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Decreased Plasma Ubiquinone-10 Concentration in Patients with Mevalonate Kinase Deficiency

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ABSTRACT. Patients with mevalonate kinase deficiency suffer from psychomotor retardation, ataxia with progredient cerebellar atrophy, and myopathy. The pathophysiology of the disease remains unclear. The mevalonate kinase product, cholesterol, is within the normal range in patient plasma and fibroblasts. In search of the pathophysiology of this disorder, another mevalonate kinase product, ubiquinone-10, was studied. The concentrations of ubiquinone-10 in patient plasma ($n = 6$) and ubiquinol-10 in patient LDL ($n = 2$) and the synthesis of ubiquinone-10 in patient fibroblasts ($n = 4$) were determined. After oxidative modification of LDL by copper *in vitro*, the concentrations of α-tocopherol and polyunsaturated fatty acids in LDL and the relative electrophoretic mobility of LDL were measured to determine the antioxidant capacity of LDL samples of two affected siblings. The ubiquinone-10 concentrations in plasma samples (median = 508 μg/L, range = 488–642 μg/L) *versus* controls (median = 613 μg/L, range = 564–809 μg/L; $p < 0.005$) were decreased. In LDL samples of two affected siblings, the concentration of ubiquinol-10 and the resistance to oxidation *in vitro* were found decreased during intercurrent patient crisis condition. In patient fibroblasts (median = 533 dpm/mg protein, range = 399–1 047 dpm/mg protein) *versus* controls (median = 40 731 dpm/mg protein, range = 12 774–54 739 dpm/mg protein), the synthesis of ubiquinone was found to be decreased. We conclude that mevalonate kinase deficiency leads to a decreased synthesis of ubiquinone-10 and that ubiquinone-10 deficiency is responsible for the clinical progression of this disease characterized by increased lipid peroxidation, cerebellar atrophy, cataract development, and myopathy with increased creatine kinase activity. (*Pediatr Res* 34: 129–133, 1993)

Abbreviations

HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A
Rf, relative electrophoretic mobility

Mevalonic aciduria is an autosomal recessive disease caused by a defect of the mevalonate kinase gene (1–3) on chromosome 12 (4). The enzyme mevalonate kinase is involved in the synthesis of cholesterol and several nonsterol isoprenes such as ubiquinone-10, also known as coenzyme Q_{10} (Fig. 1) (1, 5).

Clinical manifestations begin in early childhood and progress with great variability of severity and organ involvement (1, 6–9). In 10 patients, we observed psychomotor retardation (10 of 10), myopathy (nine of 10), ataxia (five of nine), failure to thrive (nine of 10), hepatosplenomegaly (six of 10), dysmorphic features (five of 10), and cataracts (three of 10). Neuroradiologic and postmortem investigations revealed extensive cerebellar atrophy (five of nine) with a marked progression during the first years of life. Creatine kinase activity in plasma was frequently increased (six of nine). Most patients suffered from episodic crises characterized by fever, nausea, diarrhea, and weakness. Some patients exhibited mucocutaneous rashes, edema, and arthritis.

In patients with mevalonate kinase deficiency, the concentrations of mevalonate in plasma and urine are markedly elevated (1, 3). Despite the mevalonate kinase deficiency, cholesterol concentration in patient serum (1, 2, 7, 9) and fibroblasts (10) is normal or only slightly reduced, and the pathophysiology of this disease remains unclear.

Therefore, we investigated another important product of mevalonate kinase, ubiquinone-10 and ubiquinol-10, the reduced form of ubiquinone-10, which have a protective effect on the antioxidant α-tocopherol (vitamin E) (11–13). Ubiquinol-10 has been described as one of the potent antioxidants within LDL (13). To test whether the ubiquinone-10 concentration is decreased in patients with mevalonate kinase deficiency, we determined ubiquinone-10 concentrations in plasma as well as the synthesis of ubiquinone-10 in cultured fibroblasts. Ubiquinol-10 concentration and antioxidant capacity of LDL samples of two patients were also investigated.

