Perypheral neuroblastic tumors and Immunological studies in ROHHADNET syndrome (Rapid-onset Obesity with Hypothalamic dysfunction, Hypoventilation, Autonomic Dysregulation and NEural Tumor)

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Background

ROHHADNET syndrome (Rapid-onset Obesity with Hypothalamic dysfunction, Hypoventilation, Autonomic Dysregulation and NEural Tumor) is characterized by the occurrence -in previously normal children- of:
-sudden hypothalamic dysfunctions (typically early, rapid weight gain and variable degree of pituitary hormone deficiencies and/or precocious puberty)
-autonomic dysregulations (pupillary dysfunctions, gastrointestinal dysmotility, thermal dysregulation)
-respiratory manifestations (alveolar hypoventilation)
-developmental delay/regression,behavioural disorders
Prompt recognition is important for appropriate management of endocrine deficits, and close monitoring for the need of respiratory support. If not identified or treated inadequately, the alveolar hypoventilation can be fatal
In spite of a suspicion for genetic etiology, disease-associated genetic variations have not been identified yet. A paraneoplastic/autoimmune etiology has been suggested because of the overlap with autoimmune encephalitis symptoms, the association with neural crest tumors, extensive infiltrates of lymphocytes and histiocytes in the hypothalamus of some patients and a partial response to intravenous immunoglobulin, rituximab and cyclophosphamide.

Objective and hypotheses

Aim of this study was to describe the phenotype of ROHHADNET patients, and to evaluate a possible role of autoimmunity in this disorder..
We present our preliminary results regarding autoimmunity and neural tumors in patients with ROHHADNET syndrome

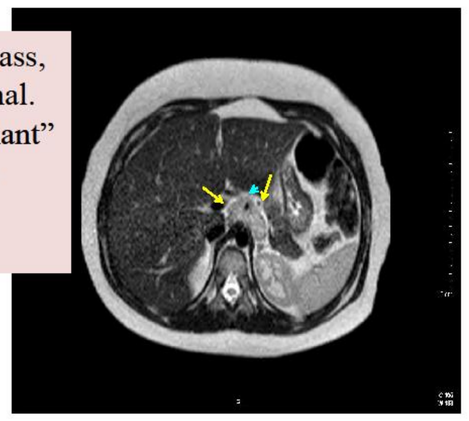

2 years old


9 years old

Subjects and Methods

Seven patients (3M, 4F, age 7-20 yrs) with ROHHADNET syndrome underwent clinical and instrumental studies; serum levels of antibodies against neuronal antigens N-methyl-d-aspartate receptor (NMDAR), LGI1, contactin-associated protein-like 2 (CASPR2), dopamine receptor, AMPAR, ganglionic AChR (acetilcholin receptor), autonomic, voltage-gated potassium channel (VGKC) and voltage-gated Ca++ channel (VGCC), often found in association with tumors,were assessed in 6 patients. Serum and CSF were tested for oligoclonal bands in 6/7 patients.

Solid retroperitoneal mass, contiguous to left adrenal. Biopsy: "stroma dominant" peripheral neuroblastic tumor: **maturing ganglioneuroma**

