Recurrent atraumatic compartment syndrome as a manifestation of genetic neuromuscular disease

Dennis T. Famili, Miguel A. Fernandez-Garcia, Maria Vanegas, Michael F. Goldberg, Nicol Voermans, Ros Quinlivan, Heinz Jungbluth

1. Introduction

Compartment syndrome (CS) is a medical emergency that occurs secondary to excessively high pressures within a confined fibro-osseous space (a compartment), with subsequent reduced tissue perfusion [1] secondary to an increase in the intra-compartmental pressure relative to the capillary perfusion pressure [2]. Causative pressure increases may be secondary to intra-compartmental volume expansion due to various etiologies [3], or extra-compartmental restriction, for example due to restrictive dressings [4].

Compartment syndrome can be divided into acute CS, most commonly due to trauma and considered an orthopaedic emergency, and chronic CS, most commonly presenting in athletes with recurrent exercise-induced pain [5,6]. Fractures [7], soft tissue injuries and other forms of trauma are the most common causes of acute compartment syndrome (ACS) [8,9]. ACS has an average incidence of 3.1 per 100,000 [10] and is most common in younger males [7]. ACS most commonly affects the lower leg and forearm [11] but may also occur in other, including abdominal [12], gluteal [13] and paraspinal [14,15], muscle groups. Chronic exertional compartment syndrome (CECS) is characterised as an overuse injury typically involving the lower leg (95 %) [5] and, like acute exertional compartment syndrome (AECS) [6], is overwhelmingly seen in athletes.

Diagnostically important symptoms of ACS include unexpectedly severe localized muscle or limb pain, particularly if refractory to analgesia [1] and/or occurring at rest, as well as severe pain on passive stretch or palpation [16]. Tense swelling and hypeaesthesia, an early feature of nerve hypoxia [4], are other
important signs. Pallor and paralysis suggestive of ischaemia may also be present, but pulses are often preserved as CS primarily arises from micro- rather than macrocirculatory compromise. Patients with CECS typically present with (intensive) exercise-induced pain, cramping and tightness in the affected compartment [17], with symptoms often persisting after cessation and recurring upon return to exercise. Where the clinical diagnosis remains uncertain, measurement of intra-compartmental pressures may be helpful [18,19].

Surgical decompression of the affected compartment by fasciotomy is the mainstay of ACS treatment [1] and ought to be performed in a timely fashion to avoid irreversible damage and long-term sequelae [20–22], but is not without its complications itself [16,23]. CECS may be managed conservatively with analgesia and physiotherapy, but fasciotomy (often endoscopically) is often performed to provide longer-term relief [17].

Although the vast majority of CS cases will be sporadic, a limited number has been reported in neuromuscular disorders, particularly in metabolic myopathies [15,24–34] but also channellopathies [35,36] and Duchenne Muscular Dystrophy [37], in the latter probably due to the pathognomonic calf pseudohypertrophy. Other (metabolic) myopathies associated with recurrent exertional rhabdomyolysis [38] may theoretically also predispose to CS.

Here we present the first case of recurrent CS associated with a heterozygous dominant gain-of-function mutation in the skeletal muscle ryanodine receptor (RYR1) gene, a common cause of exertional rhabdomyolysis and myalgia, as well as two additional cases with PYGM-related McArdle disease and recurrent CS. In all patients, the underlying diagnosis was delayed for many years despite longstanding symptoms of exercise intolerance, suggesting that closer attention to the past history of patients presenting with recurrent atrumatic CS may lead to earlier diagnosis.

2. Case histories

Case histories from patients are summarized below. Patients were identified through a family conference [8] organized by the RYR1 Foundation (www.ryr1.org), the support organization for individuals affected by RYR1-related disorders (Patient 1), and through the highly specialised UK neuromuscular service for McArdle disease and related disorders (Patients 2 and 3) led by Prof. Ros Quinlivan, one of the co-authors. Patient 1 self-reported their case; we did not approach additional patients directly to identify other RYR1-related cases. We also reviewed the literature on all previously published cases with (recurrent) CS in the context of a genetic neuromuscular disorder (summarized in Table 1); this was done by searching the terms “compartment syndrome” AND “myopathy”/“metabolic”/“hereditary”/“genetic” in PubMed and Google Scholar.

