Raised CK and acute kidney injury following intense exercise in three patients with a history of exercise intolerance due to homozygous mutations in *SLC2A9*.

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ABSTRACT

Acute rhabdomyolysis (AR) leading to acute kidney injury has many underlying etiologies, however, when the primary trigger is exercise, the most usual underlying cause is either a genetic muscle disorder or unaccustomed intense exercise in a healthy individual. Three adult men presented with a history of exercise intolerance and episodes of acute renal impairment following intense exercise, thought to be due to AR in the case of two and dehydration in one. The baseline serum CK was mildly raised between attacks in all three patients and acutely raised during attacks in two of the three patients. Following referral to a specialized neuromuscular centre, further investigation identified very low serum urate (<12 umol/L). In all three men, genetic studies confirmed homozygous mutations in *SLC2A9*, which encodes for facilitated glucose transporter member 9 (GLUT9), a major regulator of urate homeostasis. Hereditary hypouricaemia should be considered in people presenting with acute kidney injury related to intense exercise. Serum urate evaluation is a useful screening test best undertaken after recovery.

Key words: Acute rhabdomyolysis, exercise induced renal failure, renal hypouricaemia

INTRODUCTION

Acute rhabdomyolysis (AR) leads to myoglobinuria, which in turn may cause acute kidney injury requiring dialysis. The most useful biomarker for AR is the serum creatine kinase (CK) which is acutely elevated to at least 5-10x the upper limit of normal, although the level may be considerably higher due to extensive skeletal muscle damage [1]. There are many causes of acute rhabdomyolysis [2], however, the most common presentation to emergency departments follows some form of physical activity in people with either metabolic muscle disease (glycogen storage disorders and fatty acid oxidation disorders) or following intense unaccustomed exercise in otherwise healthy individuals [3, 4]. Identifying the cause of AR episodes is important so that appropriate management advice can be given to prevent future occurrences. A preceding history of exercise intolerance or previous episodes of AR may identify those with underlying metabolic muscle disorders and guide further investigation [3]. Despite this, the underlying cause in many patients presenting with recurrent episodes of AR remains undetermined.

Here, we describe three young adult males who presented with exercise intolerance associated with raised CK and recurrent episodes of acute exercise induced kidney injury (AEIKI) who were found to have hereditary renal hypouricaemia type 2 (RHUC2) caused by homozygous mutations in *SLC2A9*.

Case histories

Patient One

A previously healthy 23 year-old man of Pakistani origin was referred to our Neuromuscular Centre for further investigation following an episode of AEIKI and subsequent history of exercise intolerance to rule out a possible underlying diagnosis of McArdle disease.

Two years earlier, he had presented acutely to his local Accident and Emergency Department (A/E) with loin pain, abdominal pain, nausea and vomiting following an episode of strenuous exercises comprising 50 sit-ups. The discharge summary disclosed that he had a raised serum creatine kinase (CK) 10,373 IU/L (normal <190 IU/L), C reactive protein (CRP) 14.9 mg/ml (normal range 0-5 mg/ml), White cell count 13.6 and evidence of acute kidney injury with serum creatinine 437 umol/L (normal range 66-112 umol/L) and urea 17.1 mmol/L (normal range 1.7-8.3 mmol/L), other blood parameters, including serum electrolytes, were not reported. He did not report a change in the colour of his urine during this episode, but urinalysis was positive for blood (3+) and ketones (1+). A diagnosis of exercise induced AR was made. He was managed with intravenous fluids and discharged home a few days later with improved blood parameters (CK 330 IU/L, renal function and electrolytes were reported to be normal).

