National Narcolepsy Task Force
Interim Report
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1 Background and mandate

The Director-General of the National Institute of Health and Welfare (THL) appointed 13 October 2010 a Task Force to determine whether there exists a causal relationship between the increased incidence of narcolepsy in children in Finland in 2010 and the vaccination campaign carried out with Pandemrix vaccine during fall 2009.

The Executive Director requested the Finnish Society on Sleep Research and the Finnish Association of Pediatric Neurology to nominate suitable experts to the Task Force from their membership. Based on these proposals the following persons who gave their consent were invited to the group: Dr Päivi Olsen, MD, PhD, Oulu University Hospital, Unit of Pediatric Neurology, Dr Christer Hublin, MD, PhD, Institute of Occupational Health, Research Centre on Brain and Work, Dr Sari-Leena Himanen, MD, PhD, Päijät-Häme Hospital District, Department of Clinical Neurophysiology Unit, Turkka Kirjavainen, Helsinki University Hospital, Department of Pediatrics, Docent Markku Partinen Helsinki Sleep Clinic and Dr Outi Saarenpää-Heikkilä, MD, PhD, Tampere University Hospital, Unit of Pediatric Neurology. The Ministry of Social Affairs and Health was represented by Dr Merja Saarinen, MD, until 31 December 2010. From the scientists at the THL, the Director-General appointed Dr Terhi Kilpi, MD, PhD, THL Department of Vaccination and Immune Protection as the chairperson of the Task Force and Dr Hanna Nohynek, MD, PhD, THL Vaccination Programme Unit, as the secretary and as other members Dr Jukka Jokinen, PhD, THL Vaccine Research Unit, and Research Professor Ilkka Julkunen, MD, PhD, THL Virus Infection unit and Research Professor Outi Vaarala, THL Immune Response Unit.

The Task Force was to consult experts in the field, and it was authorised to work in sections. To clarify the issue, the group was asked to submit proposals of national and international studies and to monitor and evaluate the work carried out at the THL and the information obtained from regulatory authorities and scientists to gain insight on pandemic vaccines, narcolepsy and their possible association.

The appointment letter stipulated the Task Force to submit an Interim Report of its progress to the Director-General by 31 January 2011 and the final report after completion of the work, but no later than 31 August 2011.

2 Background information on narcolepsy

2.1 Narcolepsy symptoms and the clinical picture, especially in children and adolescents

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness and cataplexy. Cataplexy refers to sudden loss of muscular tone in connection with emotional reactions. Tiredness is prominent and it is expressed as falling asleep unintentionally, for example, during play, at school, during meals or any other situations, where a person does not normally fall asleep. Cataplexy can be provoked by laughing, e.g. while playing or watching a funny video etc. Stress or fright may cause an attack of cataplexy. Especially in children, cataplexy occurs typically on the face (change of facial expression, opening of the mouth, pushing the tongue out of the mouth, nodding of the head, double vision, etc). Bending of the knees, weakness of lower limbs, or falling down because of loss of muscular tone in the lower limbs is also common. The affected person may fall on the ground during an attack. – Unlike in epileptic seizures the fall is usually not sudden and the person usually does not get badly injured.

Other symptoms of narcolepsy are visual hallucinations when waking up or falling asleep, sleep paralysis, and restless sleep. In children, narcolepsy often begins with stronger symptoms than in adults. Children are very tired and it may involve defying and aggressive behaviour. The attacks can be extremely frequent, particularly in the early stages of the disease. The strength of narcoleptic symptoms in children is also apparent in sleep tests. For example, in Multiple Sleep Latency Test (MSLT) the latency to falling asleep is typically shorter in children than in adults, and children have more REM sleep than adults with narcolepsy. Children with narcolepsy often have nightmares, their sleep is often restless, and on average they see a variety of delusions more frequently than adults. Other symptoms such as disturbed eating pattern and metabolic disturbances are common in narcolepsy.

2.2 Short literature overview on the epidemiology of narcolepsy

The prevalence of narcolepsy when both child and adult cases are taken into consideration varies by study and from country to country. On the average, the prevalence is reported to be approximately 0,05%; i.e. one in two thousand will fall ill with narcolepsy. In Finland, the prevalence is estimated to be 0.026 %, i.e. one in four thousand will fall ill with narcolepsy. In children less than 10 years of age, narcolepsy has been extremely rare. Previous studies have estimated the annual incidence of narcolepsy at approximately 1,4 newly diagnosed cases per 100 000 inhabitants per year (children and adults together). This means that in Finland approximately 60-70 persons have been diagnosed with narcolepsy annually. Typically, narcolepsy is sporadic, although about one in ten cases has got a relative with narcolepsy. The onset of the disease can manifest from early childhood to over 60 years of age. The onset of symptoms tends to be bimodal: the highest peak is around 15 years of age, and a smaller peak around 36 years of age.

According to studies in twins, environmental factors play a very significant role in addition to the genetic predisposing factors. Globally, only two identical twin pairs have been reported, in which case both twins had narcolepsy. Twins suffering from narcolepsy are almost always nonidentical. In identical twins it is more common that only one is diagnosed with narcolepsy. In a Finnish study of more than 11 000 twins, three were diagnosed with narcolepsy. All three patients were nonindentical twins, and their close relatives had not experienced any symptoms of narcolepsy.

A variety of infections, for example streptococcal A and viral infections, have been thought as triggering factors for narcolepsy. Other triggering factors include allergic reactions, inflammatory diseases, other autoimmune disorders, brain damage, thyroid dysfunction, and severe psychological trauma. None of these factors, however, have been confirmed causing narcolepsy.

