

# Narcolepsy in children

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# Introduction

- Symptoms in childhood narcolepsy can differ from adults → lead to **misinterpretations and misdiagnosis** (e.g. epilepsy x cataplexy)
- Retrospective studies have shown that about 50% of adults with narcolepsy had the onset of symptoms in youth, **many patients remain undiagnosed** (*Morish et al. Sleep Med 2004*)
- Data on the incidence and **prevalence** of pediatric narcolepsy **is not available**
- The occurrence of **cataplexy** varies → 60-75 %, hypnagogic/hypnopompic **hallucinations** 39-50%, **sleep paralysis** 29-60%, **automatic behavior** → ≥ 50% (*Nevsimalova et al. Eur J Paed Neurol 2011*)
- **Disrupted nocturnal sleep** → 80-90% (*Serra et al. Mov Dis 2008*)

# Specific clinical features (1)

## Excessive daytime sleepiness

- sleep attacks have **longer duration**
- children are sleepy during lessons at school, returning home their naps may last up to **2-3 hours** without being restorative
- confusional arousals with features of **sleep drunkenness** may be present (*Nevsimalova Sleep Med Rev 2009*)



# Specific clinical features (2)

## Cataplexy

- **cataplectic face** with repetitive mouth opening, tongue protrusion and drooping eyelids. Semipermanent state of facial muscle weakness can be mistaken for sleepiness (*Serra et al. Mov Dis 2008*)
- duration of a single cataplectic episode may last only several seconds. A complex array of “**negative**” (hypotonia) and “**active**” **phenomena** (myoclonic, dyskinetic jerks) (*Plazzi et al. Brain 2011*)



# Specific clinical features (3)

- **Hypnagogic hallucinations** - dream-like experience during falling asleep (hypnagogic) or during awakening (hypnopompic), in kids → frequently simple forms (colored circles, images of animals or people). Emotional content is rare (*Droogleever-Fortuyn et al. Sleep, 2009*)

1. Visual
2. Auditory
3. Tactile

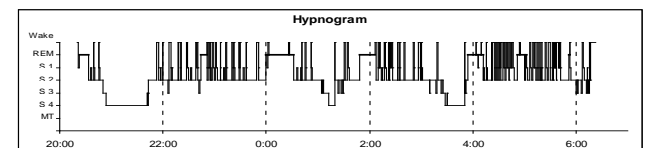
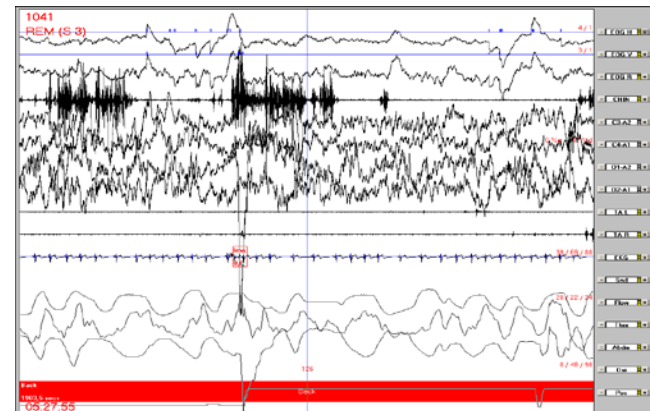
- **Sleep paralysis** – transient inability to move when falling asleep or waking up, duration from a few seconds to several minutes → in young children difficulty to recognize (*Peterson & Husain Brain Dev 2008*)



# Nocturnal sleep

- **Disrupted sleep** with vivid dreams and often **nightmares** accompanies narcoleptic patients from childhood through adulthood to old age (*Pisko et al. Sleep Med 2014*)
- **REM behavior disorder** can be rarely recognized as one of the first clinical symptoms (*Nevsimalova et al. Sleep Med 2007*)