During childhood he did not recall any problems performing intense physical activities such as running (he could sprint >100m without any difficulty). From the age of 12 years, he started to perform regular upper body strengthening exercises (weightlifting) without any difficulty. However, since the admission to A/E two years earlier, he reported experiencing symptoms of tachycardia, dizziness, nausea, muscle weakness and myalgia during strenuous physical activities such as walking up more than two flights of stairs and exercising vigorously in the gym. He had a younger brother (described below) who presented with similar symptoms. His parents, who were first cousins, were both fit and healthy. He had an uncle who was wheelchair dependent following a spinal injury and was being managed for chronic renal failure.

The patient's past medical history was unremarkable, apart from two generalised seizures in early adolescence. He was not taking any regular medication. Clinical examination was normal.

Laboratory investigation, performed at our centre, showed mildly raised serum CK 284 IU/L (normal range <190 IU/L), urea 7.8 mmol/l (normal range 1.7-8.3 mmol/l), sodium 141 mmol/l (normal range 135-145 mmol/l), potassium 4.5 mmol/l (normal range 3.5-5.1 mmol/l), creatinine 87 umol/l (normal range 66-112 umol/l), estimated GFR >90. Other investigations were normal and included: liver and thyroid function, calcium, phosphate and alkaline phosphatase, fasting acylcarnitine profile and urine organic acids. A non-ischaemic forearm exercise test was normal (table 1). However, routine serum urate was found to be undetectable <12 umol/L (normal range 280-350 umol/L). Genetic testing confirmed a diagnosis of RHUC2 and is described below.

He was advised to avoid strenuous exercise and to ensure that he was well hydrated before and during aerobic activities to prevent future episodes. The patient failed to attend further appointments and was lost to follow-up.

Patient Two

The younger brother of patient one presented to A/E at the age of 19 years, only a few weeks after his brother's first presentation with very similar symptoms of acute abdominal pain and loin pain with nausea and vomiting following strenuous exercise (weightlifting at his local gym). On examination, he was noted to have tenderness in both right and left iliac fossae and his urine was blood stained. Investigation results taken from the discharge summary demonstrated acute kidney injury: urea 16.9 mmol/L (normal range 1.7-8.3 mmol/L) and serum creatinine 219 umol/L (normal range 66-112 umol/L), serum electrolyte results were not specified. White cell count (WCC) and C reactive protein (CRP) were mildly raised (WCC 13.8 X10^9/L, CRP 14.9), vasculitic screen including: antinuclear antibodies, antineutrophil cytoplasmic (ANCA) antibodies, complement: C3 and C4 were all negative. Urine protein/creatinine ratio was normal, HIV and Hepatitis B serology were negative. Serum CK and urate were not tested during the acute episode. X ray abdomen and CT scan of kidneys and bladder showed no renal calculi. He was diagnosed with acute kidney injury secondary to dehydration and managed with intravenous fluids and discharged from hospital after a few days.

When seen in the neuromuscular clinic two years later, he reported symptoms of nausea, dizziness, myalgia and back pain whenever he performed intense exercise. His past medical history was unremarkable. As a child he had no problems performing physical activities and could run with ease. Clinical examination

was normal. Laboratory investigation showed mildly raised serum CK 480 IU/L, but normal: renal function (urea 7.2 mmol/L, creatinine 87 umol/L, sodium 141 mmol/l, potassium 4.5 mmol/l, GFR >90 mL/min/1.73 sqm), liver and thyroid function, calcium, phosphate, alkaline phosphatase, fasting acylcarnitine and urinary organic acid profiles. A non-ischaemic forearm exercise test was normal (table 1). However, serum urate was found to be undetectable <12umol/L (normal range 288-350 umol/L). Genetic testing (described below) confirmed a diagnosis of RHUC2. He was advised to avoid strenuous exercise and ensure that he was well hydrated when performing aerobic exercise. However, he failed to attend future appointments and was lost to follow-up for several years.

