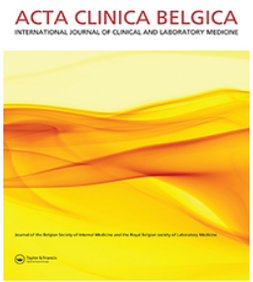

Acta Clinica Belgica
International Journal of Clinical and Laboratory Medicine

ISSN: 1784-3286 (Print) 2295-3337 (Online) Journal homepage: https://www.tandfonline.com/loi/yacb20

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To cite this article: Meltem Koca, Abdulsamet Erden, Berkan Armagan, Alper Sari, Fatih Yildiz, Sevim Ozdamar, Umut Kalyoncu & Omer Karadag (2019) Two cases of glutaric aciduria type II: how to differentiate from inflammatory myopathies?, Acta Clinica Belgica, 74:6, 451-455, DOI: 10.1080/17843286.2018.1547244

To link to this article: https://doi.org/10.1080/17843286.2018.1547244

Published online: 19 Nov 2018.

ACTA CLINICA BELGICA
2019, VOL. 74, NO. 6, 451–455
https://doi.org/10.1080/17843286.2018.1547244

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CASE REPORT

Two cases of glutaric aciduria type II: how to differentiate from inflammatory myopathies?

Meltem Koca[a], Abdulsamet Erden[b], Berkan Armagan[b], Alper Sari[b], Fatih Yildiz[c], Sevim Ozdamar[d], Umut Kalyoncu[b] and Omer Karadag[b]

[a]Faculty of Medicine, Department of Internal Medicine, Hacettepe University, Ankara, Turkey; [b]Faculty of Medicine, Department of Rheumatology, Hacettepe University, Ankara, Turkey; [c]Department of Rheumatology, Saglik Bilimleri Universitesi, Van Egitim ve Arastirma Hastanesi, Van, Turkey; [d]Faculty of Medicine, Department of Neurology, Hacettepe University, Ankara, Turkey

ABSTRACT

Muscle weakness is a nonspecific finding of myopathy of any etiology that include iatrogenic, toxic, endocrinological, infectious, immunologic, and metabolic disorders. Among the metabolic myopathies glutaric aciduria type II (GAII) is an autosomal recessively inherited rare disorder of fatty acid and amino acid metabolisms. The late onset form is heterogeneous in terms of symptomatology and severity and for the cases that chronic manifestations of lipid storage myopathy are the only clues for the disease, differential diagnosis can be challenging. Here we report two cases of GAII: the first one was 18-year old boy who presented with proximal muscle weakness and in another center, he was diagnosed as polymyositis and treated with immunosuppressive therapies. He admitted to our clinic with ongoing muscle weakness and symptoms that were related to the side effects of immunosuppressive therapies. The second case was also presented with muscle weakness. For both cases, muscle biopsies and urinary organic acid analyses were consistent with the diagnosis of GAII. To differentiate inflammatory myositis from non-inflammatory myopathies; rheumatic symptoms, accompanying complaints of the patient and autoantibody positivity can be helpful. To our knowledge this is the first report to underline the differential diagnosis of inflammatory myopathies from metabolic myopathies.

KEYWORDS

Myositis; metabolic; lipid storage myopathy; multiple acyl-coenzyme A deficiency; glutaric acidemia type II

Introduction

Glutaric aciduria type II (GAII) or multiple acyl-CoA dehydrogenase deficiency (MADD) (OMIM #231,680) is an autosomal recessively inherited rare disorder of fatty acid and amino acid metabolisms. It results from the deficiency in anyone of three molecules: the alpha and beta subunits of electron transfer flavoprotein (ETFA and ETFB), and electron transfer flavoprotein dehydrogenase (ETFDH) [1]. In GAII, urine organic acid analysis demonstrates increased excretion of lactic, ethylmalonic, butyric, isobutyric, and isovaleric acids whereas it is the only organic acid whose concentration increases in GAI is glutaric acid.

