

# Narcolepsy–cataplexy associated with precocious puberty

**Abstract**—In children, narcolepsy may be the symptom of a brain lesion or genetic disease. The authors report two cases with severe narcolepsy–cataplexy emerging in childhood in close temporal association with obesity and precocious puberty.

NEUROLOGY 2006;66:1577–1579

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The diagnosis of narcolepsy in children is challenging because it may be the symptom of a larger problem, e.g., a brain lesion or genetic disease, such as Niemann–Pick Type C.<sup>1</sup> Frequent misdiagnoses include epilepsy and psychiatric problems.<sup>1</sup>

Renewed interest in narcolepsy has led to earlier diagnosis in children and direct observation of cases closer to onset. These early-onset, rapidly diagnosed cases represent a natural model to study the effect of an acute dysfunction of the hypocretin system, a system that has widespread brain and spinal cord projections, regulating autonomic function, sleep, and metabolism.<sup>2</sup> These patients not only present sleep abnormalities but also gain weight rapidly. This feature is intrinsic to childhood narcolepsy and may correlate with a metabolic dysfunction linked to hypocretin and leptin control.<sup>3</sup>

Experimental studies also suggest the hypocretin system plays a major role in regulating the hypothalamopituitary gonadal (HPG) axis,<sup>4</sup> but clinical data are scarce.

This report describes two cases of severe narcolepsy–cataplexy emerging in childhood in close temporal association with obesity and primary precocious puberty.

**Case 1.** A 7-year-old boy presented in July 2004 with severe daytime somnolence impairing school performance, homework, and sports activities. Nocturnal sleep became disturbed, with auditory and visual hallucinations while falling asleep, frequent prolonged arousals, and nightly terrifying dreams. Within 2 weeks,

cataplexy appeared: nonemotionally triggered episodes of tripping during walking or running, or of sudden head and arms dropping while eating. In mid July, he presented with continuous drowsiness, sleep attacks, and almost continuous hypotonia. Neurologic examination disclosed bilateral ptosis, remarkable generalized hypotonia, dysmetria, and fluctuations of consciousness accompanied by head drops. Brain MRI (figure), routine CSF, search for oligoclonal bands, protein and cellular counts, muscle biopsy, fibroblast skin biopsy (for Niemann–Pick Type C), and routine screening for metabolic and autoimmune diseases were all negative. Epilepsy was suspected, and clonazepam, valproic acid, and lamotrigine were given in various associations; IV corticosteroid therapy (methylprednisolone) was also initiated, all without any clinical changes.

In December 2004, the patient was referred to us when the parents recognized his condition on a video spot on narcolepsy sponsored by the Italian Narcolepsy Association (Associazione Italiana Narcoletti [AIN]). We observed obesity (body mass index [BMI] 21.9 kg/m<sup>2</sup>)—with a progressive weight gain of 16 kg since disease onset, sleepiness, and a state of almost continuous cataplexy–hypotonia (see video—Case 1). He also displayed secondary sexual characteristics. The diagnosis of narcolepsy–cataplexy was readily confirmed by polysomnography (PSG) (table 1) and MSLT (mean sleep latency of 2 minutes and 2/5 sleep-onset REM periods [SOREMPs]). IQ (Wechsler Intelligence Scale for Children-Revised) was normal (total score 87), as were the results of neuropsychological, memory, and attention assessments. HLA typing was positive for HLA-DQB1\*0602. CSF hypocretin-1 measurement was undetectable. Hypothalamic proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS) showed low N-acetyl-aspartate to creatine ratio (NAA/Cr): 1.44—normal values range 1.54 to 2.01. The diagnosis of idiopathic central precocious puberty was confirmed on the basis of height (136 cm, 75th percentile), weight (40.5 kg, >97th percentile), testicular enlargement (both 4 mL), pubic hair, bone age (11 years), and hormonal evaluations (table 2). Narcolepsy was treated with modafinil and venlafaxine, with rapid improvement.

