Acute progressive weight gain, impending apnea and more.

Dr. Ahmad Amer

The Case

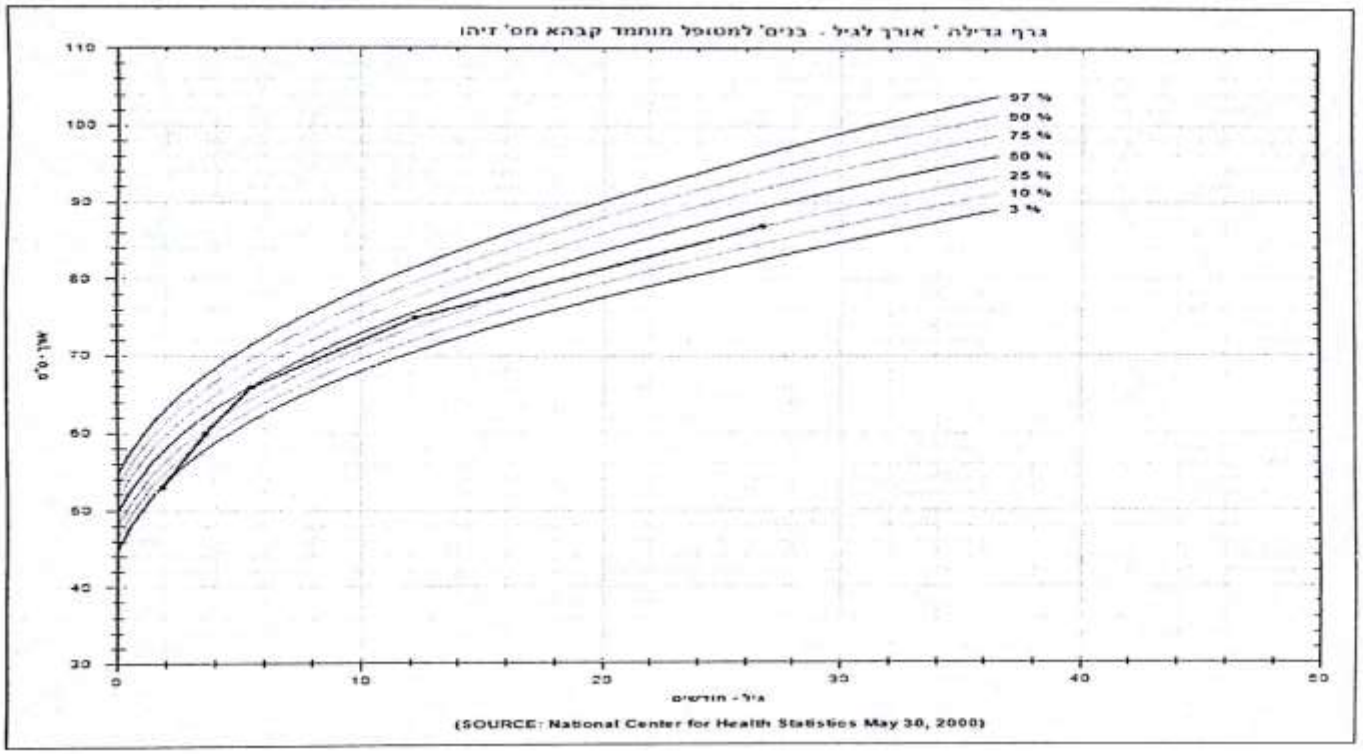
History -

- M. is a Generally healthy 4 years old boy.
- Rapid weight gain in the last 6 months.
- Referred urgently to the ER after an SMA showed **Hypernatremia** of 182 mEq/L

