

Narcolepsy with cataplexy and hyperthyroidism sudden appeared after H1N1 vaccination

Silvia Leiva¹
Jimena Madrazo¹
Claudio Podesta¹

¹ Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI), Unidad de Medicina del Sueño - Capital Federal - Buenos Aires - Argentina.

ABSTRACT

Narcolepsy type 1 (NT1) is a chronic sleep disorder, characterized by excessive daytime sleepiness, cataplexy and fragmented nocturnal sleep. It is caused by a hypocretin deficiency due to a significant reduction of the neurons producing it. In the last years, it has been postulated that an autoimmune mechanism would be responsible for the destruction of these neurons in those genetically predisposed patients. The increased incidence of narcolepsy after the pandemic H1N1 influenza vaccination campaign in 2009-2010 is known. We present below the case of an adult patient who, 10 days after receiving H1N1 vaccination, suffers a traffic accident after falling asleep. Subsequent studies revealed hyperthyroidism due to Graves disease. In spite of the treatment, the patient persisted with daily and disabling daytime sleepiness, sleep attacks and episodes of generalized muscle atony with preservation of consciousness. A nocturnal polysomnography and multiple sleep latency test (MSLT) were performed with a diagnosis of NT1. The particularity of this case is the presentation of 2 autoimmune diseases triggered by an H1N1 vaccine without adjuvant, so far there is only evidence of NT1 associated with vaccines with adjuvant and viral infection. The association of both entities has made us reflect on the autoimmune mechanism, reinforcing the theory of its role in the onset of the disease.

Keywords: Narcolepsy; Influenza A Virus, H1N1 Subtype; Influenza Vaccines; Hyperthyroidism

Corresponding author: Claudio Podesta. Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI), Unidad de Medicina del Sueño - Capital Federal - Buenos Aires - Argentina.
E-mail: cpodesta@fleni.org.ar
E-mail: sleiva@fleni.org.ar
Received: October 24, 2017; Accepted: November 28, 2017.

DOI: 10.5935/1984-0063.20180008

INTRODUCTION

Excessive daytime sleepiness (EDS) is defined as the inability to maintain wakefulness during waking hours, resulting in unintended lapses into sleep. This result either because of shortened sleep time, fragmentation of the sleep period, or central nervous system dysfunction. Possible causes can be sleep breathing disorder, periodic limb movement disorder, insufficient sleep syndrome, shift work disorder, medications, substance abuse, and certain medical condition like hypothyroidism, neurologic, and psychiatric disorders, less commonly, narcolepsy and Idiopathic hypersomnia. They must be differentiated based on adequate questioning, physical examination, laboratory testing, and a sleep study¹.

Narcolepsy with cataplexy is a sleep disorder, characterized not only by EDS, the presence of cataplexy, associated with other symptoms such as hypnagogic or hypnopompic hallucinations, sleep paralysis and fragmented nocturnal sleep.

The hypocretins are hypothalamic neuropeptides thought to play a significant part in the regulation of sleep and arousal states. The substantial reduction in their levels in cerebrospinal fluid (CSF) of NT1 patients is postulated to be due to an autoimmune mediated destruction of hypocretin-producing neurons in the lateral hypothalamus. The autoimmune etiology is possibly triggered by some environmental agent.

The neuropeptide hypocretin-1 and -2 (also known as orexin-A and -B) are produced in the hypothalamic neurons. These two neuropeptides are derived from a same precursor, prepro-hypocretin, and bind to G-protein-coupled receptors, hypocretin receptor (Hcrtr) 1 and 2².

Also it is well known hypocretin-1 binds to Hcrtr 1 with higher affinity, and, in contrast, hypocretin-1 and -2 bind to Hcrtr2 with similar affinities. Hypocretin-2 acts more effectively than hypocretin-1 in some cases. Then Hcrtr2 is critical for narcolepsy suggesting that Hypocretin-2 is also important for pathophysiology of narcolepsy hypothalamic neurons³.

Genetic predisposition is suspected because of narcolepsy's strong association with HLA DQB1*06-02, and genome-wide association studies have identified polymorphisms in T-cell receptor loci

In 2009, due to an H1N1 pandemic, massive vaccination began. Subsequently, there was an increase in narcolepsy cases in children and adolescents associated only with AS03-adjuvanted A(H1N1) vaccine, Pandermix[®]. The first cases were reported in Sweden and Finland, later in other European countries. A seasonal increase in the incidence of narcolepsy was also seen in China after pandemic influenza A virus without clear relation to any vaccine. This implicates the possibility that the H1N1 virus per se could be a triggering factor⁴.