MATERIALS AND METHODS

Patients and statistical analysis. Investigations were carried out on samples from nine patients (four boys, five girls; median age = 2 y, range = 0.3–7 y), as listed in Table 1, and healthy controls.

Values are given as mean ± SD or as median with the range. Statistical analysis was performed using the Mann-Whitney U test.

Ubiquinone-10 in plasma. Ubiquinone-10 concentration in plasma samples from untreated patients with mevalonate kinase deficiency (two boys, four girls; patients AB, BB, AA, BA, BC, and C; median age = 3 y, range = 0.3–7 y; Table 1) and from healthy children (10 boys, nine girls; median age = 2 y, range = 0.1–8 y) was determined by reverse-phase HPLC using a C-18

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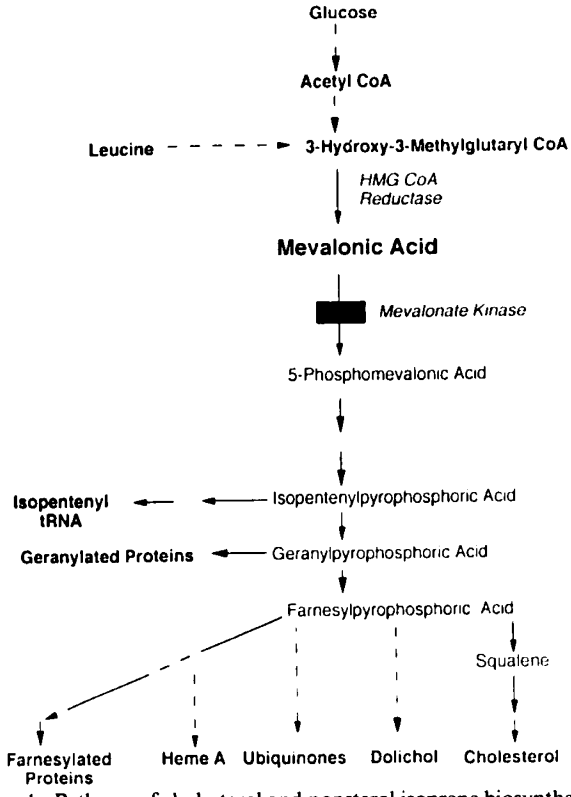

Fig. 1. Pathway of cholesterol and nonsterol isoprene biosynthesis (1, 5). The position of the defective mevalonate kinase in mevalonic aciduria is indicated by the *black rectangle.*

Table 1. *Patient group from which blood and fibroblast samples were taken for analysis**

Patient	Gender	Patient age (y) at collection of specimens: Plasma	LDL	Fibroblasts
AA†	F	5	6	
AB†	M	4	5	2
BA†	F	7		
BB†	M	2		
BC†	F	0.3		
C	F	3		
D	M			1
E	M			0.3
F	F			0.3

* $n = 9$; five females and four males.
† Two siblings of family A and three siblings of family B.

column (150 × 4 mm, 5 μm; Nucleosil, France) (14). Ubiquinone-10 was detected by UV light absorption (λ = 275 nm) and quantified using an external standard (ubiquinone-10, Sigma Chemical Co., Deisenhofen, Germany) (Table 2 and 3).

α-Tocopherol and ubiquinol-10 in LDL. α-Tocopherol in LDL from two affected siblings (patients AA and AB, Table 1; one boy, one girl; 5 and 6 y, respectively) and from healthy children (five boys, three girls; median age = 7 y, range = 5–9 y) was measured by HPLC (15). Quantities as low as 0.02 μg (46 pmol/injection) could be detected (Table 3; Fig. 2).

Ubiquinol-10 concentrations in lipid extracts (16) from LDL samples of the two affected siblings (AA and AB, Table 1) and of healthy children (two boys, three girls; median age = 5 y, range = 5–14 y; Table 3) were determined by reverse-phase HPLC using a Lichrospher RP-18 column (150 × 4 mm, 5 μm; E. Merck, Darmstadt, Germany) and a Hewlett-Packard 1049A Electrochemical Detector (amperometric mode; Hewlett-Packard, Andover, MA) set to a potential of 0.8 V (0.5 μA full scale).

