CASE REPORT

Primary carnitine deficiency in a 57-year-old patient with recurrent exertional rhabdomyolysis

Andoni Echaniz-Laguna,¹ Valérie Biancalana,^{2,3} Pauline Gaignard,⁴ Jean-Baptiste Chanson¹

¹Neurologie, Hôpitaux universitaires de Strasbourg, Strasbourg, France

²Laboratoire de Diagnostic Génétique, Hôpitaux universitaires de Strasbourg, Strasbourg, France

³Physiopathologie des maladies neuromusculaires, Institut de Genetique et de Biologie Moléculaire et Cellulaire, Illkirch, France

⁴Service de Biochimie, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

Correspondence to

Dr Jean-Baptiste Chanson, jean-baptiste.chanson@chru-strasbourg.fr

Accepted 18 May 2018

SUMMARY

Rhabdomyolysis is an emergency requiring rapid diagnosis and suitable aetiological treatment. We describe the case of a 57-year-old man with recurrent exertional rhabdomyolysis who was diagnosed with systemic primary carnitine deficiency (SPCD). Clinical examination was normal, creatine kinase levels were elevated, plasma free carnitine concentration was mildly decreased, muscle biopsy demonstrated lipid accumulation, carnitine uptake in cultured fibroblasts was decreased and genetic analysis identified a homozygous pathologic c.1181_1183del in the *SLC22A5* gene. Rhabdomyolysis did not recur after treatment with oral L-carnitine was introduced. SPCD is a rare autosomal recessive disorder of carnitine transportation usually manifesting as an infantile (hepatic) or a childhood myopathic (cardiac) condition and rarely affecting adults. Our case indicates that SPCD should be considered in the aetiological evaluation of adult patients with recurrent exertional rhabdomyolysis, even in the absence of myopathy and cardiomyopathy.

and he had no family history of neuromuscular disorders and no obvious history of consanguinity. Muscular complaints had begun in his 30s, with the patient describing diffuse muscle pain systematically appearing immediately after strenuous exercise, for example, after moving heavy furniture or trimming hedges. Laboratory studies performed during these painful episodes demonstrated markedly increased CK levels, usually in the 5.000–15.000 U/L range (normal <200), and fluid management using aggressive hydration was needed a number of times to prevent kidney damage. Interestingly, the patient had been able to practice several sports and to perform his military duties in his teens and 20s and exercise intolerance only appeared after age 30 years. At least 10 episodes of rhabdomyolysis occurred until adaptation in his lifestyle allowed him to avoid intense physical activity. No more episode happened after these changes. Clinical examination demonstrated neither muscle weakness nor muscle atrophy.

BACKGROUND

Rhabdomyolysis is a severe acute muscle injury resulting in myalgia, weakness and/or swelling with release of myofiber contents in bloodstream.¹ Symptoms develop over hours to days after a triggering factor and serum creatine kinase (CK) levels are increased. The release of intracellular muscle components into the blood stream frequently results in myoglobinuria and, in severe cases, acute renal failure.^{1,2} Acquired causes include substance abuse, medication or toxic exposures, electrolyte disturbances, endocrine disorders and inflammatory myopathies.¹ Inherited causes include disorders of glycogen metabolism, fatty acid β -oxidation and mitochondrial oxidative phosphorylation.^{1,2} Here, we describe an adult patient with recurrent exertional rhabdomyolysis caused by systemic primary carnitine deficiency (SPCD), a rare treatable metabolic disorder usually presenting as an infant-onset or childhood-onset myopathic or cardiac condition.

CASE PRESENTATION

A 57-year-old male patient with no history of alcohol abuse or toxic substance exposure was addressed to our Neuromuscular Disorders Referral Centre because he presented with exercise intolerance and recurrent rhabdomyolysis for more than 20 years. He was of Portuguese origin,

