Cushing disease in a patient with Beckwith Wiedemann: an unusual association

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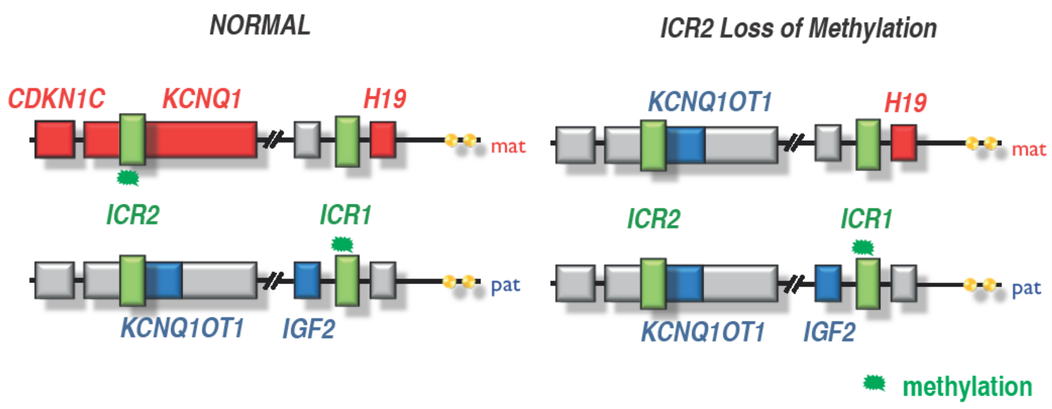
BACKGROUD

Beckwith Wiedemann syndrome (BWS) is an overgrowth syndrome with an increased risk of embryonic tumors during early childhood. About 80% of patients show a molecular defect in the 11p15 imprinted region. Loss of methylation (LOM) at the inmprinting control region 2 (ICR2) is the most frequent defect, which leads to a loss of expression of the CDKN1C gene, increasing cell proliferation



BWS has been associated for a long time with malignant neoplasms during early childhood, and especially with Wilms' tumors. However, recent works described benign neoplasms in some patients.

We report here the first case of **Cushing disease in a patient with a BWS due to an ICR2 LOM.**

CLINICAL CASE

A 19-year-old female patient was refered to an Endocrinolgy clinic for rapid weight gain, hirsutism and secondary amenorrhea. Furthermore, she presented hemihyperplasia. Macroglossia was noticed by the parents during early infancy.
Blood and urinary tests showed hypercortisolism (table 1). Dynamic tests confirmed the ACTH dependent hypercortisolsm (table 2). MRI showed a pituitary microadenoma (Figure 1)
The patient underwent transsphenoidal surgery of the microadenoma, which was positive for ACTH-staining, with a Ki67 index at 4%.
Methylation analysis on the patient's leucocytes showed an ICR2 LOM in a mosaic state (methylation index 17%). ICR2 LOM was observed in nearly all cells in the adenoma '(methylation index 1%). (Figure 2)

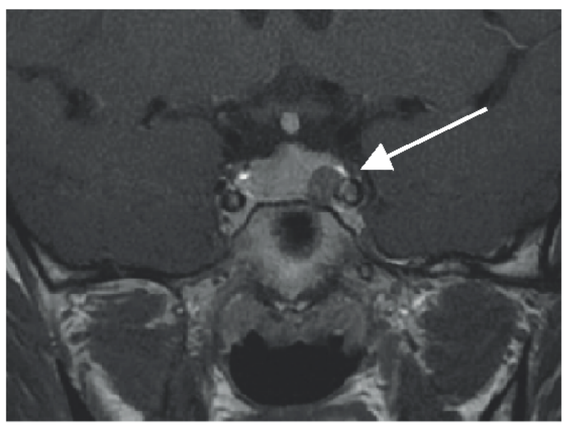


Fig. 1: MRI of the patient before surgery showing the left pituitary microadenoma.

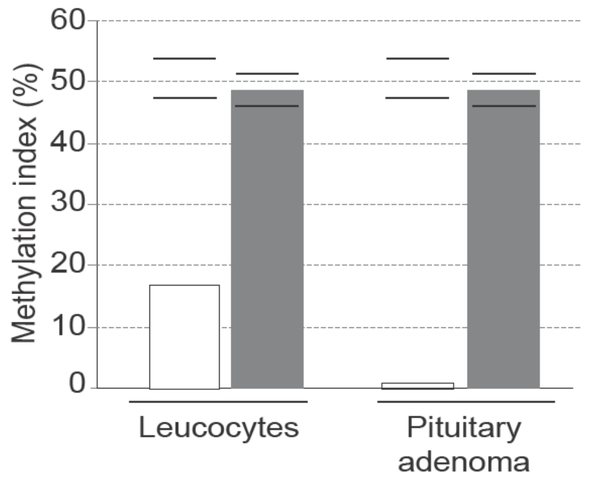


Fig. 2: Methylation indexes of ICR2 (white boxes) and ICR1 (grey boxes). Black horizontal lines figure the normal values of methylation indexes.

	Patient	Normal values
Testosterone (ng/ml)	0.38	0.08 – 0.48
Androstenedione (ng/ml)	**3.4**	**0.2 – 3.0**
DHA sulfate (ng/ml)	2159	599 – 3001
17 OH Progesterone (ng/ml)	1.5	0.11 – 1.1
Prolactin (µg/L)	17.4	4.8 – 23.3
Urinary free cortisol (µg/24H)	309	10.9 – 71.4
Urinary creatinine (mg/24H)	15.1	7 – 12
Cortisol (ng/ml) / ACTH (pg/ml)		
	8H 267 / 35.1	**62 – 194**
	12H 169.1 / 19.1	
	16H 185.5 / 30.8	
	20H 186 / <2.0	
	24H 128 / 33.4	

Table 1: basal hormonal evaluation of the patient. Estradiol, LH, FSH, prolactine, FT4, TSH, IGF1 values were in the normal range (not shown).

	Patient
1 mg Dexamethasone suppression test	
Cortisol (ng/ml)	**121**
ACTH (pg/ml)	**57.7**
8 mg Dexamethasone suppression test	
Cortisol (ng/ml)	34
ACTH (pg/ml)	4.99
CRH stimulating test	
Cortisol (basal/peak) (ng/ml)	**269/394**
ACTH (basal/peak) (pg/ml)	**44.8/133**

Table 2: dynamic explorations confirming the ACTH-dependent Cushing syndrome.

CONCLUSION

Beckwith Wiedemann syndrome should be evoked in case of pituitary adenoma when associated with uncommon symptoms, and especially hemihyperplasia. Methylation studies of the 11p15 region on sporadic isolated pituitary adenoma may identify new underlying molecular mechanisms.

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