Table 2. *Mevalonate concentration, creatine kinase activity, and ubiquinone-10 concentration in plasma samples from untreated patients with mevalonate kinase deficiency and from healthy control subjects*

	Mevalonate (μmol/L)	Creatine kinase (U/L)	Ubiquinone-10 (μg/L)
Four* of six patients			
Median	53	307	495†
Range	38–141	118–510	488–519
Two‡ of six patients			
Range	66–81	3–13	568–642
Controls			
Median	0.03		613
Range	0.01–0.04	3–80	564–809
n	10		19

* Patients AA, AB, BC, and C (see Table 1).
† Patient *vs* control values, $p < 0.002$; Mann-Whitney U test.
‡ Patients BA and BB (see Table 1).

Table 3. *Concentrations of ubiquinone-10, ubiquinol-10, and α-tocopherol in plasma and LDL samples of two siblings with mevalonate kinase deficiency (patients AA and AB, Table 1) during an episodic crisis condition with fever, nausea, diarrhea, and weakness and out of such a crisis condition under different drug therapies**

Patient during (+) or out of (−) crisis	Ubiquinone-10 in plasma (μg/L)	Ubiquinol-10 in LDL (pmol/mg total cholesterol)	α-Tocopherol in LDL (pmol/mg total cholesterol)
AA† (+)	537	ND	4 411
AB† (+)	560	ND	<46
AB† (−)	525	ND	8 823
AA‡ (−)	684	ND	21 593
AB‡ (−)	675	ND	10 448
AB§ (+)	675	<4	48 293
AA§ (−)	976	182	28 094
Controls			
Median	613	68	7 198
Range	564–809	30–143	1 161–12 538
n	19	5	8

* ND, not determined.
† Without treatment.
‡ Treated 1 mo p.o. with 30 mg α-tocopherol/kg body wt/d.
§ Treated 1 mo p.o. with 30 mg α-tocopherol/kg body wt/d, 116 mg ascorbic acid/kg body wt/d, and 3.5 mg ubiquinone-10/kg body wt/d.

The mobile phase consisted of ethanol:methanol = 1:1 with 2 g/L LiO_4Cl and 1 g/L acetic acid (E. Merck). It was delivered by a Merck L6000 HPLC pump with a flow rate of 1 mL/min. For data acquisition, a Merck D2500 Integrator was used. Quantification was performed by external standardization. The ubiquinol-10 standard was freshly prepared from ubiquinone-10 (bovine heart, Sigma Chemical Co.) as described by Lang *et al.* (17). Quantities as low as 0.4 pmol/injection (*i.e.* 4 pmol/mg LDL cholesterol) could be detected.

Ubiquinone and dolichol biosynthesis in fibroblasts. Skin fibroblasts (five to 14 passages) from patients with mevalonate kinase deficiency (three boys, one girl; patients AB, D, E, and F; 0.3–2 y of age; Table 1) and of three healthy age- and gender-matched controls were investigated. The ubiquinone and dolichol synthesis was estimated by measuring the metabolic flux of R-[5-^{3}H]-mevalonolactone (New England Nuclear, Boston, MA) through the mevalonate pathway (1, 5) in the presence of lovastatin (18). Radiolabeled intermediates were separated by phenol:chloroform and petroleum ether extraction (18, 19). Deviating from the method originally described by Maltese and Aprille (18), cells were incubated for 21 h (37°C), and delipidated FCS was used

