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PRADER -WILLI SYNDROME : CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Prader-Willi syndrome (PWS) is a complex genetic disorder, characterized by neonatal hypotonia, delayed development, short stature, childhood obesity, hypogonadism, characteristic facial features, and other features. This is a report of 12-years old girl with Prader-Willi syndrome. After birth, she had severe hypotonia, her physiological reflexes were very indolent, also she could not suck or swallow herself. All laboratory tests for newborns were performed which showed normal results, including karyotype test (46XX). After the consultation, fluorescent in situ hybridization (FISH) cytogenetic test was carried out to verify the hypothesis of Prader-Willi syndrome. The results showed 15q11 region deletion. This case shows the importance of genetic testing when patients are suffering from severe hypotonia.

INTRODUCTION

Prader-Willi syndrome is one of the genetically based syndromes which is rather good researched and during last decades the dramatically positive changes in treatment and care of such patients occurred (e.g., growth hormone therapy, children obesity control) [1-3]. One of the symptoms of this disease is not high but mild mental retardation, and it made it slightly easier for me to stay emotionally uninvolved during studying information and life cases of the patients. One of the main characteristic features of Prader-Willi is obesity based on impossibility to feel satiety. The fact is that hunger of PWS patient might be controlled only "from the outside", or basically only with psychological methods – there is no pill or procedure nowadays to help children and adults simply not to feel hunger.

CASE REPORT

Prader-Willi syndrome (PWS) is a complex genetic disorder, characterized by neonatal hypotonia, delayed development, short stature, childhood obesity, hypogonadism, characteristic facial features, and other features . It can be considered to be an autosomal dominant disorder and is caused by deletion or disruption of a gene or several genes on the proximal long arm of the paternal chromosome 15 or maternal uniparental disomy 15, because the gene(s) on the maternal chromosome 15 are virtually inactive through imprinting. This region contains genes that are epigenetically imprinted. A recent foreign study has shown that the prevalence of PWS is 1/29,000 in newborns. We report 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 asymetrical, 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, fluorescent in situ hybridization (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. This case

shows the importance of genetic testing when patients are suffering from severe hypotonia.

PWS overview

The Prader-Willi syndrome is a genetic disorder, and being not very common, it occurs in approximately our of every 15000 births (between 1:8000 and 1:25000) (statistics from the Foundation For Prader-Willi Research Canada and USA Prader-Willi Syndrome Association) [2-3]. There is no differences in affecting males and females by this syndrome, and also all ethnicities and nations are affected the same. The Prader-Willi syndrome (PWS) is recognised as the most usual genetic cause of life-threatening childhood obesity.

It was first described in 1956 by Andrea Prader, Heinrich Willi, Alexis Labhart, Andrew Ziegler and Guido Frankoni – Swiss doctors who based their findings on the examination of nine children. The initial report contained and defined such characteristics like small hands and feet, abnormal growth and body composition including small stature, low lean body mass, and early-onset childhood obesity following the first two years of life; hypotonia at birth, insatiable hunger and intellectual disability.

This syndrome is caused by abnormality of chromosome 15, and definitive diagnosis nowadays is based on genetic testing.

Symptoms

Infants with Prader-Willi syndrome commonly exhibit hypotonia, poor suck, including the requirement of gavage feeding, weak cry, and genital hypoplasia (for instance, cryptorchidism, scrotal hypoplasia, clitoral hypoplasia). Neonatal hypotonia is one of the hallmark features of this disorder and is a valuable clue to initiate diagnostic testing [4-5].

Toddlers with Prader-Willi syndrome demonstrate delay of major motor milestones: they start sitting at age 12 months, walking at age 24 months, etc.

Children of 1-6 years present with symptoms of hyperphagia with progressive development of obesity – the very characteristic symptom of PWS. Short stature is generally present during childhood; a minority of patients present later with lack of pubertal growth spurt. Also there are here sleep disturbances, ranging from central or obstructive sleep apnea to narcolepsy. Exacerbation of obstructive sleep apnea shortly after initiation of growth hormone therapy is a recent concern.

Most patients with Prader-Willi syndrome have growth hormone deficiency which was determined with provocative testing, and the growth hormone therapy is the essential part of treatment.

Pubic and axillary hair may grow prematurely in children with Prader-Willi syndrome, but other features of puberty are generally delayed or incomplete. Testicular descent has occurred as late as in adolescence; menarche may occur as late as in 30 years in the presence of significant weight loss [4]. Mild intellectual disability is common. Obesity complications like sleep apnea, cor pulmonale, diabetes mellitus, atherosclerosis, hypogonadism (osteoporosis), and behavioral issues are common problems in adults with PWS.

