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Case report

Valproic acid during pregnancy: Case report of a child with congenital malformations due to fetal valproate syndrome, and a high unbound serum level of valproic acid at birth

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ABSTRACT

We present a child in utero exposed to valproic acid with congenital malformations due to fetal valproate syndrome and with toxic effects. Directly postnatal, a high-unbound serum level of valproic acid was measured. The total serum level of valproic acid was in the therapeutic range. Measuring unbound serum levels during pregnancy and postnatal period in the child provides more information about real-time exposure than measuring total serum levels.

1. Introduction

Valproic acid (VPA) is a commonly used antiepileptic drug for juvenile myoclonic epilepsy. Superior efficacy of VPA compared to lamotrigine or topiramate was suggested in the Standard and New Antiepileptic Drugs (SANAD) trial.[1,2] Young women first diagnosed with juvenile myoclonic epilepsy and reaching the age of child-bearing potential are a challenging group to treat. Together with the patient a risk-benefit analysis should be performed by the neurologist to determine the right antiepileptic drug treatment.

The usage of VPA in women of child-bearing age is controversial due to the risk of major congenital malformations, withdrawal symptoms and poorer cognitive development later in life of the unborn child.[2,3] Spina bifida aperta, cardiovascular and urogenital malformations combined with skeletal defects and specific facial malformations, also called fetal valproate syndrome, are seen with VPA use during pregnancy.[3] Symptoms of withdrawal seen are irritability, jitteriness, abnormalities of tone, seizures, and feeding problems.[4] Alternative treatment options for VPA in juvenile myoclonic epilepsy are not always available or effective.[5] For women without the desire to become pregnant in the near future VPA treatment is a very effective treatment option when combined with effective contraception.[5]

If women become pregnant during VPA treatment stopping VPA is not always an option. Untreated epilepsy during pregnancy is associated with higher health risks for women and fetus.[3,6] Furthermore switching to another antiepileptic drug may cause additional risks of major congenital malformations and increase of maternal epileptic attacks.[5] The additional risk for maternal epileptic attacks due to stopping VPA before reaching the new steady state concentrations of the new antiepileptic drug is present.

VPA dosages and serum levels both as low as possible combined with the clinical assessment of the neurologist is a tool to optimize treatment during pregnancy. Hereby reducing the exposure of the unborn child.

We present a neonate, in utero exposed to VPA, with congenital malformations due to fetal valproate syndrome, withdrawal symptoms and toxic unbound VPA levels with a follow-up time of four years.

2. Case report

At the age of 11 years the mother was diagnosed with juvenile myoclonic epilepsy for which she received VPA. Seven years later,

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at 18 years, she had an unplanned pregnancy. At that time she used VPA 1000 mg twice daily. In the second trimester, after four months, the neurologist was informed. Considering that the embryonic phase of development had passed and organogenesis was finished VPA dosage was not adjusted. Therefore the risk for epileptic attacks with lower dosage was considered to be a higher risk than congenital malformation at that stage of the pregnancy.

After six weeks of gestation the mother started with folic acid (5 mg daily) prescribed by her general practitioner. At 36 weeks of gestation her gynecologist prescribed phytomenadione (10 mg daily).

No abnormalities were seen at the 18 and 26 weeks echo. No serum levels of VPA were obtained during pregnancy. The most recent VPA total serum level was 117 mg/L (reference 50–100 mg/L) nine months before conception.[9] The second last was 37 months before conception with total serum level of 83 mg/L (reference 50–100 mg/L) and unbound serum level of 14 mg/L (reference 5–10 mg/L) using the same dosage of 2000 mg/day. No albumin concentrations were available. Due to therapy resistance higher unbound and total serum levels were accepted. Dosage was determined based on clinical presentation and higher serum levels were deliberately accepted.

At 40 weeks a male child was born after uncomplicated vaginal delivery with a birth weight of 3095 gram. APGAR scores were 7 after one minute, 7 after five minutes and 8 after ten minutes. Because of postnatal groaning the child received PEEP (oxygen and positive end expiratory pressure ventilation) for a short period of time.

Physical examination revealed remarkable major congenital malformations of the head such as trigonocephaly due to stenosis of sutura metopica and plagiocephaly, combined with facial dysmorphic features such as deformed and small ears, epicanthic fold, long philtrum, small lips, and high-arched palate (Fig. 1). Furthermore inverted nipples, hypospadias and cryptorchidism, long fingers and toes with syndactyly at the right hand and both feet were observed.

Laboratory results showed an albumin level of 22 g/L (reference 24–39 g/L). Valproic acid levels were measured immediately after birth. Total VPA serum level was 76 mg/L (reference 50–100 mg/L). The unbound serum level was increased, i.e. 17 mg/L (reference 5–10 mg/L).

