CASE REPORT

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Importance of genetic evaluation and preconception assessment counseling in a case of Prader-Willi/Angelman syndrome

Importancia de la valoración genética y la asesoría preconcepcional, a propósito de un caso de síndrome de Prader-Willi/Angelman

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ABSTRACT

Objective: To report a case of prenatal diagnosis of Prader-Willi/Angelman syndrome using microarray. A review of the literature is made and the importance of preconceptional genetic counselling is highlighted. Case report: A 30-year-old female patient G2P1001 underwent genetic screening ultrasound at 11-14 weeks, in which increased nuchal sonolucence was detected in percentile greater than 99. She was taken to amniocentesis for microarray in amniotic fluid at 21 weeks whose result was chromosomal deletion 15q11.2q13.1 compatible with Prader-Willi/Angelman Syndrome. The patient was accompanied by maternal-fetal medicine and was informed about the prenatal diagnosis. The patient chose to terminate the pregnancy voluntarily. No anatomopathological study of the fetus was performed. Conclusions: Although in Colombia sentence C-355 of 2006 establishes the three grounds under which voluntary termination of pregnancy is legally available, it does not emphasize the importance of carrying out an anatomopathological study of fetuses with a prenatal diagnosis of a genetic pathology. This does not allow for a genotype-phenotype correlation, nor does it allow parents to receive preconception genetic counseling for future pregnancies.

Key words: Prader-Willi/Angelman syndrome, DNA microarray, Genetic counseling, preconceptional

RESUMEN

Objetivo. Comunicar un caso de diagnóstico prenatal del Síndrome de Prader-Willi/Angelman mediante el uso de *microarray*. Se hace una revisión de la literatura y se resalta la importancia de la asesoría genética preconcepcional. Caso clínico. Una gestante de 30 años G2P1001 se realizó ecografía de tamizaje genético de las 11 a 14 semanas, en la cual se detectó sonolucencia nucal aumentada en percentil mayor a 99. Fue llevada a amniocentesis para *microarray* en líquido amniótico a las 21 semanas, cuyo resultado fue deleción cromosómica 15q11.2q13.1 compatible con Síndrome de Prader-Willi/Angelman. La paciente recibió acompañamiento por parte de medicina materno-fetal y fue informada sobre el diagnóstico prenatal. La paciente optó por finalizar la gestación de forma voluntaria. No se realizó estudio anatomopatológico del feto. Conclusiones. Aunque en Colombia la sentencia C-355 del 2006 establece las tres causales bajo las cuales se puede acceder de forma legal a la interrupción voluntaria del embarazo, esta no enfatiza la importancia de llevar a cabo el estudio anatomopatológico de los fetos con diagnóstico prenatal de una patología genética. Lo anterior no permite hacer una correlación genotipo-fenotipo y tampoco que los padres reciban asesoría genética preconcepcional para futuras gestaciones.

Palabras clave. Síndrome de Prader-Willi/Angelman, Microarray, ADN, Asesoramiento genético preconcepcional

Introduction

Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are two clinically different genetic disorders that share the same chromosomal region 15q11q13[(1)].

PWS results from loss of gene expression within paternal chromosome 15q11q13, which can occur by three different genetic mechanisms: paternal deletion within the chromosomal region occurring in approximately 70%

of cases, maternal monoparental disomy of chromosome 15 (UPD15) occurring in 25% of those affected, and 2% of individuals have biparental inheritance of chromosome 15, but show an abnormal methylation and gene expression pattern. These patients have a defect in the imprinting center[2]. Its prevalence is estimated to be between 1:10,000-1:30,000 live births[3]. Due to its wide variability of clinical presentation, it can be diagnosed from 8.6 weeks of pregnancy to 3.9 years[2,4].

Its clinical presentation is progressive and varies from prenatal stages (phase 0), where there is evidence of reduced fetal movements and growth restriction. In childhood it is characterized by weight gain due to reduced metabolism and hyperphagia (phase 1 to 3) - becoming the first genetic cause of obesity -[2], to severe cases of delayed psychomotor and language development, as well as sleep apnea, scoliosis and endocrinopathies secondary to hypothalamic dysfunction such as growth hormone deficiency, hypogonadism, hypothyroidism and adrenal insufficiency[4].

