Letter to Editor

Sir,

In a recent article, Smith et al.\(^1\) reported four siblings with coenzyme-Q deficiency (CoQD) due to the COQ\(_9\) variants c.521 + 2T>C and c.711 + 3G>C who all died between 19th and 34th week of gestation. We have the following comments and concerns.

CoQD may be associated with epilepsy.\(^2\) Seizures may occur even intrauterinely.\(^3\) Did any of the four siblings develop seizures during pregnancy or during the period of extrauterine life? Was the family history positive for epilepsy or seizures? Did the pregnant mother ever observe excessive fetal movements during any of these four pregnancies?

CoQD may be associated with lactic acidosis.\(^4\) However, only in two of the four siblings were serum lactate levels documented (29 and 23 mmol/L, respectively), without providing the reference limits. Was serum lactate in these two patients elevated or normal? Also, were the lactate levels determined in the cerebrospinal fluid (CSF) by either CSF investigations or magnetic resonance spectroscopy?

In patient 3, thickening of the myocardium at the age of 29 weeks is reported.\(^1\) However, echocardiography after Caesarian section was described as normal.\(^1\) How to explain this discrepancy? Did the patient receive cardiac treatment between these two cardiac investigations? Was the family history positive for cardiac compromise?

Interestingly, patients 1 and 3 had fixed flexion contractures of the elbows at birth.\(^1\) Congenital joint contractures are frequently associated with reduced intrauterine movements. Were fetal movements indeed reduced in these two patients? Did the patient present with myopathy? Were there reduced limb movements due to quadriplegia from cerebral involvement?

CoQ not only transfers electrons from complex-I to complex-II and complex-III of the respiratory chain, but also serves as an electron carrier in the reaction catalyzed by the sulfide:quinone oxidoreductase (SQR), which catalyzes the first reaction in the hydrogen sulfide oxidation pathway.\(^5\) Thus, CoQD may lead not only to oxidative phosphorylation defects but also to altered mitochondrial sulfide metabolism.\(^5\) Reduced SQR activity secondarily leads to reduced serum glutamate, serotonin, and catecholamine levels.\(^5\) Were there any indications in the four siblings for glutamate deficiency, serotonin deficiency, or Addison’s disease?
The patient with CoQD due to a COQ9 variant described by Duncan et al.[6] developed hypertrophic cardiomyopathy. However, postnatal cardiologic examinations in the four presented siblings were described as normal, except for patient 1 who had dilated ventricles and pulmonary hypertension.[1] Particularly, there were no indications for hypertrophic cardiomyopathy.[1] How to explain this cardiac phenotypic heterogeneity?

The case described by Duncan et al.[6] had also developed renal tubular dysfunction. Were there any indications for renal insufficiency or Fanconi’s syndrome in the four presented siblings? Were renal cysts in patient 2 regarded as renal involvement?

In summary, this interesting study confirms that CoQD due to COQ9 mutations is a multisystem disease, affecting the cerebrum, the heart (cardiomyopathy and arrhythmias), the kidneys (cysts, Fanconi’s syndrome, and insufficiency), the hematopoietic system, the muscle, the bones (dysmorphism), and the endocrine organs (short stature). Cerebral involvement dominates and includes epilepsy, dystonia, spasticity, hypotonia, basal ganglia calcification, symmetric gray matter lesions, bleeding, hydrocephalus, episodic hypopnea or apnea, and cerebellar atrophy.

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Conflicts of interest
There are no conflicts of interest.

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