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Case report

So doctor, what exactly is wrong with my muscles? Glutaric aciduria type II presenting in a teenager

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Abstract

Late-onset glutaric aciduria type II (GAII) is a rare but treatable cause of profound proximal myopathy. GAII is caused by defects in intra-mitochondrial acyl-CoA dehydrogenation due to deficiency in one of three molecules: the alpha or beta subunits of the electron transport flavoprotein (ETFA; OMIM 231680, ETFB; OMIM 130410), or ETF-dehydrogenase (ETFDH; OMIM 231675). This case report illustrates that GAII may present in the teenage years and may not be associated with hypoglycaemia. It outlines some important diagnostic conundrums faced in diagnosing and managing juvenile onset myopathies. Mutational analysis from this patient revealed two mutations of the ETF-DH gene: EFTDH-334C > T/His122Tyr and EFTDH-1366C > A/Pro456Thr (OMIM 231675). An outline of this rare but important disease, its clinical characteristics and diagnostic methodology are given.

Keywords: Glutaric aciduria type II; Late-onset; Myopathy

1. Introduction

Glutaric aciduria type II (GAII) or multiple acyl-CoA dehydrogenase deficiency is a relatively recently described autosomal recessively inherited disorder of fatty acid and amino acid metabolism [1]. In most patients it results from deficiency in one of three molecules, due to mutations in their respective genes: the α- or β-subunits of the electron transfer flavoprotein (ETFA; OMIM 231680, ETFB; OMIM 130410) or ETF ubiqinone oxidoreductase (ETFDH; OMIM 231675). The heterogeneous clinical features of patients with GAII fall into three subclasses: a neonatal-onset form that is usually fatal and characterised by severe non-ketotic hypoglycaemia, metabolic acidosis, excretion of large amounts of fatty acid- and amino acid-derived metabolites with congenital anomalies (type I); a neonatal-onset form without congenital anomalies (type II); and a late-onset form (type III) [2,3]. Symptoms and age at presentation of late-onset disease are highly variable and may be characterised by recurrent episodes of lethargy, vomiting and hypoglycaemia, metabolic acidosis, and hepatomegaly, or muscle involvement in the form of pain, weakness and lipid myopathy. All the three clinical form of the disease can be caused by a defect in any of the three genes [4].

We describe the presentation of the late-onset GAII in a teenager, illustrating some of the important diagnostic difficulties of juvenile onset myopathies.

2. Case report

A 14-year old girl presented with 12-months of progressive proximal limb and truncal muscle weakness; lethargy; myalgia; dysphagia; exertional and nocturnal dyspnoea and choking. She had no antecedent illness, relevant family or past medical history of note. She had nasal dysphonia, generalised muscle wasting, and profound weakness of her neck, trunk and proximal limb muscles. Eye movements were normal. Physician's global assessment [5] scored 1/10 and childhood myositis assessment scale (CMAS [6]) scored 4/52. There was full range of passive movement of all joints; no rash, temperature, calcinosis, retinal or optic field abnormality, or cerebellar

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signs. Reflexes were reduced but symmetrical and plantars down going. Cardiorespiratory and abdominal examinations were normal.

Full blood count, renal profile, glucose, thyroid function, immunoglobulins, viral serology, and inflammatory markers, were normal. She was never hypoglycaemic. Antinuclear and anti-encapsulated nuclear antibodies were negative. Initial muscle enzymes were mildly elevated (CK 436 IU/mL, AST 150 IU/mL, ALT 115 IU/mL). Pulmonary function, compared to predicted values, was reduced (FVC 57% and FEV_1 52%). CSF and blood lactate concentrations were normal. Mitochondrial enzymes in skeletal muscle biopsies showed low complex I, II and IV levels (0.01 nmols NADH oxidised/min, 0.095 nmols DCPIP reduce/min, 0.058×10^{-3}K/s, per unit citrate synthase, respectively (controls ($n=20$) 0.166 ± 0.047; 0.208 ± 0.070 and 1.805 ± 0.550)). Screening for common mitochondrial DNA mutations (3243A > G MELAS, 8344A > G MERRF, 8993T > G NARP, duplications/deletions) was negative. Plasma free carnitine was slightly reduced at 12 μmol/L (14–74 μmol/L); plasma α-glucosidase concentrations were normal. Upper gastrointestinal contrast study confirmed lower oesophageal dysmotility. Chest CT was normal; echocardiography showed no cardiomyopathy; EMG showed gross myopathic changes but normal nerve conduction and response to repetitive stimuli. MRI of muscles was initially not possible due to an implanted hearing-aid (surgery for cholesteatoma). Two muscle biopsies pre-treatment (quadriceps and deltoid) both showed perivascular immune deposition, minimal inflammatory changes, with mitochondrial and lipid accumulation. The deltoid biopsy also showed increase HLA Class I staining and deposition membrane attack complex of complement.

