Different clinical aspects of debrancher deficiency myopathy

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Abstract

***Objective*—To characterise the main clinical phenotypes of debrancher deficiency myopathy and to increase awareness for this probably underdiagnosed disorder.**

***Methods*—The diagnosis of debrancher deficiency was established by laboratory tests, EMG, and muscle and liver biopsy.**

***Results*—Four patients with debrancher deficiency myopathy were identified in the Tyrol, a federal state of Austria with half a million inhabitants. Clinical appearance was highly variable. The following phenotypes were differentiated: (1) adult onset distal myopathy; (2) subacute myopathy of the respiratory muscles; (3) severe generalised myopathy; and (4) minimal variant myopathy. Exercise intolerance was uncommon. The clinical course was complicated by advanced liver dysfunction in two patients and by severe cardiomyopathy in one. All had raised creatine kinase concentrations (263 to 810 U/l), myogenic and neurogenic features on EMG, and markedly decreased debrancher enzyme activities in muscle or liver biopsy specimens. The findings were substantiated by a review of 79 previously published cases with neuromuscular debrancher deficiency.**

***Conclusions*—This study illustrates the heterogeneity of neuromuscular manifestations in debrancher deficiency. Based on the clinical appearance, age at onset, and course of disease four phenotypes may be defined which differ in prognosis, frequency of complications, and response to therapy.**

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Debrancher deficiency (glycogenosis type III, Cori-Forbes disease[1 2]) is a glycogen storage disease with predominantly hepatic and neuromuscular phenotypes and an autosomal recessive mode of inheritance.[3] The hepatic subtype presents in childhood with the typical clinical triad of hepatomegaly, growth retardation, and fasting hypoglycaemia.[3] Phenotypic expression and age at onset of neuromuscular disease, by contrast, are highly variable. Previous surveys suggested classifications of type III glycogenosis based on the underlying biochemical defect and organ involvement[4–6] or on the temporal sequence of liver and muscle disease.[7] The current study focused on the various clinical aspects of debrancher deficiency myopathy.

Methods

ANALYSIS OF SKELETAL MUSCLE TISSUE

Histochemical reactions were carried out on 10 m thick, fresh frozen sections (−70°C). Sections were stained with haematoxylin and eosin, periodic acid Schiff (PAS), modified Gomori trichrome, oil red O, Sudan black B, NADH tetrazolium reductase, succinate dehydrogenase, phosphorylase, and α-glycerophosphate dehydrogenase. Fibre typing was based on the myofibrillar adenosine triphosphatase reaction at pH 9.4, 4.6, and 4.2. Muscle specimens for biochemical analysis were immediately frozen in liquid nitrogen. A minimum of 20 mg muscle tissue was homogenised in HEPES-EDTA buffer (1:20). Amylo-1,6-glucosidase was determined according to the methods described by Hers *et al* in 1967,[8] with liberation of glucose from a phosphorylase limit dextrin. Measurements were done twice and average values given.

ELECTROPHYSIOLOGY

Electrophysiological examinations were all carried out on a Nicolet electromyograph (Vicking 4.0) and included nerve conduction studies (median, ulnar, peroneal, tibial, and sural nerves) and quantitative needle EMG

Case reports

The current study included four unrelated patients with debrancher deficiency myopathy. Age at disease onset ranged from 1 to 62 years. There were no inherited disorders or known consanguinity in the families of our patients. Laboratory findings are detailed in table 1.

CASE 1

This man was apparently healthy until the age of 62, when he became aware of slowly progressive muscle wasting of the calves and peroneal muscle groups. Polyneuropathy due to vitamin B_{12} deficiency (135 pmol/l, normal >148) was suspected and vitamin substitution initiated. Muscle weakness, however, further deteriorated and spread to intrinsic hand and forearm muscles. Proximal limb regions remained spared. On admission to our hospital 4 years later his gait was unstable; walking on toes and heels was not possible. Muscle strength was 3/5 (Medical Research Council scale) in the tibialis anterior and triceps surae muscles and 4+/5 in the forearm flexors and hand muscles. Deep tendon reflexes were

