Non isolated central precocious puberty: prevalence of brain lesions and other associated disorders

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INTRODUCTION

• Non idiopathic central precocious puberty (CPP) is caused either by acquired or congenital hypothalamic lesions visible on magnetic resonance imaging (MRI) or associated with complex distinct genetic and/or syndromic disorders without visible lesion on MRI.

• A knowledge of the different clinical forms of non-isolated CPP is therefore essential when evaluating children with CPP, to ensure that they are appropriate managed.

• A few groups have reported the epidemiology of non isolated CPP. These studies were limited by CNS lesions only, and other associated disorders not evaluated.

AIM OF THE STUDY

This study investigated the different types and the prevalence of non isolated CPP phenotypes in a large group of consecutive patients with CPP.

PATIENTS AND METHODS

• This **observational cohort study** included all patients identified as having non-isolated CPP in the database of a single Pediatric Endocrinology center since the last 11 years (**n=63)**. Patients were classified into **2 categories of CPP** : Those with a CNS pathology with hypothalamic lesions on cerebral MRI findings and those with non hypothalamic MRI findings in patients with associated syndromes and chromosomal or molecular disorders.

• We excluded patients with CPP known due to mutations in the maternally imprinted gene MKRN3, due to previous irradiation and those with CPP related due to international adoption or early exposure to sex steroid.

• Features of syndromic phenotypes with or without chromosomal abnormalities were carefully assessed individually, by a pediatric endocrinologist and a geneticist.

RESULTS

A total of 63 consecutive children (42 girls and 21 boys) with non isolated CPP were identified. Their phenotypes are displayed in Table 1. A broad spectrum of diseases were found according to the presence (*n* = 28; 45% of cases) or absence (*n* = 35; 55% of cases) of visible hypothalamic lesions on MRI of the CNS.

Table 1: Distribution of the phenotypes of the patients from the non-isolated CPP cohort at Robert Debre Hospital (*n* = 63), according to the presence or absence of hypothalamic lesions visible on brain MRI.

	Number (%)
Hypothalamic lesions on brain MRI	***28 (45%)***
Hamartoma	**17 (27%)**
• Isolated	14
• Syndromic or associated with: Pallister Hall syndrome + EPP Mowat-Wilson syndrome [a] Hydrocephalus	3
Glioma	**8 (13%)**
• Isolated	2
• Syndromic (neurofibromatosis type 1)	6
Others	**3 (5%)**
- Interhypothalamic adhesions (IHA)	2
• Isolated IHA	
• Syndromic IHA with optic nerve hypoplasia+ EPP	
- Arachnoid cyst	1
Without hypothalamic lesions on brain MRI	***35 (55%)***
Narcolepsy	**9 (14%)**
• Isolated (familial form, *n* = 1)	8
• Associated with MPHD	1
RASopathy	**4 (6%)**
• Cardiofaciocutaneous syndrome [b]	
• Epidermal hamartoma [c]	
• Neurofibromatosis type 1	
• Ito hypomelanosis	
Encephalopathy or autism spectrum disorder (ASD) [d]	**15 (24 %)**
Other genetic syndromic disorders	**7 (11 %)**
• Silver-Russell syndrome [e]	1
• Temple Syndrome [f]	2
• Williams Beuren Syndrome [g]	1
• Kabuki syndrome [h]	1
• T21 (Down's syndrome)	1
• Usher syndrome (type 1) [i]	1

Figure 3:
Age at evaluation in individuals, according to the differents subgroups in patients with and without visible CNS hypothalamic lesion on MRI.

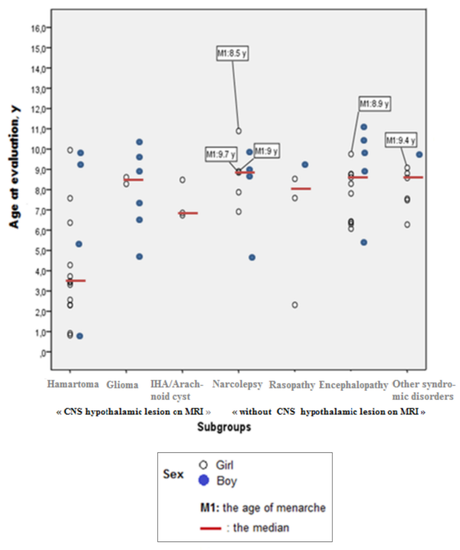

Table 2 - Characteristics of the 63 patients with non-isolated CPP according to the presence or absence of hypothalamic lesions on MRI