INVESTIGATIONS

CK levels at rest were mildly increased (250 U/L; normal <200) and plasma free carnitine concentration was mildly decreased (20 μ M; normal: 25–50 μ M). Acylcarnitine profile in plasma was normal, with the concentration of different length acylcarnitine species in the normal range. Muscle biopsy demonstrated numerous lipid vacuoles (figure 1A), and ECG and echocardiogram were normal. Targeted exons sequencing using a custom panel of 136 genes implicated in neuromuscular disorders was performed (MYOdiagHTS panel). A c.1181_1183del leading to an in-frame deletion of one amino acid p.Leu394del was detected in exon 7 of the *SLC22A5* gene (NM_003060.3). This variation was homozygous and was confirmed by Sanger sequencing (figure 1B). Skin biopsy was performed to assess carnitine transport in cultured fibroblasts. Carnitine transport in the patient's fibroblasts was reduced below 10% of control rates, that is, 0.17 pmol/min/mg proteins in the patient versus 3.02 in the control (extracellular carnitine concentration: 5 μ mol/L) (figure 1C). In view of the previous genetic and biochemical results, the patient was eventually diagnosed with SPCD, even if plasma free carnitine concentration was only mildly decreased.

To cite: Echaniz-Laguna A, Biancalana V, Gaignard P, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-224272

Figure 1 (A) Muscle pathology showing lipid accumulation (oil red O staining). (B) Sequencing chromatogram showing a c.1181_1183delTGC in exon 7 of the *SLC22A5* gene. (C) Carnitine transport assessment in cultured fibroblasts demonstrating a massive decrease in total and specific carnitine uptake in the patient's fibroblasts in comparison with a normal control.

DIFFERENTIAL DIAGNOSIS

Several inherited metabolic disorders may provoke secondary carnitine deficiency, including organic acidemias and fatty acid oxidation defects such as very long-chain acyl-CoA dehydrogenase (VLCAD), medium-chain acyl-CoA dehydrogenase (MCAD), long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) and carnitine palmitoyl-transferase II (CPT II) deficiencies.³ In the case presented here, SPCD was differentiated from other fatty acid oxidation defects by demonstration of low free carnitine levels in plasma associated with normal acylcarnitine profile.

Treatment with ciclosporine, pivampicillin and valproate, malnutrition, renal tubular dysfunction, prematurity and prolonged total parenteral nutrition feedings without carnitine supplementation may also cause secondary carnitine deficiency.³ Here, the patient had no previous pharmacological treatment and his renal function was normal.

Glycogen storage diseases and mitochondrial disorders may also provoke recurrent exertional rhabdomyolysis, and both disorders should therefore be systematically considered.^{1 2} However, low free carnitine levels associated with normal acylcarnitine profile is a pattern usually not observed in these conditions.^{1 2} Furthermore, muscle biopsy did not demonstrate pathological evidence of glycogen storage disease and mitochondrial disease, that is, glycogen accumulation, red ragged red fibres and/or cytochrome oxidase deficiency.^{1 2}

TREATMENT

Carnitine is an essential compound acting as a transporter of long-chain fatty acids into the mitochondria where their oxidation will produce energy. Carnitine and long-chain fatty acids form long chain acetylcarnitine esters which are transported across the mitochondrial membrane by CPT I and CPT II.

The lack of carnitine will thus impair the energy production in muscle and other tissues. One of the possible consequences will be recurrent rhabdomyolysis after prolonged exercises, when energy production is especially dependant on lipids. The metabolic and myopathic manifestations of SPCD can be prevented by maintaining normal plasma carnitine levels using supplementation with oral levocarnitine (L-carnitine). The patient was therefore treated with oral levocarnitine at a dose of 100 mg/kg/day divided into three daily doses.

OUTCOME AND FOLLOW-UP

The effect of levocarnitine supplementation was beneficial as rhabdomyolysis did not recur under treatment, even after exercise.

DISCUSSION

SPCD is a rare autosomal recessive disorder of carnitine transportation.^{3 4} The clinical manifestations of SPCD vary widely. The most severe forms are typically characterised by episodes of hypoketotic hypoglycaemia, hepatomegaly, elevated transaminases and hyperammonaemia in infants. Other forms present with skeletal myopathy, increased CK level and cardiomyopathy beginning in childhood or even with only cardiomyopathy, arrhythmia or abnormal fatigability beginning in adulthood.³ Interestingly, several asymptomatic adult patients have also been described.³ The diagnosis is usually established by demonstrating low plasma free carnitine concentration (<5 μM, normal 25–50 μM), reduced fibroblast carnitine transport (<10% of controls) and molecular testing of the *SLC22A5* gene.^{3 5} The case presented here is unique in that the patient presented with isolated recurrent exercise-induced rhabdomyolysis, which has not been described until now in adult patients with SPCD.^{3 6 7}