Patients with Prader-Willi syndrome often exhibit certain behavioral problems, such as:

1. temper tantrums, stubbornness, and obsessive-compulsive behaviors in young children;
2. compromised level of academic performance caused by obsessive-compulsive behaviors; perseveration are challenging for children with Prader-Willi syndrome in the classroom setting;
3. psychotic features are presented in 5-10% of young adults with PWS;
4. food-seeking behaviors may include eating garbage, eating frozen food, and stealing resources to obtain food. High thresholds for vomiting and pain tolerance can complicate binging on spoiled foods and delay treatment for GI disease. One of the reasons of death is due to choking episodes. After episodes of binge eating both thin and obese individuals with Prader-Willi syndrome could develop abdominal discomfort, with acute gastric dilation observed with radiography. Some patients could develop gastric necrosis [5].

Genomic basis

There are more than one gene is involved in PWS. These genes are near each other in a small area of the "long arm" of chromosome 15, the region marked 15q11-q13. There is still no definite answer (according to information of American PWS Association) of how many genes and which specific ones are involved [3].

The critical genes must come from the child's father for correct functioning; the mother's genes in this area are "turned off" through genomic imprinting.

There are at least three different chromosome errors that can keep these key genes from working normally, and all result in the child having Prader-Willi syndrome.

The two most common errors that cause PWS can occur in any conception, means, PWS is not usually an inherited condition; this disease just happens. Parents may have a 50-percent chance of having another child with PWS only in very rare situations.

Differential diagnosis

In the 1980s scientists were questioned by the fact why some people who appeared to have PWS ceased to have the chromosome 15 deletion and also why some the individuals with the chromosome 15 deletion appeared to have a a condition that differs from PWS. Dr. Merlin Butler and colleagues started solving the issue by reporting in 1983 that the chromosome 15 deletion in PWS was on the father's chromosome [2-3].

The next breakthrough followed in 1989, when Dr. Robert Nicholls announced their research results showing PWS is an example of genetic or genomic

imprinting, a process well described in plant genetics but not previously found in humans. The "Prader-Willi region" of chromosome 15 (the area where the deletion occurs), shows genes that must come from a baby's father are active, or "expressed," in order to work. The following genes are not active or expressed on the chromosome 15 inherited from a mother because of mother imprint that appeared to turn them off. In Prader-Willi syndrome these critical genes are either absent (deleted) from a father's chromosome 15, functioning incorrectly because of an imprinting defect, or the entire chromosome 15 from a father is absent and both chromosome 15-s come from a mother. When a deletion of chromosome 15q11-q13 region is found on a mother's chromosome 15 it results is an completely different syndrome named Angelman syndrome (AS). It is caused by the fact showing there is also one gene in the Prader-Willi region that is imprinted, or turned off, on the father's chromosome 15; people who have this gene absent from their mother have AS and not PWS. This discovery solved the puzzle concerning the cases of people who had a chromosome 15 deletion but ceased to have the characteristics of PWS – their deletion was on the chromosome 15 that came from a mother. Caused by a genetic error occurrence in the same section of chromosome 15, PWS and AS are sometimes named "sister" syndromes even though being almost completely different from one another.

Genetic forms of PWS

Three genetic forms of PWS can be found and will be described further:

1. About 70% of all cases of PWS result in paternal deletion.

In the most usual form of PWS part of the chromosome 15 inherited from a child's father is absent. In some cases the section that has vanished (deletion or sometimes microdeletion) is large enough to be seen with high resolution chromosome studies done with a microscope; in other cases, it is too small in size but it possible to be detected with another chromosome test named FISH. Today typical or common deletions are classified as Class/Type 1 or Class/Type 2, based on the size of the deletion. Often a deletion occurs for an unknown reason and is not likely to happen again in another pregnancy (less than 1% chance of recurrence can be seen). There is nothing a father had done (or not) to cause it and no chance to prevent it. In rare cases of atypical deletions imprinting defects when a chromosome change such as a translocation caused the PWS genes not to function correctly , the family could have another child with the same syndrome. The importance of genetic concealing in these case seems to be obvious [4].

2. About 25% of cases result in Maternal uniparental disomy (UPD)

In this less usual form of PWS a baby inherits both copies of chromosome 15 from a mother. In these cases a developing baby commonly starts out with three copies of chromosome 15, or trisomy 15, caused by an extra set in a mother's egg. Further the chromosome 15 that came from a father's sperm ceases to exist [2]. This results with the same effect as a deletion. A child ceases to have any active genes on chromosome 15 supposed to come from a father in order to be expressed. Even though there are two complete copies of the mother's chromosome 15, the key genes in the PWS region are imprinted in the mother's copies. As far as the error in this form of PWS is caused by an extra chromosome in the mother's egg, and older eggs are more likely to have errors of this type, older mothers are more likely than younger mothers to have a baby bearing the form of PWS described above but it is also not likely to happen to a second or following child in the same family. If a baby inherits two identical chromosome 15-s from the mother (isodisomy), there is also a chance of having additional genetic problems or conditions.

