Immunological Studies in Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, Autonomic Dysregulation, and Neural Tumor (ROHHADNET) Syndrome

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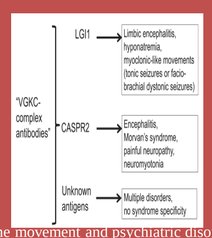
Background and Aim

ROHHADNET syndrome (Rapid-onset Obesity with Hypothalamic dysfunction, Hypoventilation, Autonomic Dysregulation and NEural Tumor) is characterized by the occurrence - in apparently 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
Up to now, no genetic cause has been identified as responsible for ROHHADNET pathogenesis; however, the frequent 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 suggests a possible role of autoimmunity in ROHHADNET syndrome
We present our preliminary results regarding the role of autoimmunity in six patients with ROHHADNET syndrome

Autoimmune encephalitis

Serum antibodies to neuronal antigens often found in association with tumours and associated with different forms of immune-mediated encephalitis

- ***NMDAR:*** anti-NMDAR encephalitis (described in 2007, is one of the most frequent and best characterized autoimmune encephalitis. Sequential presentation of symptoms, including prodromal symptoms followed by behavioral changes, psychosis, catatonia, decreased level of consciousness, dyskinesias, and autonomic instability which may require ventilatory support)
- ***LGI1:*** limbic encephalitis
- ***CASPR2:*** limbic encephalitis



- ***AMPAR:*** limbic encephalitis
- ***Dopamine receptor:*** autoimmune movement and psychiatric disorders
- ***Ganglionic AChR (autonomic):*** autoimmune autonomic ganglionopathy
- ***VGCC:*** Lambert-Eaton myasthenic syndrome, paraneoplastic cerebellar degeneration

Subjects and Methods

Six patients (2M, 4F, age 6-16 yrs) with ROHHADNET syndrome underwent clinical, neurophysiological and neuroradiologic studies.
Serum antibodies to 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 tumours, were assessed.
Serum and CSF oligoclonal bands were assessed (3 pts).

Table 1. Clinical characteristics of six patients with ROHHADNET syndrome

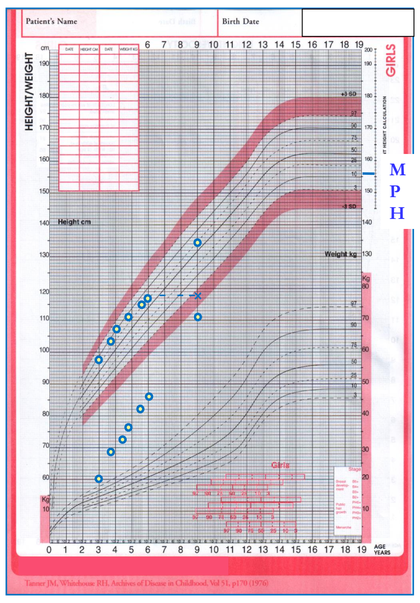
	1 ♂	2 ♀	3 ♂	4 ♀	5 ♀	6 ♀
Hypoventilation (age at diagnosis) (yr)	NO	YES (3)	YES (2)	YES (4)	YES (6.5)	NO
GH deficiency (age)	YES (14yr)	YES (4)	YES (6)	YES (7)	YES (7)	YES (16)
Precocious puberty (age)	NO	NO	NO	YES (6)	YES (6)	NO
Hyperprolactinemia	YES	YES	YES	YES	YES	YES
Central adrenal insufficiency (age)	NO	YES (3)	NO	NO	YES (4)	NO
Central hypothyroidism (age)	YES (11yr)	YES (3)	YES (4)	YES (10)	YES (4)	NO
Hypogonadotropic Hypogonadism	YES	NO	NO	NO	NO	YES
Hyper/hyponatremia	Hyper	NO	Hyper	NO	Hyper/Hypo	Hyper
Neurobehavioral disorders	NO	YES	YES	YES	YES	NO
Neural tumor (age)	NO	NO	?	YES (10)	YES (4)	YES (14)
Autonomic dysregulation	NO	NO	YES	NO	YES	NO

Results

All patients had normal birth size and no symptoms until 2-4 years
- they developed *rapid weight gain* (mean BMI Z-score +3.5SDS),
- hyperprolactinemia,
- water/salt balance disruption and
- *behavioral problems*

Central apnoeas: 4 pts. (non-invasive ventilation) at age 2-6.5 yrs
Endocrinological data: Central adrenal insufficiency: 2 pts
growth hormone deficiency: 6 pts
central precocious puberty: 2 pts
central hypothyroidism: 5 pts
Brain MRI: normal or not significant in all pts.
Retroperitoneal mass/tumor: 4 pts

The above mentioned serum autoantibodies were undetectable in all patients. CSF tested positive for oligoclonal bands in one patient.



Abdomen MRI: solid retroperitoneal mass, contiguous to left adrenal. Suspect **neural tumor**
Biopsy: "stroma dominant" peripheral neuroblastic tumor, **maturing ganglioneuroma**

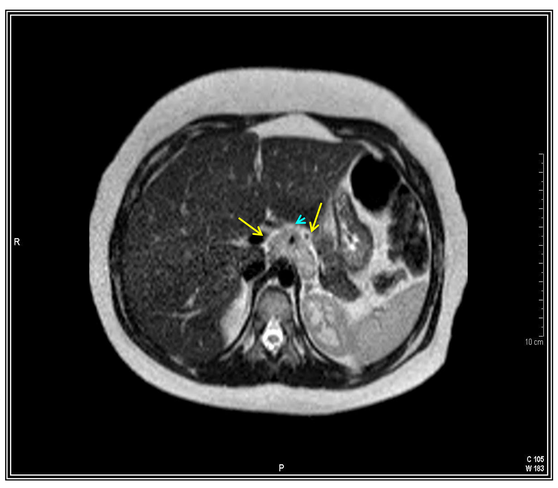


Table 2: Serum antibodies to neuronal antigens and abdominal masses in the 6 patients with ROHHADNET syndrome

	Age	BMI (SDS)	Abdominal mass	NMDA	LGI1	C2	D2	AMPA	VGKC (<100pM)	VGCC (<70pM)	AChR (<50pM)
♂	15	31,5 (+2,8)	/	0	0	0	0	0	64	38,4	6
♀	7	20 (+1,9)	/	0	0	0	0	0	63	39,4	16,8
♂	6	26,5 (+4,7)	Retroperitoneal Mass	0	0	0	0	0	77	17,8	0,1
♀	10	27,6 (+2,6)	Maturing Ganglioneuroma	0	0	0	0	0	57	-12,2	2,5
♀	8	39,1 (+4,6)	Maturing Ganglioneuroma	0	0	0	0	0	59	12	8,4
♀	17	41,7 (+3,9)	Maturing Ganglioneuroma	0	0	0	0	0	36	-6,8	7,5

Conclusions

We investigated ROHHADNET patients' sera for most of the known autoantibodies associated with different forms of immune-mediated encephalitis, but all results were negative: up to now, there is no evidence of neuron autoimmunity related to ROHHADNET syndrome at the serum level in our patients.

Lack of identification of known Abs by current available methods do not exclude the possibility of a role of autoimmunity in ROHHADNET (new antigenic targets?). Additional studies to look for novel autoantibodies are needed
There are ongoing studies testing the CSFs of patients for binding to brain tissues.

A better understanding of pathogenetic mechanisms could improve the management of this severe disorder.

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