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MEDICINE

Sturge-Weber Syndrome and Haematuria: a Case Report of an Unusual Presentation

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Abstract

Sturge-Weber syndrome (SWS) is a rare, congenital neurocutaneous disorder. SWS is the most commonly described as a 'triad' of a facial port-wine naevus in the trigeminal nerve ophthalmic distribution, leptomeningeal angiomatosis and glaucoma. Renal infarcts have not previously been described in patients with SWS. The association behind SWS and renal infarcts is unclear, however, may be a result of the same cerebrovascular malformations occurring in the renal vasculature. We report on a patient with known SWS presenting with a first episode of frank haematuria, subsequently found to be a result of a renal infarct with preserved kidney function. This proposes new challenges in the investigation and management of comorbidities associated with SWS, most notably with regard to the use of radiological imaging and anticoagulation in younger patients.

Keywords Sturge-Weber syndrome · Haematuria · Renal infarct

Background

Sturge-Weber syndrome (SWS) is a rare, congenital neurocutaneous disorder. It is most commonly described as a 'triad' of a facial port-wine naevus in the ophthalamic distribution of the trigeminal nerve, leptomeningeal angiomatosis and glaucoma [1, 2]. Cerebral vascular malformations result in the neurological manifestations of SWS, including seizures, stroke-like episodes and intellectual disabilities [3]. Disease progression has been associated with thrombotic events and venous stasis which perpetuates neurodegeneration [4].

The presence of leptomeningeal capillary-venous malformations affecting the occipital lobes or optic tract has also been described in literature as causing visual field defects [5]. The guanine-nucleotide-binding protein G(q) subunit alpha (GNAQ) gene, involved in G protein-coupled receptor signalling, has been associated with SWS; in particular, a somatic activating mutation in GNAQ has been found to cause dysregulated signalling activity [6]. In embryonic development, this leads to abnormal formation of blood vessels through dysfunction of peptide-receptor signalling, such as endothelin, leading to the malformation of the cerebral vasculature as described above [7]. More recently, GNA11 (guanine nucleotide-binding protein subunit alpha-11), the paralogue of GNAQ, has been identified as also being mutated in patients with SWS [8, 9]. In vitro, GNA11 mosaicism has been demonstrated to have downstream effects on multiple signalling pathways, which possibly explains its relevance in G protein disorders and their clinical features [10]. These encompass SWS, McCune-Albright syndrome, phakomatosis pigmentovascularis (PPV) and others.

Renal involvement in SWS is uncommon and usually consists of haemangiomas within the renal pelvis, papilla and bladder, with polycystic kidney disease also being associated with SWS [11, 12]. However, renal infarcts have not been described in patients with SWS. We describe a patient with known SWS presenting with a first episode of frank haematuria, subsequently found to be a result of a renal infarct. To our knowledge, this is the first case that SWS and renal infarcts have been described together.

Case Presentation

A 19-year-old non-verbal, intellectually impaired male presented to the emergency department with the primary

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complaint of haematuria. His carers noted frank blood, about half a teaspoon, mixed in with urine in the patient's nappy. The day before presentation, the patient's urine was observed to be darker than usual, and he was noted to be mildly irritable. Apart from this, the patient had been well with no obvious complaint of pain, and the carers denied any systemic symptoms such as fever, night sweats or recent weight loss. Oral intake and urine output had been normal.

The patient had been diagnosed with Sturge-Weber syndrome at the age of 18 months and had developed associated conditions typical of the disease, such as focal seizures, a port-wine stain on the face, bilateral pial angiomatosis and intellectual and visual impairment without glaucoma. He had a history of a stroke-like episode at the age of 10 resulting in left-sided hemiplegia, needing a wheelchair for mobilization and dysphagia. His diet consisted of minced, moist food and mildly thickened fluids.

Examination was limited due to the patient's pre-morbid condition. However, he appeared well, and his vitals were within normal limits. His chest was clear to auscultation, and his abdomen was soft and non-tender. A limited neurological examination revealed no new deficits, and indeed his carers agreed that they had noticed nothing different regarding patient safety for his frank haematuria.

The patient underwent routine initial tests in the emergency department: full blood count, electrolytes, liver and renal function, urine microscopy and a computed-tomography (CT) non-contrast scan of the abdomen.

