

# Narcolepsy: Association with H1N1 Infection and Vaccination

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Epidemiological studies have demonstrated an association between H1N1 influenza infection and vaccinations. This article reviews the various studies, and suggests the biological mechanisms explaining why and how H1N1 influenza infection or vaccine stimulates the autoimmune response, thereby resulting in narcolepsy. Among the vaccines, the effect of Pandemrix was scrutinized more than other vaccines, due to its higher association with an increase of narcolepsy onset. The consequences of using other vaccines which contain same or different adjuvants as Pandemrix, were also analyzed.

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**Key Words** Narcolepsy, Influenza, H1N1, Vaccine.

## INTRODUCTION

Virus infected B cell or antigen cross-reactive to B cell, are suggested to be possible causes of human leukocyte antigen (HLA)-related autoimmune disorders. Apoptosis of B cell, T cell specific to autoantigen, or autophagy resulting in the production of autoantibodies, may trigger an autoimmune response.<sup>1</sup> Apart from HLA class II (the widely known trigger of narcolepsy), HLA class I and HLA-DP alleles may also indirectly contribute to the onset of narcolepsy.<sup>2</sup>

Autoantibodies specific to narcolepsy have not been found in cerebrospinal fluid (CSF) or serum from narcolepsy type 1 patients.<sup>3</sup> Also, no autoantibody for hypocretin neuron has been discovered in 21 patients who recently had onset of narcolepsy type 1.<sup>4</sup> However, an autoantibody-like TRIB2 was suggested in a subgroup of narcolepsy patients.<sup>5</sup> Previous studies on the processes involved in autoimmune processes and new genes discovered, concordantly corroborate the hypothesis that narcolepsy is an autoimmune disorder.<sup>2,6</sup>

Previous studies have suggested that Streptococcal infection is a major culprit for the autoimmunization involved in narcolepsy onset, while H1N1 influenza infection/vaccination is another rising possibility due to the temporal relation between H1N1 influenza infection/vaccination and narcolepsy onset. One study in France suggested H1N1 vaccination in cataplexy patients might have sparked the autoimmune response of narcolepsy.<sup>7</sup> Moreover, in 2010, the number of narcolepsy cases increased three-fold higher than the baseline onset rate recorded at Changzheng Hospital.<sup>8</sup> Similar increase was also seen at the People's Hospital in China, thereby suggesting a close association between H1N1 and narcolepsy.<sup>8</sup> Although the detailed mechanism has not been confirmed, the antigen related to H1N1 virus is suspected to be the cause of narcolepsy.<sup>9</sup> Additionally, the virus's high association with narcolepsy could be based on molecular mimicry.<sup>6</sup>

## H1N1 INFECTION AND NARCOLEPSY

### Biological Mechanisms

The recombinant activating gene 1-deficient mice are devoid of B- and T-cells. These mice

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were infected by H1N1, and showed sleep problems similar to narcolepsy. The infecting agent targeted the brainstem and orexin/hypocretin producing hypothalamic neuron, thereby affected the stability of sleep. Thus, an H1N1 virus infection of the brain leads to sleep disturbances like narcolepsy.<sup>10</sup>

The association of H1N1 vaccine or infection with narcolepsy was studied by hypothesizing that the autoimmune CD4+ T cells specific to the hypocretin (HCRT) epitope of narcolepsy patients may affect the hypothalamus.<sup>11</sup> In 2013, *Science Translational Medicine* published a relevant study conducted by De la Herrán-Arita AK et al. This article was withdrawn due to the team's failure to replicate the results which compare the narcoleptics and healthy controls by analyzing the relationship between CD4+ T cells and two HCRT epitopes. However, one important potential mechanism was suggested to expand our quest for possible mechanisms involved in the relationship between H1N1 and narcolepsy.

