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Horse riding, energy drinks and cardiogenic shock: A clinical conundrum

Instructive Case

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Case:

A previously well 15-year-old girl dismounted during horse-riding, reporting shortness of breath, chest tightness and abdominal pain. She had consumed 3 Red Bull™ energy drinks (total 230mg caffeine) earlier that morning. Paramedics were called and administered a dose of intramuscular adrenaline to treat possible anaphylaxis. She continued to deteriorate with an altered mental state and was transferred to the nearest emergency department. On arrival, she was peripherally shut down with tachycardia and hypotension. Given a working diagnosis of cardiogenic shock secondary to either sepsis or cardiomyopathy, the patient was commenced on inotropes, vasopressors, antibiotics and steroids. Frank pulmonary oedema required

intubation and ventilation. Bedside echocardiogram demonstrated a dilated left atrium and poorly contractile left ventricle. She had cannulation for ECMO (extra-corporeal membrane oxygenation) and was transferred to a cardiothoracic tertiary centre.

Early consideration of possible underlying reasons for her clinical state included meningococcal septicaemia and septic shock due to a retained tampon, however there were no clinical signs consistent with this.

Initial investigations showed acute renal injury with an elevated creatinine, elevated lactate, neutrophilia, elevated procalcitonin and elevated troponin level. The remainder of her electrolytes were normal and preliminary blood cultures were negative.

Careful history taken after initial stabilisation revealed a three-year history of exercise induced "spells" with palpitations, nausea and shortness of breath. She had previously had a 24 hour Holter monitor, ECG and echocardiogram, all which had been reported as normal. She had occasional hypertension and had been prescribed a beta-blocker but was non-adherent to this. The family also mentioned in passing the history of a paternal aunt with a carotid body tumour and recurrent phaeochromocytoma.

On careful examination during her stay in ICU, she was felt to have a "fullness" on the left side of her abdomen. Ultrasound revealed a well-defined, left para-aortic lesion, confirmed on CT scan with MRI performed for further delineation. Her admission was complicated by evolving renal failure with a creatinine rising to 516umol/L, requiring haemofiltration. Despite cardiovascular stabilisation and being weaned off ECMO over 3 days, she remained confused and sedated with a Glascow Coma Score of 3 with evidence of right sided hemiparesis. CT brain demonstrated a left MCA infarct whilst MRI brain showed multiple foci of diffusion restriction.

As she improved clinically and was weaned off inotropes, hypertension developed, with blood pressure rising up to 180/110mmHg (systolic 95th centile 125, diastolic 95th centile 85) whilst awake, with associated tachycardia to 150bpm.

The presence of an abdominal mass with hypertension and tachycardia raised suspicion of a secretory paraganglioma. Urine and plasma metanephrines/catecholamines and Chromogranin A (a nonspecific polypeptide commonly secreted by chromaffin cells) were undertaken (Table 1). Despite the usual pre-operative management of alpha blockade prior to introduction of beta blockade, the patient had already been commenced on esmolol for management of her

hypertension in ICU. Once the underlying cause for hypertension was recognised, alpha blockade was commenced with phenoxybenzamine.
GaDOTA-TATE scan (MR-PET) confirmed the left para-aortic mass lesion seen on MRI but there was no gallium 68 DOTATATE avidity.

Surgery for removal of the paraganglioma was delayed due to significant nausea resistant to protein-pump inhibitor therapy, requiring naso-gastric feeds and intravenous fluids. A normochromic normocytic anaemia required a transfusion pre-operatively. On day 39 after admission, a large (5.4cm) left infra-renal para-aortic mass was removed through open laparotomy without capsular disruption. Histology confirmed a paraganglioma with immunohistochemical staining pattern consistent with an SDHB mutation. Microarray results confirmed a deletion in chromosome 1p36.13, spanning exon 3 of the SDHB gene, confirmed to be paternally inherited. Given the nature of the exon deletion, it was not detected on whole exome sequencing.

The lack of avidity on functional scans was considered to be due to extensive necrosis within the lesion, probably incurred at the time of severe hypotension. Metanephrines and Chromogranin A normalised post operatively. She has received counselling regarding her SDHB mutation and ongoing screening requirements. Her father and sister have since been confirmed to have the same mutation but have negative screening to date.

