The Kleine-Levin syndrome

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Outlines

- Very rare neurological disease
- Mostly teenagers
- Relapsing-remitting: episodes with hypersomnia plus cognitive and behavioral symptoms
- Cause: unknown, MRI and CSF are normal
- Tests: EEG and functional imaging: often abnormal, sleep study not very contributive
- Course : usually disappears in the thirties
- Treatment: not codified. Mostly lithium and valproate

KLS definition - ICSD 3 (2013)

A. At least 2 recurrent episodes of excessive sleepiness of 2 days to several weeks duration

B- Episodes recur usually >1/y (at least 1/18 months)

C- Normal alertness, cognitive function, behavior and mood between episodes

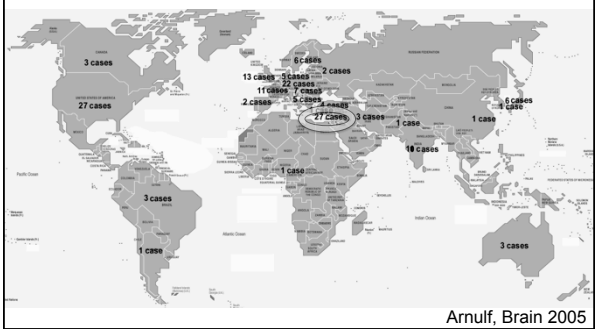
D- At least one of the following during episodes:

- cognitive dysfunction
- altered perception, derealisation
- eating disorder (anorexia or hyperphagia)
- disinhibited behavior (such as hypersexuality)

E- symptoms not better explained by other disorders

2004

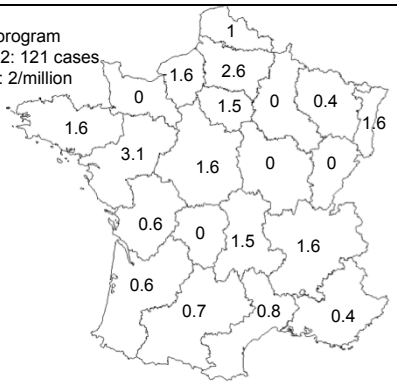
168 patients with primary KLS



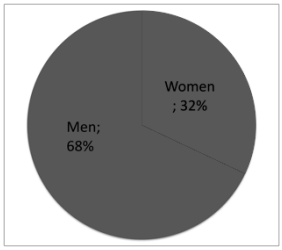
Arnulf, Brain 2005

Where were you at time of your first KLS episode ?

