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An Unusual Cause for High Creatine Kinase Levels in an Acute Care Setting

Amina Yousuf Shaikh [1]
[1] Department of Acute Medicine,
Kettering General Hospital,
Kettering, UK

Correspondence: Amina Yousuf Shaikh

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Abstract: Ryanodine receptor 1 (RyR1) group of myopathies are rare disorders with a fairly common initial presentation. A high index of suspicion while evaluating patients being readmitted with similar presentations in the Acute Medical Units (AMU) can aid diagnosis of rare diseases.

We report the scenario of a young gentleman who presented to AMU with severe myalgia for one week. His creatine kinase (CK) levels were considerably high. He was further investigated following MDT (Multi-Disciplinary Team) discussion. He was diagnosed with exercise induced rise in CK levels, and discharged.

Two months later, he represented to the A&E (Accident & Emergency department) and was admitted to the AMU with the same complaints. Thorough investigations raised the suspicion of a genetic disease and a muscle biopsy was planned. He was referred to specialised neuromuscular services in the country for further evaluation where he was diagnosed to have a RYR1-related myopathy, which is a rare congenital muscle disease, resulting from an alteration in the RYR1 gene.

Keywords: *Ryanodine Receptor 1, RYR1, Myopathy, Genetic, Creatine Kinase, Acute Medical Unit.*

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I. INTRODUCTION

Acute Medical Unit (AMU) is the point of first contact when a patient presents to the hospital with urgent medical issues, requiring immediate attention. Whilst in these units, the focus remains on mainly dealing with acute medical illnesses. However, rare diseases can sometimes be suspected, and eventually diagnosed if we maintain a high index of suspicion.

In most cases, an early diagnosis can significantly improve the quality of living by reducing morbidity, progression of disease and early mortality. The need to reconsider an established diagnosis and timely refer to the relevant specialties, if needed, cannot be emphasised enough.

II. CASE

A 28-year-old gentleman attended the Acute Medical Unit (AMU) with severe leg cramps and pain for one week. He was referred by his GP as CK levels were considerably high.

Further history revealed that these cramps were limited to the thigh muscles only. He had similar episodes in the past – 4 times in the last 2 years. Each time, he had severe pain, unable to weight bear, causing him to be bedridden. The pain and cramps subsidised within a week of the symptom onset during these past 4 episodes. The usual trigger was cycling. He felt well between episodes and denied any other symptoms. He usually took diazepam prescribed by the GP to help alleviate his symptoms. No change was noticed in the colour of his urine. This time, he had severe pain, of similar intensity and severity which failed to resolve with rest or diazepam. He hence went to his GP clinic where blood tests including CK levels were checked.

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His past history was significant for a surgery for perianal fistula and ectopic beats for which no cause was found. He had a history of atopy. No other allergies were reported. He was not on any regular medications or herbal remedies. He was a non-smoker who rarely consumed alcohol as he had bad hangovers and cramps after. He denied use of any recreational drugs, protein supplements and/or energy supplements. He did not have any family history of genetic diseases but his sister was under investigation for probable juvenile dermatomyositis.

On clinical examination, his BMI was normal and vitals were within normal limits. Neurological examination demonstrated typical muscle tone, with near-normal proximal muscle strength (4/5), normal distal muscle strength (5/5) with intact reflexes and sensation in both upper and lower limbs. Bilateral thigh muscle tenderness was noted with mild wasting; other muscle groups were unremarkable. He had no swelling of the joints or any significant deformity. No rash was identified. Remaining systemic examination was unremarkable.

Significant blood results from the GP were as follows:

- CK: 21,050 IU/L
- ALT: 436 IU/L
- RF: 1.3 IU/mL (negative)
- ANA: negative

A probable diagnosis of myositis (inflammatory versus autoimmune) was made. He was hydrated intravenously and CK levels monitored during his stay in AMU. Additional tests including ANA, RF, serum electrophoresis, ds DNA antibodies, LDH and urine for myoglobin were done. Results for these were unremarkable.

