BECKWITH-WIEDEMANN SYNDROME:
AN OVERVIEW FOR NEW PARENTS

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Abstract

As the day approaches when a newborn enters this world, it should be an exciting time filled with joy and anticipation. However, when a child is born with unusual physical characteristics, the prospect of a normal life can suddenly be diminished. One common congenital overgrowth disorder is Beckwith-Wiedemann Syndrome (BWS). It is associated with the abnormal expression of genes within a specific region of chromosome 11. Although the characterization of BWS is widespread and varies in its complexity from case to case, the primary traits include above average birth weight, an unusually large tongue, uncommonly large internal organs, umbilical hernia, low blood sugars, and kidney abnormalities, among others. Through careful evaluation from specialists such as cardiologist (heart), oncologist (cancer), nephrologist (kidney), orthopedist (limb length discrepancies), endocrinologist (blood sugar), gastroenterologist (intestinal), plastic surgeon (craniofacial/tongue abnormalities) or sometimes other specialists, the prospect of a normal life can be realized. Using ultrasound surveillance to watch for any potential malignant tumor growth can give early detection remarkable success in fighting childhood cancer for which children with Beckwith-Wiedemann Syndrome are at an increased risk of developing.

Keywords: Beckwith, Beckwith Wiedemann Syndrome, exomphalos, gigantism, hemihyperplasia, hypoglycemia, macroglossia, macrosomia, omphalocele, visceromegaly, Wiedemann, Wilms tumor
Acknowledgement or Dedication

This page is dedicated to my grandson, Finn Andrew Wooten, who was diagnosed with Beckwith-Wiedemann Syndrome at birth in November 2016. Thankfully, he no longer displays symptoms of the disorder, and is doing very well. It is because of this diagnosis that inspired me to learn more about BWS.

I also want to thank my loving and supportive husband, Greg, for cheering me on in this final stage of my degree. Without his support, this process would have been very difficult. I love you, Greg.

A special thank you goes out to Dr. Vickie Kelly and Gwen Wilson, both from Washburn University. First, Dr. Kelly deserves special recognition for mentoring me through this entire program, but especially this thesis process. She was an invaluable resource for information and support.

Gwen Wilson deserves praise for her prompt attention to my friendly Monday morning emails that I sent her throughout the thesis process. Her knowledge and advice when it came to editing my papers for APA style was extremely helpful.
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Beckwith-Wiedemann Syndrome (BWS) is a congenital overgrowth disorder associated with the abnormal expression of genes within a specific region of chromosome 11. Although the characterization of BWS is widespread and varies in its complexity from case to case, the primary traits include above average birth weight, an unusually large tongue, uncommonly large internal organs, umbilical hernia, and many others. Below is a review of the history of BWS, significance of the condition, characteristics, number of cases affected, description of chromosome 11, exams/tests, differential diagnoses, treatment, surveillance, diagnosis, complications, and the impact on health care professionals.

Significance of the Project

For families whose child is born with odd physical characteristics, the future seems a little unsettled, scary, or perhaps intimidating. Unless faced with the situation personally, most people are unfamiliar, uneducated, and misinformed about the condition. The information below is to bring awareness to the Beckwith-Wiedemann Syndrome so support and encouragement can be offered in times of crisis. Although no additional information has been offered in recent years, all the data is consistent when it comes to the signs, symptoms and causes of BWS. Having a game plan as to course of action and what to expect can ease the stress and uncertainty.

Literature Review

History

In 1964, Dr. Hans-Rudolf Wiedemann (1915-2006), a German pediatrician, began to report unusual findings in children in his pediatric clinic (Kelly, 2013). He had a number of cases where the infants displayed similar characteristic signs of exomphalos (umbilical hernia), macroglossia, and many others. Dr. Hans-Rudolf Weidemann.

Kieler Scholar Register, (n.d.)
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(enzlarged tongue), and gigantism (unusually large stature of the entire body). Independently, in 1969, Dr. John Bruce Beckwith (1933 -), an American pathologist/physician also began reporting cases of a new syndrome that displayed similar signs and initially coined it the EMG Syndrome after the first letter of each condition (exomphalos/macroglossia/gigantism) (Benjamin, 2005). Over time it became known as Beckwith–Wiedemann Syndrome, and the observable characteristics expanded. Today, infants should be suspected of having BWS if they clinically present when one or more of the following major and/or minor findings.

