Narcolepsy-cataplexy and psychosis: a case study

Francesca Cañellas-Dols, Carlos Delgado, Celso Arango-López, Rosa Peraita-Adrados

Hospital Universitari Son Espases; Institut d'Investigació Sanitaria de Palma, IdISPa; Palma de Mallorca (F. Cañellas-Dols). CIBERSAM (C. Delgado, C. Arango-López). Hospital General Universitario Gregorio Marañón; IiSGM; School of Medicine; Universidad Complutense de Madrid; Madrid, Spain (C. Delgado, C. Arango-López, R. Peraita-Adrados).

Corresponding author:
Rosa Peraita-Adrados MD, PhD. Sleep and Epilepsy Unit. Clinical Neurophysiology Service. Hospital General Universitario Gregorio Marañón. IiSGM. School of Medicine. Universidad Complutense de Madrid. Doctor Esquerdo, 46. E-28007 Madrid (Spain).

E-mail:
rosa-peraita@telefonica.net

Accepted:
22.05.17.

How to cite this paper:
Cañellas-Dols F, Delgado C, Arango-López C, Peraita-Adrados R. Narcolepsy-cataplexy and psychosis: a case study. Rev Neurol 2017; 65: 70-4.

Versión española disponible en www.neurologia.com

Aims. To report a challenging patient a girl who developed narcolepsyy with cataplexy (NT1) and a psychosis during adolescence. To discuss diagnostic and therapeutic challenges of the comorbid cases.

Case report. A 14-year-old girl was referred to Sleep and Epilepsy Unit for excessive daytime sleepiness, impaired nocturnal sleep, binge eating and weight gain, over the last year. After being diagnosed with a NT1 the patient was treated with modafinil and sodium oxybate. She was hospitalized for psychotic symptoms after starting NT1 treatment. Withdrawal of the narcolepsy treatment and initiation of haloperidol 1 mg/day (the only antipsychotic treatment she could tolerate) improved the delusions, hallucinations and dysphoria but worsened the narcolepsy symptoms. Polysomnography showed fragmented nocturnal sleep and five sleep REM onset periods in MSLT. Positive HLA-QB1*06:02 and undetectable level of hypocretine in the cerebrospinal fluid were found. MRI and CT-scan were normal. Diagnostic Interview for Genetic Studies Adapted for Narcolepsy (DIGSAN) questionnaire confirmed that patient presented a dual diagnostic NT1 and psychotic symptoms. The last sleep follow-up while on psychopharmacological treatment, showed an increased sleep efficiency index. She currently has severe somnolence, obesity, and partial cataplectic attacks along with normal mood, academic failure and social isolation.

Conclusion. The coexistence of narcolepsy with psychoses is a rare clinical entity, more frequent in adolescents than in adults. The comorbidity of the two illnesses worsens clinical and therapeutic prognosis and also suggests interesting pathophysiological hypotheses.

Key words. Comorbidity. Narcolepsy-cataplexy. NT1. Psychotic disorders. Sleep wake disorders.

Introduction

Impaired sleep patterns can take various forms and can be interpreted as a psychiatric disorder or vice-versa. This can be of particular concern in diseases such as narcolepsy. According to the International Classification of Sleep Disorders (ICSD-3) [1]. Narcolepsy with cataplexy has been renamed as narcolepsy type I (NT1). The main symptoms are excessive daytime sleepiness (EDS), irresistible sleep attacks, and disturbed nocturnal sleep, as well as cataplexy, sleep-related hallucinations and paralysis. NT1 is a disease of the central nervous system caused by a deficiency in hypothalamic neurotransmission, through a selective loss of hypocretin producing neurons causing a hypocretin 1 (Hcrt-1) deficiency [2,3]. This very specific mechanism of neural destruction and its close association with the HLA-DQB1*06:02 in almost all patients, potentially indicates an autoimmune mechanism in its pathophysiology. Although, the existence of specific autoantibodies has not yet been demonstrated.

The age of onset is variable with a peak in adolescence and another one around 35 years of age. Its prevalence in Spain is similar to other European countries and North America around 0.02% in adults. Prevalence in children and adolescents between 5 and 19 years of age in European countries was estimated to be 0.83 per 100,000 [4].

In a recent study, our data reflects a premorbid state in those individuals genetically predisposed to NT1 that begin to feel doze and prefer to be alone, a type of avoidance behaviour. This finding implies that psychological factors are involved at the beginning of the disease [5].

