SIDE EFFECT OF DEPAKINE: A CASE REPORT

Danielius Serapinas*

Mykolas Romeris University, Lithuania.

ABSTRACT
Holt-Oram syndrome is caused by TBX5 gene mutation. This condition is characterized by skeletal abnormalities of the hands and arms (upper limbs) and heart problems. The TBX5 gene mutation can be confirmed through molecular genetic testing. A case report of Holt-Oram syndrome is represented when mother has been taking a Depakine (valproic acid) during pregnancy.

INTRODUCTION
Holt-Oram syndrome (HOS) includes a number of symptoms associated with upper extremities (hands and arms) and cardiac abnormalities. Therefore, this syndrome is also known as hand-heart syndrome (Heart-hand syndrome). It was found that HOS leads TBX5 gene mutation [1-3]. This syndrome occurs in 1 in 100 000 individuals, and is inherited in autosomal dominant way in 85% cases. It also has been attributed to de novo mutations [4]. TBX5 gene is found on chromosome 12q24.1. It belongs to the T-box gene family and acts as a transcription factor, which is important in cardiogenesis and limbs formation. For gene mutation produced abnormal three-dimensional structure of a protein that is unable to perform his functions, or suspended protein synthesis [2-5]. TBX5 The most common gene mutations are missense, nonsense, deletion or local structural gene on chromosome rearrangement, for example gene inversion:
• Missense – point DNA mutation that by which the altered nucleotide replaces one amino acid codon to another amino acid codon;
• Nonsense – point DNA mutation, where one altered nucleotide replaces an amino acid codon to stop codon on the mRNA synthesis is stopped prematurely;
• Deletion - mutations that set is lost in a DNA sequence or part of the chromosome [6]. During normal embryogenesis TBX5 gene product T-box protein is responsible for the development of hand, heart growth, especially atrioventricular partition separating the left and right part of the heart formation. Also, the T-box protein affects the cardiac conduction system development [7].

As a result, in the event of mutation, leading to the HOS, as some sort of syndrome-specific symptoms. Holt-Oram syndrome clinical signs. Holt-Oram syndrome is characterized by the offense of the upper limbs, the heart of the anatomic structure and the conduction system. Upper limb disorders can be clearly seen during the inspection or required them to identify the radiography. Deformities of the hands and arms are on one or both sides, symmetrical or not. More frequent abnormal forearm and finger position, different wrist bones, radius, thumbs developmental disorders, such as triphalangial thumb or his lack of combinations. It may be limited shoulder joint movements. In rare cases, the HOS during limb malformations may be high when the upper limb portion will not develop and the only visible part of the reduced limbs. This is called phocomely. Structural cardiac malformations occur in 75 percent individuals with HOS. Generally in the form of heart atrial (atrioseptal) and ventricular (ventriculoseptal) septal defect, the size, the location and number can be varied. Malformations of the heart disrupts its normal function, causing it to certain syndromes.
Tetralogy of Fallot, which includes a ventricular septal defect, aortic change location of the pulmonary trunk stenosis and right ventricular hypertrophy. Cardiac conduction disorders is characterized by a slowdown in the rate or acceleration - bradycardia or tachycardia. There are also varying degrees of atrioventricular (AV) block, which, over time, can progress to complete AV block. Cardiac conduction disorders are possible and where there is no structural cardiac abnormalities, or they may occur in older age[2]. As a result, it is recommended to periodically check the heart ECG and ultrasound tests.

Holt-Oram syndrome is characterized by a combination of clinical signs are very different, so it was investigated what determines one or other phenotypic manifestation. The literature data [5] of the HOS phenotype and mutations local connection indicates that changes in protein closer to the N-terminus result in higher cardiac malformations, and, on the contrary, closer to the C-end leads to more changes in limb malformations. This means that the HOS clinical signs of the emergence of a significant impact on TBX5 gene product, transcription factor and its target sites of interaction.

Holt-Oram syndrome diagnosis

Holt-Oram syndrome is diagnosed based on clinical signs and is confirmed by molecular genetic testing. Clinical symptoms are determined from inspection, familial anamnesis and applying instrumental analyzes: hand X-ray, an electrocardiogram and cardioechoscopy [2].

Genetic and molecular studies confirm the clinical diagnosis, to identify the genetic changes in the visible hands and heart defects and prenatal diagnosis when the family mutation known or ultrasound visible characteristic of fetal limb abnormalities and heart development. Possible genetic and molecular studies HOS approval is TBX5 gene sequencing and comparative genome hybridization vector (Eng. Array CGH). The test substance is usually taken from blood or prenatal diagnosis of amniotic fluid. From cells isolated genetic material is multiplied by polymerase chain reaction. Mutations checked TBX5 gene exons 2-9. Vector comparative genomic hybridization is faster (lasts 3-4 weeks) as well as easier method, so this test is selected more often. The sensitivity is 74 per cent., so not all HOS cases are confirmed genetically [8,9].

Holt-Oram syndrome case report

The patient is the first child in the family, born 40 weeks of pregnancy. Caesarean section operation, 53 cm tall and 3090 g weight. She was awarded a doctor of showing genetic consultation congenital malformations. Marital history. The mother of the 14 year. epilepsy and during pregnancy, Depakine 500 mg 1.5 tab. Depakine active ingredient is sodium valproate and valproic acid. One of the side effects of the drug teratogenicity. Genealogy of the patient is in Figure 1.

Visual inspection. Both hands flexal contracture, not your thumbs on both hands are ulna reduction, clinodactily finger nail hypoplasia. Also, deformed feet and toes. Face is slightly oblique slit eyes, a small hyperelorism, flat nasal bridge, a longer filter and micrognathia. (See. Figure - 2).