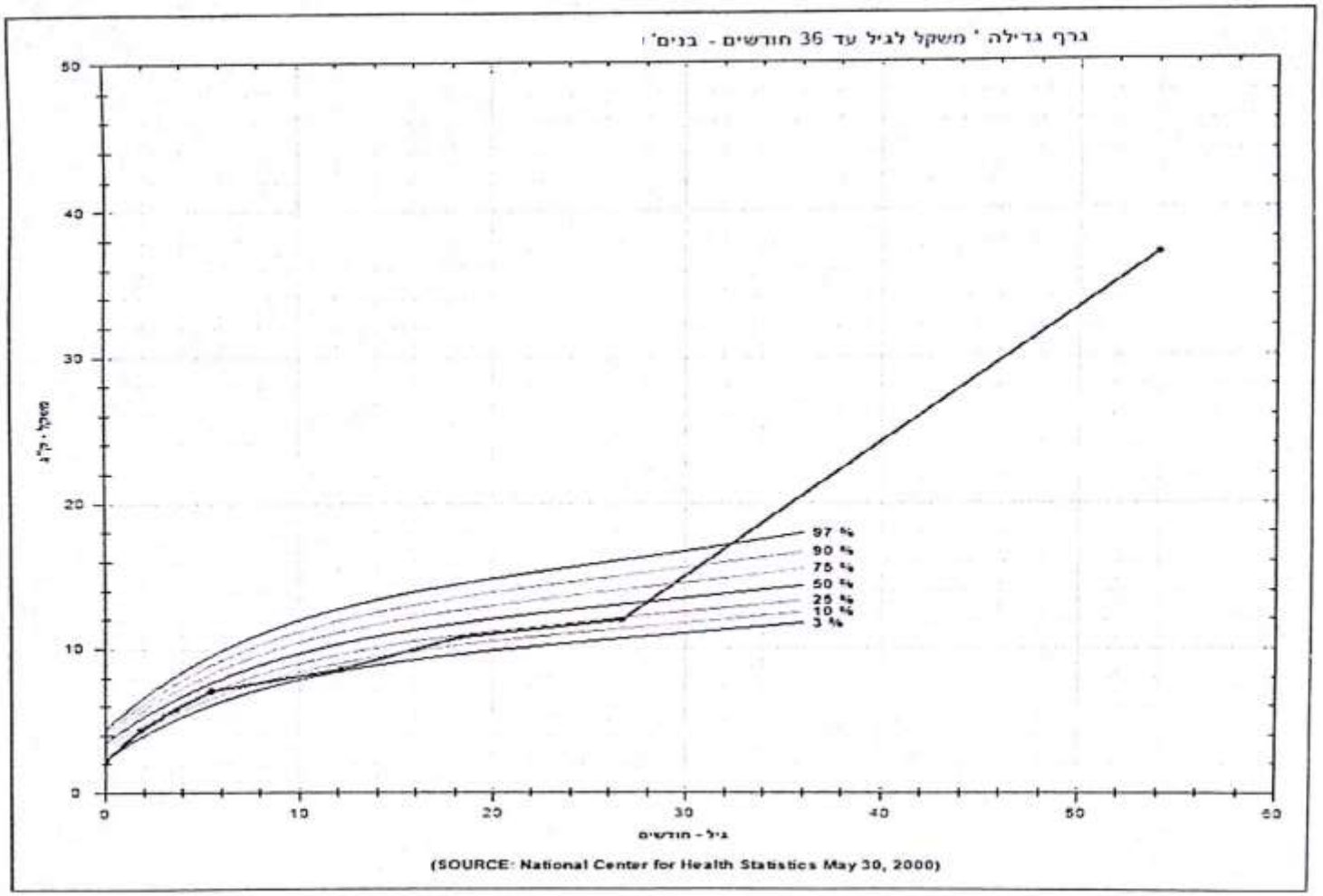
Physical -

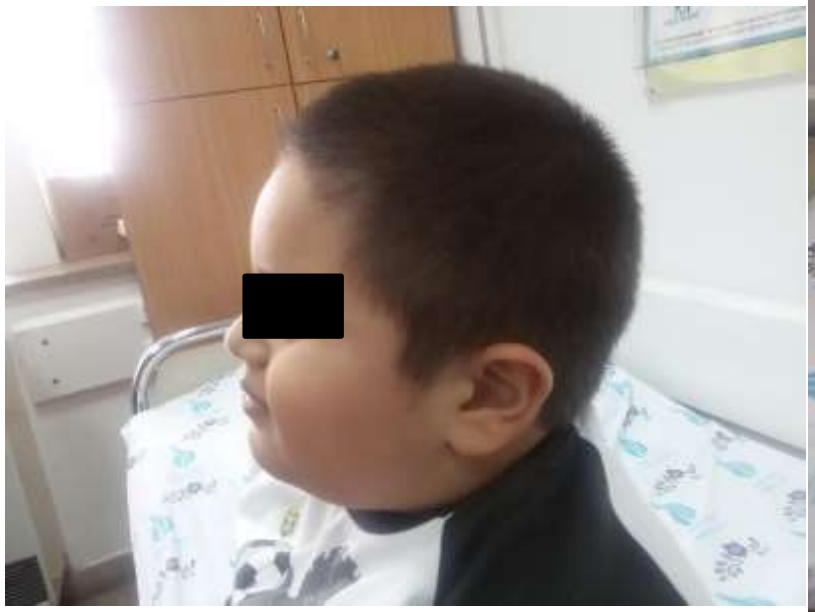
- The child was well appearing, severely overweight, easily irritated.
- Elevated BP, Mild Tachycardia, slow pupil response to light.

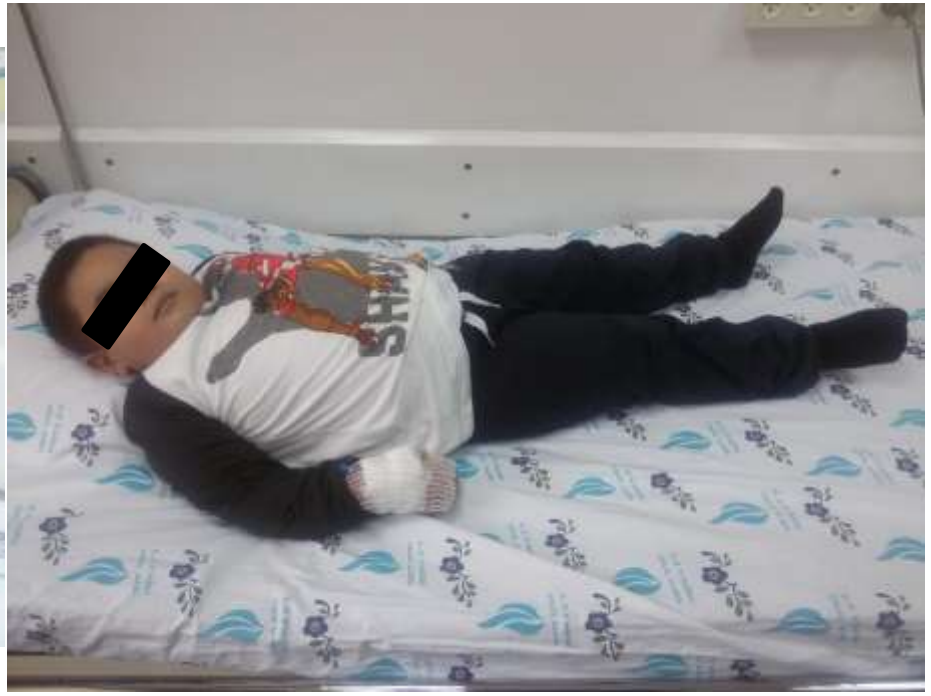
Length/height-for-age



Weight For Age







SMA

Na+ : 177
K+: 4.33
Urea : 62
Creatinine : 1.17
Uric Acid : 10.7

הזמנה : 7051298	לקיחה : -	אישור תשובה : 25/09/2016 - 22:42

**** דו"ח זה מכיל תוצאות פניקה ****

בדיקות כימיה בדם

בדיקה	תוצאה		יחידות	ת. ייחוס	טווח	הערות
Glucose - B	119	H	mg/dl	65 - 110	[.....]*	
Urea - B	62	H	mg/dl	15 - 36	[.....]*	
Sodium - B	177	PH	mmol/L	136.0 - 145.0	[.....]*	
Potassium - B	4.33		mmol/L	3.40 - 4.70	[.....*..]	בדוק
						תוצאה מתוקנת
Chloride - B	137	H	mmol/L	98 - 107	[.....]*	
Osmolality calculated - B	372	H	mOsm/kgH2O	275 - 295	[.....]*	
Creatinine-B	1.17	H	mg/dL	0.30 - 0.60	[.....]*	
Calcium-B	9.6		mg/dl	8.8 - 10.8	[...*.....]	
Phosphor-B	2.3	L	mg/dl	4.5 - 6.7	*[.....]	
Uric acid - B	10.7	H	mg/dl	2.0 - 5.5	[.....]*	
Protein, total-B	7.3		g/dl	6.4 - 8.3	[....*....]	
Albumin - B	4.63		g/dl	3.80 - 5.40	[....*....]	
Globulin - B	2.7		g/dl	2.2 - 4.0	[..*.....]	
Albumin/globulin-B	1.7		Ratio	1.2 - 2.6	[...*.....]	
Bilirubin total-B	0.27	L	mg/dl	0.30 - 1.10	*[.....]	
Bilirubin direct-B	0.06	L	mg/dl	0.10 - 0.50	*[.....]	
Alk.Phosphatase - B	109		U/l	93 - 309	[*.....]	
GGT - B	44	H	U/l	3 - 22	[.....]*	
ALT (GPT) - B	107	H	U/l	0 - 41	[.....]*	
AST (GOT) - B	96	H	U/l	0 - 48	[.....]*	
LD - B	1131	H	U/l	300 - 570	[.....]*	
						הפרעה המוליטית
Cholesterol total-B	158		mg/dl	104 - 210	[....*....]	
Triglycerides-B	268	H	mg/dl	30 - 130	[.....]*	
HDL-Cholesterl-B	23	L	mg/dl	43 - 65	*[.....]	
HDL-Cholesterol %-B	14.6	L	%	21.0 - 65.0	*[.....]	
Non HDL-Cholesterol	135		mg/dL	100 - 190	[...*.....]	
LDL-Chol. calcul-B	81		mg/dl	70 - 160	[.*.....]	
Magnesium-B	2.94	H	mg/dl	1.70 - 2.10	[.....]*	

- CBC – Normal.
- V. Blood Gases –PH – 7.36, PCO2 -45, Bicarb - 23.
- Urine Electrolytes –NA+ 154.7, Osmolarity 934.

