BECKWITH-WIEDEMANN SYNDROME (BWS)

TUMOR RISK AND SCREENING

Beckwith-Wiedemann syndrome (BWS) is a rare disorder involving changes on a region of chromosome 11p15 that influence pre- and postnatal growth. These changes disrupt the normal balance of growth gene expression and lead to the overgrowth seen in patients with BWS. This imbalance can include embryonal tumors.

What is the tumor risk associated with Beckwith-Wiedemann syndrome (BWS)?

The overall tumor risk for all patients with BWS is approximately 5% – 10%. Research has shown, however, that the tumor risk for children with BWS can vary depending on the molecular cause of BWS (Brioude, Lacoste et al. 2013, Maas, Vansenne et al. 2016, Mussa, Molinatto et al. 2016):

- IC2 loss of methylation: 2.5% – 3.1% incidence (lower risk)
- Paternal Uniparental Isodisomy (pUPD): 13.8% – 17.3% incidence (intermediate/higher risk)
- IC1 gain of methylation: 22.8% – 28.6% incidence (higher risk)

Risk for the following types have been suggested:

- *CDKN1C* mutations: ~6.9% – 8.8% incidence (intermediate risk)
- Negative genetic testing: ~6.7% incidence (intermediate risk)

We currently do not have enough data and evidence to confidently predict risk for these groups. In addition, tumor risk is not known for rare chromosome differences.

How is tumor risk managed?

To manage tumor risk, patients with BWS and hemihypertrophy/lateralized overgrowth receive tumor screening. Due to the increased risk at a young age, it is recommended that children begin the screening protocol at the time the diagnosis is suspected. The goal of tumor screening is to detect tumors at an earlier stage, as these patients tend to have more favorable outcomes. In the United States, based on the American Association of Cancer Research (AACR) guidelines, it is recommended that any child with a greater than 1% risk of developing a tumor should be screened. As a result, all children with BWS or hemihypertrophy should receive tumor screening (Kalish, Doros et al. 2017, Kamihara, Bourdeaut et al. 2017).

What kinds of tumors do we see in BWS?

The most common tumors in BWS are Wilms tumor (kidney tumor) and hepatoblastoma (liver tumor). Neuroblastoma, pheochromocytoma, rhabdomyosarcoma, and adrenal cortical carcinoma occur rarely in BWS.

- Wilms Tumor is most easily detected by ultrasound. The risk for a Wilms tumor is highest in the earliest years and decreases with age. This risk decreases to that of the normal pediatric population by age 7, which is when screening is discontinued.
- Hepatoblastoma is detected by measuring **alpha-fetoprotein (AFP)** levels in the blood and by abdominal ultrasound. The risk for hepatoblastoma is highest in the first year and decreases with age.

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What is the recommended screening in BWS?

The American Association for Cancer Research (AACR) guidelines recommend tumor screening for all BWS patients beginning at birth or at the time of diagnosis (Kalish, Doros et al. 2017, Kamihara, Bourdeaut 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

In BWS patients with CDKN1C mutations, additional screening for neuroblastoma is recommended. These include urine HVA/VMA and chest x-rays. Tumor screening tends to lead to earlier detection and more favorable outcomes, which is why tumor screening is so important in children with BWS.

What are the AACR guidelines for interpreting AFPs?

AFP values tend to be higher in patients with BWS compared to those of the general pediatric population, but AFP values alone are not diagnostic of BWS. AFP values should decrease over time. A dramatic increase in AFP levels suggests a potential hepatoblastoma and may actually detect hepatoblastomas earlier than ultrasound. Concerns about an AFP value should be discussed with the physician responsible for monitoring your child's screening.

Summary

- Tumor risk in BWS varies based on genetic/epigenetic types of BWS but the average risk is 5-10%.
- The most common tumor types seen in BWS are Wilms tumor and hepatoblastoma.
- Methods for screening include regular serum AFP testing, abdominal ultrasounds, and renal ultrasounds.

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