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Meeting report

Where are we in our understanding of the association between narcolepsy and one of the 2009 adjuvanted influenza A (H1N1) vaccines?☆

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ABSTRACT

Evaluating new rare serious vaccine safety signals is difficult and complex work. To further assess the observed increase in narcolepsy cases seen in Europe with the 2009 pandemic H1N1 influenza vaccine, the International Alliance for Biological Standardization (IABS) invited a wide range of experts to a one day meeting in Geneva in October 2015 to present data and to discuss the implications. The presentations covered the following topics: clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaigns; epidemiological studies conducted to assess the risk of narcolepsy, other neurological and immune-related diseases following 2009 pandemic H1N1 influenza vaccine; potential biases influencing the different epidemiological study designs; potential genetic contribution to the development of narcolepsy; potential biological mechanisms for development of narcolepsy in this setting including the role of the virus itself, antigenic differences between the vaccines and differences in AS03-adjuvanted vaccines. The presentations were followed by fulsome roundtable discussions. Members from affected families also attended and made informal comments to round out the day's deliberations. This meeting emphasized the value added in bringing together in a neutral setting a wide range of experts and vaccine producers to discuss such a complex new serious adverse event following immunization.

1. Objective of meeting

The overall objective of this meeting was to exchange the latest information on research on the development of narcolepsy following immunization with one of the 2009 adjuvanted influenza A (H1N1) vaccines. The meeting was organized by International Alliance of Biological Science (IABS) and took place in Geneva, Switzerland on October 23, 2015.

The specific meeting objectives were:

- To discuss new data on narcolepsy and adjuvanted 2009 influenza A (H1N1) vaccines – the epidemiology and pathophysiology of narcolepsy and hypotheses on potential biological mechanism contributing to narcolepsy;
- To discuss possible implications of these findings for seasonal and pandemic influenza vaccines as we move forward;
- To discuss options for collaboratively addressing vaccine rare event safety signals given availability of newer biomarkers, epidemiology, molecular biology and immunology tools and knowledge.

The expected outcomes were:

- A mutual understanding of a possible relationship between narcolepsy and adjuvanted 2009 influenza A (H1N1) pandemic vaccines;
- A mutual understanding of the implications of this finding for future seasonal and pandemic influenza vaccines;

☆ The meeting was conducted under Chatham House Rule: participants are free to use the information received, but neither the identity, nor the affiliation of the speaker(s) or that of any other participant, may be revealed.

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- A delineation of research steps to be taken to expand knowledge and understanding of narcolepsy, narcolepsy and biomarkers, and inciting factors for narcolepsy;
- A delineation of research steps to be taken to expand knowledge and understanding of the current hypotheses between narcolepsy and vaccination with one of the 2009 adjuvanted influenza A (H1N1) vaccines;
- A common understanding of the range of stakeholders needed to develop an effective strategy and framework for addressing vaccine rare event safety signals given the availability of newer biomarkers, epidemiology techniques, molecular biology and immunology tools and growing knowledge.

In a series of presentations the following topics were reviewed during the meeting:

- clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaigns;
- epidemiological studies conducted assessing risk of narcolepsy and other neurological as well as immune-related diseases following 2009 pandemic H1N1 influenza vaccine;
- potential biases influencing the different epidemiological study designs;
- genetic contribution to the development of narcolepsy;
- potential biological mechanisms for development of narcolepsy following H1N1 pandemic and pandemic vaccination including the role of antigenic differences between the different AS03-adjuvanted vaccines.

The presentations were followed by a roundtable discussion.

