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Sleep & Breathing in Children with PWS

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No conflict of interest

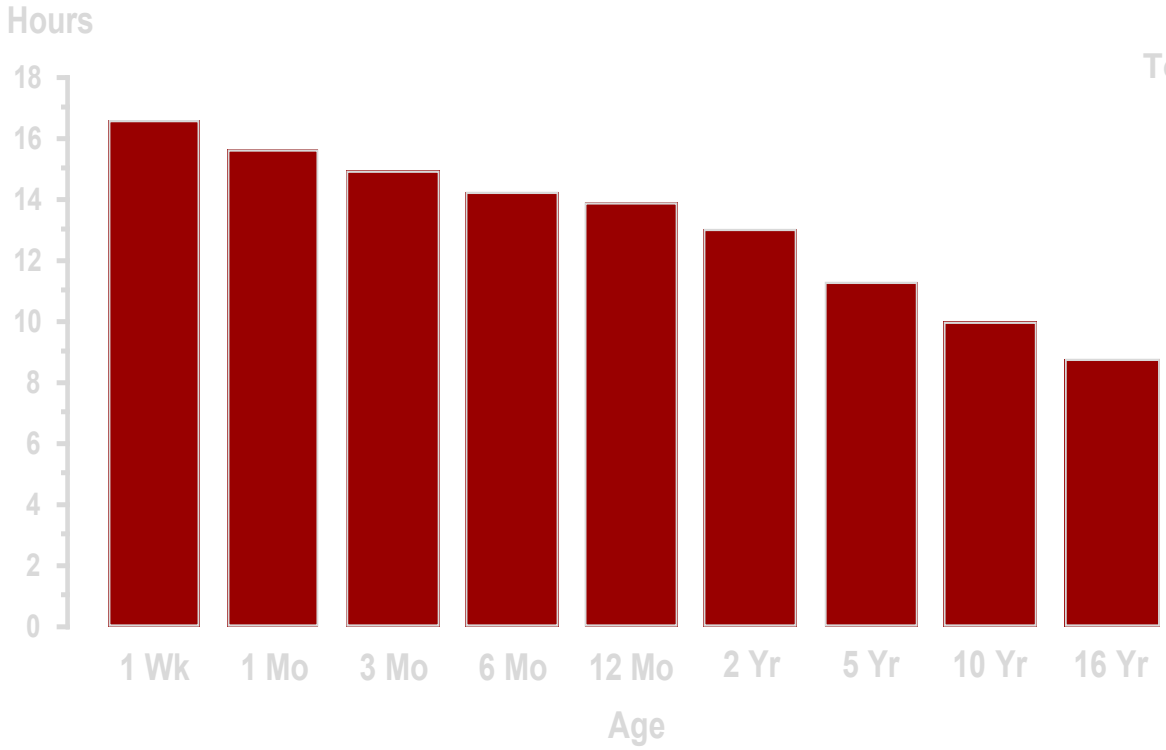
Outline

- Overview of Human Sleep
- Abnormalities of Sleep in PWS
- Assessment of Sleep Disordered Breathing
- Investigations & Management
- Growth hormone and Sleep Disordered Breathing
- Summary

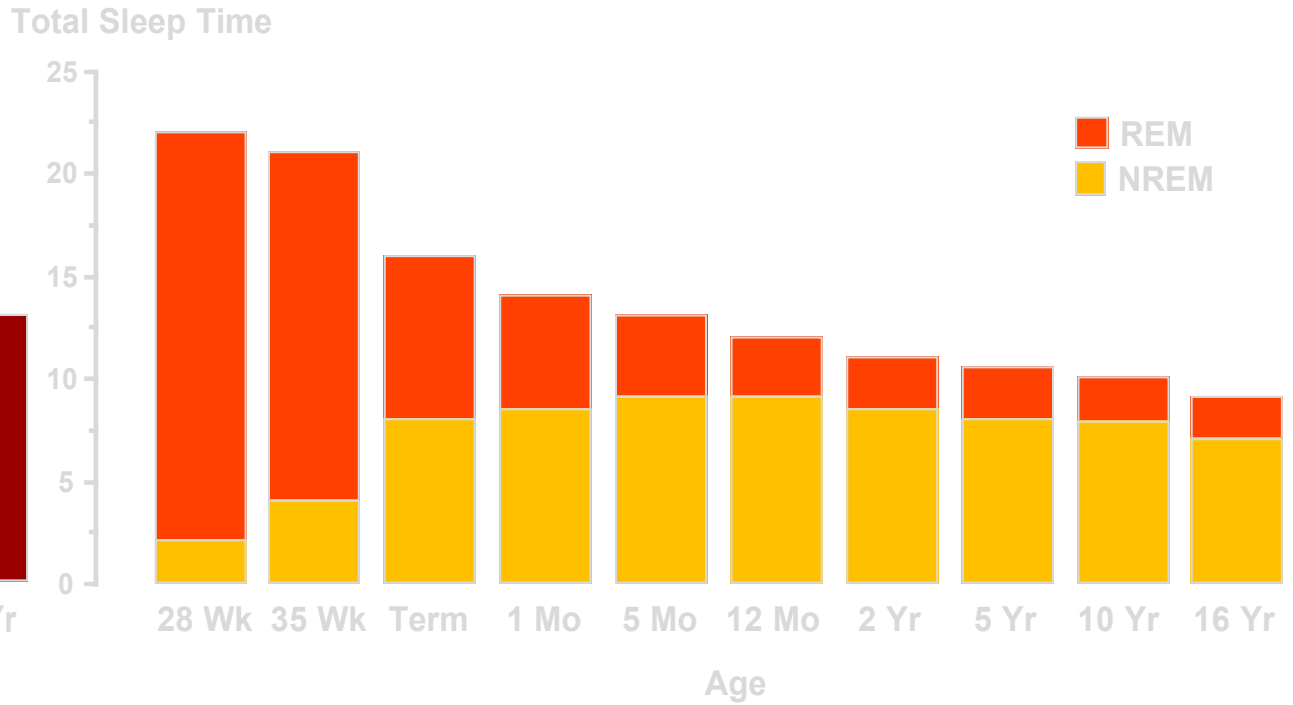
Sleep

- 1/3rd of our Lifetime
- Complex neurological state
- NREM (Non-Rapid Eye Movement) – Reparation of body tissue
- REM (Rapid Eye Movement) – Restoration of brain tissue
- Role in Central Nervous System - Neural circuitary
- Learning , Unlearning & Memory

Total Sleep Duration



REM & NREM Sleep



Modified from FERBER R.: Solve your child's sleep problems. New York. Simon & Shuster, 1985, p19

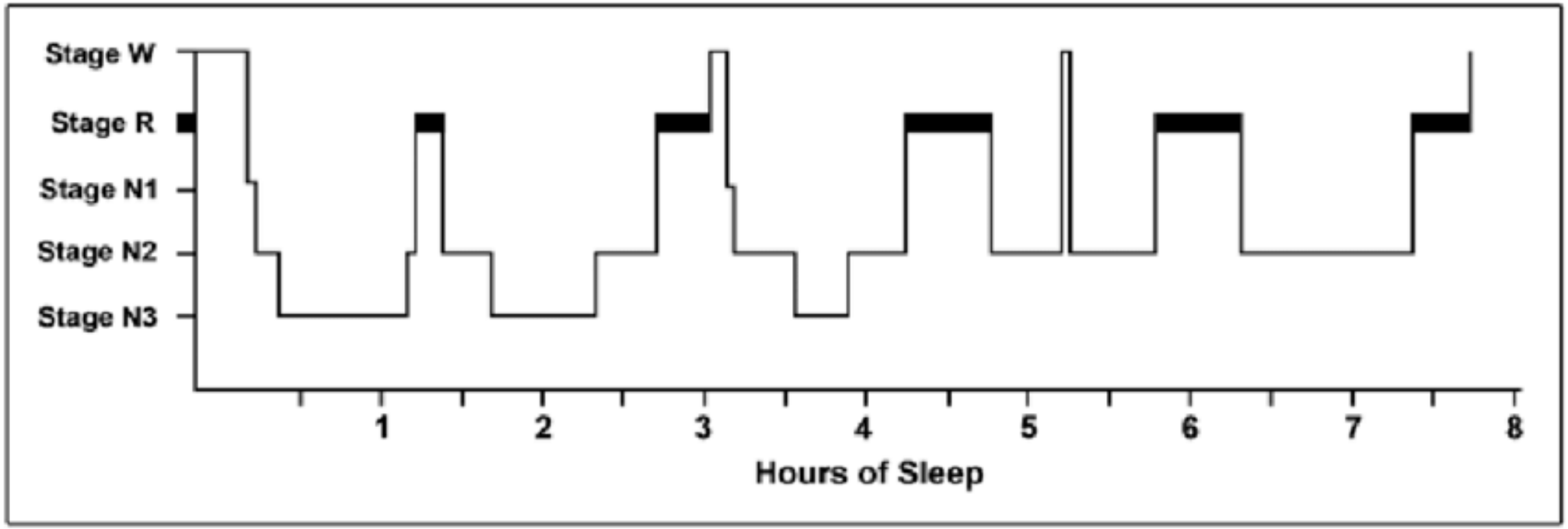
Sheldon SH, Spire J-P, Levy HB: Pediatric Sleep Medicine. Philidelphia. WB Saunders. 1992, p24