Investigations

A complete blood count was unremarkable (haemoglobin 143 g/L, white cell count 6.2×10^9/L, platelets 316×10^9/L). Electrolytes and renal function were normal (sodium 138 mmol/L, potassium 4.5 mmol/L, urea 3.8 mmol/L, creatinine 52 μmol/L). Liver function tests were slightly elevated (alanine transaminase 61 U/L, aspartate transaminase 38 U/L, lactate dehydrogenase 249 U/L, alkaline phosphatase 119 U/L, gamma-glutamyl transferase 30 U/L).

Urine microscopy revealed $< 10 \times 10^6$/L leucocytes, erythrocytes and epithelial cells. A CT non-contrast study performed of the abdomen revealed a wedge-shaped hypodensity within the upper pole of the left kidney with no other abnormalities (Figs. 1 and 2).

Upon admission to the general medical ward, the patient received further tests.

A Doppler ultrasound of the lower legs did not reveal any thromboembolus. Immunological studies were unremarkable (negative extractable nuclear antigen antibodies, anti-dsDNA, antinuclear antibodies, antineutrophil cytoplasmic antibodies). A thrombophilia screen was also unremarkable (negative lupus anticoagulant screen, activated protein-C 6.71, antithrombin 3 1.19, protein C 1.15, protein S 0.65, factor V Leiden absence). A trans-thoracic echocardiogram (TTE) did not reveal any evidence of intracardiac thrombus.

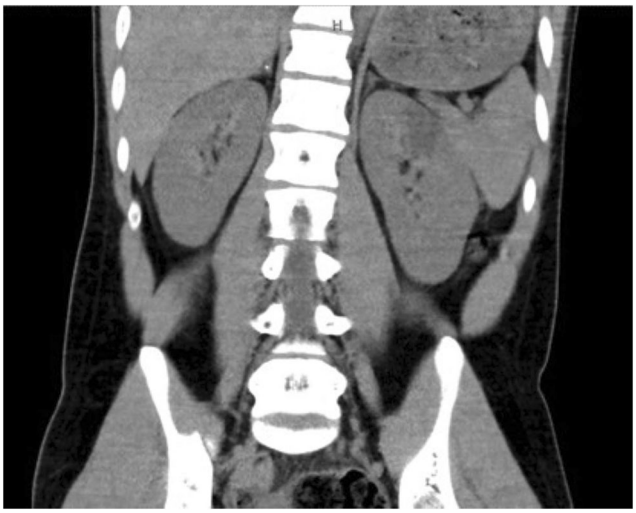

Fig. 1 CT abdomen, coronal view. This coronal view demonstrates a wedge-shaped hypodensity in the upper pole of the left kidney

Differential Diagnoses

Infections of the urinary system are one of the most common causes of haematuria [13]. As infection was shown to be an unlikely cause of the patient's presentation, the wedge-shaped hypodensity on CT imaging was identified as likely being a thromboembolism causing renal infarct and the leading cause of the patient's haematuria.

The ideal diagnostic tool for renal infarcts is a CT abdominal angiogram with a post-contrast venous phase [13]. However, given the patient's clinical presentation, alternative differentials were unlikely. For example, cystitis, pyelonephritis and lobar nephronia were considered unlikely in the absences of fevers, sepsis, flank pain, pyuria or bacteruria. The carers also noted no change in mental state or functional status which may also indicate an underlying infection. The decision was made not to unnecessarily expose the patient to further contrast and radiation given that the provisional diagnosis was made on a basis of exclusion.

Renal and ureteric stones are also a common cause of haematuria. These diagnoses were made much less likely given the findings on a non-contrast CT scan of the abdomen [13].

Benign and malignant renal tumours can also cause macroscopic haematuria. Given the patient's age, these were less likely causes; however, to be fully excluded, the patient would need to undergo a CT intravenous pyelogram (IVP) and cystoscopy. Similarly, intrinsic renal causes such as nephritis were less likely given a reassuring urine microscopy, normal

