CE 2.3 HOURS Continuing Education

Recognition and Management of the Infant With Beckwith–Wiedemann Syndrome

Pamela S. Spivey, MSN, RN, CNS, Wanda T. Bradshaw, MSN, RN, NNP-BC

ABSTRACT

Beckwith–Wiedemann Syndrome (BWS) is the most common overgrowth syndrome in infancy. The characteristic findings are macroglossia, abdominal wall defects, and macrosomia. Genetic studies in infants with BWS demonstrate 3 major subgroups of patients: familial, sporadic, or chromosomally abnormal. Recognition in the neonatal period is important because of the high incidence of childhood malignant tumors associated with BWS. This article provides an overview of the syndrome and discusses its etiology, physical findings, and diagnostic evaluation. Management and clinical implications including family support will also be discussed.

KEY WORDS: Beckwith–Wiedemann syndrome, 11p15, genomic imprinting, hemihyperplasia, macroglossia, macrosomia, omphalocele, overgrowth syndrome

Beckwith–Wiedemann syndrome (BWS) is a disorder of overgrowth with recognizable clinical characteristics of macroglossia, abdominal wall defects, macrosomia, and severe hypoglycemia.[1,2] Other clinical findings include midface hypoplasia, ear anomalies, facial nevus flammeus, hemihyperplasia, cardiac defects, visceromegaly, and tumors.[2,3] Most BWS cases are sporadic, but chromosomal abnormalities of 11p15 have been reported.[4] There is a higher incidence of polyhydramnios and prematurity associated with this syndrome.[5] A mortality rate of 20% has been seen in infants with BWS primarily because of complications of prematurity associated with omphalocele, macroglossia, neonatal hypoglycemia, and cardiomyopathy.[6]

Early identification of clinical findings associated with BWS and the neonate's response to extrauterine life provides the bedside clinician with pertinent information for managing the newborn. Prenatal and obstetrical information may help the practitioner anticipate neonatal needs after birth. Continued observation and inspection of the newborn's clinical appearance generates further evaluation of relevant findings. This article focuses on the clinical features associated with the syndrome, current medical management, and nursing implications. Family support and community resources will also be discussed.

INCIDENCE

The incidence of BWS is approximately 1 in 12,000 infants. It occurs equally in males and females and has been reported in various ethnic groups. Some cases may be unknowingly omitted because of milder phenotypic expression. Therefore, the actual prevalence may be higher.[1,4,6] An abnormal regulation of specific genes within the 11p15 region disrupts normal growth. This is a result of genetic imprinting, the occurrence of specific genes being expressed only by the maternal or the paternal allele and not by both alleles as previously assumed.[7] Genetic imprinting results in a turning on or activation of a segment on chromosome 11 that is responsible for growth. This leads to overgrowth and other clinical features of BWS.[8] Recent literature suggests a higher incidence of genetic imprinting in infants of mothers who used assisted reproductive technology to achieve pregnancy.[9,10]

ETIOLOGY

Alterations in specific genes on chromosome 11p15 have been implicated in the pathogenesis of BWS.

Address correspondence to Pamela S. Spivey, MSN, RN, CNS, Levine Children's Hospital, Charlotte, NC 28204; pamspivey43@yahoo.com.

Author Affiliations: Levine Children's Hospital, Department of Neonatology, Charlotte, North Carolina.

Imprinting control regions on chromosome 11 regulate chemical processes known as methylation. Overmethylation of the insulin-like growth factor 2 (IGF-2) gene and suppression of the *H19* gene, which restrains growth, cause the overgrowth and increased risk of tumors seen with BWS.[7]

Three major subgroups of alterations have been identified through genetic studies of infants with BWS: sporadic, familial, and chromosomally abnormal. Weksberg and colleagues[4] found at least 85% of cases to be sporadic and 10% to 15% to have autosomal dominant inheritance from maternal transmission. Translocation, duplication, or inversion of 11p15 occurred both sporadically and through inheritance. Uniparental disomy, the result of inheriting both copies of a chromosome from only one parent, has been reported. Typically infants with this syndrome have 2 paternal copies of 11p15 and no maternal copies.[4,11]

