Cases of Narcolepsy-Cataplexy Syndrome Following H1N1 Vaccination H1N1 (Domuz Gribi) Aşısını Takiben Ortaya Çıkan Narkolepsi-Katapleksi Sendromu Olguları

Mecbure NALBANTOĞLU¹, Gülçin BENBİR¹, Derya KARADENİZ¹, Ayşe ALTINTAŞ¹, Fatma SAVRAN OĞUZ²

¹Sleep Disorders Unit, Department of Neurology, Cerrahpaşa İstanbul University, İstanbul Faculty of Medicine, İstanbul, Turkey

²Department of Medical Biology, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey

ABSTRACT

Narcolepsy-Cataplexy syndrome is a rare sleep disorder related with human leukocyte antigens (HLA-DQB1*0602) caused by the loss of hypothalamic hypocretin/orexin producing neurons. Recently, in European countries, Narcolepsy-Cataplexy syndrome developing following H1N1 vaccination has attracted attention. Our first patient was a 9-year-old boy, who was referred to our clinic with the complaint of daytime sleepiness developed 1.5 month after H1N1 vaccination. After a couple of weeks, weakness of the upper extremities while laughing was added to the clinical picture. He also developed hypnopompic hallucinations and nightmares. Multiple sleep latency test (MSLT) following full-night polysomnography (PSG) showed that the mean sleep latency was 0.6 minutes; and all of the naps had sleep-onset REM periods. Our second patient was a 50 year-old man, who presented to our clinic complaining of sleep paralysis and REM sleep behavior disorder developed 4 months after H1N1 vaccination. He developed daytime sleepiness 6 months after and cataplexy 8 months after H1N1 vaccination. He was also diagnosed as having Narcolepsy-Cataplexy syndrome upon PSG and MSLT. We investigated HLA-DRB1/DQB1 locus with Polymerase Chain Reaction-Sequence Specific Primer technique. The first patient had HLA-DQB1*0602.47 and DQB1*03.01 heterozygous loci; and the second patient had HLA-DQB1*0602.47 and DQB1*02.01 heterozygous loci. These patients are the first reported cases of Narcolepsy-Cataplexy syndrome related with H1N1 vaccination in Turkey. Although there is no specific marker, temporal relationship between vaccination and onset of disease symptoms suggests a possible causal relationship. In the presence of an underlying genetic predisposition, it was thought that H1N1 vaccination could trigger Narcolepsy-Cataplexy syndrome. (*Archives of Neuropsychiatry* 2014; 51: 283-287)

Key words: H1N1 vaccination, swine flu, narcolepsy, cataplexy

Conflict of Interest: The authors reported no conflict of interest related to this article.

ÖZET

Narkolepsi-Katapleksi sendromu, insan lökosit antijenleri (HLA-DQB1/0602) ile ilişkili, uyanıklıktan sorumlu hipokretin peptit eksikliğine bağlı gelişen nadir bir uyku hastalığıdır. H1N1 domuz gribi aşısı sonrasında Avrupa ülkelerinde narkolepsi-katapleksi endemisinin ortaya çıkması dikkatleri çekmiştir. Türkiye’de H1N1 aşısına bağlı ortaya çıkan Narkolepsi-Katapleksi sendromu olgusu henüz bildirilmemiştir. İlk olgumuz, 9 yaşında erkek hasta domuz gribi aşısını takiben 1,5 ay içinde ortaya çıkan gün içi aşırı uykululuk hali, gülerken üst ekstremitelerde güçsüzlük, hipnopompik halüsinasyonlar ve kabuslar nedeniyle başvurdu. İkinci olgumuz 50 yaşında erkek hastada, domuz gribi aşısından 4 ay sonra uyku paralizisi ve REM uykusu davranış bozukluğu, 6 ay sonra gündüz aşırı uykululuk hali, 8 ay sonra güllünce/ağlayınca ortaya çıkan düşme/hareket edememe şikayetlerinin ortaya çıkması üzerine başvurdu. Hastalarımıza, Polisomnografinin (PSG) ardından Çoklu Uyku Latans Testi (ÇULT) yapılarak Narkolepsi-Katapleksi sendromu tanısı konuldu. Her iki hastamıza yüksek çözünürlüklü PCR-SSP (Polymerase Chain Reaction-Sequence Specific Primer) tekniği ile HLA-DRB1/DQB1 lokus incelemesi yapıldı. İlk olguda HLA-DQB1/0602.47 ve DQB1/03.01 heterozigot lokus; ikinci hastamızda HLA-DQB1/0602.47 ve DQB1/02.01 heterozigot lokus saptandı. Sunduğumuz iki olgu, Türkiye’de H1N1 aşısıyla ilişkili olarak bildirilen ilk olgulardır. Özgün göstergelerin olmamasına karşın, aşı ve hastalık şikayetleri arasındaki zamansal ilişki, olası neden-sonuç ilişkisini akla getirmekte; alta yatan genetik yatkınlık varlığında H1N1 aşısının Narkolepsi-Katapleksi sendromunu tetikleyebileceği düşünülmektedir. (*Nöropsikiyatri Arşivi* 2014; 51: 283-287)