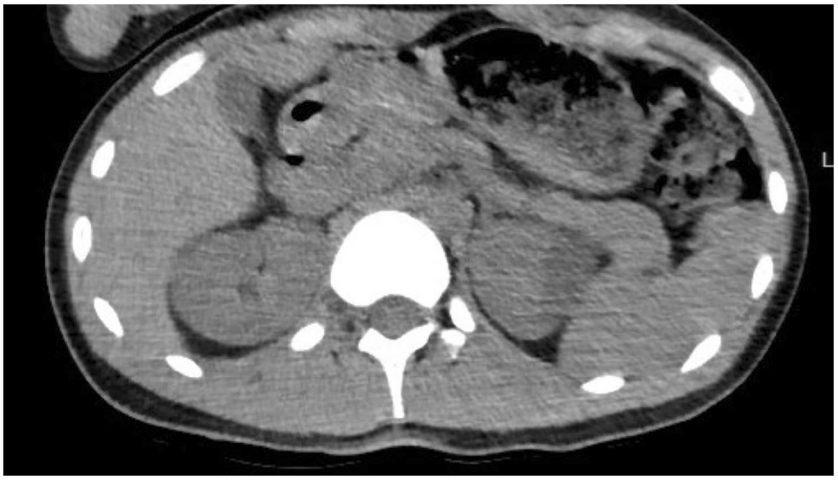

Fig. 2 CT abdomen, transverse view. This transverse view demonstrates a wedge-shaped hypodensity in the upper pole of the left kidney

renal function and negative immunological studies. A formal renal biopsy was not considered.

Treatment, Outcome, Follow-Up

The patient was treated conservatively, with supportive care on the ward. He was previously managed on low-dose aspirin to reduce thrombosis and promote neuroperfusion, though this practice remains controversial [3, 14].

The patient was discussed with specialists, who recommended initiation of a second anticoagulation agent to prevent further thromboembolic events. The benefits and risks of further anticoagulation were thoroughly discussed with the patient's carers and family.

The patient's family explained that he has previously had multiple high-impact falls, resulting in serious concussions requiring hospital admission. The patient has a high-fall risk given his hemiparesis, intellectual impairment and visual deficits. Owing to the risk of significant sequelae following a fall on anticoagulation, the family (his decision-makers by law) opted to continue only on aspirin.

A complicating factor for follow-up was the patient's age. Owing to the complex nature of his condition, at age 19, the patient was only beginning his transition from paediatric care to the adult healthcare system. His presentation with frank haematuria unfortunately occurred only 1 month post his final paediatric appointment.

The patient was discharged with a 2-month follow-up appointment at with adult internal medicine outpatients' clinic. A referral was also made to the adult neurology outpatient department. The overall unifying diagnosis was renal infarct, with the aetiology unclear, but most likely thromboembolic. At the time of writing, the patient was well, and at home waiting for this appointment.

Discussion

The capillary-venous vascular malformations in Sturge-Weber syndrome most commonly affect the brain, skin and eye [15]. Other organs are rarely involved. The patient described in our report certainly presented with the classic, well-described phenotype of neurological symptoms: namely, a port-wine stain, seizures, bilateral pial angiomatosis, cortical visual impairment—although no glaucoma was present—and hemiplegia from a previous stroke. Dysphagia was also present.

Renal involvement in SWS has been described in very few cases. If the renal system is affected by SWS, it is most likely from an angioma, which can cause haematuria [15, 16]. Rhabdomyolysis and acute renal failure have also been described in one other case [17]. However, an extensive literature search has not revealed any cases of renal infarction and SWS described together in one patient.

The GNAQ gene mutation has been described as the most likely main mutation in SWS [18]. Cells rich in GNAQ include endothelial cells in the brain, eye and skin, causing their respective disorders [19]. These organs and their vasculature are known to arise from the ectoderm and mesoderm, both of which are also affected by the phakomatoses including Klippel-Trenaunay syndrome, tuberous sclerosis and Von Hippel-Lindau disease [16].

In utero, the renal system is derived from the intermediate mesoderm, and it is supplied by the right and left renal arteries, which branch into small segmental arteries, and then lobar branches subsequently—the latter gives off interlobular arteries supplying the individual glomeruli [20, 21]. Infarction of the renal system is rare and most commonly is caused by thromboembolic events, which occlude the segmental arteries, thus giving the classical appearance of a wedge-shaped area of hypoperfusion on CT imaging [22].

Given the previous background of a cerebral infarct, our patient was admitted for further investigation for thrombophilia, deep-vein thrombosis, echocardiography and a decision on anticoagulation. These follow established clinical guidelines, especially in a patient who has had multiple presumed ischemic events [20]. As investigations revealed no clear source of emboli, nor co-existing thrombophilia state—the renal infarct was presumed to be due to SWS.