Orphan disease program
France 2006-2012: 121 cases
State prevalence: 2/million



Sex-ratio

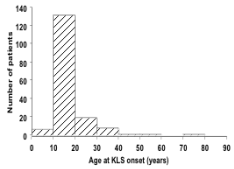


Published cases
n= 168

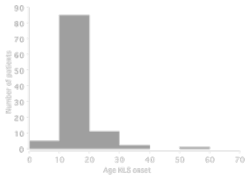
Arnulf, Brain 2005

Age at KLS onset

Litterature sample N=168

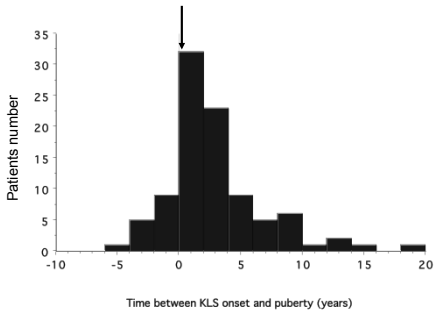


Stanford sample N=108



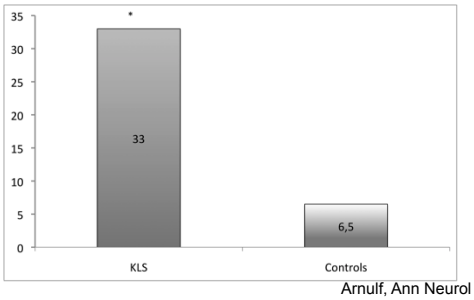
Median age at onset: 15.7 y

Puberty



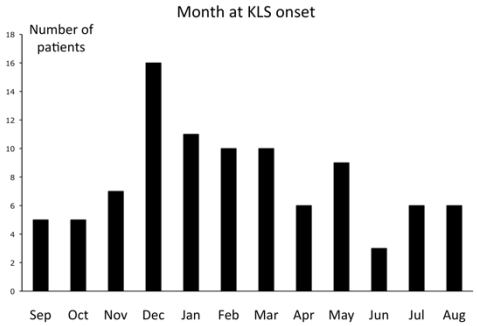
Stanford sample

Birth defect or developmental problems



Arnulf, Ann Neurol 2008

Month at KLS onset

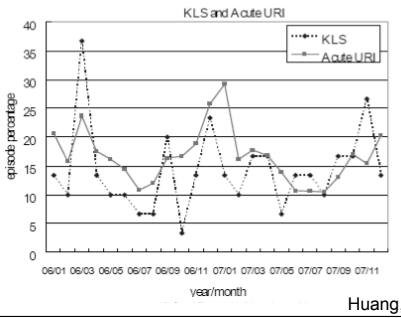


Stanford sample

	Litterature	Stanford	Paris
Event before onset	61%	72%	76%
Flu-like fever, UAW infection	25%	25%	30%
Urinary/gastro-intestinal infection	3%	4%	12%
Alcohol	3.6%	23%	25%
Sleep deprivation	1.8%	22%	
Unusual stress	1%	20%	
Physical exertion	1%	19%	60%
Head trauma	4%	9%	
Marijuana	3.4%	9%	

- Further episodes: same factors

Frequency of KLS relapses in function of upper airways infection in Taiwan



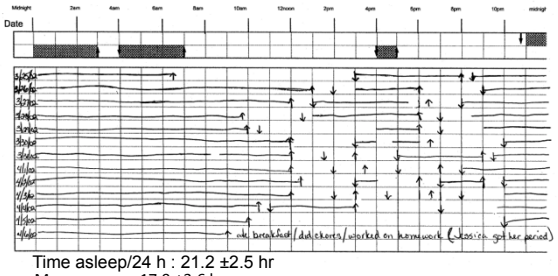
N=30

Huang, Sleep 2011

Symptoms

- Sleep symptoms (hypersomnia, end-episode insomnia)
- Cognitive symptoms (apathy, slowness, confusion/ amnesia)
- Altered perception
- Behavioral disorders
- Psychological changes
- Meningeal and autonomous symptoms

Hypersomnia



Time asleep/24 h : 21.2 ±2.5 hr
Mean: 17.9 ±3.6 hours
Max: 21.35 ±2.5 hours

Jessica, 13 y.o.

Arnulf, Ann Neurol 2008

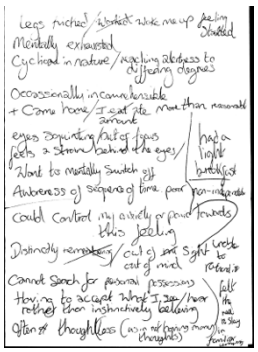
Polysomnography findings

- Many different aspects, depending on time since episode onset, and of the episodes, and on obtaining 24 h sleep monitoring
- Prolonged sleep time : TST/24 h = 701±208 min (Dauvilliers, Neurology 2002)
- Frequent sub-wakefulness rather than real sleep excess : alpha continuous rhythm
- Normal night-time sleep structure (REM sleep> SWS during the first half of the episode, SWS>REM sleep during the second half
- MSLT (if feasible):
  - 17% MSL<5 min (2 with SOREMPs)
  - 41% 5<MSL<10 min
  - 42% MSL> 10 min (Huang, Neurology 2008)

  => Sleep monitoring is neither sensitive nor specific

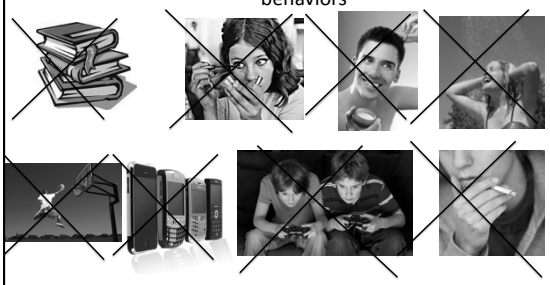
Cognitive impairment: 100% of patients

- Slow to speak and answer (94%)
- Confusion (87%), post-episode partial or complete amnesia
- Apathy



L., 21 .