2.1. Case 1

This currently 54-year-old female, a former athlete at high school and beyond, suffered 2 episodes of ACS requiring fasciotomies (Fig. 1A) at the age of 38 and 41 years before a diagnosis of a RYR1-related disorder was eventually established. Both episodes were characterized by intense lower leg swelling and pain, and associated with increased compartment pressures, exacerbated by treadmill exercise on the first occasion.

Despite being very sporty, she had a longstanding background history of severe fatigue, worsening anterior tibial pain, muscle weakness, cramping and falls, initially thought to be related to fibromyalgia and common peroneal nerve palsies. The recurrence was initially attributed to fascial scarring following the first surgery, with some signs of continuity seen intraoperatively.

At 43 years of age, she was investigated further by her local neurology services prompted by a constellation of symptoms comprising chronic myalgia, debilitating fatigue, severe cramping and muscle contractures following mild exertion, muscle spasms, muscle weakness, recurrent severe headaches/migraines and heat intolerance. Extensive metabolic investigations revealed only hyperglycaemia. Additional immunological studies, including tests for autoantibodies associated with inflammatory myopathies were negative except for weakly positive anti-N-type calcium channel autoantibody titres at 0.15 nmol/L (normal <0.03 nmol/L); subsequent nerve conduction studies ruled out Lambert-Eaton Myasthenic Syndrome (LEMS).

At the age of 51 years, genetic testing identified two heterozygous variants in RYR1, c.14918C>T (p.Pro4973Leu), a known pathogenic variant associated with Malignant Hyperthermia Susceptibility (MHS), and c.3371A>G (p.Asn1124Ser), a variant of uncertain significance; the phase of these variants could not be determined due to lack of parental samples. Screening for pathological variants in 73 additional genes implicated in genetic neurological disease did not reveal any other pathological variants.

Retrospectively, she also reported additional symptoms, in particular recurrent heavy nosebleeds and heavy menstrual bleeding, compatible with a RYR1 gain-of-function mutation [39]. Her neuromuscular symptoms are currently managed with physiotherapy and analgesia.

2.2. Case 2

This currently 50-year-old woman suffered two episodes of ACS requiring fasciotomies before a diagnosis of McArdle’s disease was finally established at the age of 41, despite lifelong symptoms of exercise intolerance.

She first presented at 14 years of age with a several hour history of sudden-onset severe pain and muscle contracture in her right forearm whilst grooming her horse (an activity requiring isometric muscle contraction), which persisted after rest. At the time she was unable to straighten her fingers or move her arm
The diagnosis of McArdle disease (P1–7) had been established based on a combination of suggestive history, clinical features, muscle biopsy and/or genetic testing. The diagnoses of LPIN1 deficiency (P8–9), GYGI deficiency (P10), hypokalaemic periodic paralysis (HYPP) and SCN4A-related paramyotonia congenita (PMC; P14) had been suspected based on suggestive clinical features and confirmed on genetic testing, whereas the diagnoses of CPTII deficiency (P11) or another fatty oxidation defect (P12) were strongly suspected based on (family) history, clinical and histopathological features but not confirmed genetically. The aetiology of (recurrent) compartment syndrome (CS) was considered idiopathic unless stated otherwise. Creatinine kinase (CK) levels showed marked fluctuations but typically decreased after fasciotomies were performed. Compartment pressures (CP) were consistently increased but variable when measured. Where muscle biopsies were performed, those showed features suggestive of the underlying condition (P2, P1, P12) and/or acute changes consistent with ongoing rhabdomyolysis and/or pressure-induced damage (P8–9, P11–P12). In addition to (often multiple) fasciotomies, patients required a range of other surgical interventions (for example, irrigation and debridement) depending on the extent of muscle damage.

(K) means “Known diagnosis” and indicates that the underlying genetic muscle disorder had already been diagnosed at the time the patient presented with acute compartment syndrome, (P) means “Presenting feature” and indicates that the diagnosis of the underlying muscle disorder was only made after (and/or prompted by) the presentation with acute compartment syndrome. ACS = Acute Compartment Syndrome; AECs = Acute Exertional Compartment syndrome; CP = compartment pressure; CS = compartment syndrome; E = number of events; ER = exertional rhabdomyolysis and/or myalgia; I + V = Intubation and ventilation; RM = rhabdomyolysis.
due to the intensity of the pain. Over the next four hours her forearm became markedly swollen and discoloured, leading to an emergency fasciotomy under the suspicion of ACS, resulting in marked scaring (Fig. 1B). Histological analysis of a muscle sample taken intraoperatively showed only severely necrotic tissue. At the time (and indeed on no other previous occasion), there was no myoglobinuria and a serum CK was not requested. At age 20, she had another episode also requiring surgical decompression by emergency fasciotomy.