Decreased cerebral perfusion in patients with SWS—leading to stroke-like events—has been previously described and imaged as a result of impaired venous drainage from multiple vascular malformations, leading to venous stasis and microvascular thrombosis [15]. Further abnormalities in cerebral vasculature can include calcium deposition and increased endothelial proliferation [3, 15]. Given that vascular-endothelial growth factor (VEGF) and its associated receptor are heavily expressed in both cerebral vasculature and renal vasculature, and that GNAQ mutations increase downstream signalling in VEGF and mitogen-activated protein kinase (MAPK) pathways, it stands to reason that these malformations and abnormalities might also be present in the renal arterial system and hence cause the infarct [15, 23, 24]. Hence, CT angiography of the renal vasculature should be worth pursuing in patients with renal infarcts and SWS. Further, since SWS can affect tissues of mesodermal origin, it is worth further exploring if there is any possible genetic link with renal vascular or parenchymal development.

Kinsler et al. [9] recently undertook deep phenotyping and DNA sequencing of 45 international patients with SWS, PPV or extensive dermal melanocytosis (EDM), and GNAQ or GNA11 mutations were found in almost half of these patients. Interestingly, renal hypertension was found in 2 patients—one with an obstructing renal cyst, and the other with renal artery stenosis. This finding could lend strength to the hypothesis that the renal system is a possible target organ in patients with SWS with GNAQ/GNA11 mutations. Unfortunately, genetic testing was not undertaken in our patient as GNAQ/GNA11 sequencing is not offered widely in Australia.

The use of aspirin in SWS patients for antithrombotic use has been described in a few studies, all of which report improvement in seizure and stroke-like episode frequency with daily 3–5 mg/kg/day dosing [25–27]. Apart from this, there is no evidence to suggest the use of other anticoagulants—more investigation is required before these could be used, and it must be noted that the use of dual anticoagulation should be considered very cautiously, as patients with SWS have a high risk of falling [28].

Given the paucity of evidence, the importance of a thorough discussion with stakeholders was critical in this case. The decision to continue aspirin alone was made with consideration of the patient's high-fall risk. However, the family was aware that this conversation would need to be revisited should another thromboembolic event occur.

As previously discussed, CT or MRI angiography would be ideal but clinically considered not appropriate. As the carers elected for conservative management, there was no benefit to expose the patient to contrast or radiation, nor could the cost of imaging be justified. Given that the aetiology of renal infarction remains unknown in 40–50% of patients following investigation, angiography should be considered in future cases [29, 30]. However, the risks and costs of the investigation must be tempered by clinical appropriateness and whether it would affect management [31].

Conclusion and Learning Points

- Haematuria in Sturge-Weber syndrome can be a result of vascular malformations and subsequent thromboembolic events.
- Investigations should exclude more common causes before proceeding to computed tomography (CT) or magnetic resonance (MR) angiography.
- Some Sturge-Weber patients are intellectually impaired or non-verbal. It is important for the immediate family/caregivers to be heavily involved in decision-making. Similarly, it is critical that stakeholders are sufficiently educated to make informed decisions.
- There is no evidence available for anticoagulation apart from aspirin. Use a second anticoagulative agent with major caution. Decisions should be made in consultation with relevant specialty services and stakeholders.
- Genetic testing, including GNAQ/GNA11 sequencing, where available and not at significant expense to the patient, could be considered to assist the clinician in further management and research towards the pathophysiology of SWS.

Patient's Perspective

The patient's parents (also the primary carers and legal decision-makers) were present during the majority of his inpatient stay and, when asked, commented on their experience.

We appreciate the time that's been taken to explain the situation to us. This was a difficult decision because of how complicated it was. We want the best for our son but it's sometimes hard to navigate medical language. We feel very grateful that the team took the time to talk to us and respected our final decision.

Author Contributions E.M. and C.D. contributed equally to the design and implementation of the case report. E.M. wrote the manuscript, and C.D. edited and provided feedback.

Data Availability Not applicable.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethics Approval Automatically exempt from review, (National Statement on Ethical Conduct in Human Research, paragraphs 5.1.22 and 5.1.23).

Consent to Participate and for Publication Informed, written consent was sought and obtained from all participants included in the study.

Code Availability Not applicable.

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