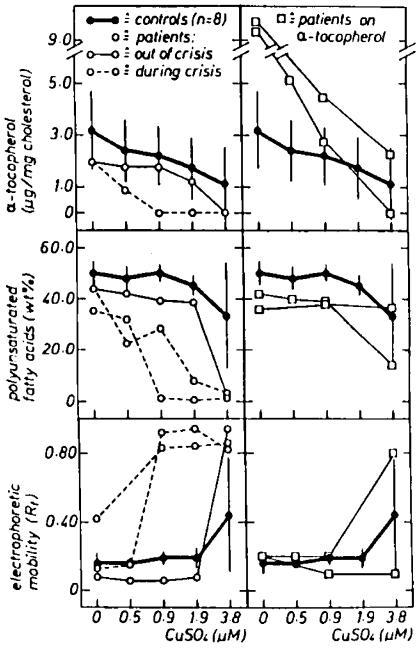

Fig. 2. Autooxidative modification of LDL by incubation in a serial dilution of $CuSO_4$ (*horizontal axis*) (20, 21). LDL samples were taken from healthy children and from two siblings with mevalonate kinase deficiency (patients AA and AB; Table 1).

in a final concentration of 10% (2). After two-dimensional, thin-layer chromatography of concentrated petroleum ether extracts, products were localized by iodine staining and quantified by liquid-scintillation spectrometry. In our experimental assay, discrimination of the dolichol region from the ubiquinone region was not possible.

Oxidative modification of LDL. LDL from two affected siblings (one boy, one girl, patients AA and AB, 5 and 6 y of age, respectively; Table 1) and from healthy children (five boys, three girls; median age = 7 y, range 5–9 y) were isolated by density-gradient centrifugation (20). Blood samples were obtained from the siblings during a crisis condition with fever, nausea, diarrhea, and weakness. A second sample was taken from one sibling without such a crisis condition (patient AB in Table 1). Further blood samples were taken after 5 mo of oral substitution with α-tocopherol (30 mg/kg body wt/d).

LDL suspension was diluted by PBS (without Ca^{++} and Mg^{++}, pH 7.3; Sigma Chemical Co.) to reach a final LDL cholesterol concentration of 0.85 mg/mL (Cholesterin Monotest, Boehringer Mannheim, Mannheim, Germany). Oxidative modification of LDL was achieved by incubation (37°C) of the LDL suspension in serial dilutions of Cu^{++} ($CuSO_4$, M_r 249.68; E. Merck) for 18 h as indicated on the horizontal axis in Figure 2 (20, 21).

Fatty acids of LDL were determined by capillary gas chromatography (20) (Fig. 2). Rf of LDL and oxidatively modified LDL was assessed on 0.83% agarose gels (20) (Fig. 2). The Rf value is defined as the distance of the LDL spot center from the starting point divided by the according distance of the bromophenol-blue–stained solvent front.

Mevalonic acid. Mevalonate concentrations in plasma samples were determined using a stable isotope dilution assay and capillary gas chromatography-mass spectrometry with both electron impact and ammonia chemical ionization (3).

RESULTS

In plasma samples of six patients (patients AA, AB, BA, BB, BC, and C; Table 1) with mevalonate kinase deficiency, the concentration of mevalonic acid was highly increased (Table 2). In four (patients AA, AB, BC, and C; Table 1) of these six patient plasma samples, ubiquinone-10 concentration was decreased, and creatine kinase activity was increased (Table 2). In two samples, plasma ubiquinone-10 concentration and creatine kinase activity were within the normal range (Table 2). These two normal plasma samples were obtained from two affected siblings (patients BA and BB, Table 1) who had a third affected sibling with pathologic plasma values (patient BC; Table 1).

Concentrations of ubiquinone-10 in plasma and α-tocopherol in LDL were determined in two siblings (patients AA and AB; Table 1) with mevalonic aciduria under different clinical and therapeutic conditions (Table 3). Ubiquinone-10 and α-tocopherol concentrations increased under simultaneously administered oral substitution with ubiquinone-10, α-tocopherol, and ascorbic acid (Table 3).

Ubiquinol-10 was determined in LDL samples taken from the two sibling patients (patients AA and AB; Table 1) only after treatment with ubiquinone-10, α-tocopherol, and ascorbic acid. One patient (patient AB; Table 1) was in an episodic crisis condition, whereas his sister (patient AA; Table 1) was not. In the female sibling, who was not in a crisis condition, ubiquinol-10 in LDL was elevated in response to the oral ubiquinone-10 substitution. However, the girl's brother, who received the identical oral treatment with ubiquinone-10 but who suffered from a crisis condition, had a markedly decreased LDL-ubiquinol-10 level when compared with his sister or with control values (Table 3).