Sleep Cycle -Hypnogram

Wake

REM

NREM



Breathing

- Required for normal oxygenation of the red blood cell to deliver oxygen to the cells
- Oxygenation and Carbon dioxide clearance
- Central drive from brain for breathing
- REM hypotonia
- Respiratory system is vulnerable in sleep
- PWS:
  - Higher arousal and Blunted ventilatory response to hypercapnia
  - Poor arousal and Cardiorespiratory responses to hypoxia

Abnormalities of Sleep in PWS

- Excessive daytime sleepiness, Narcolepsy
- Sleep-disordered breathing
    - Central sleep apnoea
    - Obstructive sleep apnoea
    - Hypoventilation

Excessive Daytime Sleepiness (EDS)

Excessive Daytime Sleepiness (EDS)

- Common feature of PWS
- EDS – occurs despite increased quantity of nocturnal sleep
- EDS in children with PWS is multifactorial
- Disruption of sleep – difficulties with initiating sleep, awakenings, behavioral issues
- Sleep disordered breathing
- Narcolepsy

Excessive Daytime Sleepiness (EDS)

- Hypersomnia:
  - Hypothalamic dysfunction
  - Narcolepsy-like phenotype: sleep-onset REM and sometimes cataplexy [1,2]

- Orexin-A (hypocretin-1) [A neurotransmitter important in maintaining wakefulness]
  - CSF - Absent or very low levels - narcolepsy type 1 with cataplexy [3].
  - Intermediate levels of orexin-A [1]

1. Manni, R et al, Clin. Neurophysiol. **2001**, 112, 800–805

2. Omokawa et al, Am. J. Med. Genet. A **2016**, 170, 1181–1186.

3. Nishino, S et al; Lancet (Lond. Engl.) **2000**, 355, 39–40

EDS - Narcolepsy

- Characterized by EDS, sleep paralysis, hallucinations and fragmented sleep

  +/-cataplexy

- Two types

  Type 1 – with cataplexy

  Type 2 – without cataplexy

EDS - Cataplexy

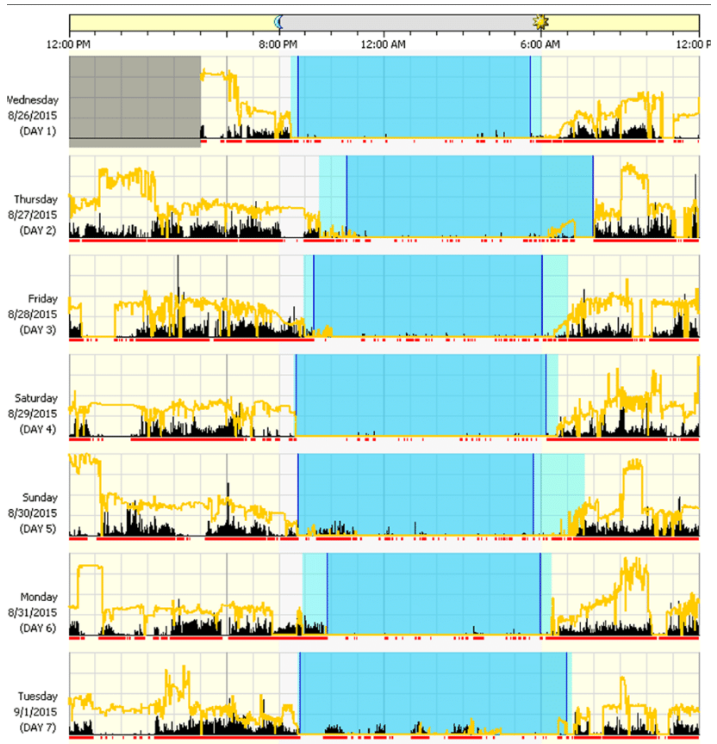
- Sudden, brief episode of muscle weakness triggered by strong emotions

- Can be difficult to detect in children as symptoms can be subtle

- Falling episodes
- Eyelid drooping/ twitching
- Slurred speech
- Facial drooping
- Lip smacking/twitching
- Clumsy

EDS - Narcolepsy

- Sleep Diary and Actigraphy – subjective and objective monitoring of sleep/wake cycle



- Diagnosis:

  Overnight PSG, followed by multiple sleep latency test (MSLT)

  - Mean sleep latency <8 minutes
  - At least 2 SOREM sleep

Excessive Daytime Sleepiness (EDS)

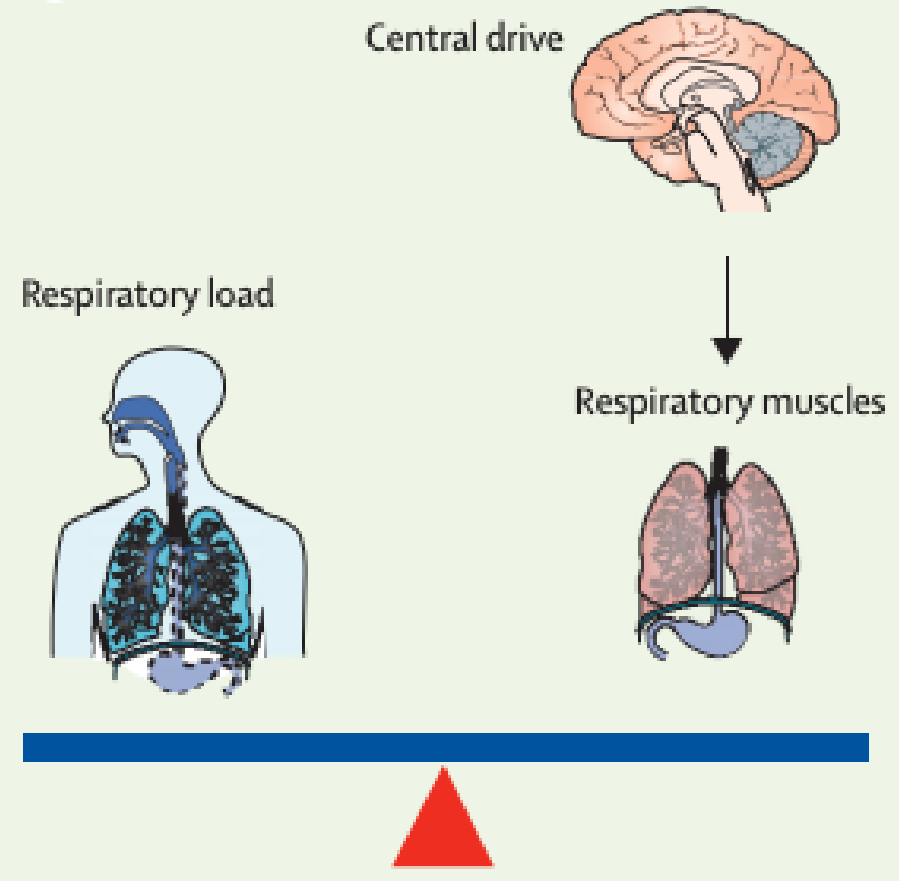
Management:

