Mitochondrial diseases represent a risk factor for valproate-induced fulminant liver failure


Abstract: We report on 3 siblings (2 females and 1 male) with chronic progressive external ophthalmoplegia (CPEO), compatible with inherited mitochondrial cytopathy. The younger of the two sisters died at the age of 37 due to progressive respiratory failure. The older one presented with a status epilepticus at the age of 39 and was treated with valproate. Five months after the start of treatment, she developed fulminant liver failure and died. The brother has suffered from CPEO since early childhood but has had so far no other symptoms of a mitochondrial disease. A muscle biopsy from the younger sister revealed ragged-red fibers and decreased activities of complex I and IV of the respiratory chain but no pathogenic mutations in the mitochondrial tRNA genes or in several locations in the coding region of the mitochondrial genome. In the older sister’s liver (obtained post-mortem), mitochondrial DNA was fragmented and could not be investigated. The clinical presentation and the biochemical findings suggest that all 3 siblings suffered from a mitochondrial dysmyopathy. Since mitochondrial cytopathies and valproate-induced fulminant liver failure are both rare events, an association between them is likely. Mitochondrial diseases should therefore be considered as a risk factor for valproate-induced liver failure and be excluded before treatment with valproate.

Valproate (VPA) is a branched-chain fatty acid composed of eight carbons used widely as an anti-epileptic. Shortly after its introduction, several cases of fulminant liver failure have been reported in patients treated with this drug (1–4). In a retrospective study, Dreifuss et al. (3) identified young age and concomitant treatment with other antiepileptics such as phenytoin, carbamazepine or phenobarbital as risk factors for fulminant liver failure. It is interesting to note that, all patients reported so far with VPA-induced liver failure and older than 10 years, were treated with VPA in combination with other antiepileptics.

The typical histological findings, namely microvesicular steatosis accompanied by necrosis of hepatocytes (2), suggest that inhibition of hepatic mitochondrial β-oxidation is a principal cause of VPA-induced liver failure (5). Since VPA is activated to valproyl-CoA, depletion of the hepatic pool of free CoA represents a potential mechanism (6). Another mechanism may be direct inhibition of mitochondrial β-oxidation by metabolites of VPA, for example, 2-n-propyl-4-pentenoic acid (Δ1-VPA). Δ1-VPA is generated by a cytochrome P450-mediated reaction (7) and has been shown to inhibit mitochondrial β-oxidation (6). A third possible mechanism is a decreased activity of complex IV of the respiratory chain, a finding shown to be associated with long-term administration of VPA in rats (8).

Since the frequency of VPA-induced fulminant liver failure is low, approximately 1:5,000 in children and 1:20,000–40,000 in adults (3), other factors not yet recognized may also be important. It has recently been proposed that pre-existing mitochondrial diseases, e.g. impaired β-oxidation and/or impaired function of the respiratory chain, may represent a risk factor for VPA-induced mitochondrial dysfunction, in particular for liver failure (9, 10). If this concept is true, it has important clinical implications, since patients should be screened for such diseases before therapy with VPA is started. In support of this view, we present three siblings with a mitochondrial disorder and
Valproate-induced liver failure

Table 1. Activities of enzyme complexes of the respiratory chain in skeletal muscle. Activities were determined spectrophotometrically as described previously (12). Control values (mean ± 95% confidence interval from n = 8 control samples) are given in parentheses. Activities of complex I and IV are reduced

<table>
<thead>
<tr>
<th>Enzyme complex (oxidoreductase)</th>
<th>Absolute value (µmol/min/g wet weight)</th>
<th>Relative to citrate synthase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex I (NADH:ubiquinone-1)</td>
<td>0.26 (2.16 ± 0.99)</td>
<td>0.034 (0.29 ± 0.15)</td>
</tr>
<tr>
<td>Complex II (succinate:dichloroindo-phenol)</td>
<td>0.57 (0.29 ± 0.18)</td>
<td>0.075 (0.038 ± 0.026)</td>
</tr>
<tr>
<td>Complex III (decylubiquinol:ferricytochrome c)</td>
<td>11.2 (5.66 ± 1.95)</td>
<td>1.48 (0.75 ± 0.35)</td>
</tr>
<tr>
<td>Complex IV (ferrocytochrome c:oxygen)</td>
<td>0.04 (1.43 ± 0.23)</td>
<td>0.005 (0.19 ± 0.06)</td>
</tr>
<tr>
<td>Citrate synthase</td>
<td>7.57 (8.57 ± 2.5)</td>
<td></td>
</tr>
</tbody>
</table>

one of them with VPA-induced fulminant liver failure.

