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CASE REPORT

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Pathophysiological aspects of posterior reversible encephalopathy syndrome in two peritoneal-dialyzed children

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Abstract

Hypotension, blood pressure fluctuation, and endothelial impairment indicate possible additive pathophysiological aspects in the development of posterior reversible encephalopathy syndrome in children on peritoneal dialysis.

KEYWORDS

arterial hypotension, blood pressure, peritoneal dialysis, Posterior reversible encephalopathy syndrome, seizures

1 | INTRODUCTION

The two described children on peritoneal dialysis show possible additive pathophysiological aspects—as hypotension, blood pressure fluctuation, and endothelial impairment—other than the commonly described hypertension, chronic kidney disease, and immunosuppressive medication, being responsible for the development of posterior reversible encephalopathy syndrome.

Posterior reversible encephalopathy syndrome (PRES) is a rare, clinically, and radiologically diagnosed disorder with typical neurological and radiological findings, first described in 1996.[1] Main clinical symptoms are comparable in children and adults, namely abnormalities of visual perception, altered mental state, seizures, and severe headache.[1-7]

Characteristic imaging findings are symmetric white matter abnormalities in the posterior regions of the cerebral hemispheres, suggesting cerebral edema.[1,2,8] Additionally atypical lesions involve frontal lobes, cerebellum and less frequently temporal lobes, brain stem, basal ganglia, and affection of adjacent cortical areas.[2,3,7-10]

The syndrome's pathophysiology is not yet fully understood, presumed being multifactorial. Dysfunction in autoregulation of brain perfusion, brain-capillary leak, and vasogenic edema in order to arterial hypertension, endothelial cell dysfunction, and toxic effects on endothelial cells may play a key role.[1] In pediatrics, few patients and case series were published.[2-7,11] Commonly described underlying conditions in pediatrics are arterial hypertension, acute and chronic kidney disease, kidney transplantation, immunosuppression with calcineurin inhibitors, and nephrotic syndrome.[2-5,11-13] Although in comparison with the adult population, it seems that PRES is more common in children having normal or only slightly elevated blood pressure (BP).[9]

We do describe two peritoneal-dialyzed children diagnosed with PRES. Other possible additive pathophysiological aspects in the pathophysiology of PRES are discussed.

2 | CASE REPORTS

2.1 | Patient 1

A 24-month-old girl presented with oliguria and arterial hypertension postnatally and was diagnosed with autosomal recessive polycystic kidney disease (ARPKD (PKHD 1 with rare heteroallelic variant: c.11338C > T (p.Pro3780Ser) and c.25A > G (p.Met9Val) and deletion of exon 57 and 58))

based on family history and ultrasound. Due to pharmacological (fourfold therapy with amlodipine, carvedilol, dihydralazine, furosemide) uncontrollable arterial hypertension and recurrent, massive vomiting leading to failure to thrive, bilateral nephrectomy was performed at the age of 6 months. Peritoneal dialysis (PD) was installed thereafter, followed by successive normalization of BP (average 95/60mmHg (P50-75) without antihypertensive treatment), minimization of vomiting episodes and catch up growth. At the age of 8 months, slightly reduced fluid intake during 3 days was noted at home, no general signs of infection were documented, and on day 3, the girl suffered a first epileptic seizure leading to hospital admission. Regular measured BP before seizure revealed hypotension (60/41 mm Hg (<P50)). At the emergency unit, the girl presented in reduced general condition and with altered conscious state. Physical examination showed no signs of infection or dehydration, and first measured BP was 91/51 mmHg (P50), as seen in Figure 1. Laboratory findings were uneventful (Table). Based on neurological signs with altered conscious state, intermittent eye deviation, and muscular hypotension, a nonconvulsive status epilepticus was suspected and confirmed by an electroencephalogram (EEG).

