Paediatric sleep overview
(and an interesting case)

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Obstructive Sleep Apnoea

- Breathing during sleep with partial upper airway obstruction and/or intermittent complete obstruction
- Disruption of normal ventilation
- Prevalence 2 - 5%
- Commonest cause = enlarged adenoids and tonsils

- Gold standard for diagnosis of OSA is PSG
- Classify severity based on Apnea/hypopnea index
  - 1-5/hr Mild OSA – Conservative, non surgical
  - 5 to 10 Moderate OSA – Most often surgical
  - >10/hr Severe OSA - Surgical+/- CPAP

- Higher risk - Complex disorders like Craniofacial syndromes, Pierre Robin, Downs, Neuromuscular disorders
Nocturnal pulse oximetry

- Specifications of overnight pulse-oximetry
  - Useful tool for screening OSA
  - TCM40, Nellcore 3000 (fast averaging)
  - Overnight monitoring for at least 6 hours
  - Averaging time 2-4 seconds
  - Well versed to differentiate between artefacts and true desaturation
  - McGill’s Oximetry score
Nocturnal pulse oximetry

- Nixon et al.; Pediatrics; 04
- Identify clusters of desaturation below 90%
  - Normal or inconclusive (>90%, 2 clusters below 90)

- Cannot rule out sleep apnea and will need further evaluation
- Low risk surgery
- Performed non-tertiary setup
Nocturnal pulse oximetry

- Mild to moderate abnormal (> 3 clusters below 90%)
  - > 3 clusters of desaturations below 90%
  - Will need ENT intervention
  - Can be done non-tertiary setup but will need to be soon
Nocturnal polysomnography

- Severe abnormal (Frequently <90%, <85%)
- Frequent desaturations below 85%
- With CO2 retention
- Urgent tertiary hospital referral
  - May need CPAP
  - ENT only where PICU is available
Sequelae of OSA

• Intermittent Hypoxia and sleep fragmentation
  – Neuro-behavior in children
    • Inattention, hyperactivity, general conceptual abilities, arithmetic skills
    • Verbal, non-verbal intelligence
    • Irritability, aggressiveness
  – Systemic hypertension during wakefulness (increased sympathetic tone)
  – Pulmonary hypertension (more with continuous)
• Present even in mild OSA (Urschitz et al)

Urschitz; Pediatr; 05
Blunden S; J Clin Exp neuro; 00
Kennedy JD; Ped Pulmonol; 04
Beebe; Review; Sleep; 06
Polysomnogram (PSG)
Developmental changes

Normal sleep in children

REM & NREM sleep by age
CPAP and non-invasive ventilation

• Challenges
  – lack of available equipment for use in small children (appropriate nasal masks and machinery)
    • maximal frequency of many commercial NIV machines is inadequate for infants with higher baseline respiratory rates.
  – need for mask training to facilitate compliance

• important potential side-effect of long-term use = mid-face hypoplasia

Interface choices

Device choices
Indications

• primary indication for nCPAP is OSA
  – emerging use is preoperatively as bridge to AT
    • 2-week treatment period (with good compliance) allows ‘re-setting’ of central chemoreceptors, with normalization of normal physiological responses

• Possible benefit in tracheobronchomalacia or extrinsic airway compression in congenital cardiac disease

• Respiratory failure from a variety of causes including
  – neuromuscular disorders
  – severe chronic lung disease
  – bronchiectasis due to end-stage cystic fibrosis or recurrent aspiration
A rare cause of childhood obesity
Introduction

• 1965 – Described a constellation of symptoms termed “Late Onset Central Hypoventilation Syndrome with Hypothalamic Dysfunction (LO-CHS/HD)“
  Fishman et al Am J Dis Child 1965

• 2007, Diego Ize-Ludlow renamed using acronym ROHHAD-NET
  – Heterogeneous medical condition
  – Natural history and aetiology is poorly understood.
  – Incidence is rare with ~100 reported cases.
  – High burden and mortality rates between 50-60%
ROHHAD & ROHHAD-NET

