СЕКЦІЯ XXIII.
МЕДИЧНІ НАУКИ ТА ГРОМАДСЬКЕ ЗДОРОВ'Я

A RARE CASE OF ISODICENTRIC CHROMOSOME 15 SYNDROME IN A CHILD. CLINICAL OBSERVATION

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The syndrome of isodicentric chromosome 15 (idic (15)) is a chromosomal anomaly that has a multiple nature of damage to the human body. A marker chromosome usually exists as an isodicentric chromosome; that is, 2 copies of a specific part of the long arm of chromosome 15q11.2-q13.1, which is mirror image and duplicated, with two centromeres and two satellite DNA. The smallest markers are usually harmless and may go unnoticed. However, if they are large enough to carry a number of important genes, they can lead to isodicentric chromosome 15 syndromes [1].

One of these regions responsible for the symptoms of the idic syndrome (15) is the SNRPN and UBE3A genes of chromosome 15 (Fig. 1). These genes are located in the critical region of Prader-Willi syndrome and Angelman syndrome on chromosome 15, respectively, imprinted and expressed by the paternal and maternal alleles. The SNRPN gene encodes a component of a small nuclear ribonucleoprotein complex that participates in pre-mRNA processing and can promote tissue-specific alternative splicing. The UBE3A gene encodes a protein that takes part in the processes of activation of neurotrophic factors in the brain [2].

Materials and methods: somatic-genetic, clinical-genealogical, instrumental, cytogenetic and molecular-cytogenetic researches.

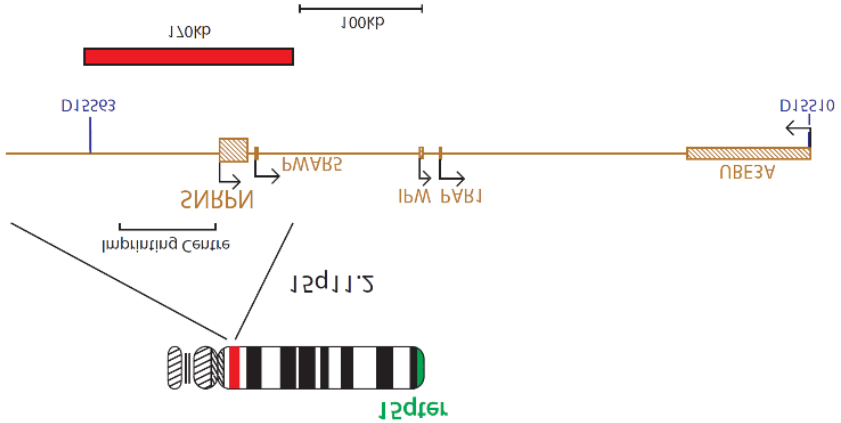


Fig. 1. **Location of the SNRPN and UBE3A genes on chromosome 15**

Results and discussion

We present our observation. A family with a sick 16-year-old child turned to the interregional medical and genetic center-the center for rare (orphan) diseases. The parents had the following complaints about the child's condition: echolalia, mental retardation, clonic-tonic convulsions (from 2-5 attacks every night), unsteadiness of walking, impaired vision (myopia), impaired swallowing, lack of self-care skills, sleep disturbances, sometimes the smell of acetone from the mouth, tendency to constipation.

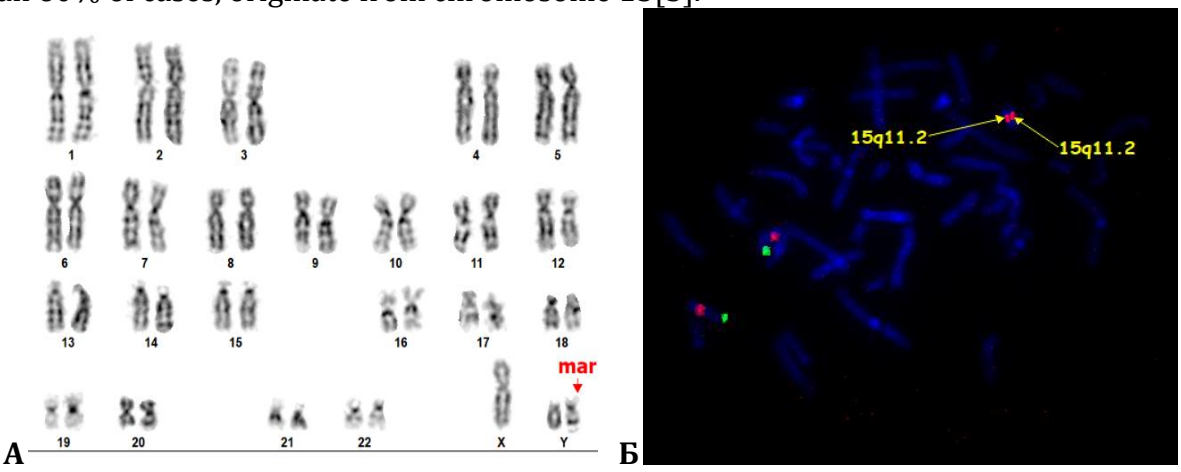
Phenotype assessment: height — 169 cm, weight — 40 kg; deformation of the chest and spine, hemangiomas on the forearm, impaired muscle tone (hypotonia of the muscles of the upper and lower limbs), impaired coordination, right-sided hemiparesis.