According to the article, the amount of CD4+ T cells strongly reacting to the two epitopes (HCRT56-68 and HCRT87-99) that bind to HLA-DQB1\*06:02, was significantly higher in narcoleptics than healthy controls. This result suggested that the T cell response to two HCRT epitopes might be specific to narcolepsy with cataplexy.

## H1N1 VACCINATION AND NARCOLEPSY

### Epidemiological Studies

2608 narcolepsy cases were investigated at the healthcare database in Netherlands, Finland, Sweden, Italy, Denmark and the United Kingdom.<sup>12</sup> It was noted that narcolepsy was increased in Sweden and Finland, compared to other countries which had a limited vaccination coverage due to age or lower rate of receiving vaccination.<sup>12</sup>

Also, according to the study conducted in Sweden 2013, the narcolepsy onset was 25-folds more than that before vaccination.<sup>13</sup> Furthermore, the age of initial onset was lower than the sporadic cases, and the onset developed more abruptly.<sup>13</sup> Among the 1198 patients in 233 sleep centers in Germany, 106 children and adolescents were investigated.<sup>14</sup> The collected data showed a 3.57-fold higher narcolepsy onset in the patients who were vaccinated.<sup>14</sup> Considering the data collected from 2007 to 2011, the narcolepsy onset of children under 18 years of age gradually increased from spring in 2009.<sup>14</sup>

One study in Finnish and Italian patients illustrated no significant differences in the condition of pediatric cases before and after vaccination.<sup>15</sup> The patients after vaccination had shorter mean sleep latency and higher rate of sleep fragmentation according to the multiple sleep latency test (MSLT) result.<sup>15</sup> However, there were no differences in anthropometric data, symptoms, the level of HCRT-1 and polysomnography data.<sup>15</sup> The

recordings of cataplexy were also similar, except for the fact that the patients who had narcolepsy before the vaccination campaign showed more pronounced hyperkinetic movements.<sup>15</sup>

Moreover, in a study comparing 69 vaccine-related narcolepsy patients and 57 vaccine-unrelated narcolepsy patients, the former displayed less diagnostic delay, lower periodic leg movement index, faster sleep-wake rhythm, and lower diagnostic age.<sup>16</sup> MSLT results indicated shorter sleep latency and more frequent sleep onset REM periods than the vaccine-unrelated narcolepsy patients; these cases were also related to age.<sup>16</sup> Additionally, when sleep patterns were examined by actigraphy, there were more sleep fragmentation and less amount of sleep in vaccine-related narcolepsy patients.<sup>16</sup>

However in another study, where the level of hypocretin for vaccine-related narcolepsy patients was lower, the scores from Ullanlinna Narcolepsy Survey and Epworth Sleepiness Scale were worse.<sup>17</sup> This suggested that the level of hypocretin is related to the narcolepsy symptoms.<sup>17</sup>

### Biological Mechanisms

After the 2009 influenza pandemic vaccination, the presence of HLA-DQB1\*06:02 and the level of A/H1N1 were associated in patients who had early narcolepsy onset.<sup>5</sup> The significance of HLA-DQB1\*06:02 was also seen in 37 pediatric narcolepsy patients investigated in Sweden, who were all HLA-DQB1\*06:02 positive.<sup>18</sup> However, not only HLA-DQB1\*06:02, but also the HLA variant HLA-DQB1\*03:01, was related with younger narcolepsy onset.<sup>19</sup> As HLA-DQB1\*06:02 homozygotes declined after H1N1 influenza, genetic variability may be significant for the association between the vaccines and the onset.<sup>19</sup>

The IgG response to 10846 human protein fragments was screened from sera samples from 57 vaccine-related narcolepsy patients, vaccine-unrelated narcolepsy patients, and controls.<sup>20</sup> Of these, 14 antigens that displayed significant response were further investigated. Methyltransferase-Like-22 and Cytosolic 5'-nucleotidase were more frequent observed in narcoleptics.<sup>20</sup>

