Coexistence of Mosaic Uniparental Isodisomy and a *KCNJ11* Mutation Presenting as Diffuse Congenital Hyperinsulinism and Hemihypertrophy

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Beckwith-Wiedemann syndrome (BWS) is an imprinting disorder that is clinically characterized by macrosomia, macroglossia, and abdominal wall defects and leads to an increased risk of tumorigenesis. It is caused by multiple epigenetic and genetic changes affecting imprinted genes. The chromosomal region in BWS is 11p15.5, which consists of two imprinting domains: IGF2/H19 and CDKN1C/KCNQ1OT1. BWS has five known causative epigenetic and genetic alterations: loss of methylation at KvDMR1, gain of methylation at H19DMR, paternal uniparental disomy (UPD), CDKN1C mutations, and chromosomal rearrangements [1].

Hyperinsulinaemic hypoglycaemia (HH) is the most common biochemical abnormality observed in patients with BWS, and this tends to be severe in patients with UPD of chromosome 11. The underlying molecular mechanisms of HH in patients with BWS are not known. Typically, patients with HH due to paternal UPD of chromosome 11 do not respond to therapy with first-line drugs, such as diazoxide, and may require a pancreatectomy.

The report by Kocaay et al. [2] and 2 previous reports [3, 4] highlight several important aspects of patients with

BWS and HH due to paternal UPD of chromosome 11. Patients with BWS and HH may not always have the classical features of macrosomia, macroglossia, hemihypertrophy, and abdominal wall defects at birth. These clinical features might be subtle and may develop later in life. Thus, a high index of suspicion of BWS is required in some patients with HH, and if suspected, then this warrants testing for paternal UPD of chromosome 11.

The molecular mechanisms of HH in some patients with BWS due to UPD of chromosome 11 may involve loss of function mutations in the *ABCC8/KCNJ11* genes that encode the SUR1 and KIR6.2 components of the potassium-sensitive pancreatic K_{ATP} channel. In the report by Kocaay et al. [2], the patient described had two novel mosaic paternally inherited *KCNJ11* mutations which potentially led to severe HH. Further analysis confirmed paternal UPD of chromosome 11 that extended across the *KCNJ11* gene at 11p15.1 and the BWS locus at 11p15.5 and was confirmed in the blood and pancreatic tissue. However, not all patients with HH and BWS due to UPD of chromosome 11 have mutations in the *ABCC8/KCNJ11* genes [4], suggesting other possible molecular mechanisms of HH in these patients.

References

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