Kleine Levin Syndrome (KLS) Symposium (March 26, 2015)

This symposium, entitled "Kleine-Levin Syndrome: New information from large series," was held during the 6th World Congress on Sleep Medicine conference in Seoul, Korea. The KLS symposium was part of the larger annual sleep conference, which provides participants from around the world with opportunities to exchange scientific ideas and experiences in sleep medicine to learn about recent advances in the field. The KLS symposium (see http://wasmcongress.com/s51) was organized by Prof Arnulf who has kindly provided the following summary of some new findings in KLS research.

- I. Arnulf (Pierre and Marie Curie University, Paris, France) reported on a study in a group of 120 KLS patients in France, finding that 28% of patients had long (>30 day) episodes and confirmed more birth and developmental problems in KLS patients than in controls, despite normal karyotypes. The findings also stressed the importance of ruling out many neurological (e.g., basilar migraine, epilepsy) and psychiatric differential diagnosis. Full results of the study was published in the Annals of Neurology, January 2015.
- I. Arnulf described a KLS imaging study showing a lower functioning of some associative cortical, thalamic and hypothalamic areas during and between episodes, with the emergence during episodes of a specific involvement of the temporo-parietal junction (possibly causing the derealization) and the prefrontal mesial cortex (possibly in link with the major apathy) in 41 patients with KLS compared to healthy controls. These results were published in the journal Brain in 2014 and received support from the KLS Foundation.
- I. Arnulf further observed in 124 French patients with KLS that attention and verbal memory (retrieval strategies) were durably lower in KLS patients than in controls. This suggests cognitive remediation and academic support as soon as there is a need for it in KLS patients, and that cognitive functions should be regularly tested (e.g., every 1-2 years).
- I. Arnulf also reported a benefit of lithium therapy over 2 years in 70 patients with severe KLS, compared to 49 patients with moderate KLS who were not given drug treatment. The patients treated with lithium spent one month less incapacitated per year than those without lithium, and had few known side effects of the treatment.

- E. Mignot (Stanford University, USA) reported finding a locus in the genes of 600 KLS patients (from around the world) compared to normal subjects. This same genetic locus has been reported to be involved (with a lower odd ratio) in the risk of bipolar disorder. The odds ratio for KLS was remarkably similar across the centers that provided DNA samples for the study (China, Taiwan, France and USA), suggesting that the phenotype and diagnosis is homogeneous across these locations. The KLS Foundation supported part of this study.

- F. Han (Beijing, China) highlighted that appetite was decreased during episodes in more than 54 % of Chinese patients with KLS, while hyperphagia was rarer.
- F. Han obtained CSF from up to 20 patients during and between episodes. He found a consistent trend for hypocretin to decrease from normal to intermediate levels between versus during episodes. Although the levels were not as low as in

narcolepsy, this result provides some support for a role of decreased arousal system during KLS episodes.

- F. Han monitored the arterial pressure and heart rate during 24 h in several patients with KLS, and found that they were consistently lower during than between episodes, suggesting a mild hypotension is common during episode.

- Y.S. Huang (Taiwan) studied 30 children with KLS in a pediatric sleep department, of whom 20 were followed up for 5 years. The frequency of episode clearly decreased with time, and the cognitive function remained unchanged since KLS onset after 5 years and (in absence of a control group) seemed normal. She also highlighted some frequent defects in SPECT imaging, especially in the left thalamus during and between episodes.
- Y.S. Huang insisted on the absence of nocturnal sleep markers during versus between episodes in the 30 children with KLS monitored during both conditions. MSLT were extremely difficult to perform because children did not comply with the MSLT conditions (being awakened and asleep on command). The MSLT latencies were shorter during (around 10 min) than between (around 14 min) episodes, but SOREMPs indicative of "narcolepsy-like" features were exceptional, ruling out any similarity between primary narcolepsy and KLS.

- G. Mayer (Germany) summarized the pathophysiology of KLS and rationale for treatment. He underlined the partial benefit of stimulants on alertness during episodes, although they do not provide benefit to other symptoms. He reported the beneficial treatment of 18 patients in Germany with lithium therapy, some of them for more than 10 years, with relapses when stopping. He discussed the mechanisms of action of lithium, which is beginning to be better identified, which has anti-inflammatory properties, a stimulating effect on dopamine, on circadian gene PER, neuroprotective and reinforce the blood brain barrier.

The session was well attended (approximately 80 people, despite being held at the end of the congress) and there were many questions from the audience.