The clinical presentation is heterogeneous and can be grouped into three forms: the neonatal-onset form with and without congenital anomalies (type 1 and 2, respectively), and the late-onset form (type 3) [1]. Severity of the clinical picture is not related to the gene which is affected (ETFA, ETFB or ETFDH), rather it depends on the nature and the location of the mutation [2]. The neonatal-onset forms are usually fatal in perinatal period and present with acute metabolic decompensations characterized by severe metabolic acidosis, nonketotic hypoglycemia, hypotonia, multisystem involvement with or without congenital anomalies which include facial dysmorphism, cystic renal dysplasia, and cerebral malformations and even coma [3]. Age and symptoms at presentation are highly variable in the late onset form and are characterized by recurrent episodes of lethargy, vomiting, hypoglycemia, metabolic acidosis, and chronic manifestations of lipid storage myopathy: myalgia, muscle weakness and exercise intolerance. Organic aciduria may be mild, atypical, or detectable only during acute metabolic decompensations [4].

Here we describe two cases who were presented with muscle weakness that may be a manifestation of some rare inborn errors of metabolism like late-onset GAII and whose clinical pictures may be confused with polymyositis (PM).

Case I

An 18-year old boy was first presented four years ago to another hospital with dyspnea, weight loss of about 10 kg, muscle weakness of proximal lower extremities, neck and jaw when chewing. His rheumatic symptom questioning was not remarkable except for weakness and fatigue. On admission, serum creatine kinase (CK) and lactate dehydrogenase (LDH) levels were 1140 U/L

CONTACT Meltem Koca meltem.koca@outlook.com Faculty of Medicine, Department of Internal Medicine, Hacettepe University, Sihhiye, Ankara 06100, Turkey

and 2036 U/L, respectively and the tests for antinuclear antibodies (ANA), extractable nuclear antigens (ENA) and rheumatoid factor (RF) were negative, erythrocyte sedimentation rate (ESR) was 6 mm/h. As the TSH and vitamin B12 levels were within normal limits and his medical history was negative for any drug/toxin induced myopathies or exercise induced myositis; he had the diagnosis of PM based on the electromyographic (EMG) examination that was found compatible with symmetrical proximal myopathy of lower extremities. 30 mg/day prednisolone was prescribed however his symptoms did not ease off. Then, he was treated with 3 days intravenous pulse methylprednisolone (MPZ) (1gr/day) followed by 64 mg/day MPZ and 15 mg/week methotrexate (MTX) as immunosuppressive therapy. As his muscle weakness and dyspnea started to improve, the steroid dose was tapered. While he was on 32 mg/day MPZ plus 15 mg/week MTX treatment, he relapsed with prominent upper extremity weakness. Although Azathioprine 150 mg/day was added to treatment regimen, his symptoms continued to deteriorate. Then, he received two injections of intravenous immunoglobulin (IVIg) with three months of interval and a Rituximab injection just before his admission to our center. During the follow-up of the patient, it was discovered that he had steroid induced-hyperglycemia treated with a short period of insulin treatment followed by a metformin 2 × 1000 mg/day. An acute back pain was added to his complaints and it was revealed that the reason was a compression fracture of the T12 vertebral body due to the osteoporosis secondary to the steroid therapy. He was suggested to wear a back brace until the fracture heal.

He admitted to our clinic with the complaints of muscle weakness, dyspnea on exertion and 12 kg of weight gain. The physical examination revealed moderate muscle weakness (grade 4/5 for upper extremities' proximal muscle groups, grade 3/5 for lower extremities' proximal muscle groups; grade 5/5 for distal muscle groups), positive Gowers' sign, swelling, and tenderness on his right knee, cushingoid appearance with facial erythema, partial alopecia, red striae, and proximal muscle atrophy. CK and LDH were 34 U/L and 299 U/L, respectively. Alanine aminotransferase (ALT) was 30 U/L and aspartate aminotransferase (AST) was 16 U/L. The capillaroscopic examination was within normal limits. His transthoracic echocardiography (TTE) and hepatic ultrasonography were in normal limits. The EMG findings was consistent with steroid myopathy and spinal MRI showed linear compression fractures of T3, T11, and T12 vertebral bodies. MRI of the right knee showed avascular necrosis of the lateral and medial condyles and subchondral fracture of the lateral condyle. The MPZ treatment was tapered and stopped. Three months later, he was presented with complaints of anorexia, nausea, vomiting, dysphagia, 8 kg of weight loss and increasing myalgia and muscle weakness. 4 mg/day MPZ was started and MTX was stopped due to his gastrointestinal symptoms. Drilling and synovectomy operation was performed to his right knee for the avascular necrosis of the both lateral and medial condyles. After that operation, he was able to walk again. He was hospitalized for the symptoms of weight loss, nausea and vomiting. His muscle biopsy from the biceps brachii demonstrated vacuolar degeneration in 50 percent of muscle fibers and the oil-red-o staining was consistent with lipid storage myopathy (Figure 1(a)). Urinary organic acid analysis showed raised concentrations of ethylmalonic, adipic, glutaric, and suberic acids and blood acylcarnitines measured using tandem mass spectrometry, showed increased concentrations of medium- and long-chain acylcarnitines. These results were consistent with the multiple acyl-CoA dehydrogenase deficiency. Subsequently, treatment with riboflavin 300 mg/day, L-carnitine 3g/