Cardiologist for advice. A patient has a congenital heart defect - tetralogy of Fallot. As a result, in 2013. February. It has undergone radical surgery, when the girl was 2 months.

Genealogy. Uninformative, family Holt-Oram syndrome have been previously found (see. Figure - 2). Molecular genetic study. TBX5 point gene mutation was not found. TBX5 gene mutation are found in 75% cases of Holt-Oram syndrome).

Based on the clinical features of the diagnosis of Holt-Oram syndrome was established.

Treatment and Care

Holt-Oram syndrome can only symptomatic treatment, ie, Surgical removal of defects. This requires close collaboration between doctors geneticists, of cardiac surgery, orthopedic and plastic surgeons. The recommended periodic monitoring of Cardiology on possible cardiac conduction occurs. Also, the patient must try to provide the best possible rehabilitation and integration into society conditions [2].

Figure 1. Pedigree of the patient. Proband is marked with filled circle.

Figure 2. Visible malformations of hands: both hand contractures, reduce elbows, thumbs are not formed, clinodactily
Valproic acid (valproate) is a first-generation antiepileptic drug, usually used to treat epilepsy and certain psychiatric diseases (e.g., Bipolar disorder). Valproic acid has good efficacy, but this material was observed side effects. In particular, it is dangerous during pregnancy as a teratogen [10]. Valproic acid is teratogenic in most animal species tested, but the human embryo seems to be the most susceptible. A daily dose of 1000 mg or more and/or polytherapy are associated with a higher teratogenic risk. It seems that several other AEDs potentiate the teratogenic effects of VPA. Thus, when valproate cannot be avoided in pregnancy, the lowest possible effective dose should be prescribed in 2-3 divided doses, preferably as monotherapy. Women exposed to valproate in pregnancy should be given periconceptional folic acid and followed up in a high risk pregnancy clinic. Appropriate ultrasonographic and other examinations, focusing on the possible different anomalies described with this agent, should be carried out.

No teratogenic effects of valproic acid until the end is not yet clarified, but this substance use during pregnancy is associated with neural tube, heart, limb defects and other malformations features. A teratogenic effect mechanism hypothesis is that valproic acid inhibits histone deacetylases, resulting in altered gene responsible for chondrogenesis and osteogenesis expression. Such epigenetic variation causes limb deformities development [11]. It is also being investigated, which seeks to establish a link between the development of defects and valproic acid daily dose. Based on study results, the higher (over 1,000 mg) daily dose of valproic acid consumption results in more frequent malformations. Therefore, during pregnancy, when it is impossible to stop drug use, it is recommended to use the lowest effective dose of valproic acid [12,13].

It was found that the greater the risk of malformations has antiepileptic drugs polypharmacy, especially when the combination is valproic acid than monotherapy. It is therefore recommended not only better for the lowest effective dose, but also to treat only one choice antiepileptic drug.

It is observed that during pregnancy antiepileptic drugs cause similar malformations, as occurred without the use of any medication. The most common cardiac, skeletal, urinary tract, and head and face deformation. However, the development of neural tube defects are more common in pregnant women taking valproic acid [14,15]. A recent study showed children of mothers taking valproate during pregnancy are at risk for significantly lower. Maternal valproate use during pregnancy has been associated with a significantly higher risk of autism in the offspring. A 2005 study found rates of autism among children exposed to sodium valproate before birth in the cohort studied were 8.9%. The normal incidence for autism in the general population is estimated at less than one percent. It is possible to duplicate features characteristic of autism in humans by exposing rat embryos to valproic acid at the time of neural tube closure. Valproate exposure on embryonic day 11.5 led to significant local recurrent connectivity in the juvenile rat neocortex, consistent with the underconnectivity theory of autism. A 2009 study found that the 3 year old children of pregnant women taking valproate had an IQ nine points lower than that of a well-matched control group. However, further research in older children and adults is needed. The influence of VPA on human chondrocytes was also monitored using histochemical, immunocytochemical, and morphological techniques. There was a decrease in mitotic activity and the extracellular matrix was modified. At human therapeutic doses, immunofluorescence revealed that type II collagen was reduced, while type I collagen increased. In addition, the alcian blue-staining matrices (i.e., sulfated proteoglycans) were reduced. Moreover, the Golgi apparatus had swelling in the trans-face cisternae suggesting that proteoglycan synthesis may be altered.

This valproic acid on nerve tube is associated with exposure to the product in folate metabolism, so pregnancy is very important that the mother's serum folate are sufficient points. In order to avoid the possibility of their lack of folic acid recommended daily dose is 0.4 mg. However, there is no evidence that the daily amount of folate reduces fatal neural tube defects in the risk of pregnant women receiving anti-epileptic drugs. [16-18] Nevertheless, it was being investigated, which sought to establish an adequate dose of folate, which protects against neural tube development defects. So now, even though research evidence yet, folic acid is recommended for up to 5 mg / day for pregnant women to have a higher risk to give birth to a new born with a neural tube defect. It is also important that the therapy is started before pregnancy, so women with epilepsy disease is proposed family planning [16, 17, 18].

CONCLUSION
Developmental disorders can lead to a number of factors that are difficult to clearly separate and complicated. It is described in Article patients. As TBX5 gene mutation molecular genetic testing has not confirmed Holt-Oram syndrome diagnosis was made according to clinical features. This diagnosis based on clinical criteria only two - in this case the upper limbs, developmental defects and cardiac structural defects (tetralogy of Fallot). Patients developmental disorders justification for particularly difficult pregnancies exposed to valproic acid, which can also cause the limbs, heart and other deformities. If anti-epileptic drugs during pregnancy can not be terminated, the lowest effective single dose in combination with folic acid.

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REFERENCES