Anahtar kelimeler: H1N1 aşısı, domuz gribi, narkolepsi, katapleksi

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Narcolepsy syndrome is a disease characterized with excessive daytime sleepiness (EDS) accompanied or not accompanied by cataplexy. Disrupted night-time sleep, sleep paralysis, and findings related with REM sleep, including hypnopompic/hypnagogic hallucinations, may accompany in addition to excessive daytime sleepiness and cataplexy. In almost all patients, the first complaint is irresistible sleep attacks in the daytime. The time of the sleep

attacks may range between a few seconds to a few minutes and may occur in inappropriate situations, including eating and driving. Although the sleep attacks are short in times, they are refreshing. Cataplexy is defined as the sudden, reversible decrease or loss of striated muscle tone triggered by emotional stimuli, including laughing, fear, or astonishment. No loss of consciousness occurs during these attacks (1,2).

Although sporadic and familial forms of narcolepsy syndrome have been reported, it sporadically occurs with a rate of 95% (3).

Correspondence Address/Yazışma Adresi

Dr. Mecbure Nalbantoğlu, İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi, Nöroloji Anabilim Dalı, İstanbul, Türkiye
Phone: +90 212 632 96 96 E-mail: mecbure03@hotmail.com Received/Geliş tarihi: 30.01.2013 Accepted/Kabul tarihi: 22.03.2013
©Copyright 2014 by Turkish Association of Neuropsychiatry / ©Telif Hakkı 2014 Türk Nöropsikiyatri Derneği

In studies performed in different countries and ethnic groups, it was demonstrated that narcolepsy–cataplexy syndrome affects .03% of populations. The prevalence of narcolepsy without cataplexy is less clear, and it is accepted that it constitutes 20%–50% of the cases with narcolepsy. In the pathophysiology of the disease, loss of hypothalamic neurons that produce hypocretin (orexin) because of an autoimmune process has been demonstrated (4). Demonstration of polymorphisms related with human leukocyte antigens (HLA) and T-cell receptors (TCR) in patients with narcolepsy syndrome supports that an autoimmune process targets a peptide in the HLA-TCR connections in the cells producing hypocretin/orexin. It has been demonstrated to have a strong relation with HLA DQB1*0602 and DQA1*0102 alleles (5,6).

Narcolepsy syndrome may also be observed as a part of other medical diseases. Rarely, cases that occurred following intracranial tumor, multiple sclerosis, encephalitis, or head trauma have been reported (7). More frequently, it is known that narcolepsy syndrome can be triggered by streptococcal upper respiratory tract infections (8). In recent years, it has been noted that narcolepsy syndrome can be triggered by H1N1 vaccination or by influenza infections caused by H1N1 (9,10,11,12,13,14). In our country, no cases of narcolepsy–cataplexy in relation with H1N1 vaccine have yet been reported. Here, we presented two patients whom we followed up with findings of narcolepsy–cataplexy syndrome following the administration of H1N1 vaccine.

Cases

Case 1

A nine-year-old male patient admitted to our outpatient clinic because of excessive daytime sleepiness that occurred 1.5 months after the administration of swine flu vaccine. The family reported that the patient developed complaints of withdrawal, decrease in speech, loss of appetite, and reluctance in the same period. Therefore, his academic success was also decreased. Daytime sleep attacks repeated 6–7 times during the daytime and lasted approximately for 30–60 min. It was learned that complaints, including weakness in the upper extremity and ptosis in the palpebrae and head, were also added to the clinical picture after 4 months. Sleep paralysis was not described. It was learned that frequent hypnogogic and hypnopompic hallucinations in the form of walking trees or fearful faces while falling asleep and hearing voices while awakening started approximately 6 months after the administration of the vaccine. It was reported that his sleep was frequently interrupted, and he frequently had nightmares and whimpered while sleeping.