It was speculated that the strong stimulation of CD4+ T-cells by AS03 adjuvant is responsible for the development of NT1. However in Canada was used Arepanrix[®], a vaccine with AS03 adjuvant, and there was no increase in narcolepsy cases, suggesting that the vaccine alone is not sufficient to trigger it, a

genetic predisposition would be necessary (which the European and Chinese populations would have).

In following investigations, was reported the presence of antibodies against the Hcrtr 2 in the serum of the NT1 patients who received the AS03 adjuvant Pandermix vaccine, this antibody in turn reacts against a nucleoprotein contained in the virus and in the vaccine. This nucleoprotein is in low amounts in other vaccines like Forcetia, which does not cause narcolepsy and has 72.7% less of the nuclear influenza protein than Pandemrix. As was also observed in Arepanrix and MF59⁵.

The infection causes a stronger immune response than the vaccine, and thus more chances of triggering narcolepsy. These findings make it unlikely that adjuvant AS03 will be the only cause of the disease⁶.

CASE REPORT

A 40-year-old woman crashes her car into a tree because of a sudden sleep attack. It enters the emergency service presenting drowsiness, oriented in time and space and without serious traumatic injuries.

The blood test revealed anemia (Hto 32% and Hb 9.7) and hyperthyroidism (TSH 0.04 IU/ml, T4L 2.47 ng/dl, T4 17.77 IU/ml and T3 216 ng /dl).

Tc-99m thyroid scan by gamma camera revealed an overall increased uptake of radiotracer, homogeneous distribution and increase in the size of the gland. The TSH receptor antibodies (TRAb) were positive. These findings were compatible with Graves' disease and standard treatment to achieve euthyroid state with Methimazole (60 mg/day) was started⁷.

During the hospitalization (May 2014), she presented several episodes of sudden drowsiness and transient loss of muscle tone with consciousness preservation. Psychiatric pathology was ruled out. A holter electrocardiogram showed supraventricular extrasystoles. Electroencephalogram, magnetic nuclear resonance and Physical-chemical analysis of the CSF were normal.

In August 2014 she was evaluated in the Sleep Medicine Unit of FLENI, although laboratory values improved TSH 3.1 IU ml, T3 99 ng/ml, T4 2.42 IU ml and TRAb reduction. The Epworth sleepiness scale was 18/24 and the symptoms were disabling. The polysomnographic night record showed fragmented sleep, conciliated to early latency of 3 minutes and reduced efficiency 72%, Respiratory Disturbance Index 0.3 events/hour, mean SatO₂ 98%, PLMS Index 2.6 per hour. The MSLT showed mean sleep latency of 4.18 minutes and 1 sleep-onset REM periods (SOREMP).

Due to high clinical pretest of NT1, a new MSLT was performed, which showed a mean sleep latency of 3.24 minutes and 2 SOREMP, which confirmed the diagnosis.

According to established criteria, NT1 was diagnosed⁸. Narcolepsy Type I criteria require cataplexy plus either 1) two SOREMPs on MSLT or a SOREMP on nocturnal polysomnography plus one SOREMP on MSLT or 2) CSF hypocretin-1 concentration ≤ 110 pg/mL or $<1/3$ of mean values.

Modafinil 200 mg/d and Venlafaxine 37.5 mg/d were initiated. Clinical control at three months showed a good clinical response and laboratory parameters were normalized. Endocrinological medication was suppressed. The asymptomatic patient returned to work with the same doses of Modafinil and Venlafaxine⁹.

The anamnesis showed a fact of transcendence, the only precedent of relevance reported was that ten days before the traffic accident, as a result of having fallen asleep, the patient received H1N1 vaccine (lot 001435 VIRAFLU[®]) due to the death of her cousin from this disease.

DISCUSSION

One of the influenza vaccines for the Southern Hemisphere, for the 2014 season authorized by the National Administration of Medicines, Food and Medical Technology (ANMAT) in Argentina was VIRAFLU, of Sinergium Biotech, an anti-influenza vaccine, inactivated surface antigens without adjuvant.

The same, on the recommendation of the World Health Organization (WHO) is formed by the following strains: A/CALIFORNIA/7/2009 (H1N1) pdm09, derived strain used (NYMC X-181), 15 μ g hemagglutinin/dose; A/TEXAS/50/2012 (H3N3) derived strain used (NYMC X-223) 15 μ g hemagglutinin/dose and B/MASSACHUSETTS/2/2012 strain derived used (NYMC BX-51B), 15 μ g hemagglutinin/dose.

To date the cases of NT1 reported were associated with Pandemrix, a vaccine with ASO3 adjuvant, and in China to virus infection. No other vaccines outside of Pandemrix demonstrated clear narcolepsy association so far¹⁰.