On a molecular viewpoint, our patient presented with the *SCL22A5*c.1181_1183del which is extremely rare in public databases. Interestingly, this is only the second clinically relevant *SLC22A5* gene in-frame deletion reported until now.^{6 8 9} Indeed, 116 mutations have been reported in the *SLC22A5* gene, including a unique c.67_69delTTC in-frame deletion.^{6 8 9} It has been observed that *SLC22A5* gene non-sense and frame-shift mutations are typically associated with lower carnitine transport and are mostly found in symptomatic individuals, whereas missense mutations and in-frame deletions may result in retained residual carnitine transport activity and are mainly observed in asymptomatic individuals.⁷ In keeping with this concept, the *SCL22A5* homozygous c.1181_1183 in-frame deletion we found in our patient is indeed associated with residual enzymatic activity that may explain his attenuated late-onset phenotype. Overall, this case demonstrates that lipid metabolism disorders should not be overlooked in adult patients with recurrent rhabdomyolysis, even in the absence of myopathy and cardiomyopathy.

On a larger perspective, identifying underlying genetic disorders in patients with recurrent rhabdomyolysis is a diagnostic challenge requiring a high degree of clinical suspicion before requesting appropriate investigation.^{1 2} Establishing a genetic

diagnosis in a patient with recurrent rhabdomyolysis is of crucial importance to provide relevant advice to prevent future episodes and also to provide cost-effective patient care. Also, in terms of global health, our report demonstrates the extreme importance of raising the awareness of the medical community on rare disorders associated with recurrent rhabdomyolysis.

Contributors AE-L drafted the manuscript. All the authors substantially contributed to the gathering of data and revision of the manuscript.

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 J-BC reports hospitality fees from LFB laboratory, Grifols and CSL Behring and speaker fees from CSL-Behring.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

Learning points

- Clinicians should bear in mind systemic primary carnitine deficiency (SPCD) as a differential diagnosis among adult patients with recurrent exertional rhabdomyolysis even in the absence of myopathy and cardiomyopathy, and even when plasma-free carnitine concentration is subnormal.
- SPCD is a treatable condition, with L-carnitine preventing clinical manifestations.
- Lipid metabolism disorders usually present as severe infantile or childhood conditions, but adult-onset attenuated presentations should not be overlooked.

REFERENCES

- 1 Nance JR, Mammen AL. Diagnostic evaluation of rhabdomyolysis. *Muscle Nerve* 2015;51:793–810.
- 2 Scalco RS, Gardiner AR, Pitceathly RD, et al. Rhabdomyolysis: a genetic perspective. *Orphanet J Rare Dis* 2015;10:51.
- 3 Magoulas PL, El-Hattab AW. Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management. *Orphanet J Rare Dis* 2012;7:68.
- 4 Laforêt P, Vianey-Saban C. Disorders of muscle lipid metabolism: diagnostic and therapeutic challenges. *Neuromuscul Disord* 2010;20:693–700.
- 5 Tein I, De Vivo DC, Bierman F, et al. Impaired skin fibroblast carnitine uptake in primary systemic carnitine deficiency manifested by childhood carnitine-responsive cardiomyopathy. *Pediatr Res* 1990;28:247–55.
- 6 Lamhonwah AM, Olpin SE, Pollitt RJ, et al. Novel OCTN2 mutations: no genotype-phenotype correlations: early carnitine therapy prevents cardiomyopathy. *Am J Med Genet* 2002;111:271–84.
- 7 Rose EC, di San Filippo CA, Ndukwe Erlingsson UC, et al. Genotype-phenotype correlation in primary carnitine deficiency. *Hum Mutat* 2012;33:118–23.
- 8 Frigeni M, Balakrishnan B, Yin X, et al. Functional and molecular studies in primary carnitine deficiency. *Hum Mutat* 2017;38:1684–99.
- 9 Li FY, El-Hattab AW, Bawle EV, et al. Molecular spectrum of SLC22A5 (OCTN2) gene mutations detected in 143 subjects evaluated for systemic carnitine deficiency. *Hum Mutat* 2010;31:E1632–51.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow