SHORT REPORT

A case of posterior reversible encephalopathy syndrome in a child with Crohn's disease treated with Infliximab

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Abstract

Background and aims: Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological entity characterised by headache, seizures, visual disturbance, altered mental status and vasogenic oedema on neuro-imaging. We report a rare case of PRES in a 8-year-old female with Crohn's disease (CD) following Infliximab administration and colectomy.

Method: Clinical case reported including a review of current literature regarding PRES and Infliximab.

Results: This is one of several cases of PRES reported recently in proximity to Infliximab administration.

Conclusions: Awareness of this rare condition in patients receiving immunosuppressive treatment is important to prevent poor outcomes for patients. The increasing number of these cases recognised in patients receiving Infliximab should be kept under close clinical surveillance due to the possibility of a link between the two.

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Introduction

Infliximab is useful in the treatment of severe active paediatric Crohn's disease (CD). We report a rare case of an eight year old girl with severe CD who developed posterior reversible encephalopathy syndrome (PRES), soon after treatment with Infliximab. PRES encompasses a reversible clinico-radiological syndrome of seizures, visual disturbance, altered mental status...
and headache. MRI is recommended for diagnosis and there are characteristic findings of oedema in the subcortical white matter in the regions of posterior vascular blood flow.

Case report

An eight year old Caucasian girl presented to our hospital with a two year history of intermittent bleeding per rectum, abdominal pain unchanged by defecation and poor appetite. The patient was progressing well in full time education. Blood results from diagnosis and at subsequent time points together with Paediatric Crohn’s Disease Activity Index are shown in Table 1 (T1) (Column(C)1). Upper GI endoscopy with ileo-colonoscopy and biopsies were performed. She underwent upper GI endoscopy with ileo-colonoscopy and biopsies. Upper GI endoscopy was macro and microscopically normal. At colonoscopy macroscopically there was erythema and ulceration in the recto-sigmoid area with a clear area of macroscopic sparing before a similar inflamed and ulcerated appearance was seen in the transverse colon before a further area of macroscopic sparing before caecal inflammation. Histological examination confirmed inflammatory bowel disease in keeping with CD with variation in the severity of inflammation, focal submucosal inflammation and with architectural preservation and lack of inflammation in the areas of macroscopic sparing. The clinico-pathological picture combined with the normal small bowel imaging was in keeping with a diagnosis of CD limited to the colon.

She initially commenced exclusive enteral feeds with Modulen IBD as is standard practice in our institution. A week later, her clinical condition had deteriorated, and oral Prednisolone was commenced at 40 mg OD (see T1 C2). There was minimal response and the patient was subsequently admitted for intravenous (IV) hydrocortisone (4 mg/kg) qds. After 1 week of IV steroids (see T1 C3) the patient was commenced on parenteral nutrition and Infliximab was administered at 5 mg/kg (see T1 C4). A week later her clinical condition was unchanged and she proceeded to emergency colectomy.

Laparotomy with total colectomy and ileostomy formation was performed 8 days after Infliximab infusion with subsequent admission to the paediatric intensive care unit (PICU) (see T1 C5). In the immediate post operative period, she experienced significant polyuria (6 ml/kg/day) leading to persistent hypokalaemia (between 2.2 and 3.8 mmol/l) and hypomagnesaemia despite aggressive replacement therapy. During this time period her blood pressure (BP) remained within normal limits for her age.

Five days post operatively, the patient complained of nausea, visual disturbance and subsequently became unresponsive (Glasgow Coma score 3). Her BP at this time was 116/71 and she was apyrexial with dilated, reactive pupils. She then had a left sided focal seizure. During seizure activity she became bradycardic and hypertensive. Fundal examination was normal. Seizure activity continued despite benzodiazepine administration and she was subsequently intubated and ventilated. Rapid sequence induction terminated seizure activity and the patient required re-admission to PICU (See T1 C6). Computer Tomography (CT) scan of the brain showed symmetrical changes of oedema in the subcortical white matter and cortex. EEG suggested right temporal lobe dysfunction. She had two further focal seizures which were controlled with Midazolam and subsequently a phenytoin infusion. After being assessed by a paediatric neurologist, she was commenced on regular phenytoin, Cefotaxime, Vancomycin and Aciclovir.

The following day clinical examination suggested signs of raised intracranial pressure; she was bradycardic, hypertensive, hyperreflexic with evidence of clonus, and had absent venous pulsation on fundoscopy. Magnetic resonance (MR) imaging showed abnormal high signal in the subcortical region, bilateral occipital lobes, and on the right side with extension to involve the right temporal region (see Figs. 1 and 2). There was prominence of sulci, gyri, ventricles and basal cisterns noted. MR angiogram revealed a hypoplastic left posterior communicating artery (a normal variant with

<table>
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<th>Column 1</th>
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<td>Post Infliximab</td>
<td>Colectomy</td>
<td>Seizure</td>
<td>Discharge</td>
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<td>Magnesium (mmol/l)</td>
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<td>0.84</td>
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a W — week.
b CS — corticosteroids.
c ND — not done.
no other abnormalities). The clinical picture and the neuro-imaging were in-keeping with PRES. She underwent neuro-protective measures and her blood pressure was treated aggressively with labetolol and sodium nitroprusside. She improved and was extubated a day later.

Cerebrospinal fluid pressure was normal with normal protein, glucose and cell count with no pathogens identified. Blood, faeces and urine cultures were all negative.