- Extend night-time sleep
- Bedtime issues
- Structured daytime activities
- Important to rule out OSA
- Stimulant medications – Methylphenidate, Modafinil, in selected patients

**De Cock, V.C et al; Am. J. Med. Genet. A 2011, 155A,1552–1557.*

Sleep Disordered Breathing (SDB)

PWS and SDB



- Delay in maturation of the central ventilatory control centers
- Higher arousal and Blunted ventilatory response to hypercapnia
- Poor arousal and Cardiorespiratory responses to hypoxia
- OSA, Obesity
- Growth Hormone

Sleep Disordered Breathing (SDB)

- Phenotype of SDB in PWS patients
  - Evolves over time
  - Predominantly central sleep apnea in infants
  - Obstructive sleep apnea (OSA) in older children
  - Hypoventilation

Assessment of Sleep-Disordered Breathing

History:

- Sleep pattern - Duration of sleep, Regularity,

  Bedtime problems, Night-time awakening

- SDB symptoms: Snoring, Restless sleep,

  Witnessed apneas, Morning headaches,

- Questionnaire based assessment of sleepiness

Examination:

- Obesity
- Neck circumference
- Adenoids, Tonsils
- Mallampatti score
- Blood Pressure

Overnight Investigations:

- Pulse oximetry
- Sleep study (Polysomnography)

Obstructive Sleep Apnea (OSA)

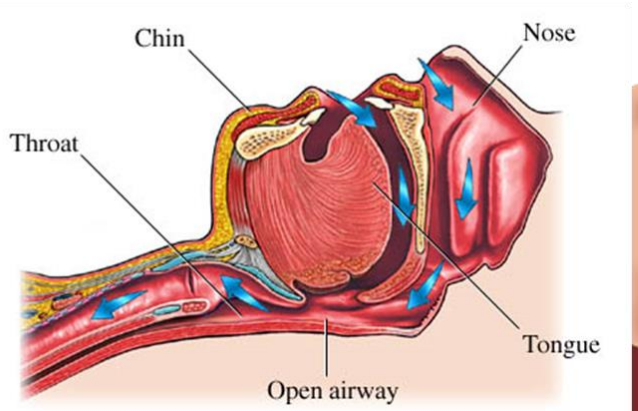
- Prevalence of OSA in children with PWS is just under 80% - meta-analysis [1] (vs 1% to 4% prevalence in the general pediatric population)

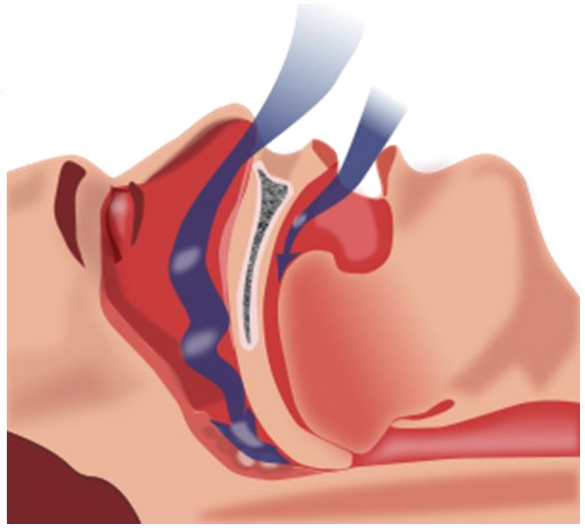
- Peak incidence: 3 to 6 years

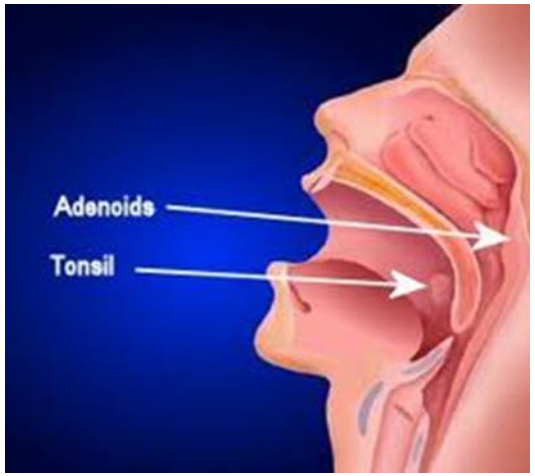
- Risk factors:
  - Altered ventilatory control
  - Obesity
  - Hypotonia
  - Micrognathia, narrowing of the upper airway

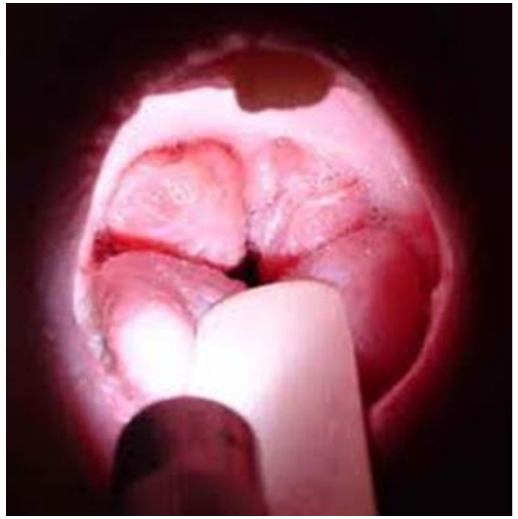
1. Sedky, K et al; J. Clin. Sleep Med. 2014, 10, 403–409.

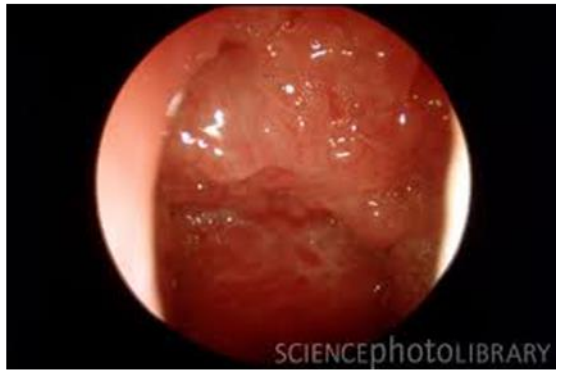
Obstructive Sleep Apnea (OSA)











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Polysomnography (Sleep Study)

Polysomnography (Sleep Study)

