Case Report with Literature Review

# Compromised gut–brain axis architecture in uremic encephalopathy: A case report with review of literature

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## ABSTRACT

Posterior reversible encephalopathy syndrome (PRES) is often clinically manifested by headaches, seizures, and altered sensorium, which coincide with clinical features of uremic encephalopathy (UE). Here, a case of a 12-year-old female with polycystic kidney and hepatic disease 1 positive polycystic chronic kidney disease (autosomal recessive polycystic kidney disease), presenting with non-specific abdominal pain, bloating, mouth ulcers, and vomiting, followed by status epilepticus, is reported. Magnetic resonance imaging of the brain showed features of atypical PRES. Gastrointestinal symptoms, UE, and PRES offer an interesting window into the common toxin-mediated damage to the gut–brain axis architecture. This report is followed by a crisp review of the literature.

**Key words:** Chronic kidney disease, Gut–brain axis, Polycystic kidney and hepatic disease 1, Posterior reversible encephalopathy syndrome, Uremic encephalopathy

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome characterized by an acute or subacute onset of neurological symptoms associated with reversible vasogenic edema, predominantly involving the posterior cerebral regions on neuroimaging magnetic resonance imaging (MRI). PRES is usually reversible and implies that the brain swelling primarily occurs in the posterior region. However, sometimes, when other brain areas are involved, symptoms may not always fully resolve and neurological sequelae may persist [1]. PRES manifests on imaging as cortical or subcortical edema within the cerebral hemispheres with parietal-occipital predominance [2]. PRES is often linked to acute hypertension, but other conditions (such as pre-eclampsia, chronic kidney disease, hemolytic uremic syndrome (HUS), severe sepsis, interferon therapy, high-dose corticosteroids, glomerulonephritis, and nephrotic syndrome) have also been identified as etiological or risk factors. In many conditions, classical PRES changes are not appreciated on MRI brain; however, certain atypical PRES signatures can be identified, especially on apparent diffusion coefficient (ADC) and diffusion-weighted images. Polycystic kidney and hepatic disease 1 (PKHD1) mutation-related autosomal recessive polycystic kidney disease (ARPKD) is characterized by primary involvement of the kidneys and liver. Prenatal/neonatal and infantile (1 month to age 1 year) are two common presentations. The third presentation in late childhood is associated with hepatobiliary manifestations. PRES is common among uremic patients. Uremic encephalopathy (UE) is an acute or chronic cerebral dysfunction resulting from severe renal failure, characterized by the buildup of neurotoxic solutes in the blood when the glomerular filtration rate falls, typically below 15 mL/min [3]. Toxin accumulation in the blood owing to kidney failure can trigger changes in brain–blood vessels in UE, leading to PRES development. PRES in UE is considered a serious complication [4,5]. It is noteworthy that in UE, patients often present with gastrointestinal (GI) manifestations before progressing to full-fledged PRES. PRES is now being conceptualized as neurovascular endotheliopathy characterized by cerebral autoregulatory failure and blood–brain barrier disruption leading to vasogenic edema [6]. Systemic inflammatory states, hypertensive volatility, and endothelial toxic exposures, common precipitants of PRES, simultaneously perturb peripheral vascular beds, including the gut–vascular barrier. Emerging gut–brain axis models suggest that intestinal barrier dysfunction, microbial translocation, and cytokine-mediated endothelial activation may amplify

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cerebrovascular permeability and autoregulatory instability [7]. Thus, GI symptomatology and PRES may represent parallel manifestations of a shared systemic endothelial–inflammatory dysregulation rather than isolated organ-specific pathology.

## CASE SUMMARY

A 12-year-old girl with genetically confirmed ARPKD PKHD1 mutation had remained clinically stable with preserved renal function and no renal complications throughout childhood, apart from chronic growth failure. She was apparently well until 12 months before presentation (May 2021), when she developed insidious onset fatigue and anorexia, followed by progressive pallor, declining urine output, and worsening hypertension over the subsequent weeks.

