BECKWITH-WIEDEMANN SPECTRUM (BWSp)

Diagnosis

Beckwith-Wiedemann syndrome (BWS) is a rare overgrowth disorder involving genetic and epigenetic changes on chromosome 11p15. BWS occurs in approximately one out of 10,500 births. Since BWS was first described by Drs. J. Bruce Beckwith and Hans-Rudolf Wiedemann in the 1960s, we have come to understand that not all children with BWS present in the same way. Patients with BWS may only have one or more of the most common (cardinal) features or perhaps only a handful of suggestive features. As a result, BWS was recently redefined as the Beckwith-Wiedemann Spectrum (BWSp) during an international consensus meeting. BWSp can be a clinical and/or molecular diagnosis.

Clinical Scoring System

To aid in diagnosis, the international consensus developed a scoring system to determine clinical criteria. Cardinal features of BWSp are assigned 2 points each and suggestive features are assigned 1 point each.

The following table can be used to help determine a patient's clinical score:

CARDINAL FEATURES	
Macroglossia	
Omphalocele	
Lateralized Overgrowth	
Hyperinsulinism	
Multifocal/bilateral Wilms tumor or nephroblastomatosis	
Pathology Findings*	
TOTAL CARDINAL FEATURES	

SUGGESTIVE FEATURES	
Large birth weight	
Facial nevus simplex	
Polyhydramnios and/or Placentamegaly	
Ear creases/pits	
Umbilical hernia and/or diastasis recti	
Organomegaly	
Embryonal tumors^	
Transient Hypoglycemia	
TOTAL SUGGESTIVE FEATURES	

*Mesenchymal dysplasia of the placenta, adenomatosis of the pancreas, or cytomegaly of the adrenal glands. ^Hepatoblastoma, unilateral Wilms tumor, neuroblastoma

Number of Cardinal Features: _____ x 2 = _____ point(s)

Number of Suggestive Features: _____ x 1 = _____ point(s)

Total Clinical Score: _____ point(s)

BWSp Molecular Testing Criteria

Score <2 Molecular testing not warranted
Score ≥2 Molecular testing for BWS warranted

Molecular testing for BWS should include:

- Methylation analysis for chromosome 11p15
- SNP array (microarray)
- *CDKN1C* gene sequencing
- Copy number analysis

A positive molecular result confirms a diagnosis of Beckwith-Wiedemann Spectrum. Patients with negative molecular testing should be re-evaluated to determine whether clinical scoring criteria is met.

BWSp Clinical Diagnosis Criteria

Patients with negative BWS molecular testing should be re-evaluated to identify if other clinical features suggestive of an alternative diagnosis are present. If other features are present, it is recommended that genetic testing for an alternative diagnosis be performed.

If an alternative diagnosis is not suspected, the patient's clinical features and score should be considered:

Score ≥4 with negative testing	Clinical Diagnosis of BWSp
Score <4 with negative testing	Referral to BWSp expert Consider BWS testing on additional tissues

Patients with a clinical score ≥4 and negative BWS testing without features suggestive of an alternative diagnosis meet criteria for a clinical diagnosis of BWSp. Patients with a clinical score <4 should be referred to a BWSp expert who can evaluate the clinical features present. Patients with at least one cardinal feature of BWSp should be suspected to have BWSp, even in the absence of a positive molecular result, with the exception of isolated omphalocele. Patients with isolated omphaloceles are less likely to be affected by BWSp compared to other isolated BWSp features and should not be considered part of the BWSp.

In patients suspected to have BWSp, testing additional tissues (such as a skin biopsy from the larger limb for patients with lateralized overgrowth or a tumor sample) can help molecularly confirm the BWSp diagnosis.

Summary

- BWS was redefined as BWSp due to varying presentations between patients
- BWSp can be a clinical and/or molecular diagnosis
- The BWSp clinical scoring system can aid in diagnosis
- Testing additional tissues can help identify molecular causes in patients suspected to have BWSp with negative blood testing

References:

Brioude, F., Kalish, J.M., Mussa, A., Foster, A.C., Bliek, J., Ferrero, G.B.,...Maher, E.R. (2018). Expert Consensus Document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. *Nat Rev Endocrinol*, 14, 229-249.