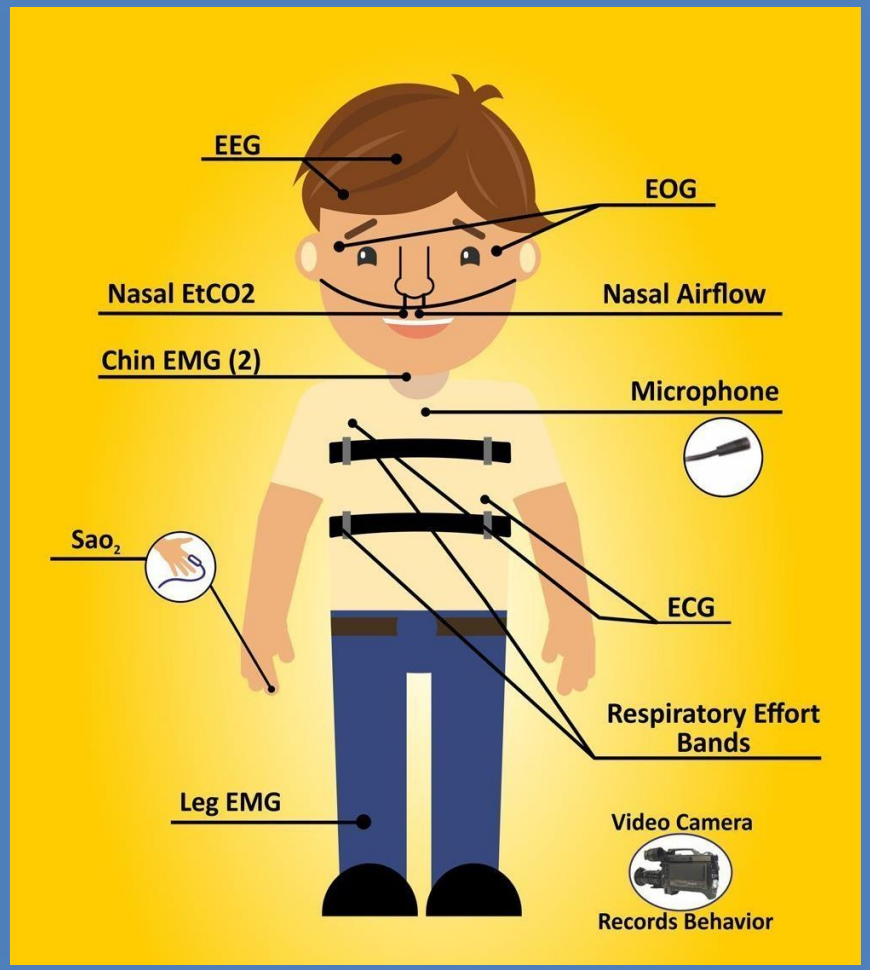
EEG – Electroencephalogram

EtCO2 - Exhaled Carbon dioxide

EMG – Electromyogram

SaO2 – Oxygen Saturation

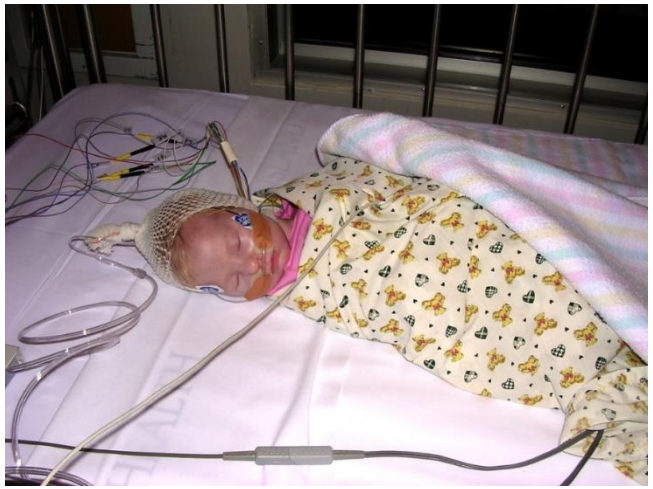
EMG – Electromyogram

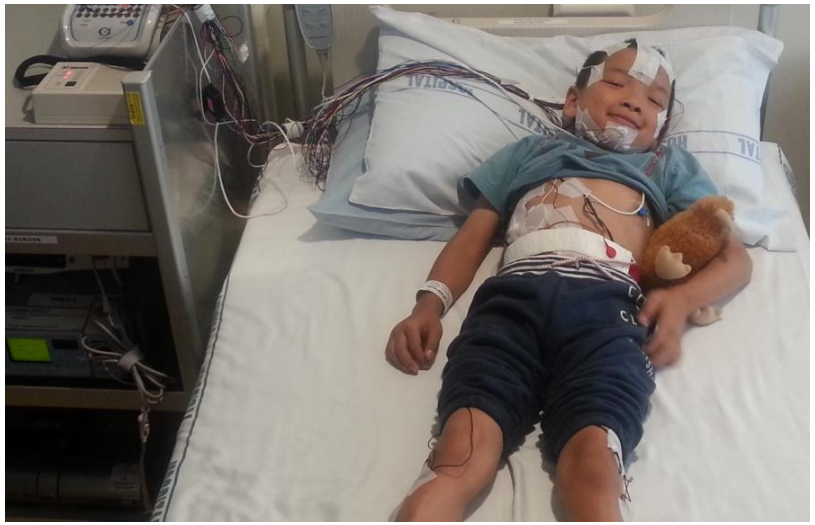


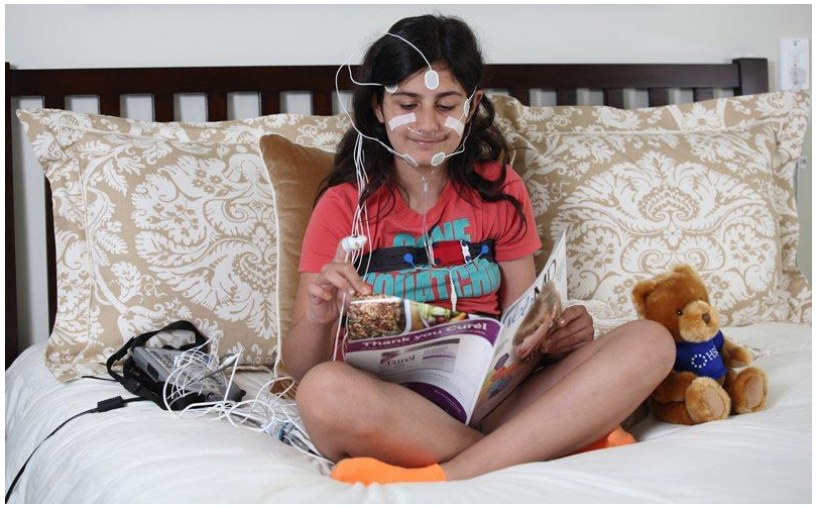
EOG – Electro-oculogram

ECG – Electro-cardiogram

PSG – Set up and Channels







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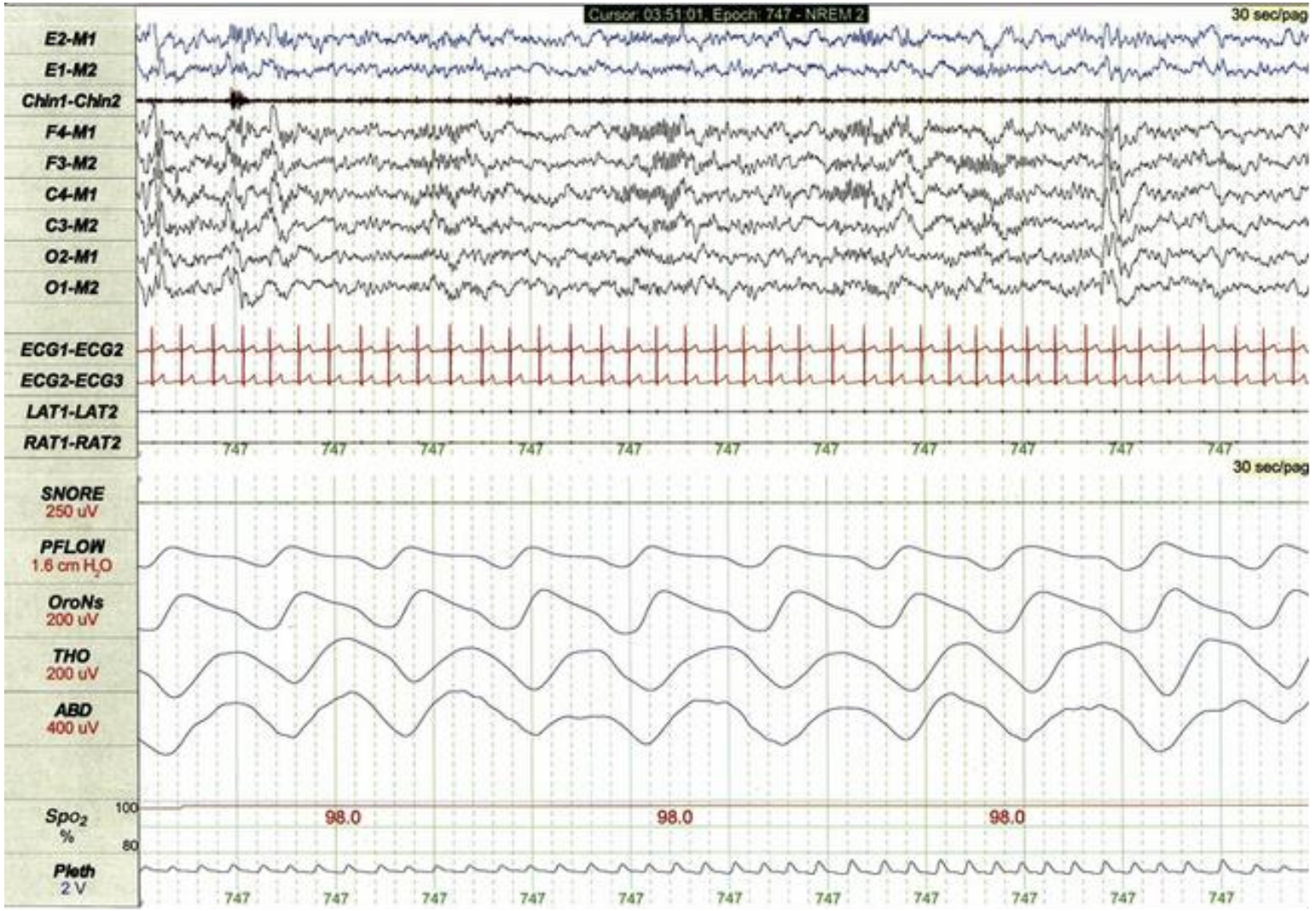
Overnight Sleep Study (PSG)