Further, 36 narcolepsy patients who had onset after vaccination, and 48 vaccine-unrelated patients, were compared. High levels of certain cytokines in vaccine-related patients demonstrated an increase in immune response.<sup>21</sup> This was regulated by the activation of normal T-cell expression and secretion.<sup>21</sup> In vaccine-related patients, the levels of CSCL10 and CXCL9 were significantly higher, while the level of CXCL10 was lower.<sup>21</sup> This study shows the relationship between interferon- $\gamma$  (IFN- $\gamma$ ) and narcolepsy onset. As IFN- $\gamma$  network developed more actively after vaccination, it is presumed to play an integral role in immune mechanisms that cause narcolepsy.<sup>21</sup>

Another study analyzed the patients who had onset of narcolepsy after Pandemrix vaccination in Sweden.<sup>22</sup> There was an increase in the *Streptococcus*-associated antigen production in response to IFN- $\gamma$  production in narcoleptics.<sup>22</sup> Specifically, IFN- $\gamma$  cellular immune response was specific to *Streptococcus* serotype

M6.<sup>22</sup> Eventually, the results indicated that  $\beta$ -haemolytic group A *Streptococcus* might have sparked an autoimmune response in Pandemrix-related narcolepsy patients.<sup>22</sup>

## PANDEMRIX AND NARCOLEPSY

### Epidemiological Studies

Among H1N1 vaccines, Pandemrix is the most widely discussed vaccine to have a close association with narcolepsy. Amongst these pediatric cases, 11 narcolepsy patients who were vaccinated with Pandemrix displayed higher rate of cataplexy and weight-gain, as compared to 65 patients who were not.<sup>23</sup> Moreover, the former had more facial hypotonia and tongue protrusion.<sup>23</sup>

According to the narcolepsy cases collected in Ireland from April 2009 to December 2010, the onset rate after the Pandemrix vaccination was 5.7/100000 in child or adolescent population.<sup>24</sup> On the contrary, the rate without Pandemrix vaccination was 0.4/100000 in child or adolescent population.<sup>24</sup> These results demonstrate the correlation between narcolepsy and Pandemrix in Finland and Sweden.<sup>24</sup>

In 2010 and 2011, the study conducted in Norway recruited 58 pediatric patients who displayed narcolepsy onset after Pandemrix administration.<sup>25</sup> The analyses showed a significant increase in narcolepsy with cataplexy.<sup>25</sup> One year after vaccination, the CSF hypocretin level declined for 10/100000 vaccinated children, and 0.5-1/100000 in non-vaccinated children.<sup>25</sup> Narcolepsy onset in those who were vaccinated with Pandemrix in Finland from 2009 to 2010 was 12.7-folds higher than unvaccinated.<sup>26</sup> Since Pandemrix appeared to affect narcolepsy onset from 4 to 19 years of age (children and adolescents), Pandemrix was alleged to be the cause of early-onset narcolepsy.<sup>18</sup>

### Biological Mechanisms

Influenza nucleoprotein NP111-121 is similar to HCRT receptor 234-45, in that they are both exposed on the surface of nucleoprotein.<sup>6</sup> Antibodies cross-reactive to anti-HCRT receptor 2 and influenza nucleoprotein peptide were detected in narcolepsy patients vaccinated with Pandemrix, and were found to be HLA-DQB1\*06:02 positive.<sup>6</sup> Thus, there is an antibody cross-reactive to influenza nucleoprotein and HCRT receptor, which disturbs the HCRT neurotransmission in narcolepsy patients and affects the immune response.<sup>6</sup> After the serum was analyzed through the peptide microarray platform, the pattern responding to epitope to neuraminidase and haemagglutinin was different between the group infected by H1N1 and the group vaccinated with Pandemrix.<sup>27</sup>

