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Posterior Reversible Leukoencephalopathy Syndrome Caused by Renal Artery Fibromuscular Dysplasia in a Six-Year-Old Child: Case Report and Literature Review

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ABSTRACT

Posterior reversible leukoencephalopathy syndrome (PRES) is a clinical-imaging syndrome resulting in subcortical vasogenic edema. Most frequently reported in young or middle-aged female adults and under-reported in the pediatric. We report a case of PRES in a six-year-old boy associated malignant hypertension secondary to unilateral renal artery trunk ostium severe stenosis, and complicated by disturbed electrolytes and abnormal kidney function. To our knowledge, in the literature, it was described in just a few case reports of unilateral renal artery stenosis as a cause of childhood PRES. Our case highlights the importance of recognizing that causes in childhood PRES and prompting intervention may offer favorable prognosis to childhood PRES patient.

Keywords: *Fibromuscular Dysplasia, Renal Artery Stenosis, Hypertension, Posterior Reversible Leukoencephalopathy*

Introduction

PRES is also known as posterior reversible leukoencephalopathy syndrome (Franco *et al*., 2019). It is characterized by reversible vasogenic edema involving the subcortical white matter of supratentorial lobes, especially in the parieto-occipital lobes (Fugate and Rabinstein, 2015). The clinical and radiological abnormalities of most PRES cases can be reversed when promptly diagnosed and properly treated (Tetsuka and Ogawa, 2019). Malignant hypertension is the most common cause of PRES. PRES is very rare in children compared to adults (Babici *et al*., 2022). Renovascular disease is one of the commonest etiology of childhood secondary hypertension, and fibromuscular dysplasia (FMD) of the renal arteries predominates in this setting (Mudalige *et al*., 2022). We report a case of PRES in a six-year-old boy who presented with malignant hypertension secondary to unilateral renal artery trunk ostium severe stenosis,

complicated by disturbed electrolytes and abnormal kidney function. So far, such case reports are rare in the pediatric.

Case Report

Patient Presentation

A six-year-old boy presented with vomiting and headache for 4 days, and suffered from four seizures in the 3 days without obvious cause. Manifested as twitching limbs, foaming at the mouth, paroxysmal tonic upgaze, deviated mouth, they were accompanied by loss of consciousness. On admission, he had a fifth seizure. His temperature was 36.7°C, pulse was 107/min, respiratory rate was 40/min and hypertension was up to 200/168mmHg.

Laboratory Findings

Laboratory examination revealed white blood cell count (WBC), C-reactive protein (CRP), interleukin-6 (IL-6), renin activity, angiotensin II, aldosterone, creatine kinase (CK) and lactate dehydrogenase (LDH) levels increased. Disturbed electrolytes included hypokalemia, hyponatremia and hypochloraemia. Cerebrospinal fluid (CSF) examination showed that protein and glucose levels were elevated, Pandy test was positive, and CSF pleocytosis. Urinalysis revealed creatinine decreased, β2 microglobulin and microalbumin increased. The specific values were shown in Table 1.

Table 1: Review of chemistries.

Chemistries	Pretreatment values	Unit	Abnormal indicate	Reference values	Posttreatment values
WBC	37.3	10^9/L	↑	4.30-11.30	5.49
CRP	17.38	mg/L	↑	＜10.00	＜10.00
IL-6	11.26	pg/mL	↑	0.00-7.00	1.50
K+	2.26	mmol/L	↓	3.70-5.20	3.79
Na+	124.0	mmol/L	↓	135.00-145.00	138.0
CL-	79.0	mmol/L	↓	98.00-110.00	101
renin activity	6.24	ng/mL/hr	↑	0.15-2.33	2.17
angiotensin II	148.40	pg/mL	↑	25.00-60.00	59.51
aldosterone	228.90	pg/mL	↑	30.00-160.00	125.70
CK	2121	U/L	↑	50.00-310.00	52
LDH	403	U/L	↑	120.00-250.00	167
PROT	1.40	g/L	↑	0.20-0.40	0.30
GLU	6.5	mmol/L	↑	2.50-4.40	3.4
WBC-BF	10.00	10^6/L	↑	0.00-8.00	4.00
Pandy	positive			negative	negative
U-CREA	3021.0	umol/L	↓	7000.00-18000.00	9000
B2MGU	2868	ug/L	↑	6.00-250.00	200
UMALB	120.10	mg/L	↑	1.70-22.90	20.9