Apathy: Quantitative reduction of voluntary, goal-directed behaviors



Altered perception- derealization
100% of patients

- "Dreamlike" 87%
  - Feeling of being in a dream, in a bubble
  - Feeling unreal, mind-body disconnection

- Abnormal/dulled senses

visual, auditory, touch, taste, temperature, or pain

'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

- 'Would try to do something to get a normal reaction i.e. would break a cup to see if it would break to reassure me things were normal. Also wanted to see if it would help me to snap out of it..' L., 21 y

- 'When episodes first began, John would ask me if he was dead or alive.' J, 10 y

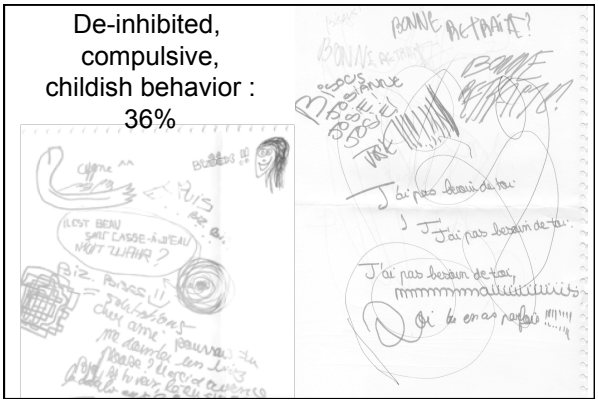
Less frequent symptoms

- Behavioral disorders
- Psychological changes
- Vegetative and meningeal symptoms

Odd, de-inhibited behaviors

- Hyperphagia in 66% (sweets), but eat less in 34%
- Sexual de-inhibition in boys (58.5%)>girls (35.6%) : masturbation in front of others, inappropriate language and sexual avances
- Irritable: 65%, frustrated, impolite
- Repetitive compulsive behaviors

De-inhibited, compulsive, childish behavior : 36%



Psychological changes

- Depression : 53% girls> boys
- Anxiety: 45 %"scared of being left alone," or afraid of novelty in their environment. "scared of going crazy and that the episode might never end"
- Delusions (megalomania, paranoid,paranoiac): 35%
- Hallucinations: 27%
- Flattened affect or on the contrary more affectionate (regressive)

Vegetative and meningeal symptoms

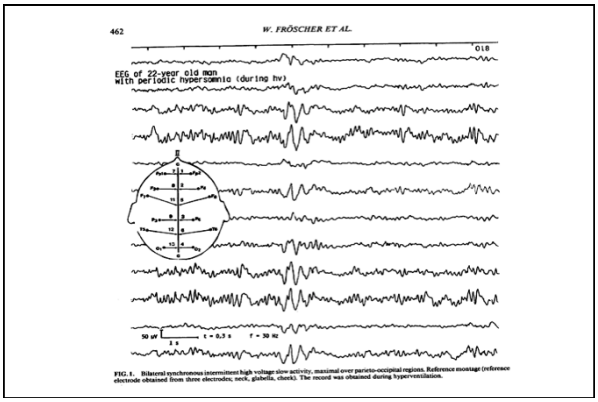
- Fever 68%
- Photophobia 59%
- Headache 48%
- Sweating 48%
- Nausea 18%

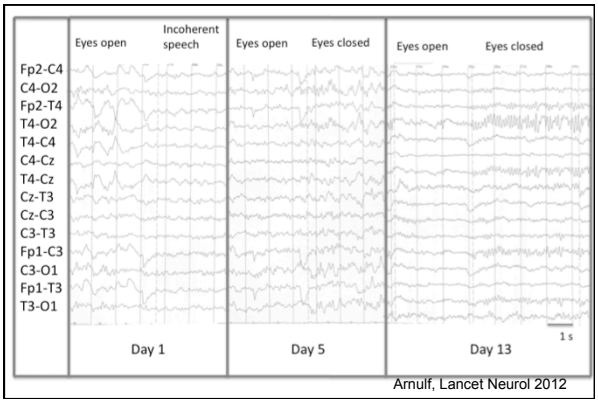
End of an episode

- After short episodes, frequent, brief overshoot with
  - Sleep: mild sleep decrease to complete sleep loss 1-3 d
  - Mood: From feeling of relief to euphoria, talk and talk
- Reaction to the episode
  - Want to check if things had happened (amnesia + dereality)
  - Ashamed
  - Depressed

