BTS Guideline for diagnosing and monitoring paediatric sleep disordered breathing

Online Appendix 10 Question 10 Evidence Review and Protocol

Q10 For children with daytime sleepiness and normal cardiorespiratory sleep studies, what characteristics are associated with a diagnosis of narcolepsy?

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Question Evidence Review

Q10 For children and young people with daytime sleepiness and normal cardiorespiratory sleep studies, what characteristics are associated with a diagnosis of narcolepsy?

Background

Narcolepsy is a chronic and lifelong neurological disorder characterised by excessive daytime sleepiness, cataplexy and other dissociations of rapid eye movement (REM) sleep, but a diagnosis of narcolepsy is often not clinically clear and there are many causes of sleepiness, especially in adolescents. The multiple sleep latency test (MSLT) consists of five scheduled naps separated by 2-hour intervals across the day. Sleep latency and REM latency are recorded, yielding a quantitative measure of sleep propensity as well as detecting sleep-onset REM episodes. Currently, polysomnography (PSG) and MSLT are necessary to confirm a diagnosis of narcolepsy, and rule out a diagnosis of sleep disordered breathing (SDB), but these are not readily available within the UK. Cardiorespiratory sleep studies (CRSS) can exclude a diagnosis of SDB, so this review will explore if there are clinical features that can confirm a diagnosis of narcolepsy when SDB has been ruled out.

Outcome

Diagnosis of narcolepsy

Evidence Review

The literature search identified 45 papers, but only one retrospective case series investigated the characteristic of narcolepsy in children.[1]

Sleep attacks

Sleep attacks (sudden sleep episodes that occur during any activity at any time of day) occur when an individual falls asleep suddenly, without warning, and are commonly associated with narcolepsy. Challamel et al. reported sleep attacks in 97% of their cohort of children with a diagnosis of narcolepsy (75/77 children) (Table 10a).[1]

Table 10a: Summary of narcolepsy characteristics in children

Study	**Characteristic**	**No. of cases** (%)
Challamel 1994[1]	Sleep attacks	75 / 77 (97%)
	Co-existent cataplexy	62 / 77 (81%)
	Cataplexy - initial presenting symptom	7 / 77 (9%)
	Hypnagogic and hypnopompic hallucinations	30 / 77 (39%)
	Sleep paralysis	22 / 77 (29%)

Sleeping in unusual situations

No study reported on sleeping in unusual situations.

Co-existent cataplexy

Cataplexy in children can manifest as various motor phenomena and may be subtle. Patients may appear floppy with an altered gait and typical “cataplectic facies”, comprising facial hypotonia, bilateral ptosis, mouth opening and tongue protrusion. These signs may be present continually, particularly close to disease onset, and are enhanced by emotional stimulation, including laughter, anger and frustration. Some patients may attempt to compensate, presenting with unusual movements or postures such as eyebrow raising, facial grimacing and neck hyperextension. The Challamel et al. study reported that cataplexy was present in 80.5%

of cases of primary narcolepsy (62/77 children); and was the initial presenting symptom in 9% of cases (7/77 children) (Table 10a).[1]

Hypnagogic and hypnopompic hallucinations and sleep paralysis

Sleep paralysis (SP) is the inability to move or speak immediately on awakening, or just before falling asleep and episodes resolve themselves after a few minutes. Hypnagogic and hypnopompic hallucinations (HH) comprise visual, auditory, tactile or other sensory events that occur when falling asleep and on awakening respectively. Challamel et al. reported on HH and SP, with 39% of their cohort (30/77 children) having HH and 29% having SP (22/77 children) (Table 10a).[1]

Though these phenomena may also occur in otherwise healthy individuals, the presence of both SP and HH in the context of excessive daytime sleepiness should arouse some clinical suspicion.

Evidence Statements

There is very limited evidence supporting this review.

Cataplexy is present in the majority of children at the onset of narcolepsy, however its manifestations may be subtle and narcolepsy may be present without cataplexy (**Ungraded**)

Hypnagogic and hypnopompic hallucinations and sleep paralysis are much more common in children with narcolepsy than in the general population (**Ungraded**)

Although sleep attacks are strongly associated with a diagnosis of narcolepsy in children, they are not specific to the disorder of narcolepsy (**Ungraded**)