Case reports

The patient with VPA-induced fulminant liver failure has already been described by us (11). This patient suffered from congenital bilateral ptosis and chronic progressive external ophthalmoplegia (CPEO) since childhood. At the age of 39, she developed a frontal status epilepticus and was treated with VPA and clonazepam. Clonazepam was subsequently stopped whereas VPA was continued. Four months later, she presented with progressive ataxia and became increasingly apathetic. Treatment with carbamazepine was started but had to be stopped after two weeks due to leukopenia. Two weeks later, she developed fulminant liver failure and died after one week due to multiorgan failure and hepatorenal syndrome. Histological examination of the liver revealed microvesicular steatosis and diffuse necrosis. Due to autolysis, liver mitochondrial DNA was fragmented and enzyme activities were low or undetectable. An underlying mitochondrial disease could therefore be suspected but could not be demonstrated definitively in this patient.

Interestingly, the younger sister suffered also from congenital CPEO. In addition, she had progressive cerebellar ataxia, axonal polyneuropathy, cognitive impairment and weakness of skeletal musculature. A muscle biopsy, obtained after her older sister had died, revealed ragged red fibers, abnormalities of mitochondrial shape and paracrystalline inclusions, indicating mitochondrial cytopathy. As shown in Table 1, activities of complex I and IV were reduced both as an absolute value and relative to citrate synthase (12), supporting the diagnosis of mitochondrial cytopathy. In DNA isolated from skeletal muscle of this patient, deletions and duplications were excluded by long PCR of the entire mitochondrial genome. Using this technique, we are able to detect mutated mitochondrial DNA at a level of less than 1% (13). Point mutations were searched by PCR, followed by single strand conformation polymorphism analysis (SSCP) and direct sequencing of polymorphic fragments (13). We analyzed all mitochondrial tRNA genes (considered as mutational “hot-spots”) and frequent pathogenic mtDNA point mutations located in coding regions (NARP 8993, LHON 11778, LHON 3460, LHON 14484). However, no pathogenic mutations could be detected in the mitochondrial genome of this patient. She finally died at the age of 37 from progressive respiratory failure despite treatment with ubiquinone and tocopherol.

The brother of these two patients suffers also from congenital bilateral ptosis but has so far not developed additional symptoms, and has not been investigated in detail for mitochondrial diseases. Their mother suffers from chronic depression and reports no typical symptoms of a mitochondrial disease whereas their father died from leukemia at the age of 61 years.

Discussion

Young age and antiepileptic polytherapy are well established risk factors for VPA-induced liver failure (3). Common antiepileptics such as phenytoin, phenobarbital and carbamazepine are inducers of the cytochrome P-450 enzyme system, favoring the microsomal formation of toxic VPA metabolites such as Δ4-VPA (7). However, even in children treated with antiepileptic polytherapy, fulminant liver failure is not more frequent than 1:5000 (3), suggesting that other factors, for example underlying metabolic diseases, may also be important.

Microvesicular steatosis, a typical finding in livers from affected patients, indicates mitochondrial damage such as impaired β-oxidation and/or function of the respiratory chain (5). Mitochondrial cytopathies (affecting the function of the respiratory chain and impairing mitochondrial β-oxidation indirectly) may therefore represent a risk factor for VPA-induced liver failure. All 3 siblings suffered from CPEO, a typical sign of mitochondrial cytopathies. The presence of a mitochondrial cytopathy was further ascertained in the younger one of the two sisters by the typical histological findings
and reduced enzyme activities in skeletal muscle. The fact that no mutations in the mitochondrial genome were found does not exclude this diagnosis, since not the whole genome was sequenced and mutations in the nuclear genome can also be responsible for this disease (14). Since both sisters and also their brother had similar symptoms, it is very likely that all three siblings suffered from an inherited form of a mitochondrial cytopathy which is normally transmitted by the mother (14).

Both mitochondrial cytopathies and fulminant liver failure are rare diseases, with a frequency in adults of less than 1:10,000 (3, 14). The combination of two rare diseases in the same patient suggests that there is an association between them. Our report therefore indicates that mitochondrial diseases represent a risk factor for fulminant liver failure in patients treated with VPA. To the best of our knowledge, this has so far been proposed only for children (9, 10), but not for adults.

Since fulminant liver failure has also been described in patients with mitochondrial cytopathies not treated with valproate (15–17), the possibility cannot be completely excluded that liver failure in the patient described was not caused by valproate. However, patients with mitochondrial cytopathies usually develop liver failure early in life and not in adulthood (15–17). The patient described in this study had no signs of liver disease before treatment with valproate (11) and also her siblings were not known to have liver disease. Based on these considerations, we believe that valproate most likely precipitated liver disease in the patient.

Our findings have important clinical implications. Before treatment with VPA is started, at least a careful family and personal history should be obtained and an accurate clinical investigation should be performed (14). Patients with findings compatible with a mitochondrial disorder (e.g. maternally transmitted myopathy, cardiomyopathy or encephalopathy) should either be excluded from treatment with VPA or be assessed more profoundly by histological, biochemical and genetic investigations. As demonstrated by our report, this is not only important in children, but also in adults.

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References