

Adrenal Insufficiency in ROHHADNET Syndrome (Rapid Onset Obesity with Hypothalamic dysfunction, Hypoventilation, Autonomic Dysregulation and Neural Tumor)



R. Tallone, F.Napoli, N.Di Iorgi, A.E.M. Allegri, A.Calcagno, M. Maghnie
Pediatric Endocrinology and Diabetology Service G. Gaslini Institute
University of Genoa



Introduction:

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation and neural tumor (ROHHADNET) is a rare condition. The disorder can mimic genetic obesity syndromes and several endocrine disorders.

The first symptom is the appearance of **rapid onset obesity** (2-4 years) followed by;

- **central hypoventilation** (with the lack of paired-like homeobox 2B mutation)
- **hypothalamic dysfunction** (central hypothyroidism, disordered water balance, growth hormone deficiency, hyperprolactinemia, disorders of puberty and corticotropin deficiency)
- **dysautonomic symptoms** (thermal dysregulation, pain insensitivity, behavioral disorders, strabismus, pupillary anomalies..)
- **neural tumors** (such as ganglioneuroma and ganglioneuroblastoma, located in abdomen or mediastinum).

Objective and hypothesis:

Aim of this study was to evaluate adrenal function in ROHHADNET patients from a single-center .

Six patients with ROHHADNET underwent clinical (BMI SDS) and biochemical evaluation for baseline cortisol and for Insulin Tolerance Test (ITT) at the mean age of 10.1±5.9 (range 4.7-19.9 yrs); 4 were also tested with low-dose ACTH test (Synacthen 1 mcg/ m²) after an interval of 0-4 years. All subjects had a morning baseline cortisol evaluation at the time of ROHHADNET diagnosis. The examinations excluded in all patients the presence of Cushing's disease as a cause of symptoms Pituitary defects were present (n=4) in one patient, (n=3) in one, (n=2) in two and (n=1) in two patients While hyperprolactinemia was documented in all of them; 5 had neural crest tumor.

P.	ITT						ACTH					
	Basal cortisol (mcg/dl)	Cortisol peak (mcg/dl)	Age (Year)	BMI Kg/m ²	BMI SDS	defects	Basal Cortisol (mcg/dl)	Cortisol Peak (mcg/dl)	Age (year)	BMI Kg/m ²	BMI SDS	defects
1	8,9	23,1	7,7	22,4	2,4	2	8,8	20,35	19,9	60,3	4,9	3
2	0,1	0,1	7,6	40,3	4,7	4	1,1	8,5	5	32,6	4,8	2
3	16,1	15,8	6	26,5	3,3	1	0,1	0,1	8,9	22,5	2,1	3
4	7,3	10,2	4,7	18,8	1,9	2	7,6	15,8	16,7	33,7	3	3
5	7,1	16,7	19,9	60,3	4,9	3						
6	11,8	19,3	14,8	36,1	3,4	1						

Figure 1 : in the figure are reported the values of the test to evaluate the adrenal insufficiency performed in 6 patients ;to the left by ITT, to the right by ACTH test.

Conclusion:

Central Adrenal Insufficiency was documented in 83% of ROHHADNET patients after dynamic testing with ITT or ACTH-low testing. Baseline cortisol value is not reliable for the diagnosis of central adrenal insufficiency (CAI). While the severity of hypothalamic dysfunction appears to be correlated with CAI, age and BMI SDS are not associated.

