Update on Kleine-Levin Syndrome

Pr Isabelle Arnulf

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Sorbonne university and Pitié-Salpêtrière
Hospital, Paris, France

Outline

- Presentation of the KLS center
- Symptoms during episodes, management
- Q&A
- Residual symptoms during « asymptomatic » periods Q&A
- Prevention of episodes - mechanisms
- Q&A

The French orphan disease program

Before 2006

- « Any MD is competent »
- You must be treated where you live

⇒ Local MDs have seen 0 to 2 cases with your disease in their entire life

The French orphan disease program

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Lobbying of patients support associations over the Health Minister

Telethon, media

« Patients with orphan diseases are neglected »
« MDs competence is highly dependant on their experience »
« Inequity between citizen »

The French orphan disease program

Before 2006

- « Every MD is competent »
- You must be treated where you live

⇒ Local MDs have seen 0 to 2 cases with your disease in their entire life

After 2006: National reference center (NRF)

All patients with a suspected orphan disease
- Should be refered at least once to an NRF
- For diagnosis confirmation
- Plus yearly follow up if requested
- For a central collection of clinical, biological and imaging measures

=> With large groups and growing experience, the clinicians improve their skills, identify subtypes, can perform research

=> Patients benefit from expert management

The French orphan disease program

Before 2006

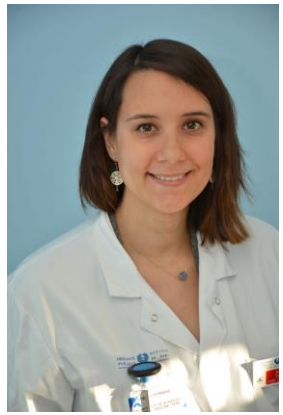
- 2 patients with KLS followed in Salpetriere Hospital

2019

- 270 patients with KLS have been diagnosed in Salpetriere Hospital
- Around 15-20 new cases/y
- Yearly check up in day hospital
- Every patient is seen by the neurologist, the psychiatrist and the neuropsychologist
- Some regional competence centers (Lyon, Nantes) are now able to ensure the follow up by themselves and refer again to Paris if problems

Pr Isabelle ARNULF
senior neurologist

Dr Smaranda LEU
senior neurologist



Dr Pauline DODET
senior neurologist

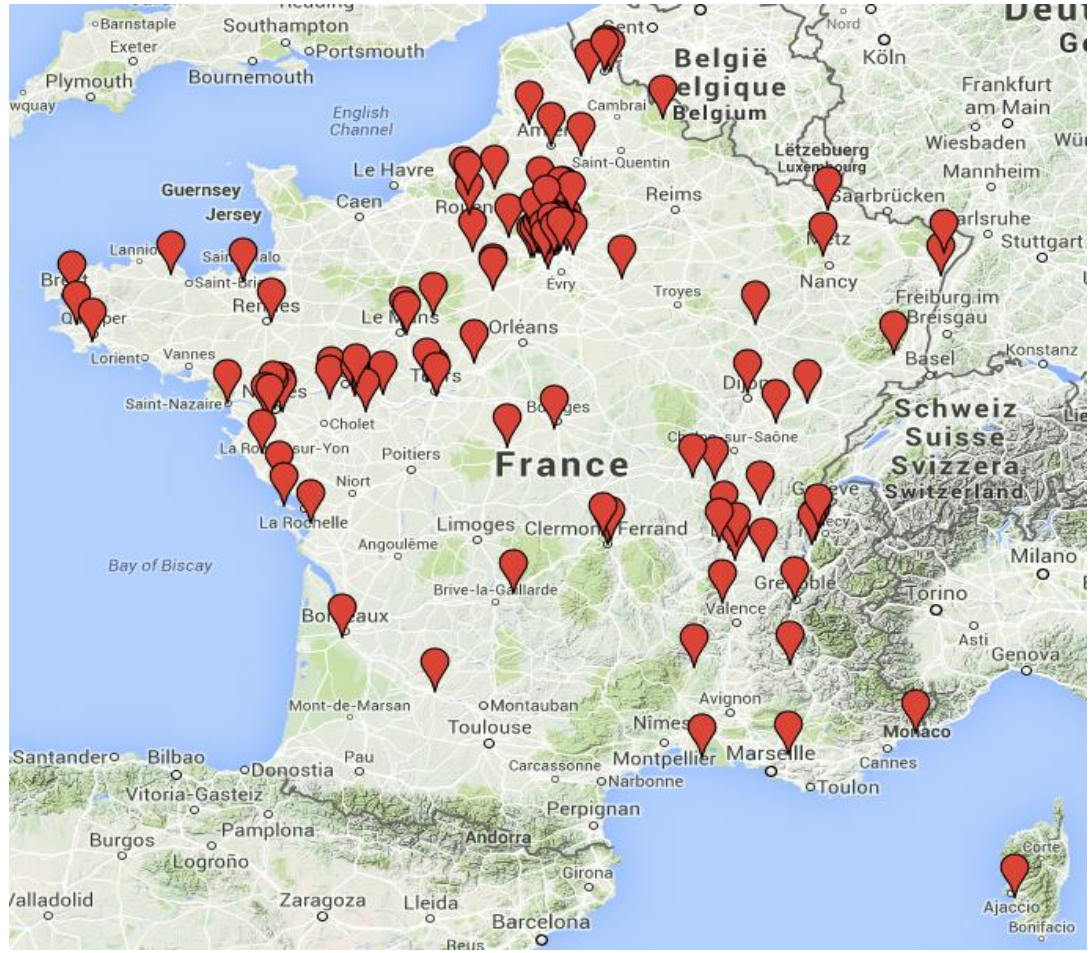
Dr Elisabeth GROOS
Dr Vanessa SLIMANI
Senior psychiatrists

Charlotte CHAUMEREUIL
Ginevra UGUCCIONI
Neuropsychologists

+ nurses

3-5 KLS Patients every Monday and Friday

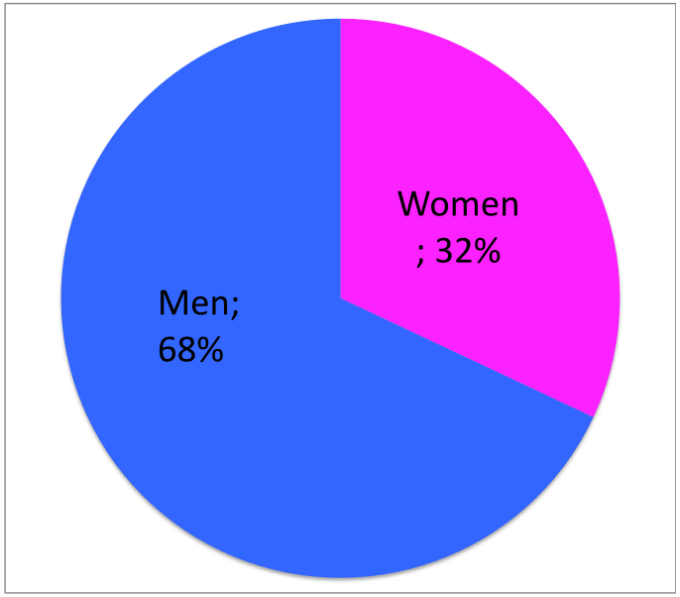
France
Prevalence: 3 to 4 cases per million
Incidence: 0.3 cases/y