Rheumatology Team was taken on board and he was further investigated. Further blood tests were done to assist with the diagnosis (Table 1). MRI of both thigh muscles was done. This revealed patchy areas of increased STIR signal within multiple muscle groups of both thighs, involving predominantly anterior muscle groups of both thighs. Some high signal in the inferior aspect of the gluteus maximus muscles was also noted. An EMG and NCS was organised and done as an outpatient – this was normal. He was diagnosed with exercise induced rise in CK levels, and discharged from the care of the Rheumatology Team.

He had developed recent interest in cycling. He used to cycle up to 150 miles/week. His first presentation to hospital coincided with his maximum exertion - cycled around 300 miles in 1 week, up and down mountains.

Two months later, he represented to the A&E and was readmitted to the AMU with the same complaints. Creatine Kinase (CK) level was 30,788 IU/L while ALT was 117 IU/L (other blood results in Table 2). A myositis screen was done which was normal. (Table 3)

Thorough investigations raised the suspicion of a genetic disease and a muscle biopsy was planned. He was referred to specialised neuromuscular services in the UK for further evaluation where he was diagnosed to have a RYR1-related myopathy, which is a rare congenital muscle disease, resulting from an alteration in the RYR1 gene.

At time of diagnosis, he had experienced 6 episodes of severe cramps in almost 3 years. These episodes sounded like ‘contractures of quadriceps’ and occurred for up to 1 to 3 weeks after strenuous exercise, alcohol intake or dehydration.

III. DIFFERENTIAL DIAGNOSIS

- myositis (inflammatory versus autoimmune)
- late-onset juvenile dermatomyositis
- metabolic myopathy
- carnitine palmitoyl transferase deficiency

IV. TREATMENT

He received supportive care (I/V fluids and regular monitoring of CK levels) throughout his admissions in AMU. Since he often experiences raised CK levels, given the nature of this disease, he continues to receive supportive care at AMU as and when required.

He is regularly followed up by the neuromuscular specialists and has received, and continues to receive necessary care. He has been educated regarding the nature of disease, the limitations involved (e.g. avoiding over strenuous activities) and complications (risk of Malignant Hyperthermia). He is under care of a multidisciplinary team and has had genetic counselling as well. His family members are being screened as well. ight author and affiliation lines of affiliation 1 and copy

V. OUTCOME AND FOLLOW-UP

Patient continues to maintain a healthy diet and lifestyle. Trying to abstain from alcohol, preventing dehydration and avoiding extended periods of strenuous activities has helped him reduce his episodes of pain and cramps.

VI. DISCUSSION

RYR1-related myopathy is a group of congenital muscle diseases and the most common type of non-dystrophic muscle diseases. [(1)] It is characterised by a change or mutation in the RYR1 gene. [(2)] This gene codes for the ryanodine receptor (RYR) calcium channel which is usually embedded in the membrane surrounding sarcoplasmic reticulum (SR).[(3)] It is usually inherited from one or both parents, who may or may not be affected by the disease. Depending on the inheritance pattern, the disease may manifest during childhood or later, during adulthood. [(4)]

Ryanodine Receptor 1 Related Myopathies’ (RYR1-RM) names were assigned according to histopathologic classification, reflecting appearance of the muscle biopsy under microscope. They present with various systemic symptoms.[(2)]

