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CASE REPORT

ABSENSE OF SUPERIOR LIMBS IN A FETUS OF A MOTHER EXPOSED TO TOPIRAMATE

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ABSTRACT

Topiramate is a new-generation pharmacological agent, used to treat partial and tonic-clonic epileptic seizures in adults and children, alone or in combination with other drugs, and as a prophylaxis of the migraine1. It also can be used in the treatment of some pathologies such as alcoholism, obesity and bipolar disorder2. In the last years, several cases of congenital malformations and restrictions in the intrauterine growth in fetuses of mothers exposed to Topiramete have been published3. We expose a clinic case of an amyelia of superior members in a fetus of a mother treated with Topiramate during the first trimester of the pregnancy, with no other possible causes related.

Key words: Topiramate, Malformation, Upper limbs (Source: MeSH NLM)

INTRODUCTION

Proper monitoring of the mother and fetus from the first weeks of pregnancy is key to reducing maternal-fetal risks and morbidity, especially in women who use potentially teratogenic drugs. Currently, it is estimated that 1 in every 250 newborns in Spain has suffered intrauterine exposure to antiepileptic drugs; This group of neonates has a higher risk of malformation, with an incidence 2-3 times higher than that of the general population. (1-3) Possible complications include intrauterine growth retardation, craniofacial and digital abnormalities, and neural tube defects (4,5). This risk is influenced by different factors, with the type of antiepileptic drug, the dose and the concentration in fetal plasma being some of the conditions with the greatest impact (6). For the specific case of Topiramate, a literature review was published in which an increased risk of palatal closure defects was confirmed, affecting 5 out of every 1000 fetuses of pregnant women exposed to this drug in the first trimester (2,7). In September 2023, the Spanish Agency for Medicines and Medical Devices (AEMPS) published a statement warning of the risk of this drug and its possible effects on the fetus (1).

We present the case of a 30-year-old pregnant woman, exposed during the first 11 weeks of pregnancy to 50 mg of Topiramate daily, whose fetus presents agenesis of the upper limbs, with no other identifiable causes that explain this malformation.

CASE PRESENTATION

We present the case of a 30-year-old patient, with a voluntary interruption of pregnancy in the first pregnancy, with the date of last menstrual period (FUR) August 28, 2023. As a history of interest, he presented a diagnosis of binge eating syndrome and difficulty in impulse control of several years of evolution, managed by his primary care physician (MAP) with Topiramate 50 mg daily, at night, and Fluoxetine 40 mg daily, in the morning. In October 2023, in the 11th week of gestation, the patient contacts her MAP to inform her that she is pregnant, at which time the interruption of topiramate is indicated due to its potential teratogenic risks.

The pregnant woman presented a deficient control of the pregnancy in the first weeks, without performing the standardized screening of chromosomal diseases and preeclampsia of the first trimester, producing the first contact in our center in the 20th week of gestation, when she went for the morphological ultrasound.

