BECKWITH-WIEDEMANN SYNDROME (BWS)

HEMIHYPERTROPHY/LATERALIZED OVERGROWTH

Beckwith-Wiedemann syndrome (BWS) is a rare disorder involving changes on a region of chromosome 11p15 that influence pre- and postnatal growth. Some of these changes act directly on the DNA itself (**genetic** changes). Other changes affect the regulation of the growth genes and whether they are turned on or turned off (**epigenetic** changes). These changes disrupt the normal balance of growth gene expression and lead to the overgrowth seen in patients with BWS.

What is hemihypertrophy/lateralized overgrowth?

Hemihypertrophy/lateralized overgrowth, also called hemihyperplasia, refers to when one side of the body is larger than the other. This may result in:

- Increased muscle bulk in one of the arms, legs, etc.
- Uneven leg length and if left untreated, scoliosis (a curved spine)
- Asymmetric macroglossia (large tongue)
- Asymmetric abdominal organs, such as the kidney and adrenal glands
- Increased risk for certain kinds of tumors

What causes hemihypertrophy in BWS?

Most cases of BWS and hemihypertrophy are caused by changes in the genes on chromosome 11p15. These genes control how and when cells grow and divide. Normally, these processes are balanced by signals that promote and limit growth equally. When this balance is disrupted, cells can grow more than usual, leading to enlarged body parts and a higher risk for certain types of tumors. The parts of the body that grow larger contain more cells with these changes.

How do we test for the different molecular causes of hemihypertrophy?

Depending on the molecular nature of each child's BWS, management plans can vary. As a result, it is important to understand the molecular causes for each child.

SNP arrays (microarrays): This test looks at all of the chromosomes to determine if there are missing or extra pieces. This test will also look at each chromosome to see if there is a copy from the mother and a copy from the father.

Methylation analysis for chromosome 11p15: This test will look at the marks on the DNA at two specific imprinted regions on chromosome 11p15 (IC1 and IC2).

How does mosaicism affect testing?

In some patients with BWS, the genetic and epigenetic changes may be present throughout the entire body, including the blood. In other patients, the changes may only occur in some parts of the body, which is called **mosaicism**. In patients with negative testing in blood, testing of an affected part of the body may be informative.

How do we treat hemihypertrophy?

Treatment depends on where in the body the overgrowth occurs. Most treatment focuses on differences in leg length to prevent scoliosis and back pain. For smaller differences, a **shoe-lift** is typically recommended. For larger differences, surgery may be recommended. Evaluation and monitoring by an orthopedic surgeon familiar with managing leg length differences is recommended. The specialist can determine if and when surgery is necessary based on each child's age, growth and the leg length difference.

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What tumor screening is recommended?

Tumor risk is not well characterized in these patients; however, the incidence is estimated at 6.7%. The American Association for Cancer Research (AACR) guidelines recommend tumor screening for all patients with BWS beginning at birth or at the time of diagnosis (Kalish, Doros et al. 2017).

Ultrasound Screening

- Full abdominal ultrasound every 3 months until age 4 years
- Renal ultrasound every 3 months from age 4 – 7 years

Alpha-fetoprotein (AFP) Screening

- AFP measurements every 3 months until age 4 years

Summary

- Children with BWS can have hemihypertrophy/lateralized overgrowth or overgrowth of one side of the body compared to the other.
- Treatment for uneven leg lengths depends on severity, ranging from shoe-lifts for mild cases to surgical options for more severe cases.
- Children with BWS or hemihypertrophy/lateralized overgrowth have an increased risk of certain types of tumors early in childhood and should be screened routinely.

References:

Kalish, J. M., L. Doros, L. J. Helman, R. C. Hennekam, R. P. Kuiper, S. M. Maas, E. R. Maher, K. E. Nichols, S. E. Plon, C. C. Porter, S. Rednam, K. A. P. Schultz, L. J. States, G. E. Tomlinson, K. Zelley and T. E. Druley (2017). "Surveillance Recommendations for Children with Overgrowth Syndromes and Predisposition to Wilms Tumors and Hepatoblastoma." Clin Cancer Res **23**(13): e115-e122.