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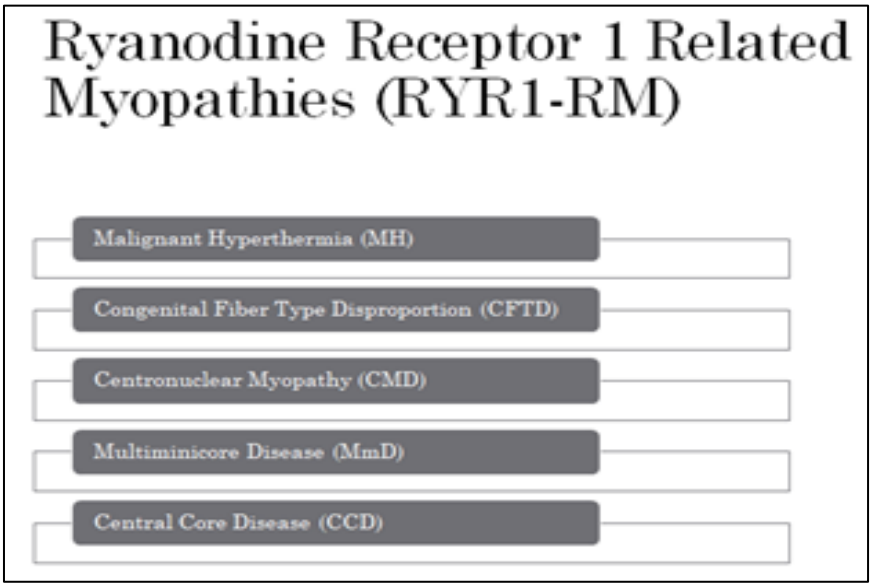

Fig 1: Classication of Ryanodine Receptor 1 Related Myopathies (RYR1-RM)

Studies suggest that the Ryanodine Receptor 1 Related Myopathies (RYR1-RM) are common but probably underdiagnosed in patients presenting with recurrent exertional rhabdomyolysis.[5] Rhabdomyolysis is often described as a clinical syndrome chacterised by intense muscle pain, a rapid increase followed by a decrease in serum creatine phosphokinase (CPK) levels with or without myoglobinuria. [6] Several case reports, small series and review articles have discussed regarding this disorder. An association of exertional rhabdomyolysis exists with RYR1 variants, including variants associated with Malignant Hyperthermia (MH) susceptibility. [7] Risk factors include intense exercise in high temperatures and humidity, inadequate hydration, insufficient recovery between physical activity and low fitness levels. This disorder requires multidisciplinary team management. Quite often, neurologists along with physiatrists (Physical Medicine and Rehabilitation Physician), sometimes orthopaedics may need to be involved in the care of patients presenting with this disorder. Genetic Counsellors (CGC) are almost always involved so that patients are well-educated about their condition and the consecutive effects it may have upon their offspring.

VII. LEARNING POINTS

- Reconsider diagnosis where relevant – esp. when patients represent with same complaints
- Multidisciplinary Team approach to help diagnose
- Timely referral to specialities can help with early diagnosis and aid in reducing progression of diseases (if possible).

CONFLICTS OF INTEREST: None

AUTHOR DECLARATION: I am the sole author of this manuscript.

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Table 1: Bloods on initial admission		
Full name of Test	***Abbreviation***	***Result***
Antinuclear antibody	ANA	negative
Complement levels	C3, C4	normal
Anti-cyclic citrullinated peptide	Anti-CCP	negative
Anti-(double stranded) Deoxyribonucleic acid	Anti-dsDNA	negative
Extractable nuclear antigen	ENA	negative
Immunoglobulins	Ig A, G, M	normal
Serum electrophoresis	EP1A	negative for paraprotein

Table 2: Bloods on subsequent admissions		
Full name of Test	***Abbreviation***	***Result***
Creatine Kinase	CK	433 IU/L
Erythrocyte sedimentation rate	ESR	2mm/hour
Anti-Jo-1 antibody	-	negative
Anti-Mi-2 antibody	-	negative
Anti-Ku antibody	-	negative
Anti-PM-Scl-100 antibody	-	negative
Anti-PM-Scl-75 antibody	-	negative
Anti-Ro-52 antibody	-	negative
Lactate levels	-	1.4 mmol/L
Aldolase levels	-	unavailable