The comorbidity of NT1 and psychosis is an uncommon but very dramatic association. The frequency of this association is unknown but appears to be more frequent in children and adolescents. In the majority of cases with NT1 reported, patients had an early onset [6] of narcolepsy often in childhood. Huang et al studied a sample of 102 of children with narcolepsy and found that 10% developed schizophrenia at follow-up [7]. Compared with other children and adolescents with narcolepsy, the onset of the disease in these cases was earlier and characteristically NT1 symptoms appeared earlier than psychotic symptoms. In relation to adolescents who presented only schizophrenia, the patients with comorbid pathology had more visual

hallucinations in addition to the auditory ones, were more obese and more resistant to the treatment with antipsychotics. In adult patients, the incidence of psychosis does not appear to be significantly higher among patients with narcolepsy than in the general population [8].

The diagnosis and treatment of patients with both pathologies is difficult because the aetiology of the clinical symptoms can be confusing. In addition, medications used to treat narcolepsy may increase psychotic symptoms, while treatment with antipsychotic drugs increases sleepiness. In some patients with NT1 the occurrence of psychotic symptoms has been considered a side effect of treatment with psychostimulants [9]. Psychotic symptoms have been reported following treatment with amphetamines but also with modafinil [10] and even with sodium oxybate [11], which are currently considered the first-choice treatments due to hyper-dopaminergia induced by these drugs. However, it is a controversial subject in the literature [12]. Treatments are not the only cause of the onset of psychotic symptoms in narcolepsy, as psychotic disorders have also been reported in patients who have not received any treatment for narcolepsy [6,7].

In this paper, we present a complex patient who was treated for an ADHD in childhood, and who later developed a narcolepsy with cataplexy and a schizophreniform disorder in adolescence. The comorbidity of the two diseases is confirmed by clinical symptomatology, HLA-DQB1*06:02 typing positive, Hcrt-1 level in cerebrospinal fluid (CSF) < 110 pg/mL, polysomnographic record (PSG) followed by the multiple sleep latency test (MLST) and the Diagnostic Interview for Genetic Studies adapted for Narcolepsy (DIGSAN) [6] and clinical evolution over the last four years.

Case report

A 14-year-old girl who was seen for the first time in the Sleep Unit of the Gregorio Marañón University Hospital in Madrid in February of 2013. A paediatric neurologist referred her because for more than a year she had excessive daytime sleepiness, impaired nocturnal sleep, binge eating and progressive weight gain. He had no family history of sleep disorders. As a psychiatric background, a mother's cousin had been diagnosed with schizophrenia. She was born after normal pregnancy and vaginal delivery. Newborn weight was 2800 g. Metabolic screening was negative and development (psychomotor and weight-to-height ratio) were normal. While in primary school, her teachers found that she had difficulties with reading and writing and attention problems. As a result, she had to repeat the fourth grade. According to parents, before the age of 7 she was a very active and short sleeper. Her appetite and weight were normal.

At age 7, she was diagnosed with attention deficit hyperactivity disorder (ADHD) and treated with methylphenidate for one year. Parents said that after starting this treatment she began to gain weight and to sleep more, which they considered as a side effect of the treatment. He experienced menarche at 10 years of age.

Episodes of irresistible daytime sleepiness occurred at age 12 years while on holidays at the beach (August 2011) associated with increased appetite. During the following school year she was always tired and sleepy and experienced 3-4 daily episodes of irresistible sleepiness as well as disturbed nocturnal sleep (trouble falling asleep and frequent awakenings) in addition to night eating episodes and terrifying nightmares.

In October 2011, she was referred to the Emergency Department for 'dizziness episodes'. The physical and neurological examinations were normal. A standard EEG preceded by partial sleep deprivation, showed normal wake pattern and sleep N1 and N2 phases. The cranial MRI and CT-scan were normal. Laboratory tests showed a low serum ferritin, treated with oral iron.

The first cataplexy attack occurred at the age of 13 while she was having lunch and laughing watching TV.

The onset of psychotic symptoms is less clear. Her mother remembers that at 11 years old she refused to go to school because she said the other children were laughing at her. She started having visual hallucinations at the age of 12; believing that a picture of her grandfather (deceased 3 years before) changed and he 'looked meanly' at her. Auditory and kinaesthetic hallucinations and delusional ideas almost simultaneously appeared. In September 2012, hallucinations worsened and a child psychiatrist put her on risperidone 0.5 mg/day, but treatment has to be discontinued due to adverse side effects (hyperprolactinemia with galactorrhoea and weight gain).

