CASE REPORT

Cluster of exertional rhabdomyolysis in three young women

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Accepted 27 March 2018

SUMMARY

Three young women, aged 18–24 years, presented to general practice with signs and symptoms of exertional rhabdomyolysis in 2016. All attended the same gym and had undertaken an intensive physical workout. Presenting symptoms were severe muscle pain and swelling, significantly reduced range of motion in affected muscles and, in two cases, dark-coloured urine. One case had presented to the out-of-hours service 4 months previously with similar symptoms but rhabdomyolysis was not considered, although retrospective history taking suggests that was the likely diagnosis. All three women were admitted to hospital, treated with intravenous fluids and discharged between 1 and 6 days later. All made a full recovery with no renal sequelae. The cases were questioned about potential risk factors, and the only commonality was unaccustomed strenuous exercise.

BACKGROUND

Exertional rhabdomyolysis (ER) results from skeletal muscle injury that alters the integrity of the muscle cell membrane, allowing the release of the muscle cell content into the plasma. Complications include cardiac arrest, compartment syndrome, acute renal failure and death. It can affect anyone regardless of age, gender and fitness level following a bout of unaccustomed exercise.

This is the first time a cluster of ER in young female gym users has been reported in the published literature. Although ER is relatively rare, the potential consequences can be severe, so timely diagnosis and treatment is important. It is possible that many cases go undiagnosed or are incorrectly diagnosed as delayed-onset muscle soreness (DOMS). This cluster of cases illustrates how ER can present within primary care. This paper will explain the main presenting symptoms and risk factors. Given the popularity of very high-intensity exercise training (such as CrossFit) and the potential for harm that can occur, it is important for general practitioners (GPs) to be aware of these risk factors and how to diagnose this condition.¹ This paper aims to raise awareness of ER only, not rhabdomyolysis caused by other factors.

CASE PRESENTATION**Case 1**

An 18-year-old girl presented to her GP 4 days after a personal training (PT) session with worsening swollen painful thighs and struggling to use

the toilet and stairs due to pain and significantly reduced range of motion. She described chocolate-coloured urine and having passed urine only once that day, despite drinking a lot of fluids. The exercise undertaken was high-volume bodyweight squat variations. On examination she was very tender over bilateral anterior thigh/quadriceps, blood pressure (BP) was 140/92 mm Hg, urinalysis trace blood (can be positive in myoglobinuria), trace protein and trace white blood cells only. Urine appeared light coloured on inspection. She had no relevant medical and social history, and the only family history is that her sister has type 1 diabetes mellitus.

Case 2

An 18-year-old girl presented to her GP 3 days after PT session with very painful swollen upper arms, tenderness mainly of biceps and was unable to straighten her arms (elbows flexed at 90°). Her urine was slightly darker but she did not have black urine. BP was 135/80 mm Hg. A similar episode occurred 4 months previously when she did an arm-dominant workout (band-assisted chin-ups, press-ups on bar, tricep dips, kettlebell chest press, bench press, bent over row, kettlebell bicep curls, shoulder press). She had never trained her arms before. She had immediate pain and swelling after the session, but saw the out-of-hours service (OOHS) GP day 7 and was reassured. Her symptoms resolved after 10 days. On this occasion the patient insisted on not doing an arm workout so did some band-assisted chin-ups and tricep dips, squat jumps off a step and box jumps. Pain and swelling was noticed immediately post workout and her arms were stuck at 90°. She had no other relevant medical, social or family history.

Case 3

A 24-year-old woman presented to her GP 5 days after attending a kettlebell class with worsening pain of her arms including scapulae and, to a lesser extent, thighs. The pain was severe enough to disturb her sleep. She described some episodes of brown urine, but never black. Her BP was 120/60 mm Hg, urinalysis trace leucocytes and no blood. She was tender on palpation of biceps and over scapulae, unable to fully flex arms but extension was normal. The class was a 45 min strength/interval training-type class using kettlebells and included sit-ups, press-ups from knees, kneeling plank, isometric kettlebell front raise with hold

To cite: Mitchell F, Henderson HJ, Gardner F. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223022

for 30 s, tricep extensions, burpees to step and squats. Pain was not immediate but started a few hours later. The only relevant medical history is this patient was 11 weeks post partum (emergency section) at the time of the injury and she is an occasional smoker. There was no family history of note other than her father having type 2 diabetes mellitus.