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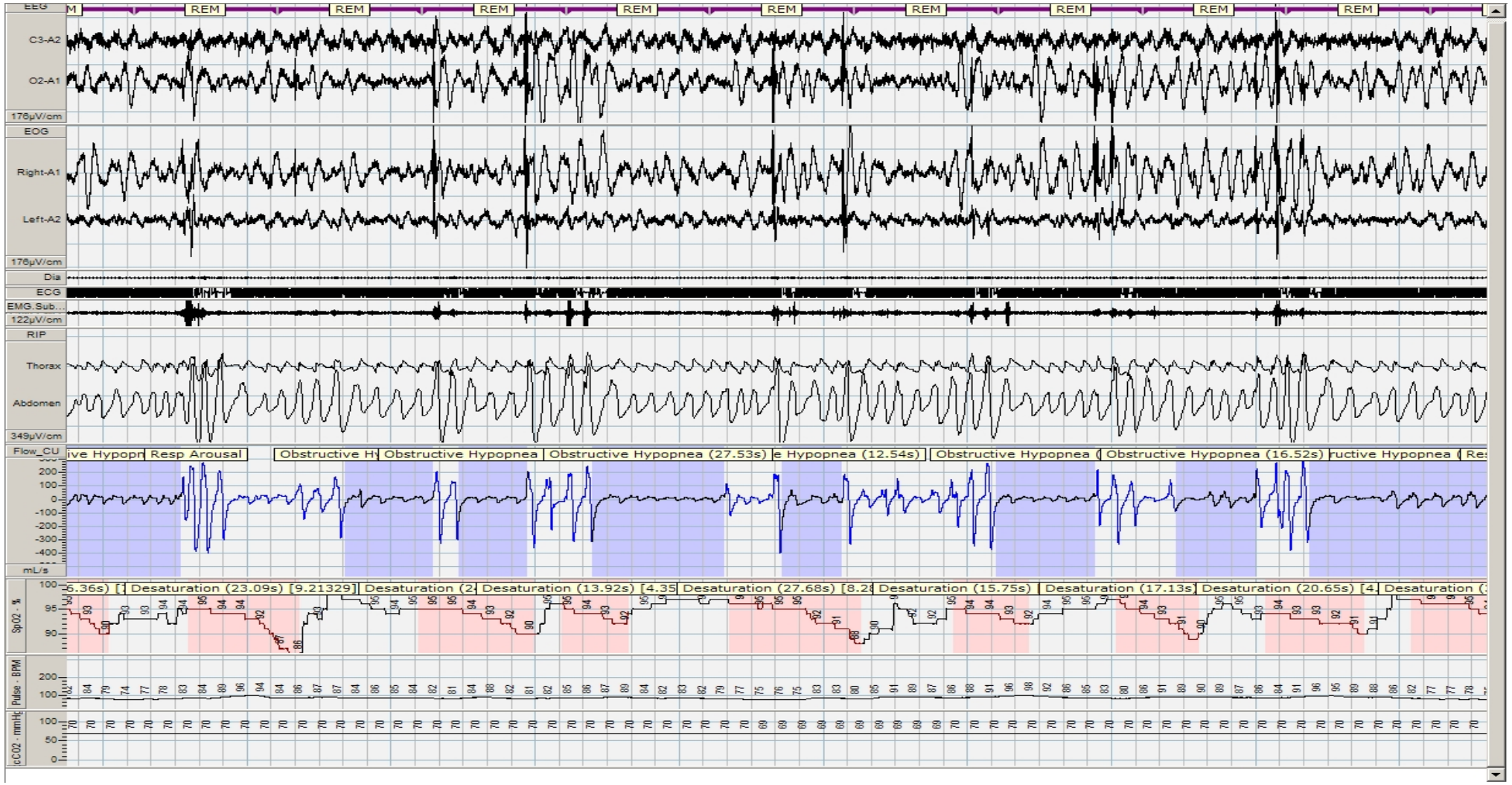
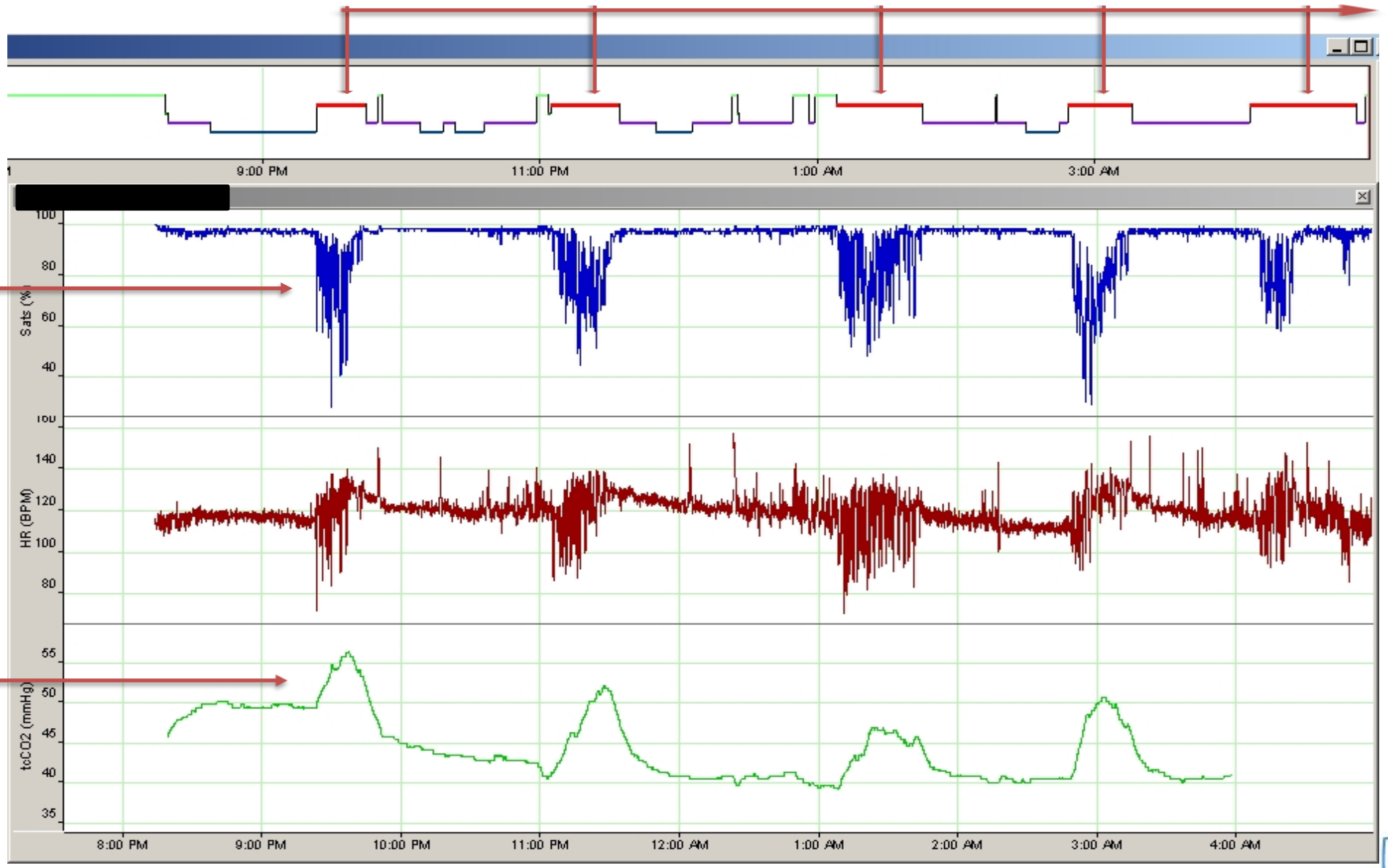
Obstructive Events