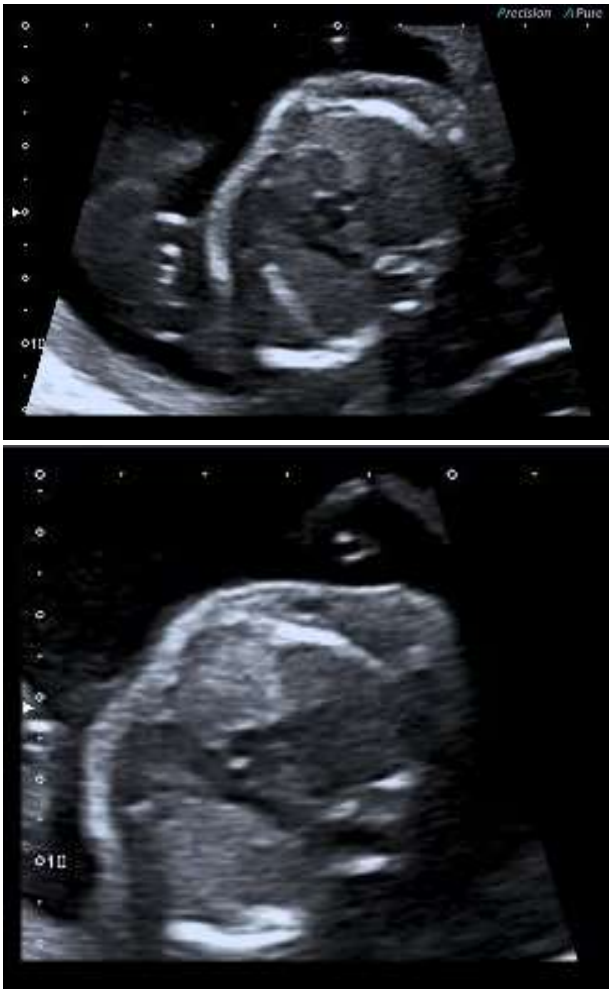

Figure 1. Total absence of both upper limbs

At week 20+3 days, the ultrasound study of the second trimester was carried out, showing a single fetus, with spontaneous active movements. Fetal biometrics are based on 20+5 weeks, with an estimated fetal weight of 378g. The umbilical cord, placenta and amniotic fluid are not apparent. During the fetal anatomical study, the total absence of both upper limbs was detected, with the presence of left and right scapulae, but without humerus (**Figure 1**). The rest of the structures studied, including the skull and face, heart, thoracic cavity, abdominal wall,

kidneys, liver, spine, lower limbs and external genitalia, corresponding to the female sex (**Figure 2**), did not present ultrasonographically visible malformations.

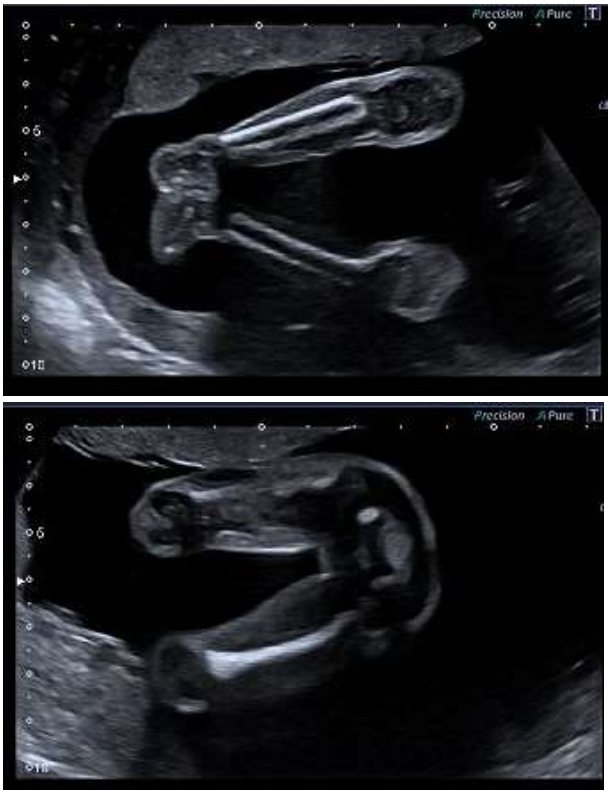

Figure 2. Lower limbs

The findings are explained to the patient and her companion, as well as the possibility of performing an invasive test for genetic study, but the pregnant woman freely decides to interrupt the pregnancy due to the malformation. During this visit, a blood draw is also carried out for the analysis of the basic serologies of pregnancy, as well as the spectrum of irregular antibodies (IAS), blood group and thyroid screening. The results obtained were:

- Serologies: negative for toxoplasma, syphilis, human immunodeficiency virus, and hepatitis B and C viruses.
- EAI: Negative
- Blood group: 0+
- Thyroid screening: TSH 1.11 g/dL

Once the decision to discontinue has been made, the patient signs the informed consents and the relevant administrative procedures are initiated. The surrogate mother is scheduled 72 hours later to perform the procedure. At the time of admission, 2 mifepristone tablets are placed vaginally, 400 mg in total; At 36 hours, 800 mcg of misoprostol is administered vaginally and then 400 mcg of misoprostol is administered every 3 hours, receiving a total of 3 doses. Subsequently, the patient goes into labor and fetal expulsion and placental delivery occur without incident (**Figure 3**). Fetus and placenta are referred to Pathological Anatomy for necrotic study. The puerperium was uneventful and after 24 hours of admission for observation, the patient was discharged.