We present a case of NT1 after the influenza vaccine without adjuvant, this suggests a mechanism not only linked to the adjuvant but possibly to a viral antigen as already mentioned above. Even if observational studies could prove strong connection between vaccination and narcolepsy, the true causative relationship requires a pathogenic-proven link.

Hyperthyroidism was also not reported associated with this vaccine. In this case the patient presented NT 1 and Graves' disease.

Autoimmune diseases (AD) tend to coexist. NT1 was associated with one and even two autoimmune diseases, including autoimmune thyroid disease. In these cases, the diagnosis of NT1 is earlier, the clinical presentation is more severe and the HLA-DQB1 * 06:02 is present when compared to cases that occur in isolation. This suggests that the disease may arise in a

context of generalized susceptibility to immunopathology. In genetically predisposed patients the autoimmune reaction could lead to the destruction of hypocretinergic neurons.¹¹ Although hyperthyroidism was diagnosed in the context of the accident, it is possible the preexistence of a subclinical hyperthyroidism that is triggered by immunization, even though NT1 was triggered at the same time, its diagnosis takes 3 months.

Although there is no clear evidence of association, the temporal relationship between the diagnosis of two autoimmune diseases and previous immunization with the influenza vaccine suggest that it could have been a possible trigger for both pathologies. If this is the case, the autoimmune pathogenesis of Narcolepsy is reinforced.

REFERENCES

1. Monderer R, Ahmed IM, Thorpy M. Evaluation of the Sleepy Patient: Differential Diagnosis. *Sleep Med Clin.* 2017;12(3):301-12. DOI: 10.1016/j.jsmc.2017.03.006 DOI: <http://dx.doi.org/10.1016/j.jsmc.2017.03.006>
2. Sakurai T, Moriguchi T, Furuya K, Kajiwara N, Nakamura T, Yanagisawa M, et al. Structure and function of human prepro-orexin gene. *J Biol Chem.* 1999;274(25):17771-6. DOI: 10.1074/jbc.274.25.17771 DOI: <http://dx.doi.org/10.1074/jbc.274.25.17771>
3. Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell.* 1999;98(3):365-76. DOI: 10.1016/S0092-8674(00)81965-0 DOI: [http://dx.doi.org/10.1016/S0092-8674\(00\)81965-0](http://dx.doi.org/10.1016/S0092-8674(00)81965-0)
4. Ahmed SS, Schur PH, MacDonald NE, Steinman L. Narcolepsy, 2009 A(H1N1) pandemic influenza, and pandemic influenza vaccinations: what is known and unknown about the neurological disorder, the role for autoimmunity, and vaccine adjuvants. *J Autoimmun.* 2014;50:1-11. DOI: 10.1016/j.jaut.2014.01.033 DOI: <http://dx.doi.org/10.1016/j.jaut.2014.01.033>
5. Ahmed SS, Steinman L. Mechanistic insights into influenza vaccine-associated narcolepsy. *Hum Vaccin Immunother.* 2016;12(12):3196-201. DOI: 10.1080/21645515.2016.1171439 DOI: <http://dx.doi.org/10.1080/21645515.2016.1171439>
6. Brown C. H1N1 vaccine and narcolepsy link discovered. *CMAJ.* 2015;187(12):E371. DOI: 10.1503/cmaj.109-5118 DOI: <http://dx.doi.org/10.1503/cmaj.109-5118>
7. Fadel A A, Gutiérrez S, Novelli JL, Orlandi AM, Parma R, Silva Croome MdC, et al. Tratamiento del hipertiroidismo por Enfermedad de Graves en pacientes adultos no embarazadas. *Rev Argent Endocrinol Metab.* 2013;50(2):107-26.
8. American Academy of Sleep Medicine (AASM). International Classification of Sleep Disorders. 3rd ed. AASM: Darien; 2014.
9. Abad VC, Guilleminault C. New developments in the management of narcolepsy. *Nat Sci Sleep.* 2017;9:39-57. DOI: 10.2147/NSS.S103467 DOI: <http://dx.doi.org/10.2147/NSS.S103467>
10. Sarkanen TO, Alakujala APE, Dauvilliers YA, Partinen MM. Incidence of narcolepsy after H1N1 influenza and vaccinations: Systematic review and meta-analysis. *Sleep Med Rev.* 2017. pii: S1087-0792(17)30001-1. DOI: 10.1016/j.smrv.2017.06.006 DOI: <http://dx.doi.org/10.1016/j.smrv.2017.06.006>
11. 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(4):414-9. DOI: 10.1111/jsr.12143 DOI: <http://dx.doi.org/10.1111/jsr.12143>