- Rapid Onset
- Obesity
- Hypoventilation
- Hypothalamic Dysfunction
- Autonomic Dysregulation
- Neural tumour syndrome
Genetics

- No specific genetic marker has been implicated.
- Some familial cases have been reported, suggesting that it may be a monogenic condition.
- Absence of PHOX2B mutation helps to rule out Congenital Central Hypoventilation Syndrome

Weese-Mayer DE et al Orphanet J Rare Dis. 2015

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Clinical presentation

• Dramatic weight gain over 6-12 months in the first 10 years of life
• Due to hypothalamic dysfunction
  – begins at the age of 2-3 years
  – rapid-onset obesity of 10-20 kg
  – almost simultaneously, height velocity will decrease
Exogenous Obesity vs. ROHHAD

<table>
<thead>
<tr>
<th></th>
<th>Exogenous obesity</th>
<th>ROHHAD</th>
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<tbody>
<tr>
<td>Sleep apnoea</td>
<td>increased</td>
<td>increased</td>
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<tr>
<td>GH unresponsiveness</td>
<td>increased</td>
<td>increased</td>
</tr>
<tr>
<td>TSH levels</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Height velocity</td>
<td>increased</td>
<td>decreased</td>
</tr>
<tr>
<td>IGF-1</td>
<td>high</td>
<td>low</td>
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<tr>
<td>Autonomic dysfunction</td>
<td>absent</td>
<td>present</td>
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<tr>
<td>Alveolar hypoventilation</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Tumours of sympathetic nervous system</td>
<td>absent</td>
<td>present</td>
</tr>
</tbody>
</table>
Clinical presentation: Endocrine

- Hypothalamic dysfunction
  - Growth failure deficiency or unresponsiveness
  - Excessive secretion of ACTH, hypercortisolism
  - Glucocorticoid deficiency
  - Hypogonadotropic hypogonadism
  - Hyperprolactinemia
  - Hypernatremia. Adipsic or Diabetes insipidus
  - Hypogonadism
  - Precocious puberty
  - Central hypothyroidism

Bougnères P et al J Clin Endocrinol Metab. 2008
Clinical presentation: Autonomic dysfunction

• Median age 3.6 years
  – inability to regulate body temperature
  – slow heartbeat
  – excessive sweating
  – altered pupil response to light
  – Strabismus
  – Gastrointestinal dysmotility with constipation and chronic diarrhoea
Clinical presentation: Respiratory

• Initially present with OSA
• Develop nocturnal hypoventilation (NH) later
• With advancing age, hypoventilation becomes apparent awake and asleep
  • Lack of normal responsivity to low $O_2$ and elevated $CO_2$→ cardiorespiratory arrest
  • Require ventilatory support (asleep or awake)
    • Bi-Level, Tracheostomy, Diaphragm pacing
Clinical presentation: Cardiac

- Arrhythmia
- Profound bradycardia requiring cardiac pacemaker
- Blood pressure dysregulation
- Right ventricular hypertrophy secondary to cor pulmonale
- Heart failure
Neural crest tumours

• Approximately 40% of the patients may develop neural crest tumours (ganglioneuroblastomas, ganglioneuromas)
  – occurs 7 -16 years after onset of obesity
  – usually found in chest or abdomen or along sympathetic nervous system chain
  – No coexisting Hirschsprung disease (think CCHS)
  – Calcification in CT is common
Developmental and neurobehavioural disorders

- Mild mental retardation and developmental regression
  - due to suboptimal ventilatory support
- Personality changes, irritability and physical aggression
- Anxiety
- Sleep symptoms: insomnia and nighttime psychosis
- Seizures
Diagnostic criteria

1. Rapid onset obesity and alveolar hypoventilation during sleep starting after 1.5 years
2. Hypothalamic-pituitary endocrine dysfunction (≥1)
   – Rapid-onset obesity
   – Hyperprolactinaemia
   – Central hypothyroidism
   – Disordered water balance
   – Failed growth hormone stimulation test
   – Altered onset of puberty
3. Absence of CCHS-related PHOX2B mutation