2. Pro-active pharmacovigilance strategy for 2009 pandemic vaccination campaigns

An overview of the pro-active pharmacovigilance strategy of the European Medicines Agency ahead of the pandemic vaccination campaigns with regulators and researchers emphasizing the importance of background incidence rates of possible adverse events of special interest was provided to meeting participants. In total eight pandemic vaccines were available for use in the large European pandemic vaccination campaigns conducted in EU/EEA Member States. Vaccination campaigns started in October 2009 at approximately the same time as the second wave of the 2009 influenza A H1N1 pandemic arrived in Europe. According to estimates conducted in the EU, at least 38.6 million Europeans were vaccinated with one of the three centrally authorized pandemic vaccines; Celvapan from Baxter (~550,000), Focetria from Novartis (6.5 million), and Pandemrix from GSK (almost 31 million) [1]. In addition ~7.5 million individuals were vaccinated with one of the nationally authorized vaccines.

3. Unexpected safety signal reported in 2010

A safety signal consisting of an increased number of narcolepsy cases reported to the medical product agencies was first recognized in Sweden June 2010 and soon thereafter in Finland. The reports led to a public announcement by EMA on August 27, 2010 that a review had been initiated [2]. By January 2015, a total of 1379 reports of narcolepsy following vaccination with the Pandemrix vaccine produced in GSK-facility located in Dresden, Germany had been received in the EMA Eudravigilance database [3].

4. Narcolepsy disease

Narcolepsy is a rare sleep disorder. The most common symptoms of narcolepsy are unintended sleep episodes, excessive daytime sleepiness (EDS) and cataplexy. Other common symptoms are hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep. Often narcolepsy starts between 12 and 25 years of age with the peak of onset at 14–16 years. An onset before age of 10 years is rare. A diagnosis is supported by a positive Multiple Sleep Latency Test (MSLT) measuring how quickly the patient falls asleep in a quiet environment during the day and analysis of cerebrospinal fluid (CSF) for hypocretin-1 concentration. Typically narcolepsy–cataplexy is characterized by the lack of or low hypothalamic hypocretin (orexin) production (<110 pg/mL in CSF) and sleep latency of less than 8 min as well as two or more occurrences of Sleep Onset Rapid Eye Movement (SOREM) periods during the first 15 min of sleep. In addition, a strong association with HLA DR15 (DR2) and DQB1*0602 has been observed. Among Caucasians over 90% of patients with narcolepsy–cataplexy are HLA DQB1*0602 positive. Environmental factors including infections have been proposed to be able to trigger narcolepsy disease in susceptible individuals; e.g. influenza A (H1N1) and *Streptococcus pyogenes*. Up until 2010, the development of narcolepsy has never been associated with a vaccine.

5. Characteristics of cases with narcolepsy following 2009 H1N1 pandemic vaccination

In a Finnish study analyzing the clinical characteristics of 50 cases <17 years with narcolepsy following the 2009 H1N1 pandemic vaccination, the mean age (±SD) at the time of vaccination was 10.8 ± 3.0 years (range 4.5–16.1 y), while the mean age at onset of disease was 11.0 ± 3.1 years [4]. Eighteen percent of the children were <8 years, 24% were 8–10 years, 38% were 11–13 years and 20% 14–16 years old at onset of symptoms (Fig. 1). The initial symptoms of narcolepsy included EDS, reappearance of regular daytime naps, and unintended sleep episodes. Further, 47 of the 50 children (94%) developed cataplexy, which started 6–359 days after the vaccination (median 77 days, i.e. 11 weeks), 53% had hypnagogic hallucinations, 18% sleep paralysis, and 88% disturbed nocturnal sleep. In addition, almost 50% of the children showed behavioral changes or psychiatric problems (conduct disorders/challenging and aggressive behavior and self-mutilation), that necessitated psychiatric treatment after onset of narcolepsy. All children had an abnormal MSLT with a mean sleep latency of 1.8 ± 1.4 min (95% CI 1.4–2.2) with at least 2 (median 4; mean 3.8 ± 0.9) SOREM periods. Among the 50 cases, 32 were HLA-typed and all were positive for the DQB1*0602/DRB1*15/DR15-DQ6 genotype.