A review of her consanguineously married parents revealed no history of or similar to chronic kidney disease in either side of the family. Despite supportive medical management, she experienced rapid deterioration in renal function over a 6-month period, progressing to end-stage kidney disease with uremic symptoms and volume overload, necessitating initiation of maintenance hemodialysis. This renal decline was followed by an acute onset of GI symptoms. On April 16, 2022, 24 h post-hemodialysis, she presented to the pediatric emergency room with abdominal pain, loss of appetite, and abdominal fullness.

She had a body weight of 28 kg <3$^{rd}$ centile (World Health Organization [WHO] growth standards) and a height of 114 cm, <3$^{rd}$ centile (WHO growth standards). The initial physical examination showed her blood pressure 95/62 mmHg, heart rate 126 beats/min, and body temperature 39.5°C. She had a hemoglobin level of 5.3 g/dL and a platelet count of 36000/μL. The blood chemistry test results revealed the levels of total protein 4.7 g/dL, urea nitrogen 97.7 mg/dL, creatinine 8.2 mg/dL, sodium 167.6 mEq/L, potassium 2.7 mEq/L, chloride 126 mEq/L, aspartate aminotransferase 83 IU/L, alanine aminotransferase 112 IU/L, and alkaline phosphatase 998 IU/L. The hepatitis B antigen and hepatitis C antibody titers were found to be within normal limits. The urinalysis results showed a urinary protein level of 1.01 g/gCr and the presence of 25–30 red blood cells per higher-power field. A chest X-ray showed a cardiothoracic ratio of 44%, which was normal. An abdominal ultrasonography was conducted for the diagnosis, showing bilateral multiple renal cysts and diffuse increases in parenchymal echogenicity in the kidneys.

Based on biochemical profile reflecting severe acute kidney injury (AKI), uremia, severe hypernatremia, hypokalemia, hyperchloremia, hypoproteinemia, transaminitis with markedly elevated alkaline phosphatase, proteinuria (~1 g/gCr), and microscopic hematuria, urgent management protocols were instituted in the pediatric intensive care. Sodium correction was performed gradually to prevent cerebral edema, potassium was replenished under cardiac monitoring, and renal function was supported with intensive fluid–electrolyte management. The patient was treated with furosemide and spironolactone to control ascites. The patient's serum levels of electrolytes, urea nitrogen, and creatinine gradually improved as ascites subsided over the next few days.

The patient had an episode of generalized tonic-clonic seizure on the 4$^{th}$ day of hospitalization. Levetiracetam (IV) was commenced at 40 mg/kg/day in two divided doses. Blood pressure fluctuated between the 90$^{th}$ and 95$^{th}$ centiles; electrolytes and metabolic profile monitoring remained within normal limits. Laboratory data supported improving renal functions with urea nitrogen 57.7 mg/dL, creatinine 3.2 mg/dL, sodium 138.4 meq/L, potassium 3.5 meq/L, and chloride 101 mEq/L. Biochemical parameters progressively normalized, urine output improved, and the patient achieved partial recovery over the next 48–72 h (day 5–7 of hospitalization). Post-stabilization and successful corrections, status epilepticus was again documented on April 23, 2022, and in the next 3 days (day 8–10 of hospitalization), her Glasgow Coma Scale (GCS) worsened between 8/15 and 6/15.

MRI of the brain was carried out in view of prolonged visual disturbances. It showed symmetrical confluent restricted diffusion areas with a lower ADC involving bilateral centrum semiovale and corona radiata with a linear signal noted in the splenium of the corpus callosum suggestive of cytotoxic edema (Fig. 1). The presence of symmetrical diffusion restriction with low ADC in the bilateral centrum semiovale, corona radiata, and splenium of the corpus callosum, indicating cytotoxic rather than purely vasogenic edema in deep white matter regions outside the classic parieto-occipital distribution, suggested characteristics of atypical PRES. With conservative management, vitals maintenance, and symptomatic support, her GCS improved to 13/15 and 15/15 on the 11$^{th}$ and 12$^{th}$ day of hospitalization, respectively.