3 Vaccines used during the H1N1 2009 pandemic

The different influenza vaccines used during the pandemic can be classified into three categories. Of these, two adjuvanted vaccines and one whole virus vaccine had a marketing authorisation granted by the European Medicines Agency in the autumn of 2009.

3.1 Vaccines similar to seasonal influenza vaccines

In Europe and North America, the seasonal influenza vaccines used since the 1970s have contained either killed and split influenza virus or only hemagglutinin (H) and neuraminidase (N) surface structures. These vaccines are produced from a combination of the original pathogen and a harmless influenza virus. This type of pandemic vaccine was used for example in the USA and Australia. In the United States approximately 80 million people received this type of vaccine, of the recipients 29 million were children. In Europe, this type of vaccine was available only in France and Spain.

3.2 Whole virus vaccines

From the 1940s until the 1970s seasonal influenza vaccines contained whole killed influenza viruses. The effectiveness of these vaccines was good, but their use as seasonal flu vaccines was discontinued mainly because of fever and local reactions. Against an entirely new kind of influenza virus, this type of vaccine was considered useful. In the fall 2009 one such vaccine was available, Celvapan®, manufactured by the pharmaceutical company Baxter. The vaccine was used in several European countries, but to a much lesser degree than the other two pandemic vaccines. Hungary produced and used a combination virus vaccine with aluminium adjuvant.

3.3 Adjuvant containing vaccines

For decades, vaccines have been used with adjuvants to improve the immune response and to gain better protection against the disease. The most commonly used adjuvants are different aluminium compounds. In Europe, the whole cell vaccine Fluval P® produced by the Hungarian company Omninvesti for national use employed aluminum phosphate as adjuvant.

Before the pandemic, clinical trials were conducted with so called model vaccines in which a new generation of squalene adjuvants proved to be effective enhancers of the immune response. Both Focetria® vaccine with MF59C.1 adjuvant (manufactured by Novartis) and Pandemrix® containing split virus with AS03 adjuvant (manufactured by GlaxoSmithKline) were widely used in Europe. In addition to Finland, Pandemrix was used for example in the other Nordic countries, United Kingdom, Ireland, Germany, France, the Netherlands and Spain. Focetria was used mainly in Italy, the Netherlands and Greece. Arepanrix® (GlaxoSmithKline) used in Canada has exactly the same composition as Pandemrix. The composition of the vaccines is illustrated in Table 1.

Table 1. Vaccines approved by the European Medical Agency for use during the pandemic 2009-10.

	Pandemrix (Arepanrix)	Focetria	Celvapan
Antigen	Inactivated split influenza virus A/California/7/2009 (H1N1)v-like strain (X-179A)	Surface structures of influenza virus A/California/7/2009 (H1N1)v-like strain (NYMC X-181)	Whole virus, A/California/7/2009 (H1N1)v virus strain
Haemagglutinin	3,75 ug	7,5 ug	7,5 ug
Produced	In eggs		Mammalian Vero cell line
Adjuvant	ASO3	MF59C.1	None
DL-α-tocoferol	11,86 mg	-	-
Squalen	10,96 mg	9,75 mg	-
Polysorbate 80	4,86 mg	1,175 mg	-
Thiomerosal	5 μg	-	-

4 Pandemic vaccinations according to age in Finland

When the objectives of the national A (H1N1) pandemic preparedness plan for autumn 2009 were agreed upon, the main target set for the pandemic vaccination was to avert swine influenza-related deaths and serious forms of disease. According to this principle, the National Advisory Committee on Vaccinations (KRAR) recommended the following prioritization of the different population groups to be vaccinated:

1. Social and health care professionals who work with A(H1N1) infected patients or patients presumably exposed to the infection, as well as ambulance personnel, and pharmacists who work in customer service;
2. Pregnant women;
3. People aged 6 months to 64 years at high risk due to their underlying illness. This category includes persons who require regular medication for heart or lung disease, metabolic disease, chronic liver or kidney disease, immune deficiency because of an underlying condition or treatment, chronic neurological disease or neuromuscular disease;
4. Healthy children from 6 to 35 months of age;
5. Healthy children and adolescents from 3 to 24 years of age as well as army conscripts, and
6. People aged 65 years and above who belong to high risk group due to an underlying illness.

After this the rest of the population was vaccinated.

Vaccination was carried out according to the recommended prioritization order as soon as the vaccines arrived in the country. Information on individuals vaccinated and batches given were recorded in the electronic patient records systems. Because Finland does not have a national immunization registry, data on immunizations needed for the investigations of the Task Force were collected during the autumn of 2010 with the help of software suppliers in charge of the design and maintenance of the patient record systems at the primary care level. In total, 2.6 million vaccine doses were given. Vaccination coverage of the entire country was approximately 50%, but varied considerably in the different age groups. The variation in vaccination coverage by age group is presented in Table 2.

Table 2. Pandemic vaccination coverage by different age groups. Ages are presented in 5-year periods.

