Children's Hospital of Philadelphia
RESEARCH INSTITUTE

# Congenital hyperinsulinism in children with paternal 11p uniparental isodisomy and Beckwith-Wiedemann syndrome (2016)

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## Background

Congenital hyperinsulinism (HI) is the most common cause of prolonged hypoglycemia in infancy. More than half of patients with HI have a mutation in one of two genes (ABCC8 or KCNJ11) that is known to cause HI. These genes are located close to the Beckwith-Wiedemann syndrome (BWS) imprinted regions on chromosome 11p15. Some patients with BWS are affected by HI, although the mechanism that causes this is unknown. A variety of treatment options are available for patients with HI depending on severity and can include removing part of the pancreas that is causing the HI, medications (typically diazoxide or octreotide), and/or continuous feeds or glucose infusions.

## Purpose

This study describes 28 children diagnosed with HI and BWS. The clinical features of the patients, medical management and molecular causes of HI were evaluated.

## Findings

The most common features observed in the patients with BWS and HI were hemihypertrophy (now referred to as lateralized overgrowth), large size at birth (macrosomia), and enlarged liver size (hepatomegaly). About half of patients also had an umbilical hernia, macroglossia, and/or ear creases/pits. In several patients, lateralized overgrowth was the only BWS feature present other than HI.

The majority of patients (26/28) were diagnosed with BWS due to paternal uniparental isodisomy of chromosome 11p15 (pUPD11p) in blood, skin and/or pancreas tissue. The other two patients were diagnosed with BWS due to loss of methylation at imprinting control region 2 (IC2 LOM). Four patients were also found to have a mutation in one of the genes known to cause HI.

The pancreas tissues of the patients with pUPD11p had unique findings that are not typically seen in pancreas tissues of patients with HI without BWS. These unique findings are considered pancreatic adenomatosis. In some patients from this study, the distinct physical appearances of the pancreas led physicians to consider pUPD11p as a possible diagnosis. Genetic testing later confirmed pUPD11p in these tissues.

Patients were treated by a combination of surgery and/or different medications (diazoxide or octreotide). Patients with pUPD11p had more severe forms of HI than the patients with IC2 LOM. Half of the patients with pUPD11p required surgery to remove part of the pancreas. Most of the patients with severe HI did not require more than two years of treatment. The four patients with HI gene mutations in addition to BWS had more severe forms and required prolonged treatment beyond two years.

## Conclusion

Patients with persistent, severe forms of HI may be affected by BWS due to pUPD11p, even if the patient does not have any other classic features of BWS. When evaluating patients with HI, it is important to consider pUPD11p due to the increased tumor risk these patients can have. Testing pancreas tissue can help detect a molecular change in patients with normal blood testing.

## Key Points

- The majority of patients with HI and BWS have pUPD11p.
- Most patients did not respond to diazoxide treatment and half required a pancreatectomy.
- Patients with HI and BWS due to pUPD11p have unique pathology findings in the pancreas that may raise suspicion for BWS.
- It is important to test for BWS in patients with severe HI, even if no other physical features of BWS are present, due to increased tumor risks.

## Reference

Kalish JM et al. Congenital hyperinsulinism in children with paternal 11p uniparental isodisomy and Beckwith-Wiedemann syndrome. *J Med Genet.* 2016;53(1): 53-61. PubMed PMID: 26545876

***Special Note:***
This article was published before the BWS International Consensus Meeting was held. As a result of the findings of this paper, both hyperinsulinism and pancreatic adenomatosis (the unique pathology finding in the pancreas samples of patients with BWS) are considered a "cardinal feature" of Beckwith-Wiedemann Spectrum.