It was learned that he had no complications during the prenatal and neonatal periods. There was no risk factor other than the H1N1 vaccine with unknown adjuvant. The stages of the motor and mental development were observed to be normal. His neurological examination was normal. His familial history revealed no pathology. Polysomnography (PSG) was found to be normal (Figure 1). The mean sleep latency in the Multiple Sleep Latency Test (MSLT) performed the next day was calculated to be 0.6 min, and sleep-onset REM periods were observed in all three tests (Figure 2). Modafinil (200 mg/day) and venlafaxine (37.5 mg/day) treatment was initiated in the patient who was

diagnosed with narcolepsy–cataplexy syndrome. In the follow-up examination performed 2 months later, the patient's complaints were observed to be under control to a great extent.

Case 2

It was learned that sleep paralysis and REM sleep behavior disorder in the form of speaking and experiencing dreams during sleep occurred 4 months after administration of swine flu vaccine in a 50-year-old male patient. It was stated that excessive daytime sleepiness was added to the picture 6 months after the administration of the vaccine; the patient stated that he could not resist sleep attacks that lasted for 30–60 min for 5–6 times a day and awakened in a refreshed state afterwards. When complaints, including falling, stroke-like state, and inability to move, occurring on laughing, crying, or getting angry developed 8 months following the vaccination, the patient presented to our outpatient clinic.

In his personal history, it was learned that he was receiving treatment for diabetes mellitus and hyperlipidemia. There was no other risk factor except for H1N1 vaccine, the adjuvant of which was unknown in terms of development of narcolepsy. In his familial

Figure 1. Hypnogram belonging to the polysomnography of case 1

Figure 2. Hypnogram belonging to the Multiple Sleep Latency Test of case 1

history, there was no pathology except for dementia and familial hypertension in his mother. His electroencephalography and cranial imaging were found to be normal. On PSG, obstructive apnea syndrome (OSAS, abnormal respiratory event index 55/h) (Figure 3) and presence of REM sleep without atonia (Figure 4) were observed. In the MSLT test, the mean sleep latency was calculated to be 2.5 min; however, sleep-onset REM periods were not observed in any of the four tests (Figure 5). Automatic continuous positive airway pressure (CPAP) treatment was initiated because of obstructive sleep apnea syndrome. However, excessive daytime sleepiness continued despite efficient treatment. Thus, a diagnosis of narcolepsy–cataplexy syndrome was made considering other complaints which accompanied. All complaints were controlled to a great extent when modafinil (400 mg/day), venlafaxine

(150 mg/day), and clonazepam (1 mg/day) treatment was initiated in addition to automatic CPAP. The patient presented in the 10th month of treatment for a follow-up visit, and it was observed that his complaints were still under control with automatic CPAP and drug treatment.

In both our patients, the HLA-DRB1 and DQB1 loci were examined using high resolution polymerase chain reaction-specific primer technique in İstanbul Medical Faculty, Department of Medical Biology that has been approved by the European Immunogenetics Federation. The PCR method was realized using PE Biosystems, CA device in 9700 thermal cycles. Presence of HLA DQB1 0602/47 and DQB1 03/01 heterozygous loci was found in our 9-year-old patient, and presence of HLA DQB1 0602/47 and DQB1 02/01 heterozygous loci was found in our 50-year-old patient.

Figure 3. Hypnogram belonging to the polysomnography of case 2

Figure 4. Example of REM without atonia observed in case 2 (increased phasic activity in jaw electromyography recordings as shown by the large arrow)

Table 1 . Clinical summary of two patients who developed narcolepsy–cataplexy syndrome following administration of H1N1 vaccine

Clinical properties	Case 1	Case 2
Age (years)	9	50
Gender	Male	Male
Vaccine type	Unknown	Unknown
The time between vaccination and onset of complaints (months)	1.5	4
Narcolepsy (sudden sleep attacks)	Yes	Yes
Cataplexy	Yes	Yes
Sleep paralysis	No	Yes
Hallucinations related with sleep	Yes	Yes
Accompanying sleep diseases	Nightmare disorder	REM sleep behavior disorder, OSAS
PSG findings	Normal	OSAS(AHI:55/h), REM without atonia
MSLT findings	Sleep latency .6 minutes; 3 SOREM	Sleep latency 2.5 min
HLA test	DQB1*0602/47 and DQB1*03/01 heterozygous	DQB1*0602/47 and DQB1*02/01 heterozygous
Treatment	Modafinil (200 mg/day), venlafaxine (37.5 mg/day)	Modafinil (400 mg/day), venlafaxine (150 mg/day), clonazepam (1 mg/day)

OSAS: Obstructive sleep apnea syndrome; PSG: Polysomnography; AHI: Apnea-Hypopnea Index; MSLT: Multiple Sleep latency Test; SOREM: Sleep Onset REM (initiation of sleep with REM stage); HLA: Human leukocyte antigen.

