Metabolic and Pubertal Alterations in Children with Narcolepsy-Cataplexy

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INTRODUCTION AND HYPOTHESIS

Narcolepsy type 1 (also called hypocretin or orexin deficiency syndrome or narcolepsy with cataplexy) is a neurological disorder characterized by excessive daytime sleepiness, cataplexy (sudden loss of muscle tone triggered by emotions), hallucinations, sleep paralysis, impaired night-time sleep and short latency to rapid eye movement sleep after sleep onset. **Narcolepsy Type 1 is caused by a deficiency of hypocretin neurons located in the dorso-lateral hypothalamus probably secondary to autoimmune destruction of hypocretin cells.**

More than half of narcoleptic patients have an onset of symptoms prior to the age of 18 years. Narcolepsy in children is usually characterized by prominent sleepiness, more spontaneous than emotion-triggered cataplexy than in adulthood. Obesity has been reported in 30% of adult narcoleptic patients[1, 2], whereas it occurs in more than 50% of narcoleptic children with increasing body weight manifested in the early course of the disease[3].

More than 50% of adults with narcolepsy have metabolic syndrome. In children, obesity and metabolic anomalies seems also to be more frequent. Precocious puberty has been also described in children with narcolepsy.

<u>Objectives of our study</u>: To study the effect of hypocretin deficiency on metabolic and pubertal characteristics in narcoleptic children. We compared the metabolic and pubertal alterations between 15 children with narcolepsy with cataplexy (narcolepsy type 1 or hypocretin deficient) and 15 control children matched for age, BMI z score.

[1]Kok SW et al Obesity research 2003; [2]Scammell NEJM 2015 ,[3] Inocente et al, CNS neuroscience & therapeutics 2013, [4]Poli et al , Sleep 2013.

Method:

Narcoleptic data were collected from the Reference Center for Narcolepsy and control common obese data from the department of pediatric endocrinology in Mother-Children's Hospital in Lyon, France.
Narcoleptic patients underwent clinical interview, polysomnographic recordings, and human leukocyte antigen typing.

Height, weight, body mass index (BMI), waist circumference, arterial blood pressure and Tanner pubertal stage were evaluated in both children groups.
Plasma lipid and glucose profiles were analyzed. For precocious puberty, plasma concentrations of hypothalamic-pituitary-gonadal axis hormones were determined.

Results: metabolic syndrome

In this study, all the narcoleptic children had cataplexy, HLA DQB10602 and were obese. Both narcoleptic and obese control children were 11 years (5 to 17), 50% male, had a median BMI 26,3 kg/m^2 (21 to 41) and BMI z score 3.6 SD (2.5 to 5).

		age	BMI	BMI z score	HOMA-IR	HbA1C	Steatosis	Advanced or precocious puberty
obese	mediane	11,0 (5,7-17)	26.3 (20.3-41.1)	3.5 (2.5-5)	1.6 (0.9-2.3)	5.4 (4.7-5.9)	1/15	2/15
Narcoleptic children	mediane	11,00 (5-17)	26.3 (20.8-41.5)	3.6 (2.5-6)	2.3 (0.8-4.5)	5.6 (5.1-5.8)	8/15	8/15

- The definition of **metabolic syndrome** have been developed in adults as the presence of at least three of the following abnormalities:
  - **abdominal obesity,**
  - **hypertriglyceridaemia**
  - **low HDL-cholesterol**
  - **fasting hyperglycaemia**
  - **elevated blood pressure.**

  There is not yet a consensus for the definition in children.

- 73% of narcoleptic children had at least one component of the metabolic syndrome compared to 11% in control obese (p=0.004) with insulin resistance.

- 7 narcoleptic children had insulin resistance with an increased HOMA-IR index and 8 had hepatitis steatosis. None of the common obese children had elevated HOMA-IR (p=0.04) and only one boy has hepatitis steatosis (p=0.008).

Results: Puberty

- <u>In the narcoleptic group</u>: 2 girls and one boy have advanced puberty and 3 girls and 2 boys have precocious puberty.
- <u>In the common obese children group</u>: only one girl and one boy have advanced puberty (NS), none had precocious puberty (p=0.02).
- Cerebral and hypothalamic pituitary region MRI were normal in both cases.

Discussion

- For children with narcolepsy, the loss of orexin neurons could be associated with other hypothalamic anomalies.
- Obesity/ metabolic syndrome and precocious puberty are frequently found in narcoleptic children.
- Complexity of all of these symptoms requires a multidisciplinary approach
- Need controlled studies to then evaluate the multidisciplinary follow and the treatment efficiency.

CONCLUSION

BMI-independent metabolic and pubertal alterations in narcoleptic children suggest that hypocretin could modify the phenotype. A careful pubertal and metabolic follow-up of these patients is mandatory as well as tailored therapeutic management.

***The authors declare no conflicts of interest**

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