At the age of 28 years, he was referred back to our service having presented to a different A/E department with severe bilateral flank pain, accompanied by nausea and vomiting, severe fatigue, loss of appetite and thirst, sweating, dizziness, shortness of breath and dysuria. Since he was last seen in the neuromuscular clinic, he reported having had at least four emergency visits to hospital a year. On this occasion, his symptoms began during circuit training which involved multiple activity stations that included cycling on a static bike, 'burpees' (a combination of squat, push up and jump), running on the spot and weight training. He did not seek medical attention for four days, at which point his symptoms had become very severe.
On admission, his urine was blood-stained and he was oliguric. His observations showed sinus bradycardia (44 beats per minute), blood pressure 117/69, respiratory rate 20 breaths per minute and oxygen saturation 98%.

On admission, there was biochemical evidence of acute kidney injury stage 3 (eGFR 18 mL/min/1.73 sqm, creatinine 364 umol/L, urea 17.5 mmol/L, sodium 131 mmol/l, potassium 3.7mmol/l), CRP was mildly raised 14mg/ml, CK was minimally raised 260 IU/L and urate 17umol/l (normal range 288-350 umol/L). He was managed with intravenous 0.9% saline, anti-emetics and analgesia. A renal ultrasound showed bilateral medullary calcinosis. Two days later his symptoms resolved, and he was well enough to be discharged, at that time, blood parameters were reported to have improved (CRP 5.3 mg/ml, creatinine 229 mmol/l, urea 12.9, sodium 144 mmol/l, potassium 4.5mmol/l).

Patient Three

A 29 year-old man of Libyan origin was referred for investigation of exercise intolerance and multiple episodes of AR requiring hospital treatment. The first episode occurred when he was 18 years of age, he had played football for about 1.5 hours, soon after he developed severe back pain and vomiting together with aching muscles in his arms and legs, there was no change in the colour of his urine, but he had elevated serum CK 6000 IU/L. The referral stated that, during this first episode, his serum creatinine peaked at 338 umol/l, parameters for serum urea and electrolytes were not mentioned. He was kept in hospital for two days and given intravenous fluids. Since then, he experienced several similar episodes each year, usually after playing football. He had three further admissions to hospital, the longest in-patient stay was 8 days, during one episode, he had a documented raised serum CK 4138 IU/L. He never required renal dialysis. During these episodes he reported pain in his back and his urine appearing darker than usual.

His most recent episode was a few weeks before he was seen in our clinic, he had drunk ½ bottle of whiskey and the following day he started to vomit and was admitted to hospital with blood and protein in his urine. Renal function was reported to have been normal on this occasion (serum creatinine 85 umol/L) serum CK was mildly raised (CK 626 IU/L).

He was able to sprint more than 100m and could go on long walks without developing any symptoms. He was able to comfortably play football for 30-40 minutes, and, if he was well hydrated, he did not develop symptoms. He went to the gym regularly, usually without any problems. Clinical examination in the neuromuscular clinic was normal.

He has a younger brother living in Libya, who has had two admissions to hospital for similar symptoms, during one of these admissions he required intensive care for acute renal dialysis. He has three younger sisters who are all well. His parents are unrelated, and both are fit and well.

Routine blood testing in our clinic showed raised CK 501 IU/L, renal function was normal (sodium 143 mmol/l, potassium 3.9 mmol/l, creatinine 78 umol/l, estimated GFR >90), other normal blood parameters included: magnesium, calcium, phosphate and alkaline phosphatase, lactate, vitamin D, full blood count, acylcarnitine profile and full blood count. However, serum urate was undetectable <12umol/L/l. Genetic testing (described below) confirmed the diagnosis of RHUC2.

Table 1

	Time (Minutes)	Ammonia (11-32) umol/L	Lactate (0.5-2.2) umol/L
Patient 1	Baseline	32	1.56
	1’	141	6.41
	2’	140	6.37
	4’	136	5.66
	6’	102	4.94
	10’	Haemolysed sample	3.47
Patient 2	Baseline	54	1.33
	1’	161	7.41
	2’	156	7.43
	4’	184	6.69
	6’	90	2.79
	10’	76	2.11

Table 1. Laboratory findings of a non-ischaemic exercise test in patient 1 and patient 2 showing a normal ammonia and lactate response to exercise.

