



CORRESPONDENCE

## Revisiting Wilms tumour surveillance in Beckwith–Wiedemann syndrome with IC2 methylation loss

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Recently Brzezinski et al. reported three individuals with Beckwith–Wiedemann syndrome (BWS) due to a loss of methylation at imprinting center 2 (IC2 LOM), who had intra-abdominal masses, and advocated strict tumor surveillance for individuals with BWS and IC2 LOM [1].

BWS is a rare imprinting disorder, with an increased risk of embryonic tumor during early infancy. It is due to various (epi)genetic abnormalities within the 11p15 region, the most prevalent one being IC2 LOM identified in about 50% of BWS patients. For years, a strong correlation between tumor risk and BWS has been reported. Present day knowledge has been summarized by Maas and co-workers [2] who collected data on all known larger series of BWS patients, with additional data from their own center, and in total representing almost 2000 patients. Tumor risk was the highest for individuals with a gain of methylation (GOM) of IC1 (28%) and paternal uniparental disomy (pUPD) of 11p15 (16%), whereas patients with IC2 LOM presented with the lowest risk (2.6%). Furthermore, they subdivided chances depending on the nature of tumors and reported the

prevalence of Wilms tumor (WT) to be high for patients with IC1 GOM and 11p15 pUPD (24% and 7.9%, respectively) and very low for IC2 LOM (0.2%) and *CDKN1C* mutations (0%). These data on the reliably diagnosed large series of BWS individuals have been taken into consideration by a group of 30 experts to establish international recommendations for tumor screening in BWS [3]. Considering the low rate of abdominal tumors in individuals with IC2 LOM, the experts recommended no abdominal screening for this subgroup of patients, but only for the three other subgroups.

Brzezinski et al. suggest in their paper that the risk of WT in patients with IC2 LOM might be underestimated, and therefore suggest that those patients should be screened for WT. However, in our opinion their data about an increased risk of WT do not allow to raise such conclusions. Indeed, patient 1 had a false initial molecular diagnosis (IC2 LOM with an IC1 “borderline” GOM, which led to a misdiagnosis of IC2 LOM). The correct molecular diagnosis was detected only after the detection of a WT in their

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patient, which was an 11p15 pUPD. Indeed 11p15 pUPD is associated with an increased risk of WT. We concur with Brzezinski and co-workers that distinguishing between the different molecular diagnosis might be challenging, especially in cases with low rate of mosaicism. Keren et al. highlighted that additional techniques such as SNP array can be needed for an accurate molecular diagnosis [4]. The description of Brzezinski is not illustrating an increased risk for WT in IC2 LOM but illustrates the need of accurate molecular diagnostic procedures, in order to provide optimal care and surveillance to these individuals and their families. Such molecular testing needs to be performed by expert laboratories, with a large experience in the field of imprinting disorders. Their patient 2 has an obvious clinical and molecular diagnosis of IC2 LOM and is described having a WT. However, the lesions in this individual are nephrogenic rests (NRs). These form a benign condition that has been associated for years with BWS. Mussa et al. reported cortical/medullary cysts in 7.5% of BWS individuals, including three of the 25 individuals with IC2 LOM. None of the latter three patients developed WT [5]. NRs are considered as benign precursors of WT. Indeed, NRs are often identified on pathological examinations of WT: in about 40% of unilateral WT and up to 93% in bilateral WT [6]. NRs are also frequently detected in the general population (up to 1% on autopsies of infants), typically by coincidence, and transformation into WT is rare, as these NR can become quiescent with age (review in ref. [7]). Long-term surveillance is recommended in a child with NRs, irrespective whether a predisposition syndrome is present or not. Follow-up of patient 2 of Brzezinski showed a spontaneous regression without any intervention. Therefore their patient 2 should not be tagged as a patient with WT. Screening programs will always also yield “false-positive” results such as the identification of benign lesions. The detection of such lesions may cause considerable psychological concerns and burdens for the affected individuals and their parents, and form a major disadvantage of any surveillance program [2]. Finally, Brzezinski presented a genuine patient with BWS and a WT in whom an IC2 LOM

was detected without clues for a pUPD 11p. This individual represents the third occurrence of the combination of findings, next to the two patients reported by Maas and co-workers. The prevalence of WT in the Canadian cohort cannot be calculated, as the total number of individuals followed by this center is not available. However, the prevalence of WT in individuals with BWS patients and an IC2 LOM is likely very low (well below 1%), and when taking world-wide figures into account, the prevalence will even be lower.

We conclude that the paper by Brzezinski and co-workers does not offer sufficient arguments to recommend screening for WT for patients with BWS due to an IC2 LOM. We remain of the opinion that the recommendations from Maas et al. [2] and those from the international consensus group [3] should be followed.

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