Table 1 Laboratory findings in four patients with debrancher deficiency myopathy

Variable	*Patient 1*	*Patient 2*	*Patient 3*	*Patient 4*	*Normal*
Creatine kinase (U/l)	424	410	810	239	Women <80 Men <140
Glutamic oxaloacetic transaminase (U/l)	25	45	101	613	6-17
Cholesterol (U/l)	6.15	4.20	4.75	5.51	2.71-5.69
Abnormal response to glucagon injection	NP	NP	+	+	
Pathological exercise test	+	+	NP	NP	
Echocardiography:					
Cardiomyopathy	+	++	+	-	
Nerve conduction study:					
Reduced nerve conduction velocity	+	-	+	-	
Electromyography:					
Fibrillation activity	+	++	++	+	
Myopathic features	++	++	++	+	
Neurogenic features	+	+	+	+	
Muscle biopsy:					
Glycogen concentration (mg/g NCP)	179	149	180	NP	60-105
Amylo-1,6-glucosidase (U/g NCP)	1.0	1.1	NP	NP	3.0-6.3
Acid maltase (U/g NCP)	2.0	2.0	NP	NP	1.2-3.5
N-acetyl-glucosaminidase (U/g NCP)	4.3	3.3	NP	NP	2.6-5.4
PAS Positive vacuolar myopathy	++	+	++	NP	
Cytoplasmatic glycogen pools in electron microscopy	++	+	+	NP	
Liver biopsy suggestive of GSD III	NP	++	++	++	

NCP=non-collagen protein; PAS=periodic acid Schiff; GSD=glycogen storage disease. NP=laboratory test not performed; −=negative or absent; +/++= evident or present (two categories).

decreased in the arms and absent in the feet. Sensation was normal. There was no clinical or laboratory evidence of liver dysfunction.

CASE 2

This woman had no history of childhood hepatomegaly or hypoglycaemia. She performed normal exercise until the age of 45, when exertional dyspnoea developed and cardiomyopathy was diagnosed. At the age of 47 she had an episode of major depression, refused nutrition, and steadily lost weight. She was admitted to hospital in a psychiatric clinic where she continued fasting but allowed substitution of vitamins and fluid. Within 2 days she developed respiratory failure with prominent hypercapnia and was intubated. She tolerated mechanical ventilation with marginal sedation, was able to get up and use her hands with normal skill, but was unable to breathe. Muscle strength was 4+/5 in deltoid and biceps muscles, normal in other limb muscles, and markedly reduced in intercostal and auxiliary ventilatory muscles. After 2 weeks of controlled ventilation and no evidence of remission a high protein diet (30%-35% of total energy intake) was started. Within a period of 4 days she was successfully weaned from the respirator. Four months after discharge muscle strength and spirometry had normalised. Cardiomyopathy, however, further deteriorated.

CASE 3

In this patient, a 60 year old man, hepatomegaly and fasting hypoglycaemia were first noticed in childhood. Motor development and milestones were normal. The patient had always been intolerant to vigorous exercise, complained of action induced myalgia, and once experienced pigmenturia after a long lasting gastrointestinal infection. Symptoms tended to regress around puberty but again worsened during adult life. At the age of 53 he was admitted to our hospital because of a hypoglycaemic coma (blood glucose, 1.22 mmol/l). He had unstable angina pectoris and advanced heart failure. The liver extended 5 cm below the costal margin. At the age of 54 the patient developed progressive muscle wasting primarily affecting proximal limb and trunk muscles. One year later he could not rise from a chair without assistance. He stopped working and soon needed help to dress. Five years after onset of myopathy he could not hold his arms over his head and was wheelchair bound.

CASE 4

This male patient was admitted to our hospital at the age of 8 months on account of muscular hypotonia, hypoglycaemia, hepatomegaly, and delayed motor development. The diagnosis of glycogen storage disease type III was established by liver biopsy (debrancher enzyme 0 nmol/min/mg non-collagen protein, normal 0.3–2.0) and therapy with frequent feeds during the day, cornstarch supplementation, and continuous feeding via nasogastric tube overnight was started. Under this treatment the child showed no more hypoglycaemic attacks and gained normal weight. Height remained at the 3rd percentile. Liver function improved. He learned to walk when he was 2 years old. Neurological examination at the age of 9 years showed mild proximal muscle weakness.

Table 2 depicts the frequency of the various clinical phenotypes in the literature[9–27] and illustrates differences in the rates of nerve involvement, complications, and response to therapy.

Discussion

THE CLINICAL VARIANTS OF DEBRANCHER DEFICIENCY MYOPATHY

On account of its phenotypic variability and the broad age range of disease onset (1 to 62 years) debrancher deficiency may be confused with a

Table 2 Debrancher deficiency myopathy: characteristics of distinct clinical phenotypes (n=83)

Phenotype	*n (%)*	*Male:female ratio*	*CK (x normal)*	*Slow NCV (%)*	*CMP [Severe CMP]*	*Liver disease [Severe LD]*	*Response to therapy*
Distal myopathy	8 (10%)	3:1	6–33	7 (88)	6 (75%) [n=0]	3 (50%) [n=0]	N/A
Generalised myopathy:							
Juvenile onset	24 (29%)	2:1	2—33	2 (8)	12 (80%) [n=0]	18 (90%) [n=1]	++
Adult onset	16 (19%)	4:1	10–45	6 (37)	9 (100%) [n=0]	8 (67%) [n=2]	(+)
Myopathy of respiratory muscles	1 (1%)	0:1	5	0	1 (100%) [n=1]	0	++
Minimal variant myopathy	34 (41%)	3:1	5–15	4 (12)	16 (76%) [n=3]	31 (94%) [n=3]	N/A

CK=creatine kinase; NCV=nerve conduction velocity; CMP=cardiomyopathy (pathological electrocardiogram and/ or echocardiography; severe CMP=heart failure; LD=liver disease; severe LD=cirrhosis; NA=data not available.

