Kleefstra Syndrome — case report

Zespół Kleefstra — opis przypadku

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ABSTRACT

Kleefstra Syndrome is a rare genetic neurodevelopmental disorder characterized by the presence of multiple congenital defects. Patients present a large variety of clinical symptoms: delay in psychomotor and speech development, intellectual disability, muscular hypotension and characteristic facial dysmorphic features. The cause of the syndrome is submicroscopic deletion in the chromosomal region 9q34.3 or an intragenic mutation of the euchromatin histone methyltransferase 1 (EHMT1) gene. Early diagnosis is extremely important for children and their families as it allows quick implementation of appropriate therapeutic management and comprehensive care, which has a great impact on improving the quality of life and prognosis for patients with Kleefstra syndrome.

We present the case of a 9-year-old girl with Kleefstra Syndrome in whom the diagnosis of the genetic syndrome was proved at the age of 2 years by chromosome analysis using CGH, which showed deletion in the terminal band 9q34.3 of the long arm of chromosome 9.

Key words: congenital defects, deletion 9q34.3, dysmorphic features, Kleefstra Syndrome,

STRESZCZENIE

Zespół Kleefstra to rzadkie, neurorozwojowe schorzenie o podłożu genetycznym charakteryzujące się występowaniem mnogich wad wrodzonych. Chorzy prezentują dużą różnorodność objawów klinicznych: opóźnienie rozwoju psychomotorycznego i mowy, niepełnosprawność intelektualną, hipotonię mięśniową oraz charakterystyczne cechy dysmorficzne twarzy. Przyczyną zespołu jest submikroskopowa delecja w regionie chromosomalnym 9q34.3 lub mutacja genu metylotransferazy histaminowej euchromatyny 1 (EHMT1). Wczesna diagnoza zespołu Kleefstra jest niezwykle istotna, gdyż pozwala na szybkie wdrożenie odpowiedniego postępowania terapeutycznego, a tym samym może mieć wpływ na poprawę jakości życia i rokowania pacjentów.

W pracy prezentujemy przypadek obecnie 9-letniej dziewczynki z zespołem Kleefstra, u której właściwe rozpoznanie zespołu genetycznego zostało postawione w wieku 2 lat na podstawie analizy chromosomów z zastosowaniem CGH (comparative genomic hybridization), w którym stwierdzono niezrównoważenie genomu w postaci terminalnej delecji długiego ramienia chromosomu 9 w prążku 9q34.3.

Słowa kluczowe: wady wrodzone, delecja 9q34.3, cechy dysmorficzne, zespół Kleefstra

INTRODUCTION

Kleefstra Syndrome is a rare genetic neurodevelopmental disorder characterized by the presence of multiple congenital defects. Patients present a large variety of clinical symptoms. The clinical picture includes delay in psychomotor development, severe or moderate intellectual disability and muscular hypotonia. The characteristic facial morphology that changes with aging helps to establish the diagnosis. Patients with Kleefstra syndrome have dysmorphic features such as microcephaly, broad, short skull (brachycephaly) and middle face hypoplasia. Also characteristic are widely spaced eyes (hypertelorism), short nose with anteverted nares, open mouth with a fleshy everted lower lip, large tongue, thickened ear helices and arched eyebrows with synophrys protruding jaw (prognatism). The syndrome often affects children with high birth weight and suffering from obesity. Structural CNS abnormalities are also observed: agenesis or corpus callosum hypoplasia or subcortical white matter anomalies. The most commonly diagnosed heart defects are ASD, VSD, Fallot tetralogy, aortic coarctation, bifocal aortic valve and pulmonary valve stenosis. Urinary tract abnormalities seen in patients

include vesicoureteral reflux, hydronephrosis, renal cysts, and chronic renal failure. Genital defects such as hypospadias, cryptorchidism and micropenis are present in some male patients. [1–5]. Moreover, in Kleefstra's syndrome epileptic seizures (tonic-clonic seizures, absence seizures and complex partial seizures), hearing loss, visual impairment, congenital hypothyroidism and a tendency to develop severe respiratory infections are observed. Psychiatric problems including behavioral disorders, autism spectrum disorders, sleep disorders, self-harm and extreme apathy or catatonic features post puberty are also found in this group of patients [6].