6. Review of epidemiological studies conducted in EU/EEA and non-EU/EEA countries to assess the narcolepsy signal

Formal epidemiological studies have been conducted in seven countries (six located in the EU/EEA and one in North America) using case–control, cohort or case-coverage methods to assess a possible association between AS03-adjuvanted 2009 influenza A (H1N1) vaccines and development of narcolepsy [5–13]. The first formal epidemiological studies (ecological and retrospective cohort) from Finland and Sweden suggested a 4–9-fold increased risk in children and adolescents who had received the AS03-adjuvanted vaccine (Pandemrix™) produced in Dresden, Germany (GSK). Subsequent studies conducted in France, Ireland, Norway, and the UK confirmed the increased risk. The Pandemrix™ vaccine was also used in these countries. One EU/EEA country, Germany has still to report the findings of their on-going study. In addition, an increased risk among young adults was been noted in Finland, France, and Sweden with a 3–5 -fold increased risk in Finland (www.julkari.fi.)

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An AS03-adjuvanted vaccine produced in Quebec, Canada by GSK using a different production protocol (Arepanrix™) was used in the 2009 pandemic vaccination campaigns conducted in Canada. Three studies conducted in the province of Quebec with a population of ~8 million and 57% vaccine coverage have assessed a possible association. The results are consistent with a risk of narcolepsy of very small magnitude, in the range one case per million doses. The existence of an excess risk of much higher magnitude as reported in the EU/EEA countries can be excluded with reasonable certainty. Further, unadjuvanted influenza vaccines containing the A(H1N1)pdm09 virus strain used in the United States were not associated with an increased risk of narcolepsy assessed in the Vaccine Safety Datalink study; however, there was limited use of any of the GSK vaccines [14]. A large global study (SOMNIA) including countries that offered AS03-containing vaccines from the two production facilities in Dresden, Germany and Quebec, Canada (Canada, Switzerland, Spain, Netherlands) as well as an MF59-adjuvanted vaccine Focetria™ (Taiwan, Argentina, Switzerland, Spain, Netherlands) produced in Sienna, Italy (Novartis) to their populations is still on-going and the report is expected in the first quarter of 2016.

7. Risks of other neurological and immune-related diseases

In a comparative registry-based cohort study conducted in Sweden an increased risk was excluded for the following neurological and immune-related diseases; Guillain–Barre syndrome, multiple sclerosis, acute disseminated encephalomyelitis, epilepsy grand mal, rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, other reactive arthritis, inflammatory systemic disease, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, myasthenia gravis, erythema multiforme, Stevens–Johnson syndrome, exfoliative dermatitis, erythema nodosum while an increased risk (3-fold with a Hazard Ratio of 2.92 95%CI 1.78–4.79) was observed for narcolepsy in individuals ≤20 years [15–17]. An increased risk for development of narcolepsy was also observed in this study in the young adults group, 21–30 years. Further studies in the adult group are on-going. A dose–response study assessing individuals receiving one or two doses of Pandemrix™, respectively is on-going with results expected in 2016.

8. Assessment of potential biases that possibly could influence study results

Several speakers addressed potential biases (e.g. ascertainment bias, random misclassification bias, differential misclassification bias, selection bias, recall bias and confounding) that could have influenced the narcolepsy observation results in the reported epidemiology studies [18]. Sensitivity analyses of biases were conducted by several stakeholders including industry. All concluded that the association between the AS03-adjuvanted 2009 pandemic vaccine produced in Dresden, Germany and development of narcolepsy persists despite strong assumptions on potential biases and confounders, but the real risk may be lower than reported. Recall bias was addressed in epidemiological studies conducted in countries with no media attention during the study period (assessed using Google trends). These confirmed the results of studies conducted in countries with a lot of media attention. Ascertainment bias was addressed in studies conducted using different primary outcomes. Studies that selected date for referral to MSLT or date of diagnosis as primary outcome had a lower but significant relative risk/odds ratio compared to studies that selected either date of EDS onset or 1st contact to health care. In conclusion, it was noted that the published observational studies meet at least 4 of the Bradford Hill causality criteria; strength, consistency, specificity and temporality while some of the on-going clinical and pre-clinical studies may address the last four Bradford Hill causality criteria: biological gradient, plausibility, coherence and experimental.

