Kleine-Levin syndrome
Update in 2015

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Outlines

• Changes in KLS diagnosis criteria
• Differential diagnosis
• Long episodes
• Brain functional imaging
• Long term cognitive functioning
• Treatments
KLS: ICSD-3 criteria

- ≥2 recurrent episodes of excessive sleepiness of 2 days to 5 weeks duration
- Episodes recur usually >1/y, and at least 1/18 months
- Normal alertness, cognitive function, behavior and mood between episodes
- ≥ 1 feature during episodes:
  - cognitive dysfunction
  - altered perception (derealisation)
  - eating disorder (anorexia or hyperphagia)
  - disinhibited behavior (such as hypersexuality)
ICSD- 2R

Recurrent hypersomnia

No other symptom → KLS

Menstrual-related hypersomnia

ICSD- 3

KLS

Menstrual-related hypersomnia = variant of KLS
Clinical features from the French cohort

Mean age: 22 ± 9 years
Male sex: 64%
Patients referred for suspected KLS
n=166

Other diagnoses
n=29

Atypical KLS
n=7

Typical KLS
n=130

Secondary KLS
n=4

Primary KLS
n=126

Continuous symptoms
n=10

Discontinuous symptoms
n=19

Incomplete data
n=6

Investigated patients
n=120

Lavault, Ann Neurol 2015
Continuous symptoms (n=10)

Symptoms

- Hypersomnia
- Disinhibited behavior
  - Megaphagia + hypersomnia
  - Megaphagia + sexual disinhibition

Diagnosis

- Idiopathic hypersomnia, n=4
- Idiopathic hypersomnia with fluctuations in sleep duration, n=1
- Idiopathic hypersomnia + single acute delusional episode, n=1
- Juvenile fronto-temporal dementia, n=1
- Attention deficit/hyperactivity disorder, n=1
- Hypothalamic hemorrhage, n=1
- Klüver-Bucy syndrome, n=1
Episodic symptoms (n=19)

- Brief (<24h) pseudo-confusional episodes + regressive behavior → Somatoform disorder, n=2
- Brief (<24h) episodes of hypersomnia + confusion → Recurrent stupor (unknown cause), n=2
- Brief (<48h) episodes of hypersomnia + headaches → Basilar migraine, n=1
- Brief (<48h) episodes of hypersomnia + confusion → Hidden alcoholic intake, n=1
- Recurrent zolpidem abuse, n=1
- Intermittent neuroleptic intake, n=1
- Short (1-3 days) episodes of hypersomnia + confusion + behavioral disturbances → Temporal lobe epilepsy, n=1
- Hyper-ammonemic encephalopathy (unknown cause), n=1
- Episodes (2-10 days) of hypersomnia + mood disorders → Psychiatric hypersomnia, n=4
- Recurrent sleepiness + anxiety → Anxiety disorder, n=1
- Recurrent sleepiness + weird contact → Malingering or personality disorder, n=3
- Recurrent sleepiness + muscle pain + tropical origin → Suspected parasitosis, n=1
3 per million
Guyane Française (n=1), Angleterre (n=3), Suisse (n=2), Allemagne (n=1), Pays-bas (n=1)
Symptoms during at least one episode

- Hypersomnia
- Cognitive impairment
- Derealisation
- Apathy
- Social disinhibition
- Depressed mood
- Megaphagia
- Hallucination/delusion
- Hypersexuality
Apathy
Apathy

Box « apathy » ticked by 54% patients in Stanford Survey
But face to face interview and clarification indicate that it is present in 100% patients
Derealization: almost 100% of patients
Stanford series, Paris series

- “Dreamlike” 87%
  - Feeling of being in a dream, in a bubble
  - Feeling unreal – derealization-mind-body disconnection

- Abnormal/dulled visual, auditory, touch, taste, temperature, pain sensations

‘The shower is an horrible experience, as I can see water flowing on my body, but at the same time I don’t feel it and don’t feel its temperature’ Romary, 30 y

‘I fumble with things more. Eg- getting an utensil from drawer, opening a box or container, finding a key in the pocket.’ Jolene, 50 y.o
Long episodes (> 1 month)

• What was known before
  – Long episodes were considered as exceptional and atypical (cf ICSD-3)
Long episodes (> 1 month)

- 28% had prolonged (>30 days) episodes
- No difference of age at onset, sex, trigger, medical history with other patients
- Longer first and mean episode duration
- Longer disease course
- Less sleep but more tired during asymptomatic periods
Brain functional imaging
What was known before

- Single patients or small (2-4 patients) samples: hypoperfusion/metabolism in various cortical and subcortical area, varying from one study to another, symptomatic and asymptomatic.

- Consistent thalamic hypoperfusion in 7 patients (Huang, Sleep 2005).