The neonate was observed at the neonatal department and received 1 mg phytomenadione. During the first day of his life the child showed hypoglycemia, tremors and apneas with decrease in saturation and bradycardia, due to withdrawal. After administration of oxygen and positive end expiratory pressure ventilation these parameters recovered to normal. After 24 hours he was transferred to the neonatal intensive care unit of the children's hospital for further examination. Due to decrease in saturation, cerebral function monitoring was performed, showing no abnormalities. Echocardiography showed no cardiac abnormalities except atypical structure of the aorta without clinical signs of

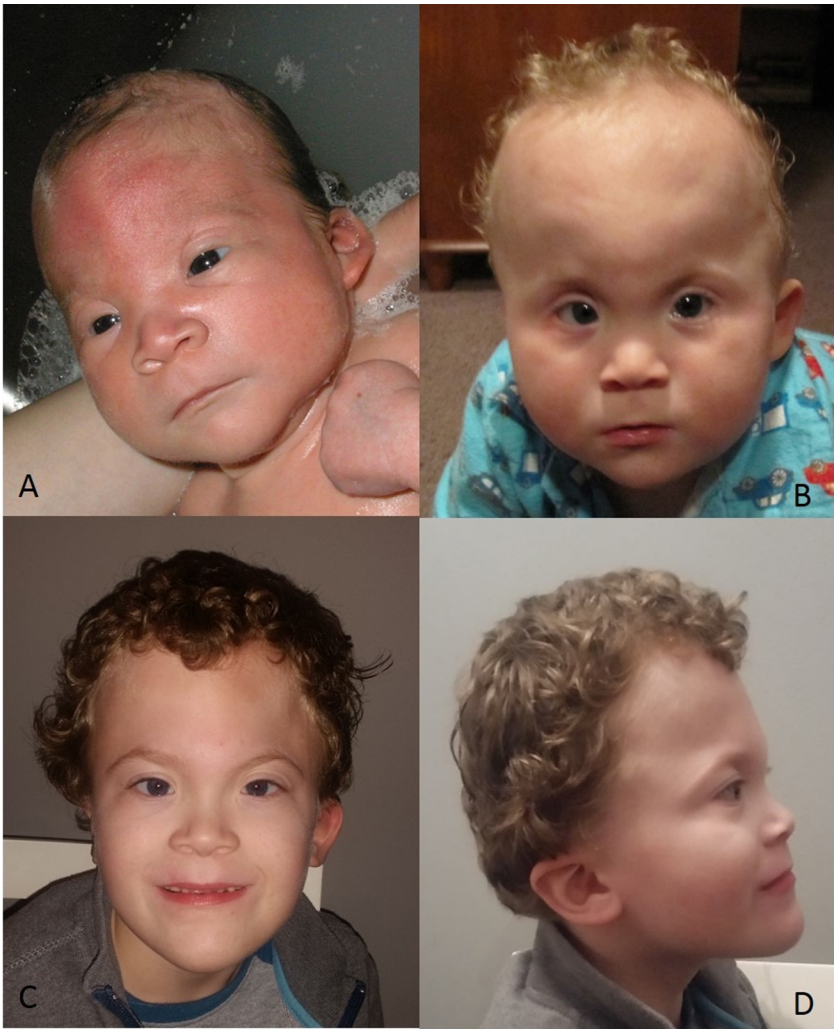

Fig. 1. Patient at the age of 3 days (A), 1 year and 11 months (B) and 8 years and 10 months (C, D). Informed consent for these photographs has been obtained.

coarctatio aortae. Feeding problems such as difficulty and sloppy drinking were observed during the first days. Sixteen days after birth he was discharged in good clinical condition.

In the first two years of life the craniosynostosis of sutura metopica was operated. Strabismus occurred for which an ophthalmologist was consulted for specialized glasses.

At the age of three years the child developed convulsions, diagnosed as myoclonic epilepsy and treated with VPA (280 mg/day). In the course of several months the dosage was increased to 600 mg/day. At age of four years psychomotor retardation was observed with reduced motor skills and speech and language development disorder. At age of six years autism was diagnosed with a developmental age of two years and three months according to the Bayles Scales of Infant Development. His development has not improved until his present age of eight years and ten months.

3. Discussion

In this case report major and minor congenital malformations, toxic effects and withdrawal symptoms were observed in a neonate with a high unbound serum level of VPA after in utero exposure.