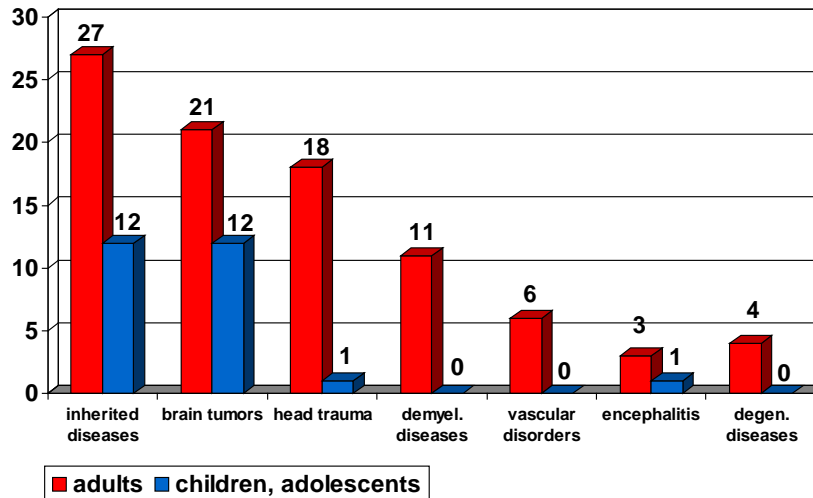
Video 1



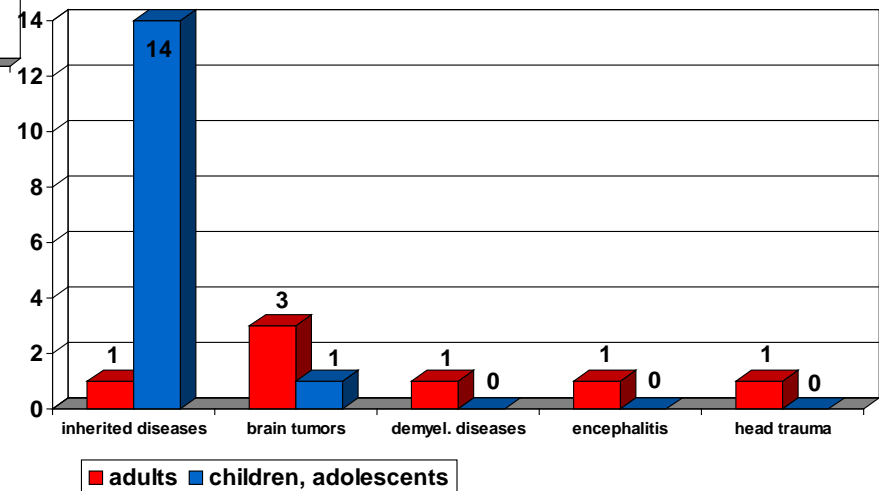
# Further specific features

- **Personality and behavioral changes:** introversion, feelings of inferiority, sorrowfulness, emotional lability, irritability or even aggressiveness, higher rates of **depression**, poor quality of life (*Inocente et al. CNS Neurosci Ther 2014*)
- **Obesity** occurs in at least 25% of all narcoleptic children, it occurs despite lower caloric intake, the mechanism is not clear. Although they eat less than healthy subjects, they tend to be overweight (*Inocente et al. CNS Neurosci Ther 2013*)
- **Precocious puberty** can arise in close temporal association with obesity, the association reflects a hypothalamic dysfunction (*Poli et al. Sleep 2013*)

# Secondary (symptomatic) narcolepsy-cataplexy



Symptomatic (isolated) cataplexy and/or cataplexy-like attacks (7 adults, 15 children and adolescents, total 22 cases)

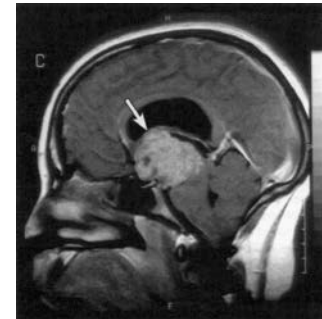


Symptomatic narcolepsy (90 adults, 26 children and adolescents, total 116 cases)