**Major findings associated with BWS:** (Shuman, Beckwith, & Weksberg, 2016)

- Macrosomia (>97th percentile in height/weight)
- Macroglossia (enlarged tongue)
- Hemihyperplasia (one-sided overgrowth of one or more regions of the body)
- Omphalocele/Exomphalos (umbilical hernia)
- Embryonal tumor in childhood (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma)
- Visceromegaly (enlarged abdominal organs) which could include liver, spleen, kidneys, adrenal glands, and/or pancreas
- Cytomegaly of the fetal adrenal cortex (enlarged cells)
- Renal abnormalities including structural abnormalities, nephromegaly, nephrocalcinosis, and/or later development of medullary sponge kidney
- Anterior linear ear lobe creases and/or posterior helical ear pits
- Placental mesenchymal dysplasia (overgrowth of cells, tissue, bone or organ)
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- Cleft palate (rare in BWS) (defect/disfigurement involving roof of mouth)
- Cardiomyopathy (rare in BWS) (disease of the heart muscle)
- Positive family history (≥1 family members with a clinical diagnosis of BWS or a history or features suggestive of BWS)

Minor findings associated with BWS:

- Polyhydramnios and Prematurity (excess amniotic fluid or pregnancy-related findings)
- Neonatal hypoglycemia (abnormally low levels of blood glucose/sugar)
- Nevus simplex (flat red or purplish stain or birth mark that usually appears on the forehead, eyelids and/or back of the neck) or hemangiomas (benign tumor made up of blood vessels)
- Characteristic facial appearances including sunken midface and skin creases under eyes
- Structural cardiac anomalies or cardiomegaly (enlarged heart)
- Diastasis recti (separation of the rectus abdominis muscle of >2.7 cm)
- Advanced bone age (common in overgrowth/endocrine disorders)

Shuman, Beckwith & Weksberg (2016) continue to report that a definitive diagnosis of BWS in a proband can only be made if the patient has three major or two major plus at least one minor findings OR “an epigenetic or genomic alteration leading to abnormal methylation at 11p15.5 or a heterozygous BWS-causing pathogenic variant in CDKN1C in the presence of one or more clinical findings” (Shuman, Beckwith, & Weksberg, 2016. p. 3). Proband (Proband, n.d.), is defined as the first person in a family who has been diagnosed with the condition.

Significance of the Condition

According to Pappas (2015), Beckwith-Wiedemann Syndrome is the most common overgrowth syndrome, affecting as many as 1 in every 13,700 births. It is possible that this
number is relatively low because many mild cases are never diagnosed and go untreated. Mainly known as a congenital condition, meaning present at birth, the clear majority of BWS cases are managed by physicians and never materialize into more serious health concerns. However, monitoring of these children is warranted as they continue to be at risk for hypoglycemia and embryonal tumors. Pappas (2015) reports the risk of tumors is about 7.5% up to the age of eight, after which the risk gradually declines.

Characteristics of BWS

The three cardinal traits thought to be characteristic of Beckwith-Wiedemann Syndrome include exomphalos, macroglossia, and gigantism. Today there are many more signs and symptoms that are diagnosed and fall under the BWS umbrella. These include nevus flammeus, visceromegaly, hypoglycemia, creases or pits in the ears, and kidney abnormalities (Genetics Home Reference, 2017a). In addition, children with Beckwith-Wiedemann Syndrome are at an increased risk of developing tumors which could potentially be cancerous. Wilms tumor and hepatoblastoma are two of the more common types (Genetics Home Reference, 2017a). Weksberg, Shuman and Smith (2005) report that physicians generally agree that if three diagnostic findings are present, then the diagnosis of Beckwith-Wiedemann is given. Below is a description of these diagnostic findings in more detail.

Exomphalos. Merriam-Webster (2017) defines exomphalos as an “umbilical hernia” and synonymous to omphalocele. According to the Centers for Disease Control and Prevention (CDC, 2017), exomphalos/omphalocele is a condition where the infant’s organs protrude through his/her umbilical cord. This could include one or more internal organs, but it almost always includes the intestines. During the sixth through 10th
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week of pregnancy, the intestines grow so large that they push out from the umbilical cord. In normal pregnancies, this is usually rectified by week 11. If there is no resolution, then an omphalocele occurs (Center for Disease Control and Prevention [CDC], 2017). Normally, the omphalocele is covered with a thin translucent sac that protects the organs. A greater risk of infection occurs if the sac ruptures. If an organ becomes twisted or otherwise entangled because it is outside its normal protective barrier, the infant risks a loss of blood flow to the organ and subsequent damage. The CDC (2017) reports that nearly 775 infants are born with this condition each year in the United States. That equates to roughly one in 5,400 births (CDC, 2017).

Treatment for exomphalos/omphalocele depends on the size of the protrusion. According to the Center for Disease Control and Prevention (2017), if the omphalocele is small, it can be surgically repaired soon after birth. An incision is made, the intestines are placed back in the belly, and the incision is stitched closed. If the omphalocele is large and involves multiple organs, then a series of surgical procedures may be necessary. Repairs may be done in stages to accommodate growth of the child. Any organ left outside of the belly is usually covered with a special protective material until it can be surgically repaired (CDC, 2017).