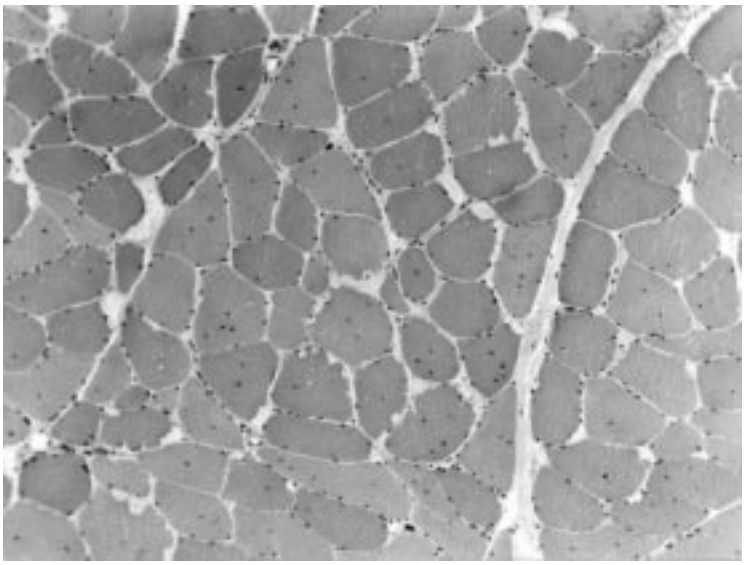
palette of other common neuromuscular disorders and thus probably represents an underrecognised disease entity. Our patients illustrate the clinical heterogeneity of neuromuscular glycogenosis type III. Four distinct phenotypes may be differentiated based on the clinical appearance, course of disease, and rate of organ involvement (table 2).

Distal myopathy

Slowly progressive distal myopathy involving calves and peroneal muscles is a typical phenotype of neuromuscular debrancher deficiency in adult life.[9 10] Apart from late onset of disease, the usually benign (non-disabling) course, comparatively low rate of hepatic involvement, and absence of severe cardiomyopathy are characteristic of this clinical variant (table 2). Mild sensory deficits and fasciculations may accompany the myopathic complaints and arise from glycogen storage in peripheral nerves.[21 26] Actually, nerve conduction studies yielded evidence of peripheral nerve involvement in most of these patients (88%; table 2). Rarely, neuropathic damage may even be the presenting feature.[21 26 27] In some patients the clinical appearance is indistinguishable from incipient motor neuron disease or common polyneuropathies. Myotonic dystrophy and inclusion body myositis are two muscle disorders that commonly show a distal pattern of weakness.

Myopathy of respiratory muscles

The most serious and at the same time least frequent clinical variant of neuromuscular glycogenosis type III is a selective myopathy of respiratory muscles (patient 2). This phenotype is characterised by a respiratory failure of myogenic origin and normal or near normal strength of limb muscles. The classic aetiology of a myopathy which selectively affects respiratory muscles is adult onset acid maltase deficiency.[28] Besides, respiratory failure may occur as a complication or initial manifestation of myasthenia gravis, Lambert-Eaton syndrome, atypical motor neuron disease, or sarcoid and inclusion body myositis.[29–32]



Cryostat section of muscle biopsy showing variation of fibre size, centrally located nuclei, and irregularly shaped subsarcolemal glycogen vacuoles in many fibres (hematoxylin and eosin originally×120).

Juvenile and adult onset generalised myopathy

Generalised myopathies account for 48% of previously published patients with debrancher deficiency myopathy (table 2). Patients with juvenile onset of disease usually experience complete or near complete recovery around puberty and in most instances enjoy normal adult lives.[3 9] Only in a few cases was myopathy unremitting or even progressive.[4 12] In adult patients the generalised form of debrancher deficiency myopathy often takes a serious course. In some cases muscle weakness rapidly deteriorates, finally causing respiratory insufficiency or making the patient wheelchair bound (patient 3). Prognosis is further aggravated by comparatively high rates of advanced liver disease (table 2) or prominent neuropathy.[12 21 27] Unexpectedly, exercise induced muscle cramps and myalgia are uncommon and only exceptionally represent the main clinical features.[13 15] A residual capacity for glucose release from peripheral chains of glycogen by the action of phosphorylase and an upregulation of alternative energy sources such as ketone bodies and fatty acids may explain this phenomenon.