- To note –
- hypoventilation and bradypnea during light sedation with midazolam while acquiring blood test

Rapid Obesity Causes
1. Endocrine

Table 47-1 Endocrine and Genetic Causes of Obesity

DISEASE	SYMPTOMS	LABORATORY
ENDOCRINE		
Cushing syndrome	Central obesity, hirsutism, moon face, hypertension	Dexamethasone suppression test
GH deficiency	Short stature, slow linear growth	Evoked GH response, IGF-1
Hyperinsulinism	Nesidioblastosis, pancreatic adenoma, hypoglycemia, Mauriac syndrome	Insulin level
Hypothyroidism	Short stature, weight gain, fatigue, constipation, cold intolerance, myxedema	TSH, FT_4
Pseudohypoparathyroidism	Short metacarpals, subcutaneous calcifications, dysmorphic facies, mental retardation, short stature, hypocalcemia, hyperphosphatemia	Urine cAMP after synthetic PTH infusion

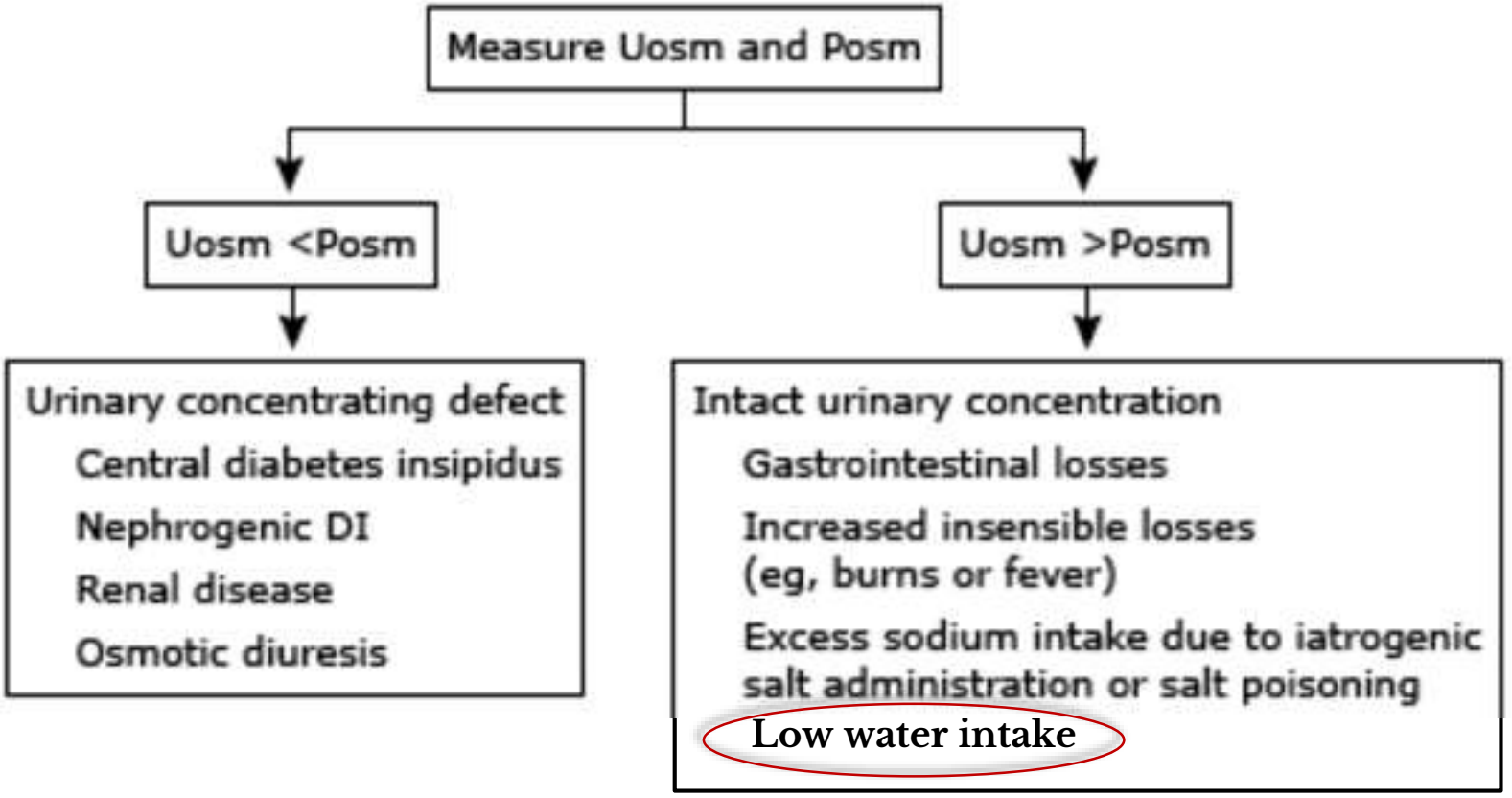
Rapid Obesity Causes
2. Genetic

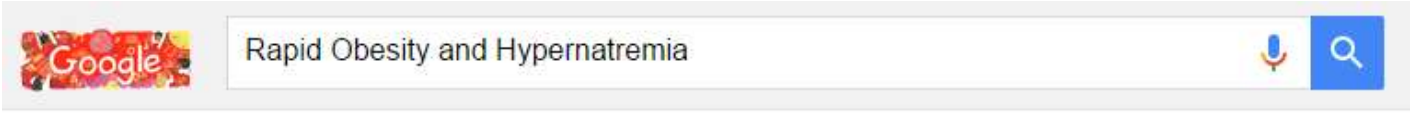
GENETIC		
Alstrom syndrome	Cognitive impairment, retinitis pigmentosa, diabetes mellitus, hearing loss, hypogonadism, retinal degeneration	*ALMS1* gene
Bardet-Biedl syndrome	Retinitis pigmentosa, renal abnormalities, polydactyly, hypogonadism	*BBS1* gene
Biemond syndrome	Cognitive impairment, iris coloboma, hypogonadism, polydactyly	
Carpenter syndrome	Polydactyly, syndactyly, cranial synostosis, mental retardation	Mutations in the *RAB23* gene, located on chromosome 6 in humans
Cohen syndrome	Mid-childhood-onset obesity, short stature, prominent maxillary incisors, hypotonia, mental retardation, microcephaly, decreased visual activity	Mutations in the *VPS13B* gene (often called the *COH1* gene) at locus 8q22
Deletion 9q34	Early-onset obesity, mental retardation, brachycephaly, synophrys, prognathism, behavior and sleep disturbances	Deletion 9q34
Down syndrome	Short stature, dysmorphic facies, mental retardation	Trisomy 21
ENPP1 gene mutations	Insulin resistance, childhood obesity	Gene mutation on chromosome 6q
Fröhlich syndrome	Hypothalamic tumor	
FTO gene polymorphism	Dysregulation of orexigenic hormone acyl-ghrelin, poor postprandial appetite suppression	Homozygous for *FTO* AA allele
Leptin or leptin receptor gene deficiency	Early-onset severe obesity, infertility (hypogonadotropic hypogonadism)	Leptin
Melanocortin 4 receptor gene mutation	Early-onset severe obesity, increased linear growth, hyperphagia, hyperinsulinemia Most common known genetic cause of obesity Homozygous worse than heterozygous	*MC4R* mutation
Prader-Willi Syndrome	Neonatal hypotonia, slow infant growth, small hands and feet, mental retardation, hypogonadism, hyperphagia leading to severe obesity, paradoxically elevated ghrelin	Partial deletion of chromosome 15 or loss of paternally expressed genes
Proopiomelanocortin deficiency	Obesity, red hair, adrenal insufficiency, hyperproinsulinemia	Loss-of-function mutations of the *POMC* gene
Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD)	Often confused with congenital central hypoventilation syndrome (CCHS), presentation ≥1.5 yr with weight gain, hyperphagia, hypoventilation, cardiac arrest, central diabetes insipidus, hypothyroidism, growth hormone deficiency, pain insensitivity, hypothermia, precocious puberty, neural crest tumors	Unknown genes May be a paraneoplastic disorder
Turner syndrome	Ovarian dysgenesis, lymphedema, web neck, short stature, cognitive impairment	XO chromosome

