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Titre de la thèse : *« Narcolepsie infantile : caractérisation clinique et implication potentielle de la neurotransmission de l'histamine »*

Résumé

Narcolepsy is a rare neurological disease characterized by irresistible excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations, dyssomnia. More than 50% of cases their disease onset before the age of 18. The difference between children and adults with narcolepsy was noted. More than 50% of narcoleptic children are obese with a rapid weight gain at the disease onset. Metabolic syndrome (MetS), a constellation of derangements associated with obesity, has increasingly been noted in narcolepsy. Narcolepsy-cataplexy would result from a loss of hypocretin (or orexin) neurons located in the posterior hypothalamus, probably resulted by an autoimmune attack. Histamine neurons, which play an important role in cortical activation and in arousal by interactions with hypocretin neurons, have also been implicated in narcoleptic children. Orexin and histamine neurons could also be implicated in the mechanism of obesity and metabolism in narcolepsy. Pitolisant, a histamine H3 receptor inverse agonist improves sleepiness and cataplexy in adult and child narcolepsy. The main objectives of the thesis were to further characterize the clinical features in children with narcolepsy and notably to investigate whether the histaminergic transmission is involved in sleepiness, obesity, metabolism. To accomplish these goals, we collected and analysed the clinical (orexin, histamine and its direct metabolite tele-methylhistamine levels), anthropometric, metabolic, polysomnographical and pharmacological data from children with narcolepsy.

In the first chapter, we compared the clinical and sleep characteristics of 46 *de novo* children with narcolepsy-cataplexy (61% male, median age 12 y) with 46 *de novo* adults who began their disease after the age of 18 years (61% male, median age 28.5 y). The frequency of obesity (54% vs 17%), night eating (29% vs 7%), parasomnia (89% vs 43%), sleep talking (80% vs 34%), and sleep

drunkenness (69% vs 24%) were higher in children than in adults, the frequency of sleep paralysis was lower (20% vs 55%) but the frequency of cataplexy and the severity of sleepiness were not different. Children scored higher than adults at the attention-deficit/hyperactivity disorder (ADHD) scale. Depressive feelings affected not differently children (24%) and adults (32%). However, adults had lower quality of life than children. There was no difference between groups for insomnia and fatigue scores. Quality of life was essentially impacted by depressive feelings in both children and adults. Obstructive apnea-hypopnea index (OAHI) was lower in children with higher mean and minimal oxygen saturation than in adults. No between-group differences were found at the multiple sleep latency test. The body mass index (z-score) was correlated with OAHI ($r = 0.32$).

Subsequently, we characterized the rapid weight gain phenotype in narcoleptic children. We defined RWG by the BMI z-score slope reported to one year (>0.67 SD) from symptom onset to disease diagnosis. We compared the clinical, metabolic, and sleep characteristics between patients with or without RWG at diagnosis. Pharmacological management, anthropometric, and clinical progression were also evaluated during the follow-up. We found RWG patients were younger at diagnosis than non-RWG patients, despite a shorter diagnostic delay. They had a higher BMI z-score and a higher prevalence of obesity at diagnosis, but not at symptom onset, and higher adapted Epworth Sleepiness Scale and Insomnia Severity Index scores than non-RWG patients. No differences on nocturnal polysomnography and multiple sleep latency tests were found between groups at disease diagnosis. After a median follow-up of 5 years, RWG patients still had a higher BMI z-score and a higher prevalence of obesity despite benefiting from the same therapeutic management and displaying improvement in sleepiness and school difficulties.

The third chapter of the thesis consists in studying the metabolic disturbances in children with narcolepsy. We included 58 *de novo* children with narcolepsy and afterwards compared the clinical and sleep characteristics in groups with different components of MS. We found a total of 17.2 % of children with narcolepsy presented MS, among whom 79.3% presented with high homeostasis model assessment for insulin resistance (HOMA-IR), 25.9% with high body mass index (BMI), 24.1% with low high-density lipoprotein cholesterol (HDL-C), and 12.1% with high triglycerides. Patients with at least 2 MS components had more night eating, lower percentage of slow wave sleep (SWS) and more fragmented sleep as shown by higher awakening and arousal indexes. On multiple sleep latency test (MSLT), they had shorter mean sleep latencies to rapid eye movement (REM) and non-rapid eye movement (NREM) sleep and more sleep onset REM periods (SOREMPs) than those with less than 2 MS components.

The following chapter is dedicated to determine the involvement of histamine transmission on sleepiness, obesity, metabolism in children with narcolepsy type 1 (NT1). We included 53 children

with NT1 (60.4% male, median age 11.6 y) and 26 clinical controls (50% male, median age 13.5 y). Then the cerebrospinal fluid (CSF) histamine (HA), tele-methylhistamine (t-MeHA) levels, spectral analysis on EEG (nighttime NREM sleep, REM sleep and daytime wakefulness) and anthropometric and metabolic parameters were compared between groups. Compared to controls, there were a lower t-MeHA level and a lower ratio of t-MeHA/HA in children with narcolepsy. Children with NT1 showed shorter total sleep time, lower sleep efficiency, shorter sleep latency and REM sleep latency, higher percentage of stage N1 sleep, lower percentage of stage N2 sleep, more waking after sleep onset (WASO) and lower OAHI on night PSG in children with NT1 compared to clinical controls. In addition, a shorter mean sleep latency and more SOREMPs on MSLT were noted in children with NT1. The theta relative power during both night NREM and REM sleep were higher in children with NT1. There were a lower delta relative power and a higher alpha relative power during night REM sleep in children with NT1. The ratio of delta/theta during both night NREM and REM sleep were lower in children with NT1. There were lower ratio of delta/gamma and delta/beta+gamma during night REM sleep. Concerning the daytime wakefulness, a higher delta relative power and lower alpha, sigma, beta, gamma relative powers were noted in children with NT1 compared to clinical controls. There was a positive correlation between t-MeHA levels and night NREM and REM theta relative powers in children with NT1. Glucose was positively associated with histamine levels and negatively associated with ratio of t-MeHA/HA in both children with NT1 and clinical controls.

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Finally, the last chapter is devoted to the therapy of the pitolisant. We included 7 de novo children with new onset of narcolepsy, we assessed polysomnographic characteristics and then these children were treated with pitolisant progressively from 4.5 mg to 36 mg for approximately 2 months. The PSG was evaluated again to observe the effects of Pitolisant on nighttime sleep. There was a tendency of lower sleep efficiency, longer waking time after sleep onset on patients receiving the therapy of Pitolisant compared to those without treatment. No other difference in terms of total sleep time, sleep latency, percentage of N1%, N2%, N3%, REM% and AHI were noted on PSG after therapy.

In conclusion, all these findings enable us to better characterize the clinical and sleep features of children with narcolepsy. Obesity is the prominent clinical manifestation compared to adults with narcolepsy. Not only obesity but also rapid weight gain were identified in children with early onset of narcolepsy. Metabolic disturbances are increasingly been reported in children with narcolepsy which could associated with nocturnal sleep disturbances, daytime sleepiness and eating behavioural alteration. There are alterations on nighttime and daytime microstructure during sleep and wakefulness in children with narcolepsy. The correlations between histamine transmission and both sleep microstructure and glucose levels probably to some extend give the answers to these phenomena.