The expression of both paternal and maternal genes is necessary for appropriate fetal growth. When the genes are altered through imprinting or in the case of uniparental disomy, absent, paternally expressed growth-promoting gene IGF-2 and maternally expressed growth-suppressing *H19* genes are affected. Mutations in the gene *CDKN1C* are identified in 5% to 10% of sporadic cases and 40% of familial forms. This gene is also involved in fetal growth regulation.[2]

Clinical Findings

The characteristic features of BWS are macrosomia, macroglossia, and abdominal wall defects (omphalocele, umbilical hernia, and diastasis recti abdominis). These findings are usually present at birth and lead the bedside practitioner to evaluate the infant for additional anomalies. Other clinicians have identified additional features (Table 1) including prominent occiput, facial nevus flammeus, hemihyperplasia, embryonic tumors, adrenocortical cytomegaly, ear anomalies, visceromegaly, renal abnormalities, and cleft palate.[2,3,6] Diagnosis is made when at least 3 diagnostic findings are present. Other findings that support the diagnosis of BWS can be noted prenatally: fetal overgrowth, enlarged placenta, polyhydramnios, visceromegaly, and discordant monozygotic twins.[4,12] Prematurity occurs in 27% of the cases.[1,3,4]

Macrosomia, commonly referred to as large body size, is seen in 75% of the cases of BWS. The infants are usually greater than the 90th percentile in both weight and height during infancy and early childhood with a slowing of growth velocity by 6 years of age. No differences in weight and height were found between male and female infants. Hemihyperplasia occurs in a small segment of the cases. Hemihyperplasia is asymmetric overgrowth of the cranium, face, trunk, limbs, and/or digits with or without visceral involvement resulting in unequal growth and an increased risk of developing tumors of embryonic origin.[13,14]

Macroglossia or tongue enlargement (Figure 1) is present in more than 80% of cases of BWS. Macroglossia can vary in size with more severe cases leading to respiratory and feeding difficulties. Angle[15] found a slightly enlarged tongue in a 4-month-old female that did not cause respiratory or feeding difficulties.[15] Additional major findings of macrosomia, facial nevus flammeus, ear anomalies, umbilical hernia, and hemihyperplasia manifested by asymmetrical limb growth assisted Angle in confirming the diagnosis of BWS. Macroglossia appears to regress with growth of the jaw and other facial structures. Speech articulation can be affected with persistent macroglossia.[1] Other craniofacial characteristics include midface hypoplasia (85%), a prominent

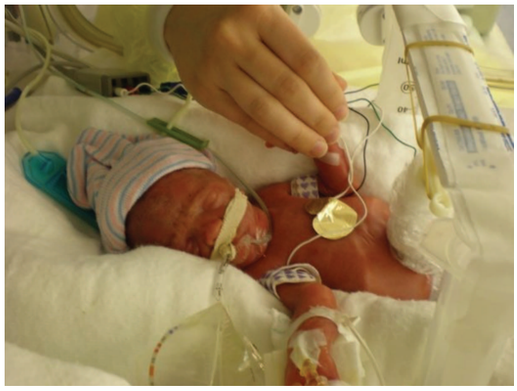
TABLE 1. Primary and Secondary Features of Beckwith–Wiedemann Syndrome

Primary	Secondary
Polyhydramnios	Enlarged placenta
Hypoglycemia	Cardiomegaly
Overgrowth	Polycythemia
Macroglossia	Hypercholesterolemia
Midface hypoplasia	Hypercalciuria
Nevus flammeus	Hypertelorism
Earlobe grooves/pits	Hypothyroidism
Abdominal wall defects	Cardiovascular anomalies
Prominent occiput	Renal anomalies
Hemihyperplasia	Tumors in childhood

FIGURE 1.