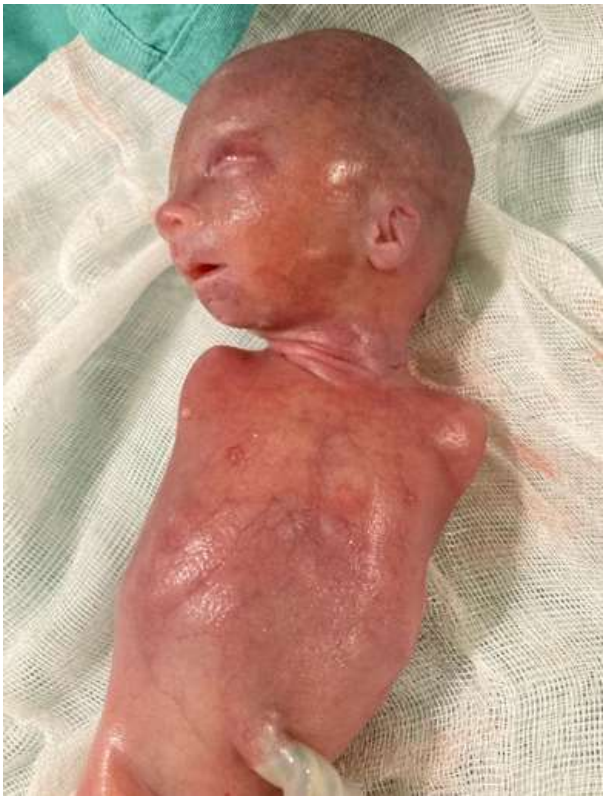

Figure 3. Fetus in Pathological Anatomy

DISCUSSION

Topiramate is a monosaccharide with a sulfamate group. It was initially developed for the treatment of diabetes mellitus thanks to its hypoglycemic action, but since the 90s it has been used as an antiepileptic agent. It acts by acting on the glutamate and carbonic anhydrase receptors of the voltage-dependent potassium, calcium and sodium channels of the neuron, where it modulates the action of the GABA receptor and increases the flow of chloride ions into the cell. Currently, its therapeutic indications are diverse, including partial

seizures, generalized epilepsy, bipolar disorder and other psychiatric disorders, as well as the prophylaxis of migraine attacks.

At the animal level, its effect on fetal growth has been proven, producing growth defects and delayed bone maturation, as well as malformations at different levels of the limbs (3).

At the human level, it has the ability to cross the placenta, and the presence of the drug in the umbilical cord has been described in the same concentrations as in maternal blood (5), presenting dose-dependent adverse effects (3). In fact, studies show the presence of the drug even in the puerperium, up to 3 weeks after delivery, both in blood and in breast milk, proving a relationship between plasma and milk concentration, with an elimination of up to 23% of the maternal daily dose through milk (8).

The safety note published by the AEMPS warned of a possible increased risk of neurodevelopmental alterations, including a greater likelihood of autism spectrum disorders, intellectual disability, attention deficit hyperactivity disorder, as well as an increased risk of congenital malformations and intrauterine growth defects (1), which is why the AEMPS currently recommends avoiding topiramate during pregnancy. except in cases for which there is no other therapeutic alternative (1). In non-pregnant women of childbearing age who are to be treated with topiramate, the use of a dual method of contraception, combining a hormonal method and a barrier method, is recommended during treatment and up to 4 weeks after discontinuation (1). It is important to emphasize the recommendation to use the barrier method since it has been proven that the effectiveness of hormonal contraceptives decreases during topiramate due to competition for cytochrome P450 (1) during its metabolism. Before starting to take topiramate, it is recommended to carry out a pregnancy test, as well as to inform of the associated risks in case of pregnancy.

In the case of breastfed newborns of mothers treated with up to 200mg of topiramate, adverse effects such as diarrhea, drowsiness, irritability, and inadequate growth have been reported (2,8).

The study of the risks derived from fetal exposure to topiramate dates back to the last years of the twentieth century, and its findings were collected by the working group of the American Journal of Obstetrics and Gynecology (7), in a meta-analysis in which several studies were included. One of them compared 785 cases of cleft lip and 6986 control cases, detecting a 10 times higher risk of developing this malformation in the group of patients exposed to the drug. Another of the included studies included 2283 cases of cleft lip compared to 8494 controls, evidencing a 3.4 times higher risk (7).

In the case described above, it has not been possible to prove a causal agent or other antecedents favoring the fetal malformation other than maternal exposure to topiramate, so the use of the drug is established as a possible cause of limb agenesis, given the health alerts published by the different scientific societies, and the cases previously published in the literature.

In conclusion, topiramate is a drug of the group of antiepileptics, used for the treatment of different neurological and psychiatric pathologies. Its use has been related to fetal malformations at different levels, so it is currently contraindicated in pregnant women and a highly effective contraceptive method should be used in patients of childbearing age who are exposed to it. During breastfeeding, there is also a risk to the neonate as it is excreted by breastfeeding in dose-dependent amounts.

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Contributions:

All authors: Literature review, translation of articles, analysis and discussion of information, writing of the document, review, correction and approval of the manuscript.