## DISCUSSION

The present case report is presented to demonstrate clinical features of PRES and GI complaints in UE. PRES's exact incidence is variable, but literature suggests an incidence of 27–31 cases/million population, with a higher female preponderance (37 cases/million vs. 16/million in males). Patients aged between 4 and 90 years have been reported to develop PRES. Hypertension is the usual condition related to PRES [8]. Usually, patients with renal disease are particularly susceptible to PRES due to the close association between renal dysfunction and hypertension.

Another interesting finding is the early reporting of GI symptoms in UE progressing to PRES. PKD-related renal dysfunction causes the accumulation of protein-bound uremic toxins that cannot be completely

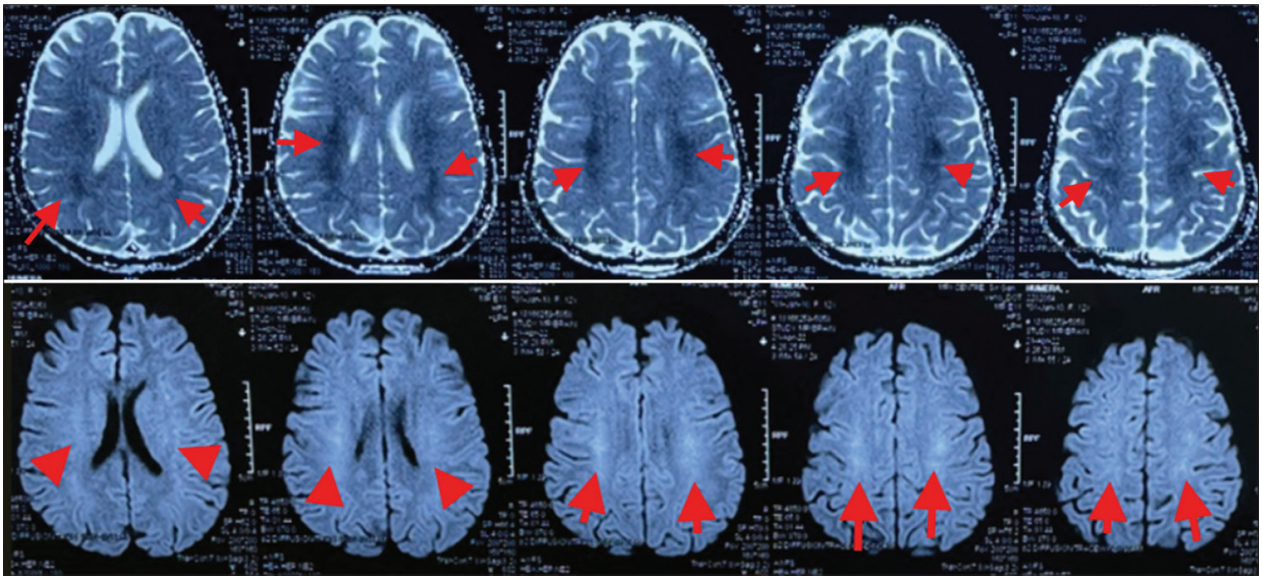

**Figure 1: Magnetic resonance imaging of the brain carried on day 2 of hospitalization in the interictal spell, showing features of cytotoxic edema, suggestive of atypical posterior reversible encephalopathy syndrome in apparent diffusion coefficient and diffusion-weighted imaging, respectively**

