CASE REPORT

Headache and inflammatory bowel disease: think cerebral vein!

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SUMMARY

Cerebral vein thrombosis is a severe complication of inflammatory bowel disease, can cause non-specific symptoms and hence lead to delay in diagnosis. We report the case of an adolescent with inflammatory bowel disease who developed extensive cerebral vein thrombosis requiring a ventriculoperitoneal shunt. Diagnosis was markedly delayed due to repeated misinterpretation of clinical signs and laboratory findings and the lack of reconsidering the working diagnosis despite the involvement of several medical subspecialties. The patient does not suffer from any neurological impairment. This case report highlights the need for clinicians to maintain vigilance for complications of chronic disease and encourages to cast doubt on the working diagnosis constantly.

BACKGROUND

Research has shown clear correlation between inflammatory conditions and a prothrombotic state.^{1–4} Cerebral vein thrombosis can be fatal and diagnosis is challenging as symptoms are unspecific. The incidence of chronic inflammatory bowel disease is increasing combined with a trend towards younger age at presentation. Thus, a raise of the complication rate is expected and hence we would like to make other clinicians vigilant by emphasising the challenges we encountered to make the diagnosis of cerebral vein thrombosis and disclosing the errors several experienced medical teams made along the way. We would like to encourage clinicians to constantly reconsider their decisions, especially if there is absence of clinical improvement after an otherwise well-established therapy.

When you assess a patient, it is hard not to glide on the predetermined track of the pre-existing condition like in this case, therefore we would like to animate clinicians to go back to basics more frequently: history and examination lead to diagnosis and the most common and the most dangerous differential diagnoses must be considered and excluded from the beginning.

Moreover, there is a lack of specific recommendation for thromboprophylaxis in children with inflammatory bowel disease and hence we would like to initiate consideration of thromboprophylaxis in children with inflammatory conditions.

This case shows an unusual clinical course: despite the large extent of the cerebral vein thrombosis, the patient does not suffer from any neurological impairment. Additionally, the need for a

ventriculoperitoneal shunt for symptom control is uncommon.

CASE PRESENTATION

A 15-year-old adolescent with inflammatory bowel disease unclassified presented to our emergency department with a 3-day history of nausea, vomiting, headache and sporadic abdominal pain along with intermittent bloody stools in recent weeks. Her pancolitis was diagnosed 18 months ago. She had been treated with sulfasalazine and three courses of steroids so far and her current medication was azathioprine. The previous weeks, her inflammatory markers were normal. Two days before presentation, she had contact with children affected by gastroenteritis. Apart from slight abdominal tenderness, the clinical examination was unremarkable. Blood tests on the day of admission showed a C-reacting protein of 86 mg/L, a normal white blood cell count and iron deficiency anaemia (haemoglobin 110 g/L). Other laboratory findings such as liver and pancreas enzymes, creatinine, urea and electrolytes were normal. Albumin was low (26 g/L) as it was during previous weeks. The working diagnosis was 'flare of inflammatory bowel disease' with headache thought to be secondary to active disease and hence she received a first dose of infliximab (5 mg/kg) as her inflammatory bowel disease had become resistant to steroids and azathioprine. Three days later, CRP raised to 191 mg/L, a white cell count was $18.5 \times 10^9/L$ and she was started on intravenous antibiotics because of possible bacterial translocation or bacterial gut infection. Subsequently she felt slightly better and the inflammatory markers decreased, therefore she was discharged home but readmitted 3 days later due to aggravation of nausea. An endoscopy to reassess her extent of disease was cancelled due to logistic issues and in view of presumed poor response to the first infliximab infusion, she received a second dose of infliximab (10 mg/kg). However, she continued to feel unwell with headache, ongoing nausea requiring parenteral nutrition and intermittent abdominal pain without marked tenderness on daily examination. Subsequent endoscopy revealed signs of chronic rather than acute inflammation. She developed a serum sodium of 127 mmol/L, interpreted as due to poor oral intake and congested conjunctival veins, interpreted as conjunctivitis. A second ophthalmology review revealed papilloedema (figure 1). Paediatric neurology advised to perform a lumbar

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Figure 1 Funduscopy showing papilloedema: blurred margins of optic disc, splinter haemorrhages and cotton wool spots.

puncture to rule out infectious causes for increased intracranial pressure and a CT head which was reported as normal. Cerebrospinal fluid showed no hints for infection. An MRI 4 days after the finding of papilloedema showed extensive vein thrombosis within the right transverse sinus, sigmoid sinus and the proximal internal jugular vein (figure 2). The patient received anticoagulation and further medical management, but ultimately required a ventriculoperitoneal shunt for effective

Figure 2 MRI head with intravenous contrast. Extensive thrombus within the right transverse sinus, sigmoid sinus and proximal internal jugular vein (red arrows).

symptom control. Overall, it took 3 weeks from initial presentation to diagnosis. Except for headache and nausea, the patient has never had any other neurological symptoms.