Age group	Vaccinated	Population	Coverage (%)
0-4	208686	298114	70.0
5-9	215496	287786	74.9
10-14	232704	302423	76.9
15-19	178920	334636	53.5
20-24	99848	324472	30.8
25-29	104958	344634	30.5
30-34	127378	337970	37.7
35-39	124262	310768	40.0
40-44	142291	358754	39.7
45-49	152718	378341	40.4
50-54	161148	378037	42.6
55-59	181278	388165	46.7
60-64	211039	396886	53.2
65-69	142332	258319	55.1
70-74	125737	225043	55.9
75-79	97188	179671	54.1
80-	116481	247408	47.1
Total	2622464	5351427	49.0

5 The incidence of narcolepsy in Finland during years 2006–2010

In early 2005, substantial changes were made to the international case definition of narcolepsy. The new case definition was gradually introduced during 2005. Narcolepsy diagnoses made prior to the early part of the year 2005 are not fully consistent and thus not comparable with the new diagnoses made after that date. Therefore, the Task Force decided to use the incidence data on narcolepsy from years 2006–2009 as baseline data. The baseline incidence data was derived from the National Hospital Discharge Register. All patients who for the first time had got the ICD-10 code G47.4 for narcolepsy qualified. The incidence of narcolepsy had gradually increased during the years 2006–2009: in 2006, a total 44 cases were diagnosed, while in 2009 the total number of new narcolepsy cases was 68.

Since the National Hospital Discharge Register data of year 2010 would not be available until the second half of 2011, THL sent an urgent request to the central hospitals and to those districts hospitals which had specialized physicians (i.e. neurologists or sleep specialists) capable of narcolepsy diagnosis as well as to private sleep clinics on 19th October 2010 and again on 16th December 2010. The aim was to obtain the most updated information on the new narcolepsy-cataplexy diagnoses (ICD-code G47.4) given in each hospital and sleep center during the years 2009 and 2010. In this way, the Task Force assumed that it would be in the best position to gather information on all new narcolepsy cases regardless of whether the patients had received Pandemrix vaccine or not. Based on these requests, extensive information on new ICD-10 G47.4 diagnoses given during the year 2010 was made available to the Task Force by mid-January 2011. The age-group specific numbers on new narcolepsy cases during the period 2006-2010 are presented in Table 3.

Table 3. The diagnoses of narcolepsy (ICD-10 G47.4), age (in years) according to the calendar year

Age* group	2006	2007	2008	2009	2010
0-4	0	0	0	1	0
5-9	0	1	0	0	18
10-14	2	1	5	3	29
15-19	3	4	9	6	15
20-24	3	10	6	14	3
25-29	2	8	4	7	7
30-34	5	5	4	8	2
35-39	1	3	6	5	4
40-44	6	3	3	3	4
45-49	4	6	3	4	4
50-54	2	4	3	3	0
55-59	3	6	4	3	3
60-64	3	4	6	1	5
65-69	3	2	4	3	6
70-74	3	1	1	3	2
75-79	2	1	2	2	0
80-	2	0	0	2	0
Total	44	59	60	68	102

*Age when diagnosis was confirmed. Situation as of mid January 2011.

Source: THL National Hospital Discharge Register (2006–2009); Discharge Registers of Hospitals (2010)

6 Narcolepsy cases occurred after vaccination with Pandemrix and notified to the THL National Vaccine Adverse Events Register

The first case of narcolepsy which was suspected to be associated with Pandemrix vaccination, was notified to the THL National Vaccine Adverse Events Register in May 2010. Subsequently, reports began to accumulate at a steady pace only in August 2010 after the Swedish National Agency for Medicines on 15 August 2009 published the observation of a cluster of narcolepsy cases temporally related to vaccination with PandemrixR. Soon thereafter, the National Advisory Committee on Vaccination in Finland (KRAR) and THL delivered a statement on 24 August 2009, as a consequence of the observation by the Finnish doctors treating narcolepsy who similarly had noted a rapid increase in cases of narcolepsy-cataplexy among Finnish children and adolescents. THL advised upon KRAR's recommendation that as a precautionary measure, Pandemrix should not be given without a specific risk assessment of the treating physician, until more information about the association between the vaccine and narcolepsy was available.

By 24 January 2011, THL had been informed of a total of 57 narcolepsy and/or cataplexy cases as suspect vaccine adverse events. Of these, 55 had both narcolepsy/cataplexy symptoms, and two mostly symptoms of cataplexy. Of these 57 cases, 33 were girls/women, 24 boys/men. Cases were on the average 12 years, median 11 years, range 4,5 to 37 years during the time of vaccination. The average time from vaccination to the onset of excessive day time sleepiness or cataplexy was 52 days. The shortest time interval was on the same day, the longest time was 8 months. In the majority of the cases, the diagnosis was confirmed with sleep polygraphy and Multiple Sleep Latency Test (MSLT), in few cases the confirmatory diagnostic tests were still pending. In the majority of the cases, other neurological diseases were excluded with brain electroencephalogram, MRI and other studies. In the majority of the patients the clinical picture is classical narcolepsy-cataplexy, characterized by compulsive falling asleep during daytime, different sleep disturbances combined with changes in the appetite and metabolism.

7 Narcolepsy cases reported after vaccination with Pandemrix / Arepanrix in Finland and abroad

Of the 57 narcolepsy-cataplexy cases notified to the National Vaccine Adverse Events Register at THL by 24th January 2011, 54 occurred in 4-19 -year-old children and adolescents. According to the National Hospital Discharge Register, in 2007–2009 an average of 59–68 narcolepsy cases were diagnosed annually, of which 6–14 cases among children and adolescents of 4–19 years of age. In 2010, based on data obtained directly from the discharge registers of hospitals and sleep centers, 102 new narcolepsy-cataplexy diagnoses were made, of these 62 cases among those 4–19 years of age. Narcolepsy has, therefore, in 2010 occurred in significantly greater numbers in those 4–19 years of age, while during the same time period among older persons narcolepsy was diagnosed slightly lower numbers than on the average during the previous years.

Of the 30 countries where Pandemrix/Arepanrix vaccine was used in the autumn winter 2009–2010, only Finland, Sweden and Iceland have observed the narcolepsy incidence increasing compared to the figures of the previous years. In Table 4, the spontaneously reported cases of narcolepsy in association with Pandemrix/Arepanrix vaccination are presented in the age group in which the increase has been observed according to the information received by 24th January 2011 from the vaccine safety authorities in Finland, Sweden, Iceland, Germany, England and Canada.