Imaging Findings

Brain MRI showed cortical and subcortical white matter lesions in the parietal lobe manifesting slightly hypointense on T1-weighted images, hyperintense on T2-weighted images and fluid attenuated inversion recovery (FLAIR) images, hypointense on diffusion weighted imaging (DWI) combined with a high apparent diffusion coefficient (ADC) mapping sequences. The subdural hematoma was crescent-shaped hyperintense on T1-weighted images (Fig. 1 a-e).

Echocardiography showed isolated left ventricular slightly hypertrophy and enlarged.

Doppler ultrasonography (US) revealed a slightly smaller right kidney with arterial flow reduction and the left with compensatory hypertrophy and hydronephrosis.

Computed tomography angiography (CTA) and Digital subtraction angiography (DSA) visualised isolated severe stenosis involving the trunk ostium of the right renal artery, and the stenosis length was about 7.12mm (Fig. 1 f-g).

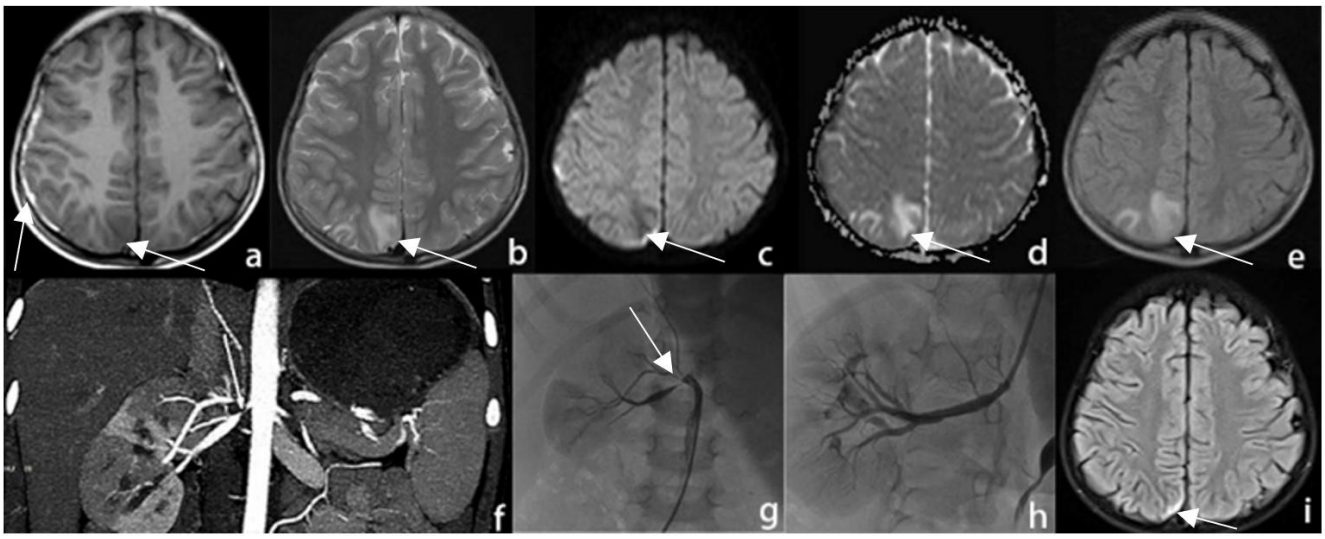

Figure 1: Brain MRI T1-weighted images: slightly hypointense lesions in the cortical and subcortical white matter of parietal lobe (a). T2-weighted and FLAIR images: hyperintense of the lesions (b,e). DWI images: hypointense of the lesions (c). ADC mapping sequences: increased ADC indicating vasogenic edema (d). Subdural hematoma of crescent-shaped hyperintense on T1-weighted images (a). Pre-renal artery balloon angioplasty CTA and DSA images showed an isolated severe stenosis involved the trunk ostium of right renal artery (f,g), the stenosis length was about 7.12mm. Post-balloon dilation DSA images showed the stenosis was significantly alleviated (h) and FLAIR images showed the lesions were absorbed (i).

Initial Diagnosis and Differential Diagnosis

The brain MRI typical findings, together with severe hypertension and neurological manifestations, suggested PRES. For possible differential diagnosis, it is necessary to consider reversible cerebral vasoconstriction syndrome (RCVS), encephalitis, posterior circulation stroke and cerebral

venous sinus thrombosis (Liman *et al*., 2019; Ban *et al*., 2017). RCVS is a group of diseases associated with classic thunderclap headache and reversible vasoconstriction of cerebral arteries, often complicated by ischemic or hemorrhagic stroke (Ducros and Wolff, 2016). A typical encephalitis patient has a fever. Cytotoxic edema is a hallmark of acute ischemic stroke, distinguished from PRES (Wagih *et al*., 2015). The typical finding of cerebral venous sinus thrombosis is the visible filling defect in the venous sinus (Capecchi *et al*., 2018). Based on the brain MRI findings and hypertension, PRES's diagnosis is not difficult. However, etiological diagnosis is crucial. Most PRES in children are associated with renovascular disease (Zhu *et al*., 2014). Subsequent biochemical tests and CTA confirmed our suspicions.