	Patient with CNS hypothalamic lesion on MRI (n = 28)	Patient with other associated disorders (n = 35)
Male (n, %)	10 (36)	11 (31)
Age at puberty onset, year	4.95 (1,60;7.50)	7.30 (6.00;7.80) *
Age at evaluation, year	6.44 (3.37;8.54)	8.61 (6.91;9.08) *
Tanner Stage at evaluation:	Tanner 2 (*n* = 15) Tanner 3 (*n* = 11) Tanner 4 (*n* = 1) -	Tanner 2 (*n* = 11) Tanner 3 (*n* = 16) Tanner 4 (*n* = 6) Tanner 5 (*n* = 2)
Target height SDS	0.73 (0.16;1.66)	0.04 (-0.37;0.88)
Height SDS	1.47 (0.57;2.45)	1.32 (-0.02;2.21)
BMI SDS	1.21 (0.73;2.34)	1.46 (0.31;2.40)
Ratio Bone age - chronological age, year	1.40 (1.18;1.83)	1.27 (1.17;1.32) *
LH peak (iU/L)	20 (12.25;35.80)	24 (9.60;30.90)
LH-FSH peak ratio	1.86 (1.18;3.27)	1.93 (0.78;2.70)
Œstradiol (pg/ml)	14.5 (10.0;22.8)	13.0 (7.5;25.0)
Testosterone (ng/ml)	0.73 (0.40;1.10)	1.19 (0.36;2.50)
Associated hormonal deficit	MPHD *n* = 5 [a] IGHD *n* = 3 [b]	MPHD *n* = 1 ** IGHD *n* = 1

*P<0.01
**P<0.02

Patients with hypothalamic lesions were significantly younger (p < 0.01) with a significantly greater BA/CA (p<0.01) at the time of CPP diagnosis and with an earlier onset of clinical signs of puberty (p < 0.01) than patients without pathological MRI findings for the hypothalamus area(Table 2).

EPP: ectopic posterior pituitary;

MPHD: multiple pituitary hormone deficiency;

a: ZFHX1B gene mutation;

b: BRAF gene mutation;

c: HRAS somatic mosaic gene mutation;

d: with or without chromosomal abnormalities including 2q24.2 deletion, 9q22.1q22.3 deletion, Trisomy 13 and mosaic Xq22.1 deletion;

e: maternal uniparental disomy of chromosome 7;

f: maternal uniparental disomy of chromosome 14 (one patient) and paternal loss of methylation at the intergenic differentially methylated region (IG-DMR) at 14q32 (one patient);

g: 7q11 microdeletion; h: MLL2 gene mutation;

i: MYO7A gene mutation.

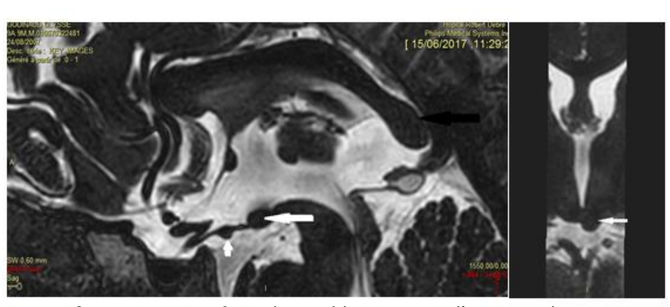

Figure 1*:* MRI of Patient with Mowat-Wilson syndrome: double hypothalamic hamartomas

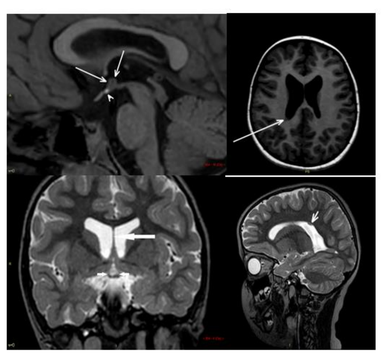

Figure 2*:* MRI of Patient with IHA + EPP+ optic nerve hypoplasia

CONCLUSION

• Our findings suggest that **a large proportion (55%) of patients with non-isolated probable non-idiopathic CPP may have complex disorders without structural hypothalamic lesions on MRI.** These disorders include **narcolepsy, Rasopathy and genetic complexes disorders and or chromosome abnormalities .** We also describe, for the first time, the association of IHA with CPP in a context of midline malformation.

• These original findings have important clinical implications for patient management, as they highlight the need for appropriate careful monitoring for the early recognition and treatment of CPP in patients with such disorders, potentially improving their long-term outcomes.

• Future studies should explore the pathophysiological relevance of mechanisms underlying precocious onset of puberty in these disorders and possible overlap between them.