Tests during episodes

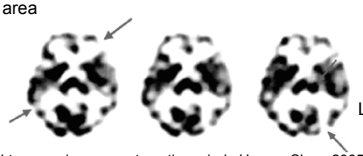
- EEG: abnormal in 70% (local or general slowing)
- SPECT or PET: hypometabolism in various area (temporal, frontal, thalamus) if compared to SPECT between episodes
- Other tests: blood, CSF, hormons, MRI: normal
- Brain autopsy in 4 patients: inflammation in ¾





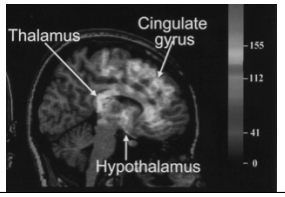
Arnulf, Lancet Neurol 2012

Brain scintigraphy: variable hypoactivity in temporal, frontal, thalamus, cingular area



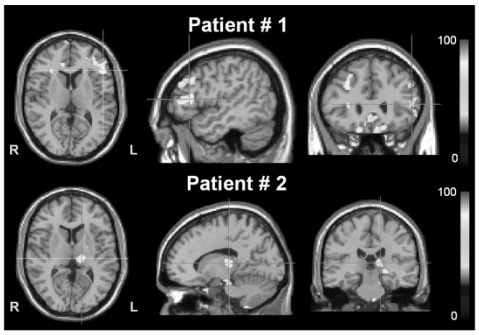
Left thalamus in 66%

Left-right comparison, symptomatic period , Huang, Sleep 2005



Symptomatic vs. asymptomatic + MRI

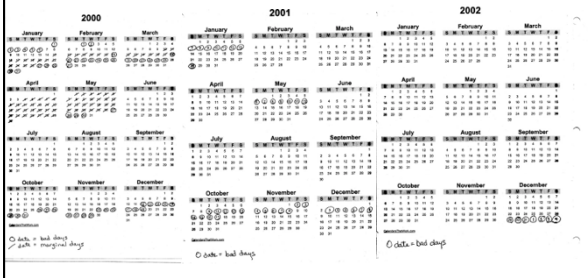
Hong, Sleep 2006



Arnulf, Lancet Neurol 2012

Disease course

Disease course



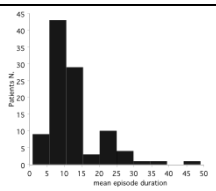
K, 15 y

During a given episode

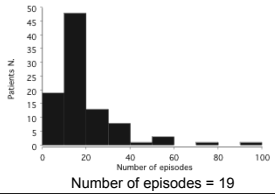
43% few h
52% few d

7-13 d

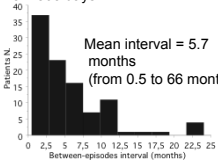
2 to xx d



Mean duration of episodes = 13 days
Max: 365 days

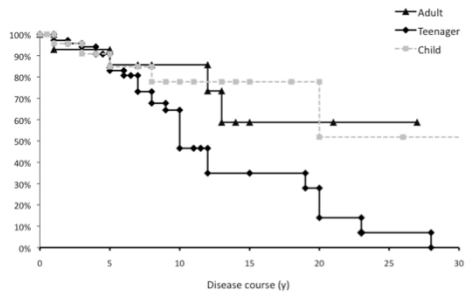


Number of episodes = 19



Mean interval = 5.7 months
(from 0.5 to 66 months)

Disease duration



Are KLS subjects totally normal between the episodes ?

Sleep symptoms between the episodes

	KLS patients	Controls
N	108	108
Night-time sleep		
Do not sleep well	17.1%	8.3%
Usual sleep latency, min	23.6 ± 25.8	18.2 ± 14.7
Usual time asleep, min	482 ± 90	465 ± 86
Restless legs syndrome	9.5%	11.6%
Sleepwalking	18.5%	18.9%
Snoring	22.9%*	11.2%
Witnessed apnea	7%*	1.4%
Daytime alertness		
Epworth sleepiness score	5.6 ± 3.9	6.1± 3.9
Hypnagogic hallucination	23.1%	26.8%
Sleep paralysis	7.4%	7.4%