The patient has no family history of thrombosis or prothrombotic conditions.

INVESTIGATIONS

Work-up of possible underlying prothrombotic state (eg, anti-thrombin-III or protein C/S deficiency, lupus anticoagulant, anti-phospholipid antibodies) was negative.

DIFFERENTIAL DIAGNOSIS

In this case, headache and nausea could have been symptoms of active inflammatory bowel disease, a space-consuming process such as bleeding, tumour or brain abscess or of any infectious disease (in particular meningitis)—especially in regard to concomitant immunosuppressive therapy.

The raised CRP and the high white cell count alongside abdominal pain should let one think of acute colitis, bacterial translocation due to inflamed bowel, appendicitis or viral/bacterial gut infection.

Raised inflammatory markers in a (presumed) flare of a chronic inflammatory condition points towards a complication such as venous thrombosis.

Papilloedema can be a sign of optic neuritis or raised intracranial pressure.

The low serum sodium can result from salt losses and dehydration due to diarrhoea and vomiting, renal or heart dysfunction or from hormonal changes (inappropriate antidiuretic hormone secretion, adrenal and thyroid glands). A central process in general needs to be taken into consideration.

Congested conjunctival veins are due to conjunctivitis, iridocyclitis (particularly with the background of inflammatory bowel disease) or venous congestion in the cerebral veins.

TREATMENT

After diagnosis, the patient was started on dalteparin and received topiramate and acetazolamide but finally needed a ventriculoperitoneal shunt for symptom control. From discharge to date, she has been treated with warfarin. In respect of her inflammatory bowel disease, she is on azathioprine and adalimumab, the latter due to an adverse reaction to infliximab several weeks after her admission.

OUTCOME AND FOLLOW-UP

At present, 11 months after diagnosis of cerebral vein thrombosis, the outcome is good, the patient does not suffer from any residual neurological symptoms. The ventriculoperitoneal shunt is still in situ and she is coping well with it.

As of yet, the patient has had five additional CT head venograms showing an unchanged extent of the cerebral vein thrombosis.

Unfortunately, her inflammatory bowel disease worsened lately and she has been commenced on a vedolizumab treatment. She has regular support from a paediatric psychologist.

DISCUSSION

To our knowledge, this is the first case reported in an adolescent with such a delay in the diagnosis of cerebral vein thrombosis and nevertheless, a very good outcome. It is very unusual, that the patient has neither shown any other neurological symptoms than headache and nausea nor has any residual neurological impairments—despite the large extent of the cerebral vein

thrombosis. Several hints in the clinical course should have alerted us: the history of predominant, constant headache—particularly with concomitant raised inflammatory markers and the background of a chronic inflammatory condition—the lack of clinical improvement after an otherwise well-established therapy (infliximab), the severity of the poor clinical state requiring parenteral nutrition and not matching the normal abdominal examination, the low serum sodium, the endoscopic signs of chronic rather than acute inflammation, the congested conjunctival veins without additional signs of classic conjunctivitis and the papilloedema which should lead immediately to appropriate cross sectional imaging regardless of a normal CT scan. The fact that due to logistic issues the extent of the inflammatory bowel disease could not be assessed sooner may have also contributed to the prolonged way to diagnosis.

Four different paediatric subspecialties (gastroenterology, neurology, general paediatrics and ophthalmology) were involved in the care of this patient but nevertheless, diagnosis was only made 3 weeks after initial presentation. It is well known that a holistic view on a patient in the sense of a multidisciplinary approach benefits the patient's care. This case in contrast stresses the difficulty several subspecialties encountered to think outside the box and therefore provide the best care.

Thrombotic complications predominantly occur in a setting of an active flare with significant inflammation. However, signs of

active and/or severe inflammation were not consistently seen in our case: during the weeks prior to admission, the patient was indeed not in full clinical remission regarding her inflammatory bowel disease. She reported intermittent bloody stools as well as periodic abdominal pain and has had repeatedly a low albumin but normal inflammatory markers. On admission, only CRP was mildly raised and a subsequent endoscopy showed rather chronic than active inflammation.