Influenza virus hemagglutinin usually binds with ganglioside, which has a crucial role in the host cell virus receptor.<sup>28</sup> Anti-ganglioside antibody is related to neurological disorders such as Guillain-Barré syndrome, which supposedly appears after

vaccination or infection.<sup>28</sup> Therefore, sulfatide and IgG anti-ganglioside antibody to ganglioside from 11 human brains was screened in narcolepsy with cataplexy patients and in healthy controls.<sup>28</sup> More anti-GM3 antibodies were discovered in the patients who were vaccinated with Pandemrix than in healthy controls.<sup>28</sup> Anti-GM3 antibody was significantly related to HLA-DQB1\*06:02 in narcolepsy patient groups who had onset before and after the vaccination.<sup>28</sup> Thus, the autoimmunity to GM3 is an attribute of Pandemrix-related narcolepsy, and the autoantibody to ganglioside may have been triggered by Pandemrix.<sup>28</sup>

## VACCINATIONS OTHER THAN PANDEMRIX

D-Pan H1N1 vaccine (Pandemrix), produced in Dresden, Germany, heightened the risk of narcolepsy onset.<sup>29</sup> In contrast, this was not observed in Q-Pan H1N1 vaccine (Arepanrix), manufactured in Quebec, Canada.<sup>29</sup> The affinity to recombinant A(H1N1)pdm09 hemagglutinin was tested in two groups of patients, who were vaccinated with Pandemrix or Arepanrix, respectively.<sup>29</sup> No difference was observed between D-Pan and Q-Pan sera with regards to the affinity.<sup>29</sup>

However, structurally modified viral nucleoprotein and the antibody of hemagglutinin and nucleoprotein, especially the detergent treated one of narcolepsy patients, were present more in Pandemrix than Arepanrix,<sup>30</sup> indicating that the viral nucleoprotein went through a detergent-induced antigenic change.<sup>30</sup> In addition, compared to the controls, nucleoprotein of the children who had DQB1\*06:02 risk allele had higher levels of antibody to the nucleoprotein,<sup>30</sup> showing an evident association between DQB1\*06:02 and vaccine levels in influencing narcolepsy.<sup>30</sup>

Pandemrix and Arepanrix are composed of viral proteins and nonviral proteins, which are all necessary for manufacturing.<sup>31</sup> The amount of neuraminidase and nucleoprotein was higher in Pandemrix than in Arepanrix, which constituted more viral and chicken proteins.<sup>31</sup> However, among the chicken proteins, the amount of Programmed Cell Death 6 Interacting Protein, Tetraspanins 8, Heart-type Fatty Acid Binding Protein, Hereditary spastic paraplegia, Tubby Bipartite Transcription Factor were higher in Pandemrix.<sup>31</sup> Although the glycosylation pattern in the two vaccines were similar,<sup>31</sup> there were different levels of deamidation and deoxidation in Pandemrix, indicating that Pandemrix and Arepanrix have different degradation patterns.<sup>31</sup> Therefore, Pandemrix's higher level of HA1 146N and the higher amount of wild type virus could be the cause of higher risk of narcolepsy displayed in subjects vaccinated with Pandemrix, when compared with those vaccinated with Arepanrix or other vaccines.<sup>31</sup>

Likewise, another vaccine Focetria showed lesser association with narcolepsy than Pandemrix.<sup>6</sup> As seen above, Pandemrix had the highest amount of cross-reactive antibody and nucleo-

protein among H1N1 vaccines, which was absent in patients who were vaccinated with Focetria or infected by H1N1.<sup>6</sup> This allows us to assume that the antibody production wanes when there is not enough amount of nucleoprotein.<sup>6</sup>

## ADJUVANTS

As explained above, the higher risk of narcolepsy onset, especially for children and adolescents, is related to the viral component of vaccine. However, adjuvants can also participate in instigating the autoimmune response.<sup>32</sup>