Two major findings in Beckwith—Wiedemann syndrome are macroglossia (enlarged tongue) and nevus flammeus. Photo courtesy of Jamie and Jason Conrad.

FIGURE 2.



Omphalocele in premature infant born at 25 weeks' gestation. Innovative wrapping held omphalocele and protected abdominal viscera until the infant is able to have surgical repair. Photo courtesy of Jamie and Jason Conrad.

occiput (58%), and nevus flammeus of the forehead (Figure 2) and eyelids (54%). Ear lobe creases and posterior helical pits are seen in 63% of BWS cases.[1,3]

Abdominal wall defects such as omphalocele, umbilical hernia, and diastasis recti abdominis are present in 80% of cases.[2,3] Cardiomegaly and structural cardiac defects have been reported in approximately 25% of BWS cases, but no specific defect has been prominent. Hepatomegaly, nephromegaly, and hyperplastic bladder, uterus, ovaries, testes, and thymus have been found.[1]

Overgrowth syndromes such as BWS are associated with an increased incidence of tumor development in early childhood. The most common neoplasms are Wilms' tumor (nephroblastoma), an embryonic malignancy of the kidney, adrenal cortical carcinoma, and hepatoblastoma. Wilms' tumor usually presents by the age of 5 years. Hepatoblastoma, liver cancer, usually develops by 2 years of age. Other less frequent neoplasms have been reported. The overall incidence of tumor development is 7.5%. The risk declines with age and is similar to the overall population by 10 years of age.[3,14,16]

Laboratory findings in BWS include hypoglycemia, polycythemia, hypocalcemia, hypercalciuria, and hyperlididemia.[1] Transient hypoglycemia is seen in the immediate newborn period. The infants may require higher glucose infusion rates initially but respond well to therapy, and hypoglycemia usually resolves with advancing age.[17,18] Severe hypoglycemia occurs in more than 50% of the cases, is caused by hyperinsulinism, and has been linked to islet cells hyperplasia.[2] Untreated severe hypoglycemia could lead to seizures and adverse neurologic outcomes. Hypercalciuria is found in 22% of the cases. This may suggest an underlying primary structural abnormality in the kidneys. Polycythemia (20%), hypocalcemia (5%), and hyperlipidemia (2%) are seen less often.[1,19,20]

Differential Diagnosis

There are several overgrowth syndromes that manifest themselves with characteristics similar to those of BWS. The differential diagnosis of infants presenting with macrosomia, macroglossia, neonatal hypoglycemia, or other findings of BWS should include Simpson–Golabi–Behmel syndrome, Perlman syndrome, Sotos syndrome, and isolated hemihyperplasia (Table 2).[1,4,21,22]

TABLE 2. Comparison of Clinical Findings Associated With Overgrowth Syndromes

Beckwith–Wiedemann syndrome	Simpson–Golabi–Behmel syndrome	Perlman syndrome	Sotos syndrome
Macroglossia	Macroglossia	Macroglossia	Macroglossia
Macrosomia	Macrosomia	Macrosomia	Macrosomia
Hepatosplenomegaly	Hepatosplenomegaly	Hepatosplenomegaly	Hepatosplenomegaly
Kidney abnormalities	Kidney abnormalities	Kidney abnormalities	Kidney abnormalities
	Macrocephaly	Macrocephaly	
	Congenital heart disease		
	Skeletal anomalies		
	Supernumerary nipples		
Abdominal wall defects			
		Facial anomalies	Facial anomalies
Neonatal hypoglycemia	Neonatal hypoglycemia	Neonatal hypoglycemia	Neonatal hypoglycemia