**Case 2.** A 7-year-old girl presented in September 2003 with overwhelming sleep attacks while playing, eating, or watching television and nocturnal sleep disturbed by vivid and unpleasant dreams. One month later, leg weakness, jaw shaking, and head dropping started to occur whenever she laughed. No diagnosis was given, and observation was suggested. A weight gain of 10 kg in 2 months, rapid height increase, and early signs of secondary sexual development (breasts and pubic hair) were noted by the parents. As in Case 1, the diagnosis was made 2 years later, after the parents recognized the condition when viewing the AIN television spot, directing their daughter to our department. Cataplexy, sleepiness, hypnagogic hallucination, and automatic behavior were all present. She presented with generalized mild hypotonia and almost continuous cataplexy. Frank cataplexy was readily elicited by laughing while watching cartoons (see video—Case 2). Clinical examination disclosed obesity (BMI 21.5 kg/m<sup>2</sup>; height 142 cm, >97th percentile; weight 43.3 kg, >97th percentile). Head circumference was more than the average for age (55.5 cm, >98th percentile). HLA typing indicated DQB1\*0602. Brain MRI (see figure) and routine CSF examination results were normal, and the result of search for oligoclonal bands was negative, whereas CSF hypocretin-1 was undetectable. <sup>1</sup>H-MRS showed hypothalamic NAA/Cr ratio below the normal range (1.36). PSG findings were typical for narcolepsy (see table 1). MSLT mean sleep latency was

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The study was partially supported by NIH grant NS232724 to E. Mignot.

Disclosure: The authors report no conflicts of interest.

Received October 3, 2005. Accepted in final form February 7, 2006.

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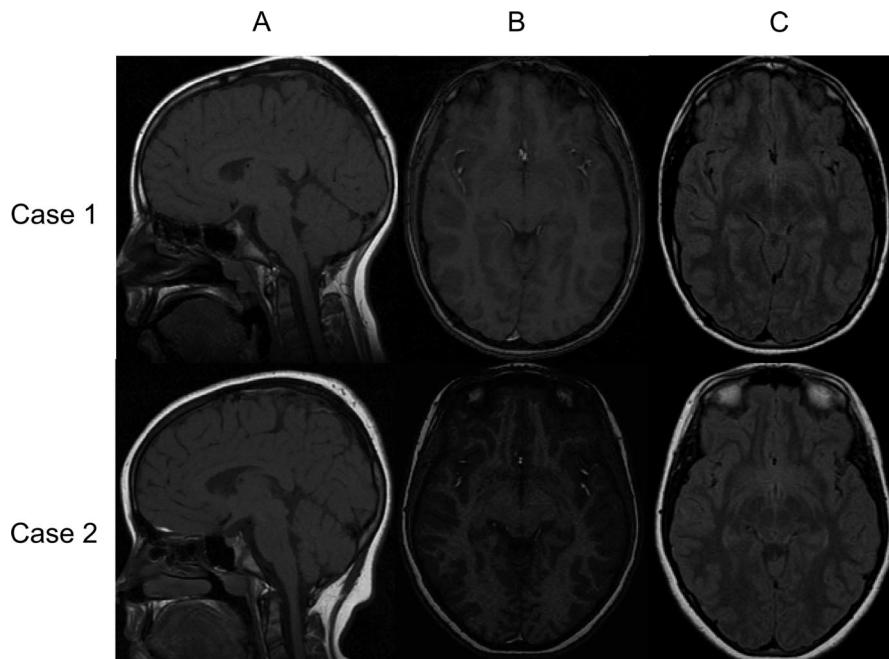


Figure. Patients 1 and 2 sagittal fast spin echo T1-weighted ( $TR = 600$  milliseconds;  $TE = 12.1$  milliseconds) (A), axial fast spoiled gradient echo ( $TR = 250$  milliseconds;  $TE = 2.4$  milliseconds) (B), and axial fluid-attenuated inversion recovery ( $TR = 8,002$  milliseconds;  $TE = 85$  milliseconds,  $IT = 2,000$ ) MRIs. All images were acquired with a slice thickness of 3 mm and slice gap of 0 mm. Normal in both cases.

1 minute, and 5/5 SOREMPs were observed. IQ (Wechsler Intelligence Scale for Children-Revised total score 114), neuropsychological, memory, and attention evaluation results were all normal. The rapid height increase, early signs of secondary sexual development (breasts and pubic hair, bone age 11 years), and hormonal examination (see table 2) indicated a central precocious puberty. Narcolepsy was treated with modafinil and venlafaxine, with improvement.