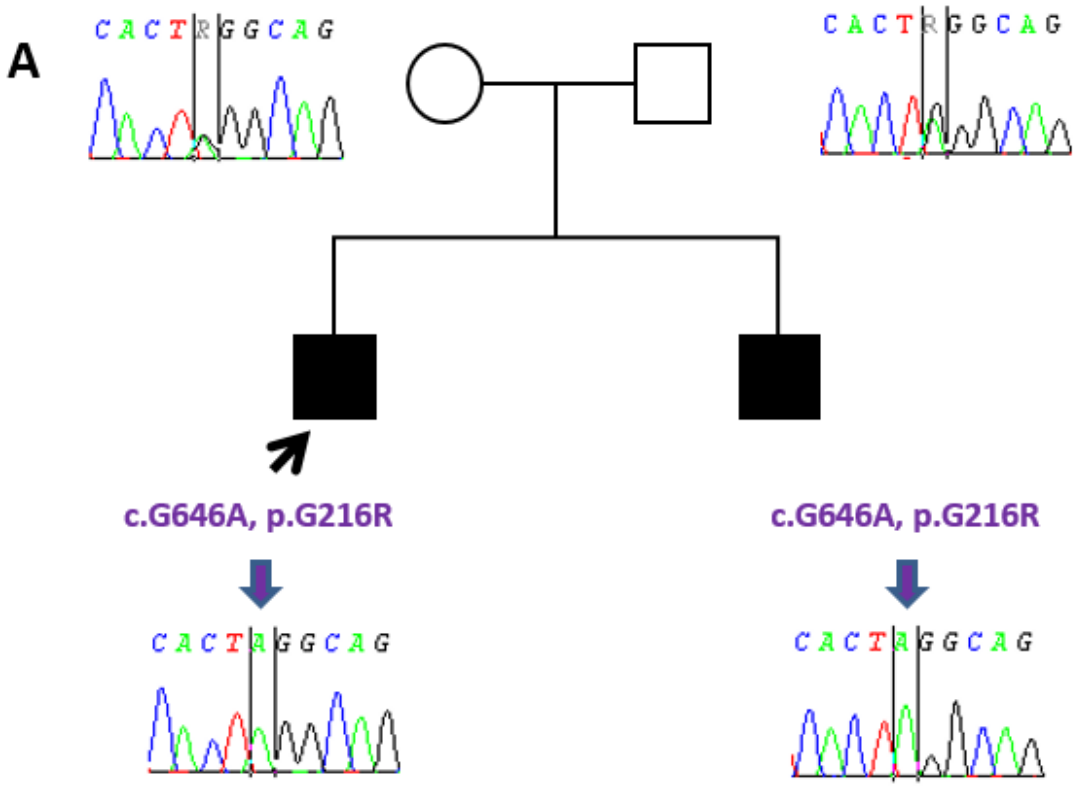
Genetic Investigation

To confirm the diagnosis of renal hypouricaemia in patients one and two, whole-exome sequencing (WES) was performed in both patients and their parents following informed consent. Analysis focused on nonsynonymous, splice-site and coding indel variants with a minor allele frequency (MAF) of <0.5% in the Exome Aggregation Consortium (ExAC; exac.broadinstitute.org), Exome Variant Server (EVS; http://evs.gs.washington.edu) and 1000 Genomes databases (1000G; http://www.1000genomes.org). From a total of 603 variants that met these filtering criteria in the proband, 186 variants in 60 genes co-segregated under an autosomal recessive model. Of these 188 variants, the only abnormal variant identified was in *SLC2A9*. This result was validated by Sanger sequencing. Segregation analysis confirmed that unaffected parents were heterozygotes for the SLC2A9 variant: NM_020041: exon5: c.G646A; p.(G216R) (Figure 1).