- No group analysis with large samples, substraction and controls.
Visit 1: 41 KLS patients
*Asymptomatic* period

15 matched paid healthy controls

11 repeated the SPECT during *symptomatic* period

Normalization with MNI and SPM8
Group analysis

Kas, Brain 2014
Asymptomatic periods

Asymptomatic KLS n=41 vs. controls n=15

L Sup temporal gyrus

Caudate

Orbitofrontal

Thalamus

Hypothalamus
During episodes

- Asymptomatic KLS, n=41 (vs. 15 controls)
- Symptomatic vs. asymptomatic periods (n=11)

Brain regions:
- R Sup temporal
- Angular gyrus
- Mesial prefrontal
- Orbitofrontal
- Thalamus
- Hypothalamus
Right and left middle temporal perfusion (BA39)

\[ r = -0.74 \]
\[ p < 0.001 \]

\[ r = -0.59 \]
\[ p < 0.005 \]
Right middle temporal perfusion (BA39)

$r = -0.53$
$p < 0.001$

Duration of episode in days

Z scores
Conclusion

• Consistant involvement of the temporo-parietal junction => derealisation ?
• Orbitofrontal and prefrontal Cx => apathy/disinhibited behavior ?
• Thalamus/hypothalamus : cognition, sleep ?

• Abnormalities persist during asymptomatic periods
During asymptomatic periods

Probable compensation
(no symptom, mild cognitive impairment)
Episodes: decompensation of the network

During asymptomatic periods

Probable compensation (no symptom, mild cognitive impairment)
Long term cognitive impairment
What was known before

• Individual reports of occasional cognitive difficulties

• A single series of 8-18 patients (Engstrom, Sleep 2009, 2014): altered working memory, use different networks in fMRI

• In our patients, 50% report academic decline since KLS onset
Visit 1: 124 KLS patients had cognitives tests

42 matched healthy controls

Visit 2: 44 KLS repeated cognitives tests, 1.3 y after visit 1
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Read the written word
Stroop color word test: speed of processing

21.4% of patients are too slow

Controls
KLS visit 1
KLS visit 2

I- Words
II- Colored words
III- Color
IV- Words with wrong color

Stroop color word test: speed of processing

21.4% of patients are too slow
Figure 3 - Stroop test stimuli. Read the colour of the word aloud and not the actual word.
Stroop: attention (number of errors)
Working memory and executive functions

- Digit span forward
- Digit span backward
- TMT-B-A
- Verbal fluency, semantic
- Verbal fluency, letter
### FCSRT Verbal Memory: Immediate Free Retrieval

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- **Controls**: 38% with 32% deficient
- **KLS Visit 1**: 38% with 40% deficient
- **KLS Visit 2**: 38% with 40% deficient
• Long term verbal memory: intact
• Visual abilities: intact
• Visual memory: intact
Determinant of long term impairment in immediate memory

- Higher episode frequency (5.3 vs 3.4/y)
- More recent episode (48 vs. 197 d)
- Shorter episode duration (9 vs 18 d)
- During episode: more difficult to awake, more dreaming and more megaphagia
Conclusion

• Long term cognitive impairment
  – Attention: the problem disappears with time
  – Speed of processing: mild, stable impairment in 21%
  – Retrieval deficit: 40%,
  – No visuospatial problems, no impact on long term memory

• Cognitive function should be regularly assessed

• => Cognitive remediation and academic support
Treatment in KLS
What was known

• Individual trials of lithium, Dr’s report (Arnulf, Brain 2005):
  – complete benefit in 41%,
  – partial in 26%

• Individual trials of lithium, patients’ report (Arnulf, Ann Neurol 2008)
  – Complete benefit 7%
  – Partial benefit 17%

=> No idea of lithium serum levels, compliance
=> No series
Methods

• Among 131 patients in Paris
  – 71 received and took lithium (serum levels of 0.8-1.2 mmol/L)
  – 49 took nothing
  – 10 took valproate or contraceptive pill
• We compared the frequency and duration of episodes
  – before treatment/abstention (mean 5 years)
  – vs. after a mean 2 years of follow-up
Frequency of episodes per year

Lithium

Nothing

Visit 1
Visit 2

Leu, Neurology 2015
Side-effects of lithium

- Tremor: 37%
- Polyuria-polydypsia: 23%
- Diarrhoea: 14%
- TSH increase: 11%
- Weight increase: 7%
- Acne: 6%
- Anxiety: 4%
- Creatinin increase: 1%
- Other: 1%

Leu, Neurology 2015
Lithium therapy

- Complete responders: 36.6%
- Partial responders: 51%
- Non responders: 12.4%
- 9.8% had « mini-episodes » (1 day) on lithium
- 13 patients had an episode after stopping lithium 2 consecutive nights
- Level IV evidence of benefit in KLS
- Lithium : 1 month less in episode per year
- The level should be high and monitored
Other preventive strategies

• Wash hand (avoid virus and bacteria)
• No alcohol ++, especially not in combination with sleep deprivation
During episodes

• Leave at home, quiet and safe, do not disturb
• No benefit of amantadine
Conclusion: large series of KLS patients

- Episodes >30 days: 1/4 patients
- Long term hypoperfusion: meso-temporal, temporo-parietal junction +, orbito-frontal cortex, thalamus and hypothalamus
- Long term cognitive impairment: speed of processing, episodic verbal memory (retrieval)
- Open, large, controlled study: Lithium therapy decreases the episode frequency and duration (-1 month incapacitated /year)
Research agenda

• Multimodal 3T-MRI in KLS in 20 patients/20 controls: in analysis

• Genetics: 5 French KLS multiplex families (11 patients, mostly horizontal): 5.8% of familial cases. Merged with Stanford cohort (total 21 familial cases/267 sporadic cases, for identifying particular features + exome sequencing

• Long term psychiatric problems: in preparation
Thanks to

• Grant PHRC 2007-2011
• KLS Foundation
• French Sleep Society (SFRMS)