CD as the cause was suspected. Duodenal biopsy demonstrated villous atrophy, meaning that the diagnosis of CD could be retained after ruling out the other causes of VTE as the neoplastic aetiologies; gynaecologic examination didn't show a lesion, neither chest radiography or colonoscopy.

The outcome of the patient was deemed favorable with anticoagulant therapy (low-molecular weight Heparin followed by Warfarin for 6 months without bleeding complications), combined with a gluten-free diet during the follow-ups over a period of 3-years in our outpatient consultation.

Discussion

CD is defined as a chronic immune-mediated small intestinal enteropathy caused by gluten intolerance in genetically predisposed individuals.⁵ The activation of both the innate and adaptive response of the immune system, following the ingestions of gluten leads to damage to the proximal mucosa of the small intestine, resulting in the malabsorption of nutrients and the appearance of extra-intestinal manifestations.

CD is a systemic disorder, with different forms of clinical manifestations, from a classic digestive clinical presentation to extra-intestinal symptoms. The intestinal form of CD is more commonly found in the pediatric population⁶ and rarely in adults. It includes diarrhea, which is a common presenting sign, in addition to malabsorption symptoms.

Nevertheless, extra-intestinal manifestations are being increasingly recognized, most likely due to better awareness of atypical presentations. They can include chronic fatigue, anemia, osteoporosis, recurrent aphthous stomatitis, elevated liver enzymes, joint or muscle pain, epilepsy, peripheral neuropathy, and infertility⁷ Therefore, it is reported that extra-intestinal manifestations may appear before the diagnosis of CD, as shown in our case.

It has been recognized that chronic inflammation is also an independent risk factor for VTE as the consequence of inflammatory cytokines and oxidative stress on the coagulation cascade is demonstrated.⁸

Our patient presented a deficiency of protein C; which has been reported in previous studies related to CD and due to vitamin K deficiency and particularly malabsorption,⁹ results in the over activity of coagulation factors V and VIII thus increasing the risk for thrombotic events.⁹ We noted also a slight increase in anticardiolipin antibodies and anti-Beta 2 glycoprotein 1 antibodies but it didn't respond to antiphospholipid syndrome criteria which was reported to be associated to CD¹⁰ and as shown in several studies where a higher prevalence of autoantibodies among patients with CD, including anti-phospholipid antibodies (see review of studies in⁹). It is possible that these anti-phospholipid antibodies might also contribute to hypercoagulability.

VTE as a presentation of CD is unusual and rarely reported, especially since this thrombosis is located in the cerebrum and its first manifestation is a status epilepticus.

In fact, other central nervous system manifestations were reported more associated to CD than cerebral thrombosis, including cerebellar ataxia, peripheral neuropathy, seizures, headache, cognitive impairment, and psychiatric symptoms.¹¹ Seizures are nonspecific and can simply be a consequence of cerebral thrombosis.^{12,13}

In addition, thromboembolic manifestations and cardiovascular disease events represent serious extraintestinal manifestations of CD due to malabsorption (vitamin B12 deficiency, vitamin B6 deficiency, folic acid deficiency, vitamin D deficiency, and carnitine deficiency), chronic inflammation, endothelial dysfunction, thrombocytosis, protein C and S deficiency, thrombophilic autoantibodies and atherosclerosis.¹⁴ So a thrombosis assessment should be considered in patients with CD.

The seriousness of these manifestations show that malabsorption syndrome should be systematically investigated to explore any symptoms due to systemic complications of malabsorption, for early diagnosis and better prognosis.¹⁵ These factors must be investigated and corrected by a gluten free diet.¹⁶

Furthermore, a long diagnostic delay may increase the risk of poor clinical response.¹⁷

A significant proportion of CD are found while screening in-at risk groups such as, type 1 diabetes T1D, autoimmune thyroidal and liver diseases, IgA deficiency, family risk, and Down, Turner, and Williams syndromes.¹⁵

Early diagnosis and treatment of CD improves the quality-of-life for patients and may spare them various long-term or even fatal complications like thromboembolic diseases.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of the clinical details and associated images was obtained from the patient.

