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CASE REPORT OF SMITH-MAGENIS SYNDROME IN LITHUANIAN UNIVERSITY OF HEALTH SCIENCES

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ABSTRACT

Smith-Magenis syndrome (SMS) is characterized by distinctive physical features, developmental delay, cognitive impairment, sleep disturbances, and behavioral abnormalities such as aggression, self-injurious behaviors due to decreased sensitivity to pain. The syndrome is caused primarily by de novo interstitial deletions of chromosome 17p11.2, which can range from 1.5 to 9 Mb in size. We present case report of 2 years girl with Smith Magenis syndrome, that was confirmed with FISH analysis. This case shows the importance of FISH testing when patient has phenotypic signs of microdeletion syndromes.

INTRODUCTION

A syndrome is a recognizable pattern of physical, behavioral, and developmental features that occur together in the same person due to a single, underlying cause. In this case, Smith-Magenis is caused primarily by de novo interstitial deletions of chromosome 17p11.2, which can range from 1.5 to 9Mb in size. Features of SMS can be categorised by the percentage of affected individuals: Major physical features (> 75% of affected individuals) include facial appearance - flat mid-face, down-turned mouth, prominent jaw as patiens get older, synophrys (eyebrows that meet in the middle), hypotonia, hyporeflexia, decreased sensitivity to pain, breast feeding problems for mothers due to oral-sensory motor dysfunction (poor suck/swallow, decreased strenght of the tongue and its movement), open mouth posture, frequent drooling, constant chronic middle ear infections and laryngeal anomalies which causes hoarse voice, hypernasal speech. Major developmental and behavioral features (> 75% of affected individuals) – development delay, mild to moderate intellectual disability, letargy, speech delay and articulation problems, chronic sleep disturbances, including frequesnt awakenings during the night, teeth grinding, increased daytime sleepiness, early morning awakenings due to inverted circadian rhythm of melatonin. Very often patients with Smith-Magenis show repetitive behaviors, the most common are arm hugging when excited, flipping through book pages with or without licking fingers, known as „lick and flip“. Self-injuries are something for parents to be constantly aware of: head banging, hand biting while young and pulling off nails while older and inserting various foreign objects into body orifices. Although positive behavior is alvo present: appealing personalities, excellent long term memory and a great sense of humor. About half to three quarters of the patiens, affected by Smith-Magenis also show signs of impaired hearing, they are shorter, have scoliosis, strabismus, myopia, microcornea and might also have iris anomalies, constipation, dyslipidemia (hypercholesterolemia or hypertriglyceridemia) and abnormal EEG even if seizures are not present. Although less common, lowered immune function, congenital heart defects, murmurs, seizures, thyroid function abnormalities, cleft lip and/or palate, detached retinas and urinary tract abnormalities were also recorded amogst people affected by SMS [1] [2] [3] [4] . The birth incidence was thought to be 1: 25 000, but it might be closer to 1:15 000 due to improved cytogenetic techniques in the past five to ten years [5]. The syndrome has been identified worldwide in all ethnic groups.

CASE REPORT

Patient was born at term (gestation age: 38 weeks) from a greenish large amount of fluid/water. During pregnancy there was a threat of miscarriage. There were no remarkable family history and it was a first child of heathy parents. After birth typical signs of Down's syndrome, stigma, skull defects were observed, and systolic heart murmur was heard. There were no signs of cardiovascular decompensation. Jaundice was in excess taking into account girls age.

Phenotypic changes: microgenia, hypoplastic lower part of the face, flat face, hypertelorism, "sandal" feature in the legs, ears below the eye line, slanting eyes, and heart disease.

Molecular cytogenetic chromosome analysis using FISH method for Smith-Magenis syndrome determination: FISH-17p11.2 (*RAI1*) was performed. Smith-Magenis syndrome diagnosis was confirmed.

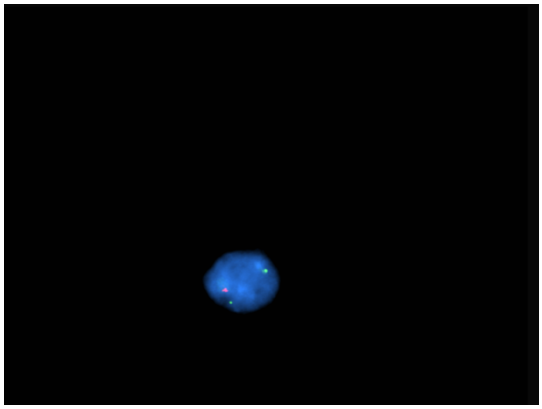

Figure 1: FISH analysis: green light shows the presence of the chromosome; red light shows the absence of parts in a chromosome

DIAGNOSIS

Smith-Magenis diagnosis is usually confirmed by performing a test, called flourescence in situ hybridization. It is a test which uses specific probes to find the exisrance or an absence of parts in a chomosome, in Smith-Magenis syndrome case, an interstitial deletion of chromosome 17p11.2 or a gene, called RAI1 (retinoic acid induced 1). It is possible to detect an interstitial deletion of chromosome 17p11.2 with routine G-banded analysis, but a mutation only in RAI1 may be overlooked. Studies show, that approximately 90% of SMS patients have a deletion, which can be detected by FISH, with approximately 70% having 3.5-Mb deletion [3]. General tactic of diagnostics is to perform a comparative genetic hybridization (CGH), which would indentify 17p11.2 deletions. If the analysis by CGH is normal and if there is a clinical suspicion of Smith-Magenis syndrome, a specific FISH test for 17p11.2 or RAI1 deletions may be performed. Both will confirm or deny SMS diagnosis.