Simpson–Golabi–Behmel syndrome shares the following characteristics with BWS: macrosomia, macroglossia, hepatosplenomegaly, and cystic dysplasia of the kidneys. Infants with this syndrome also have an increased risk for developing embryonal tumors such as Wilms' tumor and hepatoblastoma. Unlike BWS, Simpson–Golabi–Behmel syndrome has a higher incidence of congenital heart disease with additional features of macrocephaly, supernumerary nipples, and skeletal anomalies.[1,4] Perlman syndrome is an autosomal recessive disorder that presents with macrosomia, nephromegaly, hepatomegaly, and hypoglycemia. Infants with Perlman syndrome have characteristic facial features including full-round face, everted upper lip, depressed nasal bridge, and micrognathia.[21] Sotos syndrome is also characterized with overgrowth and distinctive facial features. This syndrome has been linked to 11p15 uniparental disomy much like BWS.[22]

Management

Assessment for airway sufficiency in the presence of macroglossia is crucial in the immediate newborn period. Endotracheal intubation may be difficult because of the enlarged tongue. Macroglossia may also impair feeding, necessitating the use of specialized nipples or orogastric tubes to manage feeding difficulties. If growth of facial structures does not improve moderate to severe macroglossia, then surgical intervention by a multidisciplinary craniofacial team is recommended.[4,12]

Clinical management for BWS includes early recognition and treatment of hypoglycemia to reduce the risk of a poor neurologic outcome. Glucose is important for the brain because other energy substrates are not available. Severe hypoglycemia can present with seizures and, if untreated, can lead to developmental delay. Infants with BWS will need increased requirements of glucose until hypoglycemia resolves.[18] If hypoglycemia persists, a pediatric endocrinologist consult is warranted.

Surgical intervention is necessary for neonates with omphalocele. Preoperative measures include maintenance of fluid and electrolytes, thermoregulation, gastric decompression, protection of the abdominal viscera (Figure 2), and prophylaxis against infection. A clear plastic bowel bag is often used to allow for constant visual monitoring and to decrease evaporative losses. Use of the bowel bag replaces the previous method of wrapping the intestines in warm, saline-soaked gauze as it is superior in preventing fluid and heat loss.[23] Intravenous fluids and broad-spectrum antibiotics are initiated, and an orogastric tube is placed to suction. The goal of surgical repair is the reduction of the herniated abdominal viscera into the abdominal cavity without compromising ventilation, venous return, and intestinal blood supply. In some instances, primary closure is not possible because of the size of the defect. A surgical pouch or silo is used to allow staged reduction over 1 to 2 weeks followed by final abdominal closure.[24] Hemihyperplasia, particularly asymmetric growth of limbs, may necessitate surgery during puberty to equalize different leg lengths; craniofacial surgery may benefit individuals with facial hemihyperplasia.

Children with BWS are at higher risk for developing embryonic tumors.[6,14] Screening for tumors is performed by abdominal ultrasound examination every 3 months until 8 years of age. The aim of tumor surveillance is to decrease the overall mortality and morbidity associated with childhood cancers. Serum α-fetoprotein concentration is monitored in the first few years of life for early detection of hepatoblastoma.[14] Neoplasias are treated using standard pediatric oncology protocols.

Nephrocalcinosis is treated by a pediatric nephrologist. Healthcare providers need to be aware of the many alterations associated with BWS and refer families to a geneticist or genetic counselor.[11]

Nursing Implications

Having a clinical knowledge of the associated findings of BWS provides the neonatal nurse with critical information necessary for planning care. The nurse and other multidisciplinary team members collaboratively focus care on initial airway management, stabilization of glucose levels, and protection of herniated abdominal contents of an omphalocele.[18,24] Support and education of the family is another essential role in caring for this newborn. Surgical procedures and a recovery plan of care should be discussed with the family. Pain management should be addressed pre- and postoperatively. Methods of pain relief should be reviewed with the family. After surgery, care turns to fluid and electrolyte balance, wound care, nutritional needs, and ongoing assessment and intervention to optimize patient outcomes.