Arnulf, Ann Neurol 2008

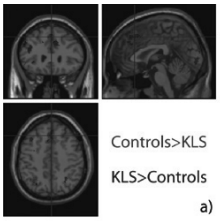
Other symptoms between the episodes

	KLS patients	Controls
N	108	108
Eating behavior		
Eating Attitude Test-26 score	5.2 ± 5.7	5.1 ± 4.7
EAT score >20	4.6%	0.9%
BMI, kg.m^2	26.1 ± 5.7*	23.3 ± 3.6
Mood and anxiety		
HADS-Anxiety score	6.1 ± 3.8*	5.1 ± 3.3
HADS-Depression score	2.7 ± 3.3	2.1 ± 2.1
Serum levels of		
Leptin (ng/mL)	8.3±11.3*[1]	5.1±7.5
C-Reactive protein (mg/mL)	2.6 ±3.8*[1]	1.2 ± 2.2

Similar BMI in patients with and without megaphagia

Asymptomatic period
Long term cognitive impairment ?

- A. Landtblom et al have first described 3 cases with subclinical impaired attention/memory



N=8 patients

fMRI during a working memory task: KLS use less the dorsomedial prefrontal and cingulate gyrus

Landtblom, Sleep 2009

Some abnormalities may persist between episodes in the brain scintigraphy

Differential diagnosis
Other intermittent disorders

- Metabolic: porphyria, OCT deficiency
- Neurology: Seizures, menstruation-linked hypersomnia, ammoniemic encephalitis, idiopathic recurrent stupor, fluctuating idiopathic hypersomnia
- Psychiatry: bipolar disorder, psychosis, generalized anxiety, non organic (nevrosis), intoxication with hypnotics, alcohol, cannabis

Cause of this recurrent inflammatory encephalitis: unknown

- Genetics: around 10 multiplex families, GWS of 380 KLS cases: negative. To be completed. Caryotype in 121 French patients: normal
- Auto-immune:
  - More HLA DQB1*0201 in KLS than in controls in a series of 30 patients (Dauvilliers, Neurology 2003)
  - No difference of HLA between 108 KLS and controls (Arnulf, Ann Neurol 2008)
  - Two trials of IvIg in French patients: negative
- Infectious: the nature of the germ at KLS onset is variable (bacteria, virus, vaccination)
- Metabolic ? Organic-aminoacid in urine, normal in 40 patients
- Abnormal brain amine metabolism (5HT-DA): 5 CSF in France: negative

Management

What we do in the reference center

- Make the diagnosis, explain it
- Evaluate the severity: frequency of episodes, duration of episodes++
- Evaluate risk factor for longer course :
  - Onset before 12 yo, after 20 yo, hypersexuality
- How is the patient between episodes ?
  - Memory: complaint, school + formal, long cognitive testing
  - Mood and psychology: no overshoot? Adjustment to disease ? No long term psychiatric problem?
  - Brain functional imaging: abnormal images correlate with median episode duration

General recommendations 1

- During the episodes, most patients
  - Are apathetic
  - Need to rest and sleep
  - Rude and exhausted if prevented to sleep
  - Fear novelty, contact with unknown people, hostility feelings
  - Ashamed to be seen by their grand parents or friends in this condition
  - Afraid of being left alone

⇒The best choice is to keep them at home (rather than in hospital), in a safe environment, asleep in a dark room, under the family supervision
⇒ Do not try to over-stimulate them (it is useless, the brain is suffering)

General recommendations 2

- During the episodes, all patients are cognitively impaired, sleepy, and have altered perception and automatic behaviors

=> Never let them drive a bike, a motorbike or a car during an episode (high risk of accident, 2 cases). Hide the key !

General recommendations 3

- During the episodes, some patients may have a decreased mood, cry, experience high frustration, feeling that the episode will never end, and that « in this case, one will die or getting mad»

⇒Check regularly their mood, hug, appease, repeat them that it will end soon (depressed mood is usually brief and frequently announces the end of the episode), that you are there. If too severe, consider using a mild benzodiazepine (Bromazepam 1/4 tablet under the tongue). If watching them is insufficient, bring them to the hospital for permanent supervision.

⇒Antidepressants seem useless at this point

General recommendations 4

- Problems that require hospitalization :
  - Major behavioral disorders (anger outburst)
  - Severe delusions => risperidone > other neuroleptics
  - Major autonomic disorders (urine retention, high blood pressure)
  - Seizures

Is there any drug helping to get out of an episode ?