Table 4. Notified narcolepsy cases after having received Pandemrix / Arepanrix

Country	Notified cases	Vaccinated 4-19 year olds	Cases / 100 000 vaccinated
Island	3	31 958	9,4
Finland	54	668 000	8,1
Sweden	58	1 193 000	4,9
Norway	8	510 000*	1,6
The Great Britain	2	295 000**	0,7
Germany	5	928 000***	0,5
Canada	2	~ 2 000 000	0,1

* 5-18 years of age
** 5-16 years of age
*** 0-17 years of age

8 Was vaccination with Pandemrix among those 5–19 years of age associated with increased risk of developing narcolepsy?

In order to ensure that the diagnoses of narcolepsy listed by the hospital discharge registries were correctly set and followed the international case definitions, THL requested the hospitals to provide the Task Force with all the relevant patient records of the ICD-10 G47.4 coded new patients who had been diagnosed during 2009 and 2010. The search was limited to those born on or after 1st January 1991, in order to concentrate efforts in that particular age group where the signal was observed. Two narcolepsy experts belonging to the Task Force independently from each other reviewed the patient records according to the suggested Brighton collaboration criteria (Level 1, Level 2, Level 3, Unknown, Not a case; for details see Appendix). In addition, the reviewers made independent estimates of the onset time of symptoms (excessive daytime sleepiness and/or cataplexy) based on the descriptions and dates noted in the medical records. After the independent review, a panel of three narcolepsy experts also belonging to the Task Force reviewed the discrepant classifications as well as those onset time estimates where the difference of the two reviewers was more than 30 days. In the discrepant cases, the final level of diagnosis and estimated onset time was set by the panel.

For the purposes of the main analysis, the onset time was defined as accurately as possible. This was done using patient records from hospitals and primary care. The primary care source documents included records from school health, health care centers and private clinics. The onset time of narcolepsy was defined as that particular day when the patient was for the first time seen by the school nurse, other public health nurse or general practitioner because of the parental observation or own complaint of unusual day time sleepiness and fatigue, and this visit and/or contact was recorded by the health care personnel in the patient records.

By 25 January 2011, based on the review of the hospital and primary care records during 2009–2010 in Finland 60 children and adolescents aged 5–19 years old fell ill with narcolepsy. Of these, 52 patients (87%) had their symptoms occur after pandemic vaccination. The vaccination coverage in this age group was 70%.

The risk of falling ill with narcolepsy was evaluated in a retrospective cohort study. The follow-up time was defined according to previously reviewed and approved protocol, and consisted of the time period from 1st January 2009 to 16th August 2010. The follow-up time was stopped at August 2010, because it was expected that the media attention to the narcolepsy cluster might have increased diagnostic sensitivity, and thus possibly biased the evaluation. The sensitivity analyses using different follow-up times did not, however, essentially make much difference to the outcome.

The incidence of narcolepsy was calculated by dividing the number of cases by the follow-up time. The follow-up time of the unvaccinated consisted of the time period of everyone before vaccination plus the follow-up time period of those not vaccinated after the pandemic vaccination campaign. The follow-up time of those vaccinated consisted of the time period after vaccination. With these definitions, the incidence of narcolepsy among those vaccinated was 9.2-fold higher in comparison to those not vaccinated (95% confidence interval 4.5–21.4). The increase in the observed incidence after vaccination is significant; this result, however, should be considered preliminary, as in some of the cases there is not sufficient information to make a robust estimation of the onset

time. In the coming months, THL will gather additional information on the diagnosed cases and confirm these findings. It is also worthy of mentioning that the information obtained of the present age cohort of those 4 to 19 years of age contains only data on narcolepsy and pandemic vaccination. Thus, the data now gathered is not sufficient to evaluate any possible confounders of the observation made.

In 2010, among adults only 40 new diagnoses of narcolepsy were made, which is a slightly lower number than in the previous years. Of these, 22 had been vaccinated. Vaccination coverage in this age group was 43%. Since it is expected that in August 2010, the publicity around narcolepsy sensitized both lay persons and professionals alike to recognize the disease, there is nothing to suggest that narcolepsy would have increased among those 20 years of age or above in general, or specifically after vaccination.

9 The more accurate detection of the association between Pandemrix vaccination and narcolepsy

The association of Pandemrix vaccination and narcolepsy found both in Finland and Sweden may be caused by several factors, either alone or simultaneously, or within a specific time period. The Task Force presented a variety of working hypotheses the verification or rejection of which guided the focus of the investigations. One working hypothesis was that the phenomenon could be due to some faulty lots of the vaccine, which had been delivered in these countries, but not anywhere else. The second working hypothesis was that when the vaccine was given in specific time window in relation to a recent or soon to be contracted A(H1N1) virus infection in genetically disposed and thus susceptible person could trigger the onset of narcolepsy. According to the third working hypothesis, there is an unknown confounding factor in the background. These different options are described below.

9.1 Was the increase in narcolepsy related to certain lots of vaccine?

Finland received vaccines from 28 production lots of Pandemrix, in total 5 286 000 doses. One production lot may consist of about a half a million to one million doses. In 2009, approximately only 100 000 doses per each production lot arrived in Finland. Doses of these same lots were taken to at least Sweden, Denmark, the Netherlands, France and Belgium.