INVESTIGATIONS

Case 1

Bloods were taken at the GP surgery when seen for urea and electrolytes (U&Es) and creatine kinase (CK). Bloods phoned to OOHs were CK 134 090 iu/L and renal function normal. She was admitted to acute medical receiving and catheterised. Her renal function was normal but she was managed with intravenous fluids and sodium bicarbonate. CK on discharge was 7000 and subsequently returned to normal by 3 weeks post admission.

Case 2

Bloods were taken at the GP surgery for U&Es and CK. Bloods phoned to OOH service were CK 47 120, aspartate aminotransferase (AST) 524 iu/L and alanine aminotransferase (ALT) 126 iu/L. The rest of her liver function tests (LFTs) and U&Es were normal. The patient was admitted to acute medical receiving and managed with intravenous fluids and sodium bicarbonate. Antinuclear antibody was negative.

Case 3

Bloods were taken at the GP surgery for U&Es, CK and LFTs. Her CK was 9482, AST 240 and ALT 109. The rest of her LFTs and U&Es were normal. She was admitted overnight only to the medical team and discharged having been referred for liver ultrasound scan (USS) and planned gastroenterology follow-up.

The GP was concerned that this cluster of cases had occurred so closely together in time, linked to the same gym. She worked with public health and a sports medicine colleague to investigate risk factors common to the three cases. The authors explored what type of physical training had been undertaken by the cases prior to developing symptoms, to identify whether a particular type of exercise could be the cause. Cases were questioned about a wide range of risk factors to help establish whether there was a single cause of this cluster.

DIFFERENTIAL DIAGNOSIS

When patients present to general practice with muscle pain following exercise, the most common reason is simple DOMS which normally starts the day after exercise, peaks at day 2 and then improves. In each of these cases, the pain came on quicker than expected and worsened instead of improving. DOMS will not cause muscle swelling and severe pain. Rhabdomyolysis is often accompanied by brown urine, which is not associated with DOMS.

TREATMENT

All cases received intravenous fluids. Cases 1 and 2 also had sodium bicarbonate infused.

OUTCOME AND FOLLOW-UP

Complete recovery and no follow-up for case 1. Case 2 was followed up by neurology 5 months later and her CK had returned to normal 1 month after the incident. Bloods taken by neurology (U&Es, LFTs, CK, lactate, carnitine palmitoyltransferase 2 gene analysis) were all normal. Her DNA has been stored. The patient is on a waiting list for muscle biopsy and

exercise testing. An underlying cause has thus far not been found. Case 3 had USS abdomen which showed an incidental finding of gallstones which initially were asymptomatic, but have since resulted in hospital admission, and the patient is being followed up by the surgical team.

On reflection, case 1 had a definite diagnosis of ER with pain and swelling of the muscle group involved and had myoglobinuria. The second case most likely has an underlying muscle condition and develops significant hyperCKaemia on exercising arms. The third case had the lowest CK but presented the latest at day 5, making us wonder what the CK was on days 2–3.

DISCUSSION

ER is caused by unaccustomed exercise, repetitive eccentric exercise, high repetition exercise and exertion beyond the point of fatigue.^{2–9} Some authors place it in a group with malignant hyperthermia syndrome.¹⁰ It has been widely reported in the literature among military recruits, firefighting and law enforcement recruits, ultra-runners, weightlifters, athletes and detrained athletes beginning an intensive training programme (having taken a break from training).^{11–22} There is some debate currently as to whether CrossFit increases risk of ER but CrossFit is a highly intensive exercise.^{23–25} This paper is the first to report a cluster of cases among young, female recreational exercisers.

This cluster of cases was only identified because the three cases attended the same GP practice. The GP's index of suspicion was raised following identification of the first case. The GP who identified the cluster of cases informed the local public health department for two reasons. First, this practice had never seen three cases of rhabdomyolysis in such a short time period (and would not expect to). Second, there was a potential ongoing risk to the public which required further investigation. The fact that all three cases attended the same gym was a particular cause for concern. With all three cases a specific type of exercise was involved; repetitive, explosive movements with a high number of repetitions. Within the UK and elsewhere, there is a current fitness trend towards more high-intensity training of the type that has been associated with rhabdomyolysis, that is, intensive training, high repetition exercise, exertion beyond the point of fatigue and repetitive bouts of eccentric exercise.²⁶