DDx

Hypernatremia

Urine Osmolarity: 934 ▶ Plasma Osmolarity : (2 x (Na + K)) + (BUN / 2.8) + (glucose / 18): 375





About 924,000 results (0.55 seconds)

Scholarly articles for **Rapid Obesity and Hypernatremia**

Rapid-onset **obesity** with hypothalamic dysfunction, ... - Ize-Ludlow - Cited by 94
Endocrine manifestations of the **rapid**-onset **obesity** ... - Bougneres - Cited by 52
... venovenous hemodiafiltration in **hypernatremic** ... - Lin - Cited by 21

Rapid-onset Obesity with Hypothalamic Dysfunction, Hypoventilation ...

https://rarediseases.org/.../**rapid**-onset-**obesity**-with-hypothalamic-dysfunction-hypove...

This **rapid**-onset **obesity** is considered a sign of hypothalamic dysfunction .... If **hypernatremic** dehydration is found, formal testing of antidiuretic hormone ...

Synonyms · Subdivisions · General Discussion · Signs & Symptoms

ROHHAD - Wikipedia

https://en.wikipedia.org/wiki/ROHHAD

Rapid-onset **Obesity** with Hypothalamic dysfunction, Hypoventilation and Autonomic ... Failed Growth Hormone Stimulation;; Adipsic **hypernatremia** (inability to feel thirst to keep normal hydration);; **Hypernatremia**;; Hyperprolactinemia; ...

Pathogenesis · Symptoms · Prognosis and treatment · See also

ROHHAD Syndrome: Reasons for Diagnostic Difficulties in Obesity

https://www.ncbi.nlm.nih.gov › NCBI › Literature › PubMed Central (PMC)

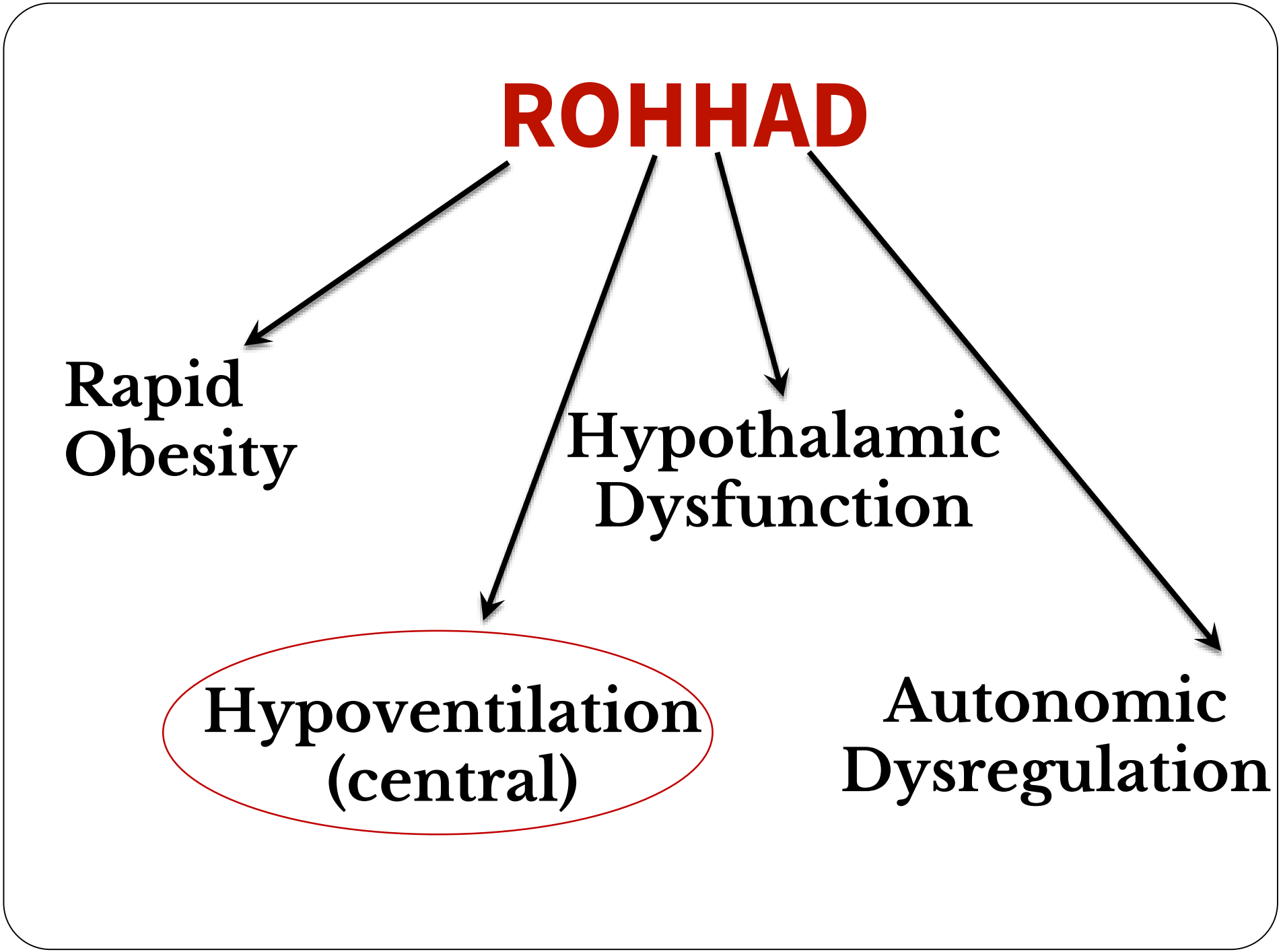
by P Kocaay - 2014 - Cited by 2 - Related articles

Dec 5, 2014 - Features matching ROHHAD syndrome such as **rapid**-onset **obesity**, ... phenomenon and hypothalamic **hypernatremia** were detected in the ...

