Beckwith-Wiedemann syndrome, characterized by the triad of omphalocele, macroglossia, and gigantism, has a population incidence estimated at 1/13,700. This is likely an underestimate, because individuals with milder phenotypes may not be diagnosed. Some cases of isolated hemihyperplasia may, in fact, represent Beckwith-Wiedemann syndrome with reduced expressivity. Additional clinical features of Beckwith-Wiedemann syndrome include hemihyperplasia, umbilical hernia, diastasis recti, embryonal tumors, cytomegaly of the fetal adrenal cortex, ear anomalies, visceromegaly, renal abnormalities, and neonatal hypoglycemia. Supportive findings may include polyhydramnios and prematurity, enlarged placenta, cardiomegaly, and characteristic facies. The latter feature is much more recognizable in early life and becomes less obvious over time. Beckwith-Wiedemann syndrome is a complex multigenic disorder caused by a variety of genomic and epigenomic alterations affecting the expression of growth regulatory genes on chromosome 11p15.

INTRODUCTION

Beckwith (1998a) has collated a comprehensive history of overgrowth and related syndromes. In his review, he provides a translation of a case report from 1861 of an individual with features suggestive of Beckwith-Wiedemann syndrome, and shows a ceramic figure from West Mexico dating back to 200 B.C. to 200 A.D. with macroglossia and a possible umbilical defect. Although there were numerous early reports of individuals with features of Beckwith-Wiedemann syndrome, a syndromic designation awaited Beckwith’s (1963) report of three unrelated children with omphalocele, hyperplasia of the kidneys and pancreas, and fetal adrenal cytomegaly. The following year, Wiedemann (1964) published a report of siblings with omphalocele, macroglossia, and macrosomia. The triad of omphalocele (exomphalos), macroglossia, and gigantism were considered characteristic of this newly described syndrome, hence the designation EMG syndrome, now commonly referred to as Beckwith-Wiedemann syndrome or Wiedemann-Beckwith syndrome.

In 1822, Meckel first documented hemihyperpertyphropy in the medical literature, whereas the first clinical case report by Wagner appeared in 1839 (Ringrose et al., 1965). Hemihyperplia, referring to increased cell size, was widely used until recently to describe “unilateral overgrowth of the body, including the structures of the head, trunk and limbs” (Viljoen et al., 1984). “Hemihyperplasia” has replaced the
term hemihypertrophy, referring to an abnormality of cell proliferation restricted to one or more regions of the body leading to asymmetric overgrowth (Cohen, 1989). Isolated hemihyperplasia is a diagnosis of exclusion, because hemihyperplasia can be a feature of numerous genetic conditions (Hoyme et al., 1998); see Differential Diagnosis below.

Incidence

The population incidence of Beckwith-Wiedemann syndrome is estimated to be 1/13,700, with equal incidence in males and females (Thorburn et al., 1970; Pettenati et al., 1986). This is likely an underestimate, as individuals with milder phenotypes may not be diagnosed. For hemihyperplasia, the incidence is estimated to be 1/86,000 (Parker and Skalko, 1969), with some authors reporting a higher frequency in females (Ringrose et al., 1965; Hoyme et al., 1998). Some individuals who present with isolated hemihyperplasia may, in fact, have Beckwith-Wiedemann syndrome with reduced expressivity. Evidence for this comes from several findings occurring in both Beckwith-Wiedemann syndrome and isolated hemihyperplasia. These include (1) increased birth weight (mean 3.8 kg) (Leisenring et al., 1994); (2) specific renal anomalies (medullary sponge kidney, abnormal collecting system) (Parker and Skalko, 1969; Tomooka et al., 1988); and (3) a well-documented increase in risk for embryonal tumors, especially Wilms tumor (Ringrose et al., 1965; Hoyme et al., 1998).

Diagnostic Criteria

Consensus criteria for Beckwith-Wiedemann syndrome are yet to be established, but the presence of at least three of the major findings or two major and one minor finding, as detailed below, is generally required to establish a clinical diagnosis. With fewer findings, such as macroGLOSSIA with umbilical hernia, the differential diagnosis should include Beckwith-Wiedemann syndrome and consideration should be given to offering molecular testing. In addition, tumor surveillance should be considered on a clinical basis even when molecular testing is negative, because a proportion of individuals with Beckwith-Wiedemann syndrome demonstrate somatic mosaicism (see below).

Major findings associated with Beckwith-Wiedemann syndrome include macrosomia (prenatal and/or postnatal gigantism), hemihyperplasia, macroGLOSSIA (typically present at birth but also reported to develop postnatally) (Chitayat et al., 1990b), abdominal wall defect (omphalocele, umbilical hernia), embryonal tumors, cytomegaly of the fetal adrenal cortex, ear anomalies (anterior linear lobe creases, posterior helical pits), visceromegaly, renal abnormalities, cleft palate, and positive family history (Pettenati et al., 1986; Weng et al., 1995a). Additional supportive or minor findings may include pregnancy-related findings (polyhydramnios, placenomegaly, placentomal mesenchymal dysplasia) (Wilson et al., 2008), prematurity, neonatal hypoglycemia, cardio-megaly and occasional structural cardiac anomalies, nevus flammeus or other vascular malformation, advanced bone age, diastasis recti, and characteristic facies with midfacial hypoplasia (Fig. 10.1A). This characteristic facial appearance tends to regress over time, especially if macroGLOSSIA and the attendant prognathism are mild or treated (Fig. 10.1B). Most individuals with Beckwith-Wiedemann syndrome have a good prognosis for long-term physical health and development, but in some, there are serious and life-threatening medical issues. Within this group, perinatal complications involving prematurity, persistent hypoglycemia, cardiomyopathy, tumors and/or severe macroGLOSSIA

FIGURE 10.1 Girl with Beckwith-Wiedemann syndrome. (A) At age 6 months demonstrating nevus flammeus, prominent eyes, malar hypoplasia, and macroGLOSSIA. (B) At age 10 years. This photo is post-partial glossectomy and demonstrates only a few residual facial features (e.g., prominent chin).
may lead to death. The frequency of early demise is likely lower than the previously quoted figure of 20%, given current approaches to medical management; however, there remains an increased rate of death in children with Beckwith-Wiedemann syndrome over that in the general population (Pettenati et al., 1986; Weng et al., 1995a; Smith et al., 2007). When dealing with apparently isolated hemihyperplasia, one must distinguish this finding from hemihypoplasia, in which the smaller body part is not normal but hypoplastic. Molecular testing may be useful in defining hemihyperplasia vs. hemihypoplasia (see below). Hemihyperplasia can involve a single organ or region of the body or several regions. When several regions are involved, these may be on one side of the body (ipsilateral) or opposite sides (contralateral). The degree of asymmetry is variable and may be rather mild in appearance. When asymmetry is limited to one limb, a measurable difference of greater than 1 cm in length and/or a significant measurable difference in girth should exist. Because hemihyperplasia can be very mild, and because some degree of asymmetry exists in the normal population, there is a “gray zone” within which it is difficult to clinically define the significance of asymmetry in some individuals. Once asymmetric overgrowth is established, other findings may point to a diagnosis of Beckwith-Wiedemann syndrome or to other diagnoses (see Differential Diagnosis).

Etiology, Pathogenesis, and Genetics

Beckwith-Wiedemann syndrome is currently understood to be a complex, multigenic disorder caused by a number of different genetic (DNA sequence) and epigenetic (DNA methylation, histone modification) alterations that result in transcriptional dysregulation of growth regulatory genes on chromosome 11p15 (Fig. 10.2 and Table 10.1) (Li et al., 1997, 1998). The genetic/epigenetic heterogeneity of Beckwith-Wiedemann syndrome is challenging, however, the most straightforward approach to understanding the etiology of Beckwith-Wiedemann syndrome involves categorizing individuals with Beckwith-Wiedemann syndrome according to family history, karyotype, and molecular data. This is further elaborated in the section below on approaches to molecular testing.