According to ultrasound: hepatomegaly.

Perinatal anamnesis: a child from the second pregnancy (the first pregnancy — a miscarriage in the early period of gestation), which occurred on the background of stress. Childbirth in termnigestation — 39 weeks (rapid) through natural birth canals. Birth weight - 3500 g, height - 51 cm. Assessment on the Apgar scale - 9 points. Breastfeeding up to 8 months. Complementary food was introduced at 6 months. Stages of motor development: sitting at 8 months, walking at 1 year 6 months. Language development from 2 years. Before 1 year of life, he was examined and treated by a neurologist for an organic lesion of the central nervous system.

Magnetic resonance spectrometry of the brain revealed peculiarities of cerebral metabolism caused by the toxic effect of ammonia accumulation in the brain tissues, which may be a consequence of a malfunction of the urea cycle.

Cytogenetic research by the GTG method determined a male karyotype with one additional marker chromosome - 47,XY,+mar (Fig. 2A). At present, despite the development and use of modern diagnostic methods, the determination of the origin of the marker chromosome and its influence on phenotypic manifestations remain unclear finally studied. The greatest success in this matter has been achieved in the identification of hotspots of chromosome 15 breaks, which lead to chromosomal rearrangements. Therefore, the majority of marker chromosomes that have been described and identified, which is more than 60% of cases, originate from chromosome 15[3].



А **Б**

Fig. 2. **Results of cytogenetic (A) and molecular cytogenetic (B) research**

In connection with the existing data, in order to determine the origin of the marker chromosome, a molecular cytogenetic study was conducted by the FISH method using DNA probes of the SNRPN and UBE3A genes. It was established that the additional marker chromosome is a derived dicentric chromosome, which consists of two equivalent sections, which include a centromeric section with a satellite block and a centromeric section of

chromosome 15, which contains the SNRPN and UBE3A genes - ish dic(15;15)(q11.2;q11.2)(UBE3A++) (Fig. 2B).

The severity of idic (15) symptoms varies among patients. People with idic (15) usually have a delay in the development of speech and motor skills, namely walking or sitting. Other signs may include low muscle tone, seizures (> 50%), short stature, and mental retardation. Most people with idic (15) have autistic traits, such as problems with communication and social interaction, disrupted sleep cycles, and repetitive, stereotyped behavior. The processing of sensory information, especially the vestibular system, is often disturbed [4].

It is known that the SNRPN gene has a monoallelic tissue-specific expression in brain tissues, so the manifestation of the idic (15) syndrome phenotype depends on a number of reasons. Various genetic mechanisms have been hypothesized to explain clinical heterogeneity, including the size of the chromosomal duplication, the gene dosage effect at this locus, and the mechanism of imprinting. Probably, when the additional chromosome has material of maternal origin, when the SNRPN gene is imprinted and the UBE3A gene is active, the clinical symptoms have a more severe course than with paternal origin. An increase in the dose of these genes can change the activity of GABA receptors, on which the main inhibitory mechanisms of the central nervous system depend [5]. These processes may represent the biological basis of some clinical manifestations in people with isodicentric chromosome 15 syndromes, namely seizures, hyperactivity, aggressiveness, and autistic disorders.

Conclusions

Based on the obtained results, it can be concluded that this patient has an unbalanced karyotype with a double copy of the UBE3A genes on chromosome 15. The clinical symptoms that were found in this case are similar to those of patients with idic (15). The pronounced symptom complex once again indicates the significant nature of the dose of genes in the karyotype.

The obtained data indicate the need for additional molecular cytogenetic diagnostics in order to determine the origin of the marker chromosomes in the karyotype. This approach is mandatory in the practice of medical and genetic counseling and enables correct diagnosis and further treatment of such patients.

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