# Secondary (symptomatic) narcolepsy-cataplexy

- The most frequent **structural abnormalities** include brain tumors particularly in the suprasellar region, predominantly **craniopharyngiomas**.
- **Niemann-Pick disease type C** prevails among genetic diseases



Careful history, neurological examination and neuroimaging methods (CT, MRI) should clarify the secondary etiology, in specific cases, genetic analysis should be added



# Diagnostic evaluation

Diagnostic symptoms are usually less typical in young children:

- **Daytime sleepiness** may be difficult to recognize in early childhood, children can be mistaken as hyperactive, learning disabled, inattentive and lazy and with consequences of severe psychosocial and social problems
- **Cataplexy** in young age may be overlooked, disregarded as clumsiness or misdiagnosed as epileptic attacks
- Young children are unable to explain their feelings during **sleep paralysis** and/or **hypnagogic hallucinations**
- Diagnostic criteria for toddlers and preschool children based on **sleep studies** are not available, nor are the criteria of MSLT-based mean latency for early school children.

*Nevsimalova Cur Neurol Neurosci Report, in press*

# Subjective evaluation of sleepiness and cataplexy

## ■ Excessive daytime sleepiness

Pediatric Daytime Sleepiness Scale (PDSS) for preschool children and early school children (*Drake et al. Sleep 2003*)

Adapted Epworth Sleepiness Score (AESS) falling asleep in car x falling asleep at school (*Snow et al. Pediatrics 2002*)

## ■ Cataplexy

Childhood Severity Rating Score (CSRS)

Score 1 = moderate weakness, e.g. head drop or jaw opening; 2 = can maintain posture with external support; 3 = loses posture and falls to the ground (*Murali & Kotagal Sleep 2006*)

# Screening methods

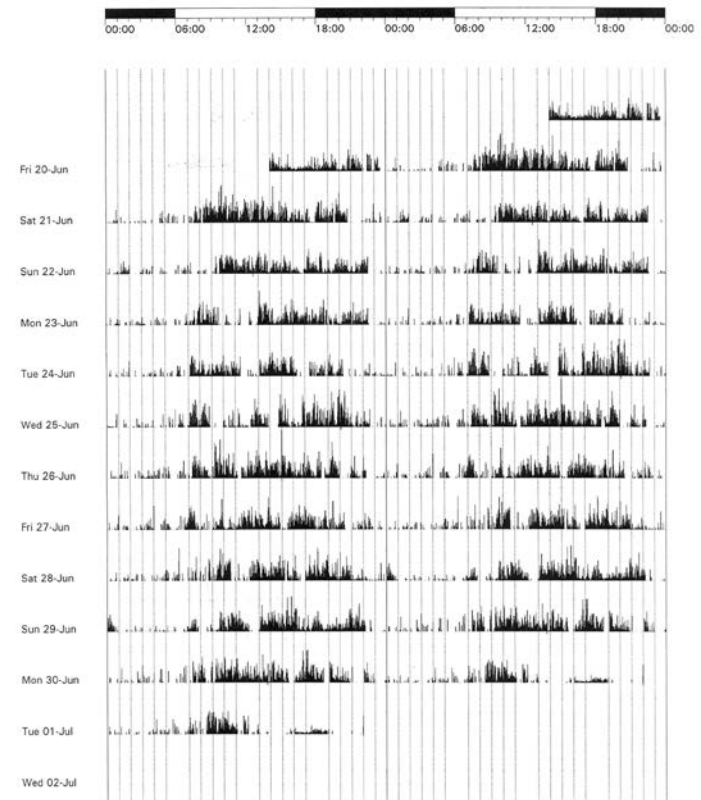
- **Sleep diary**

Filled-in by children and/or in younger ones completed by their parents

- **Actigraphy**

The method is based on quantitative recording of motor activity equating with sleep and wake states.

