Clinical Case Report

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Case report: narcolepsy type 1 in an adolescent with HIV infection—coincidence or potential trigger?

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Abstract

Rationale: Despite the acknowledged importance of environmental risk factors in the etiology of narcolepsy, there is little research on this topic. HIV as a trigger for narcolepsy has not been systematically investigated.

Patient concerns: We describe a case of narcolepsy type 1 (NT1) in an adolescent with HIV infection presenting with increased daytime sleepiness and excessive weight gain.

Diagnoses: NT1 was diagnosed according to the criteria of the third edition of the International Classification of Sleep Disorders (ICSD-3).

Interventions: Pharmacological treatment with methylphenidate.

Outcomes: Four months after initiation of methylphenidate therapy the increased daytime sleepiness improved and excessive weight gain stopped.

Lessons: Diagnosis of NT1 can be challenging at disease onset and is often delayed, especially in the pediatric population, because symptoms usually evolve gradually. The case presented here raises the possibility that the HIV infection may play a role in the pathogenesis of NT1 serving as trigger for autoimmune-mediated destruction of hypocretin-secreting neurons.

Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ATV/r = ritonavir boosted atazanavir, AZT = zidovudine, BMI = body mass index, CSF = cerebrospinal fluid, ESS = Epworth sleepiness scale, ICSD-3 = third edition of the International Classification of Sleep Disorders, MRI = magnetic resonance imaging, MSLT = multiple sleep latency test, NT1 = narcolepsy type 1, NVP = nevirapine, PSG = polysomnography, SOREMs = sleep onset REM sleep periods.

Keywords: autoimmunity, HIV, narcolepsy

1. Introduction

Narcolepsy type 1 (NT1) is a chronic neurologic disorder characterized by excessive daytime sleepiness and cataplexy that affects approximately 0.047% of the European population.[1] NT1 is caused by the destruction of over 90% of hypocretin-secreting neurons leading to a deficiency of the neuropeptide hypocretin (also known as orexin) with low or undetectable levels in the cerebrospinal fluid (CSF).[2] Epidemiological data reveal a clear association between narcolepsy and various infections.[3,4] The pathogenic mechanism underlying this observation is thought to be an autoimmune-mediated loss of hypocretin-secreting neurons[5] triggered by certain infections, such as influenza and streptococcal infections, or vaccinations, such as the AS03-adjuvanted influenza vaccine (Pandemrix, GSK United Kingdom), yellow fever and tick-born encephalitis virus vaccines.[2,6] However, the association of HIV infection and narcolepsy has not been described so far and to the best of our knowledge, there have been no reports describing an association between the 2 conditions. We present the case of an adolescent with HIV infection under effective antiretroviral treatment who presented with increased daytime sleepiness combined with excessive weight gain and eventually was diagnosed with narcolepsy.

2. Case report

The 15-year-old patient was diagnosed with HIV infection at the age of 8 years in Kinshasa, Democratic Republic of Congo. The reasons leading to the HIV testing are not known but at that time his baseline CD4$^+$ T-lymphocyte count was 228 cells/μL and no opportunistic infections were described. His parents had died under unknown circumstances and a vertically acquired HIV infection was assumed. Antiretroviral therapy (ART) with zidovudine, lamivudine and nevirapine (AZT/3TC/NVP) was

Editor: N/A.

Ethical approval: Informed consent was obtained from the patient.

Sources/Support: The authors have no funding or conflicts of interest to disclose.

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Medicine (2018) 97:30(e11490)

Received: 3 April 2018 / Accepted: 20 June 2018

http://dx.doi.org/10.1097/MD.0000000000011490

initiated in Kinshasa. At the age of 9 years he was adopted by a Swiss family and we have been following him in our pediatric infectious diseases outpatient clinic since then. He showed an uncomplicated course of the HIV infection with good compliance and full viral suppression under ART. At the age of 14 years ART was switched for simplification to a once daily regime with abacavir, lamivudine and ritonavir boosted atazanavir (ABC/3TC/ATV/r). He well tolerated the new regime and his viral load remained fully suppressed.

At the age of 15 years, 7 years after the HIV diagnosis, the patient presented with excessive daytime sleepiness. Symptoms were napping in the afternoon, falling asleep during car journeys, as well as when playing with the mobile phone, and earlier bedtimes in the evening with consequent increase of total sleep time. No hallucinations while falling asleep or cataplexy episodes were reported by the patient or by family members. However a subtle persistent hypotonic facial expression without a clear link to emotional stimuli was noted, which could be interpreted as cataplectic face.[7] At the same time excessive weight gain accompanied by increased caloric intake with a pathological rise in body mass index (BMI) from 23.1 to 27.4 kg/m^2 within a year corresponding to a weight gain of 15.8 kg within 12 months was observed (Fig. 1).

