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Short reports

Dicarboxylicaciduria and secondary carnitine deficiency in glycogenosis type IV

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SUMMARY A 3 year old boy developed an unusually mild form of glycogen storage disease type IV. Metabolic investigations showed severe abnormalities of fatty acid and carnitine metabolism. A muscle carnitine deficiency was found. Treatment with L-carnitine orally led to a notable improvement in muscle strength.

The patient was first seen at the age of 16 months with hepatosplenomegaly and hypotonia. The liver was 4 cm and the spleen 2 cm below the costal margin. Mental development was normal but motor development was severely retarded. Tendon reflexes were weak. Hypotonia was generalised but most pronounced in the legs. The child could not sit unsupported and could not stand up or walk. Computed tomography of the brain, electromyography, electrocardiography, and echocardiography all yielded normal results. Laboratory tests showed mild liver dysfunction (serum glutamic oxaloacetic transaminase activity 186 U/l and serum glutamic pyruvic transaminase activity 67 U/l). Low free and total plasma carnitine concentrations were found (table). Results of other laboratory tests were normal. No evidence of a metabolic disorder was found. Liver and muscle biopsy specimens were taken. In the liver micronodular and macronodular cirrhosis was found; periodic acid Schiff positive material which was fairly resistant to diastase was present in the hepatocytes. Electron microscopic studies showed abnormal glycogen deposits in the cytoplasm. In the muscle only mild non-specific changes were seen, but no abnormal accumulation of glycogen was found.

The combination of the clinical findings of hepatosplenomegaly and disturbed muscle function and the histological finding of glycogen storage in the liver led to a diagnosis of glycogen storage disease type IV, which was confirmed by the finding of a branching enzyme deficiency in white cells (0·5 nmol glucose-l-phosphate/min/mg; control value (n=3) 237–355) and in cultured fibroblasts (58 nmol glucose-l-phosphate/min/mg; control value (n=9) 490–1300).

At the age of 22 months high concentrations of ketone bodies and dicarboxylic acids were found in a

Table *Effect of different metabolic conditions on measurements of fatty acid metabolism*

	Plasma				*Urine*			
	Glucose (mmol/l)	*Carnitine (mmol/l)*		*β Hydroxybutyric acid (mmol/l)*	*Carnitine (μmol/mmol creatinine)*		*β Hydroxybutyric acid (mmol/l)*	*Dicarboxylic aciduria*
		Total	*Free*		*Total*	*Free*		
Aged 16 months, fasted for 10 h	4·5	21	8	Not done	56	7	Not done	Absent
Aged 22 months:								
Fasted for 10 h*					262	4	7·8	++++
Not fasted	3·6	39	27	0·48	19	2	0·01	Not done
Fasted for 16 h	2·4	22	4	1·73	84	6	2·07	+++
After treatment with L-carnitine for two months, fasted for 10 h	3·8	54	44	0·01	951	114	0·58	+

*Urine sample only.

morning urine sample (table). The patient was given a standard fasting test, which had to be stopped after 16 hours because of symptomatic hypoglycaemia. Low plasma concentrations of free carnitine were noted, in addition to dicarboxylicaciduria and ketonuria (table). Carnitine concentrations were measured in liver and muscle biopsy specimens. In the liver specimen total carnitine concentrations were normal at 6·8 nmol/mg non-collagenous protein (control value (n=3) 3·9–4·7). All the carnitine, however, was present in the form of the ester. In the muscle biopsy specimen severe carnitine deficiency was found: total carnitine concentration was 3·7 nmol/mg non-collagenous protein (control value (n=4) 13·0–19·3).

At the age of 26 months a diet rich in protein and low in fat was prescribed, with frequent meals being taken to prevent mobilisation of fatty acids. The diet was supplemented with L-carnitine 100 mg/kg/day. Within a month the boy had become more active and started to explore; muscle strength improved considerably. At the age of 33 months he could pull himself on to his feet and walk a few steps without support, but muscle strength was still mildly reduced. Fasting ketonuria and dicarboxylicaciduria had almost disappeared (table).

Discussion

Glycogen storage disease type IV is a rare recessively inherited disorder of glycogen metabolism caused by a deficiency of the branching enzyme; only about 20 other cases have been reported.[1] Clinical features include failure to thrive, hepatosplenomegaly, and early cirrhosis of the liver. Most patients die in their second year of life. The course of the disease in this patient was unusually mild as he was still well at the age of 3. McMaster *et al* suggested that neuromuscular abnormalities in these patients correlate fairly well with abnormal deposits of polysaccharides in skeletal muscle and in the central or peripheral nervous system or both.[2] In our patient, however, no abnormal storage of glycogen was found in the muscle tissue.

Ketosis with dicarboxylicaciduria and a tendency to fasting hypoglycaemia has been described in other types of glycogen storage disease but has not been reported before in patients with type IV disease.[3] The profile of the urinary dicarboxylic acids was typical of ketotic dicarboxylicaciduria.[4] It reflects the excessive flux of fatty acids through the β oxidation pathway in these patients, who are not able to use glycogen stores as a buffer for glucose homoeostasis during fasting. The high ratios of ester carnitine to free carnitine in plasma and liver are also compatible with these findings. Two factors may have contributed to the carnitine deficiency in muscle[5]: the increased urinary excretion of carnitine as acylcarnitine esters, resulting from the excessive intramitochondrial beta oxidation of fatty acids (table), and the reduced endogenous synthesis of carnitine by the liver due to liver cirrhosis. The improvement in muscle strength after starting the treatment with carnitine was rewarding. Our findings suggest that muscle carnitine deficiency is an important cause of muscle weakness in patients with glycogen storage disease type IV.

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