A case of fetal valproate syndrome with new features expanding the phenotype.

To the Editor

I read the interesting case report by Seidahmed et al,[1] on a case of fetal valproate syndrome (FVS) with new features expanding the phenotype. The authors, substantially added new phenotypes to what is already known on FVS. I have 3 comments regarding the aforementioned case report.

First, it is well-known that the common treatment strategy for a pregnancy, with epilepsy, has been to use the appropriate anticonvulsant drugs (ACDs), as monotherapy in the lowest effective dosage throughout pregnancy. The objective, is to use ACDs in such a way that generalized tonic-clonic seizures are avoided, but with minimized risks to the fetus, newborn, and breast-fed infant.[2] Exposure to ACDs, in particular valproate, in the first trimester of pregnancy, has been associated with an increased risk of major congenital anomalies in offspring.[3,4] The increase in valproate risk of major congenital anomalies compared with other ACDs, is dose-dependent, and especially evident at doses above 800-1000 mg/day.[4] The United Kingdom registry reported a higher malformation rate with valproate 5.9% (4.3-8.2%; 95% confidence interval), than with carbamazepine 2.3% (1.4-3.7%), and lamotrigine 2.1% (1-4%).[5] Moreover, retrospective and a few small prospective studies suggest that the exposure to valproate also might be associated with a lower verbal intelligence quotient (IQ) at school age, but further prospective studies are needed to draw firm conclusions.[6] Neurologists and gynecologists must be aware of the potential teratogenicity of ACDs in pregnancy, in particular valproate, and caution in prescribing should be practiced. The risks benefits ratio of these drugs during pregnancy, and their aftermaths on the fetus, neonates, and breast fed-infants, and future neuro-development need to be addressed.

Second, the aforementioned case report clearly demonstrated the marked phenotypes of FVS, but it must be kept in mind that the diagnosis must not solely rely on facial characteristics, particularly if the history of prenatal valproate exposure could not be documented. In one study,[7] nearly half (45%) of children born to mothers with epilepsy who did not receive ACDs, in particular valproate, during pregnancy, had some of the facial features associated with ACDs exposure indicating that, many of these features might be seen as part of normal variation, and that the diagnosis of the fetal anticonvulsant syndrome is difficult to make on the basis of facial gestalt alone.

Third, the ongoing extended phenotypes of FVS might indicate that, it is a heterogenous constellation of dysmorphic features. Undetermined molecular mutations, differential valproate dose exposure, physiologic immaturity, certain environmental factors, time over which polymorphism initiated in early life, and other factors could proportionally interact to continuously expand the dysmorphic phenotypes of FVS.

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Reply from the Author

With reference to the comments by Prof. Al-Mendalawi on our paper; "A case of fetal valproate syndrome with new features expanding the phenotype."[1] I would like to respond by the following comments: We thank Prof. Al-Mendalawi for his well-taken comments.

As pointed out in our paper, the mother of the propositus was on sodium valproate 1500 mg per day as monotherapy, the dose was reduced to 1000 mg per day throughout pregnancy, so she was still on a dose high enough to have teratogenic effect (800-1000 mg/day). As regarding the association of fetal exposure to valproate and low verbal IQ at school age, our case is a 4-year old, I saw her in my clinic, she seemed to be developing normally, on her speech and cognitive functions, we will perform IQ testing when she is in school age. She is still exhibiting the wide-spaced nipples and short neck, the new features, which we added to the phenotype. Regarding the second comment, we agree with Prof. Al-Mendalawi, that the facial characteristics are not pathognomonic to the diagnosis of fetal valproate syndrome. We did not base our diagnosis on the facial gestalt alone, but the presence of major limb defects "radial ray reduction" together with the facial features prompted us, to make the diagnosis of FVS, in the presence of maternal exposure to teratogenic dose of valproate taken as monotherapy before and after conception.

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