- Amantadine was signaled by several patients in USA
- Experience in France was disappointing (around 80 patients tried it without benefit)

Preventing new relapses

Between episodes: General recommendation

- KLS patients have higher BMI than controls, as a mean

=> Avoid gaining weight (healthy food, exercise)

- Some KLS patients have an impairment of sustained attention between episodes

⇒Make pauses every 30-45 min during homework

⇒Do not charge too much their school/other learnings agenda

General recommendations 1

- Relapses frequently occur after an infection

=> Avoid infections ++

- Wash hands
- Avoid contact with infected persons (distance, mask)
- Treat immediately any tonsillitis
- Vaccin: usual vaccinations do not seem to trigger relapses (Stanford and France series: no relapse after vaccination)

General recommendations 2

- Some relapses occur after alcohol intake

=> Stop any form of alcohol intake for at least three years

General recommendations 3

- Some relapses occur after sleep deprivation

⇒Avoid sleep deprivation, have regular sleep and wake rhythm

⇒ Beware of Eve, birthday and graduation parties, when alcohol, sleep deprivation and close contact with infected persons are combined

General recommendations 4

- No drug has yet proven a major efficacy in KLS
- The KLS course is unpredictable
- When considering to try a drug with the aim of preventing KLS new episodes, check for the "baseline" frequency and duration of episodes
- If episodes recur frequently (e.g. 4-12 times/year) or are long (e.g. 2-6 months), it seems beneficial to try a drug
- Benefit/risk of the drug should be regularly re-evaluated: stop or go rule

Lithium

- The drug that has been the most tried in KLS (in 18 to 27% of the patients)
- Lithium is normally present in small quantities in neurons
- Rationale: Indicated and used for >50 years in bipolar disorder (strong mood stabilizer, prevents depressive and manic relapses)
- Mechanism of action: unknown
- Narrow therapeutic window: 0.8-1.2 mEq/L (frequent blood test): inactive if lower, deleterious if higher
- AE: may partially block the thyroid (weight gain, check TSH), need to drink more and urinate more, rarely toxic for the kidney (check creatinin). Avoid if seizure or arrhythmic heart

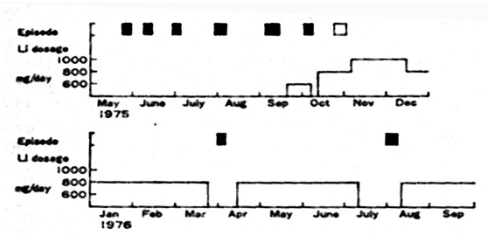
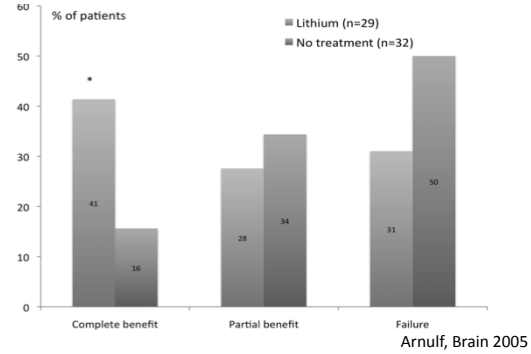
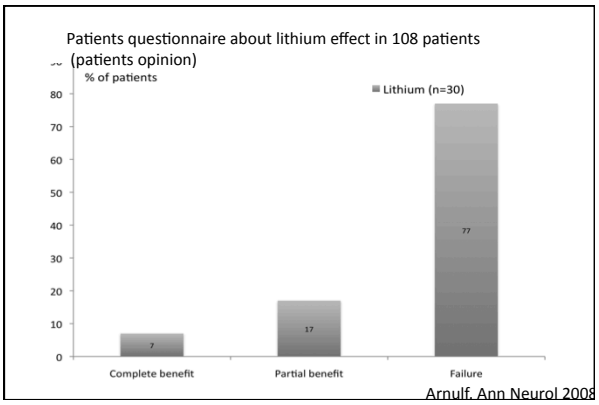


Fig 1—Hypersomniac episodes (shaded boxes) and lithium dosage. The unshaded box at the end of October 1975 refers to an episode of depersonalization.