**Table 1: Clinical manifestations of gut and brain in renal dysfunction**

| Author (Year) | Neurological manifestations | Gastrointestinal manifestations |
|---|---|---|
| Hu *et al*., 2019 [11] | Headache, altered mental status, seizures, visual disturbances | Not reported |
| Koller *et al*., 2010 [12] | Seizures, visual disturbances | Abdominal pain |
| Darwish, 2012 [13] | Seizures, headache, visual disturbances | Abdominal pain |
| Ganesh *et al*., 2014 [14] | Seizures, altered sensorium, staring spells | Gastrointestinal cytomegalovirus disease |
| Toraman *et al*., 2013 [15] | Flank pain, dark urine | None reported |
| Behera *et al*., 2020 [16] | Headache, seizures, visual disturbances, altered sensorium/ encephalopathy, focal neurological deficits (weakness) | Abdominal pain |
| Chowdhary *et al*., 2015 [17] | Headache, generalized tonic–clonic seizures, confusion/altered consciousness | Nausea, abdominal pain |
| Komur *et al*., 2012 [18] | Seizures, headache, visual disturbances | Vomiting, nausea |
| Kornilov *et al*., 2021 [19] | Severe headache, seizures, visual disturbances, confusion/disorientation | Vomiting, nausea |
| Fidan *et al*., 2016 [20] | Seizures, headache | Rectal bleeding |
| Iwafuchi *et al*., 2016 [21] | Confusion/encephalopathy | Nausea |
| Kotaru *et al*., 2021 [22] | Altered sensorium/encephalopathy, focal neurological deficits (hemiparesis) | Vomiting |

excreted by renal replacement therapy. These toxins seed complications by hemodynamic disturbances and blood–brain barrier (BBB) disruption and unfavorable changes in the intestinal microbiome. BBB disruption negatively impacts the brain through vascular dysfunction, direct toxicity of brain cells, acute inflammation, and oxidative stress in glial cells. Not just the brain, the intestinal composition of the microbiome and the intestinal environment in chronic kidney disease undergoes significant changes, leading to dysbiosis, increased protein fermentation, and therefore initiating a vicious cycle of subsequent increase in the concentration of uremic toxins. Along with dysbiosis characterized by GI symptoms, delayed equilibration of the urea level between blood and cerebrospinal fluid leads to cerebral edema and the appearance of neurological conditions (UE) sometimes manifested as PRES (headaches, visual disturbances, and seizures) [9,10]. The brief summary of cases with renal dysfunction, PRES, and GI complaints in patients is represented in Table 1 [11-22].

Based on literature review (PubMed 2020–2025), single-patient case reports and cohort-level evidence demonstrate neurological complications, renal dysfunction, and GI manifestations in systemic endothelial/immune phenotype, complement-mediated thrombotic microangiopathy (TMA), and severe pediatric systemic lupus erythematosus (SLE).

There is a near-ideal illustration of GI prodrome, with renal TMA followed by catastrophic central nervous system (CNS) involvement in a single complement-mediated episode. A 19-year old at 37 weeks of gestation presented with abdominal pain, then was found unresponsive with seizures, coma,

and diffuse encephalopathy/anoxic brain injury, and had AKI with microangiopathic hemolytic anemia and thrombocytopenia consistent with Atypical HUS (aHUS) [23]. Similarly, two more pregnancy-associated and COVID-triggered aHUS/TMA have been reported with a clear GI prodrome, severe AKI, and CNS or retinal involvement [24,25]. A case study has also reported PRES on a background of renal disease and malignant/vasorenal hypertension, with concurrent GI symptoms [19]. High incidence of CNS and GI involvement on the top of renal TMA in aHUS/HUS was documented in two case reports [26,27]. Similarly, pediatric severe SLE with mesenteric vasculitis and related GI crises have been noted, suggesting renal dysfunction and insult to gut–brain axis architecture [28,29].

Although our patient did not fulfill diagnostic criteria for TMA, aHUS, or SLE, these conditions are discussed to contextualize a shared pathobiological substrate, systemic endothelial injury with concurrent renal, GI, and CNS involvement. Complement dysregulation, microangiopathic endothelial damage, and inflammatory cytokine-mediated vascular permeability in TMA/aHUS provide mechanistic parallels to the endothelial dysfunction and BBB instability observed in UE-associated PRES.

## CONCLUSION

Bidirectional communication between gut and brain through immunological, hormonal, peripheral nervous, metabolic, and microbiota-led pathways has been well documented. The cited literature reinforces conceptual framework suggesting renal failure-associated toxin burden and endothelial activation can produce a multisystem gut–kidney–brain axis phenotype. This comparative lens strengthens the biological plausibility of the observed GI prodrome preceding neurological decompensation in our patient and situates the case within a broader spectrum of systemic endotheliopathies affecting both intestinal and cerebral vascular beds.

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