She was referred to the Sleep Unit on suspicion of narcolepsy with cataplexy (NT1). The polysomnographic study followed the following morning by a multiple sleep latency test (MSLT) and HLA-DR-DQ typing (Tables I and II) confirmed the diagnosis. Treatment for NT1 was initiated with sodium oxybate (4 g/day) and two months later modafinil (100

Table I. Clinical, complementary examinations and treatment during four years of follow up.

	February 2013	April 2015	January 2016	January 2017
Age (years)	14	16	17	18
Body Mass Index (kg/m^2)	31.4	36.5	37	39.7
Pediatric Daytime Sleepiness Scale	29	22	21	
Ullanlinna Narcolepsy Scale	24			
Treatment	None	None	Haloperidol, biperiden, metilphenidate	Haloperidol, biperiden, venlafaxine
Human leukocyte antigen class II	HLA-DRB1*15:01/ DQB1*06:02			
Hypocretin-1 levels	10 pg/mL			
Anti-NMDA receptor antibodies	Negatives			
Severity of cataplexy [a]	2	3	3	2
Hypnagogic hallucinations	Yes	Yes	Yes	Yes
Non-hypnagogic auditory hallucinations	Yes	No	Yes	No
Sleep paralysis	No	No	No	No

NMDA: N-metil-D-aspartate. [a] Cataplexy severity using EU-NN criteria [19]. Mild to moderate: 1 (≤ 1/year), 2 (≤ 1/month), 3 (≤ 1/week); severe: 4 (≤ 1/day), 5 (≥ 1/day).

mg/day) was added. A few days after initiating modafinil, the treatment of narcolepsy had to be stopped and hospitalized in the Unit for Child and Adolescent Psychiatry due to worsening of psychotic symptoms in May 2013. Symptoms included increased auditory hallucinations, irritability, mood dysphoria, suicidal ideation, and behavioral disturbances. Several therapeutic trials with different antipsychotics, including aripiprazole, were performed during admission, but the only antipsychotic treatment he could tolerate was haloperidol 1 mg/day. With this treatment, gradually disappearing delusions, hallucinations and improved her contact with the reality and mood, but worsened drowsiness and attacks of cataplexy. Three new relapse episodes with similar symptoms were observed during follow-up in outpatient psychiatric clinics. Treatment with haloperidol was maintained at a variable dose (between 1 and 3 mg day) according to severity of psychotic symptoms, as well as hallucinations and delusional ideas, together with 4 mg biperiden to control extrapyramidal symptoms as it suffered a dystonia in one occasion.

In June 2014, due to continued major somnolence and frequent cataplexy crisis, a new trial was attempted with low doses of sodium oxybate, maintaining antipsychotic treatment, but had to be discontinued again due to the appearance of delusional ideas and suicidal ideation.

In April 2015, the psychotic symptoms remitted and she was hospitalized for withdrawal of the antipsychotic medication to perform a follow-up PSG and MSLT (Table I). The last PSG follow-up in January 2016 while on psychiatric treatment, showed an increased sleep efficiency index (Table I). She is now 18, she currently has severe EDS, obesity, and partial weekly cataplexy attacks along with normal mood, academic failure and social isolation. She is treated with low doses of haloperidol (because she has bad tolerance and resistance to any other antipsychotic drug) and with venlafaxine.

In the last follow up –January 2017– a secondary amenorrhea and hirsutism signs was observed. A gynaecologic examination was performed and an ultrasound scan suggests polycystic ovaries. She is treated with venlafaxine retard 187.5 mg/day; 40 oral drops of haloperidol and biperiden 4 mg/day.

Additional diagnosis (DSM-5). Axis I: unspecified psychotic disorder (F29), unspecified psychological development disorder, ADHD (F90.1 retrospective). Axis II: specific developmental disorders of speech and language (F80.9 retrospective). Axis III: limited level of intelligence. Axis IV: narcolepsy type 1 (G47.4). Axis V: 50.

Discussion

Sleep disorders have historically been ignored in childhood and adolescent psychiatry, although sleep disturbances and psychiatric disorders may, at least in part, be due to common mechanisms [13]. Excessive daytime somnolence –usually the first symptom in childhood narcolepsy [14]– may manifest paradoxically with hyperactivity and be misdiagnosed as an ADHD. This could be the case in this particular patient. Although we do not have enough retrospective information to clarify this point, somnolence along with weight gain may have been the first symptoms of narcolepsy, which appeared almost two years before the first sleep attack.

The association of narcolepsy and mental illness has historically been challenging [15]. Narcolepsy has been misdiagnosed in some cases as a mental illness due to common symptoms to both diseases especially if cataplexy is unrecognized. In the adolescent, specific narcolepsy hypnagogic hallucina-

tions may be confused with psychotic symptoms (mainly multisensory hallucinations, irritability and altered behavior) because of a similar age of onset, behavioral problems and overlapping symptoms. Furthermore, hypnagogic hallucinations can be underrecognized due to the possible coexistence of nightmares, sleep terrors, and confusional arousals.

