Case Report

Hypertension, cerebral oedema and fundoscopy

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Introduction

In 1914, the German physicians Volhard and Fahr introduced the name ‘maligne Form der Hypertonie’ for a syndrome consisting of a severe elevation in blood pressure (BP) accompanied by signs of acute end-organ damage [1]. They noted that neurological signs and symptoms were often part of the clinical picture and emphasized the serious prognostic importance of certain fundoscopic changes. By analogy the term ‘malignant hypertension’ was applied by Keith and Wagener in 1921 when they observed papilloedema in patients with severe hypertension [2]. In 1928, Oppenheimer and Fishberg described a 19-year-old college student who suffered from severe hypertension coinciding with repeated bouts of headache, neurological deficits and convulsions and first used the term ‘hypertensive encephalopathy’ (HE) [3]. Although the characteristic retinal signs of malignant hypertension were not present at presentation but developed later in the course of the illness, fundoscopy became a very useful tool in the diagnosis of HE. Nowadays bilateral retinal haemorrhages and/or exudates are also included in the definition of malignant hypertension because further research has indicated that survival rates of patients with haemorrhages and/or exudates with or without additional papilloedema were equal [4,5]. The presence of severe acute end-organ damage decides whether a patient needs a carefully controlled immediate reduction of BP [6]. In this report we describe three patients who suffered from HE, yet in whom the classical retinal signs of malignant hypertension were lacking. The diagnosis HE could, however, be confirmed quickly by the use of recently developed techniques in cerebral imaging.

Case 1

A 21-year-old woman was transferred to the ICU of our hospital because of generalized tonic-clonic seizures complicated by respiratory insufficiency. Two weeks earlier she was admitted to another hospital because of nephrotic syndrome and renal failure. She had gained 20 kg of body weight over the previous months and generalized oedema was noted. Renal biopsy showed membranoproliferative glomerulonephritis with characteristic signs of dense deposits disease on electron microscopy. Treatment was started with prednisolone 60 mg a day. Several days later the patient complained of headache. An increase in BP was noted; metoprolol and amlodipine were prescribed. However, at the day of transfer BP still measured 160/110 mmHg. At admission she was pale, afebrile and drowsy. No other abnormalities were noted except for the generalized oedema. Laboratory examination showed a normochromic normocytic anaemia of 5.6 mmol/l. No fragmentocytes were noted in the blood film. Thrombocyte and reticulocyte counts were normal. Serum chemistry panel showed a creatinine of 334 μmol/l, albumin 22 g/l, with normal values for sodium, potassium, ionized calcium, LDH and bilirubin. ECG was unremarkable. Fundoscopic examination performed by an ophthalmologist revealed vasospastic arterioles, but no other abnormalities. Magnetic resonance imaging (MRI) of the brain (Figure 1A) revealed areas of increased signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images that were located bilaterally in the cortical grey and subcortical white matter of the frontal and parietal lobes. These lesions demonstrated increased signal intensity on diffusion weighted images (DWI) (Figure 1B), and decreased signal intensity on apparent diffusion coefficient (ADC) maps, which pattern is characteristic for cytotoxic oedema. No enhancement following gadolinium was detected. HE was diagnosed and the patient was treated with i.v. phenytoine to control seizures and i.v.
labetolol to lower BP. After a substantial BP reduction had been achieved, oral antihypertensives were initiated consisting of enalapril and nifedipine. Furosemide was also administered. The prednisone treatment was continued and azathioprine was added. The patient made a full neurologic recovery and the peripheral oedema disappeared. In 3 weeks time the serum creatinine gradually declined to 153 \( \text{mmol/l} \) and the corresponding creatinine clearance rose from 15 to 48 ml/min. Proteinuria decreased from 11.9 to 6.9 g/24 h. Two months after her admission, creatinine clearance had increased further to 74 ml/min, serum albumin was normal and proteinuria measured 1.5 g/24 h. A repeat MRI of the brain (Figure 1C) showed that most lesions had disappeared except for a small area of increased signal intensity in the cortex of the frontal lobe on FLAIR images, which may represent an area of gliosis.

**Case 2**

A 53-year-old woman was admitted with generalized tonic-clonic seizures of focal onset and a 2-day history of headache, nausea and vomiting. Her medical history included progressive severe renal insufficiency (creatinine clearance 14 ml/min) attributed to reflux nephropathy and hypertension for which a daily dose of 100 mg of metoprolol was prescribed. Further medication consisted of calcium acetate and alfacalcidol. Four days before admission, she was seen as an outpatient and an increase in her BP from 135/80 to 160/110 mmHg was recorded and the metoprolol dose was increased to 200 mg. On admission the patient was drowsy, and her BP measured 180/120 mmHg and discrete pedal oedema was noticed. Laboratory examination showed a normochromic, normocytic anaemia of 5.7 mmol/l with normal reticulocyte counts. No increase in fragmentocytes was seen in the blood film and serum LDH and bilirubin concentration was normal. Serum creatinine was stable at 391 \( \mu\text{mol/l} \), sodium, potassium, ionized calcium and phosphate was normal. Proteinuria measured 3.2 g/24 h, with a blank urine sediment. The ECG was normal. Fundoscopy revealed arteriolar vasospasm but no other pathologic changes. A CT scan of the brain was unremarkable but MRI revealed a pattern of bilateral symmetric cortically and subcortically located areas of increased signal intensity in the frontal, parietal and occipital lobes seen on T2-weighted and FLAIR images. DWI and ADC maps did not show changes indicative of cytotoxic oedema, and following gadolinium no enhancement of brain lesions was found. These signal characteristics suggest that the abnormal areas represented areas of vasogenic oedema. She was treated with i.v. phenytoine and additional BP lowering therapy consisting of nifedipine slow release and also furosemide was given. Her body weight dropped 3.3 kg, pedal oedema disappeared and BP normalized. Serum creatinine remained stable. Symptoms and signs resolved completely.