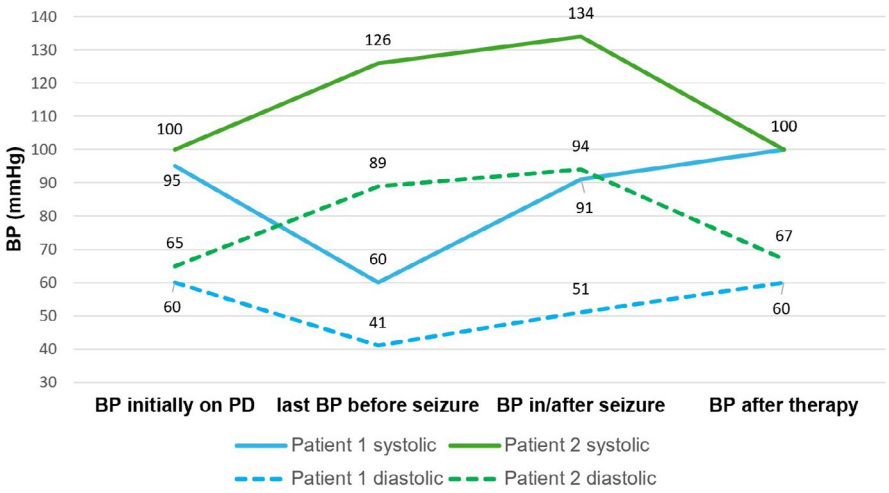
The administration of diazepam was successful and the girl underwent a cerebral magnetic resonance imaging (cMRI) indicating white and gray matter hyperintensity in T2-weighted sequences in both occipital lobes (Figure 2A) and parietal left-sided assuming the diagnosis of PRES. Additionally small, bilateral, hyperintense cerebellar areas were noted. Diffusion-weighted cMRI showed an extended area of diffusion restriction surrounded by areas of increased diffusion. Further anticonvulsive medication included levetiracetam. Based on low blood pressure, dehydration was assumed and the child was rehydrated and PD discontinued during the first 24 hours in hospital.

Minimal BP during hospitalization was 74/32 mm Hg (<P50), there were no further seizures documented, and the girl was demised 6 days after admission in a good clinical status with a blood pressure of 100/60 mm Hg (P75).

After 4 weeks of anticonvulsive therapy with levetiracetam, the medication could be tapered. There were no further signs of seizures and repeated EEG normalized. Levetiracetam was stopped after 6 weeks. Because of normal development, no focal deficits, or signs for visual problems, no further cMRI was conducted. Meanwhile, the girl is successfully transplanted and developing well.

2.2 | Patient 2

A 6-year-old girl with *Shiga toxin*–positive hemolytic uremic syndrome (STEC-HUS) was hospitalized due to acute kidney failure requiring acute renal replacement therapy. Initial physical examination showed signs of moderate dehydration, and no edemas and no neurological impairment were present. Blood pressure was in a normal range (100/65 mm Hg



	Patient 1	Patient 2
BP initially on PD	95/60mmHg (P50-75)[a]	100/65mmHg (P50)[b]
Last BP before seizure	60/41mmHg (<P50)[a]	126/89mmHg (>P95)[b]
BP in/after seizure	91/51mmHg (P50)[a]	134/94mmHg (>>P95)[b]
BP after therapy	100/60mmHg (P75)[a]	100/67mmHg (P50)[b]

BP = blood pressure; PD = peritoneal dialysis; [a] Neonatal hypertension[20]
[b] Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents[21]

FIGURE 1 Blood pressure progression

(P50)). Indication for installation of PD was anuria and uremia (36 mmol/L), electrolytes were within normal range, and metabolic acidosis was present.

Ten days after initiation of PD, BP started fluctuating and continuously increased with peak values above the 95 percentile, as Figure 1 shows. Clinically the child was slightly volume overloaded and developed mild signs of respiratory distress leading to a more aggressive ultrafiltration regimen by adaptation of PD. However, at a fluctuation of BP between 110/80 mm Hg (P90) and 130/90 mm Hg (»P95), the girl indicated vision impairment leading to total blindness and 2 hours later presented with altered conscious state, intermittent eye deviation, and muscular hypotension. Laboratory investigations did not indicate pathological values (Table 1).