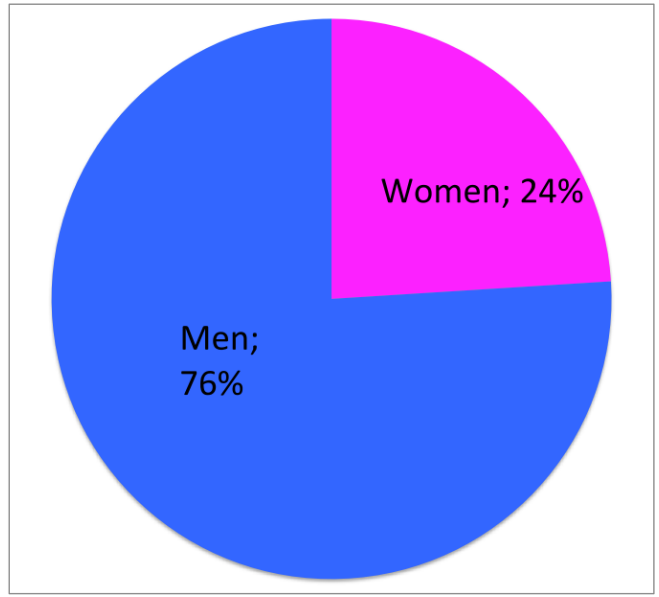
Lavault, Ann Neurol 2015

Sex ratio

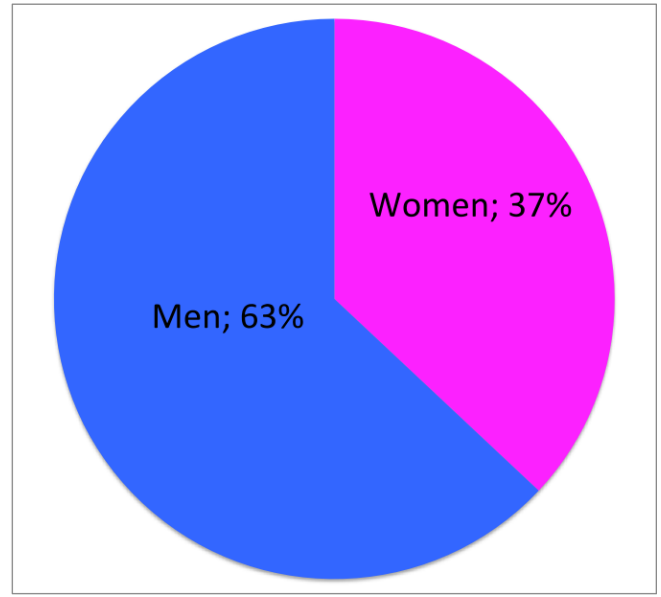
Published reports
1920-2004
n= 168



Stanford series
n= 108

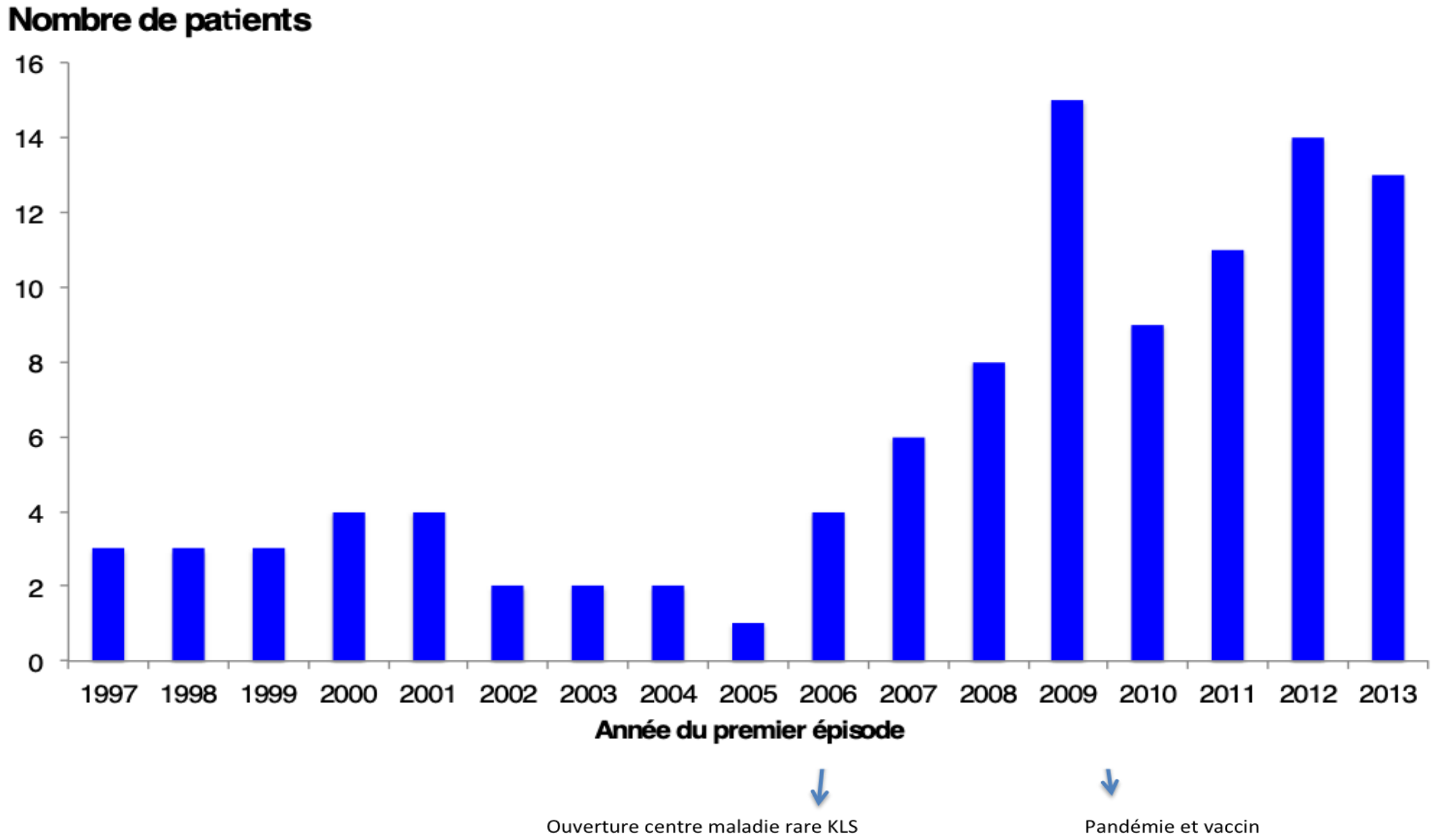


French cohort
n= 221

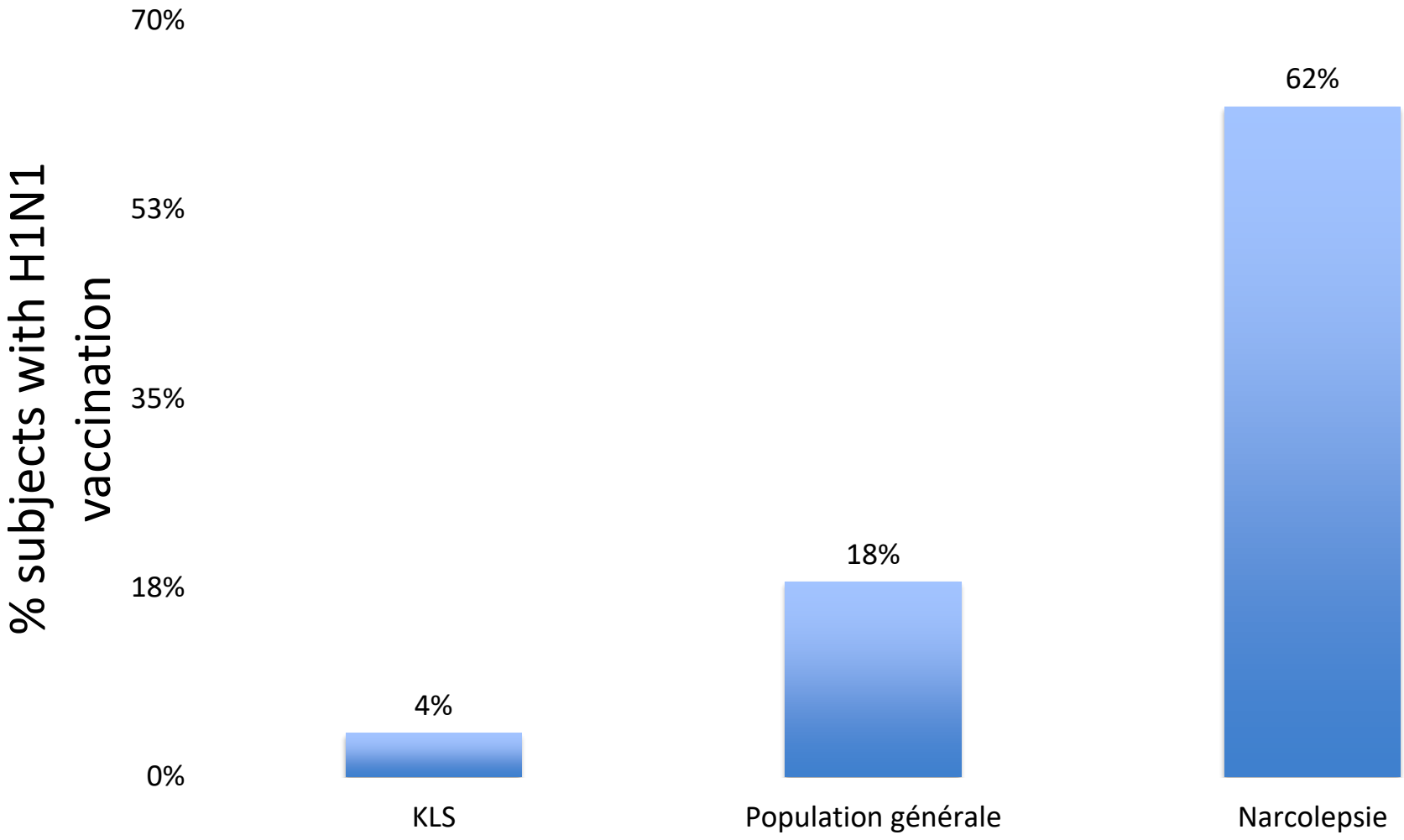


Arnulf, Brain 2005 ; Arnulf, Ann Neurol 2008, Lavault, Ann Neurol 2015

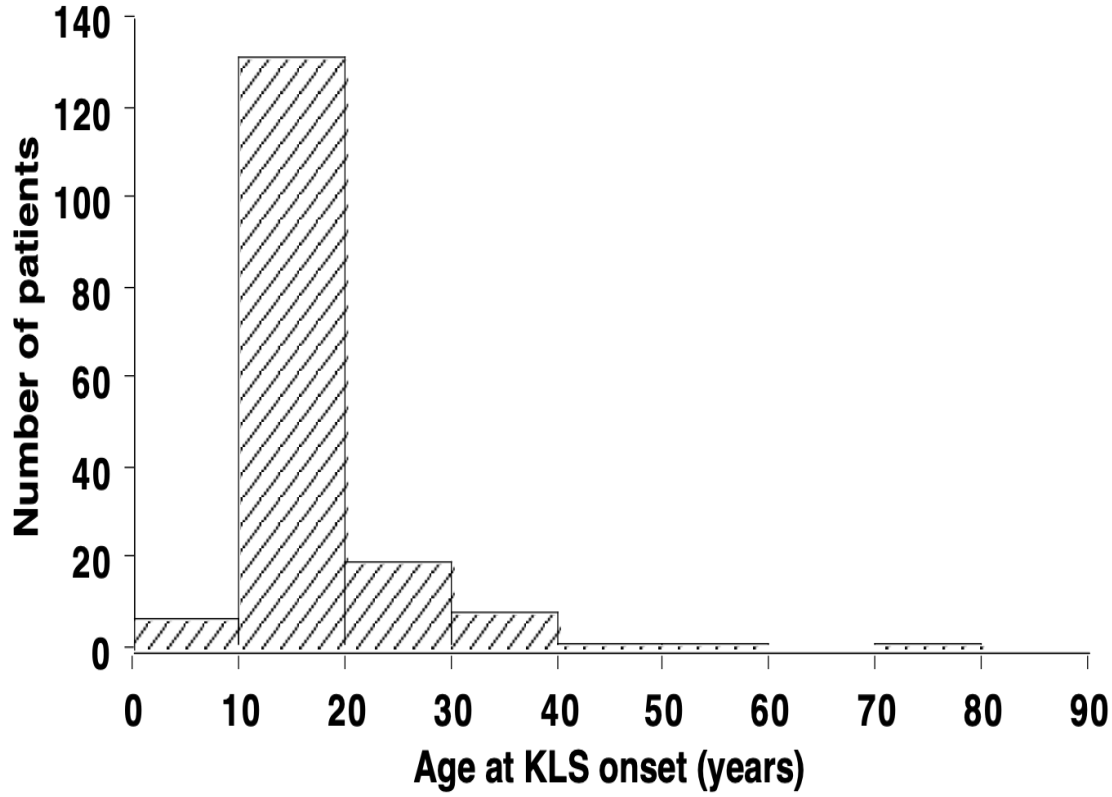

Worldwidefeatures
A REAL-LIFE 'SLEEPING BEAUTY'
RARE DISEASE CAUSES GIRL TO SLEEP FOR DAYS


Nombre de patients
16
14
12
10
8
6
4
2
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
Année du premier épisode
Ouverture centre maladie rare KLS
Pandémie et vaccin

No link with H1N1 vaccination



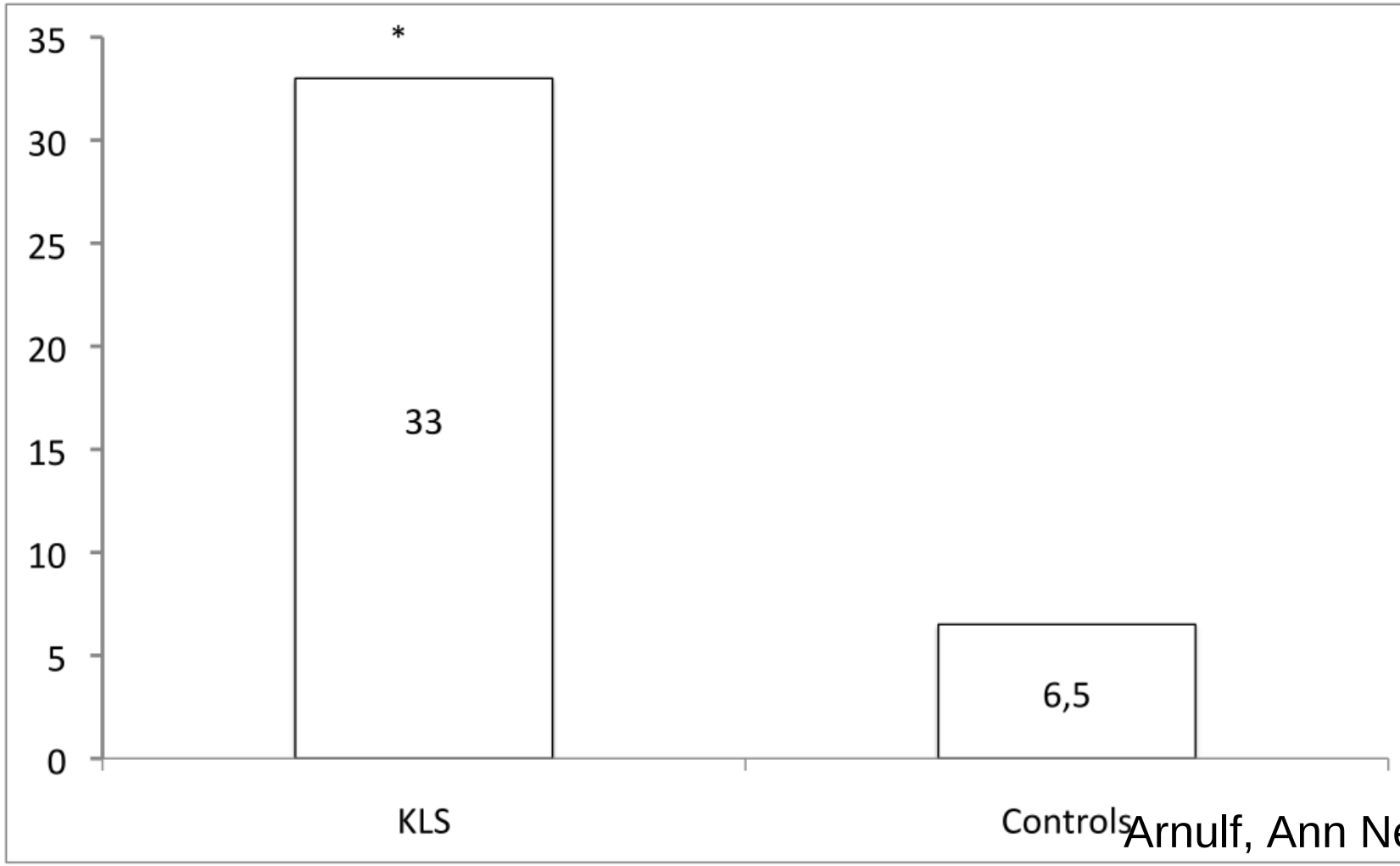
Age at KLS onset



Médiane : 15.7 ans

Arnulf, Ann Neurol 2008

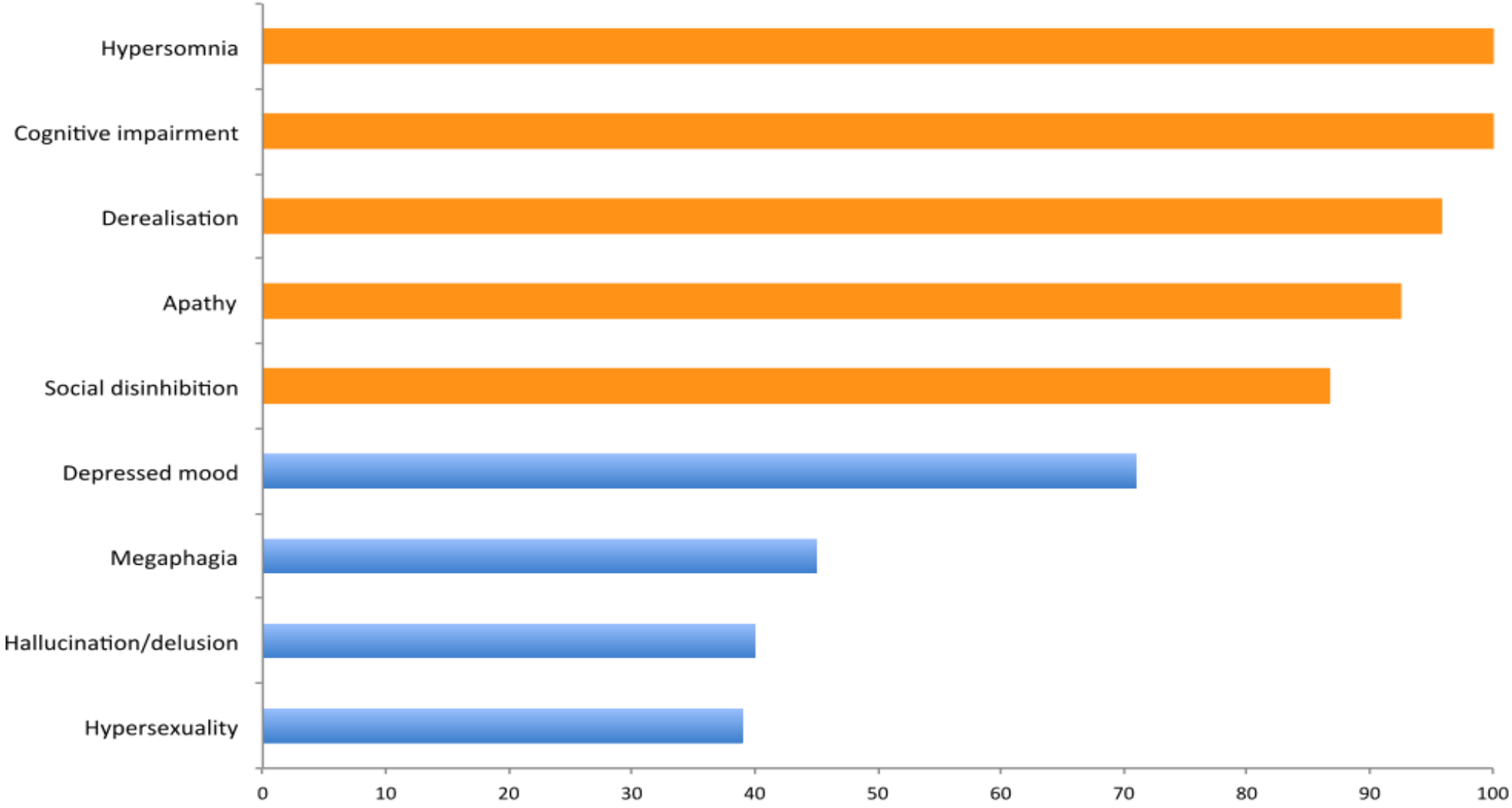
Birth or development problems



Arnulf, Ann Neurol 2008
Lavault, Ann Neurol 2015

1. Symptoms during episodes and their management

Symptoms during at least one episode



Lavault, Ann Neurol 2015

Symptoms during episodes

Neurological

- Hypersomnia (15-22h/d)
- Altered cognition
  - Slowing
  - confusion
  - Post-episode amnesia
- « Meningitis like »
  - Headache
  - Photophobia
  - Painful hyperacousia

Psychiatrical

- Irritability
- Depressive or flat mood
- Anxiety
- Psychotic symptoms
  - Reference ideas
  - Hallucinations
  - Delusion

Symptoms during episodes

Neurological

- Hypersomnia (15-22h/d)
- Altered cognition
  - Mental slowness
  - Confusion
  - Post-episode amnesia
- « Meningitis like »
  - Headache
  - Photophobia
  - Painful hyperacousia

Neuropsychiatric

- Derealisation /altered perception
- Apathy
- Disinhibition
  - Megaphagia
  - Hypersexuality
- Regressive behavior, puerility

Psychiatric

- Irritability
- Depressive or flat mood
- Anxiety
- Psychotic symptoms
  - Reference ideas
  - Hallucinations
  - Delusion

Hypersomnia

- Frequent during the first episodes, in young patients and at the begining of an episode
  - 18-22 h asleep/24h
  - Hard to wake up, sometimes lot of vivid dreams
  - May wake up in the middle of the night (« clock » problems)
  - Some have an alert period in end-afternoon

Hypersomnia

- Less common in adult patients, tends to decrease with episodes : evolve towards a major exhaustion and rather a need to rest (no major sleep excess), lying (often in a dark room), inactive

(when sleep time decreases, it may unmask the other disagreable symptoms, such as derealisation, mental slowness)

⇒Sleep monitoring during episodes: not useful

⇒No visible abnormality in this sleep (should be restorative but is not)

Practical management of hypersomnia

- Let them sleep or rest as much as they need
- Stimulants (modafinil, methilphenidate, pitolisant) do not really help=> better to sleep
- If they prefer darkness: let the curtain closed
- Avoid noise (many have a painful hyperacusia)
- Problem when in-hospital: sleep- and rest-deprived => increase their pain, increase behavioral problems, irritablity
- If possible, keep them at home during episodes
- If 1-2 nights of insomnia at the end of an episode: it is good point (like a « stop » signal)