**Case 3**

A 46-year-old female on chronic haemodialysis with renal failure of unknown aetiology presented with generalized tonic-clonic seizures preceded by headache. On admission, BP measured 190/110 mmHg and some pretibial oedema was noted. At laboratory examination no signs of thrombotic microangiopathy were found. Serum sodium, potassium and ionized calcium were normal. Phosphate level was moderately elevated at 1.58 mmol/l. The ECG was normal. No abnormalities were found at fundoscopy except for arteriolar vasospasm. MRI of the brain showed a pattern of symmetric bilateral areas of increased signal intensity.
Discussion

We describe three patients, one with glomerulonephritis, one with preterminal uraemia and one on chronic haemodialysis who developed HE. Remarkably, in none of them fundoscopic signs of malignant hypertension or laboratory signs of thrombotic microangiopathy were found.

HE represents a medical emergency characterized by the rapid onset of headache, nausea, vomiting, altered consciousness, convulsions, visual loss and a variety of other neurologic deficits. The syndrome is generally precipitated by a severe and rapid rise in pre-existing BP. After BP reduction all signs and symptoms may quickly resolve.

Newer imaging techniques, especially MRI, may now allow for a fast diagnosis. In uncomplicated cases MRI shows areas of cerebral oedema with a predilection for the posterior white matter of the brain. Lesions may be symmetric or asymmetric. The cerebral cortex, the frontal areas, the brainstem, cerebellum and basal ganglia may also be involved [7]. Although not fully correct, the name ‘reversible posterior leukoencephalopathy syndrome’ (PLS) has been adopted for this neuroradiological syndrome. The cerebral lesions usually appear isointense to hypointense on T1-weighted MR images, whereas T2-weighted images show hyperintensity. FLAIR imaging is the most sensitive conventional sequence to detect areas of cerebral oedema [8]. Diffusion-weighted imaging with ADC mapping can be used to differentiate cytotoxic from vasogenic oedema [9]. Cytotoxic oedema is characterized by increased signal intensity on DWI (Figure 1B), and decreased signal intensity on ADC maps, whereas vasogenic oedema shows a hyperintense signal on ADC maps. Cytotoxic oedema is thought to represent an increase in intracellular water as a result of ATP depletion due to ischaemia, whereas vasogenic oedema indicates an increase of extracellular water as a result of a rise in the transvascular pressure and/or increase in vascular permeability. The specific nature of the cerebral oedema in HE has not been studied extensively. Initially, it was reported in a small MRI study done on seven patients with HE that the oedema had the characteristics of vasogenic oedema on DWI with ADC mapping [10]. Recently, a few cases of HE have been reported with cytotoxic cerebral oedema and it has been proposed that severe vasogenic oedema may progress to cytotoxic oedema and cerebral infarction [9,11–13]. In this stage ADC maps may pseudonormalize or show a decreased signal intensity [12]. The MRI findings of our first patient also suggested cytotoxic oedema, which subsequently disappeared after BP lowering treatment.

Other conditions associated with PLS include eclampsia, treatment with cisplatin, calcineurin inhibitors, interferon-α or filgrastim, blood transfusion, carotid endarterectomy, AIDS and thrombotic thrombocytopenic purpura [7]. None of these were present in our patients. All our patients presented with headache, seizures and accelerated severe hypertension. Hence, a presumptive diagnosis of HE was made, which was confirmed by cerebral MRI and the favourable reaction to BP lowering therapy.

A remarkable finding in the three reported patients was the absence of papilloedema, retinal exudates or haemorrhages despite the presence of severe HE. Because they were all seen by experienced ophthalmologists it seems unlikely that these abnormalities of the ocular fundus were missed [14].

Ophthalmoscopic examination of patients with hypertension is of limited value. In mild to moderate hypertension only the degree of focal narrowing of arterioles is associated with the level of BP and no relation has been found between retinal changes and signs of chronic target organ damage such as left ventricular hypertrophy and microalbuminuria [15]. Ophthalmoscopy may be helpful in the recognition of acute hypertensive target organ damage such as HE, but the absence of retinal exudates, haemorrhages or papilloedema does not exclude this diagnosis. Our cases again clearly demonstrate that HE may occur without the classical retinal signs of malignant hypertension, as was first described >80 years ago [3]. It also shows that when clinical signs and symptoms are suggestive of HE, an MRI of the brain should be made to make a quick and correct diagnosis.

Conflict of interest statement. None declared.

References

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