6th International Prader-Willi Syndrome Caregivers' Conference

IPWSO International Prader-Willi Syndrome Organisation

Berlin, 21-23 may 2024

PRADER-WILLI FEDERAZIONE ITALIANA DELLE ASSOCIAZIONI

A case of Angelman Syndrome from a mother with Prader-Willi Syndrome

Donatella Greco, Luigi Vetri, Letizia Ragusa, Paola Occhipinti, Antonella Costanzo, Loredana Nucifora, Angela Catania*, Francesco Calì, Serafino Buono, Corrado Romano

Oasi Research Institute-IRCCS, Troina (EN) *L.C. Laboratori Campisi, Avola (SR)

INTRODUCTION

Prader-Willi syndrome (PWS) and Angelman syndrome AS) are neurodevelopmental disorders caused by lack of expression of imprinted genes in the PWS/AS critical region 15q11-q13. The clinical features of PWS include hypotonia and feeding difficulties at birth, followed by delayed psychomotor development, hyperphagia resulting in obesity. Other reported characteristics are peculiar facies (narrow forehead, almond-shaped eyes, thin upper lip and mouth turned downwards), very small hands and feet, intellectual disability, learning difficulties, behavioral disorders or serious psychiatric problems, hypogonadotropic hypogonadism with pubertal development delayed or incomplete. Infertility is a constant feature in both sexes of PWS. We report the case of a 25-year-old woman with PWS and her 3-month-old daughter with AS.

MATERIALS AND METHODS

The molecular diagnosis of PWS was achieved through methylation test of SNRPN gene (through chemical DNA modification followed by methylation specific PCR–MSP), documenting the single maternal methylated allele, compatible with PWS.

The diagnosis was confirmed by multiplex ligation-dependent probe amplification (MLPA) analysis (by SALSA MLPA Kit ME028B1 Prader Willi/Angelman) that allowed for the contemporary possibility of assessing the methylation status and the presence of alterations in the number of copies in the PWS/AS critical region.

The AS was diagnosed through the methylation test, that showed the single paternal methylated allele compatible with AS. Moreover, the diagnosis was confirmed through the molecular analysis of MLPA, showing the absence of maternal alleles including MKRN3, MAGEL2, NDN, SNRPN, UBE3A, ATP10A, GABRB3 genes, and HBII-85 snoRNA cluster in the 15q11.1–15q13 chromosomal region. The MLPA analysis was compatible with AS diagnosis due to ~5.7 Mb maternal deletion in the 15q11.1–15q13 region.

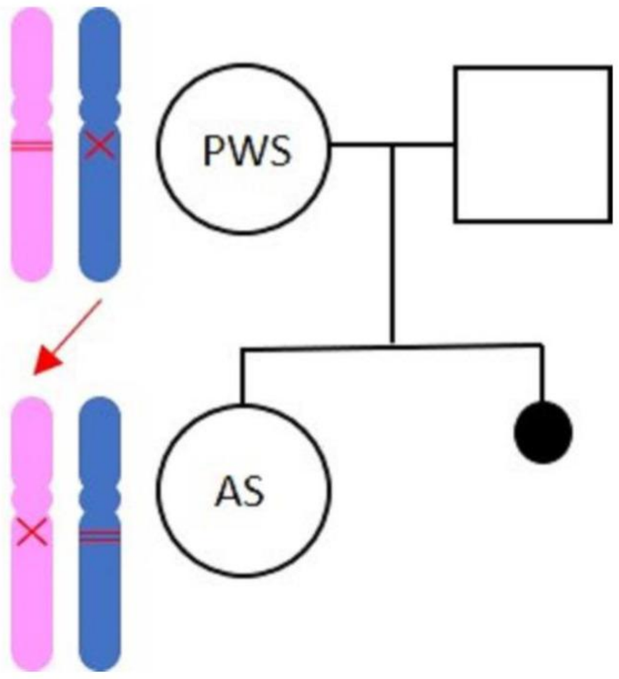

Fig.1 Genetic family tree. In the mother, the paternal allele got deleted and the maternal allele is methylated (condition compatible with PWS). The daughter inherits the deleted maternal allele, and the paternal allele is methylated (condition compatible with AS).

CASE REPORT

The diagnosis of PWS was confirmed at the age of 8 by the molecular genetics test underlying a 5.7 Mb deletion of paternal origin in the PWS/AS critical region. Moreover, the clinical diagnostic criteria according to Holm1 were fully satisfied. The patient presented obesity with BMI = 39.4 kg/m2 and type 2 diabetes mellitus. The girl developed a typical PWS behavioral phenotype, characterized by obsessive-compulsive behaviors, rigid thinking, suspiciousness, low frustration tolerance, emotional vulnerability, and self-destructive behaviors, like skin picking. Therefore, she is treated with Risperidone and Oxcarbazepine.

The menarche occurred when she was 16, with irregular menstrual cycles following. She never took sexual hormone replacement therapy. The gynecological ultrasound showed an anteverted uterus of regular size and eco structure, and normal bilateral ovaries. At the age of 26, following a physical abdominal examination, a pelvic ultrasound and a pregnancy test were performed.

Gestation, through fetal ultrasonography, was estimated to be at 28 weeks. Her partner had no neurological, psychiatric, or genetic disorders. The pregnant woman and her parents were informed about a 50% chance that the fetus was affected by AS.

Since in PWS there are a reduction of pain threshold and behavioral problems, and assuming the risk of lack of cooperation during labor, the caesarean section at 38 weeks of gestation was agreed upon and planned.

RESULTS

The diagnosis was confirmed by molecular genetic testing that revealed a ~5.7 Mb deletion in the 15q11.1–15q13 region on the paternal allele in the mother with PWS and the maternal one in the daughter with AS, respectively. Both the mother with PWS and the daughter with AS showed peculiar clinical and genetic features of the two syndromes.

CONCLUSION

Infertility is a constant feature of both male and female individuals affected by PWS, because sexual maturity does not fully develop in PWS. In people with PWS puberty is frequently delayed and/or incomplete. However, they have a premature pubarche characterized by earlier appearance of pubic hair. In girls there is mostly some breast development and in boys a degree of penile growth. Cryptorchidism, small testes, scrotal hypoplasia, and a micro-penis, are often present in boys. Hypoplasia of the clitoris, primary or secondary amenorrhea, and late menarche (frequently after their 20s) are often present in girls. Menstruation, when present, is often irregular and feeble, but some girls can have regular menstrual cycles.

Our case report reaffirms the possible fertility in PWS; therefore, it is very important to develop appropriate socio-sexual education programs and fertility assessments in order to guarantee the expression of a healthy sexuality.

REFERENCES

•Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenwag R,Whitman BY, et al. Prader-Willi syndrome: consensus diagnostic criteria. Pediatrics 1993; 91: 398–402

•Cassidy S, Schwartz S (updated 1998). Prader-Willi syndrome.In: GeneClinics available at http://www.geneclinics.org /pro. Les/pws

•Clayton-Smith J, Pembrey ME. Angelman syndrome. J Med Genet 1992; 29: 412–5

• Williams CA, Lossie AC, Driscoll DJ, et al. (updated1998). Angelman syndrome. In: GeneClinics available at http://www.geneclinics.org /pro. les/as

•Sculze A, Mogensen H, Hamborg-Peterson B, et al. Fertility in Prader-Willi syndrome: a case report with Angelman syndrome in the offspring. Acta Pediatr 2001; 90: 455-9