This mutation leads to a substitution of a small aliphatic amino acid glycine to a positively charged arginine, affecting a highly conserved nucleotide and amino acid (Figure 1) and is predicted as being deleterious by pathogenicity prediction tools.

Next generation sequencing performed for patient three confirmed a homozygous pathogenic variant in *SLC2A9* (c.224T>T; p.(Leu75Arg)). This variant has been shown to be rare in population databases and functional studies show a deleterious effect. The mutation was confirmed by Sanger Sequencing.

Figure 1 A) Results from the two affected brothers and unaffected parents are shown. Sanger sequencing chromatograms surround the symbols and show segregation of mutations. Black bars encompass the sites of interest. B) Structural conservation of the mutated amino acid residues in Glut9 across 6 species (single letters = amino acid residues; black = identical; grey = conserved substitution; purple = mutation found in this study); conservation among species of the affected amino acid residues was determined using Ensembl to retrieve the sequences and ClustalW2 software for multiple sequence alignment.



DISCUSSION

AR following intense eccentric or prolonged exercise (such as marathon running) can occur in healthy people and is relatively common [4]. People with rare metabolic muscle disorders affecting either fatty acid oxidation (Carnitine palmitoyl transferase 2 (CPT2) deficiency or very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency) or glycogen storage disorders affecting glycolysis (for example McArdle disease (GSD5) or Tarui disease (GSD7)) often present with AR following either prolonged or intense physical activities [3]. In disorders of fatty acid oxidation, there may also be a history of AR episodes occurring during times of stress either physical (infection and or fasting) or psychological.

In disorders of glycolysis, patients will usually give a history of myalgia occurring within seconds to minutes of undertaking a physical activity (the speed of onset of symptoms will depend upon the type of activity i.e. anaerobic/eccentric (within seconds) vs aerobic (within minutes)) and there may be a history of recurrent myoglobinuria with or without AEIKI. Hyperuricaemia and gout are particularly prevalent in people with glycolytic disorders due to a secondary increase in turnover of purine metabolites [5, 6]. The patients described in this manuscript were referred to our centre for investigation of a possible disorder of glycolytic metabolism, however, the clinical history was not typical for one of these disorders, where symptoms are almost always present from early childhood and include a second wind phenomenon (GSD5) or an 'out of wind phenomenon (GSD7). The unexpected finding of undetectable serum urate (performed as part of our routine panel of blood tests for muscle GSDs) led us very quickly to the correct diagnosis of hereditary renal hypouricaemia type 2 (RHUC2), confirmed by identifying autosomal recessive mutations in *SLC2A9,* which encodes for glucose transporter 9 (GLUT9).

Urate is the end-product of purine metabolism, and the serum urate level ultimately depends on the balance between the production and excretion of urate. Imbalances in homeostasis can increase or decrease serum urate levels, causing either hyperuricemia or hypouricemia. Paradoxically, hyperuricemia can be caused by heterozygous mutations in *SLC2A9* and is associated with hypertension, gout, diabetes and metabolic syndrome, cardiovascular and chronic renal disease [7]. On the other hand, idiopathic hypouricemia has been associated with certain degenerative neurological disorders such as multiple sclerosis, Alzheimers disease and Parkinsons disease [8], this has been hypothesized to be due to urate being a potent scavenger of harmful free

radicals such as reactive oxygen species [9]. In recent years several case reports describing renal hypouricemia in association with AEIKI and urolithiasis have been published, mainly in Japanese patients [10-16]. Key features are very similar to those described in our patients and include teenage or young adult age of onset, fatigue, low grade fever, abdominal pain and loin pain, nausea and vomiting in association with AEIKI. Two patients described in the literature were diagnosed after their kidneys were examined post renal transplantation, suggesting that there might be a risk of long term irreversible renal damage [17,18]

