

Valproate-associated reversible encephalopathy in a 3-year-old girl with Pallister-Killian syndrome

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Abstract: Valproic acid (VPA) is considered to be a drug of first choice for the therapy of generalized and focal epilepsies, including special epileptic syndromes. The drug is usually well tolerated, rare serious complications may occur in some patients, including hemorrhagic pancreatitis, coagulopathies, bone marrow suppression, VPA-induced hepatotoxicity and encephalopathy. We report a case of VPA-associated encephalopathy without hyperammonemia in a 3-year-old girl with Pallister-Killian-Syndrom, combined with a mild hepatopathy and thrombopathy. After withdrawal of VPA, the clinical symptoms and the electroencephalography-alterations vanished rapidly.

Keywords: pallister-killian, valproate, encephalopathy, EEG, ammonia

Case report

Pallister-Killian syndrome is an extremely rare genetic disorder that occurs due to tetrasomy of the twelfth chromosome (tissue-limited isochromosome 12p). Symptoms include varying degrees of mental retardation, epilepsy, or hypotonia. Patients also exhibit a distinctive facial structure, characterized by high foreheads, sparse hair on the temple, a wide space between the eyes, a fold of skin over the inner corner of the eyes, and a flat nose. Patients may also exhibit congenital heart defects, gastroesophageal reflux, cataracts, and congenital diaphragmatic hernias (CDH).

Because of a prenatal diagnosed sinistral CDH, the first-born of healthy, noncon-sanguine parents was a patient in our intensive care unit. The patient was born in the 36th week of gestation with a birth weight of 2.74 kg. The hernia was closed five days after birth without any severe complications. However, after a period of 5 months, the child showed typical symptoms of a Pallister-Killian syndrome with focal seizures, hypotonia, and the characteristic facial features. The diagnosis was confirmed by detection in samples of skin fibroblasts.

Anticonvulsant therapy was initiated with oxcarbazepine (OCBZ) up to a level of 30 mg/kg/BW. The seizures stopped for the next 10 months, but the electroencephalography (EEG) still showed multifocal sharp-waves. At the age of 13 months, the seizures returned with focale myoclonias and atypical absences. We decided to add VPA to OCBZ and achieved complete seizure control with a VPA-level of 25 mg/kg/BW. The child didn't show any incompatibilities or side effects associated to the antiepileptic therapy. Before the VPA-therapy was started, extended laboratory tests (including metabolic disorder screenings) were done. This included disorders in amino acid, carbohydrate, beta-oxidation, urea-cycle, and carnitin metabolism.

At the age of 38 months the girl was presented at our emergency ward with increased seizure frequency, augmented fatigue, and vomiting. On examination the girl appeared moderately ill, but the mother was worried about a significant reduction in alertness and attention. The laboratory investigations showed slight changes

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in transaminases and decreased platelets. Additionally we found generalized slowing (theta-delta-activity) in the EEG, in contrast with former EEG findings. The serum-VPA-level was 90 mg/l, the serum ammonia showed normal levels (Table 1).

We immediately stopped the VPA medication but continued the antiepileptic therapy with OCBZ. In the course of the next ten days the medical condition as well as the laboratory findings improved. The EEG-pathologies normalized within 4 days after withdrawal of VPA.

The antiepileptic medication was continued with OCBZ and topiramate (TPM) in unmodified dosages. Although a few publications showed an increased risk of encephalopathy when VPA was combined with TPM (Longin et al 2002; Cheung et al 2005), there is only one paper that shows an increased risk of encephalopathy with TPM monotherapy in adults. Long-term inhibition of cerebral glutamine synthetase and TPM as an inhibitor of carbonic anhydrase, which leads to hyperammonemia because it restricts the path of the urea cycle were appointed as possible mechanisms (Fraser et al 1999; Latour et al 2004).

The focal slowing of the EEG vanished, the seizure frequency remained acceptable, and the girl's vigilance normalized.

Conclusion

In most cases, VPA is a well tolerated antiepileptic drug with high effectiveness in seizure control. Most of the side effects are mild and transient, but there are also rare, but severe side effects, especially hepatotoxicity (Koenig et al 2006), encephalopathy (Gerstner et al 2006a), coagulation disorders (Gerstner et al 2006b), pancreatitis (Gerstner et al 2007), and bone marrow suppression (Acharya and Bussel 2000; Kohli and Golsti 2006).

In our case of a two-year-old girl with Pallister-Killian syndrome, we found a combination of encephalopathy, thrombopenia, and slight hepatopathy associated with a VPA-therapy.

Interestingly, the girl received the VPA-therapy for about 2 years at the same dosage without any signs of encephalopathy. According to previous publications, VPA-associated side effects vanish rapidly under withdrawal of VPA (Gerstner et al 2006a). A chromosomal alteration due to the underlying syndrome in this patient wasn't ever described as a predisposition for a VPA (drug) associated encephalopathy.

Especially in mentally retarded patients, the physicians should show specific advertence to VPA-associated

Table 1 Overview of laboratory findings

	Laboratory findings while presented at the pediatric ward	Laboratory findings 10 day after
Valproic acid-level	90 mg/dl	–
Ammonia	16 µmol/l	–
ALAT/ASAT	73 U/l/ 63U/l	42U/l/ 45U/l
Lipase	133U/l	159U/l
Platelets	83000/µl	220000/µl
White blood cells	6500/µl	8900/µl
Red blood cells	hb 12.2g/dl, erythr. 3.45 Mill./µl	hb 12.1g/dl, erythr. 3,88 Mill./µl

problems. An overhaul of parameters like blood count, coagulation parameters, transaminases, ammonia, and pancreatic enzymes is necessary, the EEG could provide further indices of a VPA-associated encephalopathy. As shown here, VPA-associated encephalopathy could be presented without increased ammonia and with a lack of pronounced symptoms. Additionally, every new changes in transaminases, lipase, coagulation parameters or blood count is suspicious for a VPA-associated effect. The encephalopathy could appear with hyperammonemia, but also without hyperammonemia, possibly as a direct influence of VPA on neurotransmitters (Kwan and Brodie 2001). In this case, the encephalopathy is not related to the VPA plasma level. Another possible mechanism is direct neuronal toxicity induced by increased intracellular concentrations of glutamate and ammonium in astrocytes (Ricard et al 2005), which may lead to potential neuronal injury and perhaps cerebral edema (Verrotti et al 2002).

In consideration of this approach, the side effects vanish and the patients' outcome is proper. At this time, we do not understand why most patients never have any side effects related to VPA and why other patients show such a variety of side effects related to different mechanisms. Our patient emphasizes nevertheless that VPA-associated encephalopathy has to be looked for in any individual patient and that they may be totally reversible after withdrawal of VPA. Sometimes, the EEG is the only diagnostic criteria of finding the diagnosis.

From our case we can learn, that VPA-associated side effects can occur at any time of the VPA-therapy. Especially in psychomotoric retarded patients, the physicians should show specific advertence to VPA-associated problems. An overhaul of parameters like blood count, coagulation parameters, transaminases, ammonia and pancreatic enzymes is necessary, the EEG could provide further indices of a VPA-associated encephalopathy.

In case of such side effects, an immediate withdrawal is required and a supportive therapy with intravenous carnitine could be necessary, when signs of hepatopathy occur additionally.

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