Angelman Syndrome: Sleep

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Angelman-outline (key messages)

- Why talk about sleep in people with Angelman syndrome?
- Epidemiology
- Why it matters? Does it?
- What is typical sleep?
- How do we measure it? More importantly how do we measure it in people with Angelman syndrome?
- What is different about the sleep in people with Angelman syndrome?
- What evidence is there for various therapies?
- Gaps in Knowledge and where to from here?
Angelman-outline

- Why talk about sleep problems?
- Reports of up to 80% having sleep problems
- Seem to be worse in young children and slightly better as matures
- A child that doesn’t sleep well impacts on other children and parents.…
- Impact on families..

J Trickett et al. Rev Dis Res 2017
Other genes on 15

- UBE3a is only 1 gene
- Remember all the others
- GABA A receptor subunits \textit{GABRB3}, \textit{GABRA5}, \textit{GABRG3}
- Gaba- aminobutyric acid (neurotransmitter)
- These three units form part of a receptor for GABA
- Abnormalities in these genes may result in abnormalities of function?
- Mutations/ deletions of UBE3A phenotypically important in sleep
Sleep- What is typical?

- We only know about what happens typically most of the rest is defined in small groups.
- We know that the development of the EEG in Sleep reflects the developmental attributes.
- Normal sleep allows a number of restorative processes to happen.
- Therefore would not define a sleep problem without daytime symptoms.
- These processes happen at different times and include general housekeeping processes, hormone production, memory processing.
- Abnormalities in sleep can effect many of these processes.
- Maturation of sleep is consistent with neurological development.
So- what is Normal?
Normal sleep requirements

Figure 10-1: Percentiles for total nighttime (A) and daytime (B) sleep duration during childhood.

Reprinted with permission from Iglowstein I, et al, Pediatrics. © 2003, by the AAP. pediatrics.aappublications.org/content/111/2/2352.abstract?sid=8ce3a74-5f1c-4356-9d03-57d1c604c90.
Ontogeny of REM and NREM Sleep

Sleep stages and amounts change with age

Ohayon Sleep 27(7) 2004
Classic Sleep Stages

- **Stage 1** - Drowsy sleep / sleep onset
- **Stage 2** - ‘Light sleep’ - spindles and K complexes
- **Stage 3** - Slow wave sleep
- **REM** - Rapid eye movement sleep / dream / active sleep
- **Awake** - Normal 3-5 awakenings in adults and children
Sleep stages are defined by EEG amongst other things
Typical sleep pattern

A 'good' sleep pattern for kids

Sleep Stage
Awake
REM
Stg 1: light
Stg 2: light-mod
Stg 3: mod-deep
Stg 4: deep

Hours
Settling into a pattern
Circadian Cycle

**Circadian cycle:**
Genetic control
Light controlling melatonin release
Behavioural entrainment

**Hormonal + others:**
Cortisol
Growth hormone
Immune function
Pubertal and sex hormones

It is hard to know how this sits with an atypical brain
In some dysregulated cycles
Possibly longer cycles
Visually impaired
Sleep drive

Process C
Process S

Fetal programming may be resultant upon pregnancy and early neonatal influences- Kennaway Trends in Endocrinology & Metabolism 13(9)
Circadian and ultradian rhythm
Summary

- 3 controls of sleep
- Circadian- daily cycle- often a bit longer than 24 hours
- Pressure of sleep- time since last deep sleep
- Ultradian cycle- 90 minutes

- Timing is everything….

- Controlled by genetics mostly
Sleep disturbance

- Growth failure (disturbance of rhythm)
- Cardiorespiratory problems - OSA
- Immunological (disturbance of rhythm)
Sleep Disorders

- Mood
  - Increased irritability, decreased positive mood, poor affect modulation

- Behavioral manifestations
  - Increased impulsivity, hyperactivity, mood lability, inattentiveness

- Neurocognitive performance
  - Decreased cognitive flexibility, impaired motor skills, decreased attention

- Other Effects
  - Deleterious effect on cardiovascular, immune and metabolic systems; increased accidental injuries; affect family
Sleep maturation

- Sleep onset is a learned process
- Self sleep initiation must occur prior to sleep continuity
- Awakenings are normal part of sleep
- Awake ‘bright and alert’ in mornings
- Sleep maturation [continuity] linked with intellectual development
Generic Tips - how do we measure sleep

- Good detailed history
  - Consider medical causes of sleep disruption – not always evident
  - Epilepsy
  - Exczema
  - Gastro oesophageal reflux **
  - Pain
- Parental Questionnaire
- Observation- YEAH.. the age of the smart phone
- Actigraphy
- Portable assessments ??
- In hospital observation…
- Oximetry
- PSG-
- Think about behavioural and developmental profile
Taking a good history

Sleep diary example (Teenager)

Notes: Important to distinguish between school nights and weekends
Actigraphy

Objective measure of sleep (based on gross motor movement, then automated sleep/wake algorithm applied to data)

- Similar diary recordings of sleep parameters, including:
  - Bedtime
  - Total sleep time
  - Rise time
  - Sleep latency
  - Number of awakenings
  - Naps
  - Sleep onset time
  - Wake after sleep onset
  - Regularity

- Some devices also include a light sensor
- Psychometrics good for sleep times.
- Not so good for wakefulness / sleep duration
- More useful clinically than research
- Expensive
- Cheaper versions ????
When is a sleep study worth arranging

• Sleep disordered breathing

• Remember that a sleep study can be stressful and many children particularly those that can be very anxious may struggle to keep leads on- if you can't get an EEG then unlikely..