Owing to longer duration of sleep attacks children → better applicable in younger x older children or adults



# 24h ambulatory PSG monitoring



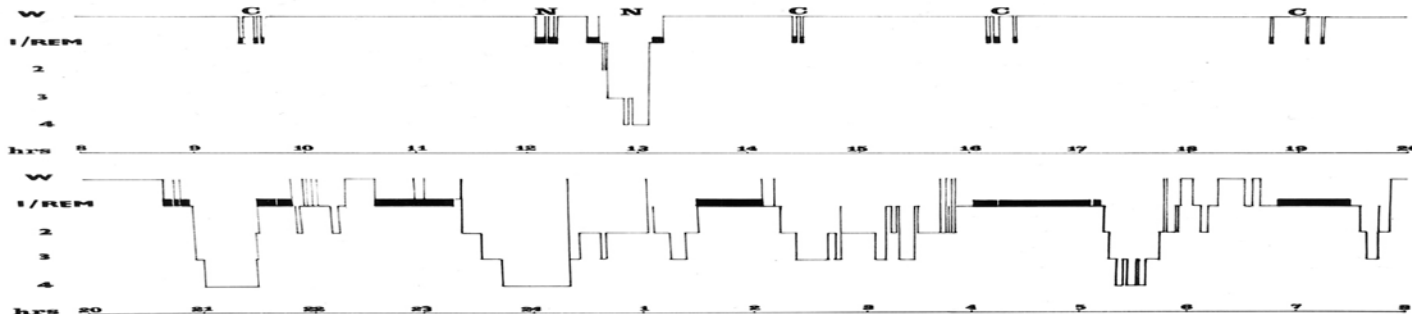
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ARTICLES

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## A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains

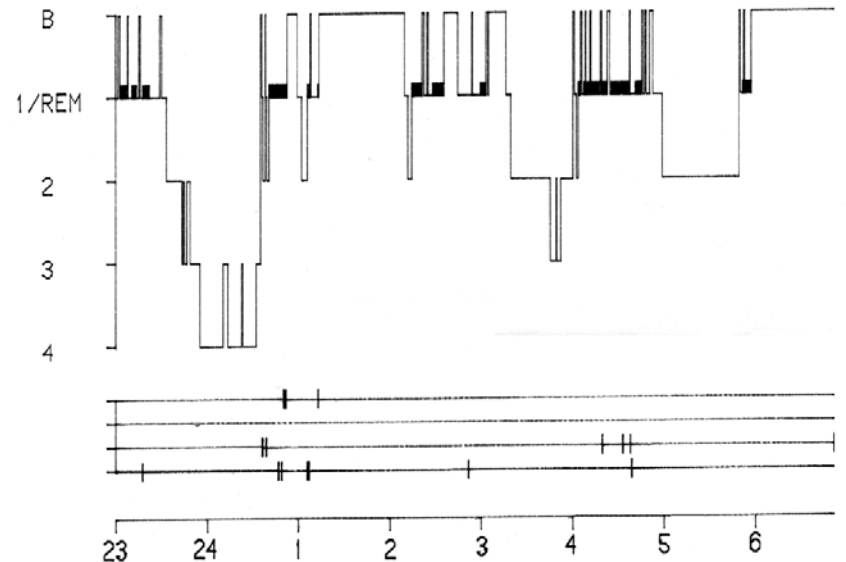
CHRISTELLE PEYRON<sup>1</sup>, JULIETTE FARACO<sup>1</sup>, WILLIAM ROGERS<sup>1</sup>, BETH RIPLEY<sup>1</sup>, SEBASTIAAN OVEREEM<sup>1,2</sup>,  
YVES CHARNAY<sup>3</sup>, SONA NEVSIMALOVA<sup>4</sup>, MICHAEL ALDRICH<sup>5</sup>, DAVID REYNOLDS<sup>5</sup>, ROGER ALBIN<sup>5</sup>,  
ROBIN LI<sup>1</sup>, MARCEL HUNGS<sup>1</sup>, MARIO PEDRAZZOLI<sup>1</sup>, MURALIDHARA PADIGARU<sup>6</sup>,  
MELANIE KUCHERLAPATI<sup>6</sup>, JUN FAN<sup>7</sup>, RICHARD MAKI<sup>7</sup>, GERT JAN LAMMERS<sup>2</sup>, CONSTANTIN BOURAS<sup>3</sup>,  
RAJU KUCHERLAPATI<sup>6</sup>, SEIJI NISHINO<sup>1</sup>, & EMMANUEL MIGNOT<sup>1</sup>