Quantification of the common chromatography region of dolichol and ubiquinone revealed a considerably lower biosynthetic activity in patient fibroblast extracts (median = 533 dpm/mg protein, range = 399–1 047 dpm/mg protein; $n = 4$; patients AB, D, E, and F; Table 1) as compared with control values (median = 40 731 dpm/mg protein, range = 12 774–54 739 dpm/mg protein; $n = 3$).

LDL was isolated and oxidatively modified by copper ($CuSO_4$) incubation *in vitro* (Fig. 2). In LDL samples isolated from healthy control children ($n = 8$), increasing concentrations of $CuSO_4$ resulted in continuously decreasing concentrations of α-tocopherol (values of native LDL *versus* respective values of LDL after oxidation by 3.8 μM Cu^{++}: $p < 0.03$; Fig. 2) and polyunsaturated fatty acids and increasing electrophoretic mobility of the LDL on agarose gel. At the copper concentration of 3.8 μM Cu^{++}, the SD of determined values increased because some of the control LDL samples were already oxidatively modified, whereas other control LDL samples with a greater antioxidant capacity were not (Fig. 2). These results clearly indicate a decrease in antioxidant capacity of LDL in controls, which is followed by the consumption of α-tocopherol, lipid peroxidation, and thus the peroxidative degradation of polyunsaturated fatty acids (21). The increased Rf of LDL on agarose gel indicates increased negative surface charge of the oxidatively modified LDL, presumably due to a modification of apo B (21).

In the two patient siblings (patients AA and AB; Table 1) with mevalonic aciduria, LDL samples were obtained during an episodic crisis condition with fever, nausea, diarrhea, and weakness (Fig. 2). A decrease in the content of polyunsaturated fatty acids was observed in these samples after incubation in only very low concentrations of Cu^{++} (0.9 and 1.9 μM; Fig. 2). α-tocopherol content of one LDL sample (patient AA; Table 1) dropped from a normal level to undetectable values after incubation in only 0.9 μM Cu^{++} (Fig. 2). In one of the two patients, blood was obtained for LDL analysis when the patient was out of crisis condition (patient AB; Table 1). Substantial LDL oxidation was observed at 3.8 μM Cu^{++} (Fig. 2), similar to normal control values.

After oral substitution of the two patient siblings (patients AA and AB; Table 1) with α-tocopherol (30 mg/kg body weight/d over 5 mo), the susceptibility of patient LDL to peroxidative damage was normalized (Fig. 2). Under this therapy, α-tocopherol concentration of patient LDL was triple normal values. Nevertheless, LDL-associated α-tocopherol was rapidly con-

sumed by challenge of LDL with increasing doses of Cu^{++} (Fig. 2).

DISCUSSION

Ubiquinone-10 concentration was found decreased in four (patients AA, AB, BC, and C; Table 1) of six patient plasma samples (Table 2), suggesting liver involvement (22, 23) in mevalonate kinase deficiency. This is supported by the above-mentioned clinical sign of hepatosplenomegaly and by the single observation that ubiquinone-10 concentration was also decreased in liver tissue (11.9 μg ubiquinone-10/g wet weight *versus* 17.1 and 17.2 μg/g in two gestational age-matched controls, respectively) obtained from an aborted fetus (19 wk of gestation) with mevalonate kinase deficiency (1, 3). The data indicate a ubiquinone-10 deficiency in patients with mevalonate kinase deficiency.

Further support for this notion comes from the finding of a decreased ubiquinone-10 and dolichol synthesis in cultured skin fibroblasts isolated from four patients with mevalonate kinase deficiency (patients AB, D, E, and F; Table 1). In our experimental assay, discrimination of the dolichol region from the ubiquinone region was not possible. However, the data suggest a primary ubiquinone-10 deficiency due to mevalonate kinase deficiency (Fig. 1). This is in contrast to findings in mitochondrial Kearns-Sayre syndrome with similar clinical signs and similarly decreased plasma ubiquinone-10 concentration but normal ubiquinone-10 synthesis in fibroblasts (24).