Apathy

- No more motivation

Apathy

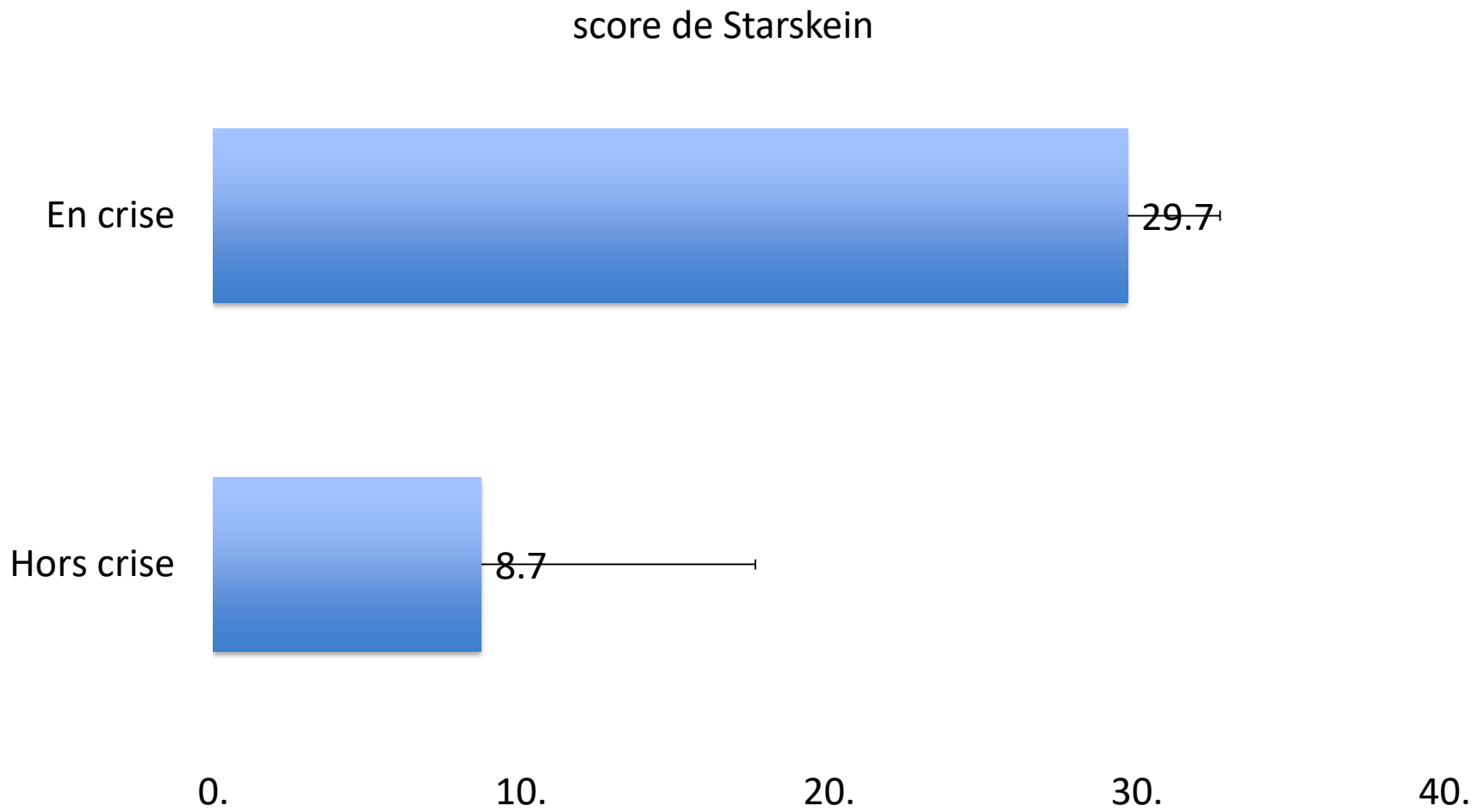
Apathy

Apathy Scale (Starkstein *et al.* 1995).

Questions	Not at all	Slightly	Some	A lot
1. Are you interested in learning new things?				
2. Does anything interest you?				
3. Are you concerned about your condition?				
4. Do you put much effort into things?				
5. Are you always looking for something to do?				
6. Do you have plans and goals for the future?				
7. Do you have motivation?				
8. Do you have the energy for daily activities?				
9. Does someone have to tell you what to do each day?				
10. Are you indifferent to things?				
11. Are you unconcerned with many things?				
12. Do you need a push to get started on things?				
13. Are you neither happy nor sad, just in between?				
14. Would you consider yourself apathetic?				

Note: For questions 1-8, the scoring system is the following: not at all = 3 points; slightly = 2 points; some = 1 point, a lot = 0 point.
For questions 9-14: the scoring system is the following: not at all = 0 points; slightly = 1 point; some = 2 points; a lot = 3 points.

Apathy scores



Consequences of apathy

- 2/3: eat less (should be called on the table or have a plate in their room when awake, too exhausted to eat, come to the family table and eat automatically then go back to bed) : loose weight in an episode, not a big problem. Check that they drink enough
- Neglect hygiene (effortful) Should be pushed to the shower
- « Empty » gaze

Management of apathy

- Nothing works to stimulate the patients
- No use to »push » them

Cognitive impairment

- Slow in answering, in speaking
- Reduced language
- Seem lost, understand nothing or with difficulty
- Lost in time (but sleep 22h) and sometimes in space : confusion
- It is a big effort for them to think

Management of slow cognition

- No homework!
- Typical medical certificate for the school:

"I hereby certify that the patient is affected by a rare disorder characterized by episodes of several days/weeks during which he/she must rest in his bedroom and cannot work. Please excuse him/her in case of missed school and help him/her catching back the missed lessons after the episode."

Communicating with patients in an episode

- Hard to call by phone (dare not answering, sleep)
- Do not want to see their friends
- Often prefer to communicate with limited language or with SMS (less stressful ?)

- Due to cognitive slowness: never drive a car during an episode! (hide the keys)

Derealisation

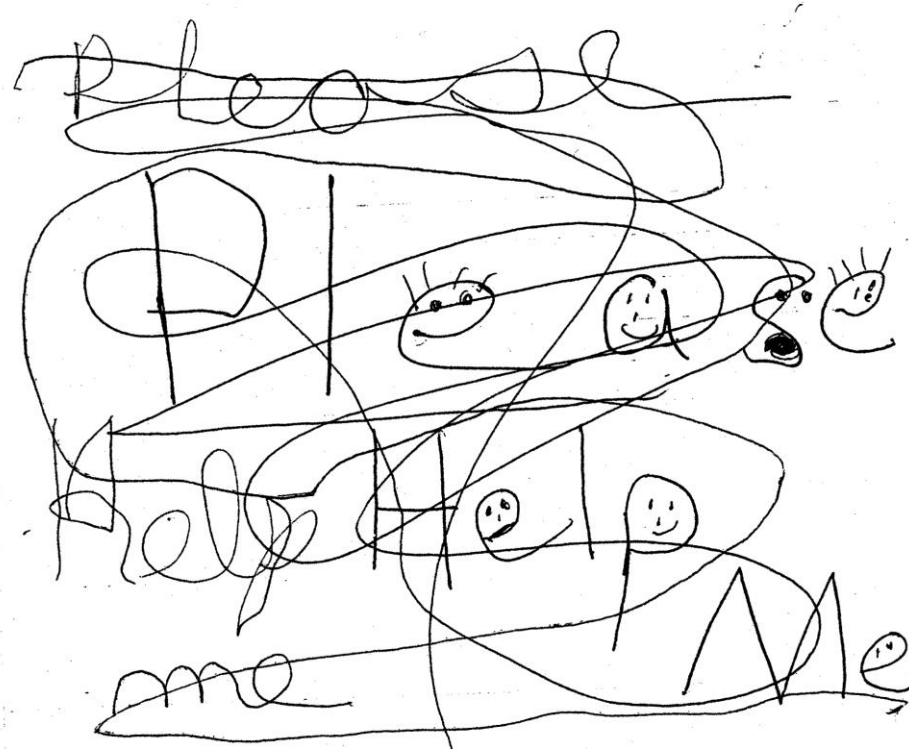
- « Feeling unreal » almost 100%
- The most disagreable symptom
- “Like being in a dream” 87% In my bubble
- Abnormal sensory feelings

(10) Feeling like I am there but nothing I do or say is happening and nothing anyone else does or say is happening (10)

(11) Needing to sleep (11)

(12) Not wanting to do anything (12)

(13) Missing doing things like playing football with my dad and brother (13)



Altered perception

- Blunted, abnormal feelings
- Changes in vision, audition, tact, temperature, pain

- ‘the shower is an horrible experience, as I see the water on my body but at the same moment I don’t feel it or its temperature’ Romary, 30 y
- Some do not recognize themselves in the mirror
- '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..’ Lee, 21 y
- 'When episodes first began, Cliff would ask me if he was dead or alive.’ Cliff, 10 y

Managing derealisation

- Reinsure the patient
- Avoid novelty (keep in the same environment)
- Avoid going outside for shopping
- Possible (not proven, little experience in our center) benefit in some patients of acetazolamide 1-2 pills/days during episode (diuretic than decreases brain swelling in other diseases, also may decrease headache)

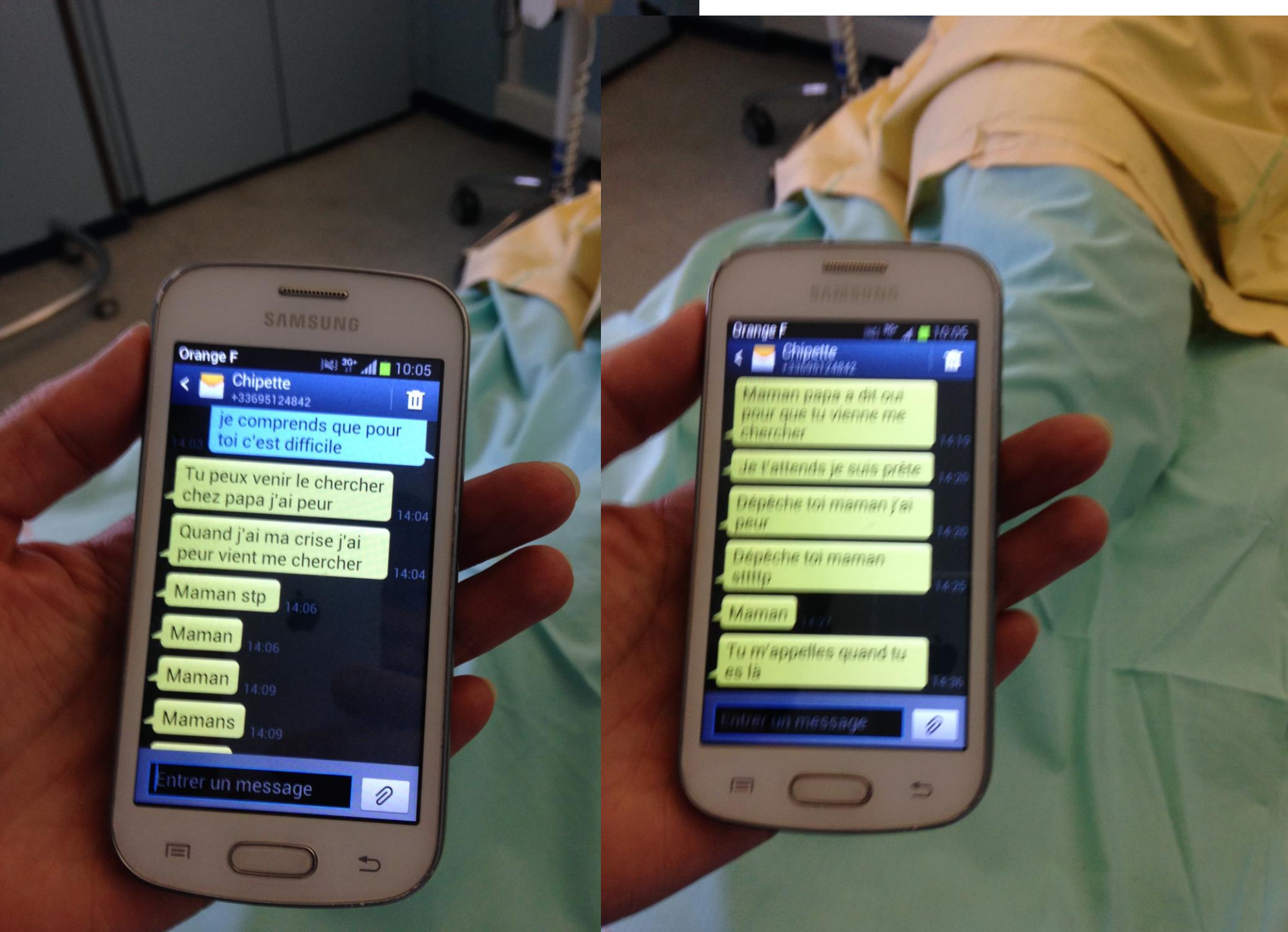
Disinhibited behavior

- Gluttonery in 51% (sweet, fixation on a certain food), but 40% eat less
- Sexual disinhibition (30%) : boys>girls
- Irritability : 65%, frustration, lack of politeness
- Childish, regressive behavior
- Some stereotyped behaviors
- In this part of the episode, some are excited, want to walk

Childish behavior: 36%

Psychological changes: sadness/anxiety

- Depressive mood 62%: girls: 75% and boys: 59%
  - Sadness, thoughts of death/suicidal idea 17-22%, 2/120 suicidal attempts
- Anxiety 51 %“panic if left alone,” “afraid of novelty”, “afraid that the disease never stops”; derealization increases anxiety


SAMSUNG
Orange F
10:05
Chipette
+33695124842
je comprends que pour toi c'est difficile
14:03
Tu peux venir le chercher chez papa j'ai peur
14:04
Quand j'ai ma crise j'ai peur vient me chercher
14:04
Maman stp
14:06
Maman
14:06
Maman
14:09
Mamans
14:09
Entrer un message
SAMSUNG
Orange F
10:05
Chipette
Maman papa a dit oui pour que tu vienne me chercher
Je t'attends je suis prête
Dépêche toi maman j'ai peur
Dépêche toi maman stttp
Maman
Tu m'appelles quand tu es là
Entrer un message

Psychotic symptoms

- Hallucinations : 46%: mostly brief, visual or “reference ideas”: feeling of being scrutinized by others when the patients are outside of their home and feeling of surrounding hostility).
- Delusive idea (megalomaniac, paranoïd,paranoiac) : 35%

Management of psychological changes

⇒If anxious: Check regularly their mood, hug, appease, repeat them that it will end soon (depressed mood is 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) or a sedative antihistaminic (hydroxyzine 25 mg).

⇒If watching them is insufficient, bring them to the hospital for permanent supervision.

