Résumé information et littérature - Narcolepsie

Résumé MSSS (Dr Bruno Turmel)

« J'ai contacté Philippe DeWals et voici les informations qu'il a été en mesure de me transmettre :

- L'étude sur les cas du Québec a été publié et nous la connaissons tous : http://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0108489&type=printable
- Suite à la publication de cette étude, le docteur Montplaisir et lui ont procédé à une nouvelle étude en utilisant un devis différent de type cas-témoins test négatif, mais en raison de limites méthodologiques importantes (difficulté à trouver des témoins, tous les cas proviennent du Québec et tous les témoins sont de Ste-Justine, donc problème de représentabilité qui remet en question les conclusions), ils ont convenu de ne pas publier ces données (qui concluaient en une absence de lien). GSK aurait manifesté le souhait de produire un manuscrit à partir de ces données, et à la lumière de la proposition soumise par GSK, les docteurs Montplaisir et DeWals ont refusé d'être associé à une éventuelle publication par GSK. Le processus de ré-écriture du manuscrit serait en cours, mais PdW n'est pas au courant d'une éventuelle publication prochaine. Mais selon ses propres termes, cette étude serait de toute façon "pourrie" et n'apporterait rien de nouveau en raison de ses limites méthodologiques.
- Pour ce qui concerne l'étude SOMNIA, l'information qu'il a pu me fournir est que la poursuite des analyses serait mise sur la glace pour des raisons obscures. Il ne semble donc pas y avoir de nouvelles analyses / publications prévues dans un avenir prochain. Il a parlé avec Jeff Kwong, et c'est la seule information qu'il a été en mesure d'obtenir.
    - La seule publication officielle est celle qui a été présentée dans le cadre du congrès ID Week 2016, dont vous possédez déjà une copie (voir pièce jointe). Nous avons contacté un expert à l'OMS, et les références fournies à ce sujet nous ramènent toujours aux données présentées dans le même poster. Le docteur Kwong a présenté les données de l'étude SOMNIA au Comité consultatif mondial pour la sécurité des vaccins (GACVS) de l'OMS lors d'une rencontre qui s'est tenue les 30 novembre et 1er décembre 2016. La position du GACVS publiée dans le Relevé épidémiologique hebdomadaire du 13 janvier 2017 est basée sur le complément d'information apporté par les données de cette étude qui ont été présentées. Ce document a été transmis à tous par courriel.
- La docteure Monique Landry a eu l'opportunité de parler récemment avec de docteur Jeff Kwong, et même si l'intention est de publier éventuellement les données, aucun échéancier n'a été fixé car ça ne semble pas prioritaire dans la situation actuelle où les résultats ont été présentés dans un congrès international et qu'il n'y aura pas de nouvelles données à présenter.
- À la lumière du point précédent, il est permis de croire qu'il n'y aura aucune publication prochaine de la part de J. Kwong à ce sujet.
- Pour ce qui est de la Saskatchewan, l'analyse a porté uniquement sur l'établissement d'un "baseline" de cas de narcolepsie. et les différences avant et après la vaccination sont non concluantes (retenir que le nombre de cas est très petit). Ma compréhension est que le même type d'analyse a été faite en Ontario (dans le cadre de SOMNIA) et que les résultats se sont avérés non concluants.

Donc, en résumé.

- Il ne semble pas y avoir de nouvelles données à venir dans avenir proche, moyen ou lointain.
- Dans la cas où une publication serait faite par GSK, les conclusions seraient à l'effet d'une absence de lien, mais des considérations méthodologiques importantes ne permettraient pas de pouvoir tenir compte de ces conclusions.

Il ne semble pas y avoir de nouvelles analyses prévues des données de l'étude SOMNIA dans un avenir proche, moyen ou lointain. La seule publication est le poster que nous avons tous vu. »