# Video-polysomnography (v-PSG)

Interrupted sleep,  
SOREMs, vivid dreams

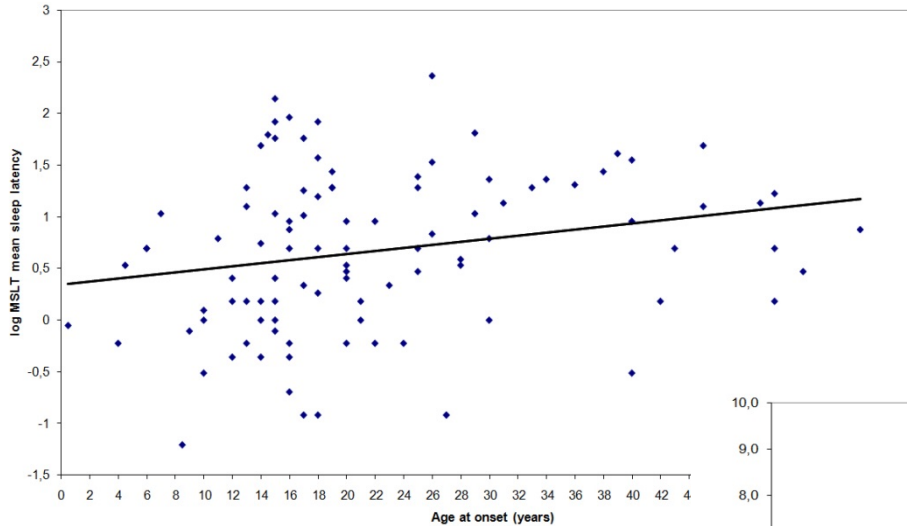
Sleep comorbidities:  
OSA, RBD, PLMs, RLS



Hodiny

# Multiple sleep latency test (MSLT)

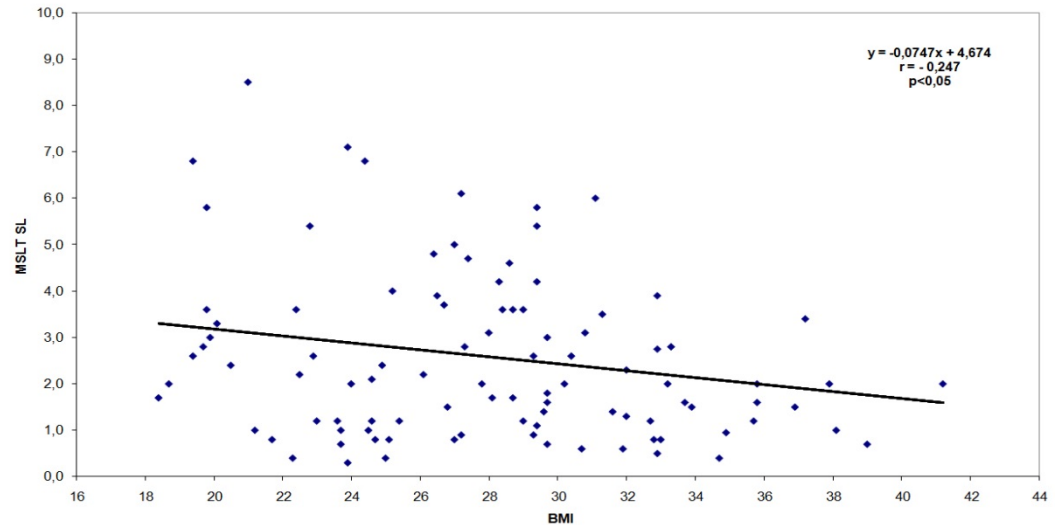
Correlation between age at onset and MSLT



