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VERY-LONG-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY – DIAGNOSTIC DIFFICULTIES AND OWN EXPERIENCE IN MULTIDISCIPLINARY MANAGEMENT

ZESPÓŁ NIEDOBORU DEHYDROGENAZY ACYL-COA BARDZO DŁUGOŁAŃCUCHOWYCH KWASÓW TŁUSZCZOWYCH – TRUDNOŚCI DIAGNOSTYCZNE I DOŚWIADCZENIA WŁASNE DOTYCZĄCE WIELOSPECJALISTYCZNEGO LECZENIA

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Abstract

A 19-year old female patient presented with a two-year history of muscle pain and weakness before she was admitted to an acute medical ward with rhabdomyolysis (creatine kinase of 83,344 IU/L) and normal renal function tests. Following admission she was under the care of the rheumatology and neurology teams, which investigated her thoroughly. As part of the belt-and-braces approach, both teams contacted the specialist Adult Inherited Metabolic Disorders team for advice, instigating definitive diagnostic investigations. An accurate diagnosis was required, as an inherited metabolic disorders can present in adult patients as a milder form of the disease.

Very-long-chain Acyl-CoA dehydrogenase (VLCAD) deficiency should always be considered as a differential diagnosis of myopathy-related symptoms. Hence, the liaison between neurologists, rheumatologists and metabolic physicians is essential in early diagnosis and the management of patients with conditions causing myopathy.

Key words: VLCAD deficiency, rhabdomyolysis, myopathy

Streszczenie

19-letnia pacjentka z dwuletnią w wywiadzie historią bólów mięśni i osłabieniem oraz z prawidłową funkcją nerek przyjęta została na oddział internistyczny szpitala. Pozostawała tam pod opieką reumatologów i neurologów, którzy ze względu na trudności diagnostyczne poprosili o konsultację lekarzy z Oddziału Rzadkich Chorób Metabolicznych. Było to celowe, biorąc pod uwagę fakt, że niektóre genetycznie uwarunkowane choroby metaboliczne manifestujące się u młodzieży i osób dorosłych, mogą mieć postać i przebieg łagodniejszy.

Z opisywanego przez nas przypadku wynika, że niedobór dehydrogenazy Acyl-CoA bardzo długich łańcuchów kwasów tłuszczowych powinien być zawsze brany pod uwagę w diagnostyce różnicowej miopatii.

Trudności diagnostyczne natomiast pokazały konieczność współpracy wielu specjalistów.

Słowa kluczowe: niedobór VLCAD, rabdomioliza, miopatia

CASE REPORT

We present a case of a 19-year-old female born to consanguineous Pakistani parents who presented with a sudden onset of weakness in her legs, and to a lesser extent in her arms, reportedly induced by vacuum cleaning the house. She also noted her urine was darker in colour. Her symptoms were not preceded by any infection, alcohol or drugs intake. Prior to her admission to a district general hospital, she was fit and healthy with no significant past medical history and she did not seek any medical advice until the age of 17, when the muscle aches started developing. Her mother was not well during the pregnancy with her, but gave birth to a healthy-looking child. Our patient lived with her parents, working as a social worker. There was no remarkable family history indicative of neurological or muscle disease.

On admission, biochemistry tests showed creatine kinase of 83,344 IU/L (<170) consistent with rhabdomyolysis, but her renal-function tests were normal. Thyroid function tests were within normal reference limits. Her autoimmune screen was normal, as was the MRI scan and lumbar puncture.

The initial diagnosis was of post-viral reactive myositis or connective-tissue disease, so her condition was treated with corticosteroids. These were subsequently stopped when creatine kinase returned to normal (52 IU/L).

In terms of medication, she was taking gabapentin, paracetamol, tramadol to help with the pain in lower limbs, vitamin D injections as her vitamin D was reported as deficient at 9.9 nmol/l, and also lansoprazole, and ferrous sulphate for iron-deficiency anaemia (MCV 68 fl).

On examination there was no muscle wasting or wasting of the limbs or face and there was no evidence of a rash. A neurological examination showed normal muscle strength and a steady gait. However, during an acute attack the patient could not move her legs at all and she had a symmetrical weakness in both lower limbs for which she required a wheelchair. However, she was still able to transfer to a couch with no assistance. Cardiovascular, respiratory and abdominal examinations were unremarkable.