Those fallen ill with narcolepsy in the age group of 5-19 years of age were vaccinated with nine different vaccine lots. A total of 1 472 000 doses were disseminated of these nine lots, and they were used to vaccinate over half a million children and adolescents between ages 5 to 19 years. The distribution of narcolepsy cases across the different vaccine lots was similar to the distribution of vaccine lots in the population of this age range in general.

Twenty one identical vaccine lots were used both in Finland and Sweden. Only four common lots were associated with the notified narcolepsy cases in both countries. Of the eleven common vaccine lots, single narcolepsy cases have been notified either in Finland or in Sweden alone. In Sweden, a cluster of 17 narcolepsy cases is associated with two vaccine lots, which were not distributed in Finland.

The fact that narcolepsy cases have occurred in association with several vaccine lots indicates that the increase in the disease cannot be attributed to one or some faulty vaccine lots alone.

9.2 The importance of genetic factors

Ninety five percent of Caucasian and Asian patients with narcolepsy carry the same genetic factor, the so-called HLA (human leukocyte antigen) DQB1*0602 allele. This HLA class II allele is responsible for presenting antigenic structures to the so-called CD4, or helper T-lymphocytes, and thus this allele regulates the activity of white blood cells. This genetic factor is found in approximately 28% of Finnish children. Its prevalence varies in the European population from 4 to 28%. In the Northern European populations (Finland, Sweden, England, Germany), genetic risk of narcolepsy can be found in approximately 25–28% of the population, while in Southern

Europe (Greece, Italy, Slovenia), the genetic risk occurs in 4–13% of the population. The HLA DQB1*0603 allele, on the other hand, seems to protect from narcolepsy. The distribution of this protective allele is very similar to the distribution of the predisposing allele, i.e. the highest prevalence is found among North Europeans (7-8%) and lowest in Southern Europeans (1-4%). Thus, the narcolepsy related HLA genotypes are very similar in the Northern European countries; the prevalence of DQB1*0602 HLA-risk genotype or HLA DQB1*0603-protective factor cannot explain the emergence of narcolepsy associated with Pandemrix vaccination in Finnish children.

So far, the HLA class II risk factor, HLA DQB1*0602, has been demonstrated in all those children with narcolepsy, in whom it has been sought (22/22) and whose narcolepsy was notified to the THL Adverse Events Register. With the current understanding, it appears that the Pandemrix vaccine associated cases of narcolepsy observed in children and adolescents do not differ genetically from the previous narcoleptic cases. Further studies are being planned to identify the genetic background in more detail among the Pandemrix vaccination associated narcoleptic cases.

The HLA class II gene polymorphism is associated with immune-mediated diseases in which the disease is caused by the abnormal function of the white blood cell activity. Such diseases are many autoimmune disorders such as type 1 diabetes, rheumatoid arthritis and multiple sclerosis. In these diseases, the white blood cell activity, either antibodies or cell-mediated reaction, leads to the destruction of the body's own tissue, either totally or partially. In narcoleptic patients, the destruction of the hypocretin/orexin producing cells in the brain results in low hypocretin/orexin content locally. This can be demonstrated by examining the cerebrospinal fluid hypocretin/orexin concentration. The hypocretin/orexin production deficiency causes the multiple symptoms of narcolepsy, such as tendency to fall asleep, cataplectic attacks, and hallucinations. The hypocretin/orexin deficiency also explains the dysfunction of appetite regulation and other metabolism-related symptoms, which result in weight gain. The strong association of narcolepsy with the HLA DQB1*0602 allele suggests that the hypocretin/orexin producing neurons are destroyed by the dysfunction of the white blood cells and that the disease is caused by immunological mechanism. In addition to the white blood cell dysfunction, other factors may contribute to the onset of narcolepsy. No single cause of narcolepsy is yet known. However, only less than one out of hundred persons who are genetically predisposed develop narcolepsy during their lifetime. Other autoimmune diseases associated with the same HLA genotype include Goodpasture's syndrome and multiple sclerosis, or MS.

9.3 The significance of the immune response

The onset of narcolepsy is considered to be mediated by immunological mechanisms, i.e. the destruction of the hypocretin/orexin producing neurons is caused by white blood cells. This is based on the fact that the disease is strongly associated with the presence of the HLA DQB1*0602 allele. Other factors favouring the role of the T-lymphocytes are the observations on the association of genetic variants of the T-receptor (important in identifying the antigen), and the purinergic receptor (controlling cellular functions) of T-lymphocytes with the risk of narcolepsy.

In addition, around the time of being diagnosed about one third of narcoleptic patients have so-called TRIBBLES-autoantibodies. i.e. antibodies against their body's own protein. The presence of these autoantibodies is not limited to narcolepsy, but the TRIBBBLES-autoantibodies also occurs in patients with autoimmune based uveitis. Thus TRIBBLES-autoantibodies cannot be regarded as a specific marker for narcolepsy. However, these findings support the theory that narcolepsy is an autoimmune disease in which the immune system attacks the body's own tissue structures. The pathogenesis of narcolepsy and the causative agent are unknown, but infections have been

suggested as triggers of the disease. The evidence is based on relatively small studies. The research on the role of the streptococcus group A bacterial infections in the onset of narcolepsy, for example, are still contradictory. All the narcoleptic cases associated with Pandemrix vaccination who so far have been tested have the HLA-risk genotype, i.e. HLA DQB1*0602 allele. The disease associated with vaccination resembles narcolepsy mediated by the so-called classical immunological mechanisms. Therefore, it is important to characterize the immune responses towards Pandemrix vaccine and the A(H1N1) virus.

