



R.C.P.U. NEWSLETTER

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Vol. XIX No. 1 R.C. Philips Research and Education Unit A statewide commitment to the problems of mental retardation July 2007

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Beckwith Wiedemann Syndrome Carrie Crain, B.S.

Introduction

Beckwith-Wiedemann syndrome (BWS) is a congenital overgrowth syndrome that affects many systems in the body. The majority of BWS cases, 85%, are sporadic and 15% are inherited in an autosomal dominant fashion (Li et al 1997, Li et al 1998). It is estimated that BWS affects about one in 13, 700 individuals. This number could be higher due to the prevalence of undiagnosed mildly affected individuals (Thornburn et al 1970.) The phenotypic expression of BWS is highly variable, but, its main characteristics include pre and or postnatal overgrowth, macroglossia and anterior abdominal wall defects. The importance of tumor screening in patients with BWS cannot be underscored as patients with BWS are at a higher risk of embryonal tumor development than the general population (WN Cooper et al 2005) Although the genetics of BWS is complex, most cases arise from abnormalities of chromosome 11p15.5.

History

The discovery of BWS as a new overgrowth syndrome illustrates the importance of communication between clinicians that is often involved in the classification of new genetic syndromes. During his residency at Los Angeles Children's Hospital in 1963, Bruce Beckwith performed an autopsy on a female infant who died at 44 hours of age with many of the clinical findings now characterized as BWS. These features included: a large ophalocele, macroglossia and enlarged kidneys (Beckwith 1998.) After his abstract was published as a "read by title only" in the June 1964 meeting of the American Pediatric Society, Dr. Beckwith began to receive inquiries from other

physicians regarding patients with similar findings. One such inquiry came from Hans Rudolph Wiedemann, a German Geneticist. Through the comparison of findings during the following years Dr's Beckwith and Wiedemann were able to establish the clinical findings for the overgrowth syndrome that is now known as Beckwith-Wiedemann Syndrome.

Clinical Description

The clinical findings of Beckwith-Wiedemann syndrome vary by individual. To date there is no consensus diagnostic criteria (www.geneclinics.org). The following clinical findings listed are agreed upon as part of the phenotypic expressions seen in patients with BWS.

Perinatal

Approximately half of all pregnancies that result in BWS are associated with polyhydramnios and are delivered prematurely (Weng et al., 1995). Fetal macrosomia is found in 90% of pregnancies resulting in BWS (Elliot et al., 1994b). Newborns with BWS have an approximately 20% increased mortality rate mostly stemming from complications associated with prematurity (Pettenati et al., 1986).

Growth

A common characteristic of BWS is macrosomia. It is estimated that 87% of individuals with BWS have birth weights and lengths at or above the 97th percentile for gestational age (Weng et al., 1995a). Macrosomia is often overlooked in patients born prematurely. By the time individuals with BWS reach mid-childhood, their growth rate begins to slow and adult heights range between the 50th and

97th percentiles (Pettenati et al., 1986; Weng et al., 1995a). Hemihyperplasia is another major finding found in BWS. Hemihyperplasia, asymmetric overgrowth of one or more regions of the body, is found in about 25% of BWS patients and is more pronounced in the first few years of life.

Craniofacial

Most patients with BWS have a noteworthy craniofacial appearance that includes both major and minor findings associated with BWS. The craniofacial characteristics found in BWS are most noteworthy early in life and become less apparent as children age. Major craniofacial findings associated with BWS are macroglossia and ear anomalies. If left untreated, severe macroglossia can cause difficulties with feeding, speech and respiratory complications (Cassidy and Allanson 2001). The ear anomalies found in BWS include anterior linear earlobe creases and or posterior helical ear pits (Pettenati et al. 1986). Minor findings regarding facial features include midface hypoplasia and intraorbital creases (Pettenati et al 1986.) Although it is rare, some patients with BWS have been reported to have a cleft palate (Pettenati et al. 1986.)

Development

Most patients with BWS have normal cognitive development. Patients whose BWS is caused by a insertion or deletions in 11p15.5 have an increased chance of having developmental delays. Other causes of delay are associated with complications of BWS such as periods of hypoxia, uncontrolled hypoglycemia or other complications associated with prematurity. It should be noted that hypoglycemia is most common shortly after birth but can persist into early infancy.

Cancer Risk

The two most common types of tumors seen in BWS are Wilms tumor and hepatoblastoma. Individuals with BWS have a tumor risk of 7.5% (Wiedmann, 1983), whereas the general population has a 1 in 10,000 or 0.01 % chance of developing Wilms tumor and a 1 in 100,000 or 0.001 % chance of developing hepatoblastoma (Cassidy & Allanson 2001). Tumors in patients with BWS are almost always seen during the first 8 years of life, and the oldest BWS patient diagnosed with Wilms tumor was 10 years and 2 months of age (Beckwith 1998).

Clinical Diagnosis

Clinical diagnostic criteria have not been established to definitely diagnose Beckwith-Wiedmann syndrome. Most patients who present with

characteristics seen in BWS are given the diagnosis of BWS if they have three findings; 2 major and 1 minor (www.geneclinics.org.)