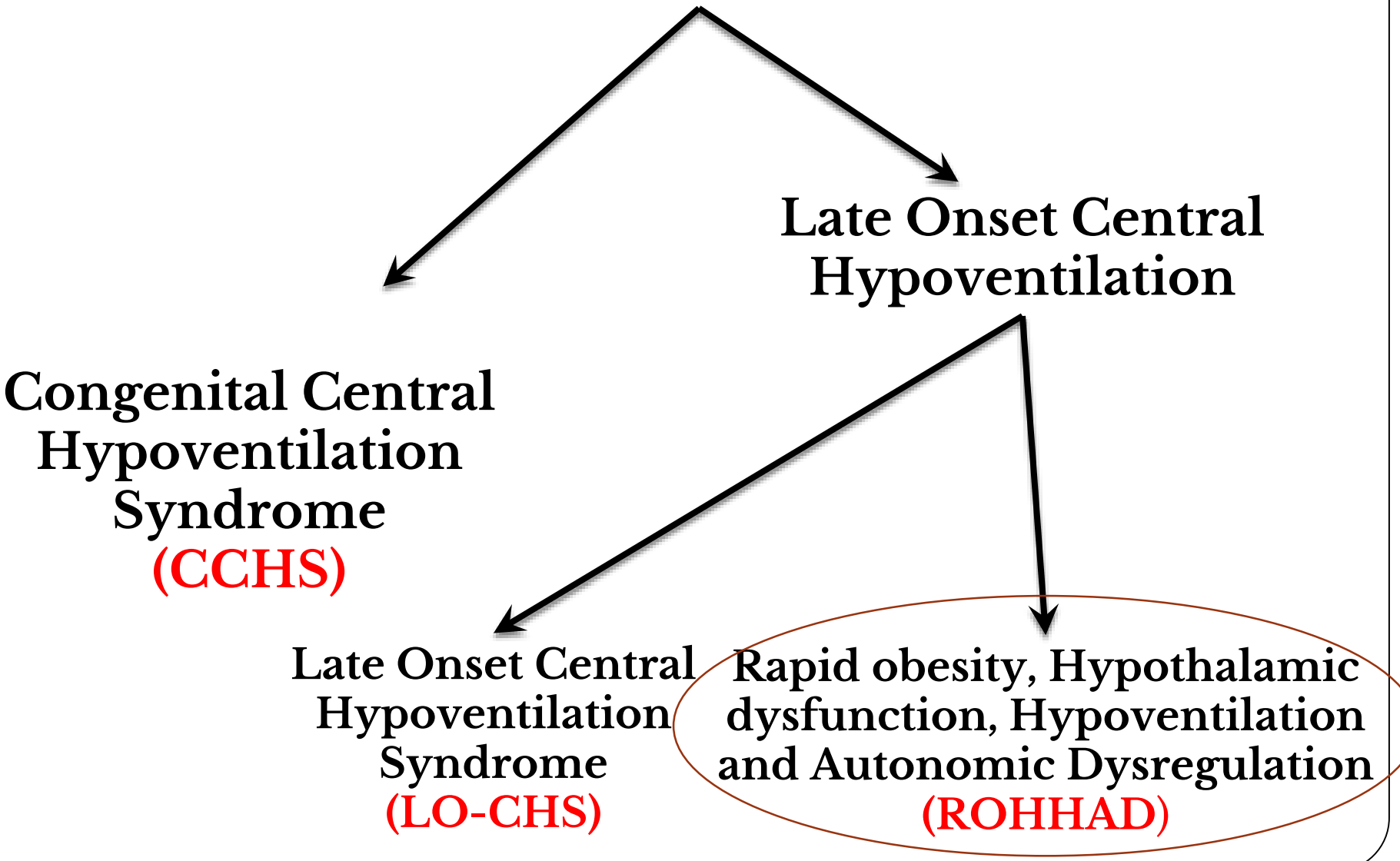
Connecting The Dots

- Rapid Obesity
- Hypothalamic Dysfunction - Impaired hunger and thirst mechanisms
- Autonomic Dysregulation - Hyperhidrosis + Tachycardia + Cold extremities

ROHHAD Syndrome

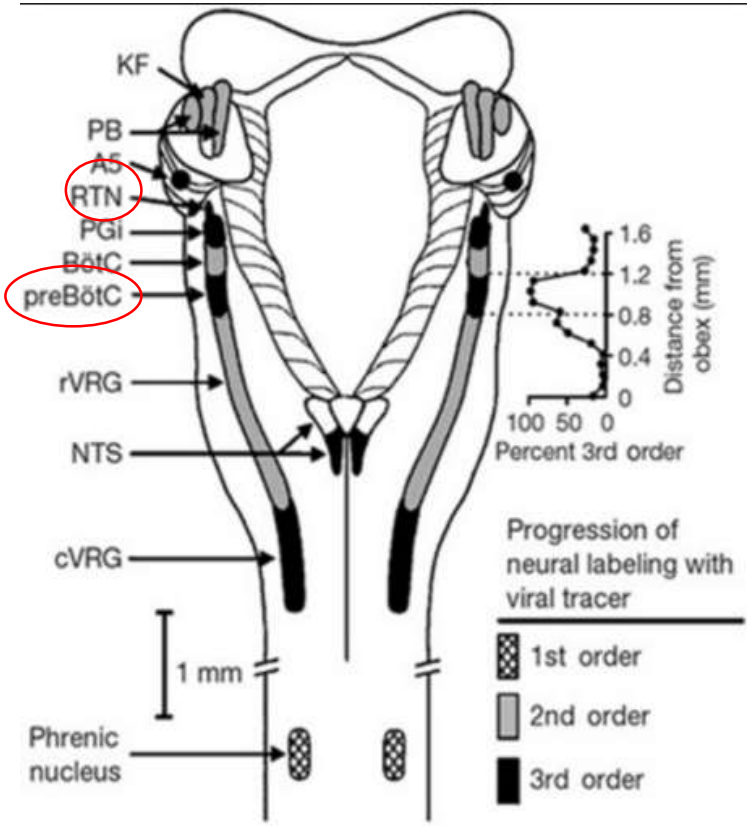

ROHHAD
Rapid Obesity
Hypothalamic Dysfunction
Hypoventilation (central)
Autonomic Dysregulation

Central Hypoventilation Syndromes



Genetics of Central Hypoventilation

- All about the PHOX2b (paired-like homeobox 2B gene).
- Located on chrom. 4p12
- The *PHOX2B* gene is expressed in both CNS and PNS.
- The retrotrapezoid nucleus (RTN)
- Hirshprung, Cardiac and ophthalmic



ROHHAD Syndrome - History

PEDIATRIC PULMONOLOGY

Late-Onset Central Hypoventilation With Hypothalamic Dysfunction: A Distinct Clinical Syndrome

Elliot S. Katz, MD, Sharon McGrath, MS, and Carole L. Marcus, MD*

Pediatric Pulmonology 29:62–68 (2000)

TABLE 2.—Summary of Reported Symptoms of LO-CHS/HD in 11 Patients[1]

Symptom	No.	%
Obesity	11	100
Hyperphagia	10	91
Hypernatremia	6	55
Hypothyroidism	6	55
GH deficiency	6	55
Diabetes insipidis	2	18
Hyperprolactinemia	5	45
Hypodipsia	3	27
Thermal dysregulation	3	27
Hypogonadism	4	36
Precocious puberty	2	18
Mood disorder	7	64
SIADH	1	8
Strabismus	3	27
Pain hyposensitivity	5	45
Pupillary anomalies	3	27
Central apnea	3	27
Decreased ventilatory response to CO_2	6 of 6 tested	100

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Idiopathic Hypothalamic Dysfunction and Impaired Control of Breathing

S. KENT DURIVAGE, ROBERT J. WINTER, ROBERT T. BROUILLETTE, CARL E. HUNT and ZEHAVA NOAH

Pediatrics 1985;75;896

TABLE. Pertinent Findings in Four Children with Hypothalamic Syndrome and Associated Central Hypoventilation