Carroll MS et al Pediatr Pulmonol. 2015
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Other Diff Diagnosis

- Prader-Willi syndrome
- Bardet-Biedl syndrome
- Leptin receptor deficiency
- Cushing’s syndrome
- GH deficiency
Initial presentation

- Referral age $5^{1/2}$
  - 4kg/month weight gain despite sensible lifestyle choices
  - Hyperphagia
  - Extreme fatigue
  - Decreased socialisation
  - Investigations by paed
    - Central hypothyroidism
    - Central adrenal insufficiency
  - CT head normal

- PMHx:
  - LSCS @ 39/40 BW 3.7kg
  - No neonatal problems
  - Growing and developing normally

- Family Hx:
  - Central American ethnicity
  - No obesity or endocrinopathy
Rapid Obesity

As of 2013

Oct 2011, 4y10m

Oct 2013, age 6y10m
Hypothalamic Dysfunction

- **Central Adrenal insuff.**
  - Rx hydrocortisone 8-10mg/m²/day

- **Central hypothyroidism**
  - Rx thyroxine to keep FT4 in upper normal range

- **GH deficiency**

- **Normal pituitary MRIs**

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<th>60 min</th>
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<td>Cortisol</td>
<td>42 nmol/L</td>
<td>222</td>
<td>301</td>
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<tr>
<td>ACTH</td>
<td>3.8 pmol/l</td>
<td></td>
<td></td>
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<tr>
<td>TSH</td>
<td>3.12 mU/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>7.2 pmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin (0-760)</td>
<td>1088 u/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-1 (6-37)</td>
<td>18.7 nmol/l</td>
<td></td>
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<tr>
<td>GH</td>
<td>&lt;1 mU/L</td>
<td>&lt;1 mU/L</td>
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<tr>
<td>αfp (0-6)</td>
<td>3 kIU/L</td>
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<tr>
<td>βHCG (0-5)</td>
<td>&lt;1 IU/L</td>
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<tr>
<td>Na</td>
<td>146 mmol/l</td>
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Autonomic Dysfunction

- Temperature instability
- Decreased HR variability
- Piloerection
- Diarrhoea – frequent, impairing sleep
- Dizziness – but no documented orthostatic hypotension
Hypoventilation: Evolution of REM hypoventilation on PSG

PSG Dec 2012 – initial OSA

PSG April 2013 – REM hypoventilation

Consistent with Reppucci et al 2016

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**Bilevel ventilation: Challenges**

- Mask fitting
- Developed parasomnias: night terrors
- Persisting daytime sleepiness: modafinil (Oct 2013)
  - No daytime hypoventilation
  - MSLT later diagnostic for narcolepsy
- Progression to tracheostomy (Dec 2013)
  - Electively planned for Jan 2014: ongoing Bilevel difficulties, inadequate ventilatory control
  - Performed Dec 2013: after acute deterioration with viral illness
Screening for Neural crest tumours

2.5cm mass - mesentery
A sign of the underlying process?

Mesenteric Lymph node biopsy

Normal - Reactive follicular hyperplasia

SA: Castleman’s Disease like pattern

- Variously sized reactive germinal centres
- Mantle of small lymphocytes
- Small atretic follicle
- Onion skinning appearance of lymphocytes
- Penetration by vessels lined by plump endothelium
Progress through 2014

- Tracheostomy
- Discharge home
- IVIG Commenced (1g/kg monthly)
- Back to school
- Cyclophosphamide (0.75g/m2)
  4 weekly  6 doses

Paz-Priel et al 2011
Evidence for treatment response: PET scan findings

Dec 2013

Oct 2014

Cervical LN  Abdominal LN  Inguinal LN
Cyclophosphamide

Prader Willi diet (<1000 kcal/day)

Increasing ventilatory needs
Progression of Hypoventilation …

Ventilatory Pressures

Episodes of lobar collapse: July and Sep 2014

Daytime Transcutaneous CO₂ O₂ trolley (Oct 2014)