The authors completed a rapid literature review to identify other potential risk factors. We looked for anything which could link the cases, and in doing so considered and ruled out use of certain prescribed drugs which could increase risk (Zyban, opiates, antihistamines, diuretics, statins); drugs of abuse (amphetamine, heroin, alcohol, caffeine, performance enhancing drugs, Methylenedioxymethamphetamine/legal highs); food ingestion around the event (overuse of liquorice, fish, wild mushrooms, fruit juice, grapefruit/pomegranate, poor vegetarian diet, C9 low-calorie diet); binge drinking; dietary supplements (synephrine, hydroxycut); and endocrine disorders including thyroid, diabetes and adrenal insufficiency.^{27–36} There were no personal or family histories of renal disease, no family histories of exercise intolerance, and no genetic disorder or genetic link between cases. All three patients were active individuals enjoying activities such as running (case 1), sports such as basketball, swimming (case 2) and some lightweight total body workouts (case 3). In each case they participated in exercises they had not done before. The one factor common to all three was that they had exercised at a level that was excessive for their ability. The only other link was that all cases had attended the same gym facility. As part of our investigation with public health, we spoke to the personal trainers involved who were very cooperative and willing to change their practice. Both were trained to Higher National Diploma standard in a fitness qualification. The studios used were

of reasonable size and fans are used to keep the rooms cool (overheating is a known risk factor). Those using the facility are encouraged during sessions to keep hydrated (dehydration is a risk factor).

Although ER is relatively rare, this paper highlights that it can go undiagnosed, and attempts to raise awareness of the condition and its clinical presentation. It has not been possible to ascertain the incidence in Scotland as codes used within secondary care are not specific enough to identify it.²¹ The following features, following a bout of exercise, should increase a clinician's index of suspicion^{10 37}:

1. Severe muscle soreness (onset 24–48 hours post exercise).
2. Significant loss of range of motion.
3. Muscle swelling.
4. Dark brown-coloured urine (not always present).

Patients may report general malaise, fever, nausea, vomiting and can be tachycardic. ER leads to vastly elevated levels of serum CK.

If ER is suspected from the history, information regarding what exercise was done and how this differs from the patient's usual activity levels should be sought. Basic observations including BP, pulse and urinalysis should be taken. If the patient is unable to provide a urine sample due to reduced urine output, is hypertensive or hypotensive, or appears unwell, then rapid admission to the medical receiving team should be arranged without waiting for blood tests. If the patient is not particularly unwell and urinalysis reveals blood, is dark coloured (suggesting myoglobinuria) or appears normal, blood tests will help diagnosis. At the very least U&E and CK levels should be measured; LFTs may also be helpful. This can be done in primary care if marked as urgent so that results can be actioned promptly. Although CK will rise after intense exercise, readings need to be interpreted bearing in mind the history and examination findings; CK results are likely to be >10000 and are often far higher.

The question of admission for inpatient management or outpatient treatment is an ongoing dilemma. A review of the literature suggests that more prospective studies are required but that cases have been managed in both settings with good outcomes. It would seem that if there is coexisting illness such as cardiac disease¹¹ or a viral infection or other factors such as analgesic use,² outcomes may be less predictable and perhaps inpatient management would be advised. In otherwise healthy individuals, the risk of acute kidney injury (AKI) appears to be low in ER compared with other causes of rhabdomyolysis.^{2 6 8 20 38–41} Indeed, a blanket management approach of alkalinising the urine in order to protect the kidneys may, in fact, result in electrolyte imbalance and further morbidity, thus reserving its use to those who are acidotic may be best.^{26 39} Although there may be a case for outpatient management in some,² there have been cases of severe ER, resulting in significant morbidity,⁴² and it is these cautionary tales which make those working in primary care more anxious.

Until recently, cases of ER have been identified more commonly in male athletes or military personnel. The current trend seems to suggest cases are being increasingly identified in both genders and in those who would not be considered athletes. Identifying case series similar to this one in non-athletes is tricky; however, trends can be identified from the literature and lessons learnt regardless. In 2008 a case series involving collegiate swimmers described seven cases of ER (four males, three females) who presented with upper body symptoms (like two out of our three cases) after participating in preseason conditioning workouts. There was no use of alcohol or dietary supplements, myoglobin was present in three cases and there was no renal or electrolyte derangement.¹⁵ All were managed with intravenous saline and there were no sequelae, all being able to return to their activities after a period of recovery. Another case series describes eight female lacrosse athletes who developed ER after undertaking the first weight training session

