

Beckwith-Wiedemann Syndrome in a Patient with Klinefelter Syndrome

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Citation

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Abstract

Beckwith-Wiedemann syndrome (BWS) is a well recognized clinical syndrome with a complex multi-genetic pathogenesis due to alterations in growth regulatory genes on chromosome 11p15. BWS has a frequency of 1 in 15000 live births. It is classically characterized by a triad of exomphalos, macroglossia and gigantism. Klinefelter syndrome is the most common cause of male hypogonadism with an estimated incidence of 1 in 500-1000 live born males. Chromosome studies most often show a 47 XXY karyotype. We report a newborn with a prenatal diagnosis of Klinefelter syndrome, and diagnosed to also have BWS after birth. This is a rare and interesting association with few previous reports in literature.

INTRODUCTION

Beckwith-Wiedemann syndrome (BWS) is a well recognized clinical syndrome with a complex multi-genetic pathogenesis due to alterations in growth regulatory genes on chromosome 11p15. BWS has a frequency of 1 in 15000 live births. It is classically characterized by a triad of exomphalos, macroglossia and gigantism.

Klinefelter syndrome is the most common cause of male hypogonadism with an estimated incidence of 1 in 500-1000 live born males [1]. Chromosome studies most often show a 47 XXY karyotype.

We report a newborn with a prenatal diagnosis of Klinefelter syndrome, and diagnosed to also have BWS after birth. This is a rare and interesting association with few previous reports in literature.

CASE HISTORY

Our patient was a male infant born to unrelated Hispanic parents. The mother was 38 years old, gravida 4 and para 1. There were 2 first trimester voluntary terminations of pregnancies. Mother had a 13 year old healthy daughter from another relationship and father had 3 other children from a previous relationship. Family history was negative for any birth defects, miscarriages, or early deaths.

Prenatal ultrasound at 17 weeks gestation showed a fetal omphalocele. FISH (Fluorescent in situ hybridization) study on amniocytes revealed a 47, XXY karyotype (Fig 1),

consistent with a diagnosis of Klinefelter syndrome.

Maternal serum and amniotic fluid alpha-fetoprotein levels were normal at that time. The parents were counseled and followed by the division of Genetics. The mother chose to continue the pregnancy and follow-up fetal ultrasound at 28 weeks gestation showed polyhydramnios with normal fetal growth.

The patient was born via repeat Cesarean section at 34 weeks gestation. Apgar scores were 6 and 7 at one and five minutes, respectively. The baby had poor cry, decreased muscle tone and respiratory distress at birth. Birth weight was 2775 grams (90th percentile), length 48cm (90th percentile) and head circumference was 33 cm (90th percentile). Physical exam was remarkable for hypoplastic flat nasal bone, hypertelorism with short palpebral features, low set ears, right ear crease, wide mouth, large tongue, widely spaced nipples, hypotonic limbs with hypoplastic fingernails, small omphalocele with umbilical cord cyst and visible small bowel, undescended testes bilaterally with right testes palpable in inguinal canal. The ear creases, macroglossia and omphalocele were all suggestive of a diagnosis of BWS and chromosomal analysis studies for the same were sent.

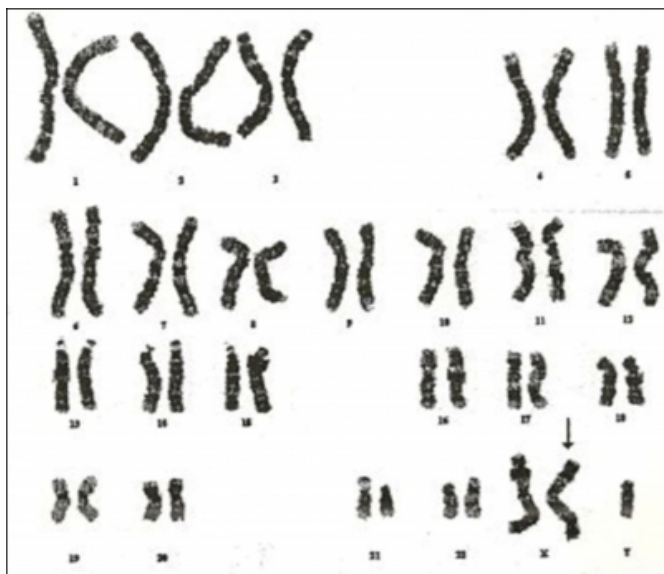
During hospital stay of this patient, the omphalocele was reduced manually and the sac ligated at the skin level hoping for skin to close naturally. Patient did not require surgical correction of the defect. The infant required respiratory support with nasal continuous positive airway pressure

(CPAP) for the first week of life. He received intravenous antibiotics for one week. He received phototherapy for physiological jaundice in the first week of life. His plasma glucose remained normal during his hospitalization. He was diagnosed with a moderate sized patent ductus arteriosus that was medically treated with intravenous Ibuprofen. There was no evidence of cardiomegaly on echocardiogram. Abdominal ultrasound did not reveal any visceromegaly and renal ultrasound was within normal limits. Scrotal ultrasound confirmed presence of right testicle in inguinal canal and absent left testicle. Cranial ultrasound and eye exam were normal and the infant passed newborn hearing screen prior to discharge.