Structure and Regulation of the Chromosome 11p15 Region

The chromosome 11p15 region associated with Beckwith-Wiedemann syndrome, spanning 1000 kb, contains several imprinted genes implicated in Beckwith-Wiedemann syndrome (Fig. 10.2). Most mammalian autosomal genes are expressed from both the maternally and paternally inherited copies of a chromosome pair. Genomic imprinting is an epigenetic phenomenon whereby the two alleles of a gene are differentially modified such that only one parental allele, parent-specific for a given gene, is normally expressed. Genomic imprinting is regulated by epigenetic mechanisms (extrinsic to changes in primary nucleotide sequence), including DNA methylation, histone modification, and non-coding RNAs. Imprinted genes, clustered in distinct regions on chromosomes, are associated with an imprinting center (IC) that controls resetting of closely linked imprinted genes during transmission through the opposite sex (Nicholls, 1994). During gametogenesis, imprinting marks from the previous generation are erased and imprinting is reset according to the sex of the current transmitting parent (Barlow, 1994). Imprinting centers, also termed differentially methylated regions (DMRs), demonstrate differential methylation of the parental alleles and regulate the expression of imprinted genes in cis (along the same chromosome) over large distances.

The regulation of imprinted genes on chromosome 11p15 is shown in Fig. 10.1. Chromosome 11p15 houses two imprinted domains, each having an imprinting center and an untranslatable RNA. Our current understanding of the role of some of these imprinted genes in Beckwith-Wiedemann syndrome is outlined below. Where possible, gene names designated by the Human Genome Organisation Nomenclature Committee are used.

In the telomeric-imprinted domain, the imprinting center, IC1, regulates transcription of two genes, H19 (an untranslated RNA) and insulin-like growth factor 2 or IGFI2. In the centromeric domain, the imprinting center, IC2, maps to the promoter region of the untranslated RNA KCNQIOT1. IC2 regulates the monallelic expression of KNCQIOT1 as well as that of several other imprinted genes including CDKN1C.

Genetic Changes Leading to Beckwith-Wiedemann Syndrome

Many types of parent-of-origin-specific and dosage-sensitive molecular alterations are observed in Beckwith-Wiedemann syndrome (see Table 10.1). These include paternal uniparental disomy, preferential maternal transmission of Beckwith-Wiedemann syndrome in autosomal dominant pedigrees, and parent-of-origin effects in chromosome abnormalities associated with Beckwith-Wiedemann syndrome. These data are consistent with the findings of alterations in imprinted genes on 11p15 in Beckwith-Wiedemann syndrome. Therefore, to understand the pathophysiology of Beckwith-Wiedemann syndrome, one must take account of the relative dosage, as well as the parent-of-origin of imprinted genomic regions. These two factors dictate the number of transcriptionally active or transcriptionally silent alleles.

Molecular Alterations Involving Domain 1

**Gain of Maternal Methylation at H19**

H19 is a maternally expressed gene encoding a biologically active nontranslated messenger ribonucleic acid (mRNA) that may function as a
A. Map of the normal chromosome 11p15 imprinting cluster

Domain 2

PAT
CDKN1C
KCNQ1
IC1
KCNQ1OT1

MAT
CDKN1C
KCNQ1
IC1
KCNQ1OT1

Domain 1

IGF2
H19

IC1

B. IC1 gain of methylation

PAT
CDKN1C
KCNQ1
IC1
KCNQ1OT1

MAT
CDKN1C
KCNQ1
IC1
KCNQ1OT1

C. IC2 loss of methylation

PAT
CDKN1C
KCNQ1
IC1
KCNQ1OT1

MAT
CDKN1C
KCNQ1
IC1
KCNQ1OT1

FIGURE 10.2  (A) Schematic representation of the chromosome 11p15.5 imprinted region, divided into two domains. In the distal domain 1 are two imprinted genes, H19 and insulin-like growth factor 2 (IGF2). IGF2 is a paternally expressed fetal growth factor, whereas H19 codes for an untranslated RNA. The H19-associated imprinting center (IC1) is differentially methylated. It is methylated on the paternal chromosome, and unmethylated on the maternal chromosome. Normally, the H19 gene is expressed from the maternal allele and IGF2 from the paternal allele. Domain 2 contains several imprinted genes including KCNQ1, KCNQ1OT1, and CDKN1C. A differentially methylated region (IC2) contains the promoter for KCNQ1OT1, a paternally expressed untranslated transcript regulating in cis the expression of the maternally expressed imprinted genes in domain 2 including CDKN1C. (B and C) are two examples of imprinting alterations leading to Beckwith-Wiedemann syndrome. (B) IC1 differentially methylated region (DMR) gain of methylation in Beckwith-Wiedemann syndrome, found in about 5% of affected individuals, leads to the biallelic expression of IGF2. (C) Loss of methylation at the KvDMR differentially methylated region (IC2) is found in 50% of affected individuals. This epigenetic alteration leads to reduced expression of CDKN1C. Arrows indicate expressed genes and reflect preferential parent-of-origin-specific expression. Lollipops correspond to methylated sites.

tumor suppressor (Hao et al., 1993). Methylation on the paternal allele and expression of H19 on the maternal allele is maintained in most individuals with Beckwith-Wiedemann syndrome (Weksberg and Squire, 1995). However, in 5%, gain of maternal methylation at IC1 is associated with loss of H19 expression and biallelic IGF2 expression, that is, from both parental alleles (Table 10.1) (Joyce et al., 1997). Gain of methylation at IC1 can be associated with genomic (DNA) alterations (microdeletions) in some individuals with Beckwith-Wiedemann syndrome (Niemitz et al., 2004; Sparago et al., 2004; Prawitt et al., 2005). Methylation changes that occur in conjunction with genomic alterations are important because of their heritability. In families carrying such H19 genomic and epigenomic alterations, the index case may or may not have a positive family history.

Biallelic Expression of IGF2  Insulin-like growth factor 2 (IGF2) is a paternally expressed embryonic growth factor. Disruption of IGF2 imprinting (biallelic expression) is observed in some individuals with Beckwith-Wiedemann syn-
TABLE 10.1 Beckwith-Wiedemann Syndrome: Genetic and Epigenetic Molecular Groups

<table>
<thead>
<tr>
<th>Molecular Group</th>
<th>Imprinted Domain</th>
<th>Frequency</th>
<th>Heritability</th>
<th>Recurrence Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC2 (KCNQ1OT1) loss of maternal methylation</td>
<td>2</td>
<td>50%</td>
<td>Sporadic</td>
<td>Low (unless associated with genomic alteration)</td>
</tr>
<tr>
<td>Paternal uniparental disomy</td>
<td>1, 2</td>
<td>20%</td>
<td>Sporadic</td>
<td>Very low</td>
</tr>
<tr>
<td>CDKN1C mutation</td>
<td>2</td>
<td></td>
<td>Almost exclusively maternal transmission</td>
<td>50% if maternally transmitted, unknown if paternally transmitted*</td>
</tr>
<tr>
<td>IC1 (H19) gain of maternal methylation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Without genomic deletion</td>
<td>1</td>
<td>5%</td>
<td>Sporadic</td>
<td>Low</td>
</tr>
<tr>
<td>• With genomic deletion</td>
<td></td>
<td></td>
<td>Heritable (maternally transmitted)</td>
<td>50% if mother carries deletion</td>
</tr>
<tr>
<td>Chromosome 11p15 duplication-cytogenetically visible</td>
<td>1, 2</td>
<td>&lt;1%</td>
<td>Heritable (paternally transmitted)</td>
<td>Increased with paternal transmission*</td>
</tr>
<tr>
<td>11p15 chromosome translocation/inversion</td>
<td>2</td>
<td>&lt;1%</td>
<td>Heritable (maternally transmitted)</td>
<td>As high as 50% if translocation is maternally transmitted</td>
</tr>
<tr>
<td>Positive family history—no molecular alteration identified</td>
<td>ND</td>
<td>ND</td>
<td>Heritable (maternally transmitted)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Overall, 85% of individuals with Beckwith-Wiedemann syndrome are the first in the family to be affected (sporadic), whereas 15% are associated with vertical transmission (i.e., have an affected parent). The molecular groups in this table do not include all individuals with Beckwith-Wiedemann syndrome and are not mutually exclusive.