Severe OSA



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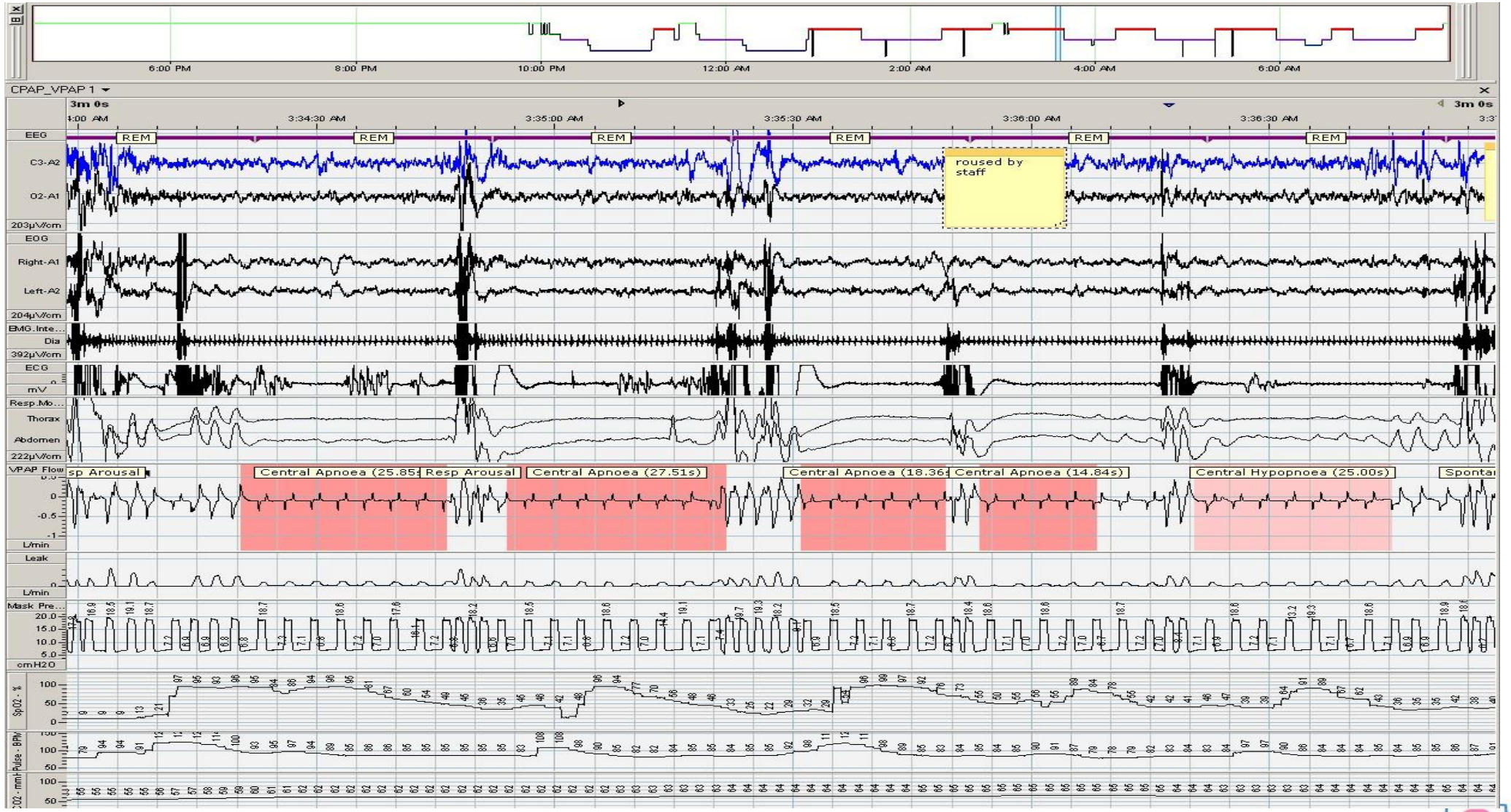
Central Sleep Apnea (CSA)

Central Sleep Apnea (CSA)

- CSA predominates in infants and children <2 years old (Peak incidence in infancy)
- Etiology: Unknown
  - Delay in maturation of the central ventilatory control centers
  - Abnormal apneic threshold (defined as the arterial pCO2 below which the drive to breathe is lost)
- Older children with PWS - still exhibit
  - Higher arousal and Blunted ventilatory response to hypercapnia
  - Poor arousal and Cardiorespiratory responses to hypoxia

→ Predispose to developing sleep-related hypoventilation during adolescence and adulthood

Central Events



Growth Hormone Therapy

Effects

- Stimulates growth
- Increase in basal metabolic rate, energy requirement, oxygen consumption
- If breathing is already at risk, GH can make it worse

Sleep & Breathing Positive effects

- Increase resting ventilation
- Central inspiratory drive
- Increased respiratory response to hypercarbia
- CSA

OSA and GH Therapy

- Accelerated growth of lymphoid tissues (Adenoidal and Tonsils)
- Onset of OSA after GH Rx

  6 weeks to up to 2 years
- Development of OSA is of particular concern - reports of sudden death in PWS undergoing GH therapy*

- Sleep study prior to starting GH therapy [2,3]
- Rx of OSA prior to starting GH treatment [2]
- NOT be initiated during an acute respiratory illness [2]
- Sleep study during GH therapy:

  - AAP recommendation - PSG - 6 to 10 weeks after starting GH [4]

  - Within 3 to 6 months after starting therapy [2] or Once a year during treatment [1]
- Worsening of SDB – needs to treated before continuing GH

** Eiholzer, U et al. Horm. Res. 2005, 63, 33–39.*

** Bakker, B et al; Horm. Res. 2007, 67,203–204*

1. *Berini, J et al; J. Clin. Endocrinol. Metab. 2013, 98, E1516–E1523*
2. *Deal, C.L et al; J. Clin. Endocrinol. Metab. 2013, 98, E1072–E1087*
3. *Vandeleur, M et al; J. Paediatr. Child Health 2013, 49, 238–241*

Consequences of Poor Sleep

- Cognitive development
- Behaviour
- Mood/Affect
- Attention/learning problems
- Cardiovascular, Neurology
- Overall quality of life
- Caregiver/Family