### ASO3

Narcolepsy with cataplexy was highly associated with ASO3-adjuvanted vaccines, as shown in the data collected by 14 narcolepsy-specialized centers in France, in 2013. A total of 62 cases were compared to 135 controls.<sup>33</sup> The onset of narcolepsy with cataplexy was 6.5-folds higher in the vaccinated patients under 18 years of age, and 4.7-folds higher for the vaccinated patients over 18 years.<sup>33</sup>

Six adult sleep centers in England studied 1446 cases and showed that the patients who were vaccinated with ASO3-adjuvanted vaccine had 4.24-folds higher onset of narcolepsy than who were not.<sup>34</sup> Considering the cases collected till November 2011, the onset was 9.06-folds higher than that of before the vaccination.<sup>34</sup>

In Quebec, 24 cases, including the 7 cases related to ASO3-adjuvanted A/H1N1 (2009) pandemic influenza vaccination, indicated a relationship between narcolepsy and vaccination.<sup>35</sup> 1/1000000 doses of vaccine presented the higher risk of the onset in patients under 20 years of age.<sup>35</sup>

$\alpha$ -tocopherol in ASO3 activates the nuclear factor-like 2 (Nrf2) transcription.<sup>36</sup> Nrf2 then activates cytoprotective genes such as the constitutive proteasome, which binds to antioxidant response element.<sup>36</sup> The above biological mechanism subsequently affects the expression and metabolism cascade of hypocretin, and elevates the amount of hypocretin  $\alpha$ -specific fragments that binds to DQB1\*06:02.<sup>36</sup> A recent study revealed a possible contributor other than ASO3 adjuvants. It focused how a component of ASO3-adjuvanted pandemic vaccines was prepared in Europe.<sup>37</sup> In fact, there was no increase in immune response in healthy children after H1N1-ASO3 vaccination.<sup>3</sup>

### MF59

MF59 is another adjuvant used in vaccines, and is prevalent in Korea and the United States. From 2007 to 2013, 41 Korean soldiers who had narcolepsy were examined.<sup>38</sup> There were 6 narcolepsy cases between April and December 2009, nine months before the MF59-adjuvanted vaccination campaign.<sup>38</sup> However, 5 narcolepsy cases were detected between January to September 2010, which is nine months after the vaccine campaign, includ-

ing three months of continuous campaign.<sup>38</sup> Thus, MF59-adjuvanted H1N1 vaccine did not show any significant relationship with narcolepsy onset in Korean young adults.<sup>38</sup> Furthermore, according to the data of narcolepsy patients from July 2006 to June 2011, not only MF59-adjuvanted but also non-adjuvanted A(H1N1)pdm09 vaccine was not related to narcolepsy.<sup>38</sup>

The study conducted in the United States analyzed 650995 people vaccinated with the 2009 pandemic vaccine, and 870530 people vaccinated with 2010-2011 seasonal vaccine.<sup>39</sup> Vaccines including the A(H1N1)pdm09 virus strain and narcolepsy were unrelated. Another study conducted in 2011 analyzed 79004 people from 115 clinical trials.<sup>40</sup> After administration of other MF59-adjuvanted influenza vaccines, the risk of sleep-related adverse events, including narcolepsy, was not escalated.<sup>40</sup>

## CONCLUSION

High association between H1N1 infection or vaccination and narcolepsy is globally evident, especially in Europe. Discovering more evidences in homologies between H1N1 influenza and hypocretin will explain how they trigger the autoimmune responses. The aforementioned discovery will pave a way to provide more evidence-based diagnosis and treatment of narcolepsy. Pandemrix possesses unique features such as detergent, adjuvant and high amount of neuraminidase and nucleoprotein. These should be studied for future protection. Further studies on vaccinations (other than Pandemrix) and their relationship with narcolepsy will be conducive to expanding our knowledge on the crucial link between H1N1 infection or vaccination and narcolepsy.

### Conflicts of Interest

The authors have no financial conflicts of interest.

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