

Case Report

Cerebral vasculitis in a teenager with Goodpasture's syndrome

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Introduction

Goodpasture's syndrome is a rare condition in childhood. We report a case in which a 14-year-old girl with Goodpasture's syndrome developed seizures due to central nervous system (CNS) vasculitis. At the time of the seizures, anti-neutrophil cytoplasmic antibodies (ANCA) were absent and her anti-glomerular basement membrane (anti-GBM) antibody titre had normalized following 3 weeks of plasma exchange and immunosuppressive therapy. This combination of events has not been reported previously in a child and raises questions as to the aetiology of the vasculitis.

Case

A previously well 14-year-old girl presented with a 3 month history of increasing lethargy followed by a 2 week history of headache, abdominal pain, nausea and vomiting. There was no history of arthralgia, rash, cough or haemoptysis. On presentation, she was pale, but otherwise alert and well perfused. She had a systolic blood pressure of 180 mmHg. Her serum potassium was 7.6 mmol/l, urea 48 mmol/l and creatinine 1726 µmol/l. She had a haemoglobin of 6.7 g/dl. Urinalysis demonstrated glomerular red blood cells with granular casts, a urinary albumin of >1600 mg/l and a urine protein:creatinine ratio of 696 mg/mmol (normal <20). Her renal ultrasound demonstrated two bright kidneys of normal size with loss of cortico-medullary differentiation. Renal biopsy showed a severe crescentic necrotizing glomerulonephritis with intense linear deposition of IgG on

glomerular capillary walls. There were no immune deposits on electron microscopy and the glomerular basement membrane was of normal thickness. Complement levels were normal. She was ANCA negative, but had a raised anti-nuclear antibody (ANA) of 320 (normal titre <10), with no double-stranded DNA antibodies, an anti-smooth muscle antibody (sm Ab) titre of 60 (normal <20) with normal liver function tests (bilirubin 8 mmol/l, ALP 99 mmol/l, ALT 8 mmol/l) and anti-GBM antibody titre of 400 U/ml (normal <20), confirming a diagnosis of Goodpasture's syndrome.

Respiratory review revealed fluid in the right horizontal fissure on chest X-ray and haemosiderin-laden macrophages on bronchial alveolar lavage. Lung function tests including carbon monoxide transfer were reassuringly normal. She was dialysed within 24 h of presentation and, in view of the respiratory findings, was started on prednisolone (1 mg/kg), intravenous (i.v.) cyclophosphamide with planned monthly infusions (500 mg; reduced in view of glomerular filtration rate <10 on presentation), and 14 sessions of daily plasmapheresis. Anti-GBM titres fell rapidly in response to treatment and were negative at 2 weeks. The non-specifically raised ANA and sm Ab titre were unaltered by treatment.

On day 29 of admission, she had three generalized convulsions over a 5 h period. She was loaded with phenytoin and subsequently started on maintenance treatment. At the time of the seizures, she was normotensive and serum biochemistry was within normal limits (Na 141 mmol/l, K 4 mmol/l, Ca 1.12 mmol/l, Mg 0.83 mmol/l, glucose 6 mmol/l). ANCA levels were still negative, as were the anti-GBM titres. A magnetic resonance imaging (MRI) scan of the brain (Figure 1) was consistent with bilateral cortical ischaemia of the occipital lobes, seen best on FLAIR (fluid-attenuated inversion recovery) sequence, but with no evidence of abnormality on diffusion-weighted imaging. Time of flight MR angiography did not show any abnormality of the major intracranial vessels. A provisional diagnosis of CNS vasculitis was made. For this reason, her treatment was intensified to 3 weekly cyclophosphamide, and plasmapheresis was re-started.