Abbreviations: ND, not determined.
*Rare cases of paternal transmission are reported.
*Specific figures are not known.

Molecular Alterations Involving Domain 2

Mutation of CDKN1C The CDKN1C gene encodes the p57Kip2 protein, a member of the cyclin-dependent kinase inhibitor gene family, which negatively regulates cell proliferation. It is both a tumor-suppressor gene and a potential negative regulator of fetal growth. Mutations in this gene, reported in 5–10% of individuals with Beckwith-Wiedemann syndrome appearing as the first case in the family, appear to be associated with the clinical findings of omphalocele (Lam et al., 1999) and cleft palate (Hatada et al., 1996, 1997; Li et al., 2001). Such mutations are found in approximately 40% of individuals with Beckwith-Wiedemann syndrome with a positive family history (O’Keefe et al., 1997; Lam et al., 1999). Although CDKN1C mutations are seen in most cases of Beckwith-Wiedemann syndrome with dominant transmission, some dominant pedigrees are associated with H19 microdeletions (Sparago et al., 2004).

Lost of Maternal Methylation at KCNQ1OT1 KCNQ1OT1 is an imprinted transcript that is antisense to KCNQ1. The promoter of this transcript is differentially methylated and represents an imprinting control element on human chromosome 11p15.5 (Lee et al., 1999; Smilinich et al., 1999). Normally, the maternally derived chromosome is methylated, whereas the paternally derived chromosome is unmethylated. Disruption of the imprinting center affects transcription and chromatin structure. Loss of maternal methylation is seen in 50% of individuals with Beckwith-Wiedemann syndrome (Table 10.1) (Lee et al., 1999; Smilinich et al., 1999).

Maternally Transmitted Translocations/Inversions of Chromosome 11p15 There are rare (1%) de novo and maternally transmitted translocations/inversions of 11p15.5 associated with Beckwith-Wiedemann syndrome. Translocation/inversions almost always disrupt the KCNQ1OT1 gene (Smilinich et al., 1999), but most do not demonstrate DNA copy number changes and very few show DNA methylation alterations (Fig. 10.2). Individuals with 11p15 translocations or inversions exhibit typical features of Beckwith-Wiedemann syndrome.
Molecular Alterations Involving Domain 1 and Domain 2

In some individuals with Beckwith-Wiedemann syndrome, the molecular alterations span both domain 1 and domain 2, impacting the expression of multiple genes. Thus, both maternally expressed growth-suppressor genes and paternally expressed growth-promoter genes are affected. This is seen in individuals with Beckwith-Wiedemann syndrome who have chromosome 11p15 chromosomal duplications or chromosome 11p15 uniparental disomy.

Paternally Derived Duplications of Chromosome 11p15

Paternally derived duplications of chromosome 11p15 are rarely associated with Beckwith-Wiedemann syndrome (1%). In those with cytogenetically visible 11p15 duplications, the duplications span both domain 1 and domain 2. Such individuals have atypical clinical features and a significant risk of developmental delay (Waziri et al., 1983; Slavotinek et al., 1997).

Paternally Derived Duplications of Chromosome 11p15.5

Paternally derived copies of chromosome 11p15.5 are seen in individuals with Beckwith-Wiedemann syndrome 1lp15 uniparental disomy. In apparently isolated hemihyperplasia, somatic mosaicism for 1lp15, chromosomal abnormality, and methylation alterations at IC1 or IC2 (Grundy et al., 1991; Martin et al., 2005; Shuman et al., 2006; Biek et al., 2008b; Voigt et al., 2008). At least a proportion of individuals with hemihyperplasia likely represent “mild” Beckwith-Wiedemann syndrome based on the risk of embryonal tumor development, the known spectrum of tumors, and certain associated clinical features (high birth weight and renal findings) (Hoyme et al., 1998).

Unique Clinical and Molecular Findings in
Beckwith-Wiedemann syndrome

Discordant Female Monozygotic Twins and Loss of Methylation at IC2

An enigmatic clinical group consists of monozygous (“identical”) twin pairs with Beckwith-Wiedemann syndrome. More than 35 such twin pairs have been reported, most commonly female and discordant for Beckwith-Wiedemann syndrome (Weksberg et al., 2002). Furthermore, the incidence of female monozygotic twinning in Beckwith-Wiedemann syndrome is dramatically increased compared with that in the general population. However, a small number of cases of male monozygotic twins discordant for Beckwith-Wiedemann syndrome, and both male and female monozygotic twin pairs concordant for Beckwith-Wiedemann syndrome, have been reported (Leonard et al., 1996; Weksberg et al., 2002; Smith et al., 2006). Male monozygotic twins have a variety of molecular defects as seen in singleton cases of Beckwith-Wiedemann syndrome. Interestingly, in skin fibroblasts from five monozygotic twin pairs discordant for Beckwith-Wiedemann syndrome, each affected twin had an imprinting defect at KCNQ1OTI on 11p15, whereas the unaffected twin maintained normal imprinting (Weksberg et al., 2002). We have proposed that in monozygotic twins discordant for Beckwith-Wiedemann syndrome, loss of imprinting at KCNQ1OTI is etiologically tied to the twinning process, both events occurring at a critical stage of preimplantation development (Weksberg et al., 2002).

Offspring of Parents with Infertility Treated with Assisted Reproductive Technology (ART)

Recently, questions have been raised regarding a possible association between the use of assisted reproductive technology and imprinting disorders in offspring. These data,
generated from both retrospective and prospective studies, suggest an increased rate of Beckwith-Wiedemann syndrome in offspring born to parents following ART. The most compelling aspect of the evidence is that the vast majority of such children demonstrate a specific chromosome 11p15 molecular alteration, loss of maternal methylation at IC2 (DeBaun et al., 1998; Gosden et al., 2003; Maher et al., 2003). Of interest, the increased rate of children with Angelman syndrome born following ART also demonstrates a specific and parallel molecular alteration—loss of maternal methylation at the imprinting center on chromosome 15q11-13 (Ludwig et al., 2005). This single mechanism—loss of maternal methylation at two independent loci—supports the hypothesis that infertility/ART is associated with an increased rate of imprinting disorders.

**Beckwith-Wiedemann Syndrome can be Associated with Methylation Defects at Nonchromosome 11 Imprinting Centers**

Recent investigation of Beckwith-Wiedemann syndrome with loss of maternal methylation at IC2 has found that a subset of such individuals also demonstrate methylation aberrations at other imprinted loci across the genome (Bliedt et al., 2008a; Lim et al., 2008; Rossignol et al., 2006). Two studies comparing individuals with Beckwith-Wiedemann syndrome born following assisted reproductive technology (ART) with those spontaneously conceived reported methylation aberrations at multiple imprinted genes. In one small study, infertility or its treatment did not appear to affect the rate of epigenetic defects in Beckwith-Wiedemann syndrome at nonchromosome 11 imprinted loci (Rossignol et al., 2006), whereas a larger study (Lim et al., 2008) did find an association between loss of methylation at nonchromosome 11 imprinted loci and assisted reproduction technology. This has generated interest in defining genes on other chromosomes that act in trans (on the other members of the chromosome pair) to regulate groups of imprinted genes across the genome. One such gene has recently been proposed for an individual with Beckwith-Wiedemann syndrome who demonstrated loss of methylation at KvDMR as well as other imprinted loci. In this case, the investigators demonstrated a recessive mutation in NALP2 in the mother as a putative cause for the imprinting defect at multiple loci (Meyer et al., 2009).

A parallel finding for infants with transient neonatal diabetes mellitus and overlapping features of Beckwith-Wiedemann syndrome has been recently reported (Boonen et al., 2008). Such individuals, in addition to loss of maternal methylation at the imprinted gene PLAG1 on chromosome 6q24, have loss of methylation at IC2 and several other imprinted regions. Recently, many reports of transient neonatal diabetes mellitus with loss of maternal methylation at multiple imprinted loci have been published (Arima et al., 2005; Mackay et al., 2006a, 2006b; Boonen et al., 2008). In some, the genome-wide maternal loss of methylation of imprinted genes was the result of a mutation in a zinc-finger protein gene (ZFP57) (Mackay et al., 2008).