5 tests at 2-hr interval

$\leq 8$  min,  $2 \geq$  SOREMs

Correlation between Body Mass Index (BMI) and MSLT sleep latency



# Human leukocyte antigen (HLA)

Parameters	Advantages	Disadvantages	Suggested indications
HLA typing <b>DQB1*06:02 +</b>	Highly specific and sensitive in cases with cataplexy  In cases without cataplexy – a possible indicator of later cataplexy development	Low specificity  Low sensitivity in cases without cataplexy	A positive finding can support diagnosis in early stages of the disease  Available at any age including infants and toddlers



# Cerebrospinal fluid (CSF) Hcrt-1 evaluation

Parameters	Advantages	Disadvantages	Indications
<p>CSF Hcrt-1 measurement</p> <p><b>Direct assay</b> <b>&lt; 110 pg/ml</b></p>	<p>Highly specific and sensitive in cases with cataplexy</p> <p>In cases without cataplexy – a possible indicator of future cataplexy development</p>	<p>Invasive and painful examination</p> <p>Method needs to be standardized at specific centers</p> <p>Low sensitivity in cases without cataplexy</p>	<p>Infants, toddlers and pre-school children as well as school children and adolescents</p>

# Narcolepsy without cataplexy (Nw/oC) and Hcrt-1 deficit

## Prognostic value of Hcrt-1 deficit:

171 patients Nw/oC and 170 controls:

Hcrt-1 deficiency → 41 patients → 30 reevaluated, in 10 of them cataplexy appeared with mean latency of 10 years

None of the patients with normal Hcrt-1 level manifested cataplexy



**Hcrt-1 deficit** - 33% sensitive, **99% specific**

*Andauler et al. Sleep 2013*

**Case report:** a boy, 16 years old:

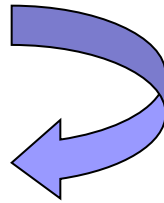
EDS from preschool age, sporadic h.h., sleep paralysis, no obvious cataplexy

At 6 years – HLA-DQB1\*06:02+, MSLT +, Hcrt-1 undetectable

At 13-14 years his weight increased (20 kg), cataplexy appeared

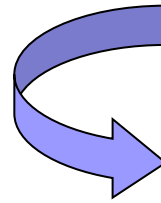
# International classification of sleep disorders ICSD-3 (2014)

Narcolepsy type 1



with Hcrt-1 deficit

Narcolepsy type 2



normal Hcrt-1 level

## **Disadvantage of new classification in children:**

Lumbar puncture: semiinvasive examination in children

Hcrt-1 examination in CSF available only in selected biochemical laboratories

Why should typical cataplexy and positive MSLT criteria be insufficient?