To complicate matters further, narcolepsy may be genuinely associated with psychosis, as in the as the girl described in this clinical note. In these cases, auditory hallucinations typical of schizophrenia are associated with sleep-related multisensory hallucinations typical of narcolepsy. Patients who present both pathologies in a comorbid manner also have delusional ideas and behavioral alterations that do not appear in patients suffering from narcolepsy alone. It is therefore essential that in these complex cases, the clinician has to be very careful in describing the clinical history and the chronology of symptoms. In front of a suspicion of narcolepsy in a patient with psychotic symptoms is very important to carry out the diagnostic study of narcolepsy including a PSG plus an MSLT before starting treatment with antipsychotics or other psychotropic drugs that could mask the symptoms. Subsequently a HLA determination and a lumbar puncture to measure Hctr levels in CSF to confirm the diagnosis of NT1 has to be performed. The Diagnostic Interview for Genetic Studies Adapted for Narcolepsy (DIGSAN) will facilitate to the non-psychiatrist clinician with the differential diagnosis of the psychotic symptoms presented by the patient. If psychotic symptoms as the hallucinations are exclusively related to REM sleep anomalies typical of narcolepsy or if they appear during wakefulness and are accompanied by delusional ideations as occurs in psychotic illnesses [6].

Obesity is more frequent in adolescents suffering from NT1 comorbid with psychosis than in those suffering only NT1 or psychotic disorders [7]. The case of this patient is very illustrative; its weight began to increase even before the appearance of typical symptoms of NT1. It has continued increasing progressively. In the last revision of January 2017 her weight was 104.5 kg. Weight gain is due to the pathophysiology of narcolepsy [16] and continued treatment with antipsychotics. In this patient she may suffer a third aggravating factor of her obesity: due to the simultaneous appearance of hirsutism and menstrual alterations the patient has recently been referred to gynecology to evaluate a possible polycystic ovary, which would partly explain the increase in weight and the excessive daytime somnolence.

Table II. Results of PSG and MSLT recordings during 3 years of follow-up.

	February 2013	April 2015	January 2016
Age (years)	14	16	17
Treatment	None	None	Haloperidol, biperiden, metilphenidate
PSG: sleep latency	3 min	8 min	9 min
PSG: sleep efficiency	59.40%	70.26%	94.09%
PSG: first REM latency	3 min	8 min	3 min
MSLT: mean sleep latency	1 min	5 min	–
MSLT: number of SOREMPs	5	5	–

The coexistence of narcolepsy with psychosis also raises interesting pathophysiological questions. The coexistence of the two illness may be a chance finding, but also could be the expression of the association of two autoimmune diseases. It has been seen that specific autoimmune diseases are associated with each other more frequently than expected by chance alone [17]. Recently has been confirmed strongest genetic association in the major histocompatibility complex (MHC) locus with schizophrenia risk [18]. This is of utmost interest as this coexistence raises the hypothesis of common pathophysiological and immunogenetic mechanisms.

References

1. American Academy of Sleep Medicine. International Classification of Sleep Disorders, third edition (ICSD-3). Darien, IL: AASM; 2014.
2. De Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, et al. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci U S A 1998; 95: 322-7.
3. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. Lancet 2000; 355: 39-40.
4. Wijnans L, Lecomte C, De Vries C, Weibel D, Sammon C, Hviid A, et al. The incidence of narcolepsy in Europe: before, during, and after the influenza A (H1N1) pdm09 pandemic and vaccination campaigns. Vaccine 2013; 6; 31: 1246-54.
5. Peraita-Adrados R, Del Río-Villegas R, Vela-Bueno A. Factores ambientales en la etiología de la narcolepsia-cataplejía. Estudio de casos y controles de una serie. Rev Neurol 2015; 60: 529-34.
6. Cañellas F, Lin L, Julià MR, Clemente A, Vives-Bauzá C, Ollila HM, et al. Dual cases of type 1 narcolepsy with schizophrenia and other psychotic disorders. J Clin Sleep Med 2014; 10: 1011-8.
7. Huang YS, Guilleminault C, Chen CH, Lai PC, Hwang FM. Narcolepsy-cataplexy and schizophrenia in adolescents. Sleep Med 2014; 15: 15-22.
8. Dauvilliers Y, Gaig C, Barateau L, Graus F, Iranzo A, López R, et al. Absence of NMDA receptor antibodies in the rare