Genome-wide epigenetic studies in Beckwith-Wiedemann syndrome will be crucial to elucidate the interaction between different chromosomal regions in the development of the Beckwith-Wiedemann syndrome phenotype. Such studies might identify unknown molecular (genetic or epigenetic) abnormalities and define new molecular defects in the 20% of affected individuals that currently defy molecular characterization. Such findings could also shed light on new molecular pathways to explain the phenotypic variability seen in Beckwith-Wiedemann syndrome.

**Recurrence Risks for Beckwith-Wiedemann Syndrome and Isolated Hemihyperplasia**

Elucidation of the molecular etiology is critical for defining recurrence risks for families. The risk of recurrence for Beckwith-Wiedemann syndrome is believed to be low in the absence of a genomic alteration or a positive family history. This low risk does not apply to families presenting with autosomal dominant transmission, as well as for individuals shown to have a specific molecular etiology for Beckwith-Wiedemann syndrome. The risk for this latter group may be increased or decreased depending on the molecular finding (see Diagnostic Testing). More specific recurrence risks (Table 10.1) for individuals or families in certain Beckwith-Wiedemann syndrome clinical groups are discussed in Manifestations and Management.

The recurrence risk for isolated hemihyperplasia appears to be very low but would be dependent on the underlying etiology. Once again, caution must be used to rule out other associated genetic syndromes for families presenting with apparently isolated hemihyperplasia.

**Diagnostic Testing**

At this time, diagnostic testing is useful for confirming the diagnosis and for determining recurrence risks rather than for guiding medical management based on phenotype/genotype correlations (Table 10.2). At present, Beckwith-Wiedemann syndrome can be categorized into distinct genetic and epigenetic groups (Table 10.1). In a large proportion, about 85%, the individual with Beckwith-Wiedemann syndrome presents as the first case in the family. In 10–15% of karyotypically normal individuals with Beckwith-Wiedemann syndrome, parent-of-origin-specific autosomal dominant inheritance is evident. Heritable chromosome abnormalities of 11p15 occur in approximately 1–2% of individuals with Beckwith-Wiedemann syndrome. Therefore, a detailed family history is an important part of the initial evaluation. Because the phenotype may be variable even within a family,
For isolated hemihyperplasia, testing should include the first four categories listed above; HI9 type analysis is required to detect rare other abdominal organs in other family members suspected of recurrence risk. Results may be found on further testing, such as testing additional tissues for uniparental disomy and/or seeking further analysis in a research laboratory, even surgically altered; hence, early childhood photographs advance in testing options for Beckwith-Wiedemann syndrome. It detects microdeletions, disomy (UPD). Because the somatic mosaicism associated with paternal uniparental disomy may generate weak signals with paternal uniparental disomy, testing should include the first four categories listed above; CDKN1C mutations have not been reported in isolated hemihyperplasia, to date. Note: All these tests are now available in diagnostic laboratories. For all the molecular tests listed, a negative test result may not be definitive. Informative results may be found on further testing, such as testing additional tissues for uniparental disomy and/or seeking further analysis in a research laboratory, followed by confirmation in a clinical diagnostic laboratory, where available.

A systematic approach to diagnostic testing for Beckwith-Wiedemann syndrome is important. All individuals should have a karyotype including high-resolution banding. Karyotype analysis is required to detect rare de novo and maternally transmitted translocations/inversions (1%). Translocations/inversions almost always disrupt the gene KCNQ1OT1 (Smilinich et al., 1999) and are not usually detectable by molecular tests that assess DNA copy number changes or DNA methylation changes on chromosome 11p15. A recent advance in testing options for Beckwith-Wiedemann syndrome is based on methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA). MS-MLPA is a variation of the polymerase chain reaction that facilitates amplification and detection of multiple targets with a single primer pair. This test evaluates both DNA methylation and DNA dosage for multiple probes across the chromosome 11p15 region (Scott et al., 2008b). MS-MLPA technology is currently the most sensitive method for detecting the majority of epigenetic and genetic abnormalities associated with Beckwith-Wiedemann syndrome. It detects microdeletions, microduplications, and changes in DNA methylation in the 11p15.5 region, including those associated with uniparental disomy (UPD). Because the somatic mosaicism associated with paternal uniparental disomy may generate weak signals on MS-MLPA, confirmation of this molecular finding by analysis of short tandem repeats may be carried out by the molecular diagnostic laboratory. Paternally derived duplications (1%) of 11p15.5 associated with Beckwith-Wiedemann syndrome will be detected by MS-MLPA, but a karyotype is still very valuable because cytogenetically detectable duplications of 11p15 have a significant association with developmental delay (Slavotinek et al., 1997), whereas microduplications (personal observation) and microdeletions (Sparago et al., 2004) of 11p15 detected by MS-MLPA are far less likely to be associated with developmental delay. If MS-MLPA testing is negative, a screen for CDKN1C mutations should be undertaken even in the absence of specific clinical indications (e.g., positive family history or cleft palate).

For individuals with a positive family history and/or a cleft palate, a screen for CDKN1C mutations can be done first. CDKN1C sequence analysis is available in clinical diagnostic laboratories. CDKN1C mutations are seen in both cases of Beckwith-Wiedemann syndrome that are the first in the family (5%) and in autosomal dominant pedigrees (40%) (Li et al., 2001). If a mutation in CDKN1C is found in a child with Beckwith-Wiedemann syndrome, the parents should be offered testing. Although mutations in CDKN1C are usually maternally transmitted, paternal transmission has been only rarely reported (Lee et al., 1997b). If no mutation is found in either parent, prenatal testing for recurrence of a CDKN1C mutation remains an option in view of the theoretical possibility of gonadal mosaicism, although there are no published reports of this.

Because all cases of uniparental disomy associated with Beckwith-Wiedemann syndrome reported to date involve somatic mosaicism, failure to detect uniparental disomy in one tissue (usually leukocytes) is not conclusive. One should consider obtaining another tissue (e.g., skin), especially in the event of surgery. Uniparental disomy for 11p15 may be found in many tissues of individuals with Beckwith-Wiedemann syndrome or may be limited to normal kidney tissue surrounding a Wilms tumor in a phenotypically normal child. The presence of mosaicism for 11p15 uniparental disomy

### TABLE 10.2 Diagnostic Testing for Beckwith-Wiedemann Syndrome

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype</td>
<td>All children presenting with features of Beckwith-Wiedemann syndrome should have a karyotype in a cytogenetics service laboratory, as there are prognostic implications if 11p15 duplication or translocation is present.</td>
</tr>
<tr>
<td>KCNQ1OT1 Uniparental disomy (UPD) of 11p15</td>
<td>This epigenetic change can be detected by methylation analysis. UPD can be detected either by methylation analysis or by analysis of DNA polymorphisms/repeat sequences. Positive results obtained by methylation analysis may be difficult to interpret because of somatic mosaicism. Therefore, such results are usually confirmed by testing DNA polymorphisms. A negative result is not conclusive.</td>
</tr>
<tr>
<td>H19 methylation analysis</td>
<td>This epigenetic change can be detected by methylation analysis. DNA sequencing of this gene detects mutations.</td>
</tr>
</tbody>
</table>

*For isolated hemihyperplasia, testing should include the first four categories listed above; CDKN1C mutations have not been reported in isolated hemihyperplasia, to date.

For individuals with a positive family history and/or a cleft palate, a screen for CDKN1C mutations can be done first. CDKN1C sequence analysis is available in clinical diagnostic laboratories. CDKN1C mutations are seen in both cases of Beckwith-Wiedemann syndrome that are the first in the family (5%) and in autosomal dominant pedigrees (40%) (Li et al., 2001). If a mutation in CDKN1C is found in a child with Beckwith-Wiedemann syndrome, the parents should be offered testing. Although mutations in CDKN1C are usually maternally transmitted, paternal transmission has been only rarely reported (Lee et al., 1997b). If no mutation is found in either parent, prenatal testing for recurrence of a CDKN1C mutation remains an option in view of the theoretical possibility of gonadal mosaicism, although there are no published reports of this.