**Discussion.** In these two cases, narcolepsy–cataplexy, obesity, and precocious puberty were associated. A similar association was recognized in one case 20 years ago.<sup>5</sup> A peculiar feature of these children was the abrupt onset, the unusual severity of cataplexy, and the significant weight gain. Because narcolepsy is rare before age 6 years, the association with precocious puberty may be more frequent than anticipated. Indeed, in most prepuberal children, onset is closer to 10 to 12 years, and it may be impossible to document an early puberty at an age already close to normal pubertal development. The temporal

association of narcolepsy onset with the recognition of precocious puberty suggests causality, although several mechanisms could be involved.

The association of hypersomnolence, cataplexy, obesity, and precocious puberty in these cases may reflect a broadly based hypothalamic abnormality that included the hypocretin cell group and adjacent

**Table 2** Clinical and laboratory features

	Case 1	Case 2
Age at puberty diagnosis, y	8*	7*
Testicular volume, mL	4*	—
Breasts	—	3–4*
Pubic hair	2*	2–3*
Bone age advanced, y	11*	11*
BMI, kg/m <sup>2</sup>	21.9	21.5
Testosterone, ng/mL	1.06*	—
Estradiol, pg/mL	—	38*
Prolactin, ng/mL	24.1	20.1
TSH, $\mu$ U/mL	1.27	1.66
GH, ng/mL	3.1	4.9
ACTH, pg/mL	23	10
LH-RH test		
Basal FSH, mU/mL	1.7	5.6
Peak FSH, mU/mL	3.3*	13.4*
Basal LH, mU/mL	2.8	4.6
Peak LH, mU/mL	12.9*	29.2*

\* Indicators of precocious puberty.

BMI = body mass index; TSH = thyroid-stimulating hormone; GH = growth hormone; ACTH = adrenocorticotrophic hormone; LH-RH = luteinizing hormone-releasing hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone.

Results are given as minutes.

TRT = total recording time; TST = total sleep time; REM = rapid eye movement; SWS = slow wave sleep.

structures. Indeed, sleepiness, obesity, and precocious puberty have been already described in an 11-year-old boy presenting behavioral disturbances (pica) and chronic lead intoxication.<sup>6</sup> In this case, however, cataplexy was absent, and narcolepsy was ruled out by polysomnographic studies. Such a case may have involved adjacent hypothalamic dysfunction while largely sparing the hypocretin cell group. In our two cases, narcolepsy was fully documented by PSG, MSLT, direct cataplexy observation, HLA-DQB1\*0602 positivity, and low CSF hypocretin-1. Hypothalamic involvement was also confirmed by <sup>1</sup>H-MRS findings mirroring those reported in adults with narcolepsy-cataplexy.<sup>7</sup> Whether or not the broader hypothalamic abnormality was of temporary (e.g., in the context of an inflammatory/autoimmune process directed toward hypocretin cells) or more permanent nature is unknown.

Alternatively, hypocretin could be involved in the regulation of the HPG axis, with hypocretin deficiency precipitating puberty. However, this is unlikely because hypocretin is reported to increase luteinizing hormone (LH) release, a factor known to trigger puberty. Further, intracerebroventricular (ICV) injections of hypocretin-1 in animals trigger LH release in ovariectomized rats, whereas ICV injection of anti-hypocretin-1 antibodies abolished the preovulatory LH surge in intact female rats.<sup>2</sup> Additionally, hypocretin-1 promotes gonadotropin-releasing hormone (GnRH) release in hypothalamic explants from male rats.<sup>8</sup> Last, hypocretin deficient adult male patients had decreased LH secretion but normal response to GnRH.<sup>9</sup>

Finally, precocious puberty could be indirectly related to the rapid weight gain or metabolic dysregulation. Obesity and precocious puberty are known to be associated in certain populations.<sup>10</sup> Rapid weight gain preceded the recognition of puberty in both of our cases.

### Acknowledgment

The authors thank Ms. Alessandra Laffi for secretarial assistance and Ms. Anne Collins for English editing. They also thank Prof. Piero Pirazzoli and Dr. Luca Vignatelli for help in revising the manuscript.

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