

## Exceptional Case

# Aggressive blood pressure control for chronic kidney disease unmasks moyamoya!

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### Abstract

Hypertensive crises in children or adolescents are rare, but chronic kidney disease (CKD) is a major risk factor for occurrence. Vesicoureteral reflux nephropathy is a common cause of pediatric renal failure and is associated with hypertension. Aggressive blood pressure (BP) control has been shown to delay progression of CKD and treatment is targeted for the 50th percentile for height when compared with a target below the 90th percentile for the general pediatric hypertensive patient. We present a case of an adolescent presenting with seizures and renal failure due to a hypertensive crisis. Hypertension was thought to be secondary to CKD as she had scarred echogenic kidneys due to known reflux nephropathy. However, aggressive BP treatment improved kidney function which is inconsistent with CKD from reflux nephropathy. Secondly, aggressive BP control caused transient neurological symptoms. Further imaging identified moyamoya disease. We present this case to highlight the consideration of moyamoya as a diagnosis in the setting of renal failure and hypertensive crisis.

**Keywords:** acute renal failure; hypertension; hypertensive emergency; moyamoya; reflux nephropathy; vesicoureteral reflux

### Introduction

Severe hypertension in pediatric patients is thought to be secondary and often related to renovascular disease. For this reason, pediatric nephrologists have become the blood pressure (BP) specialists for children with hypertension. In children, neurological causes of hypertension are often related to increased intracranial pressure whereas cerebrovascular causes are rare. The neurological consequences of hypertension are stroke, seizures and encephalopathy. Therefore, it is often presumed that renovascular disease leads to hypertension which leads to neurological disease. We report a case of neurological disease, moyamoya, causing hypertension, leading to partially reversible kidney failure. We present this case to highlight the consideration of moyamoya as a cause of hypertensive renal failure.

### Case presentation

#### *Emergent management*

A 16-year-old adolescent female awoke with severe headache early in the morning. Paracetamol (acetaminophen)

was taken, but offered no relief. Over the next 4 h the headache was unremitting and she developed nausea with emesis. She had sudden incoherence of speech with bowel and bladder incontinence. She was taken to a local hospital and was noted to have a focal seizure with left facial and hand twitching which stopped with intravenous lorazepam. A computed tomography (CT) scan of the head without contrast was normal. BP was 200/140 mmHg. A single dose of hydralazine 10 mg was administered intravenously. After stabilization she was transferred by air to a tertiary care center. Upon arrival she was admitted to the pediatric intensive care unit. BP remained elevated at 228/123 mmHg. She was encephalopathic with left hemiparesis. She began vomiting. She was intubated for airway protection. She was immediately placed on an intravenous infusion of nicardipine at 0.5 µg/kg/min without a bolus dose. An intra-arterial BP catheter was placed to allow titration of the nicardipine infusion. Chest X-ray showed bilateral perihilar infiltrates consistent with pulmonary edema. Continuous electroencephalogram did not reveal seizures, but right hemispheric slowing. The target BP for the first 8 h was to maintain above 171/105 mmHg (<25% reduction in maximum BP for both systolic and diastolic) to prevent a precipitous drop and avoid inducing irreversible neurological damage.

Past medical history was significant for grade III vesicoureteral reflux (VUR) diagnosed at age 12 after CT scan for appendicitis identified acute appendicitis and scarring of the upper poles of both kidneys. She had bilateral ureteral implantation at the age of 13. She had been seen in an outpatient pediatric nephrology clinic 9 months prior to this presentation. Systolic BP at that time was 120 mmHg; Hgb 75.1 mmol/L (12.1 g/dL); serum creatinine was 79.6  $\mu\text{mol/L}$  (0.9 mg/dL) [eGFR 78 mL/min/1.73 m<sup>2</sup>]; urinalysis with 3+ protein, without hematuria.

Current laboratory studies showed a serum creatinine of 415.5  $\mu\text{mol/L}$  (4.7 mg/dL). Urinalysis showed 3+ protein and 3+ blood without red blood cells or casts on microscopy. Drug screen was negative except for benzodiazepines. White blood cell count was 14.4K/mm<sup>3</sup> with 94% neutrophils; Hgb 67.6 mmol/L (10.9 g/dL). Magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) without contrast showed abnormal T2/FLAIR signal in the cortical and subcortical regions of the right parietal temporal lobe and basal ganglia consistent with either subacute infarction in the right MCA territory without diffusion restriction or an atypical presentation of posterior reversible encephalopathy syndrome (PRES) (Figure 1A and B). MRA revealed diminished flow in the right M1 segment (Figure 2). Renal ultrasound showed small echogenic kidneys bilaterally (right 6.9 cm; left 7.8 cm) with cortical scarring and loss of corticomedullary differentiation. Ultrasound was felt to be consistent with and supported VUR nephropathy as the cause of the hypertensive renal failure.

