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Short Communication

Ethylmalonic Aciduria Associated with Progressive Neurological Disease and Partial Cytochrome *c* Oxidase Deficiency

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Persistent excretion of elevated amounts of ethylmalonic acid (EMA) with or without concomitant acylglycinuria is a relatively frequent finding during selective screening for inborn errors of metabolism in our laboratory. One is struck by the number of cases within this group that show similar clinical features: muscular hypotonia, motor retardation, ataxia, spastic diplegia or tetraparesis develop gradually after febrile infections with vomiting and somnolence. In 3 out of 20 patients initially observed, in whom we have succeeded in obtaining the appropriate material, partial cytochrome *c* oxidase (COX) deficiency (McKusick 220110) was detected in muscle biopsies.

CASE REPORTS

Development of the girl (Bo,Ba) was uneventful up to 4 years of age. Then, after febrile infection with vomiting and somnolence, slight spasticity of both legs occurred. This progressed after a viral infection at the age of 6 years. Ten years later, following gastroenteritis with apathy and somnolence, she developed spastic paraparesis of the legs. Apart from acquired paralexia her mental development was normal. Investigation of urinary organic acids revealed persistently elevated excretion of EMA and acylglycines (Table 1). Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) (lactic acid concentration in the brain was elevated) suggested Leigh disease. Deficiency of short-chain (SCAD), medium-chain (MCAD) and multiple (MAD) acyl-CoA dehydrogenases were ruled out. Activity of COX was reduced considerably in fresh muscle tissue (Table 1).

In a second (male) patient (Ca,Ce) psychomotor retardation was noticed at the age of 7 months. Later, atactic gait (3 years) and spastic diplegia (9 years) occurred. At the age of 13 years spastic tetraparesis with considerable dysarthria was documented. Selective screening for organic acidurias revealed constantly elevated excretion of EMA. Acylglycines were detected only occasionally in slightly elevated amounts (Table 1). From these findings, MRI (characteristic lesions of basal ganglia) and MRS investigations (elevated concentrations of lactate in these regions), Leigh disease was diagnosed. COX activity in frozen muscle tissue was clearly reduced (Table 1).

Table 1 Excretion of EMA and acylglycines and muscle COX activity in 3 patients with COX deficiency and in controls

Patient	*EMA*	*IBG*[a]	*2MGB*[b]	*IVG*[c]	*COX activity* (mU/mg protein)	
		(mmol/mol of creatinine)			*Fresh supernatant*	*Frozen homogenate*
Bo,Ba	34	11–32	–	14–36	27	
Ca,Ce	34	4.5	–	3.4		17
Be,Sa	156–880	116	15	57		9.8
Controls	1–16	0.5–3.8	0.2–4.5	0–4.5	68–437	52–186

[a]IBG = *N*-isobutyrylglycine
[b]2MBG = *N*-2-methylbutyrylglycine
[c]IVG = *N*-isovalerylglycine

Patient Be,Sa was admitted at $2\frac{1}{2}$ months of age because of microhaematuria, glucosuria, and enteritic symptoms (without pathogenic agent). No other clinical or laboratory abnormalities were detected at that time. Metabolic screening revealed considerable EMA-uria (Table 1). Development of neuromuscular disease was predicted from these findings. As the clinical signs disappeared and known renal diseases had been excluded, the girl was discharged. EMA excretion, however, increased during the following months. At the age of 5 months Reye-syndrome-like disease with severe convulsions occurred and progressive motor retardation developed. EMA-uria continued to be high and acylglycine excretion increased as well. Electron-microscopic and histochemical investigations of a muscle biopsy performed elsewhere yielded completely normal results (also in respect to COX activity). Enzymatic studies in frozen muscle tissue, however, revealed pronounced COX deficiency (Table 1). The child died at the age of 16 months.

METHODS

Organic acids were separated, detected and quantitated by gas chromatography–mass spectrometry. All respiratory chain enzymes were investigated in muscle tissues as described previously (Trijbels et al 1988).

RESULTS AND DISCUSSION

Table 1 summarizes the results of urinary metabolite and muscle enzyme investigations. Until now there has existed a great deal of uncertainty concerning the diagnostic value of excretion of small but constantly elevated amounts of EMA (Duran et al 1983). During recent years we have learned to appreciate EMA, with or without concomitantly elevated excretion of short branched-chain acylglycines, as a sensitive indicator for progressive neuromuscular disorders. At this time we are aware of more than 50 such patients in 3 of whom we have detected COX deficiency so far.

Previously only isolated cases with neuromuscular disease, EMA-uria and COX deficiency (along with other defects like cytochrome *c* reductase and long-chain acyl-CoA dehydrogenase deficiency, respectively) have been described (Hoffmann et al

1990; Reichmann et al 1992). Recently a case very similar to our patients with EMA excretion, acylglycinuria, and muscular COX deficiency has been presented (Christensen et al 1993). Three patients with EMA-uria, acylglycinuria, progressive neuromuscular disease and chronic diarrhoea described recently (Burlina et al 1991) were supposed to suffer from a new but not yet confirmed branched-chain acyl-CoA dehydrogenase deficiency. However, the suggested link between branched-chain acylglycine and EMA formation, used to support this assumption, is incorrect because oxidative decarboxylation of 2-keto-3-methylvaleric to 2-methylbutyric acid is known to be irreversible. Perhaps these patients also have COX deficiency that has not been excluded. All these examples show that a urinary organic acid profile as seen here is specific neither for variant forms of MAD (Mantagos 1979) nor for SCAD deficiency (Turnbull et al 1984; Amendt et al 1985). Clearly it occurs also in certain cases of COX deficiency.

EMA is known to be formed by carboxylation of butyryl-CoA. Alternatively, it may originate from the allo-isoleucine R-pathway. At the moment we are not able to offer a well-founded explanation for the correlation between COX deficiency and urinary metabolite pattern. Perhaps lack of sufficient amounts of oxidized cofactors (NAD^+, FAD) leads to accumulation of short-chain acyl-CoA derivatives that are either conjugated or carboxylated and excreted. The nature of the disease in our patients seems to be different from common COX deficiency with lactic acidaemia and gross lactric aciduria. This may in part explain the difficulties in detecting the defect in patient Be,Sa histochemically. Because of the complexity and the dual genetic control of COX, heterogeneity of clinical phenotype is to be expected. Investigations at the molecular level are needed for further clarification.

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