Macroglossia. According to Kaneshiro (2017), macroglossia is a condition where the tongue presents abnormally large, either on one side or bilaterally. This enlargement is not from a tumor but rather from an increase in the amount of tissue. Infants diagnosed with macroglossia will potentially have an increase in difficulty breathing, swallowing, and eventually speaking (Genetics Home Reference, 2017a). Genetic and Rare Diseases Information Center (GARD, n.d.) include symptoms associated with macroglossia as “drooling, speech impairment, difficulty eating, stridor, snoring, airway obstruction, abnormal growth of the jaw and teeth,
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ulceration, and/or dying tissue on the tip of the tongue” (p. 1). Treatment of macroglossia can depend on the severity of the case. In mild cases, speech therapy may be all that is necessary. In more complex cases, surgery may be required to reduce the amount of tissue involved (GARD, n.d.).

**Gigantism.** Another cardinal sign of BWS is gigantism. Excessive growth hormones in children is generally the cause of gigantism, according to Barrow Neurological Institute (2017). This abnormal acceleration of growth hormones occurs before the growth plates close in children. The acceleration after growth plates close in adults is called acromegaly. The growth plates are located at each end of long bones such as the humerus, femur and tibia. The specific timeframe for closing of the growth plates is variable, but generally around puberty. For girls, the closing is likely between 12-14 years, and for boys 14-16 years of age (Duke Health, 2013).

According to Barrow Neurological Institute (2017), the signs and symptoms of gigantism include the following.

- Abnormally tall stature
- Abnormal growth of the face, hands and feet
- Thickened facial features
- Irregular menstrual cycle
- Excessive perspiration with slight activity
- Delayed puberty
- Double vision
- Deafness
- Headache (p. 1)
Gigantism is very rare with only about 100 cases in the United States (Barrow Neurological Institute, 2017). Boys are twice as likely to have a reported case of gigantism. Diagnosing gigantism can be made in two ways: magnetic resonance imaging (MRI) or a blood test. If a tumor is suspected, an MRI can determine its exact location on the pituitary gland. Blood tests can reveal elevated levels of prolactin or low levels of cortisol, thyroid hormone, testosterone (in boys) and estradiol (in girls) (Barrow Neurological Institute, 2017).

**Nevus flammeus.** Nevus flammeus can be a trait of Beckwith-Wiedemann Syndrome as well. Nevus flammeus is a flat red or purplish stain or birth mark that usually appears on the forehead or eyelids of newborns (Antaya, 2016). The stain consists of abnormal clusters of small blood vessels. Appearing equally among boys and girls, nevus flammeus is diagnosed in .3-.5% of all newborns in the United States (Antaya, 2016). Antaya (2016) also reports that capillary malformations grow proportionately with the child and usually pose no risk for complications.

**Visceromegaly.** Visceromegaly is another common indicator of BWS. Visceromegaly is the abnormal enlargement of internal organs, most commonly the intestines (Beckwith-Wiedemann Children’s Foundation International, 2016). According to Kalish, Duffy, and Lye (2016), “any or all of the following organs may be affected: liver, spleen, pancreas, kidneys, or adrenal glands” (p. 2).

**Hypoglycemia.** Neonatal hypoglycemia or hyperinsulinism is a condition where the newborn has unusually low blood sugar levels (Kalish, Duffy, & Lye, 2016) and can be associated with Beckwith-Wiedemann Syndrome. In normal cases, insulin acts to regulate blood glucose levels. Babies need glucose for energy, the bulk of which goes to the brain (Lee, 2015).
Mothers pass glucose on to the baby through the placenta and later through breast milk. The liver also produces glucose. Babies diagnosed with hyperglycemia and BWS generally have mild symptoms; however, “without proper detection and appropriate treatment, neurological complications may result” (Kalish et al., 2016, p. 2).

**Kidney abnormalities.** Children born with Beckwith-Wiedemann Syndrome can frequently exhibit kidney abnormalities including nephromegaly (enlarged kidneys), renal medullary dysplasia (improperly developed tissues in deepest part of the kidney), and nephrocalcinosis (increased calcium deposits in the kidney) (Kalish et al., 2016). Each of these abnormalities could prevent the kidneys from working properly, thus leading to a more substantial health risk. Healthy kidneys, located in the middle part of the back just below the rib cage, serve to extract waste from blood, balance body fluids, and create urine (Urology Care Foundation, 2017). Diagnosing kidney issues is normally done through ultrasound testing. Other symptoms that may indicate a kidney problem include pain, blood in urine, high blood pressure and urinary tract infections (Urology Care Foundation, 2017).

**Malignant tumors.** Along with the increased risk of kidney abnormalities, children with Beckwith-Wiedemann Syndrome also have an elevated risk for malignant tumors. Children’s Hospital of Philadelphia (2017) reports that the risk of developing cancer in patients with BWS is 5-10%. The two most common types are Wilms tumor and hepatoblastoma. Wilms tumor evolves from immature kidney cells which create a solid cancerous mass in the kidneys (St. Jude Children’s Research Hospital, 2017a). According to the National Cancer Institute (2017), “the incidence of Wilms tumor is 7.1 cases per 1 million children younger than 15 years” (p. 1). Although the risk factor for males and females is about the same unilaterally, females are much more likely to be diagnosed with bilateral tumors. St. Jude Children’s Research Hospital (2017a)
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reports, “Wilms tumor is the fourth most common type of childhood cancer and the most common type of kidney cancer in children” (p. 1). St. Jude also reports that children with BWS are much more likely to be pre-disposed to Wilms tumors.