#### Initial hospital course

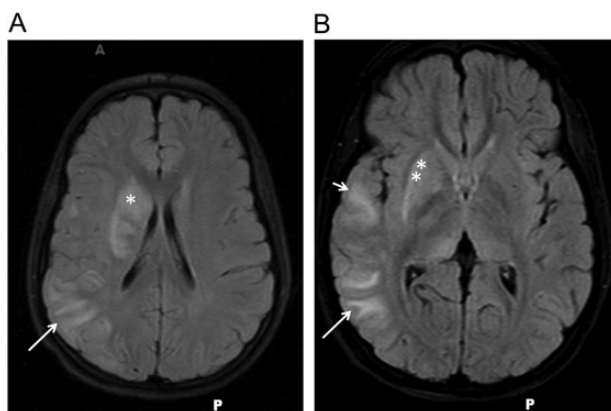
Over the next 96 h intravenous nicardipine (dose range of 2–10  $\mu\text{g/kg/min}$ ) and furosemide (0.1 mg/kg/h) were infused in an attempt to normalize BP to less than the 90th percentile for height (126/81 mmHg) (Figure 3). Her mental and neurological status returned to baseline without appreciable deficits and she was extubated. Over a 2-week hospital course she was transitioned to oral antihypertensive agents including amlodipine 5 mg twice daily, atenolol 50 mg daily, clonidine 0.1 mg twice daily, lisinopril 2.5 mg twice daily and furosemide 40 mg twice daily (Figure 3). Evaluation for autoimmune disease and vasculitis included ANA, ANCA, anti-GBM antibodies—all

were negative. Complement levels: C3 and C4 were normal. ESR was elevated at 83 mm/h. Repeat MRI/MRA without contrast showed near complete resolution of previously seen T2/FLAIR hyperintensities although there was no flow in the right M1 and A1 segment. Even with this persistent MRA abnormality, her rapid return to normal without neurological deficit and near-complete resolution of FLAIR signal abnormalities was thought to be most consistent with PRES. Furthermore, kidney function remained compromised (creatinine peaked at 645.3  $\mu\text{mol/L}$  [7.3 mg/dL]; eGFR 10 mL/min/1.73 m<sup>2</sup>), and therefore we were reluctant to proceed with a conventional angiogram as it was likely to result in the need for dialysis due to contrast nephropathy. She was discharged home on four antihypertensive agents and furosemide for a target BP at the 50th percentile for height with close follow up.

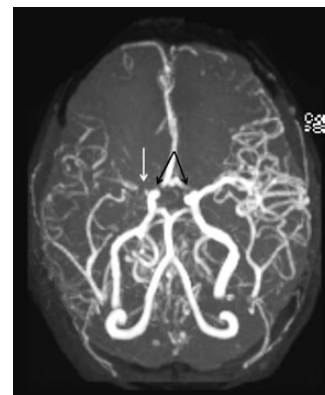
#### Long-term management

Over a 6-month period she remained on three or four antihypertensive medications which were adjusted to target a BP below 112/66 mmHg (50th percentile for height). In addition, she was started on epoetin alpha 2000 units<sup>2</sup> weekly, calcitriol 0.25  $\mu\text{g}$  daily, sodium bicarbonate 1300 mg twice daily and calcium acetate 667 mg tab with food for chronic kidney disease (CKD) management. Kidney function improved (creatinine declined to 265.2  $\mu\text{mol/L}$  (3 mg/dL); eGFR 24 mL/min/1.73 m<sup>2</sup>), anemia was treated to a target of <6.8 mmol/L (11 g/dL) (she required no transfusions), and serum phosphorous was consistently less than 1.94 mmol/L (6 mg/dL). However, she had intermittent periods of altered mental status and developed chronic headaches. Each episode was in the context of a presumed vasovagal/pre-syncopal episode.