	Present Case 1	Present Case 2	Case of Hayek and Peake[1]	Case of Fishman et al.[6]
Age at onset (yr)	3½	5	5	3½
Hypernatremia	Present	Present	Present	Absent
Obesity	Present	Present	Present	Present
Prolactin	Increased	Increased	Increased	Not reported
Thyroid-stimulating hormone response to thyrotropin-releasing hormone	Not tested	Increased	Absent	Not tested
Central hypoventilation	Present	Present	Absent	Present
Hypogonadotrophic hypogonadism	Present	Present	Not reported	Not reported
Absent adrenarche	Present	Present	Not reported	Not reported

ROHHAD
Large Case Reviews

2007

15 Cases

PHOX2B, NTRK2 and BDNF

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Rapid-Onset Obesity With Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation Presenting in Childhood

Diego Ize-Ludlow, Juliette A. Gray, Mark A. Sperling, Elizabeth M. Berry-Kravis, Jeff M. Milunsky, I. Sadaf Farooqi, Casey M. Rand and Debra E. Weese-Mayer

Pediatrics 2007;120;e179
DOI: 10.1542/peds.2006-3324

2008

13 Cases

PHOX2B, ASCL1, and NECDIN

0031-3998/08/6406-0689
PEDIATRIC RESEARCH

Delineation of Late Onset Hypoventilation Associated with Hypothalamic Dysfunction Syndrome

LOIC DE PONTUAL, DELPHINE TROCHET, SOPHIE CAILLAT-ZUCMAN, OTHMAN A. ABOU SHENAB, PIERRE BOUGNERES, YANICK CROW, STEVE CUNNINGHAM, BLANDINE ESTEVA, LADA CINDRO HEBERLE, JULIANE LEGER, GRAZIELLA PINTO, MICHEL POLAK, MAGDY HELMY SHAFIK, CHRISTIAN STRAUS, HA TRANG, ARNOLD MUNNICH, STANISLAS LYONNET, ISABELLE DESGUERRE, AND JEANNE AMIEL

ROHHAD
Methods

- 23 identified of them 15 children had comprehensive medical charts and were included. 6 male subjects and 9 female subjects.
- Criteria:
  - onset **of** **alveolar hypoventilation** after the age of 2 years (a must!!) and evidence of HD, as defined by 1 of the following findings
    - Rapid onset obesity
    - Hyperprolactinemia
    - central hypothyroidism
    - disordered water balance
    - failed growth hormone stimulation test
    - corticotropin deficiency
    - delayed or precocious puberty.
- 9 had respiratory studies as well.
- 15 were genetically tested for PHOX2B and 11 for candidate genes *NTRK2 and BDNF*.

1.Hypothalamic Dysfunction

Study

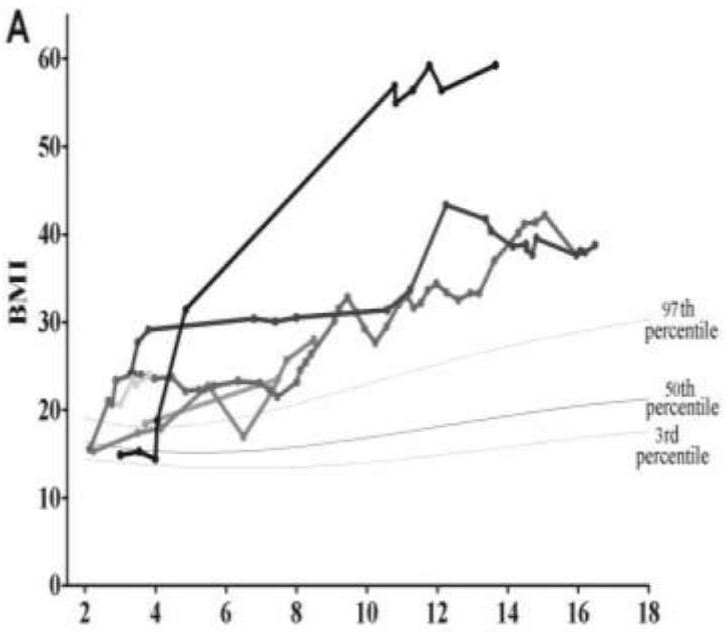
Finding	Rate	Presenting
Rapid-onset obesity	15 patients (100%)	12 patients (80%)
Failed growth hormone stimulation test	9; (60%)	
Hypernatremia	7; (46%)	2; (13%)
Polydipsia	8; (53%)	1; (6%)
Hyperprolactinemia	7; (46%)	
Hyponatremia	4; (26%)	
Hypodipsia	4; (26%)	

M.

Finding	
Rapid-onset obesity	
Failed growth hormone stimulation test	Normal GH, Low IGF1.
Hypernatremia	
Polydipsia	
Hyperprolactinemia	
Hyponatremia	
Hypodipsia	

Rapid-onset obesity

Study



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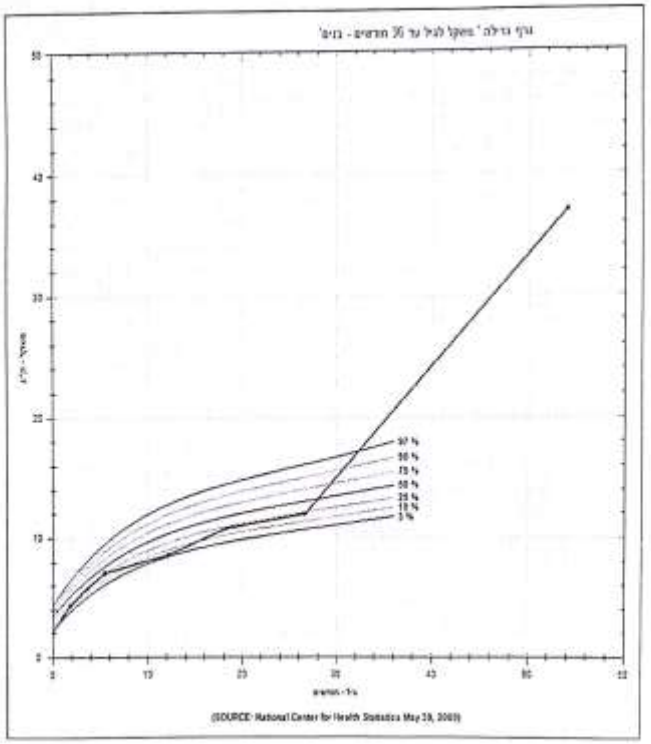


2. Respiratory Manifestation

Study

Finding	Rate
Alveolar hypoventilation	15 patients (100%)
Cardiorespiratory arrest*	9; (60%)
Reduced carbon dioxide ventilatory response*	9; (60%)
Obstructive sleep apnea	8; (53%)
Cyanotic episodes	4; (26%)
24-hour/day artificial Ventilation*	7; (46%)

M.

