Teaching Point

A patient recently transplanted with a living donor kidney develops severe neurological symptoms

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Case

One week after receiving a kidney transplant donated by his father, a 20-year-old patient was transferred to our department. The history of his kidney problems started when he was 1 year old. He had obstructive nephropathy requiring repeat urological operations and resulting in end-stage renal failure necessitating chronic haemodialysis from the age of 8 until this recent transplantation. His post-transplantation immunosuppressive regimen consisted of ciclosporin, mycofenolate mofetil and prednisone. A few days after his transfer to our department, he developed a biopsy-proven borderline transplant rejection, which was treated with high doses of cortisone. His repeated complaints of headaches were attributed to the cortisone, and they resolved without any treatment. A few days later, he developed blurred vision in the right eye, and that was followed by a generalized seizure. On the very same day—the 15th day after his kidney transplantation—he had to be transferred to the intensive care unit for a status epilepticus. His blood pressure was normal—the highest ever being 150/80 mmHg. His blood tests on the day of the onset of neurological symptoms showed the following: BUN 23 mg/dl, creatinine 1.0 mg/dl, Na 134 mmol/l, K 3.8 mmol/l, Ca 2.1 mmol/l, erythrocytes 3.7 x 10⁶/l, haematocrit 37%, haemoglobin 12.5 g/l, leucocytes 8200/l, thrombocytes 246 000/l, albumin 33 g/l, CRP 3 mg/l. Apart from the time of borderline rejection, when his creatinine rose to a maximum of 1.6 mg/dl, his blood tests were normal throughout his stay in the department. His ciclosporin trough levels had a mean value of around 250 ng/ml.

Computed tomography (CT) showed hypodense areas mainly in the posterior white matter of his brain. Our radiologist suspected a posterior reversible encephalopathy syndrome (PRES). Magnetic resonance tomography (MRT) confirmed the diagnosis of PRES by showing the characteristic hyperintense parieto-occipital white matter lesions in the T2-weighted images (Figures 1 and 2). There was no involvement of the grey matter.

Ciclosporin was discontinued immediately and replaced with rapamycin. Our patient recovered within days, showing no residual symptoms. A follow-up MRT was normal (Figure 3): all lesions had resolved. He has since been asymptomatic, with a serum creatinine of 0.9 mg/dl, and on an immunosuppressive regimen consisting of rapamycin, mycofenolate mofetil and low dose prednisone.

Discussion

The posterior reversible encephalopathy syndrome was first described by Hinchey et al. [1]. It was then referred to as the leukencephalopathy syndrome. Hinchey reported on 15 patients diagnosed with this syndrome with varying triggers. The earliest description of epileptic fits in transplant patients is by Adams et al. [2] in 1987. In their article, the authors claim the evidence implicating ciclosporin in the development of fits to be strong. The syndrome was later renamed as to posterior reversible encephalopathy syndrome, because of its greater accuracy.

PRES can be triggered by interferon-α, IV immunoglobulin, erythropoetin, cisplatin and cytarabine, or it can be associated with diseases like lupus erythematosus, panarteritis nodosa, AIDS or thrombotic-thrombocytopenic purpura. However, most cases of PRES are described in association with eclampsia, malignant hypertension and immunosuppressive therapy [3]. The most frequent triggers among immunosuppressants are calcineurin inhibitors, among those ciclosporin being more prone to cause PRES than tacrolimus [4]. The symptoms of PRES...
typically occur around day 14 of calcineurin inhibitor therapy. Though the mechanism of brain injury is not fully known, the posterior localization of the damage is thought to be due to the lack of sympathetic fibres in the posterior cerebral arteries; the hyperperfusion and oedema are suggested to be responses to a hypertensive or toxic damage to the wall of the vessels [3].

The common clinical features of PRES are headache and seizures [3]. The onset is acute, with rapid progression to multiple seizures, usually of the generalized tonic–clonic type. Other neurological symptoms, like confusional states, vomiting, visual disturbances—such as haemianopia, or cortical blindness, and occasionally focal neurological deficits may follow. Occasionally, coma may also develop [3].

The differential diagnosis of PRES includes various acute neurological conditions, such as stroke, cerebral venous thrombosis, encephalitis and demyelinating disorders. As mentioned earlier, the diagnosis is made mainly by radiologists [5]. CT scans of the brain show bilateral and mostly symmetrical hypodense areas in the parietal and occipital white matter; the involvement of the grey matter, however, is also possible. The lesions are best visualized by magnetic resonance imaging (MRI). T2-weighted MRIs show characteristic diffuse hyperintensities selectively involving the parieto-occipital white matter. The lesions are even better demonstrated by fluid attenuated inversion recovery imaging (FLAIR, another special MRI technique) where the cerebrospinal fluid signal is nulled to emphasize the oedematous lesions [6]. MRI also rules out cerebral venous thrombosis, demyelinating diseases and ischaemic stroke, the latter by diffusion-weighted imaging, another MRI technique [7]. Diagnosing viral encephalitis is difficult, and for this a lumbar puncture may be needed [3].

With PRES, it is of paramount importance to identify and treat the underlying cause rapidly,
e.g. in our case, by discontinuing calcineurin inhibitor therapy. Furthermore, it is extremely important to recognize a PRES, because an adequate therapy for PRES is different from that therapy of other neurological conditions. While moderate hypertension would not be treated in an ischaemic stroke, for example, it must be treated vigorously in PRES to reverse the pathological process before it causes permanent brain injury [3]. With rapid elimination of the cause, most PRES are fully reversible within days. There are, however, cases reported in the literature where symptoms did not fully resolve, especially when the lesions were not restricted to the white matter or when there was a delay in the administration of the correct therapy [8].

Teaching points

- If a patient develops severe neurological symptoms about 2 weeks after the initiation of calcineurin inhibitor therapy, consider the possibility of the patient having a posterior reversible encephalopathy syndrome. PRES can also occur with hypertension, eclampsia and with a variety of drugs and diseases.
- The onset of PRES is acute, and with heavy neurological symptoms, often including headache and seizures.
- PRES is diagnosed by the radiologist, based on its typical patterns in the CT scan, or more reliably, based on an MRI of the brain. Differentiation from other cerebral injuries is made by special MRI techniques.
- PRES is generally reversible, especially when treated rapidly. The treatment is simply the withdrawal of the calcineurin inhibitor therapy, or, if PRES is due to hypertension, normalization of blood pressure.

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References


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