3. Less than 5% of cases are imprinting defects [2]. In rather few cases the PWS genes on a father's chromosome are present but do not work properly or at all because of the error in the imprinting process [5]. The activity of the genes is controlled by the imprinting center on chromosome 15 in the are identical to PWS critical genes. Gene function on a father's chromosome 15 may not be set to work normally. An imprinting error can appear suddenly or it can be acquired in a father's chromosome received from his mother. If a father receives the defect from his mother, he ceases to have PWS himself being on his maternal chromosome 15 but there is a possibility he will pass it to his child. The research shows approximately 50% chance of any child he has receiving the chromosome with the defect instead of the one that is working correctly. Also a father's siblings can be carriers and pass on the mutation to their children. Further testing and genetic counselling are especially important for families parenting a child with an imprinting error.

Treatment and care

Obesity treatment

Obesity management is one of the most crucial points in dealing with PWS for individuals with this syndrome and their families. In infancy, the very important part of growing the baby is his/her nutrition, and the task for parents and other caregivers is to provide full-nutrient food in proper qualities. The typical feature of the syndrome is poor weight gaining during approximately 24 first months of life; the baby could even not wake up for eating and have to be waken up specially. Also, it is really needed to provide all necessary nutrients, including fats - cause as well as the obesity is awaited, caregivers might tend to exclude fats from the food, although they are absolutely essential part for correct physical and mental development. Systematic measurement of weight and comparison with standard rates according to the age and

other parameters, and comparison with the previous measurements are the key to healthy growth [2, 6].

During later age, it is essential to control food intake cause the hunger sense for these patients is constant and could not be satisfied. This is often the biggest obstacle keeping those with PWS from living independently. Today, no medications have proven effective in regulating appetite in PWS, and so strict environmental control and constant supervision are the only ways to prevent life-threatening overeating and extreme obesity at present. However, there are a number of novel anti-obesity drugs in clinical development, some of which might benefit the PWS population, and evaluation of these drugs in clinical trials is an important priority for researches. In the meantime, a well-balanced diet is recommended (Miller Diet 2013) along with careful control of the environment to minimize uncontrolled access to food. (FPWR) [5].

Growth hormone deficiency can be found in almost 100% of children and many adults with PWS. In various studies human growth hormone (HGH) has been found to be beneficial for successful treatment of PWS. In June, 2000, HGH was officially approved for use in patients with Prader-Willi syndrome by the Federal Drug Administration in the US. HGH is not only effective in increasing height but also in decreasing body fat, growing muscle mass, improving weight distribution, increasing stamina, and improving bone mineral density. Studies also suggest its positive effects on development and even behavior. In 2013 guidelines for HGH in PWS usage were developed as a part of an international meeting of experts [2].

Additional problems connected with PWS include sleep disorders, hormone abnormalities, scoliosis, dental issues, and skin picking. Breathing issues during sleep are also usual and periodic sleep studies are offered for all ages including newborns. Hormone abnormalities common in PWS might be taken care of by an endocrinologist with a set of standard medications [1].

Scoliosis being also extremely common in PWS should be treated by an orthopedic physician familiar with the syndrome. Dental problems appearing frequently in PWS are probably in part due to thicker saliva. Skin picking being common in those with PWS might be treated by the use of N-acetylcysteine.Management and treatment of the psychiatric and behavior problems associated with PWS also can be very challenging. A combination of behavioral therapy, environmental control, and necessary medication, followed by the strong support from the family and people around the patient also seems to be vital [1-2].

Organizations: There are a lot of organizations and associations in the world which are connecting scientific researches with issues of everyday life and give a lot of recommendations and provide support for people with this syndrome and their family members. Between these organizations there are PWS Association (USA), The PWS association (UK), Foundation of Prader Willi Research (Canada), National Organization For Rare Disorders (USA), and many others. These associations organize their own researches and studies, conduct conferences and provide correct information about the decease, actual problems of the people suffering from it and also ways of solving such problems.

The most notable organization is International Prader-Willi Syndrome Organization (IPWSO) with 102 countries included in the list of official members. The basic address of the organization is in Italy, and between the members are European countries, USA and Canada, South American countries, Japan, China, Thailand, Bahrain, Lithuania and Russian Federation. If there is no official organization and representative in a country, IPWSO is ready to provide any necessary assistance and support from medical or parent delegates for free [3-4].

The main aim of this organization is to raise the quality of life for all people with PWS and their families. They provide support for families, information for medical and educational specialists, translate materials and offer free diagnosis in the countries where diagnosis for PWS is not offered. The organization also have Scientific and Medical Advisory Board for scientific and medical support; Professional Provider Board for professional caregivers, a Family Care support group providing information in family-to-family fashion. Also, there is the international PWS conference conducted once per three years in different countries: the next host will be Toronto, Canada in upcoming 2016, and every year the organization attends the European society of pediatric endocrinologists.

CONCLUSION

In conclusion with improved possibility of testing methodologies, PWS is being diagnosed earlier, often in the first few years of life. Earlier diagnosis allowed earlier access to recombinant human growth hormone therapy, and appropriate guidance, has significantly improved the long-term health and developmental outcomes of children with PWS.

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STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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