9. Potential biological mechanisms

There is a genetic predisposition for development of narcolepsy. First degree relatives of narcolepsy patients and if available their monozygotic twins have an increased risk for also developing narcolepsy. Genome-wide association studies suggest that identified gene variants that make individuals susceptible to narcolepsy are part of the immune system. Variations in these HLA class II

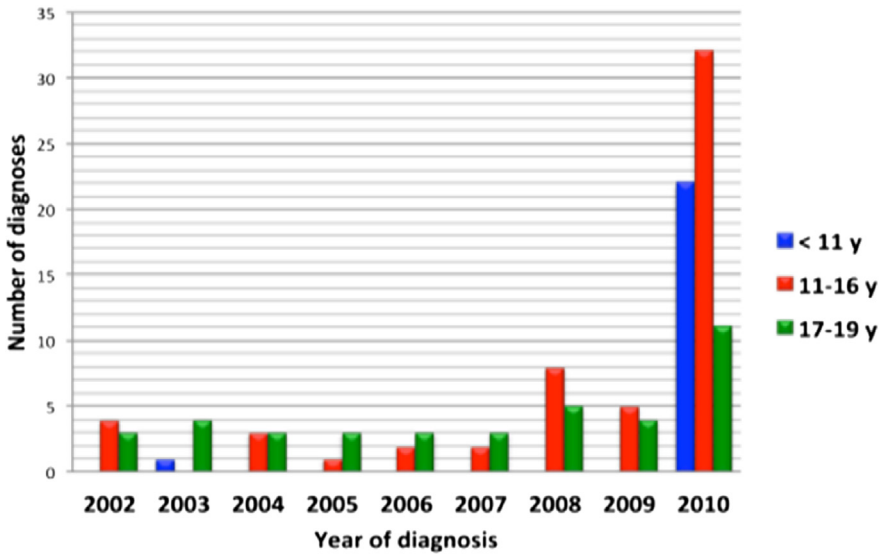

Fig. 1. The number of new diagnoses of narcolepsy among Finnish children and adolescents younger than 20 years are displayed by year of diagnosis 2002–2010 for the three age groups <11 years, 11–16 and 17–19 years of age. Narcolepsy cases were retrieved from all Finnish hospitals and sleep clinics. The average annual incidence 2002–2009 in subjects under 17 years of age was 0.31 (95% CI 0.12–0.51) per 100,000 while in 2010 the incidence for this age group was 5.3/100,000 which is a 17-fold increase (Adapted from Partinen et al. PLOS ONE published March 28, 2012). The influenza A (H1N1) vaccination campaigns started October 2009 [4].

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molecule sequences provide survival benefits for the human species including protection against infectious diseases, but provide a risk for development of auto-immune disease in the individual. It is known that each particular autoimmune disease has an association to a particular HLA class II variant. As shown above the majority of affected individuals with narcolepsy and cataplexy (>95%) express HLA class II DQB1*0602. This is viewed as a very strong association. However, this HLA class II variant is carried by ~30% of the populations in Sweden and Finland. Since this variant is co-inherited with DRB1*15:01 specific for multiple sclerosis and no increased risk for MS (15) was observed in the Swedish study presented above there is support for an immune-mediated pathogenesis, with a peptide specificity triggering disease in the affected individuals. Molecular mimicry leading to a target-specific attack is the hypothesis several investigators are pursuing, but alternative mechanisms cannot be excluded [19]. The potential target autoantigens remain to be defined.

