CASE REPORT

Herlyn-Werner-Wunderlich and Prader-Willi syndromes: more than a coincidence?

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SUMMARY

Summary A neonate with a prenatal diagnosis of left renal agenesis was born at 33 weeks gestation. A postnatal abdominal ultrasound confirmed the absence of the left kidney and revealed two non-divergent hemiuteri, consistent with the diagnosis of Herlyn-Werner-Wunderlich syndrome. During admission, significant axial hypotonia was noted, warranting additional investigations. Brain ultrasounds and MRI were normal, as were a preliminary metabolic study and comparative genomic hybridisation array. DNA methylation testing confirmed the diagnosis of Prader-Willi syndrome. The baby was discharged after 70 days, breast feeding and with modest hypotonia improvement.

BACKGROUND

Herlyn-Werner-Wunderlich syndrome (HWWS), also called Obstructed Hemivagina and Ipsilateral Renal Anomaly (OHVIRA) syndrome, is a rare congenital anomaly, characterised by uterus didelphys, vaginal septum and unilateral renal anomalies, most frequently agenesis, caused by the abnormal development of Müllerian and Wolffian ducts.^{1 2} Patients with HWWS are usually asymptomatic until menarche. However, there are a few reports describing earlier diagnosis in childhood and one case in the neonatal period.³

Prader-Willi syndrome (PWS) is a neurodevelopmental disorder that results from the lack of expression of paternally inherited genes located in the chromosome 15q11-q13.^{4 5} In the neonatal period, PWS presents with non-specific symptoms such as hypotonia, feeding difficulties and failure to thrive.⁵

We report a case of a neonate with both diagnoses: HWWS and PWS. To the best of our knowledge, there have been no previous reports of such association.

CASE PRESENTATION

We report a case of a female neonate, born at 33 weeks gestation, with an unremarkable family history. Prenatal ultrasounds revealed left renal agenesis and nasal bone hypoplasia since the 24th week of gestation. Cell-free DNA testing for fetal trisomy was negative. At 33 weeks gestation, third trimester bleeding in the mother prompted her admission to the hospital. The baby was delivered by caesarean section due to signs of fetal distress, after an incomplete course of corticosteroids for fetal lung maturation.

The neonate was born hypotonic, with inefficient respiratory effort, which responded to positive

pressure ventilation. The Apgar score was 9/10 (1st and 5th minutes, respectively) and she was transported to the neonatal intensive care unit with nasal continuous positive airway pressure (nCPAP). She was small for gestational age, weighing 1453 g (P<3) and measuring 30.5 cm (P3). At examination, significant axial hypotonia was noted, and no apparent malformations were detected.

INVESTIGATIONS

Abdominal ultrasound confirmed absence of the left kidney and revealed a uterine anomaly with two non-divergent hemiuteri. There were no signs of hydrometrocolpos.

Renal scintigraphy revealed a functioning right kidney without visible lesions.

An interventricular septal defect was found in the echocardiogram.

Additional investigations to unravel the aetiology of the baby's hypotonia were decided on after consultation with a neuropaediatrician and a geneticist. The baby was also examined by a neuro-ophthalmologist and an otorhinolaryngologist, with no additional findings.

Brain ultrasounds and MRI were normal.

A preliminary metabolic study with amino acid chromatography, redox potential, percentage of carbohydrate-deficient transferrin and the presence of reducing sugars had values within normal range.

Comparative genomic hybridisation array and karyotype were normal. DNA methylation testing confirmed PWS.

OUTCOME AND FOLLOW-UP

During admission, the baby was maintained on nCPAP for 3 days, and acquired progressive weight gain and independent oral feeding. She was discharged after 70 days, breast feeding and with modest hypotonia improvement.

DISCUSSION

HWWS is a very rare condition that results from a disorder of vertical and lateral fusion of the Müllerian ducts, around the 8th/9th week of gestation.^{1 3} Incidences of obstructive Müllerian anomalies are believed to be between 0.1% and 3.8% and HWWS accounts for approximately 5% of these.^{1 6} Studies of uterine organogenesis have implicated the Hox and Wnt genes as regulators of uterine morphology. However, specific gene mutations have not been identified or associated with most Müllerian duct anomalies.⁶

HWWS is usually asymptomatic until puberty, and an early diagnosis implies clinical suspicion or

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an incidental finding.³ Müllerian duct fusion anomaly should be suspected if renal agenesis is diagnosed in prenatal obstetric ultrasounds.⁷ The uterine malformation can be easily detected with an ultrasound in the neonatal period, because the newborn is under the influence of maternal and placental hormones and the size of the uterus increases in late gestation, showing a definable endometrial line.⁷ If necessary, further imaging studies, such as MRI or CT scan, can be considered to confirm the diagnosis.³

This syndrome usually presents in adolescent girls after menarche, with acute abdominal pain and sometimes an abdominal mass.^{1 3} A surgical approach is recommended in these cases, to prevent complications such as infertility, endometriosis, pelvic adhesions, pyosalpinx or pyocolpos.^{1 3} For newborns and girls aged below 10 years, there are no definitive treatment guidelines.¹

PWS is a neurodevelopmental disorder that occurs in approximately 1:15 000 to 1:25 000 individuals.⁸ This syndrome is caused by the absence of paternal expression of imprinted genes localised to 15q11-q13 region, which can result from paternal deletion (65–75%), maternal uniparental disomy (20–30%), from genomic imprinting centre defects (1–3%) or in sporadic cases.^{4 5 8}

Classic PWS presentation occurs in childhood, with hyperphagia, obesity, short stature, small hands and feet, mild mental deficiency, behavioural problems and hypogonadism.⁹

The prevalence of PWS among infants with hypotonia is around 10%.^{5 10} However, clinical diagnosis of PWS is difficult during the neonatal period and infancy because of absent typical phenotypic characteristics, and presence of non-specific symptoms such as hypotonia, feeding difficulties and failure to thrive.⁵

Many typical PWS features have been attributed to a primary defect in hypothalamic function, and hypogonadism has been attributed to gonadotropin deficiency.⁴ There are no references to a possible relationship between PWS and Müllerian duct anomalies such as HWWs. However, a recent study suggested that the hypogonadism in PWS may be due to combined hypothalamic and primary gonadal abnormalities.⁴ This study demonstrated that women with PWS have low levels of specific ovarian hormones—anti-Müllerian hormone and inhibin B (INB)—and small ovaries with low antral follicle count. This ovarian defect was associated with normal or high levels of follicle-stimulating hormone in the vast majority of subjects and it cannot be attributed to the hypothalamic-pituitary pathway.⁴

Although unlikely, the possibility of primary gonadal abnormalities in PWS leads to the consideration that the association of this syndrome with HWWs could be more than coincidental. Furthermore, it is known that both syndromes are forms of disorders of sex differentiation (DSD). PWS is included in the subtype with abnormalities of hormonal function, and HWWs

is part of the group with primary morphological defect of genital development, with normal sex hormones.¹¹

Decoding of the genetic causes of many DSD is occurring at an extraordinary rate, so, in the future, it may be possible to find a genetic association between these two syndromes.

Learning points

- ▶ Herlyn-Werner-Wunderlich syndrome (HWWs) and Prader-Willi syndrome (PWS) can present in the neonatal period.
- ▶ Müllerian duct anomalies such as HWWs should be suspected in all female neonates with prenatal diagnosis of renal agenesis and confirmed postnatally.
- ▶ PWS should be suspected in all newborns with hypotonia, feeding difficulties and failure to thrive.

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Competing interests None declared.

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