Hepatoblastoma is a type of liver cancer generally found in babies and young children. Willert (2017) reports it is the most common childhood liver cancer. The anatomy of the liver shows it has two lobes, a right and a left lobe. According to Boston Children’s Hospital (2017), most hepatoblastomas are diagnosed in the right lobe. The primary function of the liver is to filter and store blood as well as process food. Most children with hepatoblastoma are asymptomatic; however, the cancer can metastasize to other areas of the body which could create symptoms (Boston Children’s Hospital, 2017). Hepatoblastoma is very rare with occurrence in less than one in a million children (St. Jude Children’s Research Hospital, 2017a).

Identifying if the tumor is benign or malignant can be challenging. In some cases, a physical examination can determine additional signs and symptoms that may aid in the diagnosis. Further evaluations through blood work, liver/renal function tests, and urinalysis are always beneficial. Abdominal and chest scans using x-rays, ultrasound, CT, MRI or PET scans are also necessary to confirm the diagnosis. The gold standard for diagnosis is a histologic evaluation through a biopsy. If positive for malignancy, lymph node sampling may be required to determine the stage of the cancer (National Cancer Institute, 2017).

Chromosome 11

According to Weksberg, Shuman & Smith (2005), Beckwith-Wiedemann Syndrome “is caused by a variety of genetic or epigenetic alterations within two domains of imprinted growth regulatory genes on human chromosome 11p15” (p. 12). To begin to understand the implications of BWS, a basic explanation of genetic makeup is appropriate.
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**Cell.** The cell is the building block for the human body. It is the smallest unit within our body capable of reproducing copies of itself (British Society for Cell Biology [BSCB], n.d.). Microscopic in nature, cells provide structure, absorb nutrients, convert nutrients into energy, and perform functions necessary for survival. The human body is made up of trillions of cells. Bianconi et al. (2013) report “the total cell number of a human being ranges between $10^{12}$ and $10^{16}$” (p. 463). There are diverse types of cells within the body and their size and shape depend on their function. For example, cells in the intestinal tract have extended side walls increasing surface size to allow more absorption from food and water (BSCB, n.d.). Neural cells are elongated to account for their length from the base of the skull to the feet. Heart cells are unique in that they must process a significant amount of energy; therefore, they contain a higher number of mitochondria within each cell (BSCB, n.d.). Mitochondria are responsible for generating the energy the cell requires to functional normally.

**DNA.** Within every cell in the human body is DNA, or deoxyribonucleic acid. DNA is the hereditary information that makes us all unique. Within each person, approximately 99% of our DNA in our cells is the same (Genetics Home Reference, 2017d). There are many different DNA molecules per cell and all are located in the center, or nucleus, of the cell. DNA is
passed from adult organisms to their offspring during reproduction. DNA contains information stored as codes and consists of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T) (Genetics Home Reference, 2017d). The arrangement of these bases determines the genetic instructions contained within the DNA to ultimately help the organism grow, develop, reproduce, and ultimately die (National Genome Research Institute, 2015). Because of the vast number of DNA molecules per cell, and because the cells themselves are microscopic, the DNA is wound very tightly around proteins called histones which support its structure. This tight packaging is called a chromosome (National Genome Research Institute, 2015).

**Chromosome.** Chromosomes house the DNA within each cell nucleus. Chromosomes can be either circular or linear in shape, depending on which cell type they are housed (Mandal, 2014). According to Mandal (2014), “On cell division, the chromosomes form dense small thread-like structures that must be replicated before being equally divided between two daughter cells, to ensure each has an equal number of chromosomes” (p. 1). Liu (2017) reports “cells in the human body have 46 chromosomes, including 22 pairs of **autosomes** and one pair of **sex chromosomes** (XX in females, XY in males)” (p. 1). There are two sets of chromosomes, one received from the mother and one set from the father. Each chromosome is shaped like an “X” with the cross point being called the centromere. The location of the centromere on the “arms” is used to describe the location of specific genes. Each chromosome has a short arm and a long arm. The short arm is referred to as the “p” arm while the long arm is known as the “q” arm (Genetics Home Reference, 2017f).
Gene. A gene is the fundamental unit for heredity. With an estimated 20,000 – 25,000 human genes in a human being, genes are made up of DNA which gives us the instructions to make proteins (Genetics Home Reference, 2017g). “Genes vary in size from a few hundred DNA bases to more than 2 million bases” (Genetics Home Reference, 2017g, p.1). The purpose of genes is to store information. This information contains the instructions to give humans their unique characteristics such as hair and eye color. According to the Council for Responsible Genetics [CRG] (n.d.), “there is no such thing as a ‘typical’ gene, but there are certain basic requirements for any gene to function” (p. 1). A gene must be able to translate for any particular protein. A particular site must be available for a gene to start the translation which is called the promoter (abbreviated P) (CRG, n.d.). From there the gene requires a specific starting point for transcription (abbreviated TC). Once a translation has started, it needs a stop point (abbreviated tC). “From TC ‘start’ to tC ‘stop’ is sometimes called the transcriptional unit, meaning the DNA region that is copied into RNA” (Council for Responsible Genetics, n.d., p. 1). There are also regulatory sites (abbreviated TL and tL) within the gene.