Diagnosis is clinical, which is confirmed by genetic study. An analysis of DNA methylation status is recommended, achieving the diagnosis of PWS in 99% of cases[4]. As for treatment, it focuses on four basic pillars: diet, exercise, rhGH therapy and behavioral strategies[2].

On the other hand, there is Angelman syndrome (AS), which is generated by 4 molecular mechanisms: maternal deletions of chromosome 15q11q13 (approximately 70%-80% of patients), intragenic mutations in the maternally inherited E3A ubiquitin protein ligase (UBE3A) producing gene within chromosome 15q11q13 (10%-20% of those affected), paternal uniparental disomy for chromosome 15q11q13 (occurs in 3%-5% of patients) or chromosome imprinting defects that alter the expression of maternally inherited UBE3A (this occurs in 3%-5% of those affected)[5].

The prevalence of this syndrome ranges from 1:12,000 to 1:24,000 live births[6]. It is characterized in 100% of patients by developmental delay, intellectual disability, severely impaired cognitive ability, ataxia and tremors, easily excitable happy behavior, which is why it is called the 'happy puppet syndrome'. Additionally, seizures and microcephaly are evident in 80% of cases, and other associated features include anxiety, sleep disorders, hypotonia, and hypersalivation[7].

Diagnosis is made by testing for DNA methylation status, which is found to be abnormal in 80%-90% of cases. If this is abnormal only in the paternal imprinting pattern, the diagnosis is assured. Other techniques include fluorescence in situ hybridization and microarray to demonstrate the size of the deletion, monoparental disomy which is confirmed by analysis of DNA markers in the affected chromosome region of the parents[5]. If the methylation test is negative, but there is a high suspicion of the disease, UBE3A sequencing should be sought, which is found in 12% of cases and leads to a recurrence risk of 50%[7].

Treatment consists of syndromic approach, anticonvulsants, melatonin for sleep disorder, physical, speech and occupational therapy[7]. On the other hand, the restoration of neuronal UBE3A expression has been described, which can be performed prenatally by administering a gene therapy vector at the beginning of the second trimester, which is the period in which cortical neurogenesis ends, decreasing the severity of the syndrome; it is clarified that this is a study performed in animal models[6].

Case report

A 30-year-old female patient, G2P1001 with pregnancy of 17 weeks and 2 days by early ultrasound was referred for maternal-fetal medicine assessment due to the finding of an increased nuchal sonolucency of 2.73 mm at the 99th percentile on genetic screening ultrasound at 11 weeks and 6 days. The patient reported no significant pathological or surgical history. She was at risk of Rh-negative isoimmunization; however, she was managed with anti-D immunoglobulin in her first pregnancy and had a negative indirect Coombs' test. After signing the informed consent, amniocentesis was performed at 21 weeks for microarray in amniotic fluid, which found chromosomal deletion 15q11.2q13.1 described in OMIM (MIM6156) of autosomal dominant transmission, compatible with Prader-Willi/Angelman Syndrome. The patient was accompanied by her partner, and the risk of severe developmental delay or intellectual disability, delayed psychomotor and speech development, autism spectrum disorder, attention deficit hyperactivity disorder, among other possible neonatal complications was explained. The patient chose to have a voluntary termination of pregnancy.

Postnatal data could not be obtained due to lack of information in the clinical history. In addition, the fetus was not sent for anatomopathological study.

Discussion

Since the introduction of genetic counseling professionals, it has been possible to help patients and family members in decision making, according to ethical principles, in order to provide information on diagnostic test options according to the pathology to be studied, psychological follow-up and risk of genetic heritability, which facilitates the process of adaptation to losses, interpretation of results and, finally, decision making regarding treatment[8].

When there is diagnostic suspicion, it is necessary to rule out chromosomal/genetic causes in order to carry out an integral and directed approach that allows early therapeutic options to be established, precise follow-up and prognosis and, above all, the prevention of the appearance of new cases by means of adequate family genetic counseling[9]. Historically, the most widely used technique for chromosomal analysis has been karyotyping, which detects large losses or gains of genetic material and structural rearrangements in up to 5% of patients. However, to improve diagnostic performance, techniques such as comparative genomic hybridization arrays have been implemented that allow simultaneous exploration of multiple loci of the genome and comparison with the general population[9]. For this pathology, the technique of choice for its detection is FISH, documenting 70% of interstitial deletions of chromosome 15q11, in 2%-5% a uniparental disomy, 2%-4% a centromeric imprinting mutation and in 10% mutation of the UBE3A gene, which implies a high causal heterogeneity, being a challenge to explain the risk of recurrence[10].