The clinical examination was unremarkable except for obesity. Additional investigations revealed no signs of anemia, thyroid gland dysfunction, or Cushing syndrome. Screening for illicit drug intake was negative. HIV replication in the CSF was not present and a cerebral magnetic resonance imaging (MRI) was normal with no signs of HIV encephalopathy. The Epworth sleepiness scale (ESS) was pathologic with 15 points (normal 0 to 10) indicating a moderate excessive daytime sleepiness. Given these findings narcolepsy and sleep apnea were the most likely differential diagnosis and a polysomnography (PSG) and multiple sleep latency test (MSLT) were conducted. The tests showed increased sleep onset REM sleep periods (SOREMs) (3 of 4) and a reduced sleep latency (mean 4 minutes and 22 seconds) and were therefore highly suggestive for narcolepsy. Additionally the patient tested positive for HLA DQB1*06:02, and the finding of a pathologically low hypocretin CSF level (orexin A < 20 pg/mL) confirmed the diagnosis of NT1. Given the confirmed diagnosis of narcolepsy a pharmaceutical treatment was started. Taking into account potential interactions with the current ART methylphenidate was chosen over modafinil. Four months after initiation of methylphenidate therapy the increased daytime sleepiness improved and excessive weight gain stopped.

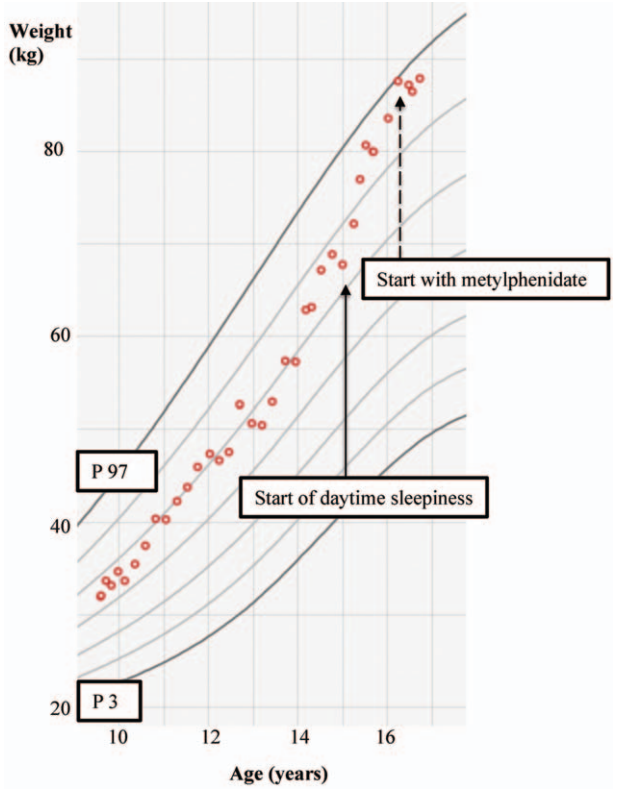

Figure 1. The patient's weight-for-age curve based on the WHO Growth Charts illustrates the sequence of presenting symptoms: start of excessive daytime sleepiness (continuous line arrow) followed by crossing upwards of major weight-for-age percentile lines and stagnation of this trend after the introduction of symptomatic treatment with metylphenidate (dashed line arrow).

3. Discussion

NT1 is one of the main differential diagnoses in patients with hypersomnia but so far was not described in children with HIV infection. Diagnosis can be challenging at disease onset and is often delayed, especially in the pediatric population, because symptoms usually evolve gradually.[8] Beyond the classical symptoms (excessive daytime sleepiness, cataplexy, hallucinations, sleep paralysis and nocturnal fragmented sleep), metabolic, endocrinologic, psychiatric, and psychosocial symptoms can be present. Excessive weight gain as observed in our patient is a common symptom in children with narcolepsy.[2] The review by Merdad et al[9] on sleepiness in adolescents can be a useful resource for planning complementary investigations. Diagnosis of NT1 according to the criteria of the third edition of the International Classification of Sleep Disorders (ICSD-3) requires both of the following:[10]

- The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.
- The presence of cataplexy and a mean sleep latency of ≤8 minutes and ≥2 SOREMs on a MSLT or CSF hypocretin deficiency.

In addition to PSG, MSLT, and CSF hypocretin levels, HLA testing is usually performed.[10] The diagnosis of narcolepsy is important, as symptomatic treatment is available.

The case presented here raises the possibility that the HIV infection in combination with a distinct genetic susceptibility such as the HLA DQB1*06:02 haplotype may play a role in the pathogenesis of NT1 serving as trigger for autoimmune-mediated destruction of hypocretin-secreting neurons.[4] Other potential infectious triggers could not be identified in this case and our patient was not immunized with 2009 H1N1 influenza vaccine (Pandemrix, GSK United Kingdom). An extensive literature research did not reveal any reports about the association between HIV and narcolepsy. This might either be because there is no association and the combination of the 2 conditions was observed by chance in our patient or because narcolepsy is underdiagnosed in children and adolescents due to its less typical presentation in this population.[7] In Europe the prevalence of narcolepsy is estimated to be 47 per 100,000 persons[1] and the HIV prevalence in Switzerland is currently at 250 per 100,000 persons. Therefore the probability to observe a patient with both conditions combined is expected to be 0.000118% meaning that 9 persons would be living with the combined condition in Switzerland. Given this fact it is surprising that no cases have been reported so far, but the question whether this is due to underreporting or lack of a causal link, remains open.

Future analysis of large HIV cohorts with a focus on vertically acquired infection can help to answer the question whether the prevalence of narcolepsy in HIV infected children and adolescent is higher compared to the general population.

Author contributions

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