Chromosome 11. The genetic causes of BWS are multifaceted. It is usually related to an abnormal regulation of genes on chromosome 11 which is directly responsible for regulating growth. According to Genetics Home Reference (2017a), Beckwith-Wiedemann Syndrome is more specifically associated with the short arm “p” within chromosome 11. Ordinarily, each parent equally passes one copy of chromosome 11 to the child, and the genes are activated in the cells. These are known as...
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parent-specific differences in gene expression (Genetics Home Reference, 2017b). However, in some cases, only the paternal copy is activated or expressed. In other cases, only the maternal copy is activated. This abnormal phenomenon is referred to as genomic imprinting (Genetics Home Reference, 2017b). “Abnormalities involving genes on chromosome 11 that undergo genomic imprinting are responsible for most cases of Beckwith-Wiedemann Syndrome” (Family Diagnosis, 2017, para. 1).

Known as the BWS critical region, the two imprinted domains on chromosome 11p15.5 include imprinting center 1 (IC1) and imprinting center 2 (IC2) (Shuman, Beckwith, & Weksberg, 2016). According to Shuman, Beckwith, and Weksberg (2016), “In more than 80% of individuals with BWS, genetic testing can detect one of five alterations” (p. 4). These genetic mechanism alterations are listed below and followed by a graphic representation (Pie Graph 1).

- Loss of methylation of IC2 on the maternal chromosome
- Gain of methylation of IC1 on the maternal chromosome
- Paternal uniparental disomy of 11p15.5
- A heterozygous pathogenic variant on the maternal CDKN1C allele
- Cytogenic (translocation, inversion, duplication)

(Shuman, Beckwith, & Weksberg, 2016, p. 4)
Miller (2017) explains the process of methylation as “the transfer of four atoms - one carbon atom and three hydrogen atoms (CH₃) – from one substance to another” (p. 1).

Methylation occurs trillions of times every second in the body. Designed to regulate many of the systems in the body, methylation plays a significant role in biochemical reactions. The systems most affected include the cardiovascular, neurological, reproductive, and detoxification systems (Miller, 2017). Routinely, methylation acts as a mechanism to turn switches on and off in the body. However, if there is a disruption in the methylation process, then activities such as DNA production, neurotransmitter production, and cell energy (among others) cannot run efficiently (Miller, 2017). According to the graphic above, approximately 55% of BWS cases are related to

*These molecular subgroups, defined by DNA methylation abnormalities, may also be the result of an underlying genomic alteration. Such genomic aberrations are most common for hypermethylation of IC1 and least common for hypomethylation at IC2. Genomic aberrations, limited to the BWS critical region on chromosome 11p15.5, can be detected by MS-MLPA or various sequencing technologies. Some deletions/duplications may be detected by CMA.

(Shuman, Beckwith, & Weksberg, 2016, p. 31)
the loss or gain of methylation at IC1 or IC2 on the maternal chromosome. Miller (2017) suggests a simple genetic test can identify low levels of enzymes that create 5-MTHF which may be a contributing factor. He also advocates for diets rich in healthy, whole-foods, which are non-processed. Foods such as asparagus, avocados, broccoli, brussels sprouts, green leafy vegetables, legumes and rice will boost the methylation cycle (Miller, 2017). In addition, lifestyles which boast regular exercise, and low-moderate alcohol and coffee consumption will also be beneficial.

**Genetic Testing.** There are five genetic tests which can be performed which relate to genes in the BWS critical region. They are DNA methylation studies, single gene testing, chromosomal microarray (CMA), karyotype, and a multi-gene panel test (Shuman, Beckwith, & Weksberg, 2016).

**DNA methylation studies.** When completing the DNA methylation studies, the IC1 and IC2 should be performed simultaneously. This test will indicate a uniparental disomy (UPD) if there are alterations at both IC1 and IC2. This means that two copies of a chromosome were inherited from one parent and not the other. If positive, parents should consider additional genetic counseling to know the risk of recurrence in future children. The following table shows the percentages of BWS alterations detected.