The THL Immune Response unit has initiated immunological studies to explore the association between narcolepsy and Pandemrix vaccination. The aim of this research is to find out whether Pandemrix vaccine and/or the A(H1N1) virus infection caused the altered immune reactivity in the narcoleptic patients. The immune response, antibodies and cell-mediated responses towards the different components of the Pandemrix vaccine (adjuvant and viral protein) and/or of the A(H1N1) virus will be examined in the patients who developed narcolepsy during 2009-2010 in order to understand whether the immune responses are deviated in comparison to healthy controls. The HLA genotype will also be taken into consideration in the interpretation of these immune responses. In addition to children and adolescents, the role of the HLA genotype in the development of vaccine and A(H1N1) virus specific immune responses will be studied among adults who have received Pandemrix vaccine. These studies are currently underway. The results will be completed during 2011.

The pandemic vaccine administration to children and adolescents was very close in time or followed very briefly the A(H1N1) virus epidemic in Finland. In immunological studies, it is very difficult to distinguish between the reaction caused by the vaccine and by a viral infection, but methods are being developed for this purpose. The studies also focus on immune responses against streptococci.

9.4 International epidemiological studies

9.4.1 Is the vaccine associated increased risk of narcolepsy only a Finnish phenomenon?

Since the observation of the increase of narcolepsy post-vaccination was so strong in both Finland and Sweden, the idea arose to set up a more comprehensive international retrospective cohort study with a similar study design as in the one now carried out in Finland alone. Countries, where researchers have access to register-based morbidity and vaccination data are, in addition to Finland, at least Sweden, Norway, Denmark and Canada. THL wrote such a study protocol, and sought for an independent international scientific advisory board for it. The start of this international research collaboration has so far been delayed due to Finland's own commitments to its national study and also because the joint European VAESCO-led baseline incidence and case-control study is already underway (see 9.4.3.).

9.4.2 Joint effect of two temporally associated factors

The swine flu swept over Finland at a rapid pace during fall-winter 2009. The number of cases reached their peak during the weeks 43–49, 2009. In Figure 1, the red vertical lines represent the laboratory confirmed swine flu cases spread over the calendar weeks (Source: THL Infectious Disease Registry). Of the Nordic countries, in both Sweden and Denmark the epidemic situation was quite similar to that observed in Finland. In Norway and Iceland, the epidemic began some weeks earlier.

In each country, the timing of vaccination was determined by the availability of vaccines, the guidance on the prioritization of the different risk groups and the population's views on the necessity and acceptability of the

vaccines. The timing of the epidemic in relation to the vaccination activities varied somewhat from country to country. In Figure 1, in addition to the laboratory confirmed swine flu cases the numbers of vaccinated persons according to age groups and calendar weeks are shown. Vaccinations of those below 19-years of age took place primarily during weeks 45–50.

The Task Force speculated whether the simultaneous occurrence of vaccination and A(H1N1) infection could have contributed to the increase in incidence of narcolepsy. A similar time wise analysis of the occurrence of vaccination and swine flu epidemic was done for Norway, Iceland and part of Sweden. The swine flu epidemic and vaccinations were in close time-association in all these countries. But since no such signal of narcolepsy was observed in Norway, it is unlikely that the proximity of swine flu and vaccinations is the explanation to the increase in narcolepsy.

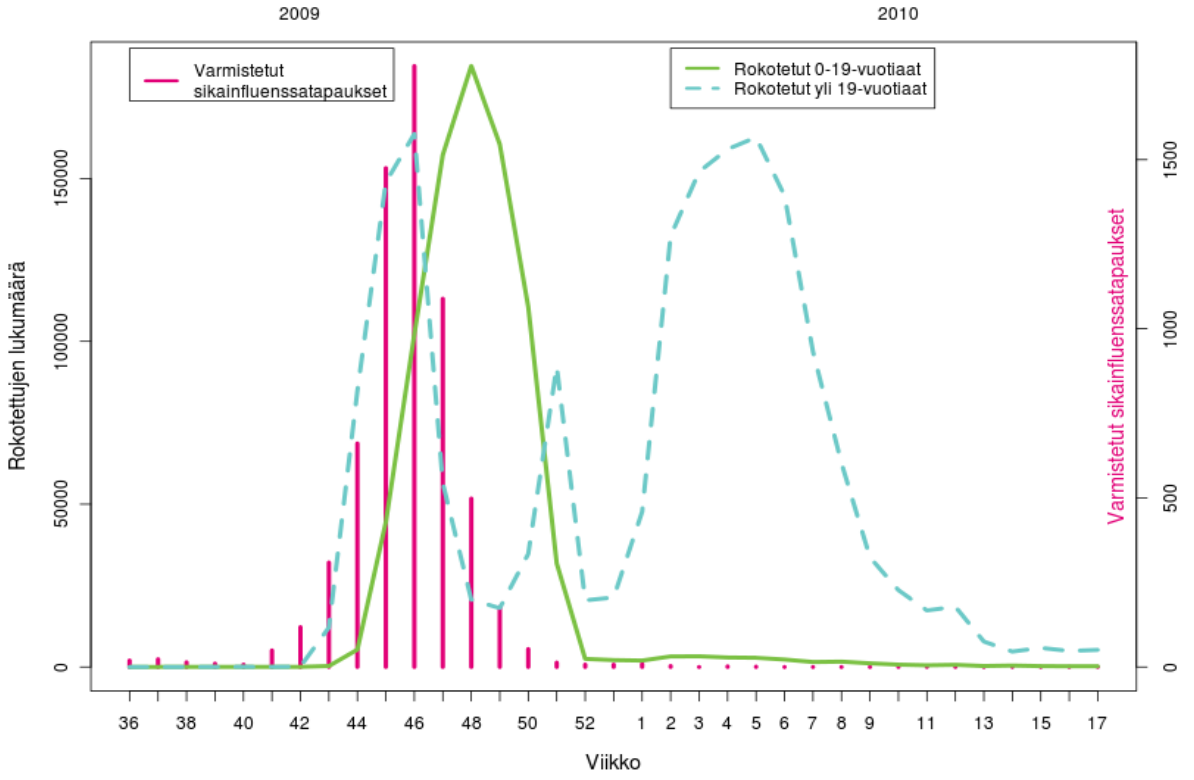

Figure 1. The swine flu epidemic and vaccinations during the calendar months in Finland. On the left Y-axis, the number of vaccinated, indicated by green line (0-19 year of age) and blue chopped line (those over 19 years of age). On the right Y axis, confirmed A(H1N1) cases, indicated by red columns. Calendar months indicated on the X-axis.