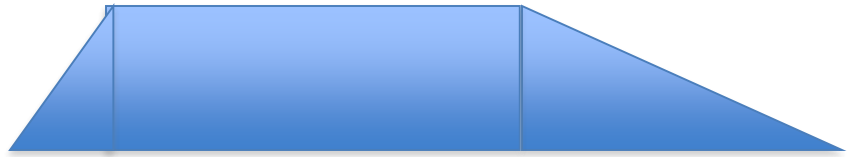
⇒Antidepressants seem useless at this point

Episodes starting when abroad/in a field trip

- Have a plan
- Sometimes not a big problem: patient sleeps…
- If abroad alone: assistance for being brought back home (we communicate with the medical assistance, explain KLS and the patient's case: usually, a simple flight back with somebody bringing back the patient at home is sufficient)
- Rare cases needing to be hospitalized abroad
- Beware of psychotic anxiety

Durations of episodes

During an episode

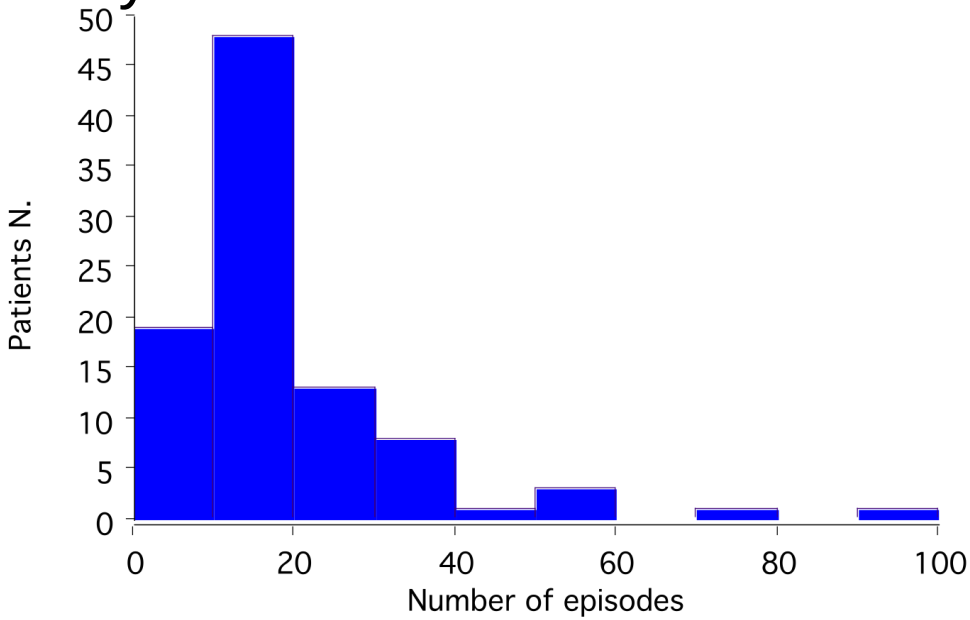


43% a few hours

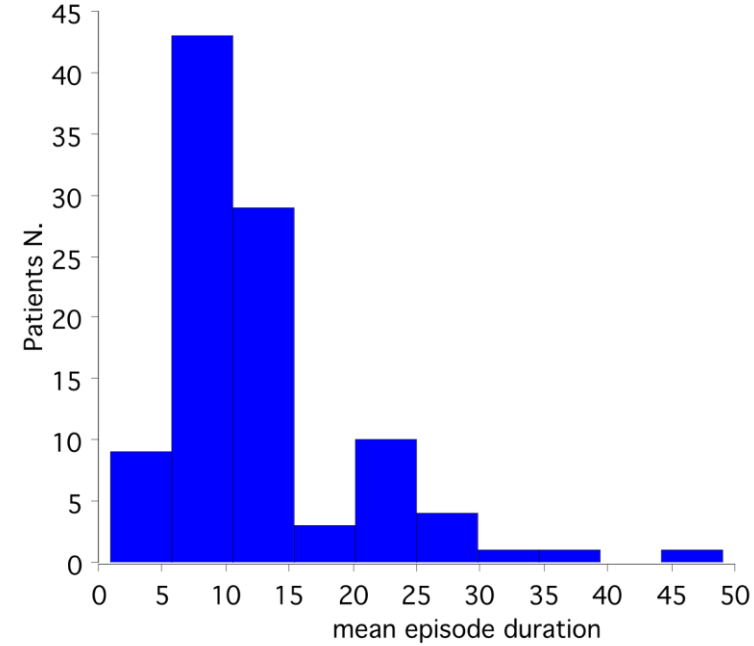
7-13 d

2 to xx d

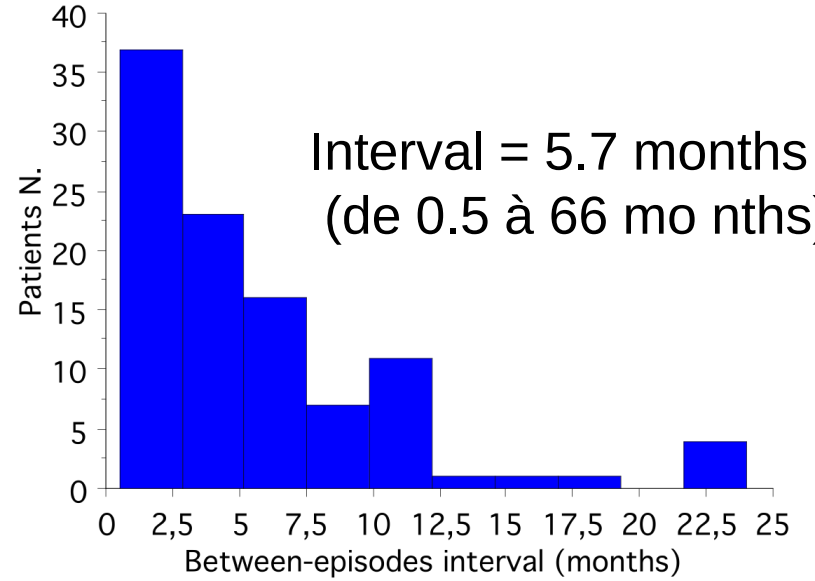
52% a few days



Mean number of episodes = 19



Median= 13 days



Interval = 5.7 months
(de 0.5 à 66 mo nths)

The problem of long episodes

In the series of Stanford, n = 108 (Arnulf, Ann Neurol 2008), as well as in the series of Paris, n = 120 (Lavault, Ann Neurol 2015):

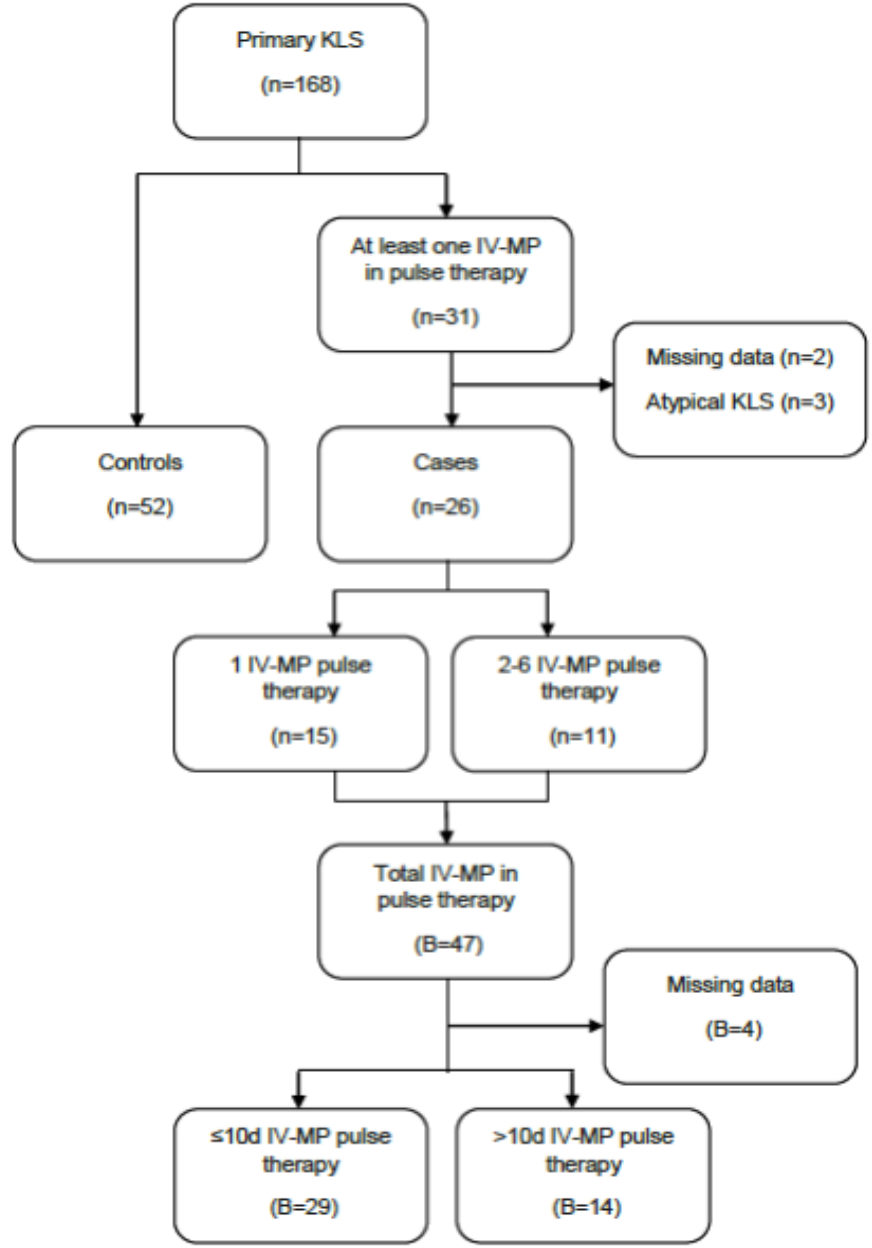
- 28% of patients have long (>30 d) episodes
- Difficult to predict who and when
- Except if the first episode was long

- => Once an episode has started, is there any mean to stop it?

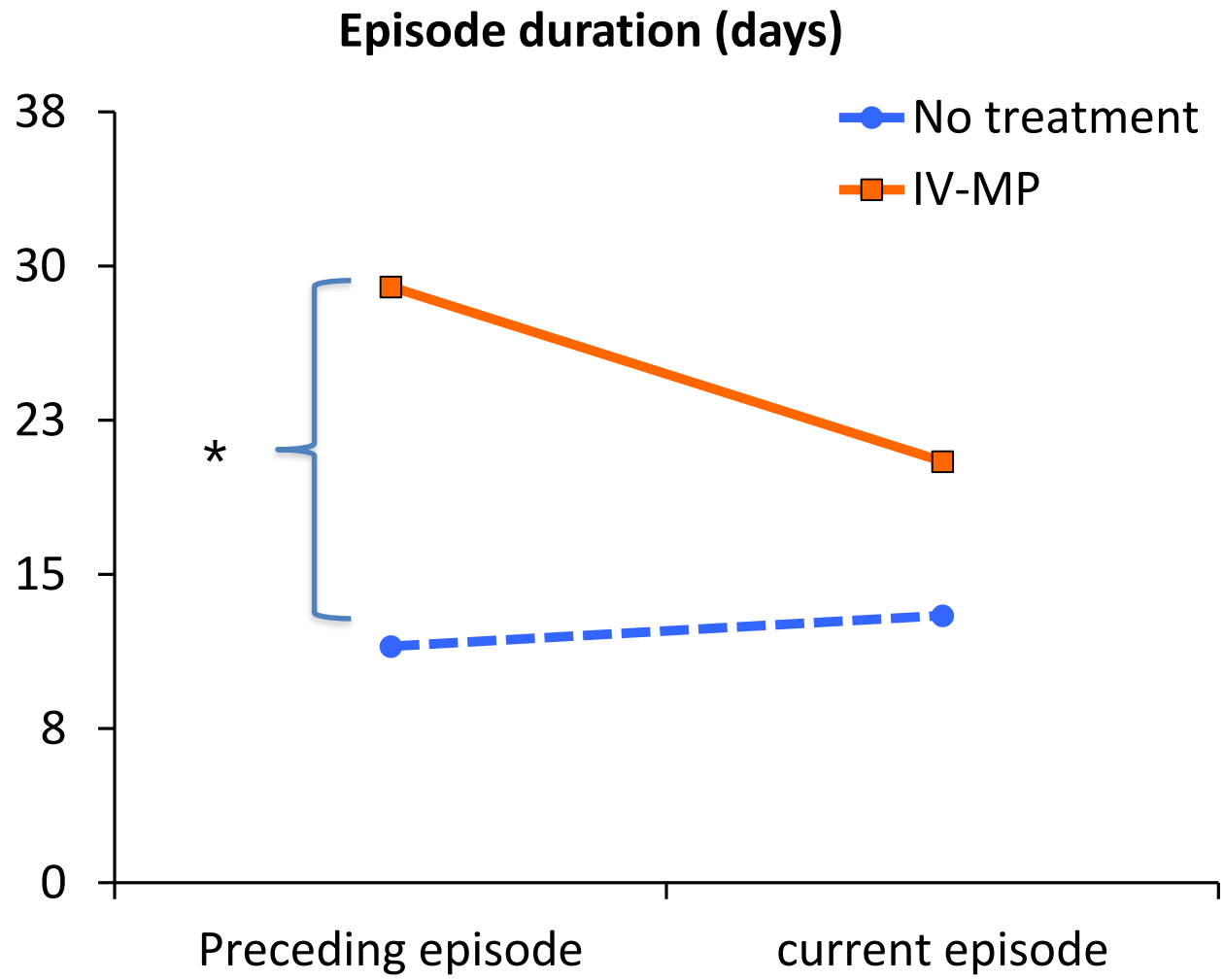
IV steroid trials

Case-control study over 3 years

- treated patients are compared to a twice greater number of untreated controls: KLS patients matched for age, sex, age at KLS onset, disease course (mean 5 y)

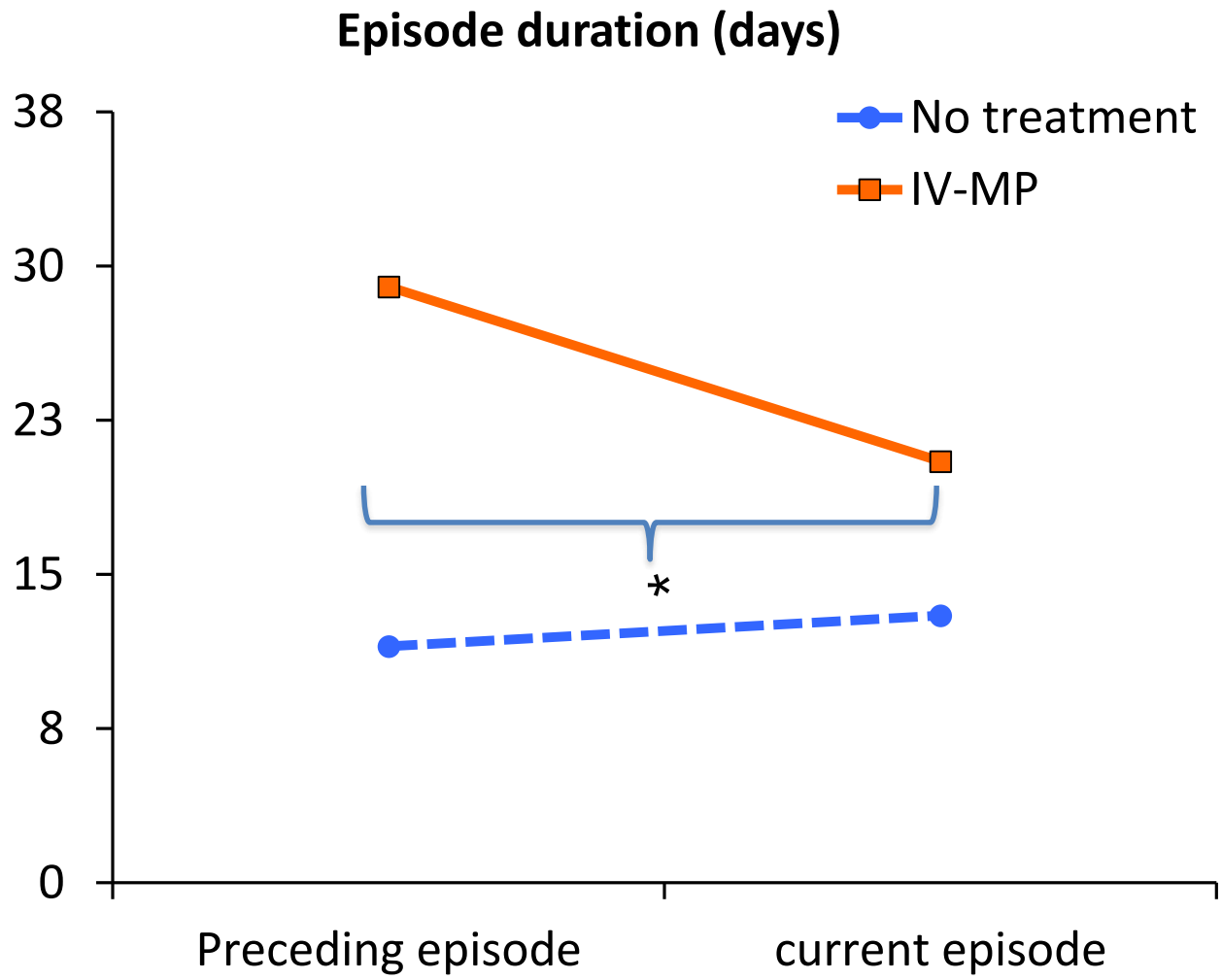


First series
(3 days IV methylprednisone, 1 gr/d)



