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BASEL-VANAGAITE-SMIRIN-YOSEF SYNDROME

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Basel-Vanagaite-Smirin-Yosef Syndrome is a rare syndrome of genetic mental retardation caused by an autosomal recessive mutation of the MED 25 gene. 112 case histories of patients aged 1 month-3 years old with seizures were analyzed. During observation symptoms, characteristic for Basel-Vanagaite-Smirin-Yosef syndrome were detected. By comparing the frequency of clinical symptoms in this patient with others, we found that this syndrome is more characterized by a combination of sparse eyebrows and hair, wide forehead, retrognathia, hypertelorism with malformations of the brain and heart, and for early diagnosis an approach based on deep research should be recommended. A multidisciplinary approach to symptom management and timely initiation of prophylaxis of complications can improve the quality of life of these patients.

Key words: Basel Vanagaite-Smirin-Yosef Syndrome (BVSYS), MED25 gene, autosomal recessive type, mental retardation, multiple congenital anomalies.

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СИНДРОМ БАЗЕЛЬ-ВАНАГАЙТЕ-СМІРІНА-ЙОСЕФА

Синдром Базель-Ванагайте-Сміріна-Йосефа – рідкісний синдром генетичної розумової відсталості, зумовлений аутосомно-рецесивною мутацією гена MED 25. Проаналізовано 112 історій хвороби пацієнтів віком від 1 місяця до 3 років із судомами. За час спостереження виявлено симптоми, характерні для синдрому Базель-Ванагайте-Сміріна-Йосефа. Порівнюючи частоту клінічних симптомів у цього пацієнта з іншими, ми встановили, що для цього синдрому більшою мірою характерне поєднання рідких брів і волосся, широкого чола, ретрогнатії, гіпертелоризму з вадами розвитку головного мозку та серця, а для ранньої діагностики слід рекомендувати підхід, заснований на глибоких дослідженнях. Мультидисциплінарний підхід до лікування симптомів та своєчасна профілактика ускладнень можуть покращити якість життя цих пацієнтів.

Ключові слова: синдром Базель-Ванагайте-Сміріна-Йосефа (BVSYS), ген MED25, аутосомно-рецесивний тип, розумова відсталість, множинні вроджені аномалії.

Basel-Vanagaite-Smirin-Yosef syndrome is a rare genetic syndrome caused by an autosomal recessive mutation of the MED 25 gene (19q13.33) [1]. This syndrome is characterised by severe developmental delay, various craniofacial, neurological, cardiac and ocular abnormalities. Currently, this disease has been reported in only a few patients in the world. Since 2015, 20 patients with common clinical features and MED25 biallelic variants have been described through whole exome sequencing, leading to a better definition of the phenotype associated with BVSYS [2, 3].

The disease has been described in 4 families from one Israeli village [2]. In addition, a report of seven patients from a related Brazilian family has been described [4]. Recently, a Lebanese family with a p.Ile173Thr variant in the MED25 gene was reported [8]. The incidence of Basel-Vanagaite-Smirin-Yosef syndrome is 1/1000000 worldwide.

This syndrome is characterized by severe developmental delay, various craniofacial, neurological, cardiac and ocular anomalies. Since 2015, 20 patients with common clinical features and MED25 biallelic variants have been described through whole exome sequencing, leading to a better definition of the phenotype associated with BVSYS [7, 10].

Patients present to the physician with the most common clinical manifestations. From infancy, they are delayed in psychomotor mental development, such as not crawling, not walking, speech delay. In Azerbaijan, Basel-Vanagaite-Smirin-Yosef is the only patient who has been diagnosed with the syndrome.

Patients with Basel-Vanagaite-Smirin-Yosef syndrome also have microcephaly, short stature and feeding difficulties, and mandibular prognathism has been observed in different adults in the same family. Other common features described include syndactyly of the 2nd and 3rd fingers, congenital heart defects (septal defects), genitourinary and ocular anomalies (cataract, microcornea, microphthalmia), hypotonia and seizures. Less common are cleft palate, hearing loss, hypospadias, kyphosis/scoliosis, camptodactyly, detached thumb, tapered fingers with ulnar deviation, overlapping fingers/feet, and super-convex nails. Brain imaging abnormalities such as thinning of the corpus callosum, ventriculomegaly, cerebral atrophy and polymicrogyria are frequently observed.

Diagnosis is based on clinical features, brain imaging, molecular and cytogenetic studies [2, 4]. The last decade has seen a dramatic increase in innovative ideas for the treatment of genetic disorders for which no curative therapies exist [6]. That is why timely diagnosis of genetic diseases can improve the prognosis of these pathologies.

The purpose of the study was to assess the clinical features of patient with seizures to improve the diagnosis of Basel-Vanagaite-Smirin-Yosef syndrome.