9.4.3 The search of potential confounding and contributing factors in collaboration with the European case-control study

The European Centre for Infectious Diseases Prevention and Control (ECDC), launched in September 2010 upon the request of the European Medicines Agency, a trans-European investigation into the association of the Pandemrix vaccination and narcolepsy. The study is being led by the VAESCO Consortium and headed by the Brighton Collaboration (www.brightoncollaboration.org). Seamless collaboration is being done also with the European Narcolepsy Research Network. The countries involved in the VAESCO collaboration on narcolepsy are Denmark, Finland, France, Italy, the Netherlands, Norway, Sweden, Spain, and United Kingdom.

The study consists of two parts: 1. the baseline incidence study of narcolepsy before Pandemrix vaccination in the participating countries, and 2. a case-control study to find out potential confounding, or contributing factors. THL Finland has participated in this study from the outset. This collaborative research has also played an important role in the standardization of the case definition of narcolepsy. It is important to guarantee that the cross-country comparisons can rely on the diagnostic criteria being similar, and thus ensuring comparability of data.

By the end of January 2011, the study protocols were finalized. In six countries, including Finland, the study plans were already reviewed and approved fully or conditionally by Ethics Committees. The data collection forms for the case-control study were finalized. With these, data will be collected from the cases and their age- and sex-matched controls on pandemic vaccination, narcolepsy-cataplexy symptoms, other neurologic and chronic diseases, especially other autoimmune diseases among the patients / controls and their close relatives, as well as different types of exposure data: history of previous infections, microbial and other drugs used including other vaccines and anaesthetic agents, smoking, menstrual onset, pregnancies and miscarriages, genetic factors predisposing to narcolepsy, and Finnish ancestry. The sample will include 250 narcoleptic cases and 1-4 controls for each case. The study will focus not only on those 4–19 year of age. The sample will include narcoleptic patients in all age groups and their age adjusted controls.

The baseline incidence data collection will be completed by February 21. According to the plan, this will allow the viewing of monthly incidence of narcolepsy in the nine European countries. Three different time periods are under review: 1. The period before the start of the pandemic, i.e. from the middle of 2000 until the end of March 2009; 2. The pandemic period prior to vaccinations, i.e. from the start of the pandemic period April 2009 up to September 2009; and 3. The vaccination period from when the virus still circulated in the population and vaccination began up to when the narcolepsy finding became known by those diagnosing and treating narcolepsy, i.e. from October 2009 to the end of June 2010. The medical records of the narcoleptic patients identified during these time periods will be reviewed in order to be certain that the diagnosis has been set correctly, and meet the internationally agreed narcolepsy-cataplexy diagnostic criteria.

The case-control study results are expected to be completed in May–June 2011.

10 Summary and conclusions

In Finland during 2009–2010, 60 children and adolescents aged 4–19 years were diagnosed with narcolepsy. This number is based on patient data collected from hospitals discharge registers and primary health care on all identified narcolepsy cases and an independent assessment of the patient records by an expert panel of neurologists and sleep researchers. When combining this information to pandemic vaccination data obtained from primary health care, it was noted that 52 persons, i.e. nearly 90 % of the cases, had received Pandemrix vaccine, when the vaccination coverage of that particular age group was 70 %.

According to these preliminary results, which still need to be confirmed, the risk of narcolepsy in the age group of 4–19 years was 9-fold among those Pandemrix-vaccinated in comparison with those unvaccinated in the same age group. The increase was most marked among those 5–15-years of age. No cases were observed in children less than 4 years of age. Among persons over 19 years of age the incidence of narcolepsy has not increased and there is no sign that the vaccine had had an effect on the risk for falling ill with narcolepsy. Overall, the observed association between the vaccine and narcolepsy in the age group of 4–19 years is so evident that it is unlikely that some underlying or so-called confounding factor could alone completely explain it.

In those countries which used similar pandemic vaccines in 2009-2010, an increased incidence of narcolepsy in children and adolescents has been observed only in Finland, Sweden and Iceland. In contrast to Finland, increased numbers of narcolepsy have been observed also among unvaccinated children and adolescents in Iceland. In Norway, United Kingdom, Germany and Canada, an estimated total of 3,5 million 4–19 year old children and adolescents have been vaccinated with the same vaccine as in Finland with no sign of an increase in narcolepsy.

So far, the studies do not indicate that narcolepsy would be related to the particular vaccine lots used in Finland and Sweden. The affected persons received pandemic vaccine from 9 different lots in Finland and from 17 lots in Sweden, with only 4 overlapping lots among these cases in the two countries. The distribution of the lots among the affected persons corresponds to the overall distribution of the different lots in the entire age group.