For the first two years the patient was under the care of the rheumatology and neurology teams and underwent multiple specialist investigations. Neurophysiological studies showed evidence of an isolated acute denervation of the left extensor digitorum brevis but no clear evidence of myopathy clear, although fibrillation potentials were present. There was no large fibre polyneuropathy.

A muscle biopsy showed no evidence of regenerating fibres, suggesting that the regeneration process was complete following her previous episode of rhabdomyolysis. There was nothing to suggest phosphorylase deficiency, an increased number of ragged red fibres or core fibres, and there was no excess accumulation of lipid or glycogen to suggest other metabolic-type problems.

Within approximately 25 months from the major episode of rhabdomyolysis, the patient had at least three further similar, although less severe, episodes requiring admission to hospital, and accompanied by creatine kinase of 3000 IU/L. Collaboration between the rheumatology, neurology and metabolic teams instigated metabolic investigations. Acylcarnitines showed C14:1 0.85 μmol/L (NR<0.39 μmol/L) and free carnitine 6.36 μmol/L (NR 20-40). Repeated analysis confirmed very-long-chain Acyl-CoA dehydrogense (VLCAD) deficiency: C14:1 0.43 μmol/L (NR<0.39 μmol/L) and free carnitine 15.3 μmol/L (NR 20-40). Organic acids did not show any abnormality. Fatty-acid oxidation flux was abnormal and consistent with VLCAD deficiency: myristate accounted for 103 (% of simultaneous controls), and palmitate 88 (% of simultaneous controls) which were within normal limits and oleate 25 (% of simultaneous controls) which was low. Genetic testing gave a definite diagnosis and showed her to be homozygous for the p. (Phe369Cys), c.1106T>G mutation in exon 11 of the ACADVL gene.

Further investigations included an echocardiogram that showed the left ventricle of normal size and normal systolic function. All heart valves were structurally normal with no abnormalities of flow. The left atrium was of normal size and the pulmonary artery pressure was in the normal range. The right side of the heart was normal.

After the last episode it took her a few months to return to normal health and she made slow but steady progress. She still had significant pain on a regular basis and this had been a recurring theme over the previous few years. She was advised on the restriction of long-chain fats to less than 20% in her diet and on avoiding fasting for more than 8 hours overnight. The patient was also made aware of an emergency regimen: the use of high-glucose polymers and fat-soluble vitamins during intermittent illnesses. Additionally, nutritional products were incorporated into her diet –medium-chain triglycerides (MCT) oil and Walnut Oil.

DISCUSSION

We presented the case of an adult female patient who developed episodic muscular symptoms induced by physical exercise.

Episodes of exercise intolerance followed by dark urine (myoglobinuria) as a result of rhabdomyolysis, and increased serum creatine kinase activity, are symptoms of skeletal muscle disease that can be acquired or inherited [1]. The first presentation of muscular symptoms in an adult person with no previous history of myopathy raises the suspicion of exogenous factors. Myoglobinuria episodes in adults are generally triggered by strenuous exercise, muscle injury, sepsis, fever, fasting, inflammatory myopathies or toxins [2].

Once external causes are excluded, inherited disorders may be considered. VLCAD deficiency is one of the differential diagnoses with later-onset episodic myopathic VLCAD deficiency probably being the most-common phenotype. It presents with intermittent rhabdomyolysis, muscle cramps and/or pain and/or exercise intolerance. Hypoglycemia is not typically present at the time of symptoms. Cases of rhabdomyolysis as a complication of adult-onset VLCAD deficiency have been previously documented in the literature [1, 3, 4]. Late-onset VLCAD deficiency has also been found to be a cause of acute hypercapnic respiratory failure [5] and acute renal failure [6].

VLCAD deficiency is a genetic disorder of mitochondrial fatty-acid ß-oxidation resulting in a defect in oxidation of long-chain fatty acids. After prolonged fasting the body switches from carbohydrates to fatty acids for energy production. In VLCAD deficiency, because of the inability to utilise long-chain fatty acids, prolonged fasting and excessive exertion predispose the patient to acute metabolic decompensation, hypoketotic hypoglycaemia, cardiomyopathy and rhabdomyolysis [7].