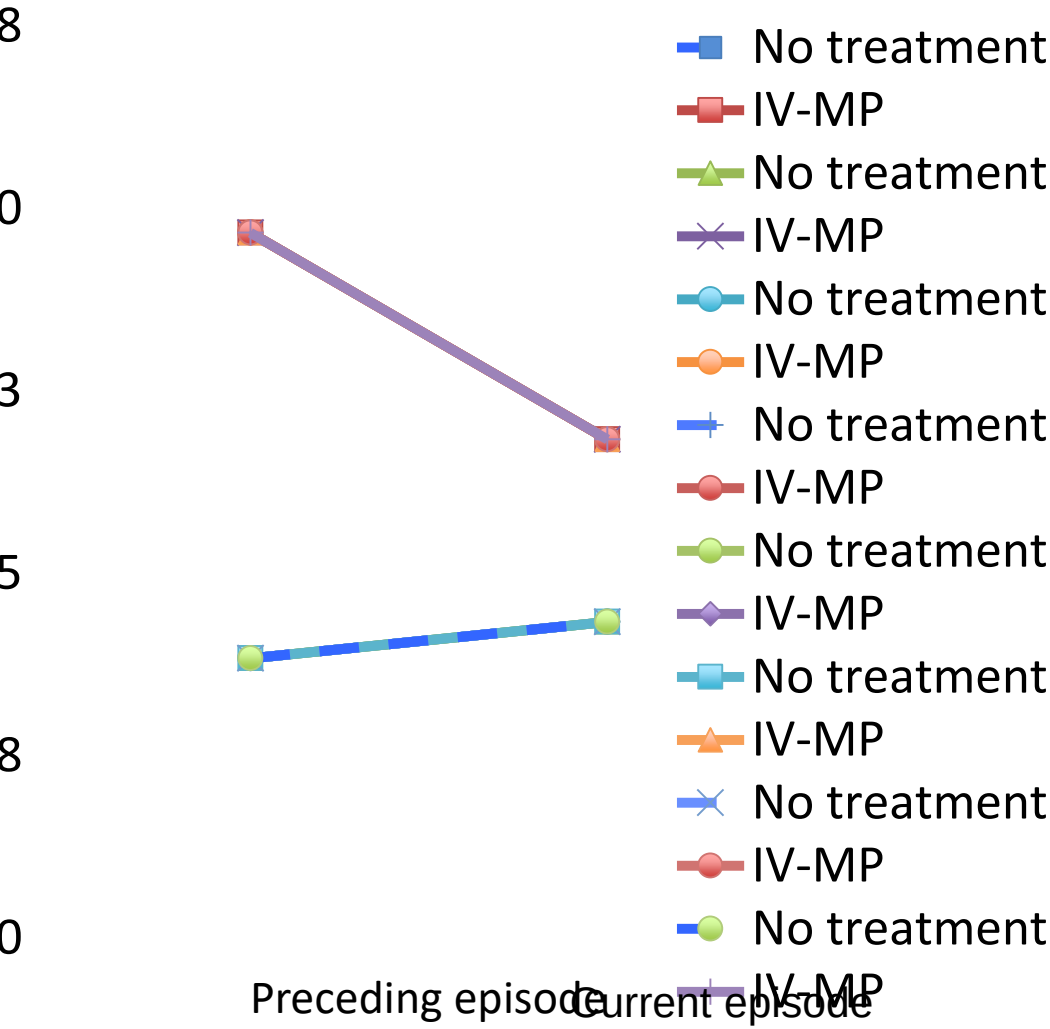
Léotard, Neurology 2018

First series



Léotard, Neurology 2018

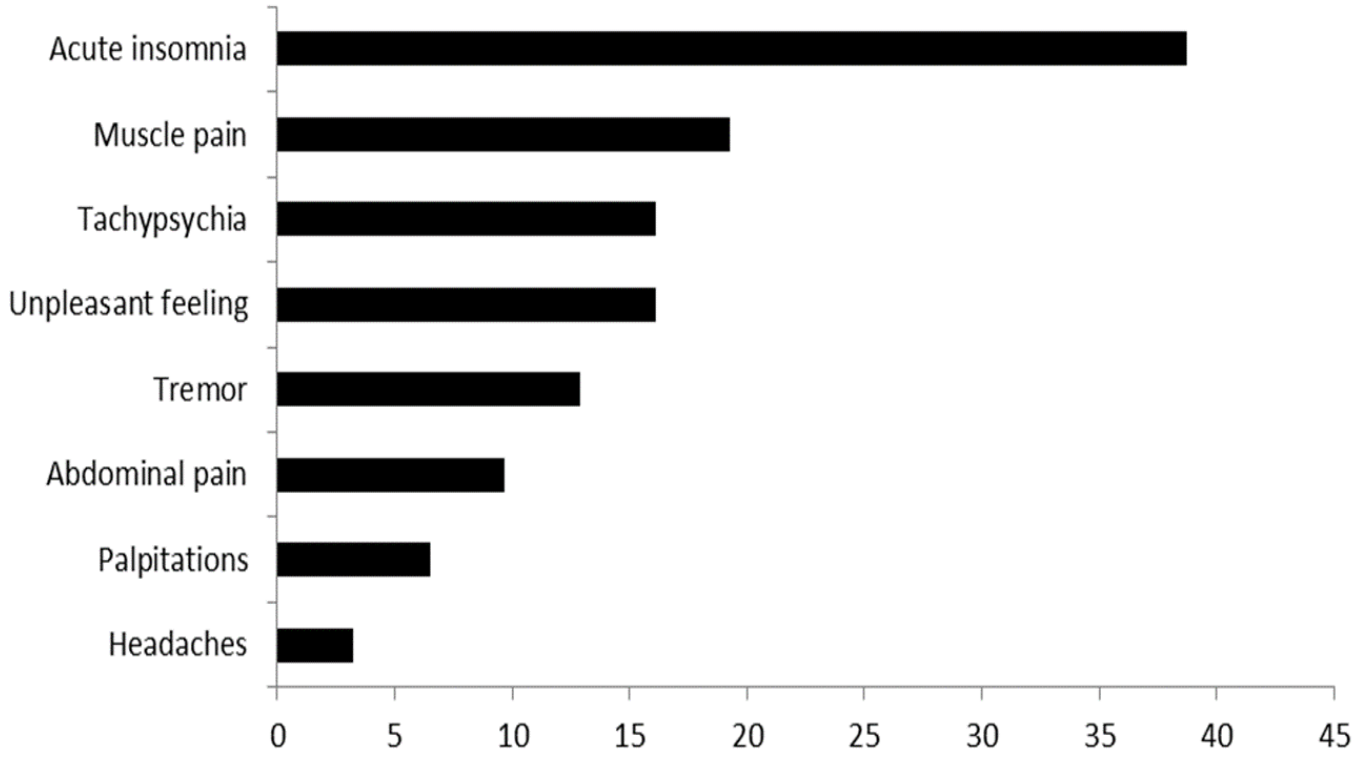
All IV series



- 43 series
- -11 d vs -0 d
- ↘ >6d : 56% vs 10%
- If infused <10 d: <u>65% of success</u> vs. 25% if >10d

Léotard, Neurology 2018

Steroids side effects



Léotard, Neurology 2018

Conclusion: IV steroids during long episodes

- Well tolerated in KLS (no serious adverse effect, no manic switching)
- 65% of benefit (-7 d in an episode) if infused during the first 10 days
- Can be repeated until 12 g (4 series) max per year
- But no benefit in 3 patients having evolved from an intermittent toward a mild chronic (>2 y with continuous fatigue and apathy) form of KLS

Léotard, Neurology 2018

Help your doctor

- Video tape your child duirng episode: face, behaviour, reaction
- Keep a diary

Episode n°#	1	2	3	4	5	
Date of onset						
Duration						
Time since last episode						
Trigger ?						
On going treatment						
Name						
Date of last lithium dosage						
Lithium dosage						
Treatment taken during the episode						
Symptoms/severity						
Hypersomnia						
Derealisation						
Apathy						
Confusion/slowness						
Cries, sadness						
Delusional idea						
Appetite						
Behaviour						

- Q and A on symptoms ?

Recent advances in KLS

- **French cohort:** n=221 patients followed in Pitie-Salpetriere hospital
- **Phenotype**
  - Hypersomnia, apathy, derealisation and slowed cognition are core symptoms (Arnulf, Ann Neurol 2008)
  - Severe forms > 1 month in 30% (Lavault, Ann Neurol 2015)
  - Familial forms (N'Guyen, Sleep 2016)
- **Pathophysiology**
  - Derealisation (Kas, Brain 2014), apathy
  - Mild hypocretin decrease (Hang, Sleep 2016)
- **Not totally normal during « asymptomatic periods »**
  - Altered cognition (Engstrom Sleep 2009; 2014 ; Uguccioni, Sleep 2016)
  - Emergent psychiatric comorbities (Groos, submitted)
- **Treatment**: Lithium (Leu-Semenescu, Neurology 2015)

2. « Asymptomatic » periods

During asymptomatic periods: what to check?

- Sleep
- Cognition
- Mood/anxiety/adjustement

=> Some patients may have « mild residual symptoms »

Sleep during « asymptomatic » periods

- Patients declare longer usual sleep time than controls (on average 30 min)
- They go to bed earlier than controls

Lavault, Ann Neurol 2015

=> This could be residual from episodes, or could be an adaptation to prevent new episodes (because sleep deprivation can trigger episodes)

Cognition:what was known before

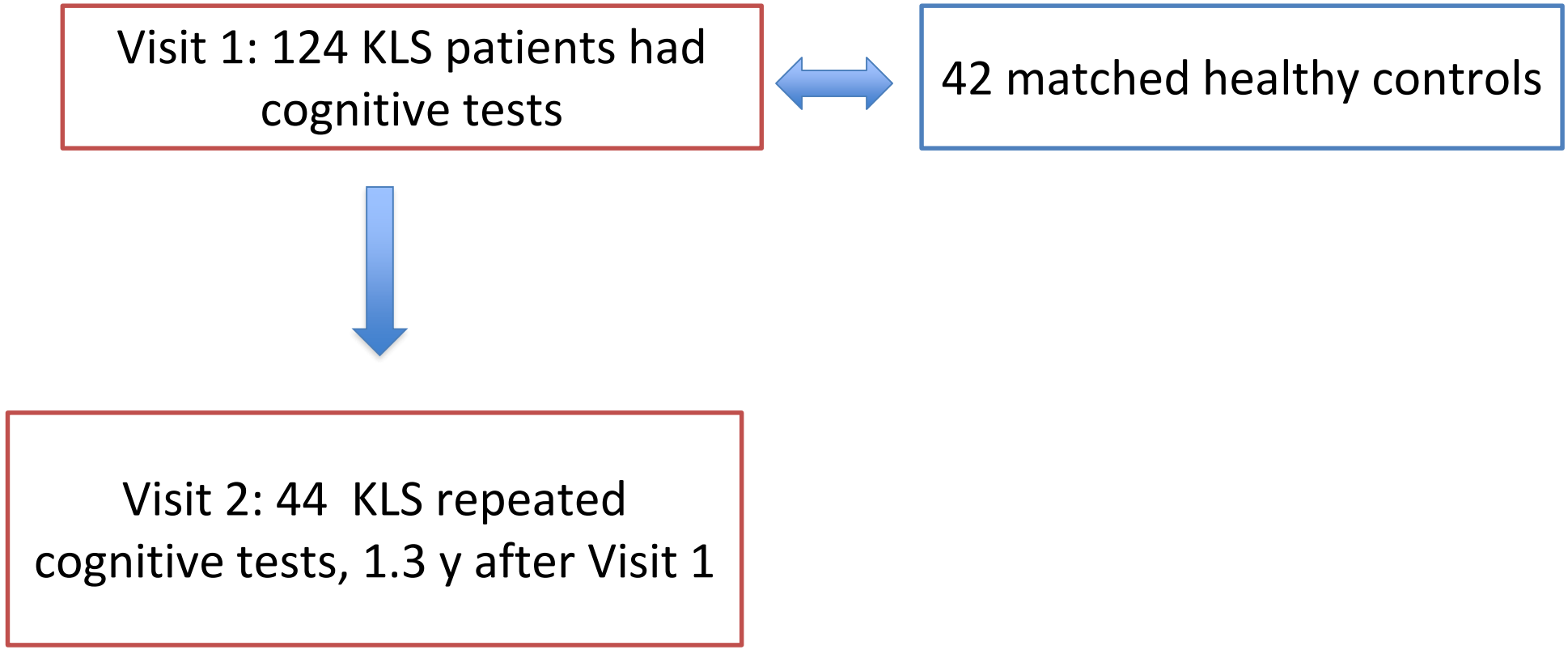
- Individual reports of occasional cognitive difficulties

- A single series of 8-18 patients altered working memory, use different networks in fMRI

Engstrom, Sleep 2009, 2014

- In our patients, 50% report academic decline since KLS onset

Uguccioni, Sleep 2015

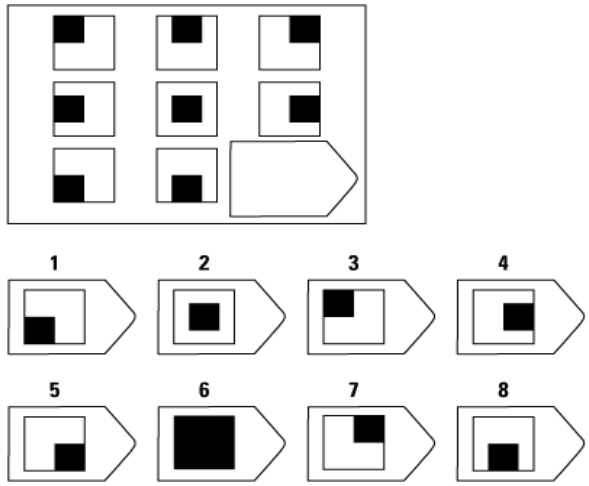


Uguccioni, Sleep 2015

FCSRT

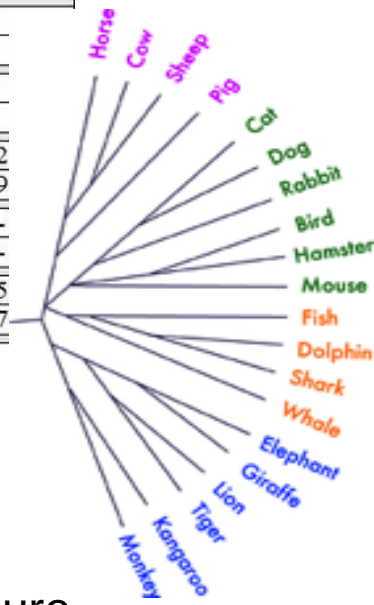
	T1	T2	T3
Throw	1		
Lily	2		
Film		1	
Discreet	2		
Loft		1	
Beef			1
Street			
Helmet		1	
Snake			1
Dug		1	
Pack	1		1
Tin	1		1

PM38

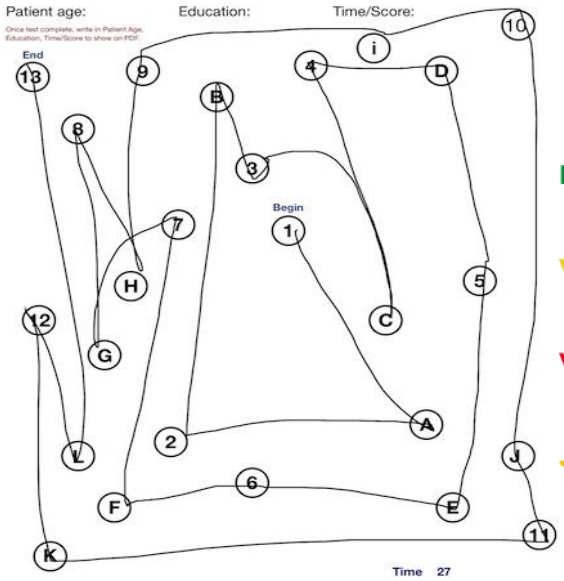


Digit span

		examiner
3 digits	Trial 1	7 - 8 - 3
	Trial 2	5 - 4 - 7
4 digits	Trial 1	7 - 9 - 6 - 2
	Trial 2	4 - 8 - 2 - 5
5 digits	Trial 1	6 - 3 - 8 - 1 - 7
	Trial 2	9 - 4 - 6 - 2 - 1
6 digits	Trial 1	4 - 8 - 3 - 9 - 7 - 2
	Trial 2	6 - 2 - 4 - 1 - 3 - 9
7 digits	Trial 1	8 - 9 - 2 - 6 - 4 - 1 -
	Trial 2	3 - 1 - 4 - 2 - 6 - 9 -
8 digits	Trial 1	7 - 1 - 9 - 2 - 8 - 3 - 5
	Trial 2	6 - 4 - 3 - 9 - 2 - 5 - 7