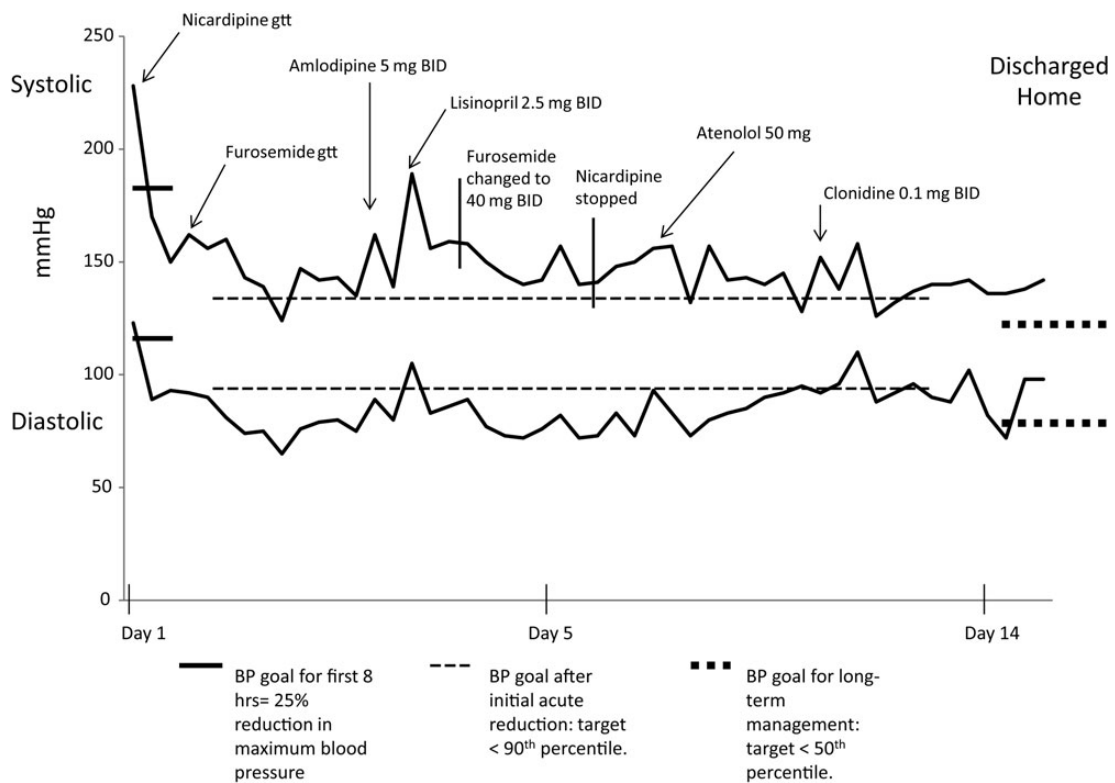
One episode occurred during a hot shower. Upon getting out of the shower, she developed vertigo and ataxia and fell to the floor. She was evaluated in an emergency room (ER). She had a normal examination. BP in the ER was 105/60 mmHg. She was given fluids and had good urine output. Her symptoms were attributed to aggressive BP control. Clonidine was discontinued and furosemide was decreased by half the dose to 20 mg twice a day. A second episode was associated with severe headache and occurred at school. When getting up from her desk



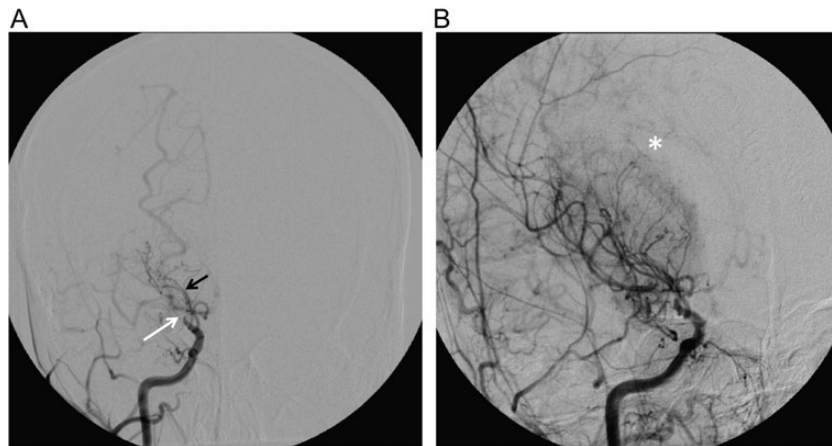
**Figure 1.** (A) MRI without contrast enhancement FLAIR signal showing hyperintensity in the right parietal lobe (white arrow), head of caudate nucleus (asterisk) and adjacent white matter. (B) Sequential image of series showing hyperintensity in the temporal lobe (short arrow), putamen (double asterisks) and right parietal lobe (long arrow). MRI, magnetic resonance imaging; FLAIR, fluid attenuated inversion recovery.



**Figure 2.** MRA without contrast enhancement using time-of-flight technique shows diminished flow in right MCA M1 (white arrow) and bilateral ACA A1 segments (black arrows). MRA, magnetic resonance angiography; MCA, middle cerebral artery; ACA, anterior cerebral artery.