Apart from the adult-onset form of VLCAD deficiency, there are two others. Individuals with the early-onset type present with cardiomyopathy, hypotonia, and hepatomegaly in the first months of life; sudden death is also frequent. Individuals with the early-childhood-onset type typically present with hypoketotic hypoglycemia and hepatomegaly without cardiomyopathy [5].

In our case initial investigations were inconclusive, as muscle biopsy was non-diagnostic, showing non-specific minor myopathic features with normal cytochrome oxidase and myophosphorylase staining and no abnormal organellar morphology in electron microscopy. Fasting lactate was normal. Consequently a fatty-acid metabolism disorder was suspected given the history of recurrent muscle pain and dark urine after prolonged exertion or fasting. The initial diagnostic approach for metabolic myopathy in an acutely-ill patient is the determination of the urinary dicarboxylic acids. The pattern in our patient did not suggest a fatty acid β -oxidation defect. The blood acylcarnitine pattern subsequently helped to differentiate the subtype of a β-oxidation defect. In this case, the serum biochemical findings and clinical picture were highly suggestive of VLCAD deficiency. Enzymatic assays in cultured fibroblasts and genetic mutational analysis confirmed the diagnosis. The defective gene of VLCAD was located in exon 11 of the ACADVL gene. The p.(Phe369Cys), c.1106T>G mutation had not been reported previously but has been found to affect a highly conserved amino-acid condition and is highly pathogenic. Importantly, the molecular basis of VLCAD deficiency is very diverse with 80 mutations reported in the literature [5, 8, 9]. Among these, some mutations in patients with the milder childhood form and the adult-onset form of VLCAD are missense mutations that can result in some residual enzyme activity [10].

From the clinical and practical point of view the early and proper diagnosis and management are important. Therefore we prepared some points to remember:

The management of VLCAD deficiency

1. Avoid fasting overnight for more than 8 hours.
2. Avoid prolonged exercise.
3. Ensure high-carbohydrate and low-fat diet.
4. Emergency Regimen: SOS 25 (glucose polymer).
5. MCT (medium-chain triglycerides) and Walnut Oil.
6. Dandrolene sodium, muscle relaxant [11].

Biochemical investigations to confirm VLCAD deficiency

1. Plasma acylcarnitines.
2. Plasma fatty-acid profile.
3. Uine organic acids.
4. Fibroblast fatty-acid oxidation probe studies.
5. Molecular testing to confirm the diagnosis.

Metabolic causes of rhabdomyolysis

Disorders of glycogenolysis/glycolysis:
– Myophosphorylase deficiency (McArdle's disease)
– Phosphorylase kinase deficiency
– Phosphofructokinase deficiency
– Phosphoglycerate kinase deficiency
– Phosphoglycerate mutase deficiency
– Lactate dehydrogenase deficiency
– Abnormal hexokinase activity

Disorders of lipid metabolism:
– CPT II deficiency
– SCAD, MCAD, LCHAD, VLCAD deficiency
– Mitochondrial trifunctional enzyme deficiency
– LIPN1 gene (phosphatidic acid phosphatase) mutations

Disorders of purine metabolism:
– Myoadenylate deaminase deficiency (MAD)

Pentose phosphate pathway
– Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Mitochondrial respiratory chain:
– Microdeletion in cytochrome c oxidase subunit I III
– Succinate dehydrogenase/complex II deficiency

Krebs cycle:
– Lipoamide dehydrogenase deficiency

Sarcoplasmic calcium adenosine triphosphate (Ca-ATPase) deficiency (Brody myopathy)

CONCLUSIONS

The genetic defects of fatty-acid β-oxidation should be at the top of the differential diagnosis list when a young adult presents with muscle pain, rhabdomyolysis and myoglobinuria induced by prolonged exercise and fasting. Collaboration between specialist teams and the prompt initiation of metabolic diagnostic investigations can prevent delays in the diagnosis and the recurrence of episodes of rhabdomyolysis that are potentially life-threatening.

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