Treatment

OSA - Rx

- Adenotonsillectomy (T & A)
- Residual OSA post T & A
  - CPAP
- Weight loss

CSA - Rx

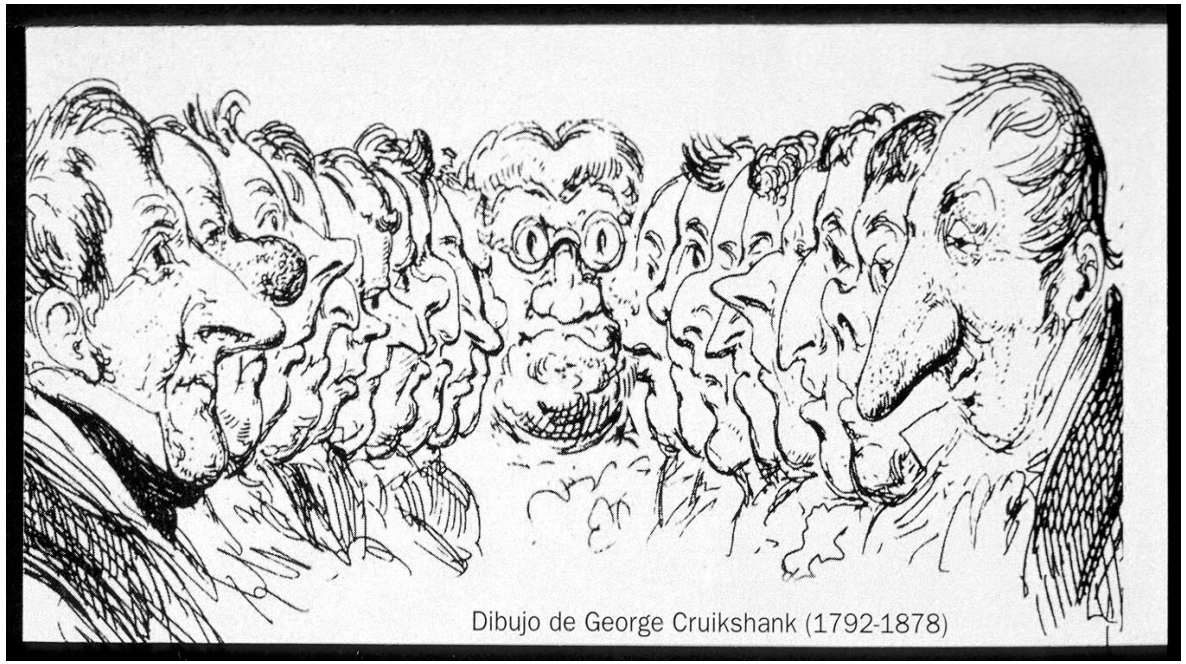
- <2 years old who exhibit CSA – Rx Supplemental oxygen
- Overnight oxygen titration PSG [1,2]
- Sleep related hypoventilation:
  Bi-level non-invasive ventilation

1. Cohen, M. et al; PLoS ONE 2014, 9, e101012.

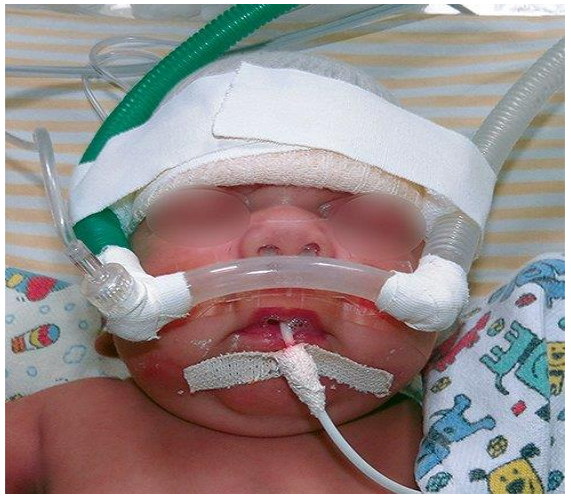
2. Urquhart, D.S et al; Arch. Dis. Child. ***2013****, 98, 592–595.*

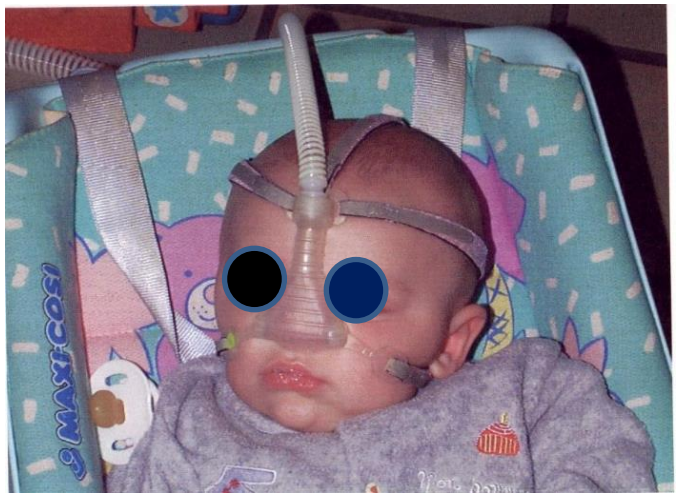
Non-Invasive Ventilation (NIV)

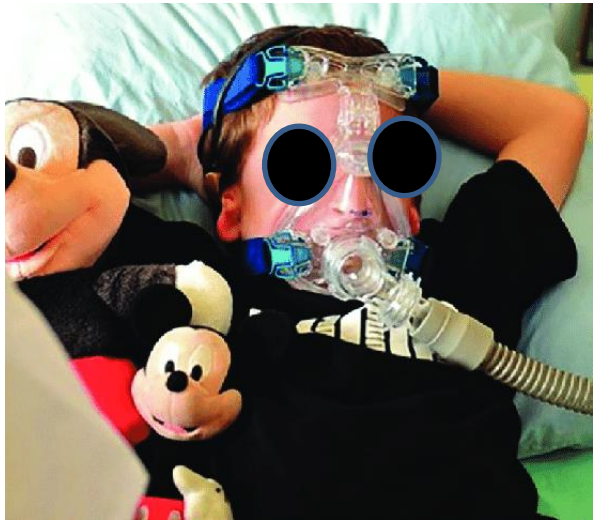
- CPAP – Continuous Positive Airway Pressure
- Bi-level Positive Airway Pressure
- Interface (Masks)
  Different size, shape

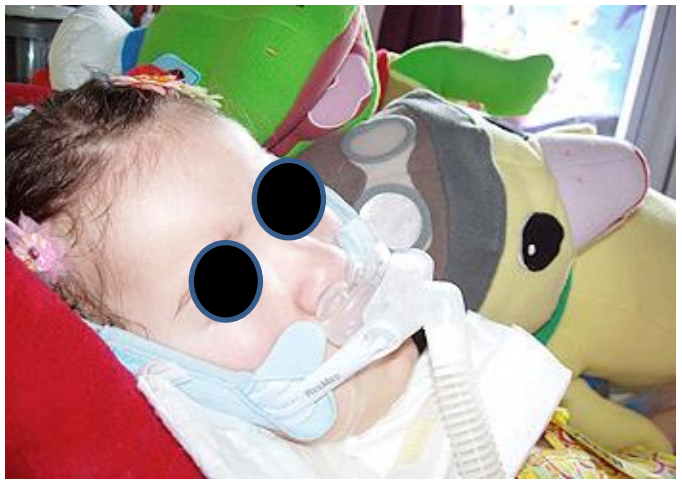


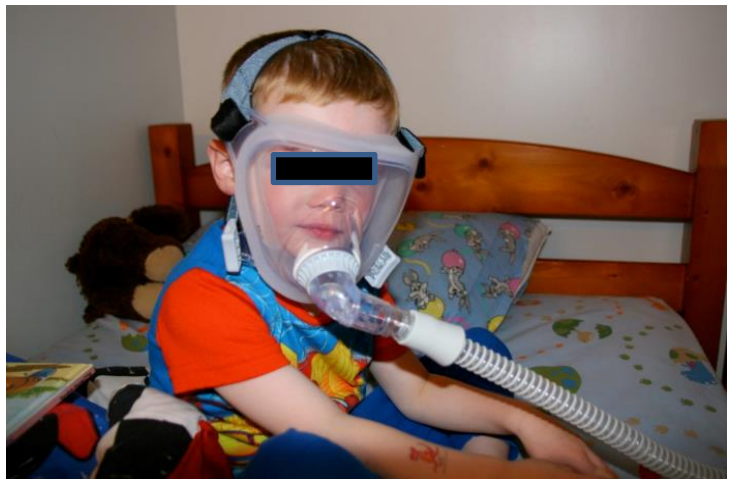
Interface (Masks)