Major Findings

- Positive family history (one or more family members with a clinical diagnosis of BWS or a history or features suggestive of BWS)
- Macrosomia (traditionally defined as height and weight >97th centile)
- Anterior linear ear lobe creases/posterior helical ear pits
- Macroglossia
- Omphalocele (also called exomphalos)/umbilical hernia
- Visceromegaly involving one or more intra-abdominal organs including liver, spleen, kidneys, adrenal glands, and pancreas
- Embryonal tumor (e.g., Wilms tumor , hepatoblastoma, neuroblastoma, rhabdomyosarcoma) in childhood
- Hemihyperplasia (asymmetric overgrowth of one or more regions of the body)
- Adrenocortical cytomegaly
- Renal abnormalities including structural abnormalities, nephromegaly, and nephrocalcinosis
- Cleft palate (rare)

Minor findings:

- Polyhydramnios
- Prematurity
- Neonatal hypoglycemia
- Facial nevus flammeus
- Hemangioma
- Characteristic facies, including midfacial hypoplasia and infraorbital creases (Pettenati et al 1986)
- Cardiomegaly / structural cardiac anomalies / cardiomyopathy (rare)
- Diastasis recti
- Advanced bone age
- Monozygotic twinning. Monozygous twins with BWS are usually female and discordant; however, both male and female monozygous twins concordant for BWS have been reported, as well as monozygous male twins discordant for BWS (Orstavik et al 1995, Leonard et al 1996).

Screening

One of the most important aspects of medical management for patients with BWS is tumor

screening. Although definite recommendations regarding tumor screening in patients with Beckwith-Wiedemann have not been agreed upon, it is the consensus of most clinicians that affected individuals receive abdominal ultrasounds every three months until they reach 8 years of age.

Another common screening technique used to assess the presence of hepatoblastoma in patients with BWS is monitoring alpha-Fetoprotein (AFP) levels through a simple blood test until four years of age. An increased AFP can be associated with the presence of tumors. If a patient is found to have elevated AFP levels, monthly repeat AFP levels are recommended in addition to further studies including imaging studies and a possible referral of oncology (Cassidy & Allanson 2001).

Genetic Testing

The genetic etiology of BWS is complex. There are several different mechanisms associated with chromosome 11p15.5. The molecular diagnosis of the specific subtype of BWS requires different modes of genetic testing.

Methylation studies are often used as the first step to determine the genetic causation of BWS because 50-60% of affected individuals have abnormal methylation of KCNQ10T1 (DMR 2) and 2-7% have abnormal methylation of H19 (DMR 1) (Bliet et al 2001, Weksberg et al 2001). Methylation analyses as well as microsatellite analysis can determine if paternal uniparental disomy for 11p15.5 is present. Paternal uniparental disomy (UPD) is present in 10-20% of BWS patients (Bliet et al 2001, Weksberg et al 2001). Karyotype and FISH studies are used to look for duplications, translocations, or inversions in 11p15.5. These cytogenetic alterations are seen in 1-2% of individuals that meet the diagnostic criteria for BWS. Sequencing of CDKN1C for mutations is important in patients that have a positive family history. Mutations in CDKN1C are the genetic causation for ~40% of patients with a positive family history for BWS and only 5-10% of patients with a negative family history (Lam et al 1999, Li et al 2001).

Genetic Counseling

The genetic counseling provided to patients with BWS is highly dependent on family history and the molecular causation of BWS. In patients with a negative family history, knowledge of the genetic basis of BWS is important in providing accurate genetic counseling regarding recurrence risk and risk to siblings of an affected individual. In patients with a positive family history, the recurrence risk for siblings and offspring of an affected individual could

be as high as 50% if the affected individual has a mutation in CDKN1C.

Table I. BWS: Genetic, Cytogenetic and Molecular Groups

BWS subgroup	Freq (%) ¹	Etiology	Inherited/sporadic	Recurrence risk
Paternal UPD	20	Post-zygotic somatic recombination	Sporadic	Low
<i>DMR2</i>	50-60	Usually epimutation, rarely deletion resulting in epimutation	Usually sporadic	Low, rarely inherited
<i>DMR1</i>	2-7	Rarely deletion resulting in epimutation	Usually sporadic	Low, rarely inherited
11p15 trans/inv	<1	Translocation	Inherited or sporadic	Up to 50% if maternal translocation ²
11p15 dup	<1	Duplication	Inherited or sporadic	Up to 50% if father is the carrier
<i>CDKN1C</i> mutations	5-10 sporadic 30-50 familial	Mutation	Sporadic or inherited	Up to 50% (preferential maternal transmission) ²

Support Groups

Support groups available to patients and families affected with Beckwith-Wiedemann syndrome include:

Beckwith-Wiedemann Children's Foundation

9031 Cascadia Avenue
Everett WA 98208
Phone: 425-338-4610
Fax: 425-357-8575
Email: BWCfcheryl@aol.com
www.beckwith-wiedemannsyndrome.org

Beckwith-Wiedemann Support Network

2711 Colony Road
Ann Arbor MI 48104
Phone: 800-837-2976 (parents only); 734-973-0263
Fax: 734-973-9721
Email: a800bwsn@aol.com

About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20 of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent

of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is run through the Division of Pediatric Genetics, University of Florida, and is funded through a contract with the Department of Children and Families.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.

Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

Acknowledgments:

The RCPU Newsletter is funded by contract with the Department of Health, Children's Medical Services.

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