Because all cases of uniparental disomy associated with Beckwith-Wiedemann syndrome reported to date involve somatic mosaicism, failure to detect uniparental disomy in one tissue (usually leukocytes) is not conclusive. One should consider obtaining another tissue (e.g., skin), especially in the event of surgery. Uniparental disomy for 11p15 may be found in many tissues of individuals with Beckwith-Wiedemann syndrome or may be limited to normal kidney tissue surrounding a Wilms tumor in a phenotypically normal child. The presence of mosaicism for 11p15 uniparental disomy
would confer a low recurrence risk, as this results from a postzygotic event.

Methylation alterations associated with Beckwith-Wiedemann syndrome, such as H19 hypermethylation and loss of methylation at IC2, can be detected by several technologies other than MS-MLPA that are currently available in clinical laboratories. These include Southern blotting and PCR-based assays. In the case of negative test results, it is important for the clinician to explore with the diagnostic laboratory whether there are options for further molecular testing. Such tests are less robust than MS-MLPA, because they target fewer regions of 11p15 for assessment of dosage and methylation. Furthermore, they do not address the possibility of presence of genomic alterations coexisting with the methylation alteration, for example, H19 deletion and H19 gain of methylation. Such a dual finding confers a high recurrence risk, whereas H19 gain of methylation in the absence of a genomic alteration is associated with a low recurrence risk.

Loss of imprinting of IGF2 is seen in multiple molecular subgroups but is not currently used as a primary molecular diagnostic tool. IGF2 imprinting status and expression studies remain research tools and should not be considered part of the routine diagnostic work-up for Beckwith-Wiedemann syndrome. IGF2 expression studies can be undertaken only on tissues expressing IGF2, which include skin fibroblast samples but not leukocytes, and only on individuals informative (i.e., heterozygous) for transcribed IGF2 polymorphisms.

Constitutional chromosome 11p15 alterations have been reported not only in Beckwith-Wiedemann syndrome, but also in a spectrum of related clinical disorders, such as isolated hemihyperplasia (Grundy et al., 1991; Martin et al., 2005; Shuman et al., 2006; Blied et al., 2008b; Voigt et al., 2008), as well as more recently in isolated Wilms tumor (Scott et al., 2008a).

Differential Diagnosis

There are a number of endocrine disorders and overgrowth syndromes that should be considered in the differential diagnosis of children presenting with macrosomia or other features of Beckwith-Wiedemann syndrome. Of immediate concern are the possibilities of maternal diabetes mellitus during pregnancy as well as congenital hypothyroidism; these should be considered and investigated. In addition, other features not commonly associated with Beckwith-Wiedemann syndrome may suggest other diagnoses. Several syndromes with phenotypes overlapping that of Beckwith-Wiedemann syndrome are discussed below. Some individuals demonstrating overgrowth do not fit into any of these defined syndromes; clearly, other new overgrowth syndromes and nonsyndromic causes of overgrowth remain to be defined.

Simpson-Golabi-Behmel syndrome shares the following features with Beckwith-Wiedemann syndrome: macrosomia, visceromegaly, macroclossia, and renal cysts. Findings of Simpson-Golabi-Behmel syndrome not seen in Beckwith-Wiedemann syndrome include coarse features, cleft lip, high frequency of cardiac defects (Lin et al., 1999), supernumerary nipples, polydactyly, and other skeletal anomalies. Simpson-Golabi-Behmel syndrome, like Beckwith-Wiedemann syndrome, has an increased risk of neonatal mortality, and an increased risk for developing embryonal tumors, including Wilms tumor and hepatoblastoma (Yong, 2000). Simpson-Golabi-Behmel syndrome is caused by mutations in an X-linked gene, GPC3, encoding an extracellular proteoglycan (glypican-3) believed to function in growth control regulation during development (Weksberg et al., 1996; Neri et al., 1998).

Perlman syndrome is defined by macrosomia, increased risk of neonatal mortality, mental retardation, nephroblastomatosis, and a high incidence of bilateral Wilms tumor occurring usually in the first year of life. There is a characteristic facial appearance: round face, up sweep of anterior scalp hair, depressed nasal bridge, and micrognathia. At present, the molecular basis of Perlman syndrome is unknown, but it likely represents a distinct genetic entity in light of its autosomal recessive inheritance (Greenberg et al., 1986; Grundy et al., 1992).

Costello syndrome (Chapter 16) overlaps clinically with Beckwith-Wiedemann syndrome only in the neonatal period, with neonates presenting with "overgrowth" because of edema and cardiac defects. Over time, they can be distinguished easily from Beckwith-Wiedemann syndrome by their distinctive facial coarsening and failure-to-thrive (Johnson et al., 1998; Van Eeghen et al., 1999). Missense mutations in HRAS are detected in approximately 80–90% of individuals with Costello syndrome (Aoki et al., 2005).

Sotos syndrome (see Chapter 51) is characterized by overgrowth involving height and head circumference as well as a typical facial appearance and developmental disability. The majority of individuals with Sotos syndrome (80–90%) have a detectable mutation or deletion in NSD1. Based on the findings of Bajjat et al. (2004), consideration should be given to testing NSD1 in individuals with suspected Beckwith-Wiedemann syndrome who do not have an 11p15.5 alteration, and similarly to testing for alterations in 11p15.5 in individuals with suspected Sotos syndrome with no detectable NSD1 mutation.

Mucopolysaccharidosis type VI (Maroteaux-Lamy disease) is a lysosomal storage disorder caused by a deficiency of arylsulfatase B. Diagnosis of this condition is typically made at age 2–3 years based on the clinical features of short stature, hepatosplenomegaly, corneal clouding, dysostosis multiplex, cardiac abnormalities, and facial findings. However, in the first year of life, accelerated growth with advanced bone age may direct the differential diagnosis toward overgrowth syndromes (Heron et al., 2004).
Hemihyperplasia may be a feature of a number of syndromes other than Beckwith-Wiedemann syndrome, including neurofibromatosis type I (see Chapter 37), Klippel-Trenauney-Weber syndrome, Proteus syndrome (see Chapter 43), McCune-Albright syndrome, epidermal nevus syndrome, triploid/diploid mixoploidy, Maffucci syndrome, and osteochondromatosis or Ollier disease (Hoyme et al., 1998). Hemihyperplasia of the face, either isolated or as part of Beckwith-Wiedemann syndrome, should be carefully distinguished from plagiocephaly (asymmetric cranial shape).

MANIFESTATIONS AND MANAGEMENT

In many cases, absolute frequencies for the clinical features associated with Beckwith-Wiedemann syndrome are not well-documented. The figures vary widely in published reports; some of the variability may be to the result of misdiagnosis because of overlapping features seen in Simpson-Golabi-Behmel syndrome and some to ascertainment bias. Therefore, the features listed below will in many instances be presented as approximate frequencies.

Growth and Feeding

A large percentage (87%) of individuals with Beckwith-Wiedemann syndrome have birth weights and lengths at about the 97th centile for gestational age (Weng et al., 1995a). However, onset of rapid growth can occur from the prenatal period to as late as 1 year of age (personal experience). Overgrowth is not an absolute requisite for clinical diagnosis. Absence of overgrowth is associated with methylation defects at other imprinting centers (Bliek et al., 2008a). Head circumference varies in that there may be a large head, in keeping with other growth parameters, or relative microcephaly. As long as the head circumference remains in the normal range, relative microcephaly does not correlate with poor developmental outcome.

The increased rate of somatic growth typically continues through the first few years of life. Growth generally parallels the normal growth curve (Pettenati et al., 1986), with bone age often at the upper limits of normal. In some studies, growth rate decreases somewhat beyond mid-childhood (Weng et al., 1995a). Adult heights range from the 50th centile to the 97th centile (Pettenati et al., 1986; Weng et al., 1995a) and are likely influenced by familial heights.

Hemihyperplasia occurs in about 25% of individuals with Beckwith-Wiedemann syndrome; it may not be evident at birth and may become more marked in the first few years of life (Elliott and Maher, 1994).

Macroglossia can occasionally lead to serious difficulties with feeding, sleep apnea, and/or speech articulation.

