

Developments in the Field:
ROHHAD
 Brooke Surran, MD
 Eastern Maine Medical Center
 Pediatric Neurology



Overview

- Nothing to disclose
- Objectives
 - Recognize the clinical features of ROHHAD
 - Understand progression of ROHHAD and possible treatments
 - Understand the possible contributing etiologic factors in ROHHAD

ROHHAD

- **R**apid-onset **O**besity with **H**ypothalamic dysfunction, **H**ypoventilation and **A**utonomic **D**ysregulation
- Diagnostic criteria:
 - Onset of alveolar hypoventilation and obesity after 1.5 y
 - Evidence of hypothalamic dysfunction
 - Obesity
 - Hyperprolactinemia
 - Central hypothyroidism
 - Disordered water balance
 - Failed growth hormone stimulation test
 - Corticotropin deficiency
 - Delayed or precocious puberty

Etiology

- Genetics?
 - PHOX2B mutations → Congenital Central Hypoventilation Syndrome
 - Not present in ROHHAD
 - Study of 7 triads including twins with whole exome found no clear genetic correlate
 - Familial case reports – Monogenic?
- Immune mediated?
 - Association with neural crest tumors (33%)
 - Lymphocytic inflammation on histology, CSF analysis
 - Intrathecal oligoclonal bands
 - No biomarker has been found
 - Partial response to immune modulatory therapies

Differential Considerations

- Congenital Central Hypoventilation Syndrome (CCHS, PHOX 2B)
- Prader- Willi syndrome
- Bardet-Biedl syndrome
- Alstrom syndrome
- Congenital leptin deficiency
- Neurometabolic disorders – mitochondrial, amino acid, and neurotransmitter
 - ROHHAD previously thought to be an isolated serotonin deficiency

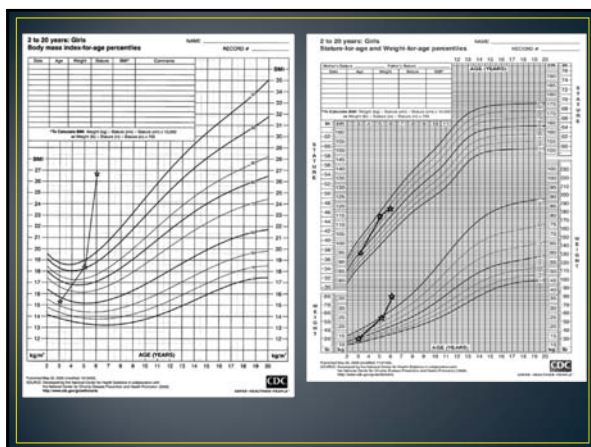
Rapid-onset Obesity



Age 2 years

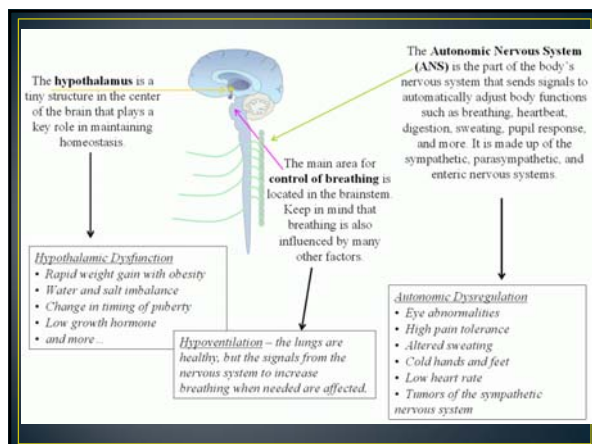
Age 3 years

- Over 6 -12 months
- Usually 30+ lbs
- Hyperphagia



Hypoventilation

- Blunted response to hypercarbia → hypoxemia
 - Obstructive sleep apnea
 - Central sleep apnea
 - Hypopnea
 - Daytime hypoventilation → Tracheostomy
- } CPAP/BiPAP
- Months to years after onset of obesity



Autonomic dysregulation

- **Respiratory**
 - Shallow breathing
 - Central sleep apnea
- **Cardiac**
 - Arrhythmia (typically bradycardia)
 - Blood pressure dysregulation
 - Cardiorespiratory arrest
- **Altered sweating**
- **Altered pupillary response**
- **Strabismus**
- **Altered GI motility**
 - Constipation
 - Diarrhea
- **Thermal dysregulation**
 - Hyper- or hypothermia