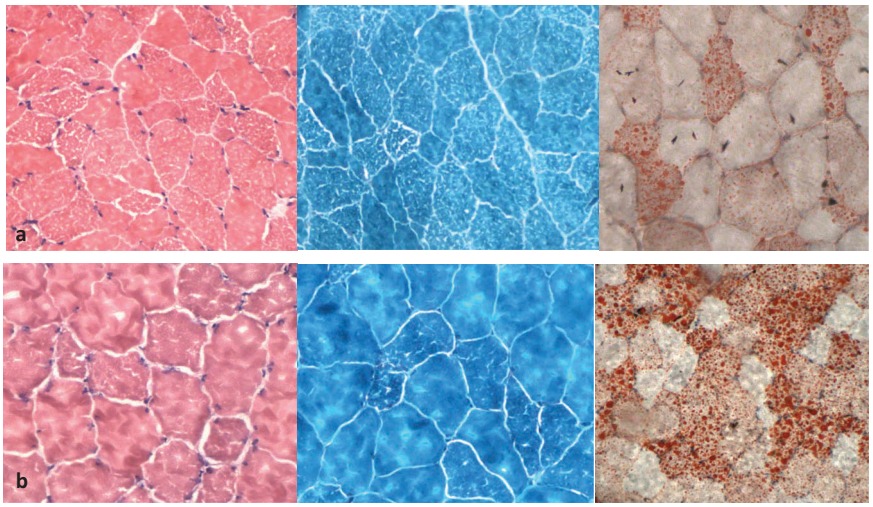

Figure 1. **a: Case I, b: Case II**: Small vacoules completely covering inside of some of the fibers, shown with hematoxylen-eosin and modified trichrome stain. Lipid accumulation was observed with Oil-Red-O stain (40x magnification).

day, and coenzyme Q 100 mg/day was started. His muscle weakness and dysphagia gradually improved.

Case II

A 23-year-old woman was presented with the complaints of myalgia and muscle weakness of proximal parts of all extremities. She described difficulty in climbing stairs and rising from chair for the last six months. She had no rheumatic symptoms; her medical history was negative for any drug/toxin induced myopathies or exercise induced myositis. On the physical examination, she had mild muscle weakness (grade 4/5 for all proximal muscle groups), and Gowers' sign was positive. Her TSH and vitamin B12 levels were within normal limits, CK and LDH were 1139 U/L and 1104 U/L, respectively. ALT was 59 U/L and AST was 101 U/L. The tests for ANA, ENA, and antineutrophil cytoplasmic antibody (ANCA) were negative, serum levels of complement proteins C3 and C4 were within normal limits (103 mg/dl and 27.5 mg/dl, respectively) and ESR was 25 mm/h. The capillaroscopic examination was also totally normal. The MRI of thigh muscles was reported as normal. The TTE and the hepatic ultrasonography were in normal limits, as well. Her EMG findings were consistent with myopathy, so we conducted a muscle biopsy from biceps brachii which showed vacuolar degeneration in fifty percent of fibers and excessive fat accumulation with oil-red-O staining (Figure 1(b)). Urinary organic acid analysis was consistent with the multiple acyl-CoA dehydrogenase deficiency and treatment with riboflavin and carnitine was started. Then, her muscle weakness gradually improved.