Evaluation

- If significant feeding difficulties are noted, evaluation by a feeding specialist is recommended.
- Height, weight, and head circumference should be measured annually. Familial heights, especially parental, should be obtained and considered in determining whether macrosomia is truly present.
- A bone age assessment may assist in predicting adult height.
- If hemihyperplasia is observed, measurements of affected regions, both length and girth, should be taken regularly. If the leg length discrepancy is greater than 1 cm, referral to orthopedics is indicated.
- It is important to follow children with hemihyperplasia over several years to evaluate relative growth potential of the two limbs so that surgical treatment, if necessary, can be carried out at the optimal time.
- Significant facial hemihyperplasia may require referral to a craniofacial surgeon.
- If hemihyperplasia involves the limbs or trunk, clinical examination of the spine is recommended for evaluation of scoliosis. Referral to orthopedics is indicated for monitoring and management of scoliosis.

Treatment

- Feeding difficulties encountered because of macroglossia may be ameliorated by use of a longer nipple such as those used for babies with cleft palate.
- Rarely, nasogastric tube feedings are indicated for a period of time.
- There is no specific treatment for macrosomia.
- For children with leg length discrepancy, annual orthopedic follow-up throughout childhood is important to determine whether shoe lifts are appropriate and if surgical intervention is indicated during puberty.
- Epiphysiodesis of the hyperplastic leg may be considered when that leg attains the final length predicted for the normal leg (typically undertaken just before puberty).
- Craniofacial surgery may be necessary for significant facial hemihyperplasia.

Development and Behavior

Contrary to early reports, development is usually normal in individuals with Beckwith-Wiedemann syndrome unless there are serious complications associated with prematurity, a period of uncontrolled or undetected hypoglycemia, or chromosomal duplication involving 11p15. Individuals with molecular alterations of 11p15 do not generally exhibit developmental delay.
Some parents have commented that their children with Beckwith-Wiedemann syndrome are behaviorally different from their other children; however, this was not confirmed in a small experimental sample (personal observation). A recent UK study indicated an increased incidence of emotional and behavioral difficulties, including autism spectrum disorder, in children with Beckwith-Wiedemann syndrome (Kent et al., 2008). Additional studies using standardized testing for autism as well as molecular testing, are indicated to elucidate this finding.

For those with isolated hemihyperplasia, which is etiologically heterogeneous, an increased incidence of developmental delay (15–20%) is reported (Viljoen et al., 1984; Ringrose et al., 1995). There may be some ascertainment bias in this figure, as hemihyperplasia is more likely to be identified if there are other associated findings such as developmental delay. The association of hemihyperplasia with developmental delay may be because of an underlying genetic syndrome or somatic mosaicism for a chromosome abnormality.

**Evaluation**

- Developmental screening should be part of every routine visit for children with Beckwith-Wiedemann syndrome or hemihyperplasia.
- Individuals with suspected Beckwith-Wiedemann syndrome and developmental delay should be carefully evaluated for other syndromes or for chromosome abnormalities (for the latter group, this may include chromosome studies of the skin).
- Those with developmental delay should have a careful, complete developmental assessment.

**Treatment**

- Any individual with developmental delay associated with Beckwith-Wiedemann syndrome and/or hemihyperplasia should be offered standard interventions such as infant stimulation programs, occupational and physical therapy, and individualized education programs.

**Cardiovascular**

Much of the information regarding cardiovascular problems in Beckwith-Wiedemann syndrome is anecdotal. The reported incidence of structural cardiac malformations ranges from 9 to 34%, with about half involving cardiomegaly (Pettenati et al., 1986; Elliott and Maher, 1994). Other reported malformations include hypoplastic left heart, mild pulmonary stenosis, and persistent foramen ovale (Elliott et al., 1994). Cardiomyopathy has been rarely reported. Cardiomegaly of early infancy in Beckwith-Wiedemann syndrome usually resolves spontaneously. Cardiomyopathies in these children can be severe and lethal despite current interventions (Smith et al., 2007). The prognosis for other structural cardiac anomalies depends on the specific defect identified and current treatment options.

**Evaluation**

- In Beckwith-Wiedemann syndrome, there should be a high index of suspicion for cardiac problems, and standard cardiac evaluation should precede any surgical or dental procedure.
- If a cardiac abnormality is suspected on clinical evaluation, a comprehensive and systematic cardiac evaluation is recommended, including electrocardiogram and echocardiogram.
- If a conduction defect is found, the alternate diagnoses of Costello syndrome or Simpson-Golabi-Behmel syndrome should be considered.

**Pregnancy and Perinatal Period**

When a fetus has Beckwith-Wiedemann syndrome, there is a high incidence (about 50%) of premature birth (Weng et al., 1995a), polyhydramnios (about 50%) and fetal macrosomia (about 90%) (Elliott et al., 1994). Other notable features are enlarged placenta, with many averaging almost twice the normal weight for gestational age (Weng et al., 1995a), placental mesenchymal dysplasia (Wilson et al., 2008), and long umbilical cord.

Prognosis depends on the severity of the presenting perinatal problem. As noted previously, there remains an increased perinatal mortality rate associated with Beckwith-Wiedemann syndrome (Pettenati et al., 1986; Weng et al., 1995a; Smith et al., 2007).

**Evaluation**

- Fetal evaluation in pregnancies with suspected fetal Beckwith-Wiedemann syndrome should include serial ultrasounds and biophysical profiles; molecular testing should be considered as it may confirm a suspected diagnosis of Beckwith-Wiedemann syndrome (Wilkins-Haug et al., 2009).
- Given the increased risk of fetal macrosomia and maternal preeclampsia/eclampsia, women suspected of carrying a fetus with Beckwith-Wiedemann syndrome should be closely monitored. Perinatal management should be undertaken in a high-risk unit.
In subsequent pregnancies, the mother of a child with Beckwith-Wiedemann syndrome could be offered serum α-fetoprotein at 16 weeks gestation and monitoring with high-resolution ultrasound at 19–20 weeks and 32 weeks gestation to look for an abdominal wall defect, to assess growth parameters (likely not detectable until late in the second trimester), and to detect organomegaly, renal anomalies, cleft palate, cardiac abnormality, and macroglossia. In addition, there has been one report of an early ultrasound, between 10 and 14 weeks gestation, revealing increased nuchal translucency and omphalocele in a fetus later found to have Beckwith-Wiedemann syndrome (Souka et al., 1998).

The same surveillance recommendations are made for pregnancies where one parent has Beckwith-Wiedemann syndrome.

If a genomic lesion has been identified in a previously affected child or an affected parent (e.g., *CDKN1C* mutation or a microdeletion), the possibility of prenatal diagnosis by chorionic villus sampling (CVS) or amniocentesis may be considered in a subsequent pregnancy. Some families may wish to undertake such testing for pregnancy and delivery management and others may consider whether or not to continue with the pregnancy. If the fetus is identified as having a genomic lesion, even in the absence of obvious clinical findings on prenatal investigation, the newborn should be considered at-risk and monitored for hypoglycemia as outlined above.

**Treatment**

- When Beckwith-Wiedemann syndrome is suspected in pregnancy, delivery planning should anticipate the possible perinatal complications such as polyhydramnios, prematurity, macrocephaly, large birth weight, macroglossia, and hypoglycemia. Less frequent complications include hypocalcemia or polycythemia (19.5%). Management of each of the complications is not different from that in the general population.
- Management may need to include the delivery of an infant with an omphalocele. Thus, it is preferable to plan the delivery in a center equipped to handle such issues.

**Endocrine**

Hypoglycemia is reported to occur in approximately 30–50% of babies with Beckwith-Wiedemann syndrome (Pettenati et al., 1986; Engstrom et al., 1988). The underlying cause of the hypoglycemia appears to be hyperinsulinemia and islet cell hyperplasia. This may be related to 11p15 uniparental disomy and/or other mechanisms involved in dysregulation of genes on 11p15. Mosaicism for 11p15 uniparental disomy is one of the recognized pathogenetic mechanisms causing focal nesidioblastosis of the pancreas (de Lonlay et al., 1997).

