Diagnosis and management of the phenotypic spectrum of twins with Beckwith-Wiedemann syndrome (2019)

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Background

The frequency of twin pregnancies is more common in the Beckwith-Wiedemann syndrome (BWS) population compared to the general population. When identical twins are affected by BWS, the features may not always be the same in both twins. One twin may have more severe features of BWS than the other, which is known as discordance. This makes it more challenging for physicians to diagnose and manage twins with BWS.

Purpose

This study evaluated the clinical features in twins with BWS and level of discordance (dissimilarity) between patients from the same pregnancy. An algorithm to diagnose and manage twins with BWS was proposed.

Definitions

- Proband: the more affected twin (the twin with the most BWS clinical features)
- Monochorionic multiple pregnancies: fetuses that share one placenta
- Dichorionic multiple pregnancies: fetuses that each have their own placenta
- Monozygotic: One egg splits into two identical twins.
- Dizygotic: Two eggs are fertilized, each by a different sperm leading to fraternal (not identical) twins.

Findings

The clinical scores of each set of twins were determined and compared. The average clinical BWS score varied greatly between the proband and the less affected twin in both the monochorionic and the dichorionic groups. Additionally, it was found that the greater the clinical score of the proband, the larger the difference is between the twins. Interestingly, if you add the clinical scores together for a proband and his/her less affected twin, you get a number that is most similar to an individual BWS patient with a typical clinical score. This suggests that there is a finite number of BWS cells in any pregnancy, and if there are more fetuses in the pregnancies, the affected cells get spread between the different fetuses. This leads to asymmetric distribution resulting in a more affected twin (proband) and a less affected twin.

Mosaicism occurs when a change can be found in some cells of the body but not others and has been understood to be a cause for the spectrum of clinical features seen in twins with BWS. The timing of when these changes occur, however, is not well understood. Therefore, a theory of *diffused mosaicism* has been proposed in this paper. Essentially, one twin is more affected than the other but both twins have the potential to show BWS features due to the timing of the change during development that creates BWS cells. We propose that the changes that lead to BWS occur earlier in embryo development for non-mosaic patients (patients with BWS in almost all of their cells) and later in embryo development in mosaic patients (patients with BWS cells in fewer cells).

Based on the findings, an algorithm for screening twins with BWS was developed. The proband and the proband's twin should both be evaluated for BWS by a geneticist. Blood genetic testing can be unreliable for the less affected twin and therefore blood genetic testing only in the more affected proband may be most informative. Management depends on the type of pregnancy:

- *Dichorionic, dizygotic pregnancies:* The twin is not expected to be affected if the cause of BWS is a non-inherited one, as the twins here are essentially typical siblings
- *Monozygotic (identical) pregnancies*: The twins can be (a) equally affected, (b) unequally affected but still both affected, (c) unequally affected with one affected and one completely unaffected. Clinical exam is the most important in this case to determine a diagnosis of BWS in the less affected twin.

Key Points

- Identical (monozygotic) twins with BWS tend to present with features of varying severity. They may not be equally affected by BWS.
- When a proband presents with a moderate clinical score (6-8 points), their twin is more likely to also be affected by BWS and meet clinical diagnostic criteria.

Reference

Cohen JL et al. Diagnosis and management of the phenotypic spectrum of twins with Beckwith-Wiedemann syndrome. *American Journal of Medical Genetics Part A,* 2019;179(7): 1139-1147. PubMed PMID: 31067005