Materials and methods. The study was carried out at the clinical departments of Scientific Research Institute of Paediatrics named after K.Y. Farajova. 112 case histories of patients aged 1 month-3 years old with seizures were analyzed. During observation symptoms, characteristic for Basel-Vanagaite-Smirin-Yosef syndrome were detected. In addition, consultations of different specialists performed to find out the disorders of internal organs.

For statistical analysis SAS 9.3 software (SAS Institute, Cary NC). Other software programs, such as Microsoft Word® 2007 (word processing), Microsoft Excel® 2007 (tabular presentation of patient data) were used. The numeral data were evaluated by descriptive statistical methods (frequency, percentage).

Results of the study and their discussion. While studying case histories we analyzed the following clinical features: congenital hip luxation, developmental delay, absence/delayed speech, short stature, muscle hypotonia, wide fontanelles, microcephaly, high forehead, sparse hair, sparse eyebrows, nevus flammeus, ptosis, hypertelorism, epicanthus, cataract, microcornea, strabismus, downslanting palpebral fissures, flat nasal bridge, broad nasal tip, short philtrum, large mouth, cleft palate, prominent chin, wide cupid bow, thin upper lip, brain malformations, heart malformations, abnormal genitalia.

According to results obtained congenital hip luxation was registered in 15 (13.4 %) of all cases, developmental delay – in 62 (54.5 %), absence/delayed speech – in 28 (25 %), short stature – in , muscle hypotonia – in 76 (67.9 %), wide fontanelles – in 57 (50.9 %), microcephaly – in 2 (1.8 %), high forehead – in 39 (34.8 %), sparse hair – 35 (31.3 %), sparse eyebrows – in 74 (66.1 %), nevus flammeus – in 6 (5.4 %), ptosis – 11 (9.8 %), hypertelorism – in 14 – (12.5 %), epicanthus – in 7 (6.3 %), cataract – 2 (1.8 %), microcornea – 0 (0.0 %), strabismus – 27 (24.1 %), downslanting palpebral fissures – 12 (10.7 %), flat nasal bridge – 38 (33.9 %), broad nasal tip – 21 (18.8 %), short philtrum – 9 (8.0 %), large mouth – 3 (2.6 %), cleft palate – 16 (14.3 %), prominent chin – 7 (6.3 %), wide cupid bow – 8 (7.1 %), thin upper lip – 22 (19.6 %), brain malformations – 46 (41.1 %), heart malformations – 26 (23.2 %), abnormal genitalia – 9 (8.0 %).

In addition, the abnormalities of gastrointestinal tract (16.1 %), urinary tract (9.8 %) and respiratory tract (4.5 %) were found out.

In 3.6 % of children observed Down syndrome was diagnosed, in 75.0 % – perinatal hypoxic-ischemic encephalopathy, in 6.25 % – cerebral palsy.

According to complex of clinical data Basel-Vanagaite-Smirin-Yosef syndrome was diagnosed in one of children. By comparing the frequency of clinical symptoms in this patient with others, we found that this syndrome is more characterized by a combination of sparse eyebrows and hair, wide forehead, retrognathia, downslanting palpebral fissures, hypertelorism with malformations of the brain and heart, and for early diagnosis an approach based on deep research should be recommended.

The case report was presented for illustration. The patient N., male, born 15.06.2019, was admitted to the paediatric department of the Research Institute of Paediatrics with complaints.

According to the mother, the child has been ill for 1 week. Hyperthermia and cough, decreased appetite, weakness were noted. Due to the severity of his condition, he was taken to the Paediatric Research Institute for detailed examination and treatment. The child is from the first pregnancy, first delivery of the mother. The child was born at term, naturally, with a body weight of 3200 g. During pregnancy, the mother was treated and examined on an outpatient basis for cytomegalovirus and rubella infection. The patient was born with a malformation of the hard and soft palate and a congenital heart defect. The patient's parents applied to a neurologist with complaints that the child could not sit, walk, bend the spine in the form of kyphosis at the age of 1 year, and as a result of genetic analysis the diagnosis: Basel-Vanagaite-Smirin-Yosef syndrome was confirmed after 1 year and 7 months. Parents are related (cousin-sister-cousin).

Fig. 1. Patient N., Basel-Vanagaite-Smirin-Yosef syndrome.

Condition on entry was severe. Symptoms of intoxication and catarrh come to the fore. Skin and visible mucous membranes pale, clean. Subcutaneous fatty fibre was poorly developed. Palate mucosal and pharynx were hyperaemic. At auscultation over the lungs hard breathing was heard. Heart tones were deaf. A systolic murmur was heard. There was hemiplegia in the lower extremities. The abdomen was soft, painless. The liver and spleen were not palpated. Physiological acts were free.

On examination, the patient had such clinical signs as sparse eyebrows and hair, broad forehead, retrognathia, downslanting palpebral fissures, hypertelorism (increased distance between the eyes), non-union of the hard and soft palate typical for the syndrome (Fig. 1.).