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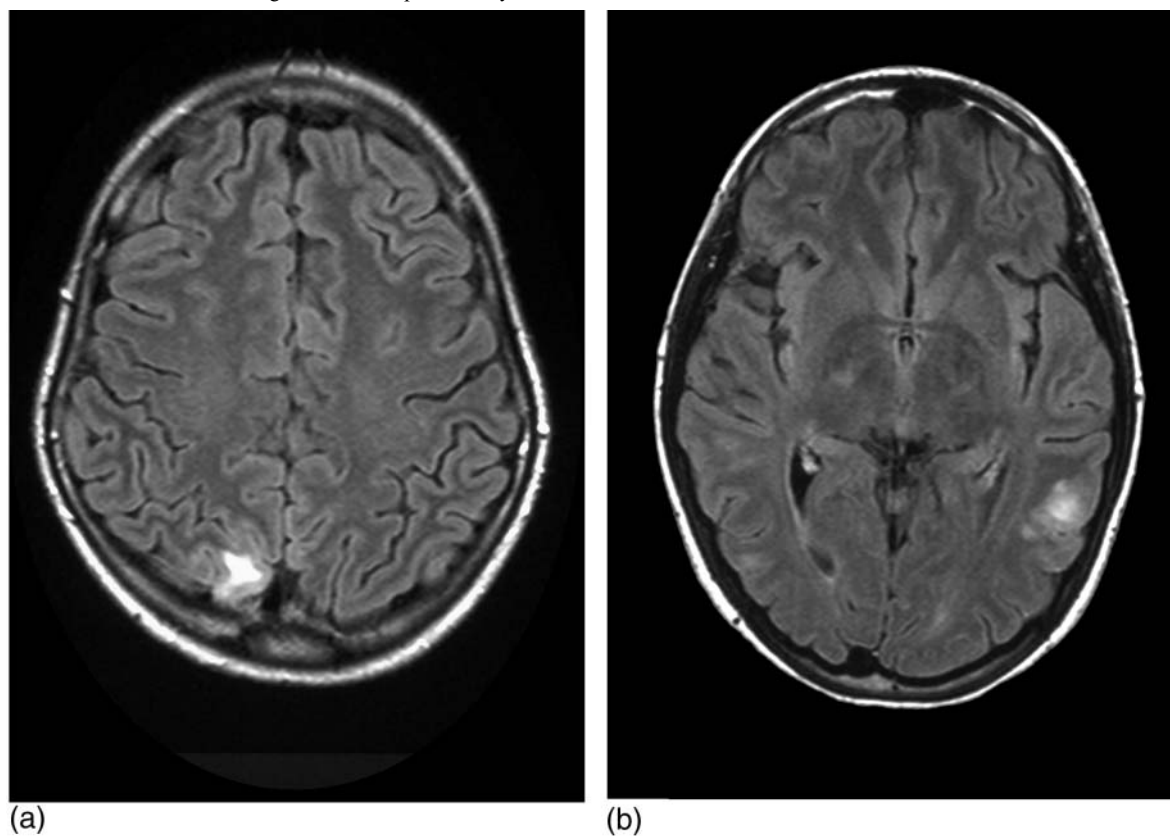


Fig. 1. MRI abnormalities on FLAIR sequence, at the time of first presentation with seizures. (a) Occipital involvement. (b) Left parietal area.

Three days after starting the intensified treatment course, the patient had a significant rectal bleed, leading to a drop in her haemoglobin by 4 g. A red cell scan delineated a possible bleeding point in the small bowel. Meckels scan was normal. In view of the previous CNS findings, the bleeding was considered to be vasculitic in origin, exacerbated by the use of heparin anticoagulation during plasmapheresis. Anti-GBM antibody and ANCA titres remained negative, and ANA and sm Ab were unchanged. Plasmapheresis was discontinued.

The patient underwent a follow-up cranial MRI scan on day 42, which showed complete resolution of the previous abnormalities. She was discharged on a weaning course of prednisolone and 3 weekly i.v. cyclophosphamide (planned for a duration of 6 months). However, 4 weeks after discharge, by which time her prednisolone had been weaned to 40 mg on alternate days, she had a second seizure. Clinical parameters remained unchanged, i.e. she was normotensive, had normal biochemistry (Na 140, K 4, glucose 6.3, Ca 1.22) and was both anti-GBM antibody and ANCA negative, with raised ANA and marginally raised sm Abs. Phenytoin levels were within the therapeutic range. A further MRI showed extensive multifocal signal abnormalities, this time with evidence of abnormality on diffusion-weighted sequence (Figure 2). Conventional arteriography was normal. She again responded well to an increase in her immunosuppressive treatment (reverting to high dose

daily prednisolone). Three weeks after this event, a fourth MRI was normal.