At age 41, she presented to hospital with acute chest pain following physical activity. Following exclusion of a cardiac cause and considering elevated serum CK levels, she underwent a diagnostic muscle biopsy which demonstrated glycogen-containing subsarcolemmal vacuoles and absent myophosphorylase, suggesting McArdle disease. Further genetic testing revealed a homozygous PYGM mutation (c.148C>T p.Arg50*). She was then referred to a specialised neuromuscular service, where she retrospectively reported lifelong symptoms typical for McArdle disease, including significant exercise intolerance since early childhood with pain and contractures in her limbs following mild exertion, associated with a clear second wind phenomenon. Her baseline serum CK was consistently raised (609 IU/L to 1651 IU/L). She has not had any further episodes of contracture since receiving appropriate management advice after her diagnosis.

2.3. Case 3

This currently 46-year-old male patient with a diagnosis of McArdle disease suffered recurrent episodes of atraumatic rhabdomyolysis and ACS induced by intense bursts of exertion, activity associated with isometric contraction and electrocution, requiring a total of five fasciotomies. In 2002, at age 25, he presented to the emergency department multiple times with acute exertional rhabdomyolysis after playing rugby. He gave a history of exercise intolerance since early childhood with a history of a clear “second wind” phenomenon, allowing him, a very keen athlete, to jog and play rugby after appropriate warm-up periods. On investigation at the time, he had an elevated baseline CK of 1980 IU/L and myopathic features on EMG. A muscle biopsy was consistent with McArdle disease, subsequently confirmed on genetic studies at a specialised neuromuscular service, which showed compound heterozygosity for PYGM mutations, c.280C>T (p.Arg94Trp) and c.1727G>A (p.Arg576Gln).

He was given activity management advice to prevent contractures and rhabdomyolysis and remained stable until 3 years later at the age of 28 years when following a short, intense sprint, he developed acute bilateral contractures of the lower limbs associated with rhabdomyolysis and a serum CK of 103,000 IU/L (normal range 190 IU/L) on admission. He was initially managed conservatively with intravenous fluids and careful monitoring of renal function, however, surgical intervention was eventually required because of symptom progression. Postoperative complications and prolonged convalescence lead to significant deconditioning, resulting in weight gain, reduced exercise ability and gout (frequently seen in McArdle patients). Exercise tolerance improved following intermittent weight loss, however, at the age of 40, he suffered another episode of acute rhabdomyolysis of both lower limbs following exercise training. He also suffered two further episodes of ACS requiring fasciotomies, bilaterally of the forearms at the age of 41 following electrocution and tight tensing of his arms, and most recently of the thigh, following unplanned isometric activity.

Recurrent episodes of ACS have triggered exercise anxiety and deconditioning, leading to excessive weight gain and likely contributing to additional diagnoses including metabolic syndrome with type 2 diabetes mellitus, hypercholesterolaemia and hypertriglyceridaemia.

3. Discussion

Here we present three cases with a history of recurrent atraumatic compartment syndrome (ACS) in the context of two genetic neuromuscular disorders, a RYR1-related myopathy (Case 1) and McArdle disease (Case 2 and 3). Fig. 2 illustrates how these neuromuscular conditions may cause atraumatic compartment syndrome along with the vicious cycles that may ensue secondary to them. Whilst the association between (exertional) rhabdomyolysis and certain neuromuscular disorders is well-recognized, particularly in those affecting calcium homoeostasis, glycogen metabolism and fatty acid oxidation, a clinically equally relevant association with CS has not been previously widely highlighted. Of note, in two of the three patients reported here, the diagnosis of the underlying neuromuscular disorder was only established after several episodes of CS, emphasizing that CS may be a presenting feature of certain genetic neuromuscular disorders even before other features of these disorders are suspected, also because presentation is often to physicians without specific experience of these rare disorders. We have previously outlined an approach of how to distinguish sporadic from genetically determined forms of (exertional) rhabdomyolysis [40,41], and, to prevent an unnecessary delay in diagnosis, a similar approach may be applied to clinically related CS.

