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CASE REPORT OF PRADER-WILLI SYNDROME IN LITHUANIAN UNIVERSITY OF HEALTH SCIENCES

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ABSTRACT

Prader-Willi syndrome is (PWS) is a genetic disorder characterized during infancy by lethargy, feeding difficulties, hypotonia, and poor weight gain, in older age of untreated patients we can find obesity, developmental delay, short stature and other symptoms. This disease is caused by a microdeletion chromosome 15 region 15q11-13. We present case report of 12-years old girl with Prader-Willi syndrome that was confirmed with fluorescent in situ hybridization (FISH) analysis which shows the importance of this method for microdeletion syndromes.

INTRODUCTION

Prader-Willi syndrome is a complex, multisystem disorder first described in 1956. Twenty-five years later it captured the interest of geneticists because it was the first recognized microdeletion syndrome identified by high resolution chromosome analysis [1]. This disease is a complex neurodevelopmental disorder occurring at a frequency of 1/10,000 – 1/20,000 births and is the leading genetic cause of marked obesity [2]. About 99% of PWS cases have deletions at a common region in chromosome bands, 15q11-q13, uniparental disomy of chromosome 15 or imprinting center defects affecting gene expression in this region. Human chromosome 15 is one of the most polymorphic chromosomes often implicated in the formation of supernumerary bisatellited chromosomes, deletions, duplications and other rearrangements. Chromosome 15 contains segmental duplications and repeated transcribed DNA sequences located at the proximal and distal ends of the 15q11-q13 region. The typical deletion of the 15q11-q13 region is the most common cause of PWS presumably due to unequal crossing over in meiosis at repeated sequences located at the ends of the 15q11-q13 region [3]. Severe hypotonia is consistently observed at birth and during the neonatal period. Other features noted during the neonatal period include lethargy, feeding difficulties, thick saliva, and increased head/chest circumference ratio, small genitalia in both males and females with frequent cryptorchidism in males. In older untreated children with obesity, developmental delay, short stature and/or decreased growth velocity, and dysmorphic features are found including a narrow bifrontal diameter, almond-shaped palpebral fissures, a thin upper lip with a down-turned mouth, small hands and feet, straight borders of ulnar side of hands and of

inner legs [4]. Hypothalamic dysfunction has been implicated in many manifestations of this syndrome including hyperphagia, temperature instability, high pain threshold, sleep-disordered breathing, and multiple endocrine abnormalities. With improved recognition and availability of testing methodologies, PWS is being diagnosed earlier, often in the first few months of life. Earlier diagnosis, allowing for earlier access to developmental resources, recombinant human growth hormone (hGH) therapy, and anticipatory guidance, has significantly improved the long-term health and developmental outcomes of children with PWS [5].

CASE REPORT

Patient was a 12-years old girl with Prader-Willi syndrome. At the day of her birth, she had severe hypotonia, her physiological reflexes were very indolent, also she could not suck or swallow herself. At the age of 12 the patient was admitted for genetic counselling. All laboratory tests for newborns were performed which showed normal results, including karyotype test (46XX). Neurosonography showed asymmetrical, rounded ventricles which suggested hypoxic ischemic changes in the brain. Phenotypically, almond-shaped eyes, prominent nasal bridge and brachydactyly were observed. Moreover, defects in the internal organs, retardation and cysts in the brain were also observed. After the consultation, FISH cytogenetic test was carried out to verify the hypothesis of Prader-Willi syndrome. The results showed 15q11 region deletion in 100% of interphase nuclei of lymphocyte culture (figure 1). The phylogenetic tree was constructed and it showed that patient's father is a carrier. This case shows the importance of genetic testing when patients are suffering from severe hypotonia.

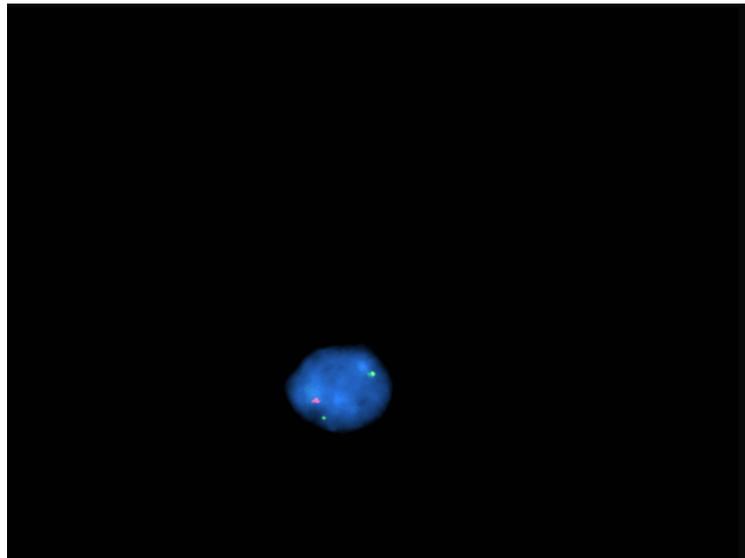


Figure 1. FISH analysis: green light shows the presence of the chromosome; red light shows the absence of parts in a chromosome.