A working diagnosis of polymyositis was made and standard immunosuppressive therapy was commenced. She was treated with 3 days intravenous (IV) methylprednisolone (1 gm) followed by high dose (60 mg) oral prednisolone. Her dysphonia and dysphagia improved and her CK normalised. Her pulmonary function continued to deteriorate, and there was no change in her CMAS score or global assessment.

Further pulses of IV methylprednisolone, weekly IV methotrexate (10 mg/m^2), and IVIG (2 gm/kg) resulted in lung function returning only to baseline, with minimal effect on muscle power. Unable to sit up she had experienced frightening nocturnal dyspnoea and choking. In view of significant ongoing symptoms, etanercept (0.4 mg/kg/dose twice a week) was commenced. Within one week she could transfer to a wheelchair unaided and by three weeks could walk unaided and climb stairs with support. Lung function improved (FVC and FEV_1 81% and 73%), and after 2 months hospitalisation she was discharged home. Two months after starting etanercept, her CMAS score was 24, her global assessment score 7, and she returned to school.

Several months later she relapsed with increasing myalgia and weakness. A stepwise increase in her immunosuppresion therefore took place. Increase in steroid dose and addition of ciclosporin stabilised symptoms for 6 months. Further deterioration failed to respond to monthly IVIG therapy.

In contrast to her original EMG, a repeat study suggested myasthenia gravis. Anti-acetylcholine receptor, anti-MusSK, anti-VGCC, and anti-thyroid-peroxidase antibodies were negative. A trial of pyridostigmine (along with weaning of immunosuppression) was associated with transient, unsustained improvement. Plasmapheresis resulted in significant deterioration. Increase in steroid dosage, re-commencing methotrexate and etanercept, and the empirical addition of carnitine and co-enzyme Q10, were associated with a modest improvement in symptoms.

Following removal of her implanted hearing-aid (infection), brain MRI was normal and muscle MRI showed diffuse atrophy with fatty infiltration. Repeat muscle biopsy (quadriceps) showed no significant change.

Urinary organic acids showed a moderately raised lactic acid, ethylmalonic acid, glutaric acid, and marked increase in adipic acid concentrations (Table 1). Acylcarnitines in a dried blood spot, measured using tandem mass spectroscopy, showed increased concentrations of short-medium-, and long-chain acylcarnitines (Table 1). This profile was consistent with a multiple acyl-CoA dehydrogenase defect.

A diagnosis of late-onset GAII was made. She was commenced on riboflavin 50 mg tds, carnitine 100 mg/kg, and a low fat, low protein, high carbohydrate content diet. This was associated with a steady improvement in her muscle strength and exercise tolerance and she was subsequently successfully weaned off all immunosuppression. Twelve months after commencement of riboflavin, she

Table 1
Blood acylcarnitine results

	Patient	Reference Range
Blood acylcarnitine concentrations ((μmol/L)		
Acetylcarnitine (C2)	25.38	6.2–27.5
Proprioylcarnitine (C3)	3.71	0.13–4.0
Butyrlycarnitine (C4)	4.26*	≤ 0.58
Isovaerylcarnitine (C5)	2.11*	≤ 0.64
Hexanoylcarnitine (C6)	0.97*	≤ 0.29
Octanoylcarnitine (C8)	0.47*	≤ 0.19
Decenoylcarnitine (C10)	0.85*	≤ 0.39
Dodecanoylcarnitine (C12)	1.26*	≤ 0.59
Tetradecanoylcarnitine (C14)	1.86*	≤ 0.96
Hexadecanoylcarnitine (C16)	3.89	0.63-5.27
Octadecenoylcarnitine (C18)	2.24*	0.15-1.43
Glutarylcarnitine (DC5)	0.13*	≤ 0.13
Urinary organic acids:	(% total organic acids)	
Lactic acid	7%	
Ethylmalonic acid	14%	
Glutaric acid	7%	
Adipic acid	17%	

*Greater or equal to upper limit of reference range.