CS has not been previously reported in RYR1-related disorders in the absence of anaesthetic exposure, although it has been rarely observed as a complication of malignant hyperthermia reactions, in only two cases published so far [42]. Like our patient, these patients had (putative) gain-of-function RYR1 mutations, suggesting possible genotype-phenotype correlations, as supported by the fact that the same class of RYR1 mutations has also been implicated in clinically similar (exertional) myalgia and rhabdomyolysis, MH, or a combination of the above [43,44]. In addition to the general pathophysiological mechanisms outlined below, the muscle hypertrophy commonly seen with RYR1 gain-of-function mutations in both humans and corresponding animal models may represent an independent risk factor for the development of CS, due to its potential effects on intracompartmental pressure, comparable to what has been postulated regarding the role of pseudohypertrophy in DMD-related CS [37]. Of note in this context, patients with RYR1 gain-of-function mutations often experience certain symptoms, in particular a sensation of muscle tightness and pain, that are not dissimilar to those experienced by individuals with CECS. In addition, our RYR1-mutated patient was a competitive athlete before the development of CS and other disabling neuromuscular symptoms, a commonly observed but currently only poorly understood clinical trajectory in individuals with RYR1 gain-of-function mutations. Profound (exertional) myalgia, fatigue and an increased bleeding tendency were additional features of a RYR1-related disorder in our patient that should be actively looked for also in other patients with otherwise unexplained recurrent CS.

In our McArdle diseases cases, on multiple occasions ACS followed muscle contracture induced by isometric muscle contraction, a known complication of the disease. Appropriate activity and exercise advice led to symptom improvement in both patients, though patient 3 suffered further ACS episodes due to sudden and unplanned bouts of isometric activity. Although recurrent rhabdomyolysis and CS are known features of McArdle disease, in most of these cases the diagnosis had already been established at the time CS developed. Case 2 in our series suggests that CS may indeed be a presenting feature of McArdle disease, and emphasizes the importance of emergency care and
orthopaedic doctors being aware of this possibility when treating patients with exertional CS, in particular as other features of this condition may be easily missed if not specifically looked for in the medical history. Table 1 provides a summary of published cases of CS occurring in the context of a genetic neuromuscular disorder, most of them within the group of metabolic myopathies.

The pathophysiology of CS (illustrated in Fig. 2) follows a regular sequence of events that occurs in sporadic forms but may be specifically amplified by genetic defects underlying predisposing neuromuscular conditions such as McArdle disease and RYR1-related disorders. In general, CS invariably starts with intra-compartmental pressure changes and results in subsequent ischaemia, reperfusion injury and inflammation, primarily affecting nerve and muscle tissue. Increases in pressure may stem from factors including intracompartmental haemorrhage and muscle swelling secondary to crush injury, rhabdomyolysis [45] and/or strenuous exercise, where swelling can cause muscle fibres to reach up to 20 times their normal size [5]. It is of note that the latter two factors feature prominently in RYR1-related disorders due to RYR1 gain-of-function mutations, suggesting potential for a shift to more pathophysiological conditions enabling CS.