Finding	Rate
Alveolar hypoventilation	NO
CXR	Normal
Polysomnography	Normal
continuous SAT. monitoring	Normal
Hypoventilatory response to anesthesia	✓

3. Autonomic Dysregulation

Study

Finding	Rate
Ophthalmologic: - Pupillary dysfunction - Strabismus	13 patients (86%) 7; (46%) 8; (53%)
Thermal dysregulation	11; (73%)
Gastrointestinal dysmotility	10; (66%)
Neural crest tumors	5; (33%)

M

Finding	Rate
Ophthalmologic: - Pupillary dysfunction - Strabismus	✓
Cold extremities	✓
Thermal dysregulation	?
Gastrointestinal dysmotility	✗
Neural crest tumors	✗

4. Developmental Disorders

Finding	Rate
Developmental Delays	3; (20%)
Developmental Regression	3; (20%)

5. Behavioral Disorders

Finding	Rate
Developmental Delays	8; (53%)

ROHHAD Timeline

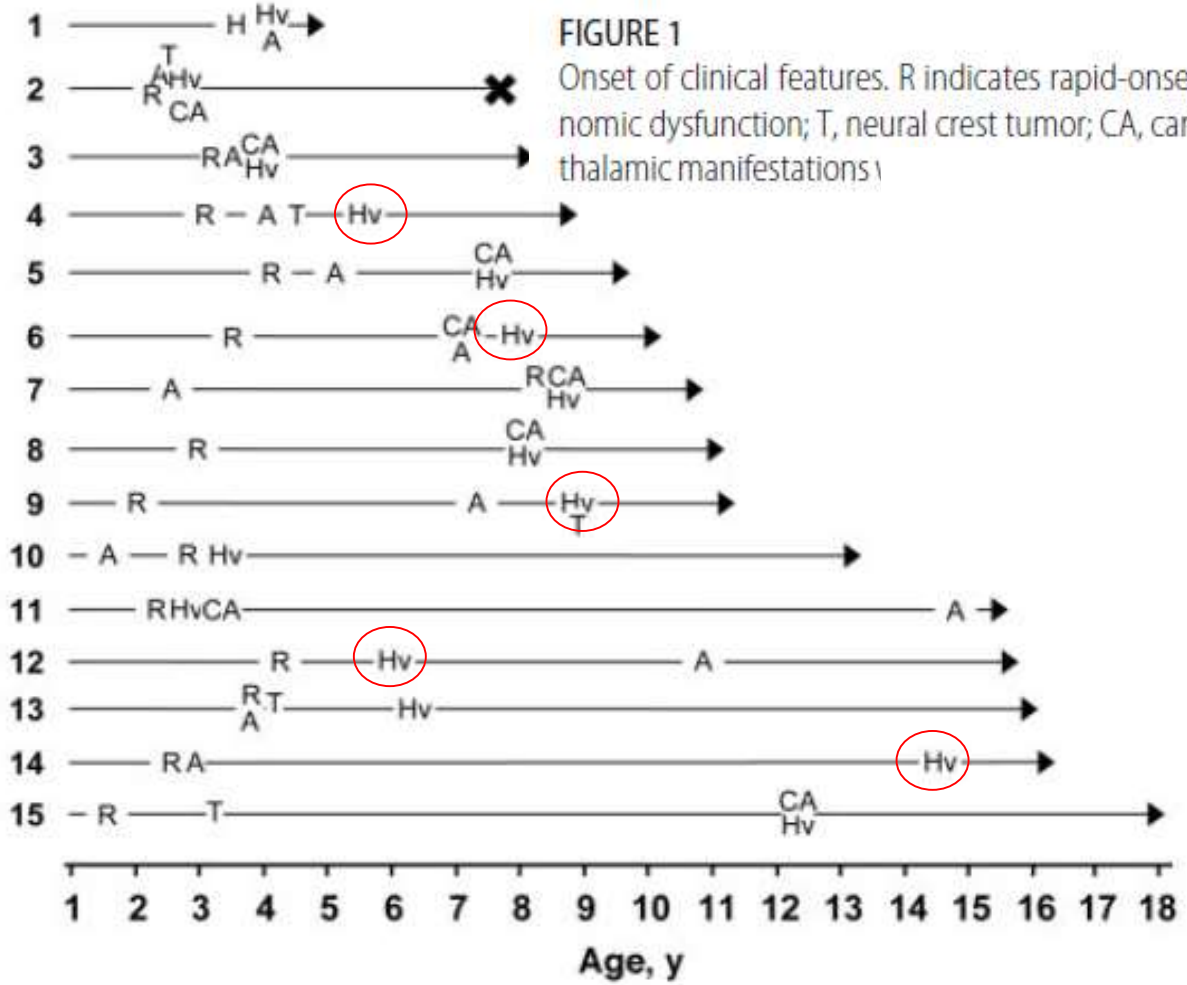


FIGURE 1

Onset of clinical features. R indicates rapid-onset obesity; Hv, hypoventilation; A, autonomic dysfunction; T, neural crest tumor; CA, cardiorespiratory arrest; X, death; H, hypothalamic manifestations

ROHHAD
Genetic Testing

- **None** of the tested children with the LO-CHS/HD phenotype had a CCHS-related mutation in the *PHOX2B* gene.
- **No novel or rare variants** were identified in the coding regions of either *NTRK2 or BDNF* for these patients.

Initial Evaluation

- **Evaluation of the hypothalamic-pituitary axis**
- **Respiratory physiologic assessment**
- **MRI or computed tomographic** - chest and abdomen.
- **Water deprivation tests**- if indicated
- **Brain imaging**

Follow up

- Serial **respiratory assessment** at **3- to 6-month** intervals.
- **Chest and abdominal imaging** every 12 to 18 months.
  - If no tumor is identified in 10 years, then it would be reasonable to decrease the frequency of imaging to every 2 years.

Back To our Case

Pulmonary	Hypothalamic	Autonomic	Other
Hypoventilatory response to anesthesia	**Rapid obesity** –Weight: 3 SD above 97% BMI. Height: 50% Perc., **Hyperphagic**	Sinus **Tachycardia** alternately. Normal ECG holter and ECHO.	Metabolic syndrome – elevated trig, elevated BP.
CXR: Normal	**Hypodipsic/Hypernatremic**	Abnormal pupil response to light	Severe caries
Polysomnography :OSA, no hypoventilation	High TSH (around 6) Normal fT4	Recurrent fever with no apparent source	Adequate ventillatory response to stress test
Normal continuous SAT monitoring	**Hyperprolactinemia – 932 (upper limit 15).**	**Hyperhidrosis**	
	Normal synacthen test, Normal 24h urine cortisol.	**Cold extremities**	
	LH, FSH adequate for age.	**NO tumors on Chest+Abdomen CT**. Negative urine catecholamine.	
	Low IGF, Normal GH.		
	Normal brain MRI		

Correspondence

- Prof Debra Weese-Mayer -

"we suspect that your patient is early in his ROHHAD course."

Recommended continuous home monitoring during sleep, more frequent PSG (monthly).