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Reviewer Report 16 September 2021

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Bouomrani Salem

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The authors have made the requested changes. The paper in its revised version can be indexed without any further modifications.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Autoimmune diseases, Internal Medicine, Thrombophilias

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 13 September 2021

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Juha Taavela

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I accept the article by Wiem et al. entitled "Case Report: Cerebral venous thrombosis revealing celiac disease". The authors have made significant improvements to the intellectual content of the article and I have no further remarks.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Celiac disease, gluten sensitivity

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 27 August 2021

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Bouomrani Salem

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The authors present an original case report of cerebral venous thrombosis occurring in a patient with celiac disease and discuss the causal link between these two pathologies. Indeed, thromboembolic complications are part of the possible extra-intestinal manifestations of this disease with several cases and different locations reported.

The authors insist on the fact that the revealing character, as well as the status epilepticus, is the element which makes the originality of their observation.

Some modifications are necessary before the indexing of this manuscript:

1. Keywords: add "cerebral venous thrombosis" to the list of keywords
2. Introduction: remove the last sentence "This presentation has not been reported previously in the literature." and replace it with "this clinical situation remains exceptional and unusual during CD". Indeed, several cases of cerebral venous thrombosis as the first manifestation of CD have been reported in the literature, some of which are associated with convulsive seizures or epilepsy. Seizures are nonspecific and can simply be a consequence of cerebral thrombosis. This possibility must be mentioned.
3. Case report: the assessment of thrombophilia is incomplete. The other tests should be noted (if they were performed): prothrombin G20210A mutation (Factor II Mutation)? Tumor markers? Anti nuclear antibodies? Lupus anticoagulant?
4. Discussion:

The causal link between CVT and CD must be well discussed and the possible mechanisms of hypercoagulability during this disease well explained i.e. deficiencies in B12, folate and

vitamin K, persistent chronic inflammation, hyperhomocysteinemia, the presence of anti-phospholipids antibodies, fibrinolysis abnormalities, endothelial dysfunction, thrombocytosis, etc.

The presence of antiphospholipid antibodies in this patient should also be discussed: simple positivity of these autoantibodies already reported during CD, or an authentic antiphospholipid syndrome associated with CD (venous thrombosis + positive anticardiolipin antibodies and anti-Beta 2 glycoprotein 1 antibodies). The association of these two autoimmune diseases remains a possible eventuality! ¹ Is the control of these autoantibodies carried out at 12 weeks?

The possible origin of protein C deficiency must also be discussed: a real thrombophilia? protein loss through diarrhea? or the received anticoagulant treatment (Warfarin)?

5. Bibliography: the list of bibliographic references is not well selected. Indeed, to support the discussion, the cases reporting CVT and CD, in particular the inaugural forms and associated with epilepsy, may be cited and used in the discussion: [refs 2-6]

Likewise, the very latest update on thromboembolic and cardiovascular complications associated with CD should be cited in the list of bibliographic references and used to discuss the different possible mechanisms of thrombogenesis during this disease ⁷.

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Is the background of the case's history and progression described in sufficient detail?

No

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Autoimmune diseases, Internal Medicine, Thrombophilias

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 23 August 2021

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Juha Taavela

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The authors have found celiac disease in a patient with venous thromboembolism. I especially like the conclusion that early diagnosis of CD is needed which is an important topic in CD (Popp *et al.*, 2019). The case report is interesting, however, I have some comments:

- The link between celiac disease and VTE is unknown. The authors suggest in the discussion that a thrombosis assessment should be considered in CD patients. Such a conclusion cannot be drawn from a couple of case reports. And the suggestion of thromboembolic prophylaxis is also not supported by such small data. I believe the situation is similar as in IBD, in which the acute phase causes a risk for VTE (Grainge *et al.*, 2010). However, celiac disease is a much easier disease to treat than some IBDs, and such acute situations in the ER are not seen in CD. This must be changed in the discussion.
- Another thing to discuss is that is the cause of protein C deficiency, coagulation factors and anti-phospholipid antibodies CD or just the fulminant diarrhea and nutrition deficiency?

- As a minor remark the article should also mention that a significant proportion of celiacs are nowadays found while screening in-at risk groups such as Graves disease, type 1 diabetes etc (2). And these patients are without any symptoms but they benefit from treatment (Kurppa *et al.*, 2014).

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Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Celiac disease, gluten sensitivity

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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