Dependent on the age of onset, the list of potential differential diagnoses includes muscle dystrophies, acquired myopathies, and especially polymyositis. Polymyositis shares several clinical and laboratory features with generalised debrancher deficiency myopathy, such as (markedly) elevated creatine kinase concentrations and fibrillation activity on EMG.

Minimal variant myopathy

In patients with primarily hepatic forms of debrancher deficiency neurological examination may show mild hypotonia and proximal or generalised muscle weakness (patient 4), which is sometimes not recognised by the patients affected. As in all other types of debrancher deficiency myopathy men are more often affected than women (ratio 2–4 to 1). Cases with minimal variant myopathies have repeatedly been described in the literature (table 2). Myopathic disease expression is either reversible, stable, or only slowly progressive but may become clinically relevant at higher ages when acquired gait disorders and diseases of fibroskeletal tissues limit compensatory resources. Prognosis primarily relies on the severity of liver dysfunction or cardiomyopathy. In rare instances, the minimal disease variant may convert into a predominantly distal or progressive generalised myopathy.

The aetiology of the prominent clinical variability in debrancher deficiency has not yet been fully elucidated. There is some evidence of a tissue specific control of debrancher enzyme expression which may be subject to specific mutations.[33] Apart from the well known genetic variability,[33–35] environmental factors such as nutrition may achieve some relevance.[36]

LABORATORY FINDINGS

If the diagnosis of debrancher deficiency is suspected, results of several laboratory tests may offer supportive evidence such as an insufficient rise of venous lactate after standardised ischaemic exercise of the forearm (95% of previous patients tested), a pathological glucagon test (100%) and a "diabetic" response to a standard oral glucose challenge (80%). Our patients and all previously published cases of debrancher deficiency myopathy had serum creatine kinase concentrations two to 45 times beyond the upper range of normal. Triglycerides, cholesterol, and urate concentrations are sometimes increased.

Electromyography may disclose pure myopathic changes (51%), predominant neuropathic features (6%), or a mixed pattern along with fibrillation activity (43%). Nerve conduction studies yield variable results depending on the clinical phenotype (table 2).

Muscle biopsy shows a vacuolar myopathy sometimes superimposed by slight neurogenic atrophy. The vacuoles are strongly positive on periodic acid Schiff staining (figure) and correspond to pools of subsarcolemal glycogen not limited by membranes in electron microscopy.[9] The overall content of glycogen with many short outer chains is variably raised. Biochemical analyses demonstrate a selective loss of debrancher enzyme activity. Measurement of glycogen concentrations and debrancher enzyme activity in erythrocytes or leucocytes represents a non-invasive alternative to muscle and liver biopsy and permits the correct diagnosis to be established in most cases.[23 37 38]

INVOLVEMENT OF OTHER TISSUES

Evidence of cardiac involvement is found in four of five patients with type III glycogenosis, with the disease expression ranging from minor ECG abnormalities without clinical relevance to severe cardiomyopathy and congestive heart failure (<5%[17 39 40]). About one half of patients with adult onset debrancher deficiency myopathy have manifest liver disease or report childhood hepatomegaly, whereas in patients with juvenile manifestation of disease symptomatic liver involvement is an almost obligatory finding (table 2). Less than 10% of patients with hepatic dysfunction develop hepatoma or progressive liver cirrhosis.[7 40 41]

THERAPEUTICAL APPROACHES

A high protein diet may be efficient in reversing growth retardation and improving muscle strength in childhood glycogenosis type III.[7 12 36] Effects of dietary measures on myopathies in adults are less well established. In our series, patient 2 had subacute severe myopathy of respiratory muscles; she required prolonged mechanical respiration and recovered completely after a high protein diet. Slonim *et al* reported a dramatic response of generalised debrancher deficiency myopathy on administering a high protein diet in two adult patients.[12]

Conclusions

Debrancher deficiency myopathy is a heterogeneous disease with various distinct clinical phenotypes and age at onset ranging from 1 to 62 years. It may be regarded as a chameleon among neuromuscular disorders, capable of mimicking muscle dystrophies, inherited metabolic and acquired myopathies, polyneuropathies, and even motor neuron disease. A history of childhood hepatomegaly or hypoglycaemia or a mixed EMG pattern may help establish the correct diagnosis, whereas normal creatine kinase largely rules out this type of glycogen storage disease. The current study intends to increase awareness for this probably under diagnosed and potentially treatable disease. Most patients with juvenile onset and some patients with adult onset debrancher deficiency benefit from a high protein diet.

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