Discussion

These two patients who were believed to develop narcolepsy–cataplexy syndrome in relation with H1N1 vaccine are the first cases reported from Turkey (Table 1). Although there were no specific indications proving a definite cause and effect relation, the temporal relation between the flu vaccine and the initiation of complaints suggested a possible cause and effect relation and that H1N1 vaccine could lead to triggering of narcolepsy–cataplexy syndrome. In our second case, the presence of OSAS made additional contribution to excessive daytime sleepiness. However, the presence of cataplexy, sleep paralysis, and hallucinations related with sleep supported narcolepsy–cataplexy syndrome triggered by the H1N1 vaccine on a background of previously present OSAS. Similarly, REM sleep behavior disorder that is observed in one fourth of patients with narcolepsy also suggested a neurodegenerative process triggered by the H1N1 vaccine in this patient.

Two mechanisms have been mentioned in the cause and effect relationship between narcolepsy syndrome and H1N1 vaccine (9,10). According to the first hypothesis, a specific immune response against H1N1 targets hypocretinergic neurons by way of cross-reaction and leads to neuron loss. In the second hypothesis, it has been proposed that the vaccine stimulates the immune system in a generalized manner and thus triggers narcolepsy syndrome.

Narcolepsy–cataplexy syndrome following H1N1 vaccine was defined for the first time by the Swedish Medical Products Agency in six patients (10). Afterwards, a history of H1N1 vaccination before the onset of symptoms was found in 69 of the 87 patients aged 19 years and younger who were diagnosed with narcolepsy–cataplexy syndrome between 2009 and 2010 in a study published from Sweden. The annual incidence was found to be 4.2/100.000 in vaccinated cases and .64/100.000 in unvaccinated cases (11,12). With publication of cases of narcolepsy–cataplexy syndrome triggered by H1N1, history of H1N1 infection and vaccine was initiated to be

interrogated in cases with acute onset. In China, it was observed that the onset of narcolepsy revealed a seasonal character (most commonly in the beginning of April and least commonly in the beginning of October) and was related with upper respiratory tract infection, including the H1N1 flu infection; however, no significant correlation was observed with the H1N1 vaccine in a retrospective study conducted with 629 patients diagnosed with narcolepsy between 1998 and 2010, 86% of whom were pediatric patients. However, it was noted that the onset of sudden narcolepsy developed 6 months after the H1N1 pandemic according to the statistics of the Chinese government (13).

Another question that flashes is if there is a difference between vaccine types and development of narcolepsy–cataplexy after vaccination. In one study, the patients who were vaccinated with influenza vaccine with MF59-adjuvant in 2010 were followed up for a period ranging between one week and 3 months in terms of development of symptoms; however, the development of narcolepsy or side effect related with sleep was not observed in any patient (15). In another study published from Finland, a population comprising children and adolescents (4–19 years) was retrospectively screened between 2009 and 2010, and it was found that 75% of this population received the H1N1 vaccine that included AS03-adjuvant containing a higher rate of squalene and alpha-tocopherol. In the same period, it was recorded that 46 of the 67 patients who were diagnosed with narcolepsy syndrome received the H1N1 vaccine which contained AS03 adjuvant and only seven patients were not vaccinated. In other words, the incidence of narcolepsy was found to be 9/100.000 in the vaccinated group, whereas it remained at a level of 0.7/100.000 in the unvaccinated group. Accordingly, a 12.7-fold increased risk of narcolepsy was demonstrated in a period of approximately 8 months following the administration of the H1N1 vaccine that contained the AS03 adjuvant in the 4–19-year-old age group, and the risk of narcolepsy associated with vaccination was calculated to be 1:16000 (14). In our country, H1N1 vaccines, including both AS03 and MF-59 adjuvants, are being used. The information regarding the type of vaccine could not be reached for the patients we presented in this article (16,17). Although these two patients were reported to be the first cases of narcolepsy that developed after vaccination in Turkey, it is probable that the cases of narcolepsy–cataplexy syndrome related with H1N1 vaccine are more common also in our country. Therefore, the history of the H1N1 vaccine should be interrogated in addition to other triggering factors particularly in cases with acute onset and atypical course. Establishment of epidemiological data belonging to our country waits for narcolepsy–cataplexy syndrome to be demonstrated in large vaccinated and unvaccinated populations by retrospective and prospective evaluation.

References

1. Thorpy MJ. Cataplexy associated with narcolepsy: epidemiology, pathophysiology and management. *CNS Drugs* 2006; 20:43-50.
2. Öztura İ. Narkolepsi. Kaynak H, Ardiç S, editörler. *Uyku fizyolojisi ve hastalıkları içinde*. Nobel Tıp Kitabevi; 2011; s. 309-315.