Recommendations

- If sleep disordered breathing is excluded, or effectively treated, and excessive daytime sleepiness (EDS) persists, other diagnoses including narcolepsy, with possible coexistent cataplexy, sleep paralysis, hypnagogic and hypnopompic hallucinations and circadian rhythm disorders should be considered (**Conditional** – by consensus)
- As cataplexy may be subtle, both child and parents/carers should be asked about head nods, neck/shoulder posturing and eyelid/facial droop. These are typically associated with laughter but may also be associated with anger or frustration (**Conditional** – by consensus)
- Both child and parents/carers should be asked about sleep paralysis, hypnagogic and hypnopompic hallucinations (**Conditional** – by consensus)
- Both child and parents/carers should be asked about sleep onset and wake up times to elicit total sleep time and sleep latency to exclude a circadian rhythm disorder (that can be associated with EDS) (**Conditional** – by consensus)

Good Practice Points

- ✓ An awareness of rare conditions in children, which may primarily present with excessive daytime sleepiness, should always be maintained
- ✓ As the associated symptoms of narcolepsy may be subtle or may not be volunteered, directed questions in the clinical history should be used to elicit a possible diagnosis of narcolepsy in children and initiate referral to a specialist paediatric sleep service for specialist assessment and investigation. Current standard of diagnostic investigation is a one-week period (minimum, preferably two weeks) of actigraphy with polysomnography (PSG) and multiple sleep latency testing (MSLT). These investigations should be performed in line with AASM/ESRS guidance[2,3]
- ✓ Children with narcolepsy should be under the care of a clinician with special expertise in the management of narcolepsy. This may be a paediatric neurologist or a sleep physician, depending on local service arrangements

Research Recommendations

- Further research is needed into the incidence and prevalence of narcolepsy in children
- Research is needed into the co-existence of obstructive sleep apnoea (OSA) and narcolepsy in children

References

1. Challamel MJ, Mazzola ME, Nevsimalova S, Cannard C, Louis J, Revol M. Narcolepsy in children. *Sleep.* 1994;17(8 SUPPL.):S17-S20.
2. Smith MT, McCrae CS, Cheung J, et al. Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med.* 2018;14:1209-1230.
3. Bassetti CLA, Kallweit U, Vignatelli L, et al. European guideline and expert statements on the management of narcolepsy in adults and children. *Eur J Neurol.* 2021;28:2815-2830.

Question Protocol

Field	Content
Review Question	For children with daytime sleepiness and normal cardiorespiratory sleep studies, what characteristics are associated with a diagnosis of narcolepsy?
Type of review question	Prognostic review
Objective of the review	Currently the received wisdom is that full polysomnography (PSG) along with multiple sleep latency testing (MSLT) is necessary for a firm diagnosis of narcolepsy. This is necessary both to confirm features of sleepiness and abnormal sleep architecture and to rule out another cause of which the commonest is sleep disordered breathing (SDB). A CRSS can rule out SDB and so this question aims to explore whether there are clinical features that can confirm a diagnosis of narcolepsy when SDB has been ruled out. The recommendations should provide guidance on which clinical features are the key ones associated with narcolepsy in a child with sleepiness that is not due to SDB.
Eligibility criteria – population / disease / condition / issue / domain	Children (<17 years) with daytime sleepiness and normal CRSS
Eligibility criteria – exposure(s)	Sleep attacks Sleeping in unusual situations Co-existent cataplexy Hypnagogic hallucinations Sleep paralysis
Eligibility criteria – reference(s)	No sleep attacks No sleeping in unusual situations No co-existent cataplexy No hypnagogic hallucinations No sleep paralysis
Outcomes and prioritisation	Diagnosis of narcolepsy
Eligibility criteria – study design	Case series Superiority studies

Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but **DO NOT** use in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	Children <2 years Children 2-16 years
Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus

Methodology will depend on data type. If sensitivity / specificity data, follow as below, if tabulated data, use a narrative approach and further instruction will be given

Data management (software)	RevMan5	Pairwise meta-analyses (if data in the correct format) Evidence review/considered judgement. Storing Guideline text, tables, figures, etc.
	Gradeprofiler	Quality of evidence assessment
	Gradepro	Recommendations
Information sources – databases and dates	MEDLINE, Embase, PubMED, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews No date restriction	
Methods for assessing bias at outcome / study level	RevMan5 prognostic review template (follow instructions in '*BTS Guideline Process Handbook – Prognostic Review (May 2019)'*)	
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (if data appropriate) Contact BTS to discuss best method for combining data if not suitable for meta-analysis (follow instructions in '*BTS Guideline Process Handbook – Prognostic Review (May 2019)'*)	
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler	Intervention review quality of evidence assessment for each outcome
	(follow instructions in '*BTS Guideline Process Handbook – Prognostic Review (May 2019)'*)	

Rationale / context – what is known	The diagnosis of narcolepsy is often not clinically clear and there are many causes of sleepiness especially in adolescents. The full investigation package of polysomnography (PSG) and multiple sleep latency tests (MSLT) is not readily available.