The patient has remained clinically well since, with no further seizures or neurological sequelae. Her prednisolone has been weaned to 5 mg on alternate days, and she has completed a 6 month course of 3 weekly i.v. cyclophosphamide. Recurrence of CNS disease is being monitored by serial MRI scanning. Her ANA and sm Ab have remained marginally elevated but with no clinical suggestion of progression to other autoimmune disease. She has remained dialysis dependent, and a renal transplantation is planned once she has remained well and anti-GBM antibody negative for 12 months. She does have an identically matched living related donor. However, a recent case report has highlighted a potential concern that an identical HLA-matched kidney may be at increased risk of recurrent anti-GBM disease, which is otherwise extremely rare [1].

Discussion

In 1919, Goodpasture reported an 18-year-old male who developed glomerulonephritis and pulmonary haemorrhage during a probable influenza epidemic [2]. At autopsy, there was also evidence of systemic vasculitis with haemorrhagic changes in the small intestine and focal necrosis of the spleen. No evidence of vasculitis in other organs was found, although there is

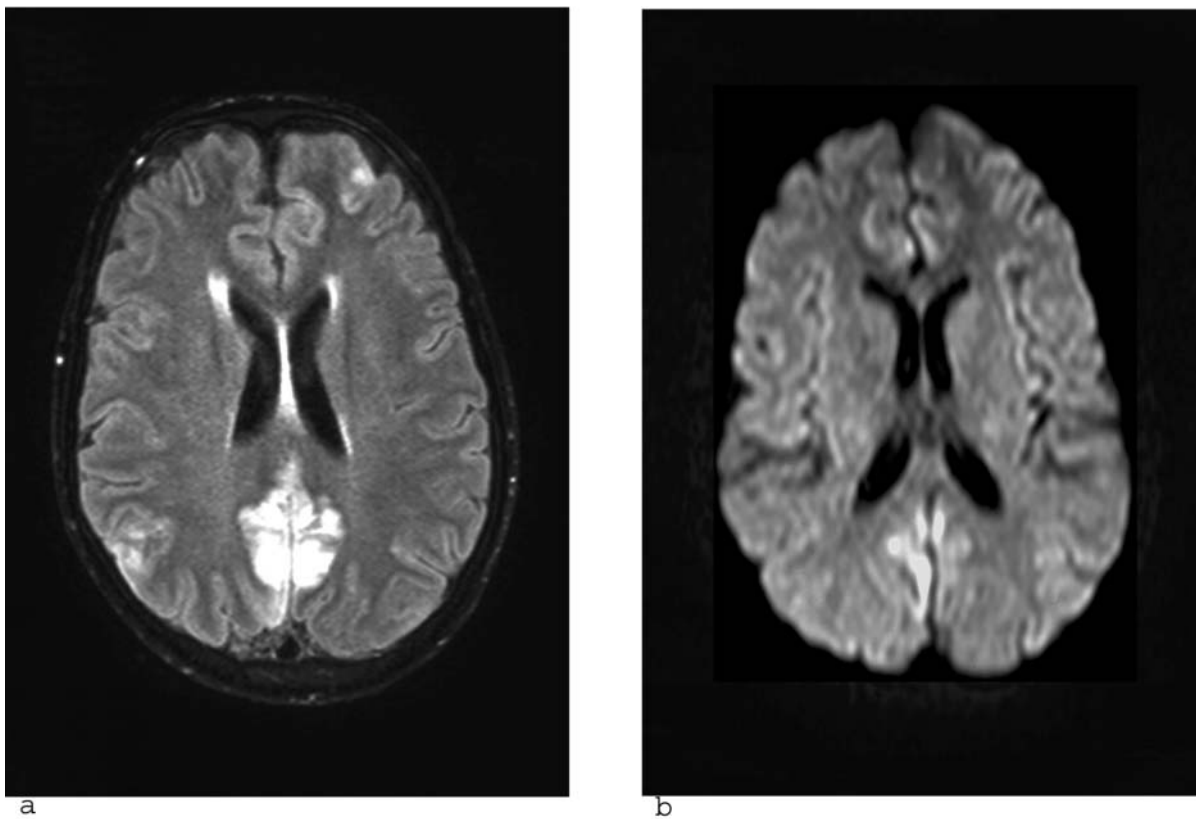


Fig. 2. MRI abnormalities at the time of second presentation with seizures. (a) Transverse section, FLAIR sequence. (b) Abnormalities on diffusion-weighted imaging.

no specific mention of whether the brain was studied. Goodpasture's syndrome has since been defined on the basis of rapidly progressive glomerulonephritis and pulmonary haemorrhage in the presence of anti-GBM antibodies. The Goodpasture antigen has been identified within the non-collagenous domain (NC1) of the α -3 chain of type 4 collagen [3].