Differential diagnosis:

Smith-Magenis syndrome should be differented from other syndrome that include infantile hypotonia, distinctive facial features, short stature, a behavioral phenotype and development delay. Similar syndroms can be distinguished by using fluorescent in situ hybridization. The most common are:

Prader-Willi syndrome – a syndrome, when a deletion in chromosome 15q11-13 occurs. Main symptoms are infantile hypotonia, behavioral problems, lack of eye coordination, poor sucking reflex, difficulty waking up, development and cognitive delays, short stature. [6]

DiGeorge syndrome – also known as 22q11.2 deletion syndrome. Features of this syndrome cary widely, and often include learning disabilities, problems with the immune system, convulsions due to hypocalcemia, which is caused by malfunctioning parathyroid glands, feeding difficulties as babies, below-borderline normal IQ, autism-like behavior. [7][8]

Miller–Dieker syndrome – caused by chromosome 17p13.3 deletion. Characterised by sunken appearance in the middle of the face, prominent forehead, small jaw. [9] Mental retardatio, reduced pre- and postnatal growth, feeding difficulties.

Cri du chat syndrome – karyotype 5p-, with the signs of feeding problems becouse of difficulty swallowing and sucking, reduced birth

weight and postnatal growth, cognitive, speech and motor development delay, hyperactivity, aggression, repetitive movements, hypotonia, growth retardation.

Angelman syndrome – a disorded, mostly characterised by severe intellectual and developmental disability, seizures, sleep disturbance, laughter, smiling and generaly happy demeanor, developmental delay, speech disability, minimal use of words, delayed growth, abnormal EEG, hypopigmented skin and eyes. It is caused by a deletion, maternally inherited by a deletion in chromosome 15. [10]

Smith-Magenis management

When the diagnosis of Smith-Magenis syndrome is confirmed, a series of evaluation tests are suggested to help with medical management of the disease:

- Full neurological and physical examination
- Spinal X-rays due to possible scoliosis
- Echocardiogram for possible cardiac anomalies
- Renal ultrasound to evaluate urologic anomalies
- Detailed ophtalmologic evaluation due to multiple possible anomalies – microcornea, strabismus, iris anomalies
- Otolaryngologic evaluation to assess throat, nose, ear problems. Common otitis media might require tympanostomy tubes.
- Audiologic evaluation for possible hearing loss
- Multidisciplinary developmental evaluation with language/speech pathology evaluation
- Keeping up a sleep diary might be helpful in diagnosing obstructive sleep apnea
- Thyroid function tests

  Recommended annually:
- Neurodevelopmental evaluation
- Ophthalmologic evaluation
- Scoliosis monitoring
- Thyroid function
- Fasting lipid profile
- Urinalysis
- Otolaryngologic assessment for otitis media
- Adiologic evaluation for conductive or sesorineural hearing loss

  Recommended as clinicaly indicated:
- EEG and brain CT or MRI scans in case of seizuresand for treatment to improve behavior and attention
- Urologic tests if the patient has frequent urinary infections
- Adrenal function screening
- Treatment for hypercholesterolemia or dyslipidemia

  Recommendations for treatment are very slim due to inefficient data and mostly experimental findings.
- Sleep disorder treatment with β1-adrenergic antagonists and melatonin seems to show promise due to an uncontrolled trial, which combined the daytime use of Acebutolol and a dose of melatonin a few hours before sleep found that nocturnal awakenings disappeared and subjective improvements in behavior during the day improved, with no reports of major adverse reactions. [11]

Diagnostics of microdeletion syndromes

Microdeletion syndromes are caused by chromosomal deletions smaller than 5 million base pairs and are too small to be detected by the usual cytogenetic methods (G-banding, spectral karyotyping, high resolution karyotyping). Microdeletions are usualy found by fluorescence in situ hybridization (FISH).

The principles of Fish method

Fluorescence in situ hybridization is a cytogenetic technique which is used to detect the absence or presence of specific DNA sequences in chromosomes. Fluorescent probes are like a mirrored copy of specific genome sequesnces, but marked with various chemical compounds which can be observed in fluorescent light. Probes can bind to the parts of a chromosome with high degrees of complementarity.

Non-Invasive Prenatal Diagnosis

Simple Non-Invasive Prenatal Diagnosis (NIPD) can be used at 9th+ week of pregnancy. Mother‘s blood sample can be taken as there are blood cells of the fetus already circulating in the system. These cells can then be tested with fluorescence in situ hybridization. Because Smith-Magenis syndrome is caused by a de novo deletion of chromosome 17p11.2, indications to test all pregnancies using FISH are not present. Only high-risk pregnancies with one or both parents having a diagnosis of genetic mosaicism should be tested with FISH and other routine cytogenetic studies. Ultrasonography is not specific to Smith-Magenis, but any anomalies found should indicate prenatal cytogenetic testing and FISH. Possible signs during US include, but are not limited to microcephaly (occipitofrontal diameter <5th centile), tetralogy of Fallot, overriding aorta, ventricular septal defect, atrial septal defect, small pulmonary trunk, polidactyly, cleft palate, micrognathia, low weight (<5th centile). There are a few cases, where SMS was detected prenatally following amniocentesis because of low maternal serum AFP on routine screening [12][13] and abnormal elevation of hCG [14].

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