No data are available concerning long-term outcome of hypoglycemia associated with Beckwith-Wiedemann syndrome. In general, children without Beckwith-Wiedemann syndrome who have had significant hypoglycemia have significantly smaller head circumferences and more neurological deficits, including lower IQ scores at 5–7 years of age, than their unaffected counterparts. Neonates with seizures secondary to hypoglycemia tend to have the worst overall neurological prognosis (Halamek and Stevenson, 1998). Newborns with asymptomatic hypoglycemia, although not completely without risk for sequelae, have the best prognosis. None of these studies adequately assesses the risks faced by neonates who do not experience seizure activity (Halamek and Stevenson, 1998).

Other abnormal laboratory findings noted in Beckwith-Wiedemann syndrome include hypocalcemia (4.6%), hypercholesterolemia, and hyperlipidemia (2.3%) (Engstrom et al., 1988). Hypothyroidism has been reported in several individuals with Beckwith-Wiedemann syndrome (Martinez y Martinez et al., 1985).

**Evaluation**

- Any neonate suspected of having Beckwith-Wiedemann syndrome should be screened for hypoglycemia for the first few days of life. Serial blood glucose measurements to detect asymptomatic hypoglycemia as well as frequent examination for clinical signs of symptomatic hypoglycemia are recommended. The level at which neonatal hypoglycemia becomes clinically important, warranting intervention, is poorly defined (Boluyt et al., 2006; Burns et al., 2008). Hypoglycemia may persist in a small percentage of babies, requiring longer-term monitoring.
- If early discharge is planned, health care professionals should advise parents about the typical clinical manifestations and treatment of hypoglycemia and should ensure that rapid access to medical care is available.
- If hypoglycemia persists beyond the first few days, evaluation by a pediatric endocrinologist is suggested because hypoglycemia, in a small number of cases, can be very refractory to baseline treatment.
- A high index of suspicion should be maintained for hypocalcemia and hypothyroidism. Evaluation is standard.

**Treatment**

- Either intravenous or oral glucose should be administered while awaiting laboratory confirmation of
hypoglycemia if clinical manifestations of hypoglycemia are present. The route of administration should be guided by the level of glucose and the severity of the clinical manifestations.

- Any individual treated for hypoglycemia should be carefully followed with serial glucose determinations at 15-30-minute intervals until the level rises to 60-100 mg/dL.
- A number of drugs, such as diazoxide or somatostatin, can be used for refractory hypoglycemia (Halamek and Stevenson, 1998).
- Early intervention for hypocalcemia or hypothyroidism is indicated. Treatment for such issues in children with Beckwith-Wiedemann syndrome is standard.

Craniofacial

Distinctive facial features of Beckwith-Wiedemann syndrome include macroglossia, anterior ear lobe creases and posterior helical pits, facial nevus flammeus, prominent eyes with infraorbital creases, and broad lower jaw leading to square-face shape. Macroglossia can occasionally lead to serious difficulties with respect to feeding and to respiratory complications. Macroglossia may also lead to difficulties with speech articulation and to local trauma (Tomlinson et al., 2007). Later childhood problems may include malocclusion, as mandibular, or lower jaw, growth accelerates in response to tongue size. A prognathic jaw may develop even after tongue-reduction surgery, meriting consideration of further surgical intervention (personal observation). In addition, hemihyperplasia may affect one side of the face and/or tongue, leading to an asymmetric appearance.

Evaluation

- Concerns about speech difficulties as a result of macroglossia should be assessed by a speech pathologist familiar with the macroglossia associated with Beckwith-Wiedemann syndrome and its natural history.
- Referral to Respiratory Medicine and/or Otolaryngology along with a sleep study should be considered for children with significant macroglossia, especially if there is any concern about sleep apnea.
- Issues related to facial appearance are optimally assessed by a multidisciplinary team including plastic surgeons, speech pathologists, and orthodontists. It is recommended that health care providers who have experience with the natural history of Beckwith-Wiedemann syndrome be selected so that growth patterns and potential long-term impact of macroglossia and/or hemihyperplasia can be anticipated and medical, dental, and surgical interventions can be optimally planned.

Gastrointestinal

Abdominal wall defects are a very common finding in children with Beckwith-Wiedemann syndrome. Such defects include omphalocele, umbilical hernia, and diastasis recti. Other less common findings are inguinal hernia, prune-belly sequence, and gastrointestinal malformations including atresia, stenosis, and malrotation.

The outcome for omphalocele surgery for children with Beckwith-Wiedemann syndrome depends on the size of the defect and on whether or not the liver is involved, as for children without Beckwith-Wiedemann syndrome. In addition, the prognosis may be affected by the presence of associated medical and surgical complications. Early detection and surgical intervention of gastrointestinal malformations are important for a good outcome.

Visceromegaly is a common finding and may involve any or all of the following: liver, spleen, pancreas, kidneys, and adrenals. Adrenocortical cytomegaly is a cardinal feature of Beckwith-Wiedemann syndrome. Renal findings are further discussed in a separate section below. Functional problems associated with enlarged liver and spleen are generally not reported. However, hyperplastic changes in the pancreas are associated with the hypoglycemia seen in this condition (see Endocrine).

Diaphragmatic eventrations, which are uncommon, may be detected during ultrasound screening for embryonal tumors.

Treatment

- Children with only mild to moderate macroglossia tend to be able to better accommodate their tongues as their facial bone structures grow, so that they can keep their tongues fully in their mouths. They can be followed longitudinally by an experienced craniofacial team.
- Partial tongue resection is generally considered for children anticipated to encounter significant orthodontic and/or cosmetic concerns or rarely, severe airway obstruction (Weng et al., 1995b). In such cases, consideration should be given to early tongue reduction by a surgeon experienced in this procedure.
- Many procedures have been described for tongue reduction. The most common ones involve excision of either the central or the anterior portions of the tongue (Tomlinson et al., 2007).
- Orthodontic treatment as well as plastic surgery may be considered when there is significant prognathism.
- Implementation of therapeutic exercises for the tongue has not been a successful intervention (personal experience).
Evaluation

- Evaluation of abdominal wall defects and visceromegaly, including standard physical examination as well as ultrasound, should be undertaken at the time of diagnosis.
- There should be a high index of suspicion for gastrointestinal malformations, which may require imaging for diagnosis of stenosis, atresia, or malrotation.
- Ultrasound findings of an abnormal relationship between the superior mesenteric artery and superior mesenteric vein may indicate a possible malrotation. They should be investigated with an upper GI series.

Treatment

- In general, abdominal wall defects and gastrointestinal malformations are amenable to early surgical treatment with good outcomes. Standard surgical intervention is indicated.
- Surgical risks may result from hypoglycemia or intubation difficulties related to macroglossia or to any associated cardiac abnormalities.

Genitourinary

Individuals with Beckwith-Wiedemann syndrome frequently have renal anomalies, including nephromegaly, which may be unilateral or bilateral. Reports also note the following findings: renal medullary dysplasia, duplicated collecting system, nephrocalcinosis, medullary sponge kidney, cystic changes, hydronephrosis, nephrolithiasis, and renal diverticulae (Choyke et al., 1998; Borer et al., 1999; Goldman et al., 2002).

Prognosis for renal function is generally good. However, it is important to identify individuals at high risk for loss of renal function from congenital malformation, nephrocalcinosis, medullary sponge kidney, or medullary dysplasia. Active surveillance and appropriate treatment are required to maximize long-term renal function.

Enlargement of the bladder, uterus, phallus, clitoris, ovaries, and testes have been reported. The natural history of other genitourinary organomegalias is not well-documented but has not been reported as problematic. Given the natural history of other types of somatic overgrowth in Beckwith-Wiedemann syndrome, surveillance without active intervention should be the first course of action.

Evaluation

- Renal ultrasound is recommended at diagnosis to assess the integrity of the renal tract.

- If congenital malformations are identified, further imaging studies may be indicated and referral to a pediatric nephrologist and/or urologist is suggested.
- Evaluation of urinary calcium excretion (calcium-to-creatinine ratio) is indicated, especially if ultrasound findings suggest possible nephrocalcinosis (Goldman et al., 2003). When abnormalities of urinary calcium-to-creatinine ratio are found, referral to a pediatric nephrologist is recommended.
- Reported symptoms of polyuria and polydipsia should prompt evaluation for medullary sponge kidney disease as renomedullary dysplasia may lead to reduction in renal concentrating ability.
- Prospective studies are underway to evaluate whether individuals with Beckwith-Wiedemann syndrome over 8 years of age should continue to have annual clinical assessments with renal ultrasound. The primary reason for study is to define the risk of developing renal changes such as nephrocalcinosis or medullary sponge kidney at a later age. The risk for such renal complications is believed to be low.