• Not many people with Angelman syndrome can tolerate the set up

• So how do we measure this?
Normal structure to sleep – central events
Mats – remote technology
Sleep pattern disorders

- Acceptable sleep patterns differ from household to household
- All children are “DIFFERENT”
- Infants & young children
  - Self initiation of sleep first step
  - Enhanced by routine
  - Parental separation
  - No night light
So How do children and adults with Angelman syndrome sleep?

- Literature
- Registry data

- Severity of sleep problems decreases with age
- Sleep behaviours improving with age
  - Refusing to go to bed (3)
  - Night time sweating (16)
- Sleep behaviours worsening with age
  - Hard to wake up in the morning (22)
Themes to Angels sleep- literature

Settling problems 2%
Night waking 37%
Early waking 10%
Enuresis
Bruxism
Sleep terrors
Sleep walking
Nocturnal movement (hyperkinesia)
Snoring
Waking with sleep stage change

No difference between different genetics

Diddens et al 2004, Bruni et al 2004
Why Angels might not sleep?

- Snoring? Obstructive sleep apnoea
- Epilepsy (seizures)
- Variable levels of melatonin/other genetic
- Animal studies with mouse models demonstrate absence of ube3a has no effect on daily (circadian)cycle or expression of clock genes in the SCN ... has no effect on cycles when in darkness and likewise responds normally to light and behavioural changes with light BUT DOES SEEM TO HAVE AN EFFECT ON SLEEP PRESSURE—Ehlen jones et al J Neuroscience 9(15)2015
- Similarly NREM sleep was much more fragmented in UBE3a absence
- Behaviour/habit
- Secondary gain
- Abnormal electrical activity resulting in initiating and sleep stage changes being difficult
Sleep and Age

- Severity of sleep problems decreases with age
- Sleep behaviours improving with age
  - Refusing to go to bed (3)
  - Night time sweating (16)
- Sleep behaviours worsening with age
  - Hard to wake up in the morning (22)- sleepiness
Stage change- OSA-central apnoeas

OSA- Treatment

OSA - mechanical
- Tonsil and Adenoidectomy results in improvement in 65-80%
- CPAP ??
Neurological

- Seizures- onset < 3 years
- Abnormal EEG- characteristic pattern with large amplitude, slow spike waves
- Seizures more prone in sleep
- Epilepsy in Angelman syndrome is associated with sleep problems
- Epilepsy medications also associated with poor sleep and daytime sleepiness

- ? Does this cause increased susceptibility to waking at sleep stage change
- ? Does this cause difficulties and resulting decreased REM and SWS( deep sleep)
- Some evidence for differing patterns in the EEG
Behavioural

- Often the behaviour when awake is most problematic
- Issues of safety
- Issues of learned behaviour
- Issues of improved behaviour with better sleep
- Issues of increase in seizures if sleep deprived
Sleep

• What to do about it?

• Sleep hygiene works in at least 20-30%
  – Dark
  – Light and bright in am
  – Quiet
  – Bed and self settle in beginning of night like later in night
  – Routine
  – Bed for sleeping
  – Calming activities (might look different in this population)

• Behavioural strategies reward avoidance

• Are no different to general population?

• BUT with modifications..
Strategies

• Limit setting- good routines clear communication, social stories
• Rewards for staying in bed (not sleeping)- appropriate
• Calming activities preferably with low light- dim screens
• Work through some of sensory things – e.g. touch
• Teach to stay in bed

• Camping out
• Checking in & out
• Out of bed card
Melatonin in children with Angelman syndrome

- Melatonin variation
- Variation in metabolism
- (fast and slow metabolisers)
- Means that some lose effect
- Some respond better to very low doses
Melatonin

- Melatonin
- ¼ have different genes that make us high or low metabolisers of melatonin
- Some recent interest in maternal melatonin and effect on fetus
- Melatonin follows the circadian rhythm
- If given is at very high doses so if it works for a short time then it doesn't may need to stop and restart
- REMEMBER bright light in morning and dim light in evening
Pain

- Prevalence: Unknown but in some developmental disorders with ASD up to 80% of behavioural presentations with pain

- **VARIES in all people** as to how people interpret Pain

- **Change** in demeanour

- More or less Irritable

- Quieter or louder

- Moving more or less

- Wearing clothes differently

- Letting you touch in some places but not others

- Eating patterns changing

- Sleep changing
How do we know

- They tell us
- Pain scales
- Observation of protection of limb etc
- Facial features - FLACC scale
Pain

• What might it be?
• Gastro-oesophageal Reflux (C Oliver et al)
• Fractures
• Gut pain
• Headaches/ migraines
• Leg pains
• Hip pains
• Teeth
• Ears
“A few of our favorite things”