



# An Intriguing Confluence of Unusual Diseases



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## INTRODUCTION

- Beckwith-Wiedemann syndrome (BWS) is a rare congenital disorder with an incidence of 1 in 13,700 newborns [1]. Patients often present with macroglossia, macrosomia, and omphalocele. Persons affected by BWS are at increased risk for neoplasms such as Wilm's tumor, pancreatoblastoma, and hepatoblastoma [6]. BWS has been associated with mutations on the short arm of chromosome 11 as well as abnormal genomic imprinting of parent specific gene expression.
- Pseudohypoparathyroidism (PHP) has a prevalence of 0.79 in 100,000 [2]. The disease process is linked primarily to resistance of parathyroid hormone (PTH), however can present in several different ways as outlined in the accompanying table. Phenotypically, patients can present with Albright Hereditary Osteodystrophy which involves hypogonadism, shortened 4th and 5th metacarpals, rounded facies and possible mild intellectual disability. PHP is caused by imprinting defects at the GNAS protein complex.
- Bartter's syndrome has a prevalence of 1 in 100,000 [3]. It is caused by a defect in the thick ascending loop of Henle. Symptoms include alkalosis and hypokalemia in most cases. Diuretic abuse can cause similar symptoms. There are multiple subtypes as seen in the associated table.
- There has been a very rare association between BWS and PHP shown in few case reports and even rarer association between PHP and Bartter's. PHP and BWS are both associated with genomic imprinting defects at the GNAS locus. [4] This is a unique case report regarding a patient that has a confluence of all three processes.

## CASE PRESENTATION

- A 37 year old caucasian male with a past medical history of BWS and PHP-1b presented to the ER with prolonged QT interval of 492 milliseconds.
- Phenotypically, his BWS only manifested itself with macroglossia. He was diagnosed with PHP during childhood after presenting with hypocalcemia and managed with calcitriol and calcium. In his early 20's he had multiple ER visits for severe hypocalcemia due to intermittent compliance with his regimen.
- On presentation, he had no complaints. On exam, the patient displayed Chvostek's sign on the left. Laboratory testing is shown in the results table.
- The prolonged QT interval was attributed to hypokalemia and hypocalcemia. He received aggressive IV calcium gluconate and potassium chloride with improvement to 390 ms. High TSH in light of negative TPO antibodies was noted and levothyroxine was started with clinical improvement.
- He had persistent hypokalemia. Further testing suggested patient's hypokalemia, hypomagnesemia and hypochloremic alkalosis were due to type 3 Bartter's syndrome although renin and aldosterone were normal once fully hydrated. Type 5 Bartter's syndrome was felt to be less likely due to elevated iPTH, although it was complicated by PHP.

## BARTTER'S SYNDROME

Type	Gene	Protein	Findings
Type 1	SLC12A1	NKCC2	Prematurity, polyhydramnios, nephrocalcinosis, hypokalemic alkalosis
Type 2	KCNJ1	ROMK1	Prematurity, polyhydramnios, nephrocalcinosis, hypokalemic alkalosis
Type 3	CLCNKB	CLC-Kb	Hypokalemia, hypochloremic alkalosis
Type 4a	BSND	Barttin	Prematurity, polyhydramnios, nephrocalcinosis, deafness, hypokalemia, hypochloremic alkalosis
Type 4b	CLCNKA/CLCNKB	CLC-Ka/CLC-Kb	Prematurity, polyhydramnios, nephrocalcinosis, deafness, hypokalemia, hypochloremic alkalosis
Type 5	CASR	CASR	Hypokalemia, hypochloremic alkalosis

## RESULTS

Date	3/2012 (Date of Admit)	8/2013	4/2014	9/2015
Sodium (136-145 mmol/L)	135	136	136	137
Potassium (3.1 - 5.1 mmol/L)	2.9	3.8	3.3	3.7
Bicarbonate (21-32 mmol/L)	33	28	28	26
Chloride (98-107 mmol/L)	96	96	98	98
Calcium (8.5-10.1 mg/dL)	6.8	8.6	8.5	7.1
Ionized Ca (4.48 - 5.28 mg/dL)	3.59			
Magnesium (1.8 - 2.5 mg/dL)	1.7	2.2	1.9	1.9
iPTH (15 - 65 pg/mL)	140			131
TSH (0.358 - 3.74 uIU/mL)	7.70	5.67	6.37	3.99
TPO (<0.9 IU/mL)	0.7			
Vit D 25-OH (25-80 ng/mL)	11			20
Vit D 1,25 (18-64 pg/mL)	11			

## PSEUDOHYPOPARATHYROIDISM

Classification	Hormone Resistance	Albright Hereditary Osteodystrophy	GNAS defect	PTH level
PHP 1a	PTH, TSH, Gn, GnRH	Yes	Maternal Mutation	Elevated
PHP 1b	PTH, TSH	No	Imprinting Dysregulation	Elevated
PHP 1c	PTH, TSH, Gn	Yes	Maternal Mutation	Elevated
PHP 2	PTH	No	Unknown	Elevated
Pseudo-PHP	None	Yes	Paternal Mutation	Normal

## CONCLUSIONS

- In the literature, there are case reports of patients with both PHP and BWS due to multiple imprinting defects likely at the GNAS locus [4]. Additionally, case reports have documented a relationship between pseudohypoparathyroidism and Bartter syndrome [5]. We present the case of a patient who appears to have all three disease processes.
- This could be suggestive of a potential epigenetic link that warrants further investigation.
- Although the elevated TSH may have been due to TSH resistance seen in PHP 1a, the clinical improvement on levothyroxine suggested mild primary hypothyroidism.

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