We present the case of a 9-year-old girl with Kleefstra Syndrome born in September 2010, a patient of Department of Pediatric Neurology, and review the related literature.

CASE REPORT

The presented patient was diagnosed with Kleefstra Syndrome. Immediately after birth, due to the child's features of trisomy 21, diagnostics was carried out which allowed the exclusion of Down Syndrome. Then the girl was ob-

served for the neuromuscular disorders. In 2012 the patient began to be suspected of Kleefstra syndrome. The diagnosis was confirmed by genetic test – CGH in which genomic imbalance – a terminal deletion of the long arm of chromosome 9 in band 9q34.4 was detected.

Perinatal medical history: pregnancy was complicated by preterm uterine contractions in 20th week. A girl was born vaginally at 41st week of pregnancy with a birth weight 3840g. The Apgar score was 10. There was no genetic disease in the girl's family. On physical examination some dysmorphic features were found: narrow palpebral fissures, fleshy ears, short neck, broad chest, large tongue and dental excrescences in mandible. She did not have a breathing or feeding disorder. The pathological changes which were observed in the first days of the child's life also included periodically occurring silent murmur along the left edge of the sternum requiring cardiological consultation. The echocardiographic examination revealed the presence of a patent foramen ovale (PFO), secondary type of atrial septal defect (ASD II) and patent ductus arteriosus (PDA). Spontaneous closure of them occurred at 2 years of age. The girl was regularly consulted in a neurological clinic every 3–6 months. She had been reaching the milestones in psychomotor development with a delay: she has been sitting unsupported at 11 months, started walking holding onto furniture at about 2,5 years of age, reached functional walking in the next two months. The abnormal and delayed development of the speech was also worrying – she began to speak single words at about 1,5 years of age. From the infancy axial and peripheral decreased muscle tone was being found. For this reason the child has been rehabilitated, thanks to which she obtained an improvement in muscle tone, but it is still lower both axially and peripherally. Moreover, during follow-up visits signs of focal central nervous system (CNS) damage were not observed. Normal, symmetrical, equal tendon reflexes, without pathological reflexes from the CNS were examined. Patient was implemented multi-profile rehabilitation – initially NDT Bobath, speech therapy, early development support. In head imaging (CT, MRI) partial agenesis of the corpus callosum, were diagnosed Recurrent respiratory infections and chronic exudative otitis were a big problem in this patient. At the age of 3 an audiometry test was conducted but it did not reveal any signs of hearing loss. The girl was also diagnosed with hyperopia which is frequently recognised vision defect in patient's with Kleefstra syndrome and it is corrected with eyeglasses. The patient required rehabilitation due to a walking abnormality – wide-based gait and the presence of deformed knees and flat feet. At the age of 2 the girl had an episode of loss of consciousness with urination which occurred after waking up from sleep in the morning and was not related to the infection or fever. In the emergency department a neurological consultation was performed and an EEG was ordered, but it did not show any abnormalities. The girl did not require hospitalization and the incident did not reoccur. From birth she was also under endocrine care due to congenital hypothyroidism. In addition, the patient is currently being diagnosed in the En-

docrinology Department for short stature.

The girl has facial dysmorphic features which are characteristic for the Kleefstra syndrome. Brachycephaly and hypoplasia of the middle part of the face can be seen as well as hypertelorism, arched eyebrows, short nose with anteverted nares, open mouth with a fleshy everted lower lips, large tongue and thickened ear helices (Fig. 1, 2, 3). The patient has also atypical hands with short, curved, distally tapering fingers (Fig. 4). The girl manifests the features of an autism spectrum disorder in her behaviour. She has mild intellectual disability and she attends special education classes. The patient is still undergoing speech therapy and psychotherapy. Due to speech difficulties the girl uses augmentative and alternative communication (AAC).

DISCUSSION

Kleefstra syndrome can be a diagnostic challenge mainly due to the rarity and ignorance of the clinical features of this genetic syndrome. From year to year the number of reports about the syndrome is increasing. Initially, this disorder was known as the 9q subtelomeric deletion syndrome. In 2005, Dr T. Kleefstra and colleagues, based on numerous studies, pointed to abnormalities in the *EHMT1* gene as the cause of the characteristic phenotype. Kleefstra syndrome should be suspected in the presence of a child's characteristic facial morphology, childhood hypotonia, delayed psychomotor development and speech, intellectual disability and co-occurrence of malformations of various organs [1].