An EEG confirmed a nonconvulsive status epilepticus. Anticonvulsive treatment including midazolam and levetiracetam was successful. After cessation of nonconvulsive status epilepticus, slight left-sided hemiparesis was noted for 3 hours and was interpreted as Todd's paresis. Cerebral magnetic resonance imaging revealed symmetric hyperintensity in both occipital lobes (Figure 2B) in T2-weighted images. Diffusion-weighted cMRI showed small areas of diffusion restriction with surrounding areas of increased diffusion. Taken together, the diagnosis of PRES was made. Further treatment consisted of antihypertensive medication (Ca^{+}-channel blockers, β-blockers, dihydralazine) and further adaption of PD was due. Follow-up of BP is indicated in Figure 1. Due to total neurological recovery within 24 hours and EEG normalization within 10 days, no further cMRI was performed. Total duration of PD was 28 days. Anticonvulsive treatment was stopped after one week, antihypertensive treatment tapered, and stopped at dismission at a BP of 100/67mmHg (P50). At one-year follow-up, the girl presented in a good clinical condition with normal neurological examination, normal renal function, BP was 108/71 mm Hg (P50-90) without medication, and only a mild proteinuria of 100g/mol creatinine persisted.

TABLE 1 Laboratory findings at presentation with seizures

	Patient 1	Patient 2
potassium	4.5 (3.5-5.0) mmol/L	5.6 (3.5-5.0) mmol/L
sodium	139 (134-144) mmol/L	141 (134-144) mmol/L
Ca^{++}	1.36 (1.22-1.37) mmol/L	1.16 (1.22-1.37) mmol/L
magnesium	1.36 (0.74-1.03) mmol/L	1.07 (0.74-1.03) mmol/L
glucose	8.1 (2.1-4.9) mmol/L	7.4 (2.1-4.9) mmol/L
pH	7.38 (7.35-7.45)	7.35 (7.35-7.45)
base excess	-8.5 (−2 to + 2) mmol/l	-9.6 (−2 to + 2) mmol/l
creatinine	375 (<35) µmol/L	811 (<60) µmol/L
urea	12 (<7) mmol/L	13.7 (<7) mmol/L

Note: Reference ranges for age in brackets.

3 | DISCUSSION

We describe two peritoneal-dialyzed patients with PRES, both presenting with nonconvulsive status epilepticus and typical and atypical lesions in cMRI. In contrast to other patients on PD,[11,14] the here described children did not have severe hypertension. One suffered from hypotension, and the other presented with fluctuating blood pressure with intermittent peak values above the 95 percentile.

Our first patient slowly developed hypotension. She clinically showed no signs of infection or dehydration and laboratory findings showed no hypoglycemia or electrolyte shift. Her cMRI revealed typical posterior lesions compatible with PRES with extended areas of diffusion restriction indicated to cytotoxic edema. We postulate that not only arterial hypertension and following excessive vasoconstriction and hypoperfusion but also arterial hypotension can result in long lasting cerebral hypoperfusion and deranged endothelial cell metabolism with consecutive breakdown of blood-brain barrier followed by vasogenic and cytotoxic edema.

The second patient revealed fluctuating blood pressure accompanied with BP spikes in hypertensive range. We assume that beside the BP spikes this blood pressure fluctuation resulted in concomitant hypo- and hyperperfusion causing PRES. Blood pressure fluctuation could be due to fluid shifts in intermittent PD. Supporting this hypothesis, cMRI diagnostic revealed both, restriction and increase of diffusion. Besides blood pressure alterations, also HUS in the second patient and uremia in both might be a supplemental cause developing PRES.