The association between narcolepsy and Pandemrix vaccine requires much further investigation. In the coming months, the register-based preliminary study results will be confirmed in Finland. In additional studies, the focus will be on exploring the role of infections and other stimuli in close temporal association with the vaccination and on identifying the importance of potential joint effects. In addition, the epidemiological, immunological and genetic studies will evaluate additional factors impacting the onset of narcolepsy. The main objective of the immunological studies is to elucidate whether the immune response in the affected or genetically predisposed persons is different for the Pandemrix vaccine, its components and the swine influenza virus, compared with other children and adolescents. It is very important to determine whether the association can be detected elsewhere than in Finland. Together with several European countries, Finland participates in a case-control study to clarify the role of the pandemic vaccine and other risk factors in the onset of narcolepsy.

Based on the investigations done so far, the Task Force considers in probable that the Pandemrix vaccine administered during winter season 2009–2010 contributed to the increased incidence of narcolepsy in Finland in the age group of 4–19 years. Because the increase in narcolepsy has been observed in only a few countries with wide use of Pandemrix, the Task Force considers it most likely that the vaccine increased narcolepsy in joint effect with genetic and/or environmental factors.

11 Literature

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Annex

1. The tentative diagnostic criteria of narcolepsy according to the Brighton collaboration and the European Narcolepsy Network

Case definition criteria

General note:
In rare cases, a suspected narcolepsy case may not be classifiable according to the levels below (e.g. when there is cataplexy, no sleepiness, and hypocretin-1 levels are unavailable). In these instances, the case definition committee will examine the clinical data and decide whether or not the patient can be classified as having narcolepsy, and if yes, at which level.

Level 1

In the *presence* of:
criterion 1: Excessive daytime sleepiness[a] and/or suspected cataplexy
AND
criterion 2: CSF hypocretin-1 deficiency[c]

Level 2

In the *presence* of:
criterion 1: Excessive daytime sleepiness[a]
AND
criterion 2: Definite cataplexy[b]
AND
criterion 3: Level 1 or 2 MSLT abormalities[d]

Note: criterion 3 has only been added to add some form of 'objectivity' (without sacrificing sensitivity)

Level 3

In the *presence* of:
criterion 1: Excessive daytime sleepiness[a]
AND
criterion 2: Level 1 MSLT abnormalities[d]

In the *absence* of:
criterion a: Other mimicking disorders, see [e]

[a]Excessive Daytime Sleepiness

definition in adults (>= 16 years):

An acquired condition, characterized by:
-involuntary sleep episodes during the day
-present almost daily for at least one month

definition in children (< 16 years):

An acquired condition, characterized by:
- -clear increase in daytime sleep episodes
- -usually in combination with feelings of subjective sleepiness and impaired concentration
- -present almost daily for at least one month

[b]definite cataplexy

definition in adults (>= 16 years):

Presence of all of the following criteria (*before* initiation of treatment):
- -episodes of muscle weakness
- -with preserved consciousness
- -at least 2 attacks with a clear trigger
- -majority of attacks lasting < 30 seconds

Episode with documented reversible areflexia will also qualify as definite cataplexy, regardless of the above criteria.

definition in children (< 16 years):

Children may present with cataplectic episodes that fulfill the criteria for adult cataplexy.

There may also be another phenotype that is restricted to children, with the following criteria:

-Acute-onset movement disorder, characterized by
- -Falls to the ground (i.e. while walking or running), and/or
- -Generalized hypotonia, and/or
- -Head drops and/or
- -Prominent facial involvement resulting in “cataplectic facies”, with ptosis, mouth opening, tongue protrusion, remarkable facial weakness, grimaces.

-Preserved consciousness
- -Triggered by possible ‘emotional’ circumstances, such as when watching funny cartoons, eating certain food, playing games.

-Emotional triggers can be absent in the first weeks after onset
- -Duration of a few seconds to several minutes, but often present in protracted clusters due to continuing emotional triggers
- -Episodes can be clearly distinguished from epileptic seizures or neuromuscular disorder

[c]hypocretin-1 deficiency

Hypocretin-1 concentration below 110 pg/ml using the Phoenix radioimmunoassay in crude, unextracted CSF. Performed in a laboratory according to published guidelines, using the Stanford reference sample.[1]

[1]Lin et al. Guidelines for the appropriate use of CSF measurements to diagnoste narcolepsy and accrediation of measurement sites. In: Narcolepsy and Hypersomnia, 1st edition, 2006. Edited by Bassetti, Billiard and Mignot.

[d]Multiple Sleep Latency Test Criteria

4 or 5 nap MSLT performed according to the AASM protocol[2]

A. Mean sleep latency of less than 8 minutes (adults) or less than 12 minutes (children <16 years)[3, 4]
B. At least 2 sleep-onset REM periods

Level 1: A AND B

Level 2: A OR B

Note: "level 2 MSLT" has only been added to have a certain form of 'objectivity' without sacrificing sensitivity.

[2]Littner et al. Practice parameters for clinical use of the multiple sleep latency test and maintenance of wakefulness test. Sleep 2005; 28:113-121

[3]Guilleminault et al. Narcolepsy in children: a practical guide to its diagnosis, treatment and follow-up. Pediatr Drugs 2000;2:1-9

[4] Serra L, et al. Cataplexy features in childhood narcolepsy. Mov Disord. 2008 Apr 30;23(6):858-65.

[e] to be excluded

The following conditions should be excluded:

-Other sleep disorders, according to ICSD-2 criteria:
Sleep disordered breathing
Behaviorally Induced Insufficient Sleep
Circadian Rhythm Disorders
Recurrent hypersomnias
Hypersomnias secondary to medical or psychiatric conditions

-Use of sedating medication

-Focal cerebral lesions, indicated by neurological examination and/or brain imaging