<table>
<thead>
<tr>
<th>Table 1 Test Method</th>
<th>Pathogenic Variants/Alterations Detected</th>
<th>Proportion of BWS Alterations Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylation analysis</td>
<td>Loss of methylation at IC2 (maternal)</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Gain of methylation at IC1 (maternal)</td>
<td>5%</td>
</tr>
<tr>
<td>Test Method</td>
<td>Pathogenic Variants/Alterations Detected</td>
<td>Proportion of BWS Alterations Detected</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Loss of methylation at IC2 AND gain of methylation at CI1 (paternal UPD)</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Sequence analysis / gene-targeted deletion/duplication analysis</td>
<td>Heterozygous maternal <em>CDKN1C</em> pathogenic variants</td>
<td>5% in persons with no family history of BWS</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Cytogenetic duplication, inversion, or translocation of 11p15.5</td>
<td>~40% in persons with a positive family history of BWS</td>
</tr>
<tr>
<td>Microarray (SNP based)</td>
<td>Microdeletions, microduplications, paternal UPD</td>
<td>~ 9%</td>
</tr>
</tbody>
</table>

(Shuman, Beckwith, & Weksberg, 2016)

**Single gene testing.** In single gene testing, a sequence analysis is conducted to identify variants. These variants could include everything from benign to cancerous deviations. These are usually followed by gene-targeted deletion/duplication analysis for individuals who have a family history of BWS or in individuals with a strong suspicion of BWS but have no chromosome 11 abnormalities (Shuman, Beckwith, & Weksberg, 2016).

**Chromosomal microarray (CMA).** Chromosomal microarray (CMA) can determine alterations in the chromosomes, either by deletion or duplication. A nonconventional, high powered microscope can detect molecular level anomalies in chromosomes. According to Vogels and Fryns (2004), “Microdeletions are often characterised [sic] by a complex clinical and behavioural [sic] phenotype resulting from the imbalance of normal dosage of genes located in that particular chromosomal segment” (p. 1). In the same respect, microduplications are the gain of pieces of chromosome to an area. The exact size and area of duplication can vary, but they
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are typically in the same critical region for each identifiable syndrome. Similar to the
microdeletions, microduplications can only be identified through specialized equipment that can
ascertain at the molecular level. Bacino (2017) reports “The phenotype of microduplication
syndromes is often less clear and less well defined than for the corresponding microdeletion
syndrome” (p. 1). Microarray can also detect for uniparental disomy (UPD) (Uniparental
disomy, 2017) which is the inheritance of two chromosomes from the same parent and none from
the other parent (Shuman, Beckwith, & Weksberg, 2016).

**Karyotype.** Karyotyping is a test which evaluates the chromosomes in a sample of body
cells. It specifically evaluates for the number, size and shape of the chromosomes to see if there
are any deviations from normal. When it comes to Beckwith-Wiedemann Syndrome,
karyotyping is used to determine if the fetus has any chromosome deficiencies, to establish if a
parent has a chromosome issue that could potentially be passed on to an offspring, or to find out
the cause of a baby’s birth defect (WebMD, 2017).

According to Children’s Hospital of Philadelphia (CHOP, 2017), of all cases diagnosed
as Beckwith-Wiedemann Syndrome, approximately 85% occur by chance and without a family
history of the condition. Most of them result from a genetic abnormality on chromosome 11. “It
is presumed that the overgrowth associated with Beckwith-Wiedemann syndrome and
hemihypertrophy may develop because of improper inactivation of one or more growth-
suppressing genes, or, alternatively, because of overexpression of genes that encourage cell
growth” (CHOP, 2017, p. 3). It is encouraging to know that individuals that fall into this chance
or sporadic categorization of the condition are not likely to pass the condition on to their children
or of having other children with the same diagnosis.
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In the remaining 10-15% of cases, Beckwith-Wiedemann syndrome is inherited from one or both parents. Of this 10-15%, approximately 50% of those cases have an elevated risk of passing the genetic abnormality on to their offspring or of having additional children with the condition (Children’s Hospital of Philadelphia, 2017). It is recommended that all children who present with a sign of symptom of BWS be evaluated by a geneticist for correct diagnosis.

Experts at CHOP recommend that all children who have features consistent with a clinical diagnosis of Beckwith-Wiedemann syndrome or isolated hemihypertrophy – but who receive negative genetic test results – receive the same medical management and cancer surveillance protocol as children who have a confirmed genetic diagnosis. (Children’s Hospital of Philadelphia, 2017, p. 4)

Differential Diagnosis

Differential diagnoses are the diagnoses that present with similar signs and symptoms which doctors and healthcare professionals need to consider when officially diagnosing a patient with Beckwith-Wiedemann Syndrome. Some considerations include Simpson-Golabi-Behmel Syndrome type 1, Perlman Syndrome, Costello Syndrome, Sotos Syndrome, Mosaic-Genome-wide Paternal and finally Uniparental Isodisomy (Shuman, Beckwith, & Weksberg, 2016).

**Simpson-Golabi-Behmel syndrome type 1.** According to Genetics Home Reference (2017c), Simpson-Golabi-Behmel syndrome is also classified as an overgrowth syndrome. Like BWS, Simpson-Golabi-Behmel can also presents with gigantism, enlarged organs, enlarged tongue, kidney abnormalities and an increased risk for tumors (Shuman, Beckwith, & Weksberg, 2016).

Distinguishing features for Simpson-Golabi-Behmel include...
more defined coarse facial features, cleft lip, heart problems, and an unusual number of fingers and toes. In some cases, there can be a developmental delay as well.