Renal hypouricaemia type 1 (RHUC1) is caused by mutations in *SLC22A12* which encodes for the urate transporter 1 (URAT1). Although rare, population screening in Japan has identified a prevalence of 0.3% [19, 20], the prevalence is also higher in Iraqi Jews [21] and European Roma families [22]. When AEIKI is caused by homozygous mutations in *SLC22A12*, the serum urate is reduced but the level may not as low as that seen in RHUC2. Only a small number of patients with RHUC2 have been reported in the literature. In both RHUC1 and RHUC2, during an acute episode of AEIKI, there is renal vasoconstriction causing acute kidney injury and the serum urate may consequently increase (as seen in patient two, although the level remained below normal), thus potentially masking the underlying diagnosis of RHCU. Follow up testing once the acute episode has resolved is therefore recommended if the condition is suspected.

Since the 1950s, it has been known that urate is actively reabsorbed in the renal tubular lumen so that, normally, the fractional excretion of urate (FE_{UA}) is very low (10% net absorption). In RHUC1 and RHUC2 there is increased renal urate clearance caused by an isolated inborn error of membrane transport for urate in the renal proximal tubule. Thus, patients with renal hypouricemia manifest low levels of serum urate (less than 2.0 mg/dL) without any underlying renal or systemic diseases such as Fanconi syndrome, Wilson disease, or drug-induced tubulopathy. The majority of people with RHUC1 and RHCU2 remain asymptomatic, but a proportion will develop nephrolithiasis and/or AEIKI [23, 24, 25].

A mouse model of RHUC2 (kiKO) exists and studies comparing renal output with control unaffected mice shows that the kiKO mouse produces 20% more urine volume and the usual concentrating capacity was challenged by a water deprivation test [26]. This suggests that patients with RUHC may be more prone to dehydration leading to hypotension, a likely mechanism for acute renal vasoconstriction leading to acute kidney injury during strenuous exercise. Thus, management advice should include ensuring a high level of hydration during exercise.

From a neuromuscular perspective, during acute presentations the finding of raised serum CK levels >10x normal in patients two and three (CK was not measured acutely in patient one), is an interesting phenomenon especially given that RHUC2 is primarily an inherited disorder of renal tubules. Myalgic symptoms and raised CK have also been described in other patients with RHUC1 and RHUC2 [27], the cause is unclear. Hellsten et al. [28] demonstrated that high metabolic stress to skeletal muscle, induced by intensive exercise, leads to an oxidation of urate in the exercised muscle, it remains unclear whether this happens in the muscle tissue of people with RHUC1 and RHUC2 since none of the affected individuals have ever had a muscle biopsy. Another possible explanation might be that the acutely raised CK is due to the normal physiological rise in CK seen with intense exercise [29] and that delayed onset muscle stiffness (DOMS) might explain the myalgia symptoms. Further research is clearly needed in this area to fully understand the processes involved.

Consensus clinical practice guidelines for the diagnosis and management of RHUC1 and RHUC2 have been very recently published [27]. These guidelines do not advocate the use of the xanthine oxidoreductase (XOR) inhibitor, allopurinol, which inhibits oxygen radicals and urate synthesis due to a lack of available safety data, one or two case reports suggest that allopurinol treatment might reduce the risk of AEIKI, but the potential risk of giving allopurinol to people with RHUC1 and RHUC2 remains unknown [27]. Recommended management to prevent complications is currently based upon advice to make lifestyle changes including the recommendation to adequately hydrate before and during exercise and to avoid or limit strenuous exercise.

Conclusion

Confirming the diagnosis of RHUC is important so that patients can be given appropriate advice to prevent future episodes and possible long term kidney damage. RHUC can often be mistaken for AR due to the presentation of AEIKI and raised CK. A presenting history that includes abdominal and back pain associated with nausea following strenuous exercise are good diagnostic clues. The diagnosis is easily confirmed with a blood urate sample taken post recovery and targeted genetic studies for mutations in *SLC22A9* and *SLC22A12*.

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