Although Goodpasture's syndrome is only rarely associated with other autoimmune diseases [4], its association with ANCA-positive vasculitis has become increasingly recognized [5]. Goodpasture's syndrome is a rare diagnosis in childhood, with <10 confirmed anti-GBM-positive cases reported in the recent literature. It is, however, our patient's ANCA-negative status in the presence of CNS vasculitis that has proven to be the most unusual feature. This has only been reported in two previous cases, both in adults.

The first case [6] was an 18-year-old man with Goodpasture's syndrome who developed seizures progressing to status epilepticus. MRI showed multiple lacunar infarcts suggestive of a vasculitis which was subsequently proven on meningeal biopsy. In this instance, the anti-GBM antibodies were still elevated (83 U, having fallen from a peak of 1780 U). The patient made a good neurological recovery following an increase in his immunosuppression. He received a living-related renal transplant 1 year after initial presentation.

A second such case was reported in 2003 [7] in a 55-year-old woman who developed episodes of confusion in the year following her diagnosis with Goodpasture's syndrome. Neurological signs varied but included aphasia and evidence of frontal lobe dysfunction. An MRI showed a left parietal area infarct, and cerebral angiography showed multifocal stenoses affecting the distal branches of the middle cerebral artery bilaterally. Her anti-GBM antibody status during each episode is not quantified other than normalization after the resolution of the first confusional episode. Repeat angiography 9 months later was normal following immunosuppressive treatment. Interpretation of the findings in this case is complicated by the presence of hypertension (BP 190/140).

In our subject, the diagnosis of Goodpasture's syndrome was made on the basis of a significantly elevated anti-GBM antibody, intense linear deposition of IgG along the GBM on immunofluorescence and normal thickness basement membrane on electron microscopy. The diagnosis of cerebral vasculitis was made on the basis of clinical presentation and MRI findings and supported by the rapid response to immunosuppressive treatment. The finding of normal vessels on either conventional or MR angiography does not exclude a diagnosis of small vessel vasculitis. In fact, in one series of 14 patients with biopsy-proven primary cerebral angiitis, 64% had normal angio-

grams [8]. Although brain biopsy is still considered the gold standard in diagnosing CNS vasculitis [9], it was not performed in this case in view of the clinical response to treatment and the potential risks involved.

The aetiology of the vasculitis is unclear. Rydel *et al.* speculate on the role of anti-GBM antibodies in CNS vasculitis in Goodpasture's syndrome [6]. However, in our patient, anti-GBM antibodies were in the normal range at the time of the CNS symptoms on both occasions and the anti-GBM titre was normalizing in Rydel's patient at the time of presentation with seizures. The findings of a raised ANA and marginally raised sm Abs in our patient are non-specific, and diagnostic criteria for other autoimmune disorders have not been met.

In conclusion, we report the case of a 14-year-old girl with Goodpasture's syndrome in end-stage renal failure who developed CNS vasculitis in the absence of ANCA or of persisting anti-GBM antibodies. This has raised several important issues. First, how should the cerebral vasculitis be monitored in order to tailor immunosuppressive treatment? This was particularly relevant in our case, with her second seizure occurring whilst still on a substantial dose of prednisolone. As cranial MRI scans reflected her neurological state, and in the absence of other reliable markers, we elected to use serial MRI scans to monitor the course of her CNS disease. However, the sensitivity of MRI scans in angiogram-positive CNS vasculitis is ~75% [10] and as such may not be appropriate for less significant disease. Secondly, the benefit of an identically matched donor must be weighed against the potential risk of recurrent disease and perhaps even recurrent CNS vasculitis. The most challenging issue, however, remains the aetiology of the vasculitis. Without this

knowledge, markers for monitoring effective treatment remain elusive.

Conflict of interest statement. None declared.

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