Kellett, BMJ 1977



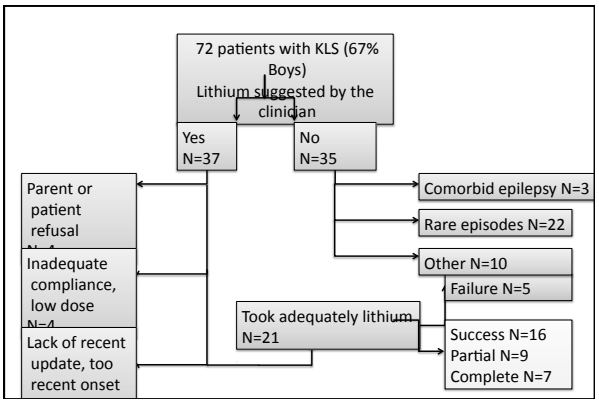
Arnulf, Brain 2005



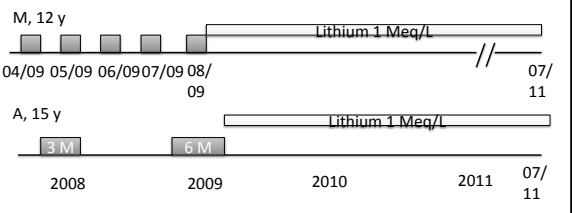
Arnulf, Ann Neurol 2008

2005-2011
How we decided to manage treatment in Paris, France (update on 72 followed patients)

- General recommendations in all patients
- Less than 4 episodes per year: no preventive treatment
- ≥ 4 episodes/y : « Stop or go rule »
  - try a drug for 6 months
  - If 0 or 1 episode : go ahead for 6 months, etc…
  - If 2 or more episodes : stop it
- 2005-2007: valproate first; 2008-2011: lithium first; except in women: contraceptive pill first

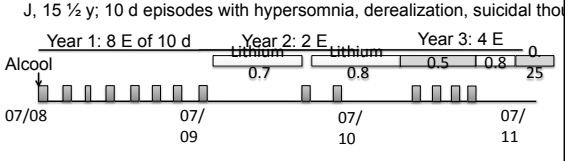


Examples of complete success

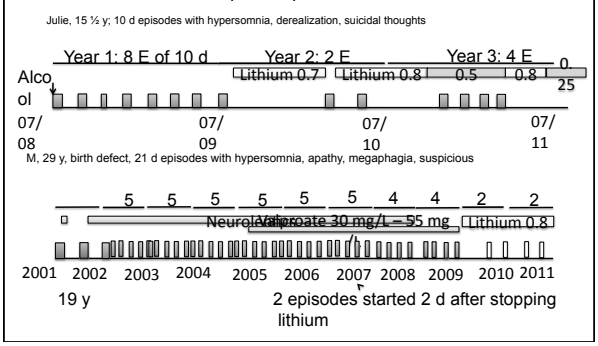


We asked them to take it at least 3 years « episode-free » before stopp

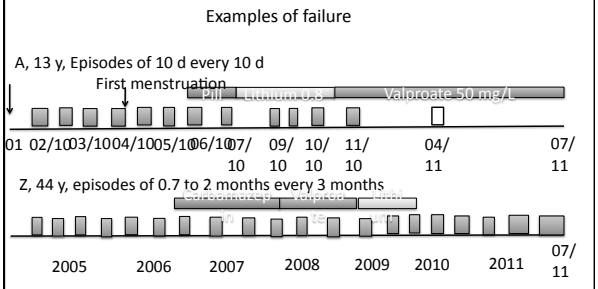
Examples of partial benefit



Examples of partial benefit



Examples of failure



Side effects amongst 25 patients

- N=6 with mild side-effects (24%)
  - Asymptomatic increase of TSH: n=2 girls
  - Increased acnea : n=1 boy
  - Tremor: n=1 girl
  - Anxiety, sensation of not being oneself n=1 girl
  - Weight gain : n=1 man
- In 19/25 patients, well tolerated (rarely increased drinking, rarely increased weight -less than with valproate)

- Compared to results from the litterature and ours in the Stanford survey, it suggests that when patients are selected with frequent episodes (4 or more per year), they benefit more consistently (ITT: 27% to 66%) from Lithium
- The occurrence of relapses when the dosage is low or 2 days after the drug is stopped reinforces the concept of « true » benefit => compliance/adequate dosage is an issue

Conclusion

- KLS : core symptoms (hypersomnia, abnormal cognition, apathy and derealization), while megaphagia and hypersexuality are optional
- Often benign, but longer than expected (risk factors: male sex, hypersexuality, adult onset), some have long-lasting episodes, "malignant" KLS, long lasting brain imaging abnormalities
- More familial cases, but no genetics findings yet
- Large cohorts bring important findings

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