association between type 1 narcolepsy and psychosis. Sci Rep 2016; 6: 252-30.
9. Dahmen N, Kasten M, Mittag K, Muller MJ. Narcoleptic and schizophrenic hallucinations. Implications for differential diagnosis and pathophysiology. Eur J Health Econ 2002; 3 (Suppl 2): S94-8.
10. Ivanenko A, Tauman R, Gozal D. Modafinil in the treatment of excessive daytime sleepiness in children. Sleep Med 2003; 4: 579-82.
11. Crosby MI, Bradshaw DA, McLay RN. Severe mania complicating treatment of narcolepsy with cataplexy. J Clin Sleep Med 2011; 7: 214-6.
12. Lecendreaux M, Bruni O, Franco P, Gringras P, Konofal E, Nevsimalova S, et al. Clinical experience suggests that modafinil is an effective and safe treatment for paediatric narcolepsy. J Sleep Res 2012; 21: 481-3.
13. Tarokh L, Hamann C, Schimmelmann BG. Sleep in child and adolescent psychiatry: overlooked and underappreciated. Eur Child Adolesc Psychiatry 2014; 23: 369-72.
14. Rocca FL, Pizza F, Ricci E, Plazzi G. Narcolepsy during childhood: an update. Neuropediatrics 2015; 46: 181-98.
15. Fortuyn HA, Lappenschaar GA, Nienhuis FJ, Furer JW, Hodiamont PP, Rijnders CA, et al. Psychotic symptoms in narcolepsy: phenomenology and a comparison with schizophrenia. Gen Hosp Psychiatry 2009; 31: 146-54.
16. Poli F, Pizza F, Mignot E, Ferri R, Pagotto U, Taheri S, et al. High prevalence of precocious puberty and obesity in childhood narcolepsy with cataplexy. Sleep 2013; 36: 175-81.
17. Martínez-Orozco FJ, Vicario JL, Villalibre-Valderrey I, De Andrés C, Fernández-Arquero M, Peraita-Adrados R. Narcolepsy with cataplexy and comorbid immunopathological diseases. J Sleep Res 2014; 23: 414-9.
18. Sekar A, Bialas AR, De Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia risk from complex variation of complement component 4. Nature 2016; 530: 177-83.
19. Luca G, Haba-Rubio J, Dauvilliers Y, Lammers GJ, Overeem S, Donjacour CE, et al. Clinical, polysomnographic and genome-wide association analyses of narcolepsy with cataplexy: a European Narcolepsy Network study. J Sleep Res 2013; 22: 482-95.

Narcolepsia-cataplejía y psicosis: estudio de un caso

Objetivo. Describir una paciente que en la adolescencia desarrolló narcolepsia con cataplejía (NT1) y psicosis.

Caso clínico. Niña de 14 años remitida a la unidad de sueño por presentar somnolencia diurna, sueño nocturno fragmentado, hambre compulsiva y aumento de peso durante el último año. Tratada inicialmente con modafinilo y oxibato sódico, tuvo que ser hospitalizada por presentar síntomas psicóticos. Se suprimió el tratamiento antinarcoléptico y se administraron antipsicóticos. El único que toleró fue el haloperidol 1 mg/día, con mejoría del delirio, las alucinaciones y los síntomas disfóricos, pero con empeoramiento de los síntomas narcolépticos. La polisomnografía mostró un sueño nocturno muy fragmentado, y en la prueba de latencias múltiples del sueño, la latencia de sueño fue de un minuto, y tuvo cinco adormecimientos directos en la fase del sueño REM. Presentaba HLA-DQB1*06:02 positivo y nivel de hipocretina-1 en el líquido cefalorraquídeo indetectable. La entrevista diagnóstica para estudios genéticos adaptada para narcolepsia (DIGSAN) ayudó a confirmar que presentaba una doble patología de NT1 y síntomas psicóticos. La última revisión de su sueño con tratamiento psicofarmacológico muestra un aumento del índice de eficacia del sueño. Clínicamente presenta somnolencia diurna excesiva, ataques parciales de cataplejía y una obesidad muy importante. No muestra alteraciones del humor, pero tiene fracaso escolar y aislamiento social.

Conclusión. La coexistencia de narcolepsia con psicosis es una entidad clínica rara, más frecuente en adolescentes que en adultos. La comorbilidad de ambas enfermedades tiene un mal pronóstico clínico y terapéutico, y sugiere hipótesis fisiopatológicas interesantes.

Palabras clave. Narcolepsia con cataplejía. NT1. Psicosis. Trastornos de la vigilia y del sueño.