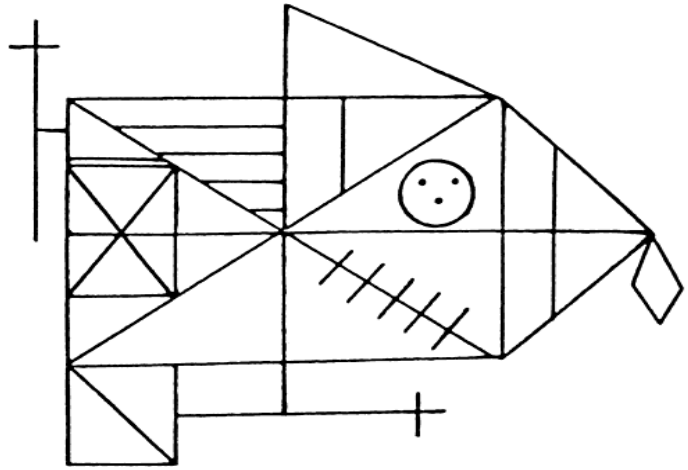
TMT



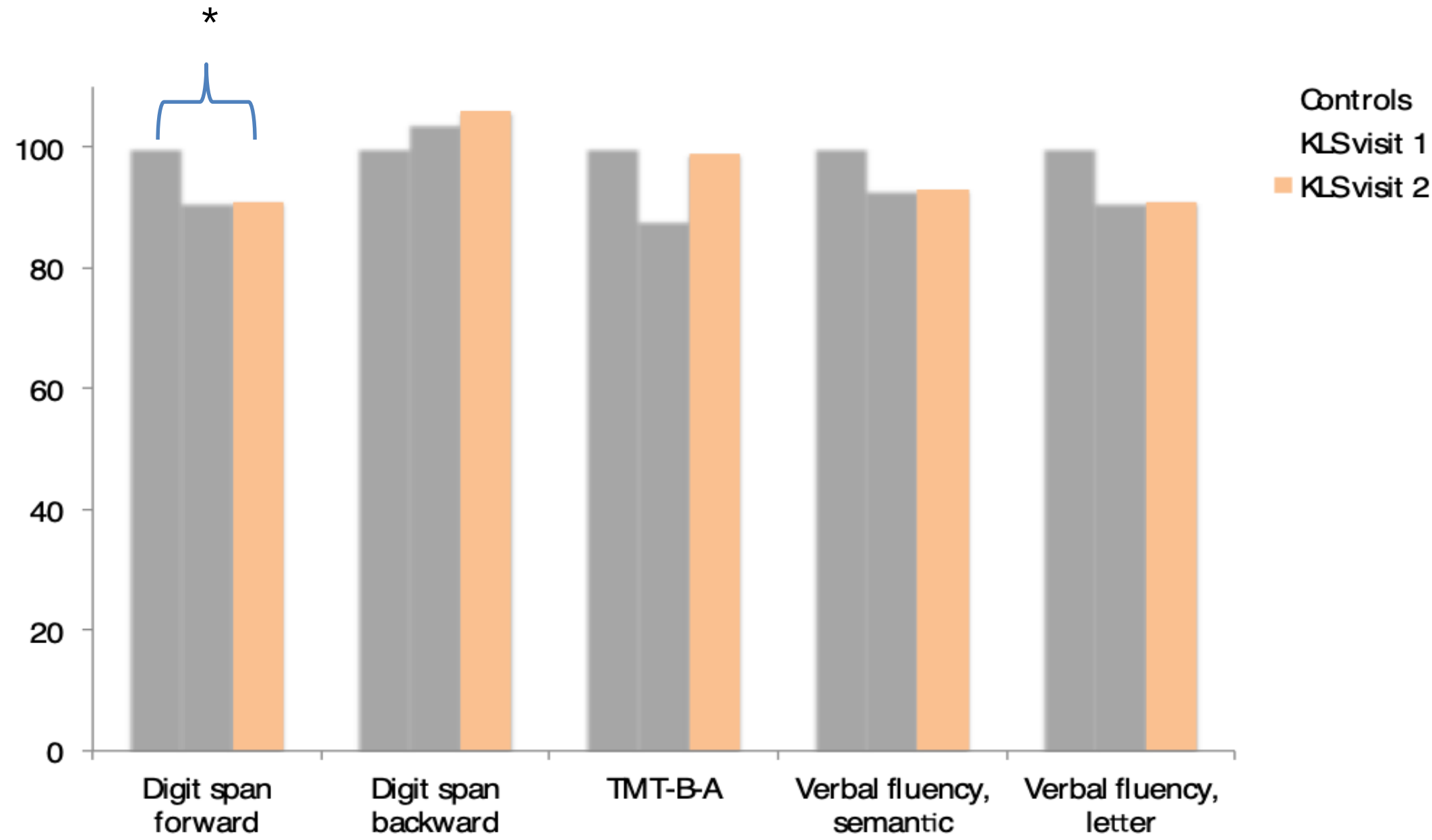
Stroop

BLEU	JAUNE	BLEU	ROUGE	BLEU
VERT	JAUNE	ROUGE	VERT	JAUNE
VERT	ROUGE	VERT	JAUNE	JAUNE
JAUNE	ROUGE	JAUNE	VERT	BLEU

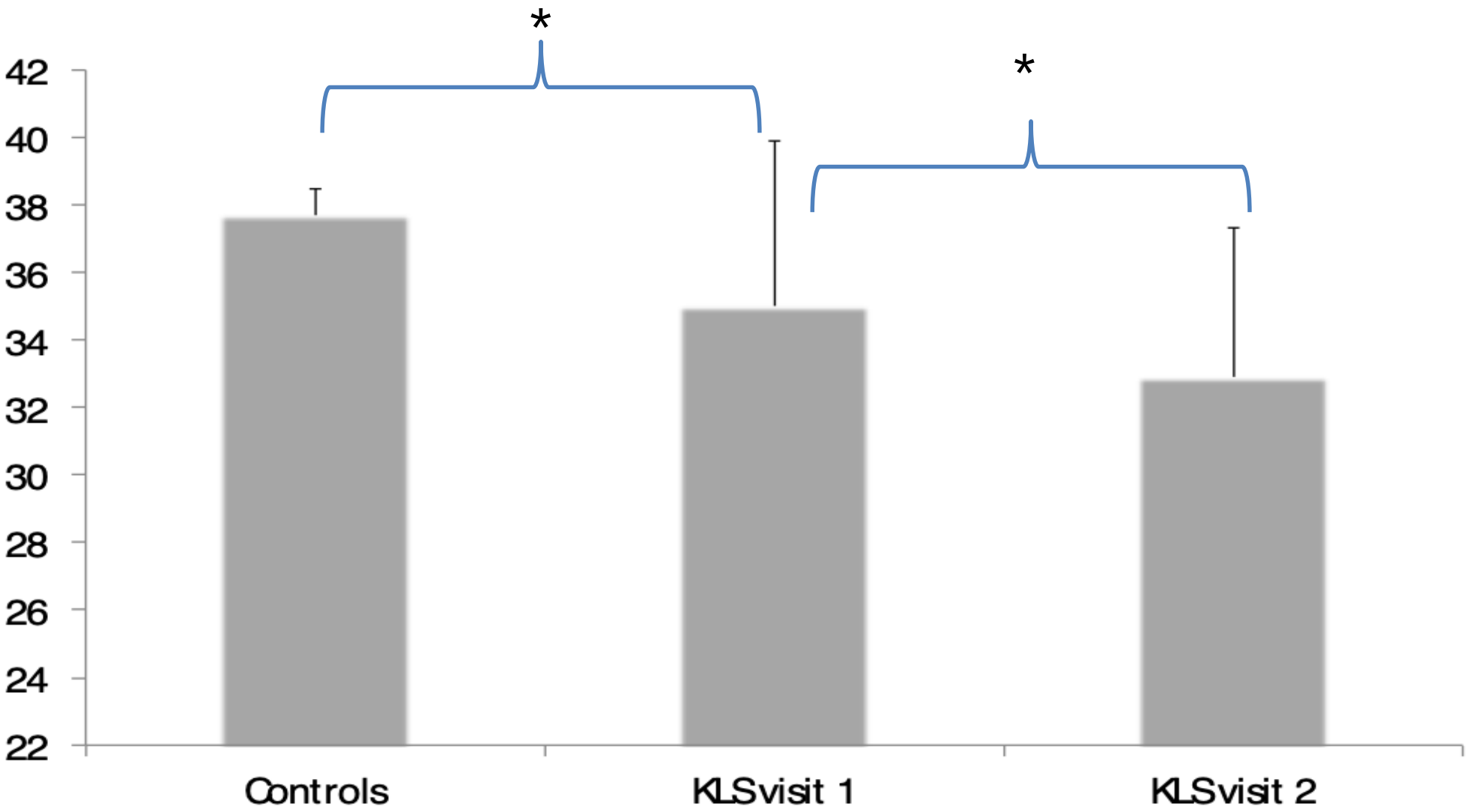
Rey-O figure



Attention and executive functions



FCSRT: Immediate free retrieval



Uguccioni, Sleep 2015

Long term cognitive impairment

- 15% of patients have impaired attention, processing speed or verbal free retrieval
- => regularly (1/y) check cognitive functions, feeling of making an effort

- => remediation and support (eg, make a pause every 45 min, reduce the academic load)
- => we prescribe methylphenidate when needed, just after an episode or when a cognitive effort is requested (eg, tests)

Uguccioni, Sleep 2015

Mental status during « asymptomatic » periods

- On average, patients score almost as controls do on anxiety/depression scale

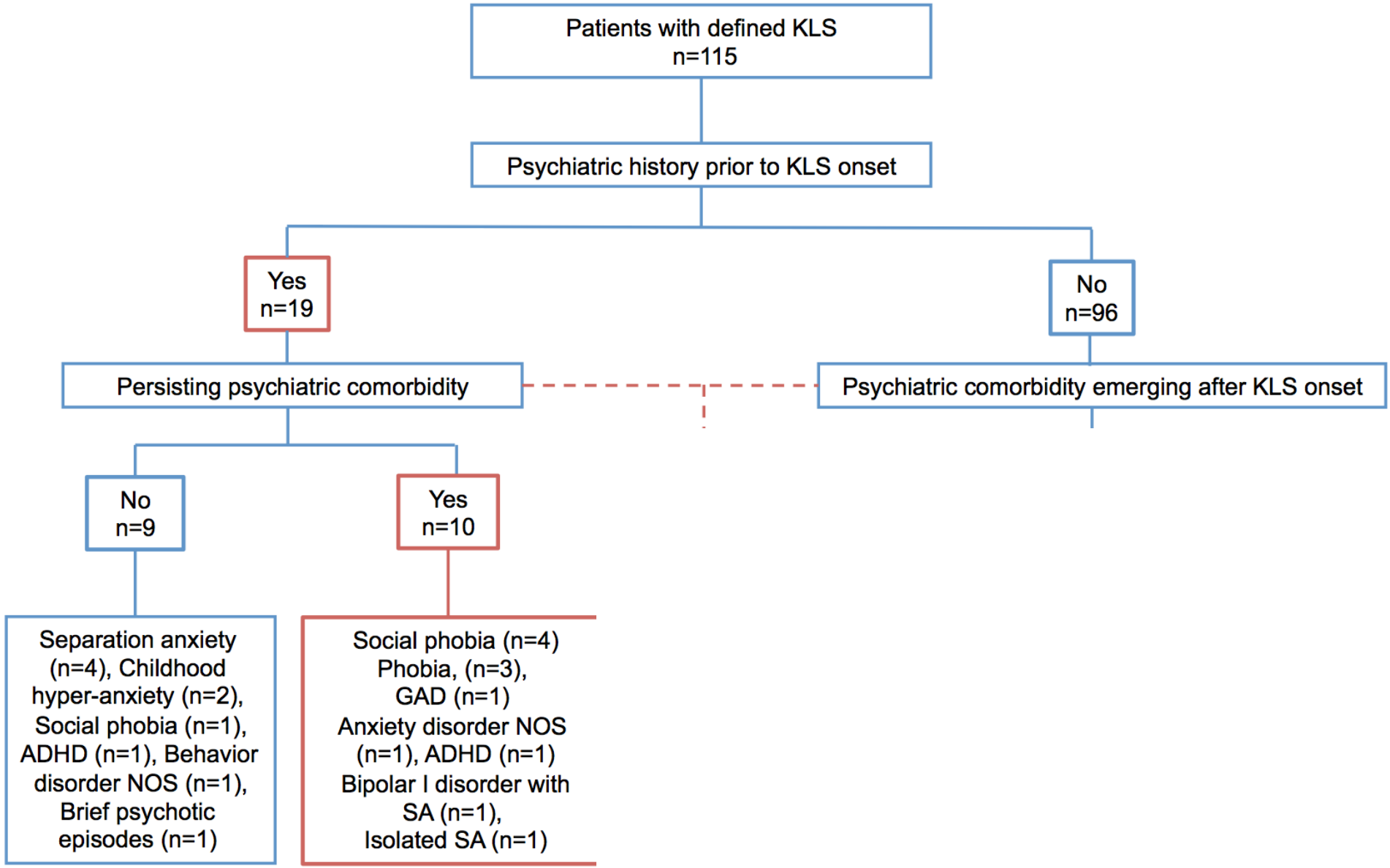
- Their psychiatric history is similar to what is seen in the general teenager population (16% with a history, mostly child anxiety)

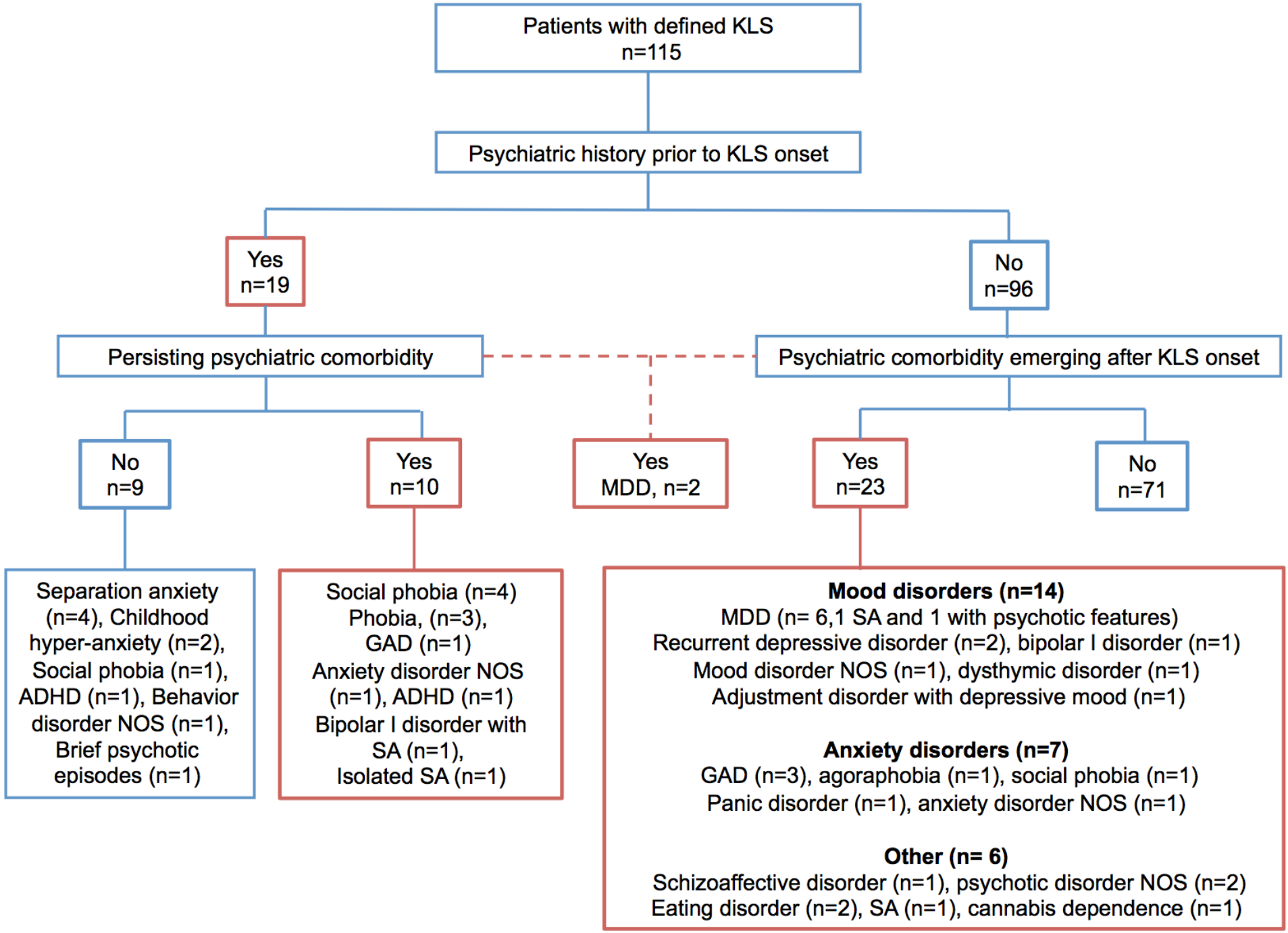
Mental status during « asymptomatic » periods