Considerable amounts of ubiquinone-10 have been found in human brain cortex and cerebellum (25). Ubiquinols are potent antioxidants in synaptosomes from brain gray matter (26), and investigations on rodents revealed that the cerebellum is the brain region most vulnerable to lipid peroxidation (27, 28). These findings suggest that the described clinical signs of psychomotor retardation, as well as progredient cerebellar ataxia and atrophy in mevalonic aciduria patients, are related to a ubiquinone-10 deficiency in the brain. The single finding of decreased ubiquinone-10 concentration in brain tissue (188 μg ubiquinone-10/g wet wt *versus* 255 and 263 μg/g in two gestation-age-matched controls, respectively) obtained from the above-mentioned aborted fetus with mevalonate kinase deficiency (1, 3) is consistent with this hypothesis. Increased susceptibility to oxidative stress may also account for the observed cataract formation (29) and myopathy in these patients.

The enzyme HMG-CoA reductase immediately precedes mevalonate kinase in the pathway (Fig. 1). Drugs that inhibit HMG-CoA reductase decrease the plasma concentration of cholesterol but also of ubiquinone-10 (30). Treatment with these HMG-CoA reductase inhibitors can lead to side effects, such as myopathy with increased plasma creatine kinase activity (31). Creatine kinase release from myocytes is related to lipid peroxidation and activation of the phospholipase A_2 pathway within the sarcolemma (32, 33). In light of this concept, it is notable that in two of our six patients (BA and BB; Table 1) with normal ubiquinone-10 plasma concentration, the creatine kinase activity was also normal (Table 2), and in the four patients (AA, AB, BC, and C; Table 1) with decreased ubiquinone-10 plasma concentration, the creatine kinase activity was increased (Table 2). No explanation can be given to date for the normal creatine kinase and ubiquinone-10 plasma data in two (BA and BB; Table 1) of three patient siblings (BC is a third sibling; Table 1).

Using the well-established method of copper-induced oxidative modification of LDL (20, 21), an increased susceptibility to oxidative attack could be observed in LDL taken from two siblings with mevalonic aciduria within crisis condition with fever, nausea, diarrhea, and weakness (patients AA and AB; Table 1). A normalized antioxidative capacity was found in an LDL sample taken from one (patient AB; Table 1) of the two affected siblings out of crisis condition (Fig. 2). These results are consistent with the concept of ubiquinone-10 deficiency leading to an unstable ubiquinol-10 concentration in LDL of mevalonic aciduria patients. This notion is supported by the demonstration that α-tocopherol levels were within lower normal ranges in native LDL of patients during and out of crisis condition (Table 3), but decreased more rapidly than in controls during oxidative modification of an LDL sample taken from a patient (patient AA; Table 1) during crisis condition (Fig. 2). Moreover, the enhanced α-tocopherol concentrations in LDL samples taken from patients (AA and AB; Table 1) treated with vitamin E and the sharp decrease of α-tocopherol concentration in these LDL samples under oxidation (Fig. 2) indicate an increased consumption of α-tocopherol in patient LDL, probably as a second step after ubiquinol-10 consumption (13). Unfortunately, we lack data on ubiquinol-10 concentration in LDL samples *in vitro* (Fig. 2) as well as in native LDL samples *ex vivo* of untreated patients (Table 3). We could find a drastic decrease of ubiquinol-10 concentration in LDL taken from one patient (patient AB; Table 1) during a crisis condition, despite oral substitution with α-tocopherol, ubiquinone-10, and ascorbic acid, whereas the ubiquinol-10 concentration in LDL taken from an affected sibling (patient AA; Table 1) under identical conditions, but out of such a crisis condition, was not decreased compared with control values (Table 3). We assume that a decrease of ubiquinol-10 is involved in the pathophysiology of the episodic crises that are a most characteristic feature of the disease.

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