**Perlman syndrome.** Perlman syndrome’s similar features include gigantism and cancerous tumors such as Wilms tumor (Shuman, Beckwith, & Weksberg, 2016). Distinguishing features for Perlman syndrome include facial features consisting of an unusually small lower jaw, lowered ears, and depressed nasal bridge. Perlman syndrome also records a high infant mortality rate and is usually associated with intellectual disabilities (Shuman, Beckwith, & Weksberg, 2016).

**Costello syndrome.** Costello syndrome is another similar diagnosis that can be mistaken for Beckwith-Wiedemann syndrome. Newborns who are measured as part of the gigantism spectrum may be considered for both syndromes. However, Costello’s identifying features include heart issues, high infant mortality rate, developmental delays, and coarse facial features (Shuman, Beckwith, & Weksberg, 2016).

**Sotos syndrome.** Gigantism is the only common denominator between Sotos syndrome and Beckwith-Wiedemann Syndrome. Healthcare professionals may distinguish between the two when considering the additional symptoms associated with Sotos. These include a long, narrow head, pointed chin, sparse hair
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distribution, intellectual disabilities, and macrocephaly or enlarged head (Shuman, Beckwith, & Weksberg, 2016).

**Mosaic genome-wide paternal.** There is minimal overlap between Mosaic genome-wide paternal and BWS; however, the similarity is in the size of the baby for its gestational age as well as an enlarged placenta. When presented with these, the doctor needs to consider both syndromes as a possible diagnosis. Mosaic genome-wide paternal’s primary distinguishing feature is that it has multiple imprinting disorders associated with it (Shuman, Beckwith, & Weksberg, 2016).

**Uniparental Isodisomy.** There are many overlapping characteristics between Uniparental Isodisomy and Beckwith-Wiedemann syndrome. To begin, they both can show the following characteristics: enlarged tongue, blood sugar disorders, umbilical hernias, enlarged liver, hemangiomas, and increased risk for cancerous tumors. The distinguishing feature with Uniparental Isodisomy is an increased rate for developmental delay and typically the presentation of symptoms is far more severe (Shuman, Beckwith, & Weksberg, 2016).

**Surveillance**

It is important that all children diagnosed with Beckwith-Wiedemann Syndrome undergo continuous surveillance to monitor for any additional complications, particularly cancer. Children’s Hospital of Philadelphia (2017) suggests such surveillance include an abdominal ultrasound every three month until the child is seven years old. The ultrasound should include abdominal
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organs such as kidney and liver. Children’s Hospital of Philadelphia (2017) reports that after age four, the ultrasound should focus on the adrenal glands because the risk of hepatoblastoma (form of liver cancer) drops significantly. Because ultrasound technology does not involve the use of radiation, ultrasounds are considered painless and safe for the infants.

Another area of surveillance which is recommended is to monitor the alpha-fetoprotein (AFP) concentration in patients with BWS. Every three months until age 4 years, a blood sample should be taken to determine the AFP levels. “AFP is a protein released by immature or damaged liver cells, and it is released at higher levels by hepatoblastoma tumor cells” (Children’s Hospital of Philadelphia, 2017). Normally, the AFP levels continue to drop as the infant ages. Therefore, each subsequent blood test would optimally indicate a decrease in AFP levels.

Treatment

Addressing the more severe signs and symptoms of Beckwith-Wiedemann is the first place to start. Issues pertaining to blood sugar, abdominal wall defects, enlarged tongue, and cardiac problems certainly get high priority. To reduce the risk for further complications including within the central nervous systems, the infant’s blood sugar levels need to be leveled out. Initial monitoring is required every few hours, three to five times per day for the first two days. If blood sugar levels have not yet regulated, continued monitoring might be needed up to 72 hours (Caring for Kids, 2013). Consultation with a medical professional to help guide through this process is essential.
Abdominal wall defects will need to be addressed shortly after birth if the infant is deemed strong enough for surgery. Surgical repair is usually well tolerated by infants. According to Mancini (2017), the infant is placed under general anesthesia so it will not feel any pain. The surgeon places an incision at the belly button and inspects the organs within. Any damaged tissue is removed and signs of birth defect are addressed at this time. The organs are then returned through the incision and the cut is repaired.

Macroglossia, or enlarged tongue, is a significant concern for a newborn. The inability to eat and take in nutrients must be addressed immediately. Most hospitals have specialists who can assess an infant’s sucking technique and can suggest longer feeding nipples that will make it easier for the infant to drink milk. Occasionally, a feeding tube is placed through the nose to ensure adequate nutrients are obtained.

Depending on the severity of each case, the infant may be referred to more than one specialist to address certain symptoms. These specialists might include a cardiologist (heart), oncologist (cancer), nephrologist (kidney), orthopedist (limb length discrepancies), endocrinologist (blood sugar), gastroenterologist (intestinal), plastic surgeon (craniofacial abnormalities) or any other specialist that might be consulted (Shuman, Beckwith, & Weksberg, 2016).