In conclusion, the treatment in the first patient aimed at an increase in blood pressure and consisted in rehydration and adaption of PD with initial break for 24 hours then gentle restart. In the second in lowering and stabilizing blood pressure with antihypertensive medication and adaptation of PD. Changes to augment ultrafiltration were made, initially rapidly achieved then more gentle to minimize further fluid shifts and blood pressure fluctuation. Additionally, further effort was made to achieve lower urea levels. A shift to hemodialysis (HD) was not needed as there was no severe hypertension or fluid overload. In contrast, further

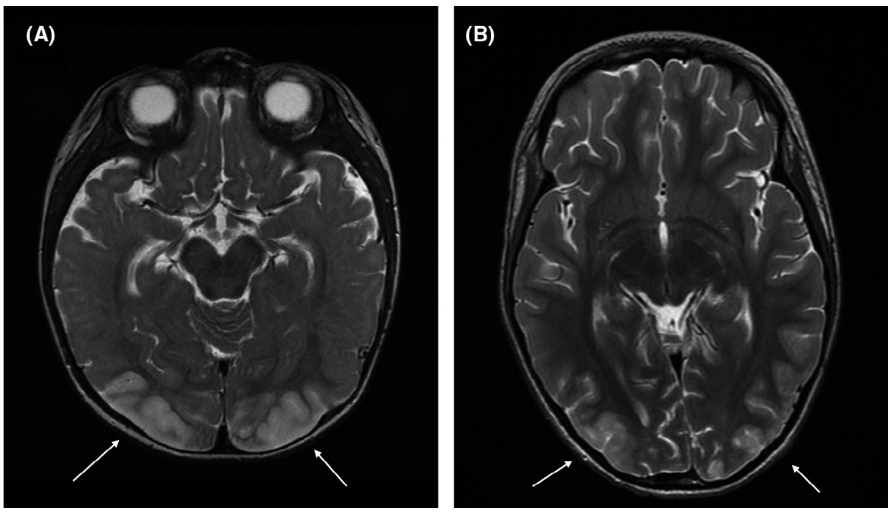


FIGURE 2 Radiographic findings. Cerebral magnetic resonance imaging showing bilateral symmetric hyperintensity of the parieto-occipital regions (arrows) in both patients in T2-weighted sequences. Patient 1: A; Patient 2: B

fluid shifts and blood pressure fluctuation could have been provoked.

The two here described patients showed rapid clinical recovery without any noticeable neurological sequela. Even the first patient with extended areas of cytotoxic edema with proposed irreversibility shows no neurological abnormalities on follow-up.

In literature overview, described typical clinical symptoms of PRES are altered mental state, abnormal visual perception, seizures, and severe headache. Symmetric hyperintensity in the subcortical white matter of the parieto-occipital regions and fluid-attenuated inversion recovery (FLAIR) images are typical signs on cMRI.[3,10] Additional lesions, described as "atypical," involve frontal lobes, cerebellum and less frequently temporal lobes, brain stem, basal ganglia, and affection of adjacent cortical areas.[3,7-10] Even affected children with isolated cortical involvement were described.[4] In difference to adults, cerebellar involvement is more often present in children.[9] Diffusion-weighted MR-sequencing nowadays allows differentiating between vasogenic and cytotoxic edema.[3,5,9,10] In the adult population, diffusion restriction can be seen in 15 - 30% of patients with PRES[15] and is thought to be caused by prolonged hypoperfusion or ischemia and generally is irreversible.[15,16] Indicated diffusion restriction in children varies between 15%[9] and 33%[7] and is mostly limited to small areas. In children undergoing a control cMRI, irreversibility or infarction has rarely been described.[5,7]