# Recommendation of age-distributed diagnostic tools

## Subjective

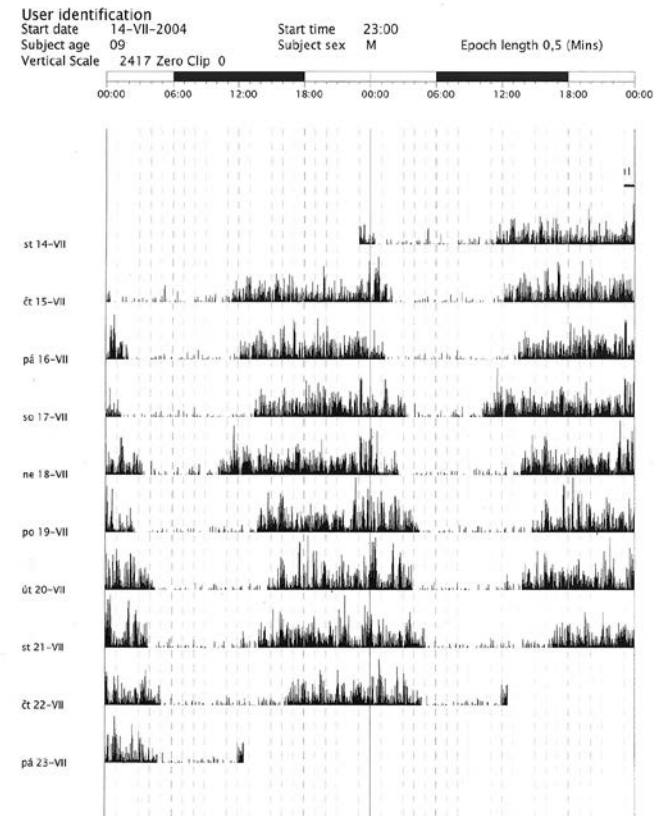
- **Sleep diary:**  
the whole age spectrum
- **Pediatric Daytime Sleepiness Scale:**  
preschool and school children
- **Adapted Epworth Sleepiness Scale:**  
predominantly adolescents
- **Cataplexy Severity Rating Score:**  
the whole age spectrum

## Objective

- **Actigraphy:**  
toddlers and preschool children
- **24-hour PSG:**  
toddlers and preschool children
- **Overnight PSG followed by MSLT:**  
school children and adolescents
- **HLA typing:**  
the whole age spectrum
- **Hcrt-1 estimation:**  
the whole age spectrum

# Differential diagnosis

- Excessive daytime sleepiness:
  - idiopathic hypersomnia
  - sleep related breathing disorder
  - sleep delay phase
  - periodic leg movement disorder
- Cataplexy:
  - epileptic seizures
  - pseudocataplexy
- Hypnagogic hallucinations:
  - schizophrenia



# Treatment and management

- **Non-pharmacological treatment:**

repeated naps during the day (at least 2 planned naps at lunchtime (1-2 p.m.) and during afternoon (4-5 p.m.)

after school and sports physical activities

monitoring emotional problems and depression

avoidance of alcohol, driving, dangerous activities

- **Pharmacological therapy:**

↓ sleepiness and cataplectic attacks



**Treatment generally used in adults is mostly off-label in childhood**

# Treatment experience ↓ sleepiness

- Modafinil (100-400 mg)\*  
school children and adolescents
- Armodafinil (50-400 mg)\*  
school children and adolescents
- Methylphenidate (10-30 mg)  
school children and adolescents
- Atomoxetine (10-25 mg)  
school children and adolescents
- Sodium oxybate (2-8 g)\*  
the whole age spectrum

\* = off label medication in children according to EMA and FDA rules

# Treatment experience ↓ cataplexy

- Sodium oxybate (2-8 g)\*  
the whole age spectrum
- Venlafaxine (75-150 mg)\*  
school children and adolescents
- Fluoxetine (10-40 mg)\*  
school children and adolescents
- Clomipramine (25-75 mg)\*  
school children and adolescents
- Imipramine (25-75 mg) \*  
school children and adolescents

\* = off label medication in children according to EMA and FDA rules



# Conclusion



Our attention should be focused on:

- **Improvement of diagnosis** – necessity to apply to appropriate criteria for different child age
- **Treatment** – urgent need to establish adequate therapy → controlled multicentric clinical trials are needed to verify that effective treatment of adults (particularly modafinil and sodium oxybate) is safe and beneficial in children, too
- **Psychological support** – not only from medical professions (pediatric neurologists or psychiatrists), but also from teachers, psychologists, patients' organizations, ↑ information in the media...)
- The aim is to **improve the quality of life** (depression !)