If there are any perceived development delays, an infant may be referred to programs that encourage infant stimulation such as physical, occupational or speech therapy. These programs can be tailored for each individual case. Physical therapy would address issues related to overall strength and endurance. If the patient had previous abdominal surgery to repair umbilical hernia, a core strengthening program may be initiated. If surgery to correct a leg length discrepancy was
necessary, physical therapy could address the strength, balance, and coordination of both lower extremities.

Occupational therapy would be necessary for more functional appropriate activities at home to make activities of daily living easier and safer. Getting in/out of the bathtub, bathing, dressing, eating, toileting and transferring are all areas that occupational therapy would address in the home.

Speech therapy plans a significant role in a developing child with Beckwith-Wiedemann Syndrome, particularly if the child’s sign and symptom involved an enlarged tongue. If a tongue resection was necessary, a speech therapist may be beneficial to help evaluate and treat speech, language, communication, and swallowing disorders.

In the event that cancer was detected in the individual, additional treatment may be required along the oncology realm. The following therapy sessions maybe prescribed by a referring physician: Radiation therapy, chemotherapy, hormone therapy, immunotherapy, watchful waiting, targeted therapy, and/or gene therapy. Additional information should be obtained through the doctor’s office regarding these therapies (Children’s Hospital of Philadelphia, 2017).

Impact on Healthcare Professionals

The most important thing that healthcare professionals need to know is the telltale signs and symptoms characteristic of Beckwith-Wiedemann Syndrome. By understanding these characteristics, doctors, nurses, and medical staff can refer patients to specialists who can monitor and track changes in conditions as the child grows. Using genetic testing and ultrasound surveillance to look for any potential tumors will help ensure the early response to treatment for an improved prognosis.
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In addition, more genetic testing needs to be done to identify why chromosome 11 deviates away from normal. Identifying environmental issues mothers may be exposed to when conceiving may play a role in this. Perhaps the intake of certain foods or the elimination of other foods in the diet could be affecting the gene expression. At the very least, more needs to be investigated regarding chromosome 11.

Conclusion and Indications for Further Research

As one of the most common congenital overgrowth disorders, Beckwith-Wiedemann Syndrome is associated with the abnormal expression of genes within a specific region of chromosome 11. Although the characterization of BWS is widespread and varies in its complexity from case to case, the primary traits include above average birth weight, an unusually large tongue, uncommonly large internal organs, umbilical hernia, low blood sugars, kidney abnormalities, and many others. Through careful evaluation from specialists such as a cardiologist (heart), oncologist (cancer), nephrologist (kidney), orthopedist (limb length discrepancies), endocrinologist (blood sugar), gastroenterologist (intestinal), plastic surgeon (craniofacial/tongue abnormalities) or sometimes other specialists, the prospect of a normal life can be realized. Using ultrasound surveillance to watch for any potential malignant tumor growth can give early detection remarkable success in fighting childhood cancer. In addition, improved education to healthcare professionals to be aware of signs and symptoms can speed up referrals to specialists and boost overall prognoses. Furthermore, increased genetic testing to assist in identifying the causes of chromosome 11 abnormalities would be beneficial to the overall understanding of this overgrowth disorder.
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Appendix A

Quick Reference Medical Terminology and Definitions as obtained through The Free Dictionary online (2017).

- **Acromegaly** - excessive enlargement of the limbs due to thickening of bones and soft tissues.

- **Cardiomyopathy** - is a chronic disease of the heart muscle (myocardium), in which the muscle is abnormally enlarged, thickened, and/or stiffened. The weakened heart muscle loses the ability to pump blood effectively, resulting in irregular heartbeats (arrhythmias) and possibly even heart failure.

- **Cytomegaly** - abnormal enlargement of a cell or group of cells.

- **Exomphalos** - hernia of the abdominal viscera into the umbilical cord.

- **Hemihyperplasia** - overdevelopment or excessive growth of half of a specific organ or part of all the organs and parts on one side of the body.

- **Hemihypertrophy** - overgrowth of one side of the body or of a part.

- **Hepatoblastoma** - a malignant intrahepatic tumor consisting chiefly of embryonic tissue, occurring in infants and young children.

- **Hepatomegaly** - enlargement of the liver.

- **Macroglossia** - enlargement of the tongue.

- **Macrosomia** - abnormally large size of the body.

- **Medullary dysplasia** - improperly developed tissues in deepest part of the kidney.

- **Nephrocalcinosis** - deposition of calcium phosphate in the renal tubules, resulting in renal insufficiency.

- **Nephromegaly** - enlargement of the kidney.

- **Nevus flammeus** - a congenital vascular malformation involving mature capillaries, present at birth. It consists of a reddish-purple lesion that is flat or barely elevated and does not fade with age.

- **Omphalocele** - protrusion, at birth, of part of the intestine through a defect in the abdominal wall at the umbilicus.

- **Neonatal hypoglycemia** - familial onset of symptomatic hypoglycemia during infancy, with persistently low blood glucose.

- **Visceromegaly** - excess size of one or more organs.

- **Wilms tumor** - a malignant renal tumor of young children.