**Figure 3.** Graphical representation of patient’s blood pressure, target ranges and medications prescribed during initial hospitalization.



**Figure 4.** (A) CNS angiogram shows an early time point of the study highlighting a tightly stenosed terminal right internal carotid artery (white arrow) with collateral lenticulostriate vessels (black arrow). (B) Later time point of study with asterisk indicating ‘puff of smoke’ appearance because of the collateral flow through the numerous lenticulostriate vessels.

she became ‘dizzy’, began seeing ‘spots’, and was nauseated. The school nurse recorded her BP at 110/63 mmHg. Neurological examination in the ER was normal with a BP of 117/72 mmHg. The headache was characterized as band like, associated with photo- and phonophobia. She was diagnosed with a migraine headache. Atenolol was changed to extended release metoprolol 25 mg and amitriptyline 10 mg nightly was prescribed.

A few weeks later the patient noticed a subtle numbness in her left hand and leg. She preferred receiving the epoetin alpha injection in her left thigh because she noticed that it hurt less. Two days prior to readmission, her father stepped on her foot and it did not hurt! On the

day of readmission, she developed facial numbness ‘I felt like I was at the dentist and somebody gave me novocain’. Her left arm felt heavy and clumsy. She presented to her primary medical doctor who referred her to the ER. On physical examination, BP was 126/75 mmHg. She had new left-sided arm weakness with numbness to light touch as well as decreased sensation to pin and temperature on the left side of the face. Although in the past we had been reluctant to use iodinated contrast, in the setting of a new focal deficit, a conventional angiogram of the central nervous system (CNS) with iodinated contrast was performed. It was consistent with moyamoya disease (Figure 4).

Upon the diagnosis of moyamoya, aggressive BP control for a target below the 50th percentile was recognized as potentially detrimental and contributory to her neurological symptoms. She recovered left-sided strength within 24 h. The target BP was revised to maintain a goal between the 50th and 95th percentile (she remained on lisinopril 10 mg twice daily, amlodipine 10 mg daily, metoprolol ER 25 mg daily and furosemide 20 mg twice daily). Two weeks after the angiogram identified moyamoya, she underwent a right-sided encephaloduroarteriosynangiosis (EDAS) with pial synangiosis revascularization. BP medications were held 24 h prior to surgery. She was discharged on post-operative day 6. Since the surgery BP targets remain above the 50th percentile and the calcium-channel blocker and beta-blocker have been discontinued. BP is controlled on lisinopril 10 mg twice daily and furosemide 20 mg daily.

## Case discussion

Hypertensive crises are caused by severe hypertension and can be divided into two categories: emergent or urgent. Hypertensive emergencies are occurring when there is evidence of evolving injury to the cardiovascular system (heart failure, pulmonary edema), kidneys (renal failure) or CNS (seizures, altered mental status, transient ischemia, stroke) due to endothelial damage from shear stress. Hypertensive urgency is defined as the presence of severe hypertension with no acute end-organ damage. Pediatric hypertensive emergencies are rare. This is in stark contrast to adult medicine where it is reported that of the 27% of the adult population affected by hypertension, 1% of these patients will at some point develop a hypertensive crisis [1]. Furthermore, 25% of all adult patient visits to the ER are related to hypertension and in one-third of these cases a hypertensive emergency is occurring [2]. In pediatrics, the causes of hypertension and hypertensive crisis vary by age although after the age of 6 years, primary hypertension is the most common cause. However, severe pediatric hypertension, which is commonly defined as a level 20 mmHg above the 95th percentile for height is most often secondary [3]. Renal disease is the most common cause of secondary hypertension and hypertensive crises [4]. In our patient, it was presumed that the presentation of hypertensive encephalopathy was due to renal failure from reflux nephropathy.

Reflux nephropathy is a recognized cause of both renal failure and hypertensive renal crisis in adolescent patients [3]. Although our patient's renal failure was precipitous, hypertension is a major risk for progression of CKD and we believed that the hypertensive crisis further accelerated the progression. A kidney biopsy was not performed because it was felt that the renal ultrasound was consistent with chronic VUR and therefore was unlikely to change management; while at the same time there would be a high likelihood of bleeding complications due to the uncontrolled hypertension and renal failure during biopsy. Her neurological status returned to baseline without any focal deficits. She was discharged home with a diagnosis of PRES and CKD. She was placed on an intensive BP regime with twice daily monitoring and target BPs at or below the 50th percentile based upon favorable outcomes from the Effect of Strict Blood Pressure control and ACE inhibition on the Progression of CRF in Pediatric patients (ESCAPE) trial group [5]. We originally deferred cerebral angiogram because of the renal failure.