Examinations performed**:** Molecular genetic study of the patient was performed at the Centre for Genomic Medicine in Germany. By exome sequencing we identified a homozygous mutation p.(C.518 T>C p.Ile173Thr) in MED25 in our patient as the cause of the syndrome characterised by eye, brain, heart, palate and growth abnormalities. mental retardation, microcephaly and severe mental retardation we were able to identify.

Test result and interpretation: Homozygous variant of uncertain significance consistent with phenotype detected (Table 1).

Table 1

Results of genetic test

Location	Phenotype	Variant	Zygosity	Gene/Locus	Inheritance	Classification
19q13.33 Exon 5	Basel-Vanagaite-Smirin-Yosef syndrome	c.518 T>C (p.ile173Thr)	Homozygous	MED 25	Autosomal recessive	Uncertain singnificance

Otorhinolaryngologist consultation**:** Other acute upper respiratory tract infections with multiple localisation. Worm's mouth. Consultation of a neurologist: Infantile cerebral palsy.

Echocardiography: PDA (patent ductus arteriosus) is monitored, with a gradient of 40 mmHg, 1st degree tricuspidal insufficiency, minimal mitral insufficiency, minimal pulmonary insufficiency.

Computed tomography of the brain**:** foci of periventricular gliosis in both parietal regions of the brain. Dilatation of the third and lateral ventricles, areas of subarachnoid fluid in the temporo-basal regions. Retrocerebellar arachnoid cyst.

Changes in the eyes were foun out: lacrimal duct closure, sensitivity to light.

On the basis of objective examination, anamnestic, clinical data and results of laboratory and instrumental studies the patient was diagnosed with pneumonia, Basel-Vanagaite-Smirin-Yosef syndrome.

Treatment: Sol.NaCl 0.9 %, Sol.Glucosae 5 %, Sol.Ceftazidime, Sol.Metranidazole, intravenous immunoglobulin G.

Condition and recommendations at the time of discharge**:** the general condition of the child is relatively satisfactory. Relativity of the condition was due to genetic syndrome. He was active, the symptoms of intoxication have disappeared, the body temperature was normal. The breathing was rhythmic, on auscultation, respiration was equal on both sides, heart tones was rhythmic. Food and fluid

intake were adequate. Physiological acts are free. The patient was discharged home under the supervision of a field physician and a neurologist. The prognosis depends on the severity of the disease.

The descriptions available in the literature are characterized by a phenotype of patients very similar to our case and those previously described with Basel-Vanagaite-Smirin-Yosef syndrome.

There is also evidence of more complex phenotypes of ataxia, seizures, congenital hip dislocation, microcephaly, sparse hair, and elevated serum lactate and pyruvate levels [8]. In our case, the symptoms were closer to classic phenotypes.

Researchers associate the main problem with the manifestation of such rather rare genetic syndromes with a high level of consanguinity. This problem is typical for many countries. In such highly related populations, it is not uncommon to see rare genetic disorders occurring in several supposedly unrelated families with the same underlying causative variant. In such cases, the variant in question is assumed to be a founder mutation that arose either sporadically as a de novo event or introduced from a closely related population [9].

However, there are indices of the possibility of the occurrence of Basel-Vanagaite-Smirin-Yosef syndrome in families that are clearly not related to each other. It is believed that this variant appears to have independent origins of the two alleles, ruling out the presence of a founder mutation.

Maini I, et al (2021) reported two young sisters, born to consanguineous parents, presenting with intellectual disability, neurological findings, and dysmorphic features typical of BVSYS, and also with bilateral perisylvian polymicrogyria [7].

Haynes D, et al (2020) described three patients showing clinical variability for this newly defined syndrome. The major features determined by “reverse phenotyping” include significant to profound developmental delays/intellectual disability with absent or delayed speech, epilepsy, ocular abnormalities, cleft lip and/or palate, congenital heart disease, urogenital anomalies, skeletal abnormalities, brain malformations and/or microcephaly, failure to thrive, and dysmorphic features [5].

Thus, some authors point out the lack of specific signs due to wide variability of symptoms that which limits clinical diagnose of this condition. Although the clinical phenotypes of the patients are consistent, all reported cases exhibit only developmental delay, absence of speech, and short philtrum. Thus, there is a possibility that this condition may be underdiagnosed and effectively detected only using molecular techniques such as whole exome sequencing [8].

Conclusion

In conclusion, our clinical observation reflects the clinical features characteristic of the syndrome as shown in the literature. Our goal is to achieve early diagnosis in children with Basel-Vanagaites-Smirin-Yosef syndrome, a multidisciplinary approach to symptom management, timely initiation of prophylaxis and prolongation of their life, and improvement of their quality of life.

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