Her post operative period was later complicated by three small intra-abdominal/pelvic collections and a femoral deep vein thrombosis. She was commenced on antibiotics and treatment dose enoxaparin and subsequently warfarin. Her condition gradually improved and she was discharged 8 weeks after admission on azathioprine and warfarin.

At follow up, neuropsychology opinion was sought due to concerns about her memory, verbal comprehension, and possible behavioural regression. On cognitive assessment she had average intellectual functioning but had poor working and phonological memory, which may have been confounded by low mood and high levels of anxiety. She experienced three focal seizures post discharge, one requiring admission to the hospital and treatment with Levetiracitam 300 mg BD and Midazolam as required. She underwent a repeat MRI (11 months post diagnosis) which showed complete resolution of the signal abnormalities identified previously.

The patient’s CD is currently well controlled, and there have been no further seizures at two year follow up.

Discussion

PRES is an acute clinico-radiological syndrome characterised by seizures, visual disturbance, headache and altered mental state. Characteristic MRI findings are oedema of the subcortical white matter in the regions of posterior vascular blood flow shown on T2 weighted and fluid attenuated inversion recovery images (FLAIR). Numerous aetiological factors have been suggested in development of PRES in paediatric patients. Indeed, PRES has been recognised as a neurological complication of hypertension and calcium-neurin administration. The majority of reported cases are in leukaemic patients, and renal disease with limited reports in solid organ tumours. However, there are only two paediatric case reports implicating Infliximab as a possible cause, and one adult case of postoperative PRES in a CD patient recently treated with Infliximab.

In this case, the patient developed PRES whilst a number of pathological processes were taking place. Infliximab is implicated as a possible cause, however the patient developed PRES in the post-operative period (following colectomy) whilst hypokalaemic and on corticosteroids. There has only been one case of PRES reported when the only therapeutic agent was corticosteroids and it is highly unlikely that there is a causal link due to the wide spread use of steroid therapy and the rarity of the clinical syndrome. However, corticosteroid therapy may induce hypertension and subsequently PRES. Furthermore, to date, there is a lack of evidence to suggest hypokalaemia is a contributing factor to developing PRES, with only one previous report of hypokalaemia at the onset of seizures.

The most common side effects of Infliximab treatment are infections and infusion reactions; however neurological complications have been reported. Aside from neurological infections, demyelinating diseases such as isolated optic neuritis, multiple sclerosis and Guillain–Barré syndrome have been reported in association with anti-TNF alpha therapy. In a large cohort study of patients with juvenile idiopathic arthritis 17 neuropsychiatric adverse events occurred during 81 Infliximab treatments. The possibility of infection was considered in view of our patient’s seizure onset 13 days after Infliximab infusion whilst on concomitant corticosteroid treatment. However, the patient was on prophylactic broad spectrum antibiotics and all virology and bacteriology results showed no evidence of infection.

The exact pathogenesis of PRES remains unknown. Two theories have been reviewed by Bartinski. Firstly, the popularised theory is hypertension leading to failed auto-regulation, hyperperfusion and disruption of the blood brain...
barrier (BBB) causing vasogenic oedema. A review by Laat et al. reported 56 children diagnosed with PRES undergoing cancer treatment. They identified 86% of children had an acute hypertensive episode before or during the onset of symptoms. In our case, the patient was normotensive before onset of symptoms and only became hypertensive after seizure onset. In support, Bartinski identified that PRES is commonly seen without hypertension or with BP rarely reaching auto-regulatory limits. Furthermore, there is scant evidence documenting hyperperfusion, with a recent case series demonstrating watershed hypo-perfusion. It also typically develops in patients with a significant systemic process and the extent of brain oedema does not appear to increase with the severity of hypertension.

The second theory suggests endothelial dysfunction/injury of the BBB from direct toxic effect of an offending mechanism. This may be autoimmunity or cytotoxic/immunosuppressive drugs causing subsequent damage to the endothelium, vasoconstriction, hyperperfusion and extravasation of fluid. This can occur with drugs levels within normal ranges. Bartinski concluded that the current literature and current vascular/perfusion imaging renders stronger support for this theory. Infliximab acts by binding to TNF alpha, facilitating cell destruction by antibody dependent cellular toxicity or complement dependent cytotoxicity. This latter theory could explain the mechanism by which Infliximab causes PRES.

In a study looking at acute cerebrovascular complications of IBD in children, 2 of 468 developed PRES but both had recent disease exacerbations with escalation of immunosuppression. The absence of hypertension before onset of symptoms, any other recognised aetiologies and recovery whilst taking corticosteroids possibly implicate Infliximab as a contributing factor to the development of PRES in this case. However, noted in two previous paediatric cases reported, high dose IV steroids were administered for over a week, previous to Infliximab administration and development of PRES. This could indicate high dose steroids or indeed colectomy as a predisposing factor for PRES post Infliximab too. Although considered benign and reversible, prompt recognition, supportive measures and treatment/removal of the cause is vital in ensuring there are no long term sequelae.

In conclusion, it has been consistently highlighted that PRES needs to be suspected in children undergoing immunosuppressive or cytotoxic treatment for cancer or renal disease. However, this case emphasises the need to be vigilant in any patient receiving biological therapy, with a low threshold for removal of the offending therapeutic agent in order to minimise possible morbidity for patients.

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