In hindsight, it was appreciated that the episodes of altered mental status were ischemic in nature and not vasovagal. The aggressive BP control in an attempt to slow progression of CKD and avoid dialysis actually induced transient CNS ischemia—unmasking moyamoya. Moyamoya is an occlusive disease of the cerebral vasculature involving the internal carotid arteries with the development of collateral circulation from the leptomeninges and branches of the external carotid [6]. The collateral circulation has the appearance of a 'puff of smoke'—the translation for the Japanese word 'moyamoya'. Although pediatric moyamoya has been associated with severe hypertension [7–10], we believe that this case is the first to present as a hypertensive emergency with renal failure and highlights this disease for consideration in the differential diagnosis of hypertensive renal failure (Table 1).

There are two possible mechanisms of hypertension related to moyamoya disease: (i) systemic compensation due to cerebral hypoperfusion or (ii) fibromuscular dysplasia of the renal arteries with resultant renovascular hypertension. The occlusive vasculopathy of moyamoya can be systemic and affect the vasculature of a number of organ systems. Renal artery stenosis (RAS) occurs in 7% of the Japanese population with moyamoya [11]. However, children are disproportionately affected (a breakdown shows that 45% were children) [8, 11, 12]. In a more heterogeneous population, 20% of children with moyamoya also had RAS according to a study from Great Ormond Street Hospital [8].

A renal angiogram was performed at the time of the CNS study (Figure 5). No evidence of RAS was found, although there was 'pruning of the distal arteries consistent with chronic kidney disease'. Therefore, it seems that in our patient the hypertension was due to compensation from cerebral hypoperfusion. This is again unique as all previous cases of renal failure associated with moyamoya have documented RAS. We appreciate that the occlusive vasculopathy of moyamoya can involve small arteries and therefore cannot entirely ascribe the findings of the angiogram to CKD with absolute certainty. Therefore, we support that in the setting of hypertension and moyamoya disease, evaluation of the renal vasculature with imaging and plasma renin levels should be performed and a strong suspicion for RAS should be maintained [13].

Our patient underwent an indirect revascularization of the CNS by an EDAS procedure. This technique involves

**Table 1.** Differential diagnosis of severe hypertension and renal failure

Glomerulonephritis
Acute post-streptococcal glomerulonephritis
Lupus nephritis
Ig A nephropathy with nephritic presentation
Pauci-immune crescentic glomerulonephritis (see vasculitis below)
Membranoproliferative glomerulonephritis
Anti-glomerular basement membrane antibody disease
Vasculitis
Granulomatosis with polyangiitis
Microscopic polyangiitis
Churg-strauss
Polyarteritis nodosa
End-stage renal disease
VUR nephropathy, PUV/CAKUT, nephronophthisis
Hemolytic uremic syndrome
Scleroderma renal crisis
Moyamoya

VUR, vesicoureteral reflux; PUV, posterior urethral valves; CAKUT, congenital anomalies of the kidney and urinary tract.





**Figure 5.** Renal angiogram. Single renal arteries (white arrows) with no ostial stenosis. Both renal arteries show distal pruning consistent with CKD.

placement of vascularized tissue supplied by the external carotid artery (which is not typically affected by moyamoya) in direct contact with the brain. This then leads to in-growth of new blood vessels ‘vascularizing’ the underlying ischemic area [6]. Surgical revascularization has gained acceptance as a primary treatment for moyamoya. The greatest risk for stroke after revascularization is within the first 30 days (reportedly 4% per hemisphere). However, thereafter the probability of being stroke-free at 5 years is 96% [6, 14, 15]. Since surgery we have been able to wean antihypertensive agents, a phenomenon which has been previously described [16]. This further supports that hypertension was not renovascularly but cerebrovascularly driven.

In conclusion, this case highlights that moyamoya must be considered in the differential diagnosis of patients presenting with hypertensive emergency and renal failure. Although CKD is a major risk factor of hypertensive emergencies with reports indicating that 79% of adult patients have CKD stage 2 or greater [17], there are a number of causes that must be considered (Table 1). We attributed the hypertensive emergency to CKD causing acute kidney injury and PRES. We were pleased as neurological status and kidney function improved potentially inducing diagnostic inertia. However, the long-term management of CKD with aggressive BP control induced transient ischemia because of moyamoya. Recognition of moyamoya led to surgical revascularization and has changed our medical management to accept higher blood pressures up to the 90th percentile.

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**Conflict of interest:** None declared.

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