Discussion:

In any patient presenting with shock, a clear history and examination are of the utmost importance in coming to a diagnosis. In this case, there were confounding features which made the road to diagnosis more difficult.
For our patient, the history of caffeine intake on the morning of her collapse would be expected to have precipitated hypertension, rather than the hypotensive state in which she was found. In retrospect, it was likely a combination of high dose caffeine and a secretory adrenaline surge caused a hypertensive crisis with subsequent cardiogenic shock.
Family history in this case was paramount. If a clear family history (and family medical record review) had been undertaken at an earlier stage, this would have informed not only a correct diagnosis of paraganglioma at an earlier point but also the likelihood of an SDHB mutation as compared to other familial syndromes. Unfortunately, in the acute care scenario with a critically ill patient, these details are often delayed.

Given the lack of prodrome for our patient, sepsis was less likely, however septic shock in adolescent patients can present atypically and always needs to be considered. A thorough physical examination is critical in narrowing the differential diagnosis, in this case guided by the abdominal mass.

The underlying cause of her stroke remains unclear and not thought to be solely caused by either hypertension or hypotension, rather in the setting of her critical illness and management including a possible complication of ECMO.

Paragangliomas were first reported by German pathologist Max Schottelius in 1886, after he described an 18-year-old woman with panic attacks, tachycardia and sweating[1]. The term phaeochromocytoma (an adrenal paraganglioma) was first described by German pathologist Ludwig Pick in 1912[1]. Diagnosis requires proof of excessive catecholamine release and anatomical tumour identification. Tumours can have fluctuating levels of catecholamine release related to their activity and hence this measurement can be less sensitive. Metanephrines, as metabolites of catecholamines, have a more constant and steady release and are hence better measured – reported as 97% sensitive and 93% specific to paragangliomas[1,2].

The imaging modalities recommended for identification of paragangliomas have changed over time. Historically, the gold standard was the metaiodobenzylguanidine (^{123}I-MIBG) scan, which uses a functional analogue of noradrenaline. MIBG scans are more likely to have false negatives (sensitivity <70%) in extra-adrenal tumours or patients with SDHB mutations and may also miss metastatic disease[3,4].

^{68}Ga-DOTA-TATE PET has a high affinity for somatostatin surface receptor type 2 and is now considered the gold standard imaging modality for paragangliomas.

^{18}F-FDG PET (flurodeoxyglucose) can also be used but is non-specific, portraying glucose metabolic activity of tumours. The uptake and retention is unrelated to catecholamine uptake and storage.

SDHB mutations are the most common of the SDH group and carriers of this mutation can have multiple and recurrent tumours[5]. Affected patients present with more aggressive tumours, a younger age of presentation and higher rates of metastasis, reported as up to 35%[6]. Malignant disease occurs in up to one third of paragangliomas/phaeochromocytomas and the presence of metastasis <18 years carries a poorer prognosis[7]. Genetic transmission is autosomal dominant except in some subtypes of SDH (SDHD and SDHAF2) where maternal imprinting occurs so

inheritance is only paternal[1,2]. Carriers of SDHB mutations have a lifetime tumour risk up to 76% with 50% penetrance by age 35[5,8]. Due to the propensity for genetic anticipation, carrier screening should start in the first decade. Surveillance is crucial, with the EviQ guidelines providing current screening recommendations[7].

This case highlights an unusual presentation of shock in an adolescent female as the index case of a familial SDHB mutation. Clear and thorough history taking at the first opportunity is essential to define the scope of disease. Early identification and understanding of a dominant mutation in a family allows reduced risk in subsequent generations by screening and follow-up of affected individuals.

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Learning Points:

- Differential diagnosis of cardiogenic shock for an adolescent girl should include possibilities of hypertensive crisis and toxic shock syndrome
- Succinate dehydrogenase B (SDHB) mutations can present in childhood and adolescence
- SDHB mutations have higher rates of malignant behaviour and metastatic disease than other SDH complex mutations
- Paragangliomas may not be detected on nuclear imaging in the case of extensive necrosis
- Genetic diagnosis requires specific gene testing as deletions may be missed using whole exome sequencing

Table 1. Elevated urinary and plasma metanephrines as well as elevated Chromogranin A.

Plasma Catecholamines	Value	Normal range
Noradrenalin (nmol/L)	**6.4**	1.0 - 5.0
Adrenalin (nmol/L)	**3.3**	0 – 1.0
Dopamine (nmol/L)	**1.1**	0 – 0.5
Plasma Metanephrines		
Normetanephine (pmol/L)	**1618**	<900
Metanephrine (pmol/L)	178	<500
3-Methoxytyramine (pmol/L)	103	<110
Urine Metanephrines		
Normetanephrine (umol/day)	**7.4**	<2.3
Metanephrine (umol/day)	1.4	<1.7
3-Methoxytyramine (umol/day)	0.8	<1.3
Normetanephrine/Cr (mmol/mol)	**1.02**	<0.25
Metanephrine/Cr (mmol/mol)	**0.19**	<0.1