of the season.¹⁶ They presented within 24 hours, and of the eight, two had a history of ER (like one of our cases). All athletes were given intravenous saline and at no point was renal function or electrolytes found to be abnormal, nor did compartment syndrome develop. There were daily follow-up visits with the team doctor and complete rest and oral hydration was advised. By 3 weeks post injury, all eight athletes had returned to full participation and unrestricted weight training. Interestingly, these athletes were managed as outpatients but with intense medical supervision. Although this may be possible in the USA, it is unlikely such outpatient support could be provided in the UK from primary care National Health Services due to lack of resources. We do need to have a higher pick-up rate for diagnosis especially with the advent of more intense forms of exercise becoming popular. Perhaps we should consider the possibility that our 'normal' population may present like athletes affected by preseason workouts, especially those who participate in CrossFit. The case report from 2017, which describes an otherwise healthy and active 31-year-old woman who developed ER after a CrossFit workout,¹ has similarities to our cases due to her not being an athlete and she also developed a transient liver transaminitis which resolved over time. Like the other cases she had no electrolyte or renal function disturbance but was managed with intravenous and oral rehydration. Many previous reported cases have been of lower-limb ER; however, in two/three of our cases and in the cases cited above, upper-limb ER is now being reported too.

It would seem from the evidence we have perused that long-term outcomes from ER are more favourable compared with other forms of rhabdomyolysis. Assuming immediate complications either do not evolve or are corrected, complete recovery is expected following appropriate treatment and there would be no long-term implications for patients affected by ER unless a genetic cause is found. Thus, after a period of recovery and normalisation of blood tests, patients can expect to go back to normal function and exercising.^{38 43–45}

Protocol for initial identification and management of ER

Given that primary care physicians do not come across such presentations very frequently, a protocol to aid identification and initial management may be helpful and, as such, we have created one as follows:

1. A history of unaccustomed exercise, repetitive eccentric exercise, high repetition exercise and/or exertion beyond the point of fatigue with severe muscle soreness within 24–48 hours of exercise. One or more episodes of having passed dark brown urine may or may not be present.
2. The patient may complain of general malaise, nausea or vomiting.
3. Examination findings may reveal swollen tender muscles; significant restriction in range of motion of affected muscles; raised, normal or reduced blood pressure; a reduction in urine output and tachycardia. Urinalysis may reveal blood.
4. If the patient appears unwell, is hypotensive (<90/60 mm Hg) and tachycardic (>100 bpm) with oliguria or anuria (suggesting shock), immediate transfer to hospital should be arranged.
5. If vital signs are stable, bloods should be taken in the community for a minimum of U&E LFT CK. These should be marked as being urgent.
6. Bloods may reveal AKI (or normal renal function) with CK levels of >1000 U/L; however, levels may be in excess of 10 000 U/L. Transfer to hospital for inpatient monitoring should be arranged.

Learning points

- ▶ Although relatively rare, exertional rhabdomyolysis can cause significant short-term morbidity although no cases of mortality have been reported thus far.
- ▶ The main risk factor is unaccustomed exercise, regardless of the individual's fitness level.
- ▶ Current trends towards high repetition exercise, repetitive bouts of eccentric exercise and exertion beyond the point of fatigue may lead to an increase in number of cases presenting to primary care.
- ▶ Presenting symptoms are severe (and worsening) muscle soreness with onset 24–48 hours post exercise; significant loss of range of motion, muscle stiffness, dark-coloured urine (not always present). Patients may also report general malaise, fever, nausea vomiting and can be tachycardic. Serum creatine kinase (CK) levels will be vastly elevated.
- ▶ If exertional rhabdomyolysis is suspected and the patient is unwell, they need rapid admission to hospital for intravenous fluids and monitoring. If the history and examination suggests rhabdomyolysis but the patient does not require direct admission, bloods should be taken and marked as urgent for urea and electrolytes, liver function tests and CK at the very least.

Acknowledgements The authors would like to thank Fiona McKinnon for her support in managing this cluster of cases. We would also like to thank Dr Rachel Thomson for proof reading the article.

Contributors HJH made a substantial contribution to the conception and design of this article, and to the rapid literature review; coauthored the article, making a substantial contribution to writing and revising the article; had final approval of the version to be published; and is accountable for all aspects of the work, in ensuring questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. FM made a substantial contribution to the conception and design of this article; gained written consent from patients; coauthored the article, making a substantial contribution to writing and revising the article; had final approval of the version to be published, along with the coauthors; and shares accountability for all aspects of the work, in ensuring questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. FG made a significant contribution to the conception and design of this article; coauthored the article, making a significant contribution to writing and revising the article; had final approval of the version to be published, along with the coauthors; and shares accountability for all aspects of the work, in ensuring questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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