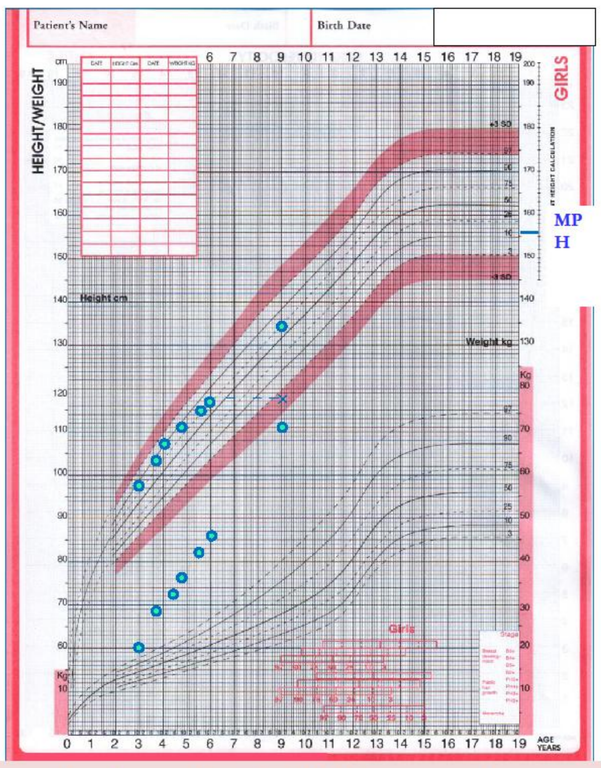


Results

All patients had normal birth size and no symptoms until 2-4 years (table 2), thenthey developed:
- *Rapid weight gain* (mean BMI Z-score +3.5SDS)
- Water/salt balance disruption,
- B*ehavioral problems*
- **Central sleep apnoeas**: 6 pts. (non-invasive ventilation or invasive ventilation) at age 2-16 years

Serum neural receptors autoantibodies were undetectable in all tested patients. CSF and serum tested positive for oligoclonal bands in 3/6 patients (one had been previously described (4)
- **Endocrinological dysfunctions:** Central adrenal insufficiency: 3 pts (partial or complete)
growth hormone deficiency: 7 pts
central precocious puberty: 2 pts
central hypothyroidism: 6 pts (1 transient)
Hyperprolactinemia (7 pts)
Brain MRI: normal or not significant
Retroperitoneal mass/tumor: 4 pts (3 ganglioneuroma)

The serum autoantibodies were undetectable in all patients. CSF and serum tested positive for oligoclonal bands in 3/6 patients. One patient has celiac disease.



Growth chart of pt 5 (GHD, central precocious puberty, severe obesity

Conclusions

We aimed to evaluate whether most of the known autoantibodies associated with different forms of immune-mediated encephalitis could be detected in serum of patients with ROHHADNET syndrome.
The results of our study were negative, but serum and CSF tests have shown autoimmune activation in 50% patients so far.
Lack of identification of known antibodies by current available methods do not exclude the possibility of a role of autoimmunity in ROHHADNET (new antigenic targets?).
Additional studies in order find novel autoantibodies are needed.
There are ongoing studies testing the CSFs of patients for binding to brain tissues.
A better understanding of underlying pathogenetic mechanisms could improve the management of this severe disorder.

Table 1. Characteristics of patients with ROHHADNET syndrome

	1 ♂	2 ♀	3 ♂	4 ♀	5 ♀	6 ♀	7 ♂
Hypoventilation (age at diagnosis) (yr)	YES (16?)	YES (3)	YES (2)	YES (4)	YES (6.5)	NO	YES (?)
GH deficiency (age)	YES (14yr)	YES (4)	YES (6)	YES (7)	YES (7)	YES (16)	YES (?)
Central precocious puberty (age)	NO	NO	NO	YES (6)	YES (6)	NO	NO
Hyperprolactinemia	YES	YES	YES	YES	YES	YES	YES
Central adrenal insufficiency (age)	NO	YES (3)	NO	NO	YES (4)	NO	YES (?)
Central hypothyroidism (age)	YES (11yr)	YES (3)	YES (4)	YES (10) (transient)	YES (4)	NO	YES (?)
Hypogonadotropic Hypogonadism	YES	NO	NO	NO	NO	YES	YES
Hyper/hyponatremia	Hyper	NO	Hyper	NO	Hyper/Hypo	Hyper	Hyper/Hypo
Neurobehavioral disorders	NO	YES	YES	YES	YES	NO	YES
Neural tumor (age)	NO	NO	?	YES (10)	YES (4)	YES (14)	NO
Autonomic dysregulation	NO	NO	YES	NO	YES	NO	YES
CSF and serum oligoclonal bands	YES	Not done	YES	NO	YES (borderline)	NO	NO
Other	Chiari I	Nocturnal enuresis	//	//	//	//	Celiac disease

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