Discussion

In present two cases, we describe late-onset GAII as a rare cause of muscle weakness in adults and want to emphasize the importance of the differential diagnosis regarding all possible etiologies that include iatrogenic, toxic, endocrinological, infectious, immunologic, and metabolic disorders. GAII is a rare metabolic cause of myopathy and may closely mimic inflammatory myopathies in adults, until the definite diagnosis is established. It is of utmost importance to diagnose GAII as early as possible to start proper treatment.

Although age of onset, symptomatology and course of disease in late-onset form are highly variable, common features of presentation are proximal muscle weakness and myalgia due to lipid storage myopathy, hepatic dysfunction with hepatomegaly, episodic nausea-vomiting, easy fatigability, and intermittent metabolic decompensations precipitated by catabolic conditions or metabolic stresses like infections [4,5]. In these two cases, proximal muscle weakness and fatigue were common symptoms. Myalgia was also present in the second case however none of these symptoms are specific for a certain etiology. Muscle weakness is the most common symptom of all types of myopathies and is nonspecific. Thus, history, laboratory findings and accompanying symptoms that may help to differentiate between inflammatory myopathies and metabolic myopathies can be diagnostic clues for the clinician.

Inflammatory myopathies comprise a group of acquired myopathies and polymyositis, dermatomyositis (DM) and inclusion body myositis (IBM) are the most common types. Clinically, PM can be distinguished from DM by characteristic skin findings which include heliotrope rash and Gottron papules and are seen in DM but not in PM. IBM can also be differentiated from other myopathies with its pattern of muscle involvement that tends to be asymmetric and distal. PM is presented with symmetric proximal muscle weakness and like the other inflammatory myopathies, extramuscular manifestations may accompany the clinical picture. These manifestations include constitutional symptoms like fever, arthralgia, Raynaud's phenomenon, anorexia, morning stiffness, and weight loss. Pulmonary symptoms are seen up to 50% of all patients and may be secondary to respiratory muscle involvement or primarily due to the interstitial lung disease which has a strong association with anti-Jo -1 antibody (autoantibody against histidyl-tRNA synthetase) positivity. Cardiac involvement may also accompany inflammatory myopathies as pericarditis, arrhythmias, ventricular dysfunction, and even cardiac failure [6]. For these two cases, absence of constitutional and other extramuscular rheumatic symptoms was making the diagnosis of inflammatory myositis less likely.

Autoantibody positivity can be seen in more than 50% of inflammatory myopathies and this frequency may reach up to 80% with the increased sensitivity of the measurement techniques [7]. Myositis-related autoantibodies including ANA and other collagen-vascular disease markers like anti-PM-Scl 75, anti-PM-Scl 100, anti-Ku, anti-Mi-2, and anti-SS-A/Ro-52 kDa are seen more common than myositis-specific autoantibodies, most of which are targeting components of translation process and include anti-Jo-1 (histidyl-), anti-PL-7 (threonyl-), anti-PL-12 (alanyl-), anti-EJ (glycol-), anti-OJ (isoleucyl-tRNA synthetase), anti-SRP (signal recognition particle), and anti-Mi-2 [7]. Autoantibody positivity is yet to be studied for the differential diagnosis of myopathies. Suzuki et al. studied anti-SRP which is known to be an antibody specific for the diagnosis of PM, for the differential diagnosis of PM and muscular dystrophies (MD); and it was detected in 8.3% of the patients with PM but in none of the patients with MD [8]. For our cases, although negative autoantibodies could not exclude inflammatory myositis, it would be an important clue to evaluate other possible etiologies.

Serum CK level measurement is one of the initial laboratory tests in the diagnostic evaluation of myopathies. It is the most sensitive marker of muscle fiber

injury but a normal CK level does not exclude the diagnosis of myopathy. In PM and DM, CK is generally found elevated up to 50 times of upper limit of normal, but in IBM it can be normal or mildly elevated. Also in rare cases of PM and several instances of DM, serum CK level may be normal [9]. In GAII, CK levels are usually slightly or moderately elevated or even can be normal [10]. Moreover, in GAII muscle weakness and CK level may fluctuate and worsen during infections and catabolic stress [11]. In these two cases, CK levels were found to be moderately elevated on admission. Additionally, during follow-up, episodic elevations of CK and liver enzymes (like ALT, AST and LDH) which are characterized in the milder forms of fatty acid oxidation disorders were observed in our cases.