Neoplasia

Children with Beckwith-Wiedemann syndrome and/or hemihyperplasia are predisposed to certain malignancies (Sotelo-Avila et al., 1980; Wiedemann, 1983; Pettenati et al., 1986). The overall risk for tumor development in individuals with Beckwith-Wiedemann syndrome is estimated to be 7.5% with a range from 4 to 21% (Sotelo-Avila et al., 1980; Wiedemann, 1983; Pettenati et al., 1986; Elliott et al., 1994; Weng et al., 1995; Schneid et al., 1997; DeBaun et al., 1998; Tan and Amor, 2006). For the two most common tumors, Wilms tumor and hepatoblastoma, the general population risks are 1/10,000 and 1/100,000, respectively. Most of the increased tumor risk in both Beckwith-Wiedemann syndrome and isolated hemihyperplasia occurs in the first 5–8 years of life.

The tumors reported in Beckwith-Wiedemann syndrome are primarily embryonal, such as Wilms tumor, hepatoblastoma, rhabdomyosarcoma, adrenocortical carcinoma, and neuroblastoma. Also seen are a wide variety of other tumors, both malignant and benign (Sotelo-Avila et al., 1980; Wiedemann, 1983). Several factors appear to be associated with tumor development in Beckwith-
Wiedemann syndrome. These include the presence of hemihyperplasia (Wiedemann, 1983), nephromegaly (DeBaun et al., 1998), and nephrogenic rests or nephroblastomatosis (Coppes et al., 1999). Beckwith and colleagues proposed the term nephrogenic rest for a focus of abnormally persistent nephrogenic cells that can be induced to form a Wilms tumor, and nephroblastomatosis for the diffuse or multifocal presence of nephrogenic rests (Beckwith et al., 1990). Recent data suggest that specific molecular subgroups within Beckwith-Wiedemann syndrome carry different tumor risks and susceptibilities for specific tumor profiles. Individuals with 11p15 uniparental disomy and H19 hypermethylation carry the highest tumor risk and preferentially develop Wilms tumors, whereas those with loss of methylation at IC2 have a lower tumor risk and are susceptible to non-Wilms tumors (Bliek et al., 2001; Weksberg et al., 2001). These data, however, should not be incorporated into clinical management until they are replicated in a larger series.

For children with isolated hemihyperplasia, the risk for tumor development is reported to be approximately 5.9% (Hoyme et al., 1998). The anatomic site of the tumor does not always correlate with the laterality of the hemihyperplasia (Hoyme et al., 1998). For hemihyperplasia, the reported range of tumor types overlaps significantly with that of Beckwith-Wiedemann syndrome (Hoyme et al., 1998). This suggests that some individuals with hemihyperplasia may represent a forme fruste of Beckwith-Wiedemann syndrome and that the majority of tumors arise from genetic events that overlap the underlying mechanisms responsible for Beckwith-Wiedemann syndrome. However, some tumors, such as leiomyosarcoma, are more likely to be related to disorders other than Beckwith-Wiedemann syndrome.

Although the oldest individual with Beckwith-Wiedemann syndrome who developed a Wilms tumor was 10 years 2 months, 96% of all Wilms tumors in a series of 121 individuals with Beckwith-Wiedemann syndrome presented by 8 years (Beckwith, 1998b). In one study, the outcome in children with Beckwith-Wiedemann syndrome was not improved through regular abdominal ultrasound screening (Craft et al., 1995). However, another report found that a regular screening protocol reduced the percentage of stage III and IV Wilms tumors at diagnosis (Choyke et al., 1999). As imaging studies improve, the need for invasive follow-up investigation resulting from such screening (Choyke et al., 1999) should be considerably reduced.

No specific data are available for long-term survival of children with Beckwith-Wiedemann syndrome who have tumors. In general, it is appropriate to counsel those with Beckwith-Wiedemann syndrome and Wilms tumor, hepatoblastoma, or other tumors that the prognosis is not known to be different in children with Beckwith-Wiedemann syndrome than in those without Beckwith-Wiedemann syndrome. Although one study reported a better prognosis for 10 children with Beckwith-Wiedemann syndrome and Wilms tumor than for Wilms tumor alone (Vaughan et al., 1995), in another small cohort, there was no difference in prognosis for the two groups (personal experience). Prognosis is generally very good (>80%) for long-term survival. The best prognostic indicators are smaller tumor size (Breslow et al., 1991), absence of anaplasia, and absence of metastatic spread.

**Evaluation**

- It is recommended that children with suspected or diagnosed Beckwith-Wiedemann syndrome or isolated hemihyperplasia be followed on a 3-monthly basis with abdominal ultrasound until the age of 8 years (Beckwith, 1998b). Common ultrasound findings include hepatomegaly, nephromegaly, and splenomegaly. As ultrasound technology continues to improve, findings such as “bulky” pancreas and/or mesenteric nodes may be detected more commonly. Generally, the above findings are not associated with neoplasm, but they should be carefully followed for several intervals of ultrasound screening.

- Masses detected in the liver or kidney must be distinguished from lesions such as hemangiomata. Depending on the type of lesion, appropriate imaging studies such as CT or MRI can be used for better definition.

- A baseline MRI study has been recommended for individuals entering a tumor surveillance program (Clericuzio et al., 1992; Beckwith, 1998b).

- Consultation with an oncologist and/or relevant subspecialist may be useful to evaluate specific imaging findings.

- If nephrogenic rests are detected or suspected, careful follow-up should be undertaken. In future, better MRI technology should facilitate visualization of macroscopic nephrogenic rests (Gylys-Morin et al., 1993), possibly identifying individuals with Beckwith-Wiedemann syndrome most likely to develop Wilms tumor.

- In some centers, parents are advised to perform abdominal palpation for tumor surveillance. Some concern has been raised that this might place undue pressure on the parent-child relationship and lead to feelings of guilt in the event that a mass was not detected via palpation. However, some parents may feel empowered by becoming more actively involved in their child’s medical management.

- Screening for neuroblastoma with urinary homovanillic acid (HVA) and vanilmandelic acid (Chitayat et al., 1990a) as well as chest X-ray has been suggested, but such screening is generally not incorporated into baseline tumor screening protocols because of the relatively low risk for this tumor (Tan and Amor, 2006). However, in an unwell child, or if enlarged
mesenteric lymph nodes are detected on abdominal ultrasound, such tests are warranted.

- α-Fetoprotein (AFP) can be measured every 2–3 months to 4 years of age as an additional marker for early detection of hepatoblastoma (Clericuzio et al., 2003; Tan and Amor, 2006). AFP levels tend to be somewhat higher in children with Beckwith-Wiedemann syndrome in the first year of life (Everman et al., 2000), but the most important indicator for management is whether the AFP is falling or rising. When AFP is elevated, a high index of suspicion must be maintained. Follow-up at monthly intervals should be scheduled with repeat AFP (to determine whether it is falling), liver function studies, and repeat imaging, including chest X-ray. In any case of a rising AFP, an exhaustive search for an underlying tumor, including germ cell tumors, is indicated. Consultation with an oncologist may also be useful.

- Clinically unaffected monozygotic co-twins of affected individuals should also be followed with tumor surveillance because of the possibility of somatic mosaicism or seeding of Beckwith-Wiedemann syndrome-positive cells secondary to vascular anastomoses in utero.

**Treatment**

- For all tumors detected, treatment follows standard oncology protocols with the added caveat that such children are at risk for second primaries.

- Children with Beckwith-Wiedemann syndrome appear to respond well to chemotherapeutic agents, and the nephrogenic rests in the kidneys of such children have shown a marked reduction in size in response to chemotherapy (Regalado et al., 1997).

- Treatment should be aimed at preserving as much functional renal tissue as possible.

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