Pathophysiological mechanisms of PRES are not yet fully understood. Major key components of the development of PRES seem to be severe hypertension, immunosuppressive medication, and kidney disease.[1-5] Two published theories describe the pathway leading to vasogenic edema based on the role of arterial hypertension: severe hypertension is thought to cause an excess of autoregulation of brain perfusion, followed by hyperperfusion or/and excessive vasoconstriction, the later leading to hypoperfusion and therefore transient ischemia. Hyperperfusion then causes a breakdown of the blood-brain barrier followed by vasogenic brain edema. Hypoperfusion and transient ischemia also lead to vasogenic edema through the activation of vascular endothelial growth factor which augments vascular permeability.[3] In children, the upper limit of cerebral blood flow regulation is lower than in adults and needs to be adapted to the child's baseline and age-related blood pressure.[15] Not only high blood pressure, but also blood pressure fluctuation might cause PRES.[10,15]

A third theory describes the role of endothelial dysfunction and activation which also leads to alterations in blood-brain barrier with following vasogenic edema.[17] In contrast to the first two theories, the last one explains PRES in patients without hypertension but various conditions leading to endothelial dysfunction and activation. Thus, in patients with kidney disorders such as hemolytic uremic syndrome or general uremia (which leads to general inflammation[18]), sepsis or autoimmune disease, this might be a causative factor for PRES. Vasculature is one of the most important targets of the immune response, as activation of the immune system leads to a systemic endothelial activation and dysfunction. This increases the vessel permeability, followed by a subsequent fluid leakage.[17] Whether end-stage kidney disease with uremia alone is an independent risk factor for developing PRES is still unclear, as most of these patients are also affected by severe hypertension.[2]

Immunosuppressive medication is thought to have a direct toxic effect on endothelial cells leading to impaired cerebral vasoregulation and damage to the blood-brain barrier. This effect is more pronounced in patients with preexisting perturbation of the blood-brain barrier (eg, hypertensive BP, uremia, sepsis, or fluid overload).

Supporting all theories, most MRI images with PRES show vasogenic edema. Furthermore, extensive vasogenic edema can increase tissue pressure and impair microcirculation, and may thereby lead to a cytotoxic edema.[10] Prolonged ischemia itself can lead to a cytotoxic edema as well.

Treatment of PRES in general includes the correction of the underlying factors. The same principles apply for patients on PD. Furthermore, PD adaptions have to be made according to BP and fluid status. In literature, only few patients are reported with PRES on PD and even fewer children. Nearly all of them showed hypertension and volume overload.[19] In those, PD dose and ultrafiltraton were increased to achieve lower BP, euvolemia, and lower urea levels. Even a shift to hemodialysis is reported to achieve high ultrafiltration and efficient dialysis. However, there is a risk of exacerbation of brain injury because of rapid ultrafiltration and dialysis and brain hemorrhage related to anticoagulants. Once acute correction of BP and volume status is achieved, we assume that prophylactic measures are a narrow balance between gentle dialysis to avoid big fluid shifts and blood pressure fluctuation and achieving good enough dialysis to avoid hyper- or hypotension and keep urea level as low as possible. As prolonged seizures and hypoperfusion can result in cytotoxic edema and probable irreversibility of PRES, early diagnosis with adequate consecutive treatment is due.[5]

In general, prognosis of PRES is benign except for patients with intracranial hemorrhage and extended areas of cytotoxic edema. Reported clinical and/or imaging residuals in children range between 8% and 23%.[3,7] Described clinical deficits are developmental delay, learning problems, visual disturbances, and focal neurological deficits in cases of infarction. In cMRI, few children showed incomplete resolution of edema, infarction, hemorrhagic lesions, or laminar necrosis.[7] However, cMRI is not repeated, if total clinical recovery is present.

In summary, not only hypertension, but also hypotension and blood pressure fluctuations might cause posterior reversible encephalopathy syndrome. In patients on PD, special attention has to be laid in adaption of PD as therapy. It is essential including posterior reversible encephalopathy syndrome as possible diagnosis in children presenting with the typical clinical sings as altered mental state, abnormal visual perception, seizures, and severe headache in order to treat adequately and consequently and therefore preventing irreversibility of posterior reversible encephalopathy syndrome.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

TK: idea of the manuscript, followed up the patients, collected the data, and drafted the manuscript. TK and GL: analyzed and interpreted data. TK, GL, and DW: reviewed literature. DW and GL: revised and approved the manuscript. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work.

