KLS Family Day

16th September 2018

Update on Research

Clinical Research

- Paris Group Update
 - A historic cohort of 220 patients, with 20 new patients per year
 - Recommendations largely based on expert opinion
 - 2 "case-controlled" retrospective studies
 - No prospective RCTs

Paris Group Update

- During bouts
 - Best off at home
 - Limit noise (including mobile phones!), don't try to keep awake
 - No driving hide keys
 - Liaison with school or work
 - Avoid stimulant drugs not helpful
 - Manage headache with standard painkillers or Diamox
 - Admission for suicidal ideation or severe behavioural problems
 - May rarely require antipsychotics, or management of autonomic dysfunction

Paris Group Update

- For long bouts
 - About 1 in 4 patients have bouts over 30 days can these be terminated?
 - Amantidine or IV steroids



First IV steroids series (3 days)



First IV steroids series (3 days)



All IV series



Steroids side effects



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

Paris Group Update

• In between bouts

- Some patients sleep more than usual
- Occasional cognitive complaints between bouts
- 15% of deficits on formal neuropsychometric testing attention, processing speed and verbal abilities
- What about preventing relapses?
 - Avoid infection
 - Flu vaccine
 - Avoid all alcohol for three years
 - Regular sleep wake pattern
- Prophylaxis

Case-Controlled Retrospective Study

- 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







Side-effects of lithium



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 Li level should be high and monitored

Understanding The Origins of KLS

168 primary cases in Literature – cluster of 27 cases in Israel – 80% Ashkenazi



Familial Occurrence of KLS: 4 cases out of 108 probands



Personal medical history in KLS patients and controls

	KLS Patients	Controls	Significance, OR		
	(108)	(108)			
Birth difficulties	25%	7.4%	P=0.0005; OR=4.2		
Development delay	14.8	0%	*P<0.0000011 OR=∞		
Birth or development	34.2%	7.4%	P<0.000001; OR=6.5		
problems					
Genetic diseases ¹	5.5%	0%	* P=0.04; OR= ∞		
Attention deficit disorder	5.5%	0%	* P=0.04; OR= ∞		
Depression	5.5%	3.7%	NS		
Autoimmune diseases	5.5%	3.7%	NS		
Right-handed	48.6%	51.4%	NS		
Age at puberty	12.9±1.5 yrs	12.7±1.2 yrs	NS		
Irregular menstruations	30.1%	21.4%	NS		

¹ Klinefelter Syndrome, von Willebrand syndrome, polycystic kidney, and two cases of mental retardation (one associated with atrophy and ataxia in one brother; the other case with autism and seizure).

 χ 2 or Fisher's exact test (*) whenever most appropriate.

Differentially expressed proteins

- 74 CSF proteins differentially expressed (FDR p-value < 0.005).
- Increased CSF levels in KLS cases associate with microglial/macrophage/monocy tes axis.
- KLS cases appears to have elevated levels of innate immune factors



7.5

5.0

2.5 0.0

-2.5

Top proteins enriched in KLS

- TGF-b2 (Transforming growth factor beta) - also secreted by macrophages, can drive both pro and anti inflammatory responses, wound healing.
- ON (Osteonectin SPARC) & SPARCL1 expressed by astrocytes, macrophages - implicated in cell adhesion, migration and wound repair.
- IGF-1 (Insulin Growth Factor -1) secreted by macrophages dampens immune response and drives injury response

CTRL IN.EPISODE OUT.OF.EPISODE



Summary & Conclusions - Ambati

- 1123 CSF proteins profiled in 22 in-episode KLS cases & 75 controls.
- Elevated levels of innate immune associated proteins in KLS cases Vs controls.
- Clusters relate to Macrophage/microglial innate immune axis.
- May suggest a neuroinflammation and response to wound healing dominated by macrophage related proteins.

Emory Update

Between KLS spells: hypersomnolence meeting ICSD criteria for narcolepsy without cataplexy AND hypersomnia

Sample	Sex	Age	BMI	Age at	Weekly sleep	ESS	TST (min)	SE%	RDI	di plmi	MS (min) SOREMps	SOREMps	CSF- hypocretin (pg/ml)	GABA receptor enhancement		Primary sleep	Additional
		2		onset	(hours)									CSF	Plasma	diagnosis	alagnoses
7	М	21	27.	5 8	84	14	463	89	0.8	0	5.3	3	307	80.6 ± 4.0	44.5 ± 1.8	N-C + LS	Kleine-Levir syndrome
							531	88.3	1.6	0	NP	NP	172				

KLS subjects between spells often exhibit hypersomnolence AND/OR hypersomnia

CASE	ESS	TST (min)	Sleep Efficiency%	SSS	MSL (min)	SOREMps	Nap TST (min)	Nap sleep efficiency %	Overall Sleep (hrs)	"Diagnosis"?
1	7	372	82	2.6	5.5	0/5	64	76.5	7.3	IH
2	4	394	99	NA	4.3	0/5	88.5	96.5	8.04	IH
3	9	443	81	2.2	2.2	0/5	72	91	8.6	IH
4	4	447	94.4	1	4.1	0/5	81.5	97.4	8.8	IH
5	1	588	92	3.7	4.7	0/3	51.5	96.7	10.7	IH
6	14	665	93	1.4	5.7	0/5	90.5	94.3	12.6	IH







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Kleine-Levin Syndrome Treated With Clarithromycin

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CASE REPORTS

Kleine-Levin syndrome (KLS) is a rare sleep disorder characterized by periodic hypersomnia and various degrees of cognitive and behavioral disturbance, hyperphagia, and hypersexuality. Effective treatment is challenging. Stimulants marginally address sleepiness, but may increase irritability and do not improve cognitive and behavioral disturbances. Modafinil may shorten the symptomatic period but not the recurrence rate. Lithium and carbamazepine are beneficial in some cases, possibly related to similarities between KLS and affective disorders. Currently, no single medication is consistently successful in treating the syndrome. Here we report the shortterm effect of clarithromycin in a patient with KLS. **Keywords:** Kleine-Levin, hypersomnia, clarithromycin **Citation:** Rezvanian E; Watson NF. Kleine-Levin syndrome treated with clarithromycin. J Clin Sleep Med 2013;9(11):1211-1212.



Future Directions

- Your samples are being used to support genetic work
- Discussions regarding blood collection during and between bouts
- Migraine study