Neurobehavioral Disorder

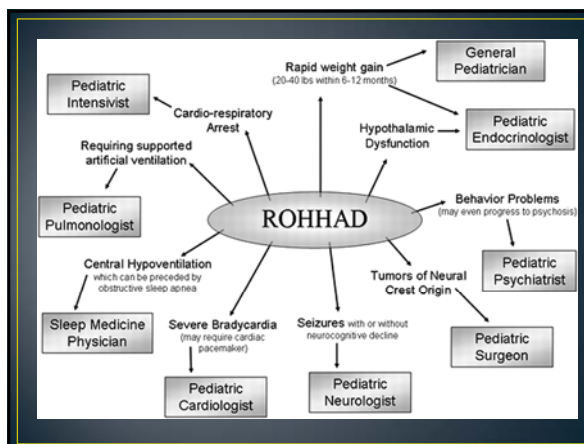
- Behavioral dysregulation
- Mood instability
- Developmental delay
- Seizures
- Ataxia

Evaluation

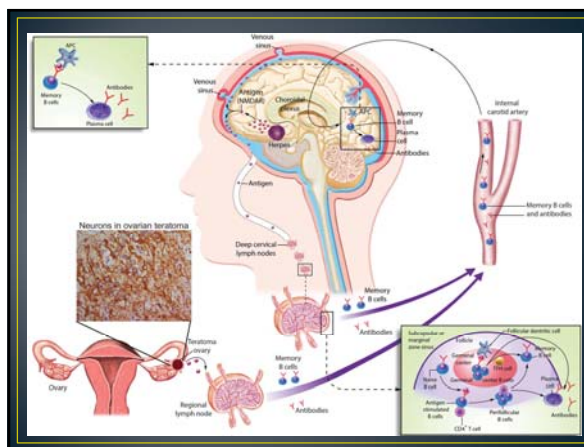
- Polysomnography
- Chest/abdomen imaging
- Cardiac evaluation
- Nutrition evaluation
- Endocrine evaluation
 - Water balance
 - Pituitary function

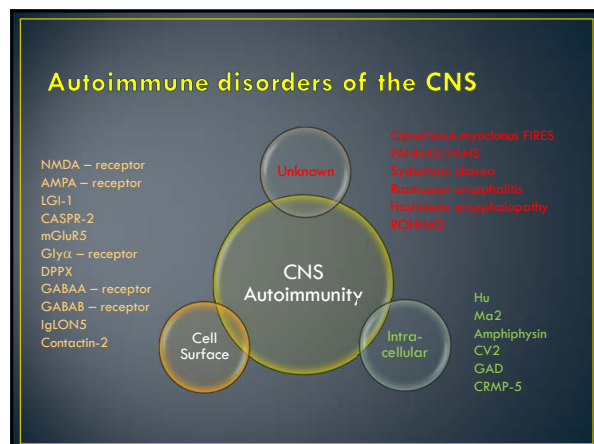
Evaluation

- MRI brain
 - Bilateral basal ganglia hypodensities
 - Rathke's cleft cyst
 - Hypointensity of pons, midbrain
 - Diffuse cerebral atrophy
 - Normal
- CSF
 - Normal
 - Inflammatory markers
 - Oligoclonal bands
 - Normal neurotransmitters



CNS Autoimmunity?





Future Directions:

- Studies currently enrolling – Use of cyclophosphamide in treatment of ROHHAD
- International ROHHAD Registry
 - 10-year observational period

Resources:

- Sartori S, Priante E, Pettenazzo A, Marson P, Suppiej A, Benini F, et al. Intrathecal synthesis of oligoclonal bands in rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation syndrome: New evidence supporting immunological pathogenesis. *J Child Neurol.* 2014;29:421–5
- Aylton AB, Conill CA, Erhan BA, Erhan B, Toliga K, Hatice NO, et al. A case of ROHHADNET syndrome. *Endocr Pract.* 2013;19:12–6
- Paz-Pitel J, Cooke DW, Chen AR. Cyclophosphamide for rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation syndrome. *J Pediatr.* 2011;158:337–9
- Ramanathan S et al. Autoimmune encephalitis: Recent updates and emerging challenges. *J Clin Neurosci* (2013)
- Carclay S, Rand C, Borch, L, Nguyen L. Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation and Autonomic Dysregulation (ROHHAD): exome sequencing of trios, monozygotic twins and tumors. *Orphanet Journal of Rare Diseases* (2015) 10:103