One investigator team working on the hypothesis of molecular mimicry reported that a mimic peptide was identified from a surface-exposed region of the influenza nucleoprotein A that shared protein residues in common with a fragment of the first extracellular domain of the hypocretin receptor 2 [20]. A significantly higher proportion of sera from HLA-DQB1*0602 haplotype-positive narcoleptic Finnish patients with a history of Pandemrix™ vaccination (vaccine-associated narcolepsy) had antibodies to hypocretin receptor 2 compared to sera from non-narcoleptic individuals with either 2009 A(H1N1) pandemic influenza infection or a history of Focetria™ vaccination. Antibodies from vaccine-associated narcolepsy patient sera cross-reacted with both influenza nucleoprotein and hypocretin receptor 2, as demonstrated by competitive binding using a 21-mer peptide (containing the identified nucleoprotein mimic) and a 55-mer recombinant peptide (first extracellular domain of hypocretin receptor 2), on cell lines expressing human hypocretin receptor 2.

Another investigator team is also working on the hypothesis of molecular mimicry, focusing their work on analyzing possible T cell cross-reactivity between hemagglutinin and hypocretin itself but no results are available yet.

Finally, several differences in the production protocols for the two AS03-adjuvanted 2009 influenza A (H1N1) vaccines have been determined: 1) higher amounts of structurally altered viral nucleoprotein in Pandemrix™ than in Arepanrix™, 2) detergent-induced antigenic changes in the influenza NP that are recognized by antibodies from children with narcolepsy, and 3) increased antibody response to NP in association of the DQB1*06:02 risk allele of narcolepsy [21,22]. Although a mechanism for Pandemrix™ triggering narcolepsy remains elusive, these results are moving the focus somewhat from the adjuvant to the influenza viral proteins. However, a possible contributing role of the adjuvant needs to be investigated.

10. Patient's view

The development of narcolepsy has had a huge impact on the injured childrens' and adults' current and future lives including negative impacts on their physical, intellectual, educational development, quality of life and well being. As narcolepsy has occurred during important developmental years for these children/young people, the disease is shaping their future. Every year “lost” impacts their entire future.

Therefore it is important to understand what caused narcolepsy and to focus on restoring the injured to full health. Additional funding and resources should be aimed at finding better treatments and cures for narcolepsy and a more fulsome understanding of the disease.

11. Conclusions

The roundtable discussion concluded that signal detection of a rare and unexpected adverse event worked well, although with some delay. However, signal validation needs to occur at a faster speed for the future. A better and more open collaborative approach to manage signals is required. Preapproved IRB approvals in all Member States could facilitate the initiation of the epidemiological association studies e.g. retrieving cases from databases or the health care system, required for signal validation assessment. Reinforcement of active surveillance during vaccination campaigns could be a useful additional approach.

The conducted and published observational studies assessing narcolepsy following Pandemrix™ vaccination meet at least 4 of the major Bradford Hill causality criteria; strength, consistency, specificity and temporality. Conducted sensitivity analysis for possible biases concluded that the observed association persists. More biological mechanistic studies are urgently needed to further understand possible biological mechanisms how Pandemrix™ could have triggered narcolepsy in susceptible individuals. The current reported hypotheses of molecular mimicry need to be confirmed by independent laboratories. The analytical framework for pandemic influenza vaccine recommendations, the risk assessment of influenza pandemics themselves and the framework for studies when needed needs to be improved.

A number of outstanding questions remain: did Pandemrix™ and to a lesser extent Arepanrix™ trigger onset of narcolepsy in individuals who would have developed narcolepsy later in life if the right trigger was encountered? Are any other pandemic influenza vaccines associated with narcolepsy? This will hopefully be answered in on-going studies expected to report in 2016. Could the preparations of regulatory authorities for speedy detection of safety signal with pandemic vaccine been better? Would a rare unanticipated safety signal be detected equally efficiently in other parts of the world? How can benefit-risk analyses be improved to inform regulatory and public health decision-making for the future?

This meeting focused on the risk-side of the equation, and future discussions should also address potential benefits from the use of vaccines. Future discussions should also include vaccine developers and vaccine quality control experts.

Finally, it was acknowledged that the IABS platform provided a good forum for the discussions.

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