As previously mentioned, feeding can be challenging in infants with BWS because of macroglossia. Feeding advancement is further compromised by the potential for surgery-related intestinal adhesions.[24] Educating parents and assisting them to master feeding skills is a major role for the bedside nurse. Nurses play an important role in providing information and support to the family of an infant requiring neonatal intensive care. Early involvement in caregiving may help the family establish the parental role and empower parents to advocate for the child in the hospital and after discharge.[25-27]

Appropriate follow-up is needed after discharge to monitor development and growth. Developmental delay was noted in patients who had complications of prematurity, untreated hypoglycemia, or duplication of 11p15.[1] Anticipatory guidance for parents including

FIGURE 3.

Toddler with noted macroglossia, nevus flammeus, and slight asymmetry of facial features. Photo courtesy of Jamie and Jason Conrad.

monitoring the infant's growth will assist parents in recognizing abnormalities such as asymmetry (Figure 3) or enlargement of the infant's limbs. Speech therapy is indicated if macroglossia affects feeding or articulation. Educating parents about the increased risk of tumor development is also necessary. Quarterly follow-up with abdominal ultrasound is recommended. Providing information about community resources is another way to support the family and provide them additional means to advocate for their child's health. The Beckwith-Wiedemann Children's Foundation is a nonprofit organization that provides information and support to parents.

CONCLUSION

Beckwith-Wiedemann syndrome can be recognized in infancy by the characteristic features of macrosomia, macroglossia, and abdominal wall defects. Other clinical findings that assist in making a diagnosis are hypoglycemia, ear anomalies, visceromegaly, and a positive family history. A clear understanding of these clinical findings will enhance the recognition of this disorder. Appropriate care can then be initiated so that optimal outcomes can be achieved for the infant and family. Additional strides in prenatal diagnoses may enhance a healthcare provider's abilities to anticipate infant care needs. Recent studies suggest the potential link between assisted reproductive technology and imprinting alterations at 11p15 and may increase the incidence of BWS in women who choose this procedure.[9,10] Also advances in genetic and molecular testing have identified atypical cases of this syndrome bringing up the question of whether or not these infants have received adequate care and follow-up. Further investigation into the various epigenetic alterations is warranted.