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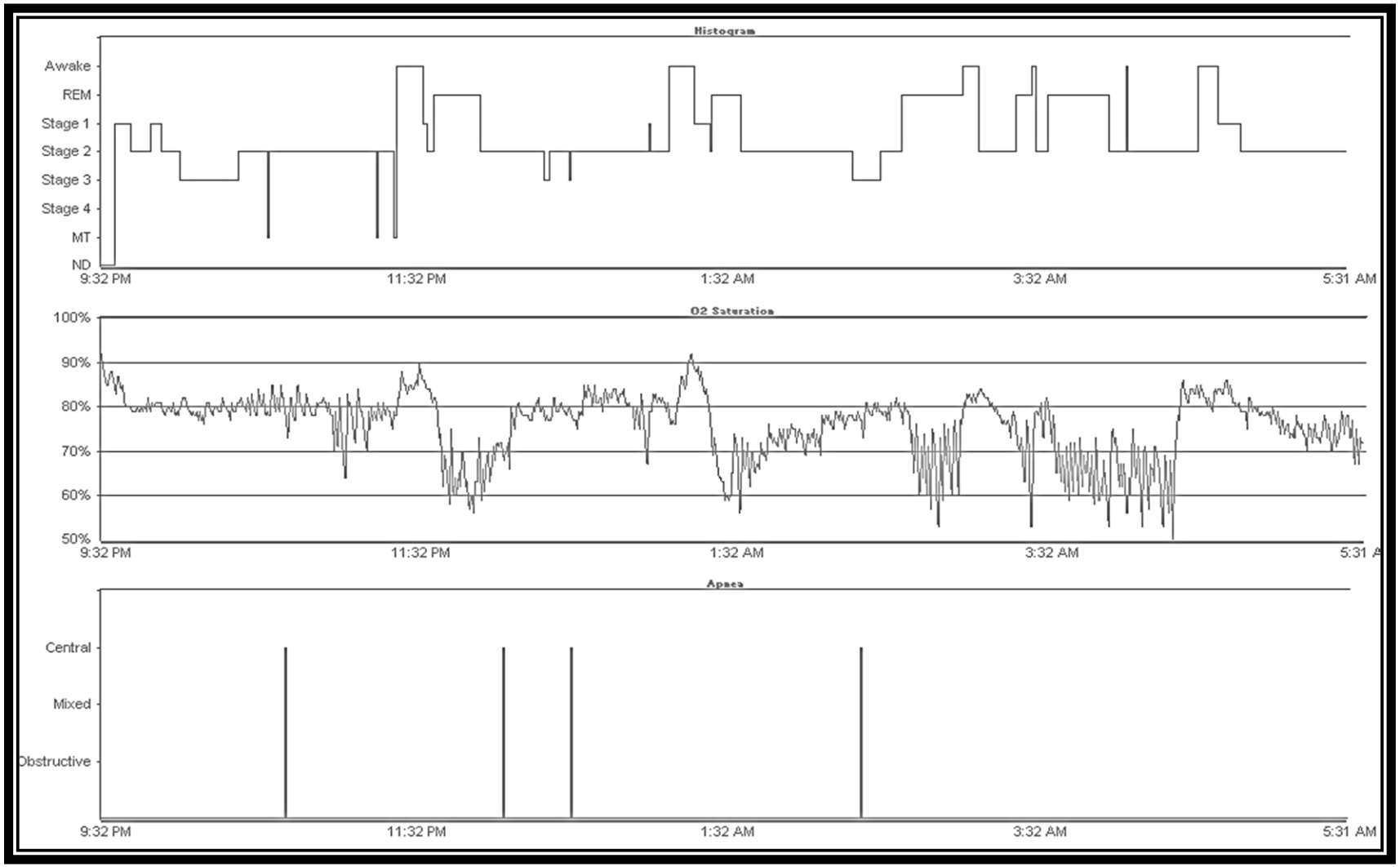
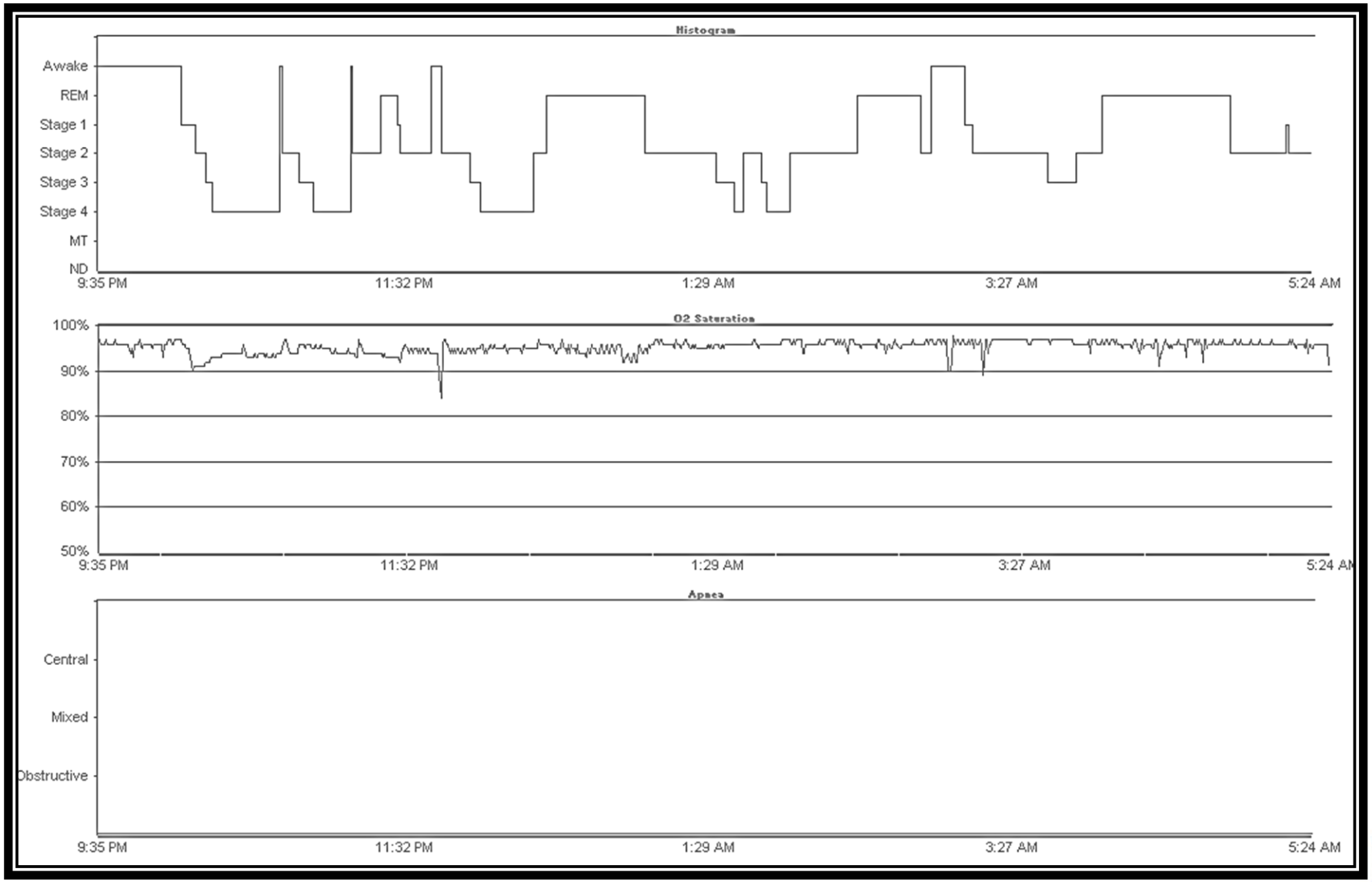
Severe Obstructive Sleep Apnoea



Non-Invasive Ventilation



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Summary

- Sleep problems are common in patients with PWS
- PWS are at risk of SBD – both central and obstructive
- Daytime sleepiness in very common in PWS
- Sleep problems and SDB can affect/worsen – Cognitive, Developmental, Behavioral problems
- Active screening for SDB:
  - Clinical assessment,
  - Pulse Oximetry, PSG

Management:

- Behavioral modifications
- Sleep hygiene
- EDS – consider stimulant medication (methylphenidate, modafanil)
- Supplemental Oxygen
- ENT surgery
- NIV: CPAP/Bi-level
- Weight management

During Growth Hormone Treatment:

- Careful monitoring
- Pre and Post-GH Sleep Study
- Treatment of SDB

Thank You

Questions?