There is no published, evidence-based recommendation for thromboprophylaxis in children with inflammatory bowel disease except for acute severe colitis,⁵ certainly something that the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) might consider as a useful topic in a future position statement.

Our literature review in PubMed revealed very few case reports of children or adolescents with cerebral vein thrombosis and inflammatory bowel disease.^{6–9} There is one published case of retinal vein occlusion in conjunction with inflammatory bowel disease.¹⁰

One retrospective study by Nylund *et al* in over 68 000 hospitalised children revealed an absolute risk for cerebral vein thrombosis of 5.4 and 15.5 per 10 000 hospitalisations in Crohn's disease and ulcerative colitis, respectively.¹¹ Thus, cerebral vein thrombosis is rare but with the increasing incidence of inflammatory bowel disease in children, the likelihood of encountering this potentially fatal complication raises.

Patient's perspective

Last October I was admitted into Addenbrookes hospital. I wasn't very active during it so I don't remember all the details very well. I had been ill with IBD symptoms for most of the summer (since June) and was put on many courses of steroids of prednisolone including a week in hospital having steroids intravenously. They didn't really do anything all summer so when I went back to school in September I was still quite ill. In late August I was put on azathioprine, although I was told that it possibly wouldn't start taking any effect for a few months (It still hasn't taken effect). I started getting the headaches late September/early October, however I don't remember noticing it very much since I was already experiencing lots of discomfort and side effects from steroids (eg, depression, exhaustion, weight gain) and my mum thought it was just a side effect. I can't really describe how it felt different from a normal headache, but it was very painful at points. I had an iron infusion in early October. I also remember getting the headache when I went to see my friend at her house and her younger siblings were sick. When I began getting ill in October we told the hospital this and I was given antibiotics as they thought it may be a bug. I was hospitalised for a few weeks and then sent home, but after the headaches continued and my eyes started looking bloodshot me and my mum called the hospital and we went to clinic 6 to check. I ended up staying at the hospital from then until mid-December.

I experienced bad stomach pain and sickness, especially during the night, until mid-October. My IBD mostly flared down during my stay, and this was helped by my loss of appetite during most of my time admitted at the hospital. I was fed through an IV tube and had many G-tubes as I kept vomiting them out. I felt mostly very sick and my eyes hurt a lot under bright lights. I had to have eye drops for about a month, because of the bloodshot nature of my eyes. I can't remember when or how but I was diagnosed with a blood clot in my head. I had to have many trips to the eye clinics and have regular photos taken of my eyes. I also had multiple MRI scans, CT scans, X-rays, lumbar punctures and an endoscopy while I was there. It was difficult because I wasn't able to move about a lot because I felt very sick, I mostly lay in bed when I could and tried to sleep. I had the shunt surgery in late November and the recovery from the operation made me very sick. In December I began to have a few hours leave from the hospital as I felt a lot better after having adjusted to the shunt.

I think the doctors could have possibly considered that I had a blood clot in my head slightly earlier, as therefore I would have been discharged earlier and may have avoided surgery. I also would have preferred to get off the steroids much quicker as I found their side effects pretty unpleasant. I don't really know what could have been done to make me better faster, however I would have preferred to have got the shunt surgery a lot earlier as I had to have two dalteparin injections every day which was very painful and now I am on warfarin.

I was worried to be discharged as I struggled to start eating again even after the shunt surgery. I feel like the doctors could have explained to me what having a shunt would be like a bit more, like how it feels very noticeable on my neck and head. I also would have preferred not so many attempts at G-tubes, as I ended up vomiting up at least 10 of them, which was very unpleasant.

During my admission, I think the nurses and play specialists were very helpful, especially in helping me understand most of the procedures. Also, everyone involved in the lumbar punctures were very helpful and calming. I also found that the doctors explained everything really well and listened to me, despite me being very ill and reluctant to talk to anyone. All the doctors I met were very kind and patient with me.

Learning points

- ▶ Symptoms that do not easily fit with those of the primary condition must be reviewed with caution and the presence of headache and nausea should prompt cross-sectional imaging in a timely manner.
- ▶ History and exam lead to diagnosis—consider all differential diagnoses and always think outside your ‘specialty box’.
- ▶ Do consider thromboprophylaxis in all hospitalised or immobilised children with a chronic inflammatory condition.

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