- Long term psychological follow up in the reference center identified emerging psychiatric problems in 20% of the patients

- Mostly mood disorders and adjustement disorders

Groos, J Sleep Res 2018


Patients with defined KLS
n=115
Psychiatric history prior to KLS onset
Yes
n=19
No
n=96
Persisting psychiatric comorbidity
Psychiatric comorbidity emerging after KLS onset
No
n=9
Yes
n=10
Separation anxiety (n=4), Childhood hyper-anxiety (n=2), Social phobia (n=1), ADHD (n=1), Behavior disorder NOS (n=1), Brief psychotic episodes (n=1)
Social phobia (n=4) Phobia, (n=3), GAD (n=1) Anxiety disorder NOS (n=1), ADHD (n=1) Bipolar I disorder with SA (n=1), Isolated SA (n=1)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Persisting psychiatric comorbidity
Psychiatric comorbidity emerging after KLS onset
No
n=9
Yes
n=10
Yes
MDD, n=2
Yes
n=23
No
n=71
Separation anxiety (n=4), Childhood hyper-anxiety (n=2), Social phobia (n=1), ADHD (n=1), Behavior disorder NOS (n=1), Brief psychotic episodes (n=1)
Social phobia (n=4)
Phobia, (n=3),
GAD (n=1)
Anxiety disorder NOS (n=1), ADHD (n=1)
Bipolar I disorder with SA (n=1),
Isolated SA (n=1)
Mood disorders (n=14)
MDD (n= 6,1 SA and 1 with psychotic features)
Recurrent depressive disorder (n=2), bipolar I disorder (n=1)
Mood disorder NOS (n=1), dysthymic disorder (n=1)
Adjustment disorder with depressive mood (n=1)
Anxiety disorders (n=7)
GAD (n=3), agoraphobia (n=1), social phobia (n=1)
Panic disorder (n=1), anxiety disorder NOS (n=1)
Other (n= 6)
Schizoaffective disorder (n=1), psychotic disorder NOS (n=2)
Eating disorder (n=2), SA (n=1), cannabis dependence (n=1)

Risk factors for long term psychiatric comorbidities

- 20% of patients (25 vs 90)
  - Female sex
  - Number of episodes (20 vs. 13) and time spent in episodes (366 d vs 155 d)
  - Psychiatric symptoms during episodes

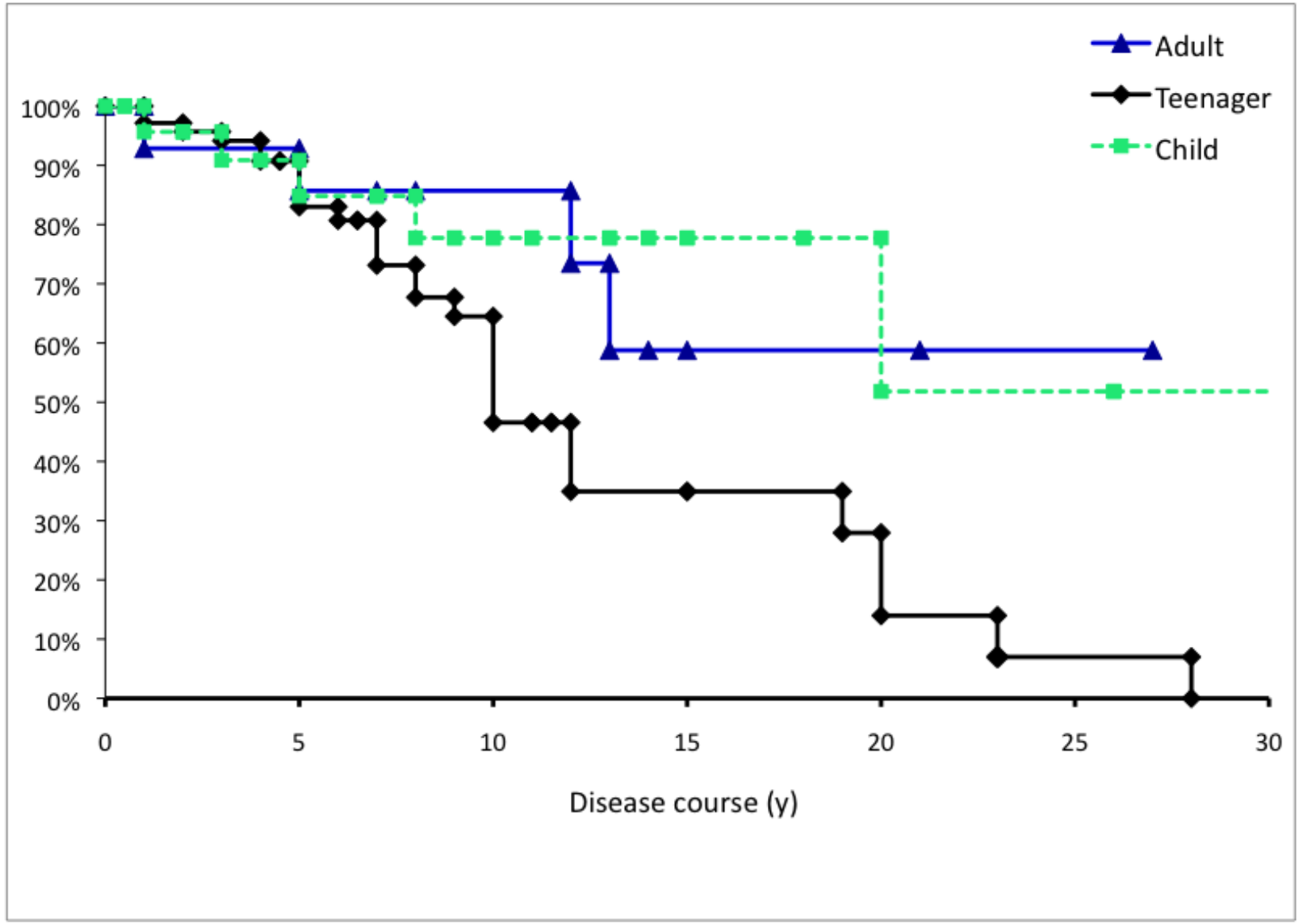
$\Rightarrow$ Identifying vulnerable patients,

$\Rightarrow$ psychological support

Groos, J Sleep Res 2018

3. Preventing new relapses

Disease course



Arnulf, Lancet Neurol 2012

General recommendations 1

- Relapses frequently occur after an infection

=> Avoid infections ++

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

General recommendations 2

- Some relapses occur after alcohol intake

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

Treatment in KLS

- Simple preventive measures:
  - No alcohol intake
  - No infection : wash hands, avoid infected people, make seasonal flu vaccine
  - Keep regular sleep/wake reason (sleep enough)

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

- 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) or contain psychotic symptoms (red flags) => it seems beneficial to try a drug
- Benefit/risk of the drug should be regularly re-evaluated: stop or go rule