Figure 5. Hypnogram belonging to the Multiple Sleep Latency Test in case 2.

3. Mignot E, Wang C, Rattazzi C, Gaiser C, Lovett M, Guilleminault C, Dement WC, Grumet FC. Genetic linkage of autosomal recessive canine narcolepsy with a mu immunoglobulin heavy-chain switch-like segment. *Proc Natl Acad Sci USA* 1991; 88:3475-3478.
4. Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, Cornford M, Siegel JM. Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 2000; 27:469-474.
5. Mignot E, Lin L, Rogers W, Honda Y, Qiu X, Lin X, Okun M, Hohjoh H, Miki T, Hsu S, Leffell M, Grumet F, Fernandez-Vina M, Honda M, Risch N. Complex HLA-DR and -DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. *Am J Hum Genet* 2001; 68:686-699.
6. Hallmayer J, Faraco J, Lin L, Hesselton S, Winkelmann J, Kawashima M, Mayer G, Plazzi G, Nevsimalova S, Bourgin P, Hong SC, Honda Y, Honda M, Högl B, Longstreth WT Jr, Montplaisir J, Kemlink D, Einen M, Chen J, Musone SL, Akana M, Miyagawa T, Duan J, Desautels A, Erhardt C, Hesla PE, Poli F, Frauscher B, Jeong JH, Lee SP, Ton TG, Kvale M, Kolesar L, Dobrovolná M, Nepom GT, Salomon D, Wichmann HE, Rouleau GA, Gieger C, Levinson DF, Gejman PV, Meitinger T, Young T, Peppard P, Tokunaga K, Kwok PY, Risch N, Mignot E. Narcolepsy is strongly associated with the T-cell receptor alpha locus. *Nat Genet* 2009; 41:708-711.
7. Nishino S, Kanbayashi T. Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system. *Sleep Med Rev* 2005; 9:269-310.
8. Aran A, Lin L, Nevsimalova S, Plazzi G, Hong SC, Weiner K, Zeitzer J, Mignot E. Elevated anti-streptococcal antibodies in patients with recent narcolepsy onset. *Sleep* 2009; 32:979-983.
9. Korum BR, Faraco J, Mignot E. Narcolepsy with hypocretin/orexin deficiency, infections and autoimmunity of the brain. *Curr Opin Neurobiol* 2011; 21:897-903.
10. Dauvilliers Y, Montplaisir J, Cochen V, Desautels A, Einen M, Lin L, Kawashima M, Bayard S, Monaca C, Tiberge M, Filipini D, Tripathy A, Nguyen BH, Kotagal S, Mignot E. Post-H1N1 narcolepsy-cataplexy. *Sleep* 2010; 33:1428-1430.
11. Swedish Medical Products Agency. Swedish medical products agency publishes report from a case inventory study on Pandemrix vaccination and development of narcolepsy with cataplexy. *Euro Surveill* 2011; 16:19904.
12. Bardage C, Örtqvist A, Bergman U, Ludvigsson JF, Granath F. Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden. *BMJ* 2011; 343:1-14.
13. Han F, Lin L, Warby SC, Faraco J, Li J, Dong SX, An P, Zhao L, Wang LH, Li QY, Yan H, Gao ZC, Yuan Y, Strohl KP, Mignot E. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. *Ann Neurol* 2011; 70:410-417.
14. Nohynek H, Jokinen J, Partinen M, Vaarala O, Kirjavainen T, Sundman J, Himanen SL, Hublin C, Julkunen I, Olsen P, Heikkilä SO, Kilpi T. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. *PLoS ONE* 2012; 7:1-9.
15. Tsai TF, Crucitti A, Nacci P, Nicolay U, Della Cioppa G, Ferguson J, Clemens R. Explorations of clinical trials and pharmacovigilance databases of MF59-adjuvanted influenza vaccines for associated cases of narcolepsy. *Scand J Infect Dis* 2011; 43:702-706.
16. Öztürk N, Ayvazoğlu B, Öztürk EK, Orman HO. Domuz gribi aşısının etki ve yan etkileri. *Başkent Üniversitesi Mezuniyet Öncesi Çalışma*. 2012; 1-10. <http://tip.baskent.edu.tr/egitim/mezuniyetoncesi/calismagrpo/grsmpzsn-m12/8.3.pdf>
17. Yaman G, Berktaş M, Güdücüoğlu H. Tartışılan adjuvan: skualen. *ANKEM Derg* 2012; 26:46-54.