Treatment

The main treatments included antihypertensive and balloon angioplasty. Continuous sodium nitroprusside and nimodipine infusion were given to decrease blood pressure. After identification of right renal artery stenosis, considered the slightly smaller right kidney with only partial ischemia (Fig. 1f), and the adequate kidney function, the etiological treatment consisted in renal artery balloon angioplasty. After repeated balloon dilation, finally only 20% localized stenosis was observed at the ostium, as shown in Fig. 1h, without dissection and the distal blood flow was TIMI grade 3. The symptomatic and supportive treatments consisted in reducing intracranial hypertension, anti-epileptic and correcting of electrolyte disturbances.

Outcome and Follow-Up

Blood pressure returned to normal for the patient's age immediately after right renal artery balloon angioplasty. Abnormal results of laboratory examination returned to normal, and the specific values were shown in Table 1. Reexamination-MRI showed cortical and subcortical white matter abnormal signals of parietal lobe disappeared, most of the subdural hematoma was absorbed, and a small amount of hemorrhage in the right parietal lobe (Fig. 1i). US showed mild stenosis of the right renal artery ostium, and distal blood flow was basically normal.

The patient was discharged home without residual neurological impairments. His blood pressure and kidney function had remained normal at 1.5 years of follow-up.

Discussion

PRES is a rare clinical-imaging syndrome dominated by reversible nervous system damage and specific imaging findings, most frequently reported in young or middle-aged female adults (Gewirtz *et al*., 2021). The incidence in the pediatric population is low, between 0.04 and 0.4% (Thavamani *et al*., 2020). Clinical presentation is highly nonspecific, mainly including: suddenly increase in blood pressure,

headache, nausea, vomiting, seizures, encephalopathy, optical and consciousness impairment, focal neurological deficits and altered mental status, with seizures and encephalopathy being the most common symptoms (Tetsuka and Ogawa, 2019).