The general risk of major congenital malformations for neonates exposed in utero to VPA ranges from 6.2–17.4%.[3] The combination of congenital malformations and specific facial features seen in fetal valproate syndrome are described in Table 1, including the comparison with the congenital malformations found in the child.[7,8,10–13]

The high unbound serum level in the child is related to the high dosage VPA of 2000 mg/day used by the mother during pregnancy. Tomson et al. found a relation between the dosage of VPA and the occurrence of major congenital malformations. Twenty four percent of the infants of mothers using VPA dosage higher than 1500 mg had major congenital malformations compared to 11.0% for dosage below 1500 mg.[13] Similar risks of 11.1% were found for dosage below 700 mg elsewhere.[10] These percentages are higher than the general risk for major congenital malformations of 2.3%.[5] Kaneko et al. found an increased risk for major congenital malformations at dosage above 1000 mg/day or total serum levels above 70 mg/L.[14] Due to the large interindividual difference seen with VPA dosage, serum levels can give more information regarding real-time exposure compared to dosage alone.[15]

Table 1
Congenital malformations associated with VPA usages during pregnancy.

Fetal valproate syndrome[11,20]	Observed in case
Neural tube defects	–
Congenital heart disease	–
Cleft lip and palate	High-arched palate
Genitourinary malformations	Cryptorchidism
Tracheomalacia	–
Radial ray defects	Long toes and fingers, partial syndactyly of the fourth and fifth digit of the right hand
Overlapping digits and abdominal wall defects	–
Trigonocephaly	Trigonocephaly due to stenosis of sutura metopica and plagiocephaly
Tall forehead with bifrontal narrow wing	–
Epicanthic folds	Epicanthic fold
Infraorbital groove	–
Flat nasal bridge	–
Broad nasal root	–
Anteverted nares	–
Shallow philtrum	Long philtrum
Long upper lip with thin vermilion border	Small lips
Thick lower lip and small downturned mouth	–
Hypospadias	Hypospadias
–	Inverted nipples
–	Deformed and small ears

In the mother the VPA unbound serum level before pregnancy was 14 mg/L (reference 5–10 mg/L) and the total serum level 83 mg/L (reference 50–100 mg/L) while using 2000 mg/day. No serum levels were obtained during pregnancy. During pregnancy serum levels of VPA change due to several reasons, i.e. the effect on albumin concentrations, hepatic metabolic activity and glomerular filtration. An increase in unbound VPA serum levels occurs due to a decrease in albumin with 10 g/L.[10,11] VPA binds for approximately 90% to albumin. At the end of the third trimester of pregnancy VPA metabolism is increased due to increase in liver activity, most likely due to increased glucuronidation.[10,12] Up to 50% VPA decrease in the last weeks of pregnancy have been found in other studies,[10,12] however no significant changes were found in unbound serum levels due to simultaneous decrease in albumin concentration.[12] The effect of increasing glomerular filtration during pregnancy on the serum levels will be minor due to the fact that less than 5% of the VPA is excreted unchanged by the kidneys.[10,15] The described mechanisms affect the total and unbound serum levels of VPA,[12] resulting in the necessity to measure VPA levels during pregnancy to maintain adequate serum levels.

Unbound VPA is known to cross the placenta leading to high exposure in the unborn child. Levels in umbilical cord serum may range from 0.52 to 4.6 times the levels in maternal serum.[11] In our infant an unbound serum level of 17 mg/L (reference 5–10 mg/L) and total level of 76 mg/L (reference 50–100 mg/L) were measured directly after birth. This potential toxic unbound VPA serum level might explain the major congenital malformations and toxic effects found. The relatively high ratio of unbound/total of 22.4% might be explained by the low albumin concentration of 22 g/L in the infant (normal ratio approximately 10%).[9]

No clear evidence is available to support routine use of TDM of antiepileptic drugs including VPA.[16] Some individuals require VPA levels outside the standard reference range.[14] In a systematic review authors concluded that TDM of classic antiepileptic drugs can lead to better seizure control with fewer side effects in a cost effectiveness manner.[17] TDM can be useful in situations of compliance issues, drug-drug interactions, unexplained seizures persist or toxicity and specific patient populations.[14] Pregnant women are such a specific group. The pregnancy-induced pharmacokinetic changes combined with great inter-individual variability and exposure of the unborn child are the main reasons for therapeutic drug monitoring during pregnancy.[15,18–21] The Dutch Society of Neurologist also recommends TDM including unbound levels during pregnancy.[22]

In this case report, a pregnant woman presented herself to her neurologist after 4 months of gestation. After careful consideration VPA was continued in the same dose. The organogenesis was completed at the time of presentation and the risk of developing epileptic attacks and this additional risk for the unborn child were reasons to continue VPA.

4. Conclusion

If valproic acid is used during pregnancy we strongly recommend therapeutic drug monitoring of valproic acid levels. Both total levels and unbound levels should be monitored. Also VPA levels before pregnancy need to be measured. High VPA exposure in the early stage of pregnancy during organogenesis is to be avoided. We suggest monthly measurements during pregnancy. At the end of the pregnancy toxic unbound serum levels of mother and therefore of the neonate are to be avoided to prevent toxic effects during the first days of life of the neonate.

Conflicts of interest

The authors have none to declare.

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