DIAGNOSIS

Usually the diagnosis of PWS is confirmed by presence of clinical symptoms, such as hypotonia, lethargy, difficulty swallowing and sucking, obesity, and using FISH test. It is a test which uses specific probes to find the existence or an absence of parts in the chromosome. When diagnosing this syndrome using FISH method, we find a deletion in 15q11-q13 region of the chromosome 15 [3]. Although DNA methylation analysis is the most efficient way to start the genetic workup if PWS is suspected clinically. The differential DNA methylation of several imprinted maternal and paternal loci in the 15q11-q13 region provides a powerful tool for assessing paternal-only, maternal-only, and normal (biparental) inheritance. DNA methylation analysis is the only technique that will diagnose PWS in all three molecular classes and differentiate PWS from Angelman syndrome (AS) in deletion cases, and a methylation analysis consistent with PWS is sufficient for clinical diagnosis, but not for genetic counseling purposes [6].

DISCUSSION

Differential diagnosis

Prader-Willi syndrome (PWS) must be differentiated from other child diseases or syndromes when severe hypotonia, lethargy, difficulty swallowing and sucking, and obesity in elder age are observed. Those could be:

Smith-Magenis syndrome (SMS) is a multisystem disorder characterized minor craniofacial anomalies, sleep disturbances, short stature, behavioral, and neurocognitive abnormalities, as well as variable multisystemic manifestations. By performing fluorescence in situ hybridization (FISH) test, we can find an interstitial deletion of chromosome 17p11.2 [7].

Angelman syndrome (AS) is a neurodevelopmental disease that is characterized by severe intellectual disability, lack of speech, happy disposition, ataxia, epilepsy and distinct behavioural profile. AS phenotype included maternal deletion of chromosome 15q11-q13 allele, the same as for PWS [8].

DiGeorge syndrome (DGS), one of the 22q11deletion syndromes, is a group of signs and symptoms associated with defective development of the third and fourth pharyngeal pouch system. Clinical

features of the disease may include developmental delay, especially speech delay, feeding difficulties, ocular anomalies, endocrine problems [9].

We must have in mind that not only genetic diseases may cause hypotonia in the newborn and infantile period. This may include neonatal sepsis, hypoxic ischemic encephalopathy, muscle diseases such as myasthenia syndromes, congenital myopathies, and congenital myotonic dystrophy, craniofacial malformations, peroxisomal and mitochondrial disorders, and congenital glycosylation defects. These diseases have similar clinical findings to those seen in PWS, and invasive or expensive tests like muscle biopsy or molecular analysis might be required for the differential diagnosis [10,11].

Management

Treatment of manifestations:

1. In infancy:
 - Special nipples or enteral tube feeding to assure adequate nutrition;
 - Physical therapy may improve muscle strength;
 - Hormonal and surgical treatments can be considered for cryptorchidism.
2. In childhood:
 - Strict supervision of daily food intake based on height,
 - Weight, and body mass index (BMI) to provide energy requirements while limiting excessive weight gain (keeping BMI Z score <2 or better) and encouraging physical activity.
 - Growth hormone replacement therapy to normalize height, increase lean body mass and mobility, and decrease fat mass.
 - Evaluation and treatment of sleep disturbance.
 - Educational planning should be instigated and speech therapy provided if needed. Firm limit-setting to manage behavioral problems;
 - Serotonin reuptake inhibitors are helpful for most teenagers and adults.
 - Replacement of sex hormones at puberty produces adequate secondary sexual characteristics.

- N-acetylcysteine or topiramate may help reduce skin picking.
 - Modafinil has been successful in treating daytime sleepiness in many children.
3. In adulthood, a group home for individuals with PWS that regulates behavior and weight management may prevent morbid obesity, and growth hormone may help to maintain muscle bulk [12].

Diagnostics of microdeletion syndromes

Microdeletion syndromes are caused by chromosomal deletions of less than 5 megabases (Mb). Because of their small length (<5 Mb), the deletions are difficult to detect using conventional cytogenetic methods and light microscopy. A method that is commonly used for microdeletion detection is fluorescence *in situ* hybridization (FISH), which is a molecular cytogenetic technique based on fluorescently labeled DNA probes specific for a chromosomal region of interest [13]. FISH is a cytogenetic technique that uses fluorescent probes that bind to only those parts of the chromosome with a high degree of sequence complementarity and is used to detect and localize the presence or absence of specific DNA sequences on chromosomes. Fluorescence microscopy can be used to find out where the fluorescent probe is bound to the chromosomes. FISH is often used for finding specific features in DNA for use in genetic counseling, medicine, and species identification [14].

Non-invasive differential diagnosis

Non-Invasive Prenatal Diagnosis (NIPT) involves analyzing the cell-free fetal DNA (cffDNA) present in a sample of maternal blood to determine the likelihood of a fetal aneuploidy or other chromosome abnormalities. NIPT is more accurate than serum screening and produces fewer false positives, but is not currently diagnostic. The only physical risks associated with the procedure are those normally

associated with a blood draw and there is no risk of miscarriage. cffDNA can be detected in maternal plasma as early as 5-7 weeks, however, test results are more accurate after 10 weeks because the amount of cffDNA increases over time. Prader Willi syndrome is caused by a de novo deletion of chromosome 15p11, indications to test all pregnancies using FISH are not present. Currently, NIPT has only been validated in women with an increased risk of fetal aneuploidies or chromosome abnormalities [15].

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