Beckwith Wiedemann syndrome: first international consensus regarding diagnosis and clinical management.


Introduction

Beckwith Wiedemann syndrome (BWS) is a rare overgrowth disorder associating macroglossia, exomphalos, lateralised overgrowth, organomegaly, hyperinsulinism, and an increased risk of embryonic tumor during early life. BWS is an imprinting disorder, with about 80% of children presenting a molecular defect (mostly a methylation defect at either ICR1 or ICR2, two differentially methylated regions, or paternal uniparental isodisomy) in the imprinted 11p15.5 region which contains the IGF2 and the CDKN1C genes.

To establish recommendations regarding clinical and molecular diagnosis of BWS, and clinical management of patients with BWS, and after a large review of the literature performed by a small group of international experts to establish a first draft document, a 3-day face-to-face meeting involving 35 participants was organized in March 2017 to discuss, formulate and vote on 72 consensus recommendations.

A new clinical scoring system

Cardinal features (2 points per feature)
- Macroglossia
- Exomphalos
- Lateralized overgrowth
- Multifocal, bilateral Wilms tumour or nephroblastomatosis
- Hyperinsulinism (> 1 week and requiring escalated treatment)
- Pathology findings: adrenal cortex ectomegaly, placental mesenchymal dysplasia or pancreatic adenomatosis

Suggestive features (1 point per feature)
- Birth weight > 2SDS above the mean
- Facial naevus simplex
- Polyhydramnios and/or placentomegaly
- Ear creases and/or pits
- Transient hypoglycaemia (lasting < 1 week)
- Typical BWSp tumours (neuroblastoma, rhabdomyosarcoma, unilateral Wilms tumour, hepatoblastoma, adenocortical carcinoma, phaeochromatosis)
- Nephromegaly and/or hepatomegaly
- Umbilical hernia and/or diastasis recti

≥ 2 points  ➔  Genetic testing
≥ 4 points  ➔  Classical BWS

BW Spectrum

Isolated lateralized overgrowth  ➔  BWS (score ≥ 4)
Atypical BWS (score < 4)  ➔  Clinical BWS

11p15 imprinted region defect

A consensus for tumour screening... stratified according to the molecular defect

<table>
<thead>
<tr>
<th>Molecular anomaly</th>
<th>Type of tumour</th>
<th>Protocol for tumour screening</th>
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</thead>
<tbody>
<tr>
<td>IC 1 GOM</td>
<td>Wilms</td>
<td>Abdominal US scan /3 months until 7 years</td>
</tr>
<tr>
<td>IC2 LOM</td>
<td>No screening</td>
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<tr>
<td>UPD(11)pat</td>
<td>Wilms / Hepatobl.</td>
<td>Abdominal US scan /3 months until 7 years</td>
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<td>Paternal dup.</td>
<td>Wilms / Hepatobl.</td>
<td>Abdominal US scan /3 months until 7 years</td>
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<tr>
<td>CDKN1C mut.</td>
<td>Neurobl.</td>
<td>Abdominal US scan /3 months until 7 years</td>
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<td>Clinical BWS</td>
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Ref: Brioude et al., Net Rev Endocrinol 2018

Clinical and molecular diagnosis, screening and management of Beckwith–Wiedemann syndrome: an international consensus statement