References

1. Cohen MM. Beckwith-Wiedemann syndrome: historical, clinicopathological, and etiopathogenetic perspectives. *Pediatr Dev Pathol.* 2005;8:287-304.
2. Kalhan SC, Parimi PS. Metabolic and endocrine disorders. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal–Perinatal Medicine: Diseases of the Fetus and Infant.* Vol 2. Philadelphia, PA: Mosby Elsevier; 2006:1467-1596.
3. Elliot M, Bayly R, Cole T, Temple IK, Maher ER. Clinical features and natural history of BWS: presentation of 74 new cases. *Clin Genet.* 1996;50:272-274.
4. Weksberg R, Shuman C, Smith AC. Beckwith-Wiedemann syndrome. *Am J Med Genet C Semin Med Genet.* 2005;137C:12-23.
5. Gilbert-Barness E, Opitz JM. Congenital anomalies and malformation syndromes. In: Stocker JT, Dehner LP, eds. *Pediatric Pathology.* Philadelphia, PA: Lippincott Williams & Wilkins; 2001:129-140.
6. Pettenati MJ, Haines JL, Higgins RR, Wappner RS, Palmer CG, Weaver DD. Wiedemann–Beckwith syndrome: presentation of clinical and cytogenetic data on 22 new cases and review of the literature. *Hum Genet.* 1986;74:143-154.
7. Jonas JM, Demmer LA. Genetic syndromes determined alterations in genomic imprinting pathways [Internet]. *NeoReviews.* 2007;8(3):e120–e126. http://neoreviews.aappublications.org/cgi/content/full/neoreviews;8/3/e120. Accessed October 8, 2008.
8. Bishara N, Clericuzio CL. Common dysmorphic syndromes in the NICU [Internet]. *NeoReviews.* 2008;9(1):e29–e38. http://neoreviews.aappublications.org.cgi/content/full/neoreviews;9/1/E29. Accessed October 8, 2008.
9. DeBaun MR, Niemitz EL, Feinberg AP. Association of in vitro fertilization with Beckwith–Wiedemann syndrome and epigenetic alterations of L1T1 and H19. *Am J Hum Genet.* 2003;72:156-160.
10. Gicquel C, Gaston V, Mandelbaum J, Siffroi JP, Flahault A, Le Bouc Y. In vitro fertilization may increase the risk of Beckwith Wiedemann syndrome related to the abnormal imprinting of the *KCN1OT* gene. *Am J Hum Genet.* 2003;72(5):1338-1341.
11. Matthews AL, Robin NH. Genetic disorders, malformations, and inborn errors of metabolism. In: Merenstein G, Gardner S, eds. *Handbook of Neonatal Intensive Care.* St Louis, MO: Mosby Elsevier; 2006:812-837.
12. Williams DH, Gauthier DW, Maizels M. Prenatal diagnosis of Beckwith–Wiedemann syndrome. *Prenat Diagn.* 2005;25:879-884.
13. Shuman C, Smith AC, Weksberg R. Beckwith–Wiedemann syndrome [Internet]. *Geneclinics.* 2005. http://www.geneclinics.org/servlet/access?db/geneclinics&site=gt&id=888889&key=DQNYFvmbINHci&gry=&fcn=y&fw=5FXn&filename=/profiles/bws/in ex.html. Accessed March 15, 2008.
14. Tan TY, Amor DJ. Tumor surveillance in Beckwith–Wiedemann syndrome and hemihyperplasia: a critical review of the evidence and suggested guidelines for local practice. *J Paediatr Child Health.* 2006;42:486-490.
15. Angle B. A 4-month-old girl with an enlarged tongue and limb asymmetry. *Pediatr Ann.* 2007;36(5):261-262.
16. Debaun MR, Tucker MA. Risk of cancer during the first four years of life in children with Beckwith–Wiedemann syndrome registry. *J Pediatr.* 1998;132:398-400.
17. McGowen JE, Price-Douglas W, Hay WW. Glucose homeostasis. In: Merenstein G, Gardner S, eds. *Handbook of Neonatal Intensive Care.* St Louis, MO: Mosby Elsevier; 2006:368-390.
18. Saitta SC, Zachai EH. Specific chromosome disorders in newborns. In: Taeusch H, Ballard R, Gleason C, eds. *Avery's Diseases of the Newborn.* Philadelphia, PA: Elsevier Saunders; 2005:204-215.
19. Martinez Y, Martinez R. Clinical features in the Wiedemann–Beckwith syndrome. *Clin Genet.* 1996;50:272-274.
20. Goldman M, Shuman C, Weksberg R, Rosenbaum ND. Hypercalciuria in Beckwith–Wiedemann syndrome. *J Pediatr.* 2003;40:188-195.
21. Cohen MM, Neri G, Weksberg R. O*vergrowth Syndrome.* New York, NY: Oxford University Press; 2002.
22. Baujat G, Rio M, Rossignol S, et al. Paradoxical NSD1 mutations in Beckwith–Wiedemann syndrome and 11p15 anomalies in Sotos syndrome. *Am J Hum Genet.* 2004;74:715-720.

23. Sheldon RE. The bowel bag: a sterile transportable method for warming infants with skin defects. *Am Acad Pediatr.* 1974;53(2):267-269.
24. Roaten JB, Bensard DD, Price FN. Neonatal surgery. In: Merenstein G, Gardner S, eds. *Handbook of Neonatal Intensive Care.* St Louis, MO: Mosby Elsevier; 2006:838-862.
25. Bruns DA, McCollum JA. Partnerships between mother and professionals in the NICU: caregiving, information exchange, and relationships. *Neonatal Netw.* 2002;21(7):15-23.
26. Heermann JA, Wilson ME, Wilhelm PA. Mothers in the NICU: outsider to partner. *Pediatr Nurs.* 2005;31(3):176-200.
27. Jackson K, Ternestedt B, Schollin J. From alienation to familiarity: experiences of mothers and fathers of preterm infants. *J Adv Nurs. 20*03;43(2):120-129.