- Prof. David Gozal

"OK to treat him as ROHADD with the concern that he may develop the ventilatory problems unexpectedly"

PSG at least every 6 months

M. - Further Follow up

1. Endocrinology and Pulmonary FU.
2. Repeat Polysom. In 3 months.
3. Repeat urinary Catecholamines in 3 months.
4. Continuous Pulse oximetry during sleep
5. Strict hypocaloric diet
6. Strict hydration regime
7. Social assistance

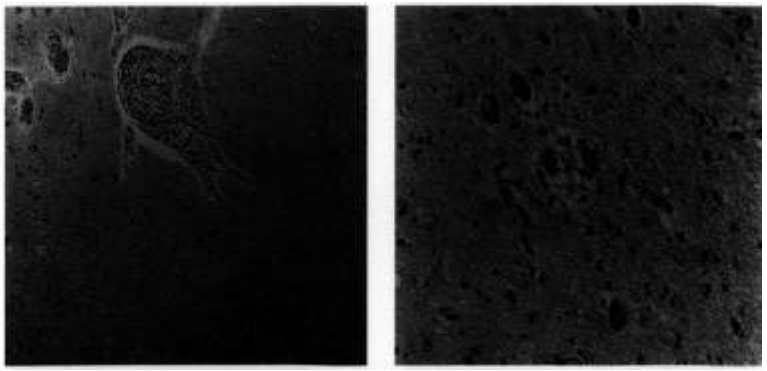
Possible Pathogenesis

1. Genetic
   - paired-like homeobox 2B [**PHOX2B**], brain-derived neurotrophic factor [**BDNF**], tyrosine kinase receptor B [**TRKB**], achaete-scute complex–like 1 [**ASCL1**], Necdin [**NDN**], 5-hydroxytryptamine receptor 1A [**HTR1A**], orthopedia [**OTP**], and pituitary adenylate cyclase activating polypeptide [**PACAP**] – **ALL NEGATIVE.**
2. Paraneoplastic
   - Neural crest tumors
   - Similarly to what happens in opsoclonus myoclonus syndrome.
   - Chronicity problem.
3. Auto-Immune
   - Evidence?

I – Pathological + Anatomical

1. Ouvrier R, Nunn K, Sprague T, et al. Idiopathic hypothalamic dysfunction: a paraneoplastic syndrome? *Lancet*. 1995;346: 1298.
2. Nunn K, Ouvrier R, Sprague T, Arbuckle S, Docker M. Idiopathic hypothalamic dysfunction: a paraneoplastic syndrome? *J Child Neurol*. 1997;12:276-281.

"*On microscopic examination, the brain showed a diffuse, **lymphocytic infiltration** within the hypothalamus, thalamus, and around the periaqueductal gray tissue of the midbrain and pons and around the fourth ventricle*"



Pediatric Neurology 52 (2015) 521–525

Pediatric Neurology

Rapid-Onset Obesity With Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation (ROHHAD) Syndrome May Have a Hypothalamus–Periaqueductal Gray Localization

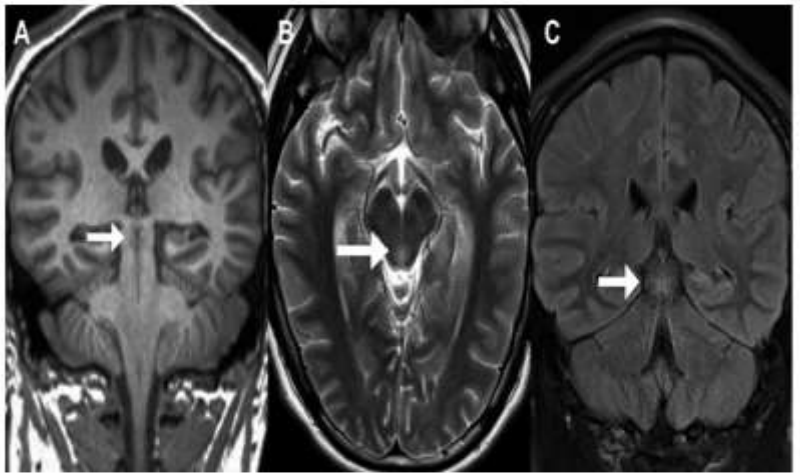


FIGURE 1.
Brain magnetic resonance imaging study at day 7 of illness demonstrating focal edema of the periaqueductal gray matter, as evidenced by hypointensity in an axial T1-weighted image (A) and hyperintensity in axial T2-weighted (B) and coronal T2 fluid-attenuated inversion recovery (C) images (white arrows).

II – Biochemical/Immune - Oligoclonal Bands in CSF

I.

Journal of Child Neurology
2014, Vol. 29(3) 421-425

Intrathecal Synthesis of Oligoclonal Bands in Rapid-Onset Obesity With Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation Syndrome: New Evidence Supporting Immunological Pathogenesis

II.

Pediatric Neurology 52 (2015) 521–525
Pediatric Neurology

Rapid-Onset Obesity With Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation (ROHHAD) Syndrome May Have a Hypothalamus–Periaqueductal Gray Localization

Possible Treatment? - I

- IVIG

Pediatric Neurology

Volume 41, Issue 3, September 2009, Pages 232–234

Immunoglobulin Therapy in Idiopathic Hypothalamic Dysfunction

Peter Huppke, MD*, , , Alexander Heise, MD†, Kevin Rostasy, MD‡, Brenda Huppke, MD*, Jutta Gärtner, MD*

"There was no immediate or drastic improvement during treatment with immunoglobulins, but her behavioral problems improved, an effect that was repeated when immunoglobulins were administered for a second time."

Table 1.
Clinical and paraclinical parameters

Behavioral changes
Hyperphagia [0 mo]
Social withdrawal [2 mo]
Poor concentration [2 mo]
Aggressive outbursts [6 mo]
Endocrine disturbances
Hypothalamic hypothyroidism [7 mo]
Growth-hormone deficiency [8 mo]
Hyperprolactinemia (3545 μE/mL (normal range, 100-500)) [7 mo]
Other signs of hypothalamic or brainstem dysfunction
Abnormal sleep/wake cycle [4 mo]
Hyperthermia (41°C) [7 mo]
Hypothermia (29°C) [8 mo]
Hypernatremia (165 mmol/L (normal range, 136-145)) [7 mo]
Hyponatremia (130 mmol/L) [7 mo] [7 mo]
Sinus bradycardia (35/min) [7 mo]

A. Possible Treatment? - II

J Pediatr. 2011 February ; 158(2): 337–339. doi:10.1016/j.jpeds.2010.07.006.

Cyclophosphamide for Rapid-Onset Obesity, Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation Syndrome

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Within 2-3 weeks from the initiation of therapy, the patient improved

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Worsening Under cyclophosphamide and tapered prednisone

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Improvement after high dose cyclophosphamide

Possible Treatment? – The Against

Hypothalamic Dysfunction Associated With Neuroblastoma: Evidence for a New Paraneoplastic Syndrome?

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Case 1
"The hypothesis of a complex hypothalamic dysfunction (HD) of paraneoplastic origin prompted treatment with immunosuppressive therapies (Ig IV, corticosteroids) that proved unsuccessful. "

Case 2
"The possibility of a complex HD of paraneoplastic origin prompted initiation of sequential immunosuppressive therapies (Ig IV, corticosteroids, cyclophosphamide) which failed to produce any improvement."

Should We Treat?

- No definitive diagnosis or pathogenesis
- Small number of patients
- Reported failed attempts
- Aggressiveness of disease
- Cost-Effectiveness issues

Take home messages

- Potentialy fatal and probably under diagnosed.
- Gradual appearence of symptoms
- Etiology yet to be descovered
- Though not curable, greatly manageable
- Requires constant follow-up

Many thanks!

Dr. Dorit Ater

Dr. Avigdor Mandelberg

Prof. Ilan Dalal

Thank You

תודה רבה

شكرًا جزيلًا