ETHICAL STATEMENT

Consent for Publication: Written informed consent was obtained from the participants for publication of this article and accompanying images.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med*. 1996;334(8):494-500.
2. Onder AM, Lopez R, Teomete U, et al. Posterior reversible encephalopathy syndrome in the pediatric renal population. *Pediatr Nephrol*. 2007;22(11):1921-1929.
3. Ishikura K, Hamasaki Y, Sakai T, Hataya H, Mak RH, Honda M. Posterior reversible encephalopathy syndrome in children with kidney diseases. *Pediatr Nephrol*. 2012;27(3):375-384.
4. Kwon S, Koo J, Lee S. Clinical spectrum of reversible posterior leukoencephalopathy syndrome. *Pediatr Neurol*. 2001;24(5):361-364.
5. Ishikura K, Ikeda M, Hamasaki Y, et al. Posterior reversible encephalopathy syndrome in children: its high prevalence and more extensive imaging findings. *Am J Kidney Dis*. 2006;48(2):231-238.
6. Incecik F, Herguner MO, Altunbasak S, Erbey F, Leblebisatan G. Evaluation of nine children with reversible posterior encephalopathy syndrome. *Neurol India*. 2009;57(4):475-478.
7. Siebert E, Spors B, Bohner G, Endres M, Liman TG. Posterior reversible encephalopathy syndrome in children: radiological and clinical findings - a retrospective analysis of a German tertiary care center. *Eur J Paediatr Neurol*. 2013;17(2):169-175.
8. Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol*. 2007;28(7):1320-1327.
9. Donmez FY, Guleryuz P, Agildere M. MRI Findings in Childhood PRES: What is Different than the Adults? *Clin Neuroradiol*. 2016;26(2):209-213.
10. Lamy C, Oppenheim C, Meder JF, Mas JL. Neuroimaging in posterior reversible encephalopathy syndrome. *J Neuroimaging*. 2004;14(2):89-96.
11. Gera DN, Patil SB, Iyer A, et al. Posterior reversible encephalopathy syndrome in children with kidney disease. *Indian J Nephrol*. 2014;24(1):28-34.
12. Giussani A, Ardissino G, Belingheri M, et al. Posterior reversible encephalopathy syndrome after kidney transplantation in pediatric recipients: Two cases. *Pediatr Transplant*. 2016;20(1):68-71.
13. Zhou J, Zheng H, Zhong X, et al. Reversible posterior encephalopathy syndrome in children with nephrotic syndrome. *Nephrology*. 2015;20(11):849-854.

14. Jellouli M, Gargah T. The posterior reversible encephalopathy syndrome in a boy on peritoneal dialysis. *Pan Afr Med J*. 2015;22:287.
15. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol*. 2015;14(9):914-925.
16. Moon SN, Jeon SJ, Choi SS, et al. Can clinical and MRI findings predict the prognosis of variant and classical type of posterior reversible encephalopathy syndrome (PRES)? *Acta Radiol*. 2013;54(10):1182-1190.
17. Marra A, Vargas M, Striano P, Del Guercio L, Buonanno P, Servillo G. Posterior reversible encephalopathy syndrome: the endothelial hypotheses. *Med Hypotheses*. 2014;82(5):619-622.
18. Girndt M. Clinical issues with uremia. *Der Internist*. 2012;53(7):817-822.
19. Moreiras-Plaza M, Fernández-Fleming F, Azkárate-Ramírez N, et al. Peritoneal dialysis: A factor of risk or protection for posterior reversible encephalopathy syndrome? Review of the literature. *Nefrologia*. 2018;38(2):136-140.
20. Flynn JT. Neonatal hypertension. *Pediatric nephrology*. 2000;14(4):332-341.
21. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressue in Children and Adolescents. *Pediatrics*. 2017;140(3):e20171904.

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