More specifically, non-regarding its multifactorial aetiology, the critical reduction of intra-compartmental perfusion and subsequent tissue hypoxia related to increased intra-compartmental pressure has several cellular downstream effects [46–51] that may act in a synergistic manner with downstream mechanisms caused by the genetic defect in RYR1-related disorders and McArdle disease: At the cellular level, reduced ATP production and increased oxidative stress secondary to hypoxia leads to failure of Na⁺-K⁺ ATPase exchangers that maintain cellular osmotic balance and membrane potential, the loss of which causes an influx of Cl⁻ resulting in cellular oedema and increased tissue swelling, further worsening hypoxia. Damage to non-perfused capillaries by inflammatory changes, an important aspect in the pathophysiology of CS [21,52–54], appears to render them ineffective at gas exchange, even after pressure release [55], while those capillaries that remain patent may allow oxygen delivery sufficient to generate reactive oxygen species (ROS), further compounding the problem. In McArdle disease, patients are deficient in myophosphorylase, creating an inability to mobilise glucose-1-phosphate from glycogen during anaerobic exercise [56], with initial aerobic metabolism also compromised due to reduced pyruvate availability from glycolysis, reducing substrate flow through the citric acid cycle. Insufficient ATP production in myocytes during exercise may then precipitate oedema and a vicious cycle propagating CS [24], which may also occur secondary to rhabdomyolysis following the failure of calcium ATPase pumps and excessive intracellular calcium build-up [57], a mechanism likely to be enhanced with RYR1 gain-of-function mutations implicated in RYR1-related disorders that predispose to exercise-induced rhabdomyolysis [43]. Excessive calcium release into the myocyte cytosol under these circumstances activates proteolytic enzymes that cause cell membrane injury [42] and excessive ATP consumption by overactive calcium ATPase pumps, predisposing cells to ischaemia, further enhancing the main pathophysiological mechanisms implicated in CS. Persistent contracture [58] may result from the inability to break actin-myosin cross-bridges (an ATP-dependant process), contributing to increased pressure. In athletic patients, muscle hypertrophy, which increases muscle size without increasing compartment volume, likely acts synergistically with exaggerated muscle contraction, impaired relaxation and myocyte swelling to increase the risk of compartment syndrome,
by reducing the available space that muscles can expand into. The contribution of muscle hypertrophy to CS is most notable in anabolic steroid users. [59–61]. These mechanisms may also have important therapeutic implications: while surgery is the mainstay of ACS treatment, CECS may be amenable to management with muscle relaxants, such as low-dose botulinum toxin [62–64] to break the cycle of impaired relaxation and excessive contracture worsening ischaemia, which further worsens the excessive contracture. RyR1 antagonists such as dantrolene may also be considered in this setting, particularly where patients harbor RYR1 mutations. In McArdle disease, patient education on activity management can prevent recurrent episodes.

Another important mechanism of ACS is reperfusion injury [65], which may occur not only following the full re-establishment of blood supply following prolonged ischaemia [66] but likely also during microcirculatory fluctuations resulting in an imbalance between the proportion of continuously perfused capillaries (the majority under normal circumstances) and the proportion of intermittently- and non-perfused capillaries [50,51,65]. Tissue ischaemia results in locally reduced ATP generation, reduced antioxidant production, failure of ion pumps, cytosolic calcium accumulation and metabolic acidosis due to lactic acid accumulation, thus creating a biochemical environment that favours ROS generation upon the return of oxygen delivery, produced from various sources including dysfunctional mitochondrial electron transport chains and the NAPDH oxidase and xanthine oxidase systems [66]. Such a biochemical environment promotes endothelial dysfunction [53] (and subsequent increased capillary permeability and/or decreased capillary blood flow), DNA damage and subsequent inflammatory cascades which may worsen cell damage [57]. Mitochondrial dysfunction may also contribute directly to cell death [68], in addition to necrosis occurring due to the above mechanisms [69]. Of note in this context, mitochondrial abnormalities and reduced antioxidant capacity are a recognized feature of RYR1-related disorders [70,71], which may promote a shift of the biochemical environment under these conditions that potentially promotes CS. In McArdle disease, the “second wind” phenomenon associated with increased blood flow and increased metabolism of free fatty acids and blood glucose [72] is known to cause significant metabolic stress during the adaptation phase, which may cause muscle injury in a manner analogous to ischaemia-reperfusion injury.

Taken together, these observations suggest a novel aspect of RYR1-related and metabolic disorders, and synergy between the cellular mechanisms implicated in these conditions and (recurrent) CS. RYR1 involvement in Case 1 highlights that anaesthetists and surgeons treating patients with (recurrent) compartment syndrome ought to be aware of the potentially associated Malignant Hyperthermia (MH) risk.

Declaration of Competing Interest

None

Acknowledgements

We like to thank the patients for their participation in this study, and the RYR1 Foundation, Pittsburgh, PA, United States (www.ryr1.org) for their support of this work. MF and NV are members of the European Reference Network for rare neuromuscular diseases (EURO-NMD).

References

pathophysiology | genetic | Kruijt | RYR1 | syndrome

rodent | of | proprietary | diagnosis | D, Pre-operative | RJ, 2016;01. RS, AR, N, Evans 0

case | R, Snoeck | SJ. Acute | myopathy? |

Can | A, KA, MT, 10.1097/0 | 

skeletal | muscle. | . 