The severity of the phenotype in this syndrome depends on the molecular etiology. Those with a deletion present more severe phenotypes, compared to those patients without a deletion where the clinical picture tends to be more variable. Intrauterine and postnatal growth as well as neurocognitive development depend on the genotype presented, which implies a correct prenatal diagnosis, as well as evaluation at birth[11], in order to be able to provide timely interventions.

The risk of recurrence is case-specific. It has been described to be less than 1% when normal paternal karyotypes are present, but it rises to 50% when there is a mutation of the maternal UBE3A gene or in cases in which a defect occurs in the imprinting center[10] and, although unlikely, a recurrence risk of up to 100% can occur in scenarios in which the mother is a carrier of a Robertsonian translocation 15;15[12]. Parents of children with PWS should be offered FISH to analyze the 15q11.2-q13 region. Maternal UPD15 usually occurs spontaneously, so a chromosomal study can be performed on the mother. If the result is normal, the father should undergo genetic testing to rule out a Robertsonian translocation[12].

Throughout history, great scientific and technological advances in the diagnosis and treatment of different diseases have been evidenced in the health field. Traditional medicine and its care models have been fundamentally focused on curative processes. However, in recent years a new conception of medicine has been born from advances in molecular genetics, genomic surveillance, bioinformatics, as well as the use of BigData[13], in order to study genetic pathologies and provide clear and accurate information to families for decision-making.

With the beginning of the knowledge of the cause-effect relationships of diseases, preventive medicine appeared, whose primary objective was to eliminate risk factors or, failing that, to prevent them, thus giving greater emphasis to the need for preventive medicine through the use of molecular biology techniques and genomic sequencing techniques[13].

When talking about health determinants, it is known that the genetic predisposition of an individual was established as a non-modifiable determinant. However, the advent of the study of the genome has allowed the development of a new paradigm in public health and prevention called 5P medicine, which implies personalized medicine, since it is based on the needs and genetic characteristics of individuals, predictive through genetic analysis to predict the appearance of diseases before they occur, preventive to define measures or treatments, participatory between the individual, the family and the health team in order to carry out adequate planning and necessary changes in lifestyle and treatments to improve the quality of life and,

finally, population-based, whose objective is to guarantee access to health and generate a more efficient system that allows optimal use of health resources[14].

According to clinical practice guidelines, all women with genetic or family history should be referred for reproductive assessment and counseling by a specialist in gynecology and obstetrics in order to initiate the multidisciplinary pathway and management, depending on each condition. Candidates for this assessment include women over 35 years of age in order to evaluate the association with aneuploidies and chromosomopathies, family or personal history of known genetic alterations, and patients with hemophilia, in order to provide information on the possibility of voluntary termination of pregnancy[15].

In Colombia, sentence C-355 of 2006 indicates the three grounds under which voluntary termination of pregnancy is legally available: if the pregnancy is the result of rape or incest, if the woman's life is at risk, or when the fetus presents congenital malformations incompatible with life.

Given the above, preconception genetic counseling for this entity is indicated to evaluate the risk of recurrence according to the genetic subtype. In addition, it allows estimating the prognosis and therapeutic options for future offspring[16].

Currently, there are no prevention methods to reduce the risk of having a child with Prader-Willi/Angelman syndrome. Nor have specific population groups been identified as being at risk for this pathology, since it occurs randomly. However, an association has been found with advanced maternal age and maternal disomy 15[16].

Conclusion

In Colombia, sentence C-355 of 2006 indicates the three grounds under which voluntary termination of pregnancy is legally available. Although this has allowed these procedures to be performed safely, there are no sections that explain the importance of the anatomopathological study of the fetuses, even more so when the cause is derived from a genetic pathology diagnosed prenatally as in the case presented. The genotype-phenotype correlation and the preconception genetic counseling provide information on the risk of heritability, natural history and treatment of a pathology and help in decision making, considering personal values and beliefs.

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