In both of our cases, capillaroscopic examinations were totally normal. Sclerodermic pattern nailfold capillaroscopic abnormalities such as giant loops and ramified capillaries with intense neoangiogenesis are seen in 71% of DM and its variant, antisynthetase syndrome. Additionally, although in patients with PM these specific capillaroscopic changes are less commonly seen, nonspecific capillaroscopic abnormalities are present in 31% [12,13]. Thus, capillaroscopic examination can be helpful for the differential diagnosis of PM and noninflammatory myopathies one of which is GAII.

Urinary organic acid profile is used for the diagnosis of GAII and it shows increased glutaric, adipic, suberic, malonic, and ethylmalonic acid excretion. In some cases, urinary organic acid profile consistent with GAII can be evident only during periods of catabolic conditions. Blood spot samples analyzed with tandem mass spectrometry for acylcarnitines show increased concentrations of short-, medium-, and long-chain acylcarnitines in MADD patients [14]. The cases here we have reported both were diagnosed with the help of urinary organic acid analysis, blood acylcarnitine analysis together with the muscle biopsy. Urinary organic acid profile could be included in initial diagnostic work-up when evaluating a patient with nonspecific muscle weakness.

GAII is caused by defects of ETF or ETFDH which are the parts of electron transfer chain. High energy electrons which are produced in the mitochondrial matrix by several acyl-CoA dehydrogenases are transferred to ETF. ETFDH then conducts dehydrogenation to carry electrons to ubiquinone in the respiratory chain. Vitamin B2 (riboflavin) is the co-factor for ETF, ETFDH and acyl-CoA dehydrogenases. Therefrom in case there is a defect in ETF or ETFDH, all acyl-CoA dehydrogenases in beta oxidation of fatty acids are affected [15,16]. Riboflavin supplementation dramatically improves clinical symptoms in a group of GAII patients. There is an association with riboflavin responsiveness and having ETFDH mutations and these patients are usually those with late-onset form [17]. Knowing that GAII may cause secondary carnitine and CoQ 10 deficiency, supplementation of CoQ 10 and carnitine can be added to treatment regimen [11,17]. In the first case, CoQ 10 and carnitine were added to treatment with this point of view. The patient in the second case whose muscle weakness was less severe at presentation, improved with riboflavin plus carnitine, and her muscle strength returned to normal.

Being a disease of autosomal-recessive inheritance, GAII may result from homozygous or compound heterozygous mutations in the genes which encode ETFA, ETFB (alpha and beta subunits of ETF, respectively) or ETFDH. Thus, consanguity is an important aspect in the patients' history [1]. Both of the patients in our cases were born to first cousin parents.

GAII is one of the four genetically diagnosable lipid storage myopathies [5,18]. Other three are primary carnitine deficiency, neutral lipid storage disease with ichthyosis and neutral lipid storage disease with myopathy. For management these two cases, one of the most important limitations was lack of genetic testing which were not available in our hospital yet.

Here we have described two patients presented with myopathy symptoms. GAII is a rare cause of myopathy and may closely mimic inflammatory myopathies in adults. CK levels were high in both cases but it is not specific for inflammatory or noninflammatory myopathies. Although it cannot exclude inflammatory myopathies definitely, capillaroscopic findings and autoantibody negativity can be important clues to differentiate noninflammatory myopathies from PM or DM. With the working diagnosis of PM, the patient in the first case had received several immunosuppressive therapies including corticosteroids, MTX, IVIg, azathioprine and rituximab each of which has important side effects and thus his morbidity significantly increased. For the patient in case II, muscle biopsy revealed lipid storage myopathy and helped us to establish diagnosis of GAII earlier and to start proper treatment with riboflavin and carnitine. Muscle weakness that is the first symptom of myopathy, should be evaluated carefully regarding all possible etiologies.

In conclusion, proximal muscle weakness is an easy symptom to recognize however what is important to treat a patient with myopathy is to find the correct diagnosis.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Meltem Koca http://orcid.org/0000-0003-3013-8556

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