The common causes associated with PRES are malignant hypertension, eclampsia, preeclampsia, various severe kidney diseases (such as acute glomerulonephritis, chronic renal insufficiency, etc.), tumor chemotherapy drugs (ifosfamide, cisplatin, etc.), use immunosuppressive drugs and cytotoxic drugs after organs tissue transplantation (immunoglobulin, interferon, cyclosporin, etc.) (Li *et al*., 2020). Hakan *et al*. reported nine pediatric patients presenting with the clinical and laboratory findings of PRES, in which acute and chronic nephropathy act as etiology of PRES. PRES patients with nephropathy have generally disturbed electrolytes and abnormal kidney function (Gümüş *et al*., 2010). Our patient's cause associated with PRES is rare, which is secondary hypertension resulted from severe stenosis of the right renal artery trunk ostium. So far, reports of this have been extremely rare, only case reports. Combined with our patient's age and imaging findings, we consider that renal artery stenosis is caused by FMD. FMD of the renal arteries predominates in childhood renal artery stenosis, representing 60% of cases (Pilato *et al*., 2020). DSA is the gold standard for diagnosing FMD and visualised classical isolated stenosis involving the renal artery trunk or first-order branches.

The pathophysiological mechanism of PRES has not been elucidated. Three main theories about the pathophysiology of PRES are included: the breakthrough theory of cerebral perfusion pressure, vasospasm theory and endothelial dysfunction theory (Fischer and Schmutzhard, 2017). The “breakthrough” theory hypothesizes that arterial blood pressure increased rapidly beyond the autoregulation threshold of cerebral blood flow, and the blood-brain barrier (BBB) had a breakdown to develop vasogenic edema. The breakthrough hypothesis was previously prevalent, although its shortcomings and contradictions have been brought out in recent years. The fact that around 30% of patients with PRES have normal or slightly increased blood pressure that does not surpass the upper autoregulatory limit. As a result, the breakthrough theory alone cannot adequately explain the pathophysiology of PRES (Allen *et al*., 2019). According to the vasospasm theory, vasoconstriction and hypoperfusion may lead to hypoxia with upregulation of vascular endothelial growth factor (VEGF), consequently, endothelial permeability increases (Chen, 2020). Endothelial dysfunction theory hypothesizes endothelial dysfunction is due to circulating endogenous or exogenous toxins. The excessive production of proinflammatory cytokines, which leads to endothelial activation, the release of vasoactive agents, increased vascular permeability and edema (Jadib *et al*., 2021; Wittgrove *et al*., 2018). Our case is likely to explain by endothelial dysfunction theory. Hypertention can increase cerebral blood flow, however, it is much less in the occurrence and progression of PRES (Feske, 2011). Renal artery stenosis

may result in critical renal ischemia, leading to renin hypersecretion. Downstream modulators such as angiotensin II and aldosterone elevated, which amplify hemodynamic alterations (Parikh *et al*., 2015). The prior reason may be due to the internal environmental dysfunction, including hyponatremia, hypokalemia, hypochloraemia and hyperaldosteronemia etc. Furthermore, these endogenic toxins may further induce endothelial dysfunction, consequently, vascular endothelial permeability increases, and vasogenic edema occurs (Marra *et al*., 2014).

CSF protein level is elevated in 70% patients with PRES. A positive correlation between elevated protein level and severity of vasogenic edema (Ellis *et al*., 2019), which might reflect the breakdown of the BBB due to the endothelial dysfunction. However, pleocytosis is rare, and its presence is a marker of hemorrhage or infarction. A common finding is that the majority of PRES patients have "albumino-cytologic dissociation," which means CSF protein levels elevated without CSF pleocytosis (Tetsuka and Ogawa, 2019). This also explained that the typical imaging finding of PRES is vasogenic edema, and infarction or hemorrhage are rare complications of PRES. We reported the child PRES patient with elevated CSF protein level and pleocytosis, and the imaging findings were vasogenic edema and subdural hematoma.