The cause of the disorder is the haploinsufficiency of the *EHMT1* gene (euchromatin histone methyltransferase 1). In most cases it is the result of microdeletion in the 9q34.3 region. In some patients the presence of intrinsic loss-of-function mutations can be determined. In both cases the clinical picture is similar. The protein encoded by the *EHMT1* gene, euchromatin histone methyltransferase together with the G9a protein are involved in 9-methylation of lysine, which is important in the formation of chromatin structure, transcriptional gene silencing, X inactivation and DNA methylation.

High expression of euchromatic histone methyltransferase 1 is found in embryonic stem cells as well as in the brain and eyeball during embryonic development. In adults, however, it is definitely smaller but retained in the heart muscle and some areas of the central nervous system: olfactory bulb, ventricular walls, hippocampus and piriform cortex. These structures are characterized by the presence of cells with high proliferative potential. The location of increased expression of euchromatin histone methyltransferase 1 may suggest that it plays an important role in the development and differentiation of the cells in central nervous system [4].

Suspicion of Kleefstra syndrome based on the characteristic phenotype features requires confirmation of the diagnosis based on genetic testing. One of the methods used in diagnostics are chromosomal microarray analysis (CMA) enabling the identification of large genomic deletions and duplications. To search for small intragenic mutations, techniques such as MLPA (multiplex ligation-depended

Ryc. I–III. Twarz 9-letniej pacjentki z zespołem Kleefstra. Widoczne są brachycefalia, hipoplazja środkowej części twarzy oraz inne cechy dysmorficzne charakterystyczne dla Zespołu Kleefstra

Fig. I–III. The face of the 9 years-old patient with Kleefstra Syndrome. We can see brachycephaly, hypoplasia of middle part of face and other dimorphic characteristics for Kleefstra syndrome

Ryc. IV. Dłonie dziewczynki z krótkimi, zakrzywionymi, zwężającymi się dystalnie palcami.

Fig. IV. Girl's hands with short, curved, distally tapering fingers

probe amplification) or quantitative DNA polymerase chain reaction (qPCR) are used. Multi-genic panels including the detection of other molecular causes of intellectual disability are also used and in special cases the karyotype test, because it does not provide the possibility of finding the microdeletion of the 9q34.3 region. When deciding on the choice of method it should be remembered that due to low sensitivity in detecting small deletions the FISH technique (fluorescent in situ hybridization) cannot be routinely used. Differential diagnostics include: Down Syndrome, Smith-Magenis Syndrome, Pitt-Hopkins Syndrome or Angelman Syndrome, autism spectrum disorder (ASD) and attention deficit and hyperactivity disorder (ADHD) [7].

Due to the fact that Kleefstra syndrome is caused by abnormalities in the *EHMT1* gene, an important issue for the patient's family is genetic counseling. Most of the cases identified so far have been de novo. In the presence of complex chromosomal rearrangement or mosaicism in a parent the inheritance of 9q34.3 deletion is possible. For asymptomatic parents of the proband it is suggested to perform routine karyotyping with additional FISH analysis in order to find a balanced translocation [7].

Care of the patients with the Kleefstra syndrome requires the collaboration of many specialists. Recommendations for patients who were diagnosed include constant monitoring by a pediatrician or neurologist and a psychiatrist. The child's height and weight should be monitored and dietary advice should be considered if obesity occurs. The attending physician of the patient with Kleefstra syndrome should be alerted to frequent ailments occurring in these patients, such as hearing loss, refractive defects,

heart defects and arrhythmias, urinary and digestive tract defects, convulsions, sleep disorders, behavior, speech, intellectual disability and, if necessary, refer to appropriate specialist. Currently, the treatment is only symptomatic and supportive [7].

Pediatricians' knowledge of the literature on the syndrome may prove useful in their daily clinical practice and may limit the diagnostic delays of the Kleefstra syndrome. Early diagnosis is extremely important for children and their families as it allows quick implementation of appropriate therapeutic management and comprehensive care, which has a great impact on improving the quality of life and prognosis of patients with Kleefstra syndrome.

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