Venous pCO₂ 38 pH 7.43
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Venous pCO₂ 54 pH 7.28
Cyclophosphamide  
Rituximab  
Prader-Willi diet (<1000 kcal/day)  
Increasing ventilatory needs  
Max ventilator settings  
Permissive hypercapnia  
Rapid drop  
Deteriorating autonomic dysfunction  
Very restricted diet (<600 kcal/day)  
Dietary challenges  
Sirolimus  
+ Azathioprine  
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Evolving complexity and issues

- Sleep: Narcolepsy, Partial arousals
- Chronic headaches
- Obesity
  - Liver (Severe NASH), Acanthosis nigricans, hyperinsulinism, mobility
- Behavioural issues
  - Body image effects, Low mood, Impact on family relationships
  - Medications: Fluoxetine, Amitriptyline
- Cardiac arrhythmias – SVT
- Enuresis
- Autonomic dysfunction
  - Significant recent deterioration
  - Recurrent Aspiration, swings in temp/BP/Na
Current status

• To minimise aspiration risk
  – Epiglottis oversewn with small tube to facilitate voice
  – Gastrostomy inserted and used for part of oral feed
• Azathioprine added with effect. Remains on sirolimus and IVIG
  – Low threshold for review
• Challenges achieving dietary restriction
  – CHO based thickeners, Enjoyment of eating/drinking
  – Weight stabilised at 95kg
• Stable ventilation
• Home carers at night, Remains at school each day
• Structured approach to behaviour management
• No evidence of neural crest tumours to date
• Palliative care involved for discussions regarding limiting treatment
Fluctuating ventilation needs

Cyclophosphamide  Sirolimus  + Azathioprine
Genetic vs. autoimmune process?

- Genetics negative to date
  - Whole exome sequencing negative (Brisbane), targets including
    - PHOX2B negative (excludes CCHS)
    - Coding regions for Hypothalamic-specific expression/development and CNS development
  - Note: Reports of monozygotic twins discordant for ROHHAD
    Patwari et al Ped 2011

- Autoimmune process?
  - Castleman’s disease like changes in lymph node
  - Narcolepsy component Mahlios et al Curr Opin Neurobiol. 2013
  - Evidence of response to IVIG
  - Evidence of response to cyclophosphamide Jacobsen et al Ped 2016
  - Evidence of response to Sirolimus (but not Rituximab)
  - Serum CRP trend
    - Note: No evidence of CNS inflammation (2013, 2016)
      - CSF no oligoclonal bands, Normal neurotransmitters
Discussions points

- The challenges of treating a condition with an unknown but probably poor prognosis
- Quality of life balance
  - Tracheostomy, periods of cuffed tracheostomy (voice), getting to school
  - Managing aspiration risk – oversewn epiglottis
  - Risks of medications used
- Unclear prognosis and course of the condition
- Role of overseas consultation…
- Next steps in management…
Meet Sebastian, 7, whose weight has TRIPPLED in two years because of a rare condition which affects just a handful of people around the world... and it could kill him

- Sebastian Aguiar is seven-years-old and weighs almost 70kg
- The boy from western Sydney suffers from ROHHDAS syndrome
- He weighed a healthy 25kg less than two years ago
- He is one of only about 75 people in the world with the condition
- He is believed to be only person in Australia suffering from the disease
- ROHHDAD syndrome is potentially lethal and incurable
- It affects breathing, body temperature, heart rate and blood pressure
- A fundraising page has been set up to send him to Chicago for tests
- It is his only hope as the syndrome is potentially lethal and incurable

By LEESA SMITH FOR DAILY MAIL AUSTRALIA

Acknowledgements

• The multidisciplinary teams involved
  – Endocrinology: Shubha Srinivasan
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  – ENT: Alan Cheng, Sue Trapani
  – Cardiology: Christian Turner
  – Physiotherapy
  – Occupational therapy
  – General Paediatrics: Joanne Ging
  – Palliative Care

• Chetan Pandit
• Arthur Teng

With special thanks to all the nurses who have looked after this child to date....and everyone at his school!!