Neuro-imaging is the cornerstone of PRES confirming diagnosis. Cranial CT is the emergent neuro-imaging, and brain MRI is the first choice of suspected PRES patients. Studies show abnormalities predominate in the parieto-occipital lobes cortical and subcortical white matter, the likely mechanisms that posterior circulation more prevalent than anterior circulation are the relative lack of sympathetic innervation in the vertebrobasilar system and its autoregulation impaired. White matter is more susceptible than gray matter due to its looser than gray matter, and fluid is easily retained (Tetsuka and Ogawa, 2019). But the involvement of frontal and temporal lobes, splenium of the corpus callosum, brainstem, cerebellum, basal ganglia, posterior limb of internal capsule and thalamus have been reported. Vasogenic edema manifested as patchy low-density shadows without mass effect on non-contrast CT. Brain MRI showed slightly hypointense lesions on T1-weighted images, and hyperintense lesions on T2-weighted images and FLAIR images, especially the T2-weighted and FLAIR images are much more sensitive (Saad *et al*., 2019). DWI combined with ADC mapping sequences can distinguish cytotoxic edema from vasogenic edema. Hyperintense on DWI and hypointense on ADC mapping sequences are typical appearances of cytotoxic edema, whereas isointense or hypointense on DWI and hyperintense on ADC mapping sequences are a hallmark of vasogenic edema (Wagih *et al*., 2015). However, due to the breakdown of the BBB, the findings of post-contrast T1WI show a superficial leptomeningeal and gyral cortical enhancement in about one third of patients. Intracranial hemorrhage is encountered in PRES patients with an incidence of 15%, presenting multiple or single small hematomas or microbleeds

(Mizuma *et al*., 2016). The clinical outcome may fluctuate from complete recovery to death due to intracranial hemorrhage and diffusion restriction (Schweitzer *et al*., 2017). The imaging findings of our PRES patient showed no intracranial hemorrhage and diffusion restriction, that indicated our patient's favorable prognosis and eventually got cured. But have subdural hematoma, is associated with an increase sharply in blood pressure.

PRES has no specific treatment. In patients with acute hypertension, starting a continuous antihypertensive-drug infusion as soon as possible to gradually decrease blood pressure (no more than 20–25% in the first 8h followed by gradual normalisation over 24–48h) to avoid the risk of cerebral, coronary and renal ischemia (Jadib *et al*., 2021). Contributory factors in the etiology of RRES are complex and the exact mechanism is unclear. However, it is vital for treatment. As for our case, the cause seems relatively distinct. Malignant hypertension, hyponatremia and hypokalemia secondary to renal artery stenosis resulted in PRES. In addition to symptomatic and supportive treatment, prompt intervention may offer near complete resolution of the physiologic and symptomatic effects of PRES due to renal artery severe stenosis. Studies have shown high success rates of revascularization procedures in patients with FMD (Parikh *et al*., 2015). When promptly diagnosed and treated, the clinical and radiological abnormalities associated with PRES can be reversed entirely in 2–3 weeks, and the prognosis is generally favorable. Otherwise, some patients can progress to having hemorrhage, ischemia, and even death (Li *et al*., 2020). Our case was diagnosed timely and accurately, and succeeded in right renal artery balloon angioplasty, so the child patient's prognosis is favorable.

Conclusion

PRES is under-reported in the pediatric, and investigations for underlying causes are mandatory. Malignant hypertension secondary to unilateral renal artery stenosis caused by fibromuscular dysplasia is the most common cause of PRES in pediatrics (such as our patient). In this setting, revascularization with balloon angioplasty resulted in the resolution of this child patient's hypertension. The patient without residual neurological impairments due to diagnosed and treated timely and accurately.

Author Contribution Statement

N.H. and C.W. contributed equally to this work. N.H. contributed to clinical data collection and wrote the manuscript. C.W. revised the manuscript. R.M.S. and H.Z. collected imaging data. T.J.G. designed the protocol. Y.R.M. and L.Y.M. analyzed imaging findings. J.Z. is the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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