Chromosome BAC (Bacterial Artificial Chromosome) array with 607 targets was unrevealing, aside from confirmation of the 47, XXY karyotype. Subsequent methylation analysis of the LIT1 gene was abnormal and consistent with a diagnosis of BWS.

Figure 1

Fig 1. XXY Karyotype



DISCUSSION

Beckwith-Wiedemann syndrome is a congenital overgrowth disorder classically characterized by the triad of exomphalos, macroglossia, and gigantism but may have a wide range of clinical manifestations that include hemihyperplasia, craniofacial abnormalities, ear anomalies, umbilical hernia, diastasis recti, visceromegaly, adrenocortical cytomegaly, renal abnormalities, neonatal hypoglycemia, embryonal tumors, and also cryptorchidism.

The genetics of BWS is complex. Approximately 85% cases

are sporadic but autosomal dominant inheritance has been identified with preferential maternal transmission in 10-15% cases.

The critical causative region for BWS is located on chromosome 11p15, a region of highly imprinted gene clusters. Variations in paternal and maternal expression of genes, such as paternal duplications, unipaternal disomy, maternal translocations and inversions, and methylation abnormalities, may lead to the pathogenesis of BWS through increased expressions of paternally expressed growth promoter genes and loss of maternally expressed growth suppressor genes [2].

Klinefelter syndrome is classically defined as 47, XXY karyotype with variants that demonstrate additional X and Y chromosomes. It is characterized by hypogonadism (small testes, azoospermia/oligospermia), infertility, gynecomastia in late puberty, psychosocial problems, hyalinization and fibrosis of the seminiferous tubules, and elevated urinary gonadotropin levels. Most diagnoses are not made until adulthood and indications for karyotyping are commonly hypogonadism and infertility. Our patient was diagnosed antenatally as a result of work up for his omphalocele.

The association of Beckwith-Wiedemann and Klinefelter syndrome is rare. On review of literature we came across two previous reports of this association. Fryns et al [3] in 1986 described a clinical case of Beckwith-Wiedemann syndrome found to have karyotype 47, XXY only on chromosomal analysis.

Delicado et al [4] later reported a patient with prenatal diagnosis of Klinefelter syndrome with karyotype 47, XXY and “de novo” pericentric inversion of chromosome Y, whose growth characteristics in the subsequent years of life pointed towards a diagnosis of Beckwith-Wiedemann syndrome. Molecular analysis revealed a partial trisomy 11p15.5 and monosomy 18q inherited as a result of paternal translocation between chromosome 11 and 18.

Currently genetic testing is available for many of the genetic abnormalities of BWS. Cytogenetic study is warranted because of prognostic implications of duplication of 11p15 and the association with developmental delay [5]. LIT1 methylation abnormalities appear to less likely be associated with cancers [6]. Early diagnosis would also enable routine screening for embryonal tumors with periodic abdominal ultrasounds and serum alpha-fetoprotein measurements.

CONCLUSION

This case has been reported because of the unique association of the two discrete genetic entities of BWS and Klinefelter syndrome. This warrants special multidisciplinary care to monitor for future phenotypic expressions of BWS, potential complications and developmental delays.

References

1. Bhasin S, Ma K, Sinha I, Limbo M, Taylor WE, Salehian B. The genetic basis of male infertility. *Endocrinol Metab Clin North Am*. Dec 1998; 27(4):783-805
2. Weksberg R, Shuman C. Beckwith Wiedemann Syndrome and Hemihyperplasia. *Management of Genetic Syndromes*, Second Edition 2005
3. Fryns JP, Kleczkowska A, Van den Berghe H. 47 XXY Karyotype in a patient with Beckwith Wiedemann syndrome. *Ann Genet*. 1986; 29(2): 112-3
4. Delicado A, Lapunzina P, et al. Beckwith-Wiedemann syndrome due to 11p15.5 paternal duplication associated with Klinefelter syndrome and a "de novo" pericentric inversion of chromosome Y. *Eur J Med Genet*. 2005 Apr-Jun; 48(2):159-66. Epub 2005 Mar 2.
5. Slavotinek A, Gaunt L, Donnai D. Paternally Inherited duplications of 11p15.5 and Beckwith Wiedemann syndrome. *J Med Genet* 1997; 34:819-26
6. DeBaun MR, Niemitz EL, McNeil DE, Brandenburg SA, Lee MP, Feinberg AP. Epigenetic alterations of H19 and LIT1 distinguish patients with Beckwith-Wiedemann syndrome with cancer and birth defects. *Am J Hum Genet* 2002 Mar; 70(3):604-11

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