References

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Results

BMI SDS was of 3.4±1.2 at the time of ITT and 3.7±1.4 at the time of ACTH test. None of the patients displayed hypercortisolism. Baseline cortisol pre-ITT was 8.5±5.3 mcg/dl with a peak cortisol of 14.2±8.1 mcg/dl. Baseline cortisol pre-ACTH test in those who underwent ACTH test was 4.4±4.4 mcg/dl with a peak cortisol of 11.1±8.8 mcg/dl (Figure 2). Five patients received the diagnosis of Central adrenal Insufficiency (CAI). Baseline cortisol was not related to BMI SDS at any time point and it was variably associated with age (r's 0.02-0.94)

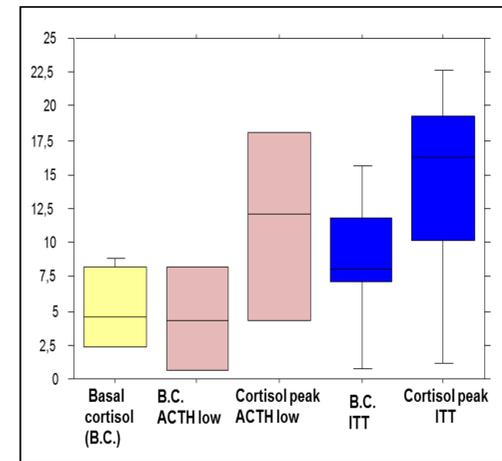


Figure 2

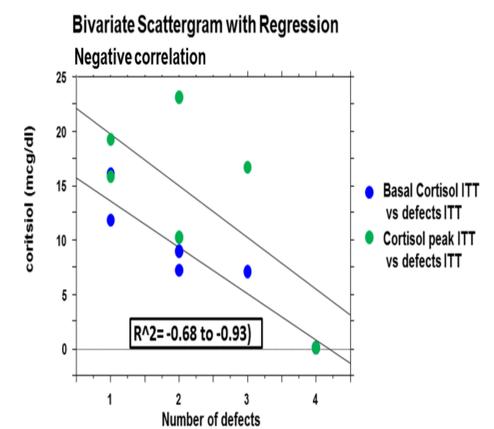


Figure 3a

The correlations between baseline cortisol levels at 3 different time points were variable (r's from 0.1-0.87). The association between baseline cortisol and peak response was strong after ACTH (r=0.95, P0.07), and moderate after ITT (r=0.7, P0.13). (Figure 3 b-c) The relation between peak cortisol responses after the 2 tests was significant (r=0.97, P0.04). Both baseline cortisol and peak cortisol after ITT are negatively correlated with the number of pituitary hormone defects (r's=-0.68 to -0.93) (figure 3a).

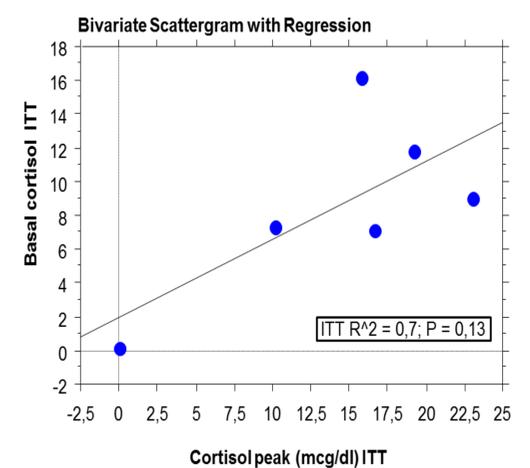
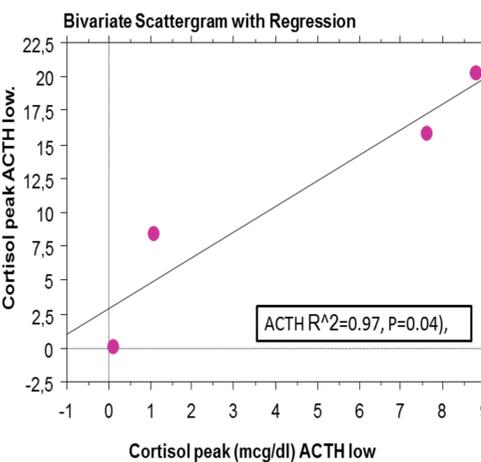


Figure 3 b-c: bivariate analysis with regression; the association between baseline cortisol and peak response was strong after ACTH (r=0.95, P0.07), and moderate after ITT (r=0.7, P0.13).