Lithium therapy in KLS

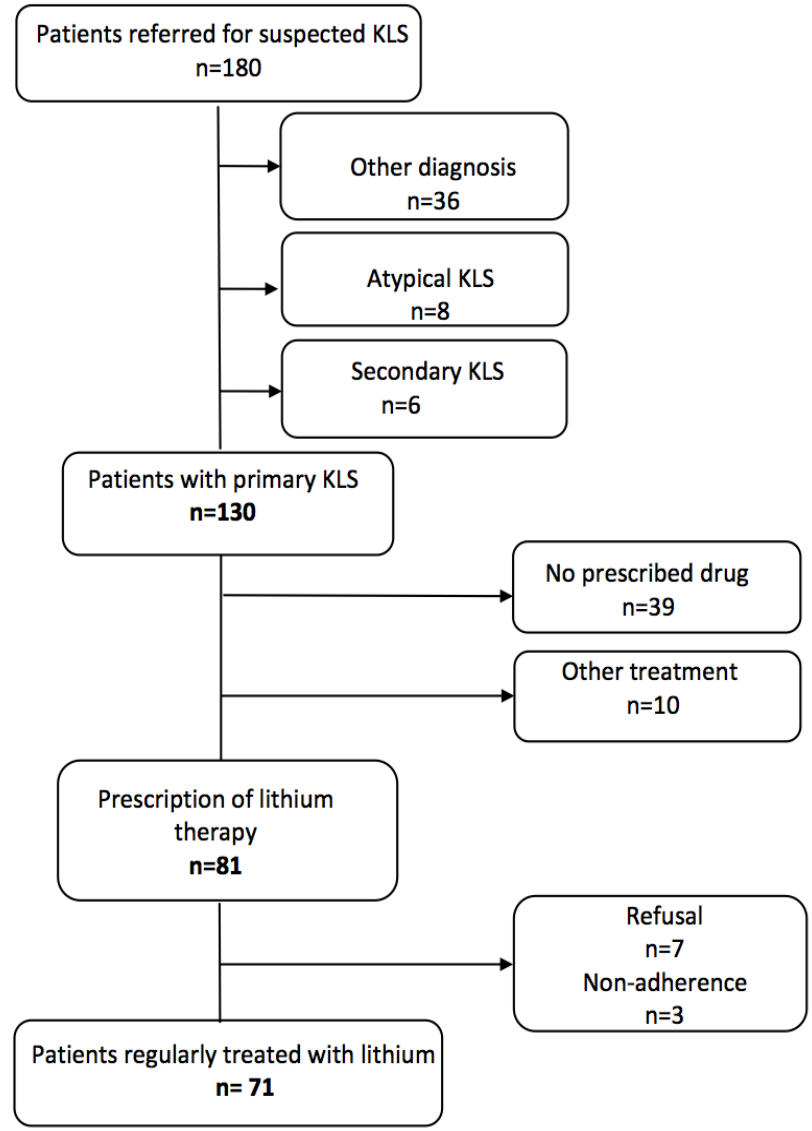
Methods

- 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

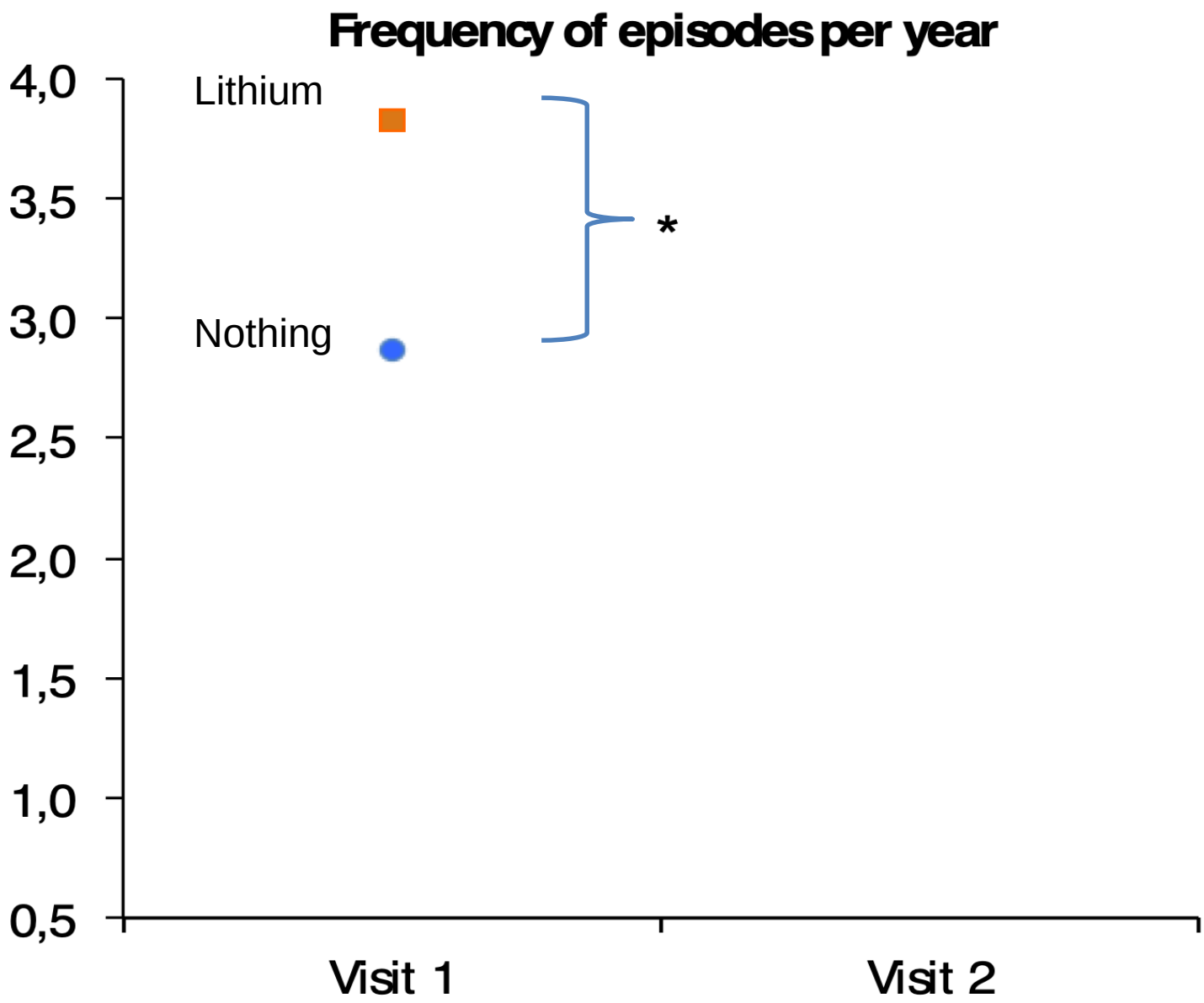
Leu-Semenescu, Neurology 2015

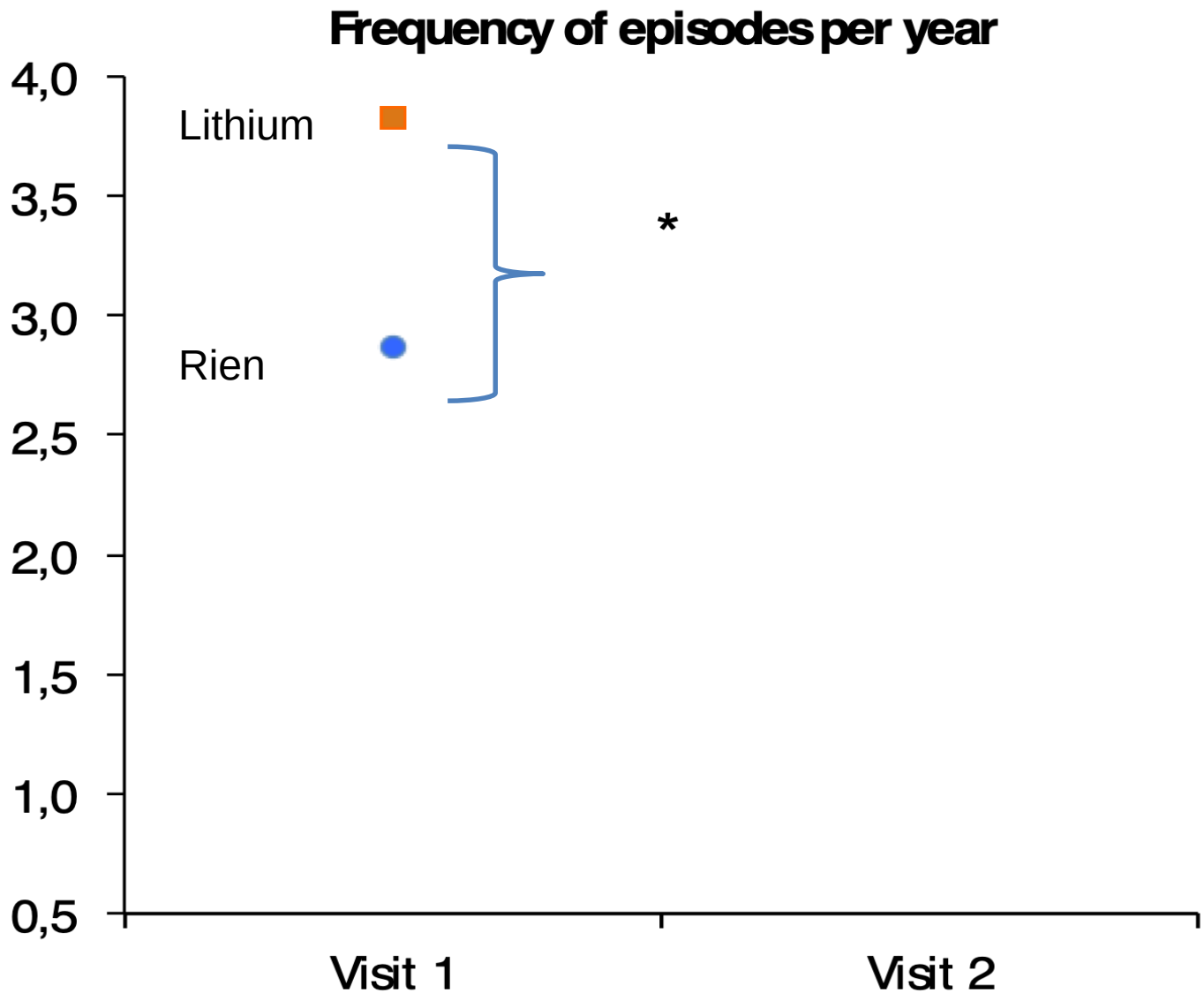
Smaranda Leu-Semenescu



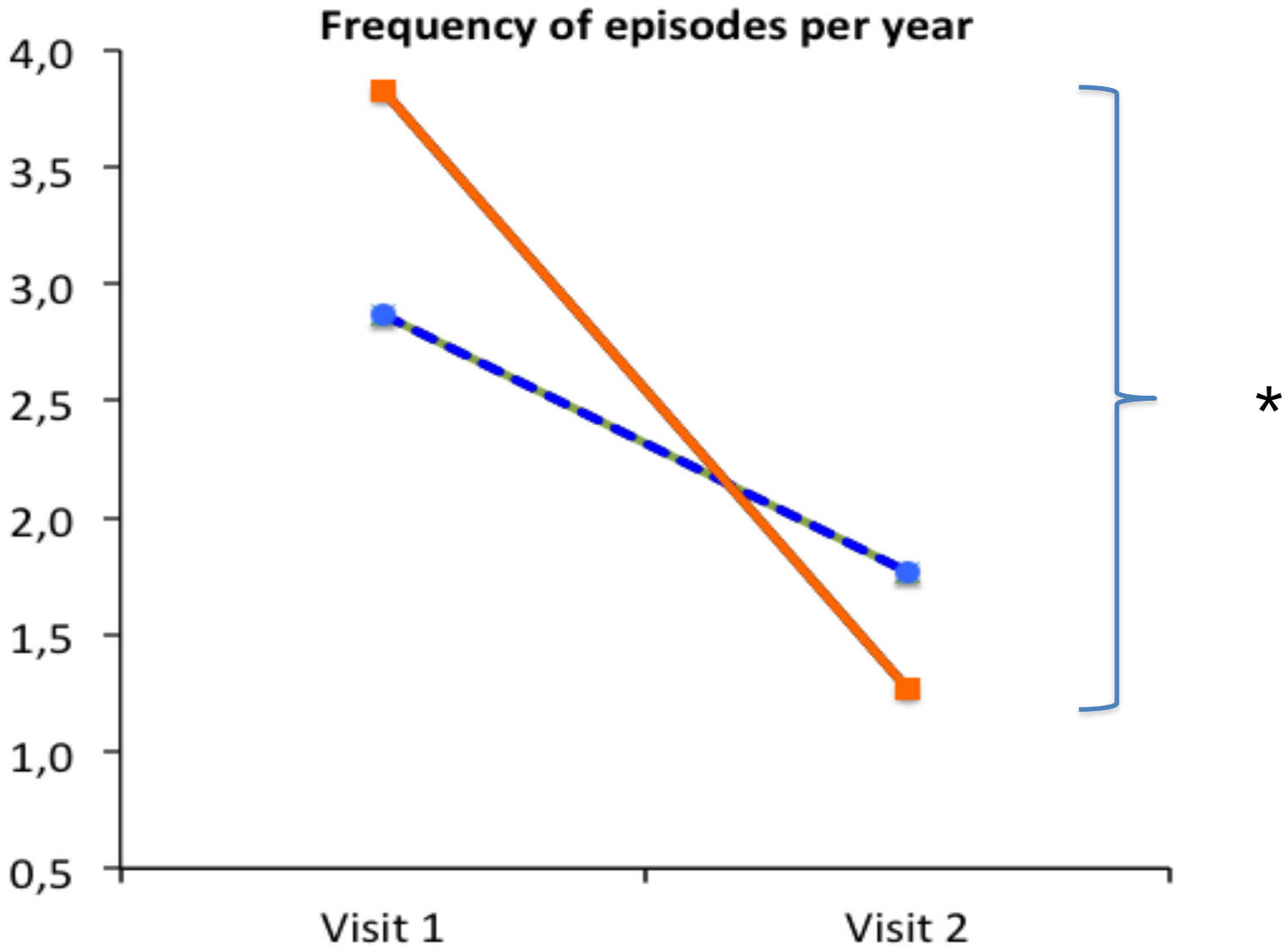
Leu, Neurology 2015

Leu-Semenescu, Neurology 2015

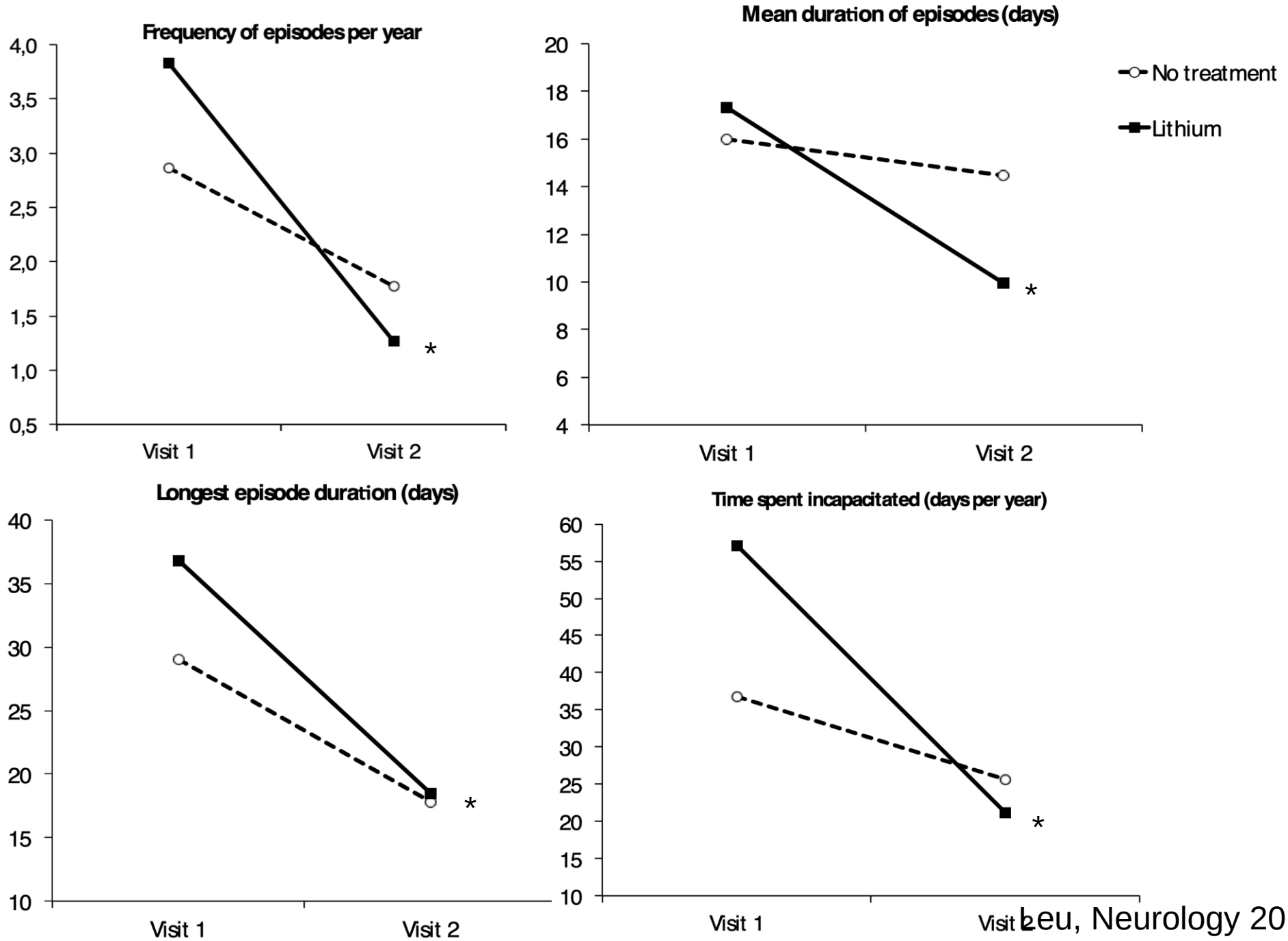




Leu-Semenescu, Neurology 2015

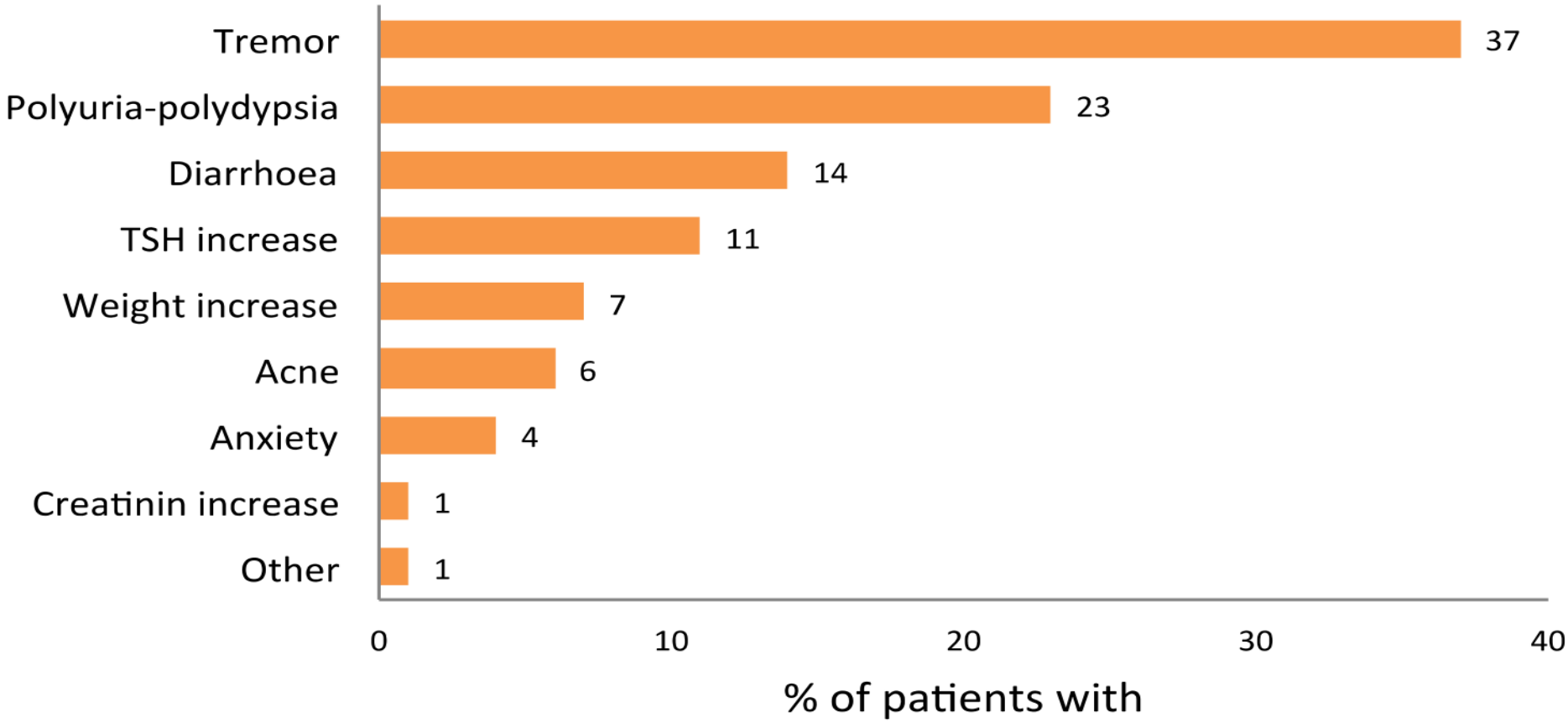


Leu-Semenescu, Neurology 2015



Leu, Neurology 2015

Lithium side effects



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 Lithium level should be high and monitored

Other preventive therapies

- Acetazolamide (Diamox): N=1 published benefit. In Paris, trials in 3 patients, without success

- Valproate: may help (first choice in boys with a mild KLS, but forbidden now in girls as it is deleterious if pregnant), lower level of evidence than Lithium

- Contraceptive pill: no clear preventing effect, but worth trying (+ teenager, sexual disinhibition when in an episode, decrease the fatigue in link with menstruation…)

Mechanisms: still unclear

- Brain functional imaging is often abnormal during symptomatic and asymptomatic periods (associative cortex)
- 5% Family cases + DNA bank (we send all DNA to Stanford) => some genetics advances by Mignot : - Gene TRANK1 does not cause but promotes the disorder
- Inflammatory/autoimmune disorder ? Benefit of lithium and steroids

Conclusion: large series of KLS patients

What has changed in the last 5 years ?

- Check every year for long term cognition (impaired: 15%) and psychiatric health (impaired: 20%) during « asymptomatic periods »: support if needed
- During episodes: consider IV steroids if long episodes
- Prevention: Open, large, controlled study => benefit of lithium therapy
- Treat patients with red flags: long or frequent episodes, psychotic symptoms in episodes

Thank you!

- Health Ministry: French Orphan Disease Program

- KLS Foundation (supported the functional imaging study)
- KLS-France (supported the retrospective study on steroid)