Posters et extraits instances internationales

1. OMS, 2017 :

2017, 92, 13-20 No 2

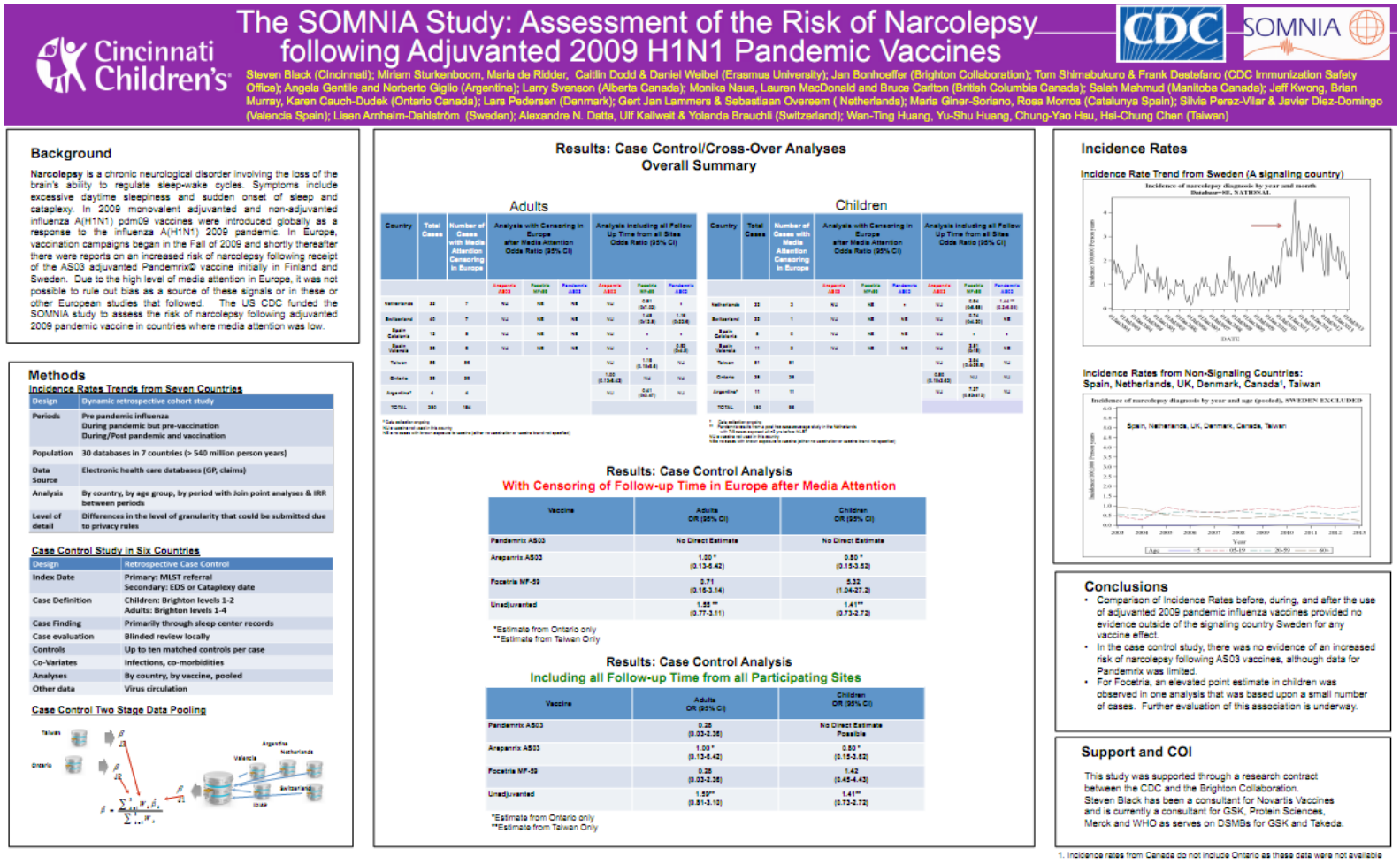
World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

13 JANUARY 2017, 92th YEAR / 13 JANVIER 2017, 92e ANNÉE
No 2, 2017, 92, 13–20
http://www.who.int/wer

Les taux de narcolepsie dans la population avant et après la pandémie ont été calculés à partir des cas diagnostiqués contenus dans les bases de données des systèmes de santé. Les analyses provisoires n'ont pratiquement pas révélé de signaux, sauf en Suède, l'un des 2 pays ayant notifié des signaux (l'autre étant la Finlande), où le Pandemrix était le seul vaccin utilisé, avec une forte couverture vaccinale. Le recrutement des témoins pour les études cas-témoins a été réalisé soit en population, soit en milieu hospitalier selon le pays, avec un appariement avec les cas selon l'âge, le sexe et le temps. Les résultats préliminaires des études cas-témoins étaient rassurants pour le Focetria et l'Arepanrix. Pour le Pandemrix, les données issues de cette étude étaient trop peu nombreuses pour permettre de tirer de nouvelles conclusions. Le GACVS est conscient que des données supplémentaires sur le Pandemrix pourraient provenir de plusieurs pays européens, notamment dans le cadre d'un suivi prolongé d'études déjà publiées, permettant de mieux comprendre le lien entre la narcolepsie et le Pandemrix. Les données présentées à ce jour rassurent sur le fait qu'à l'exception du Pandemrix avec l'adjuvant ASO3, administré à de nombreux adolescents et jeunes adultes dans plusieurs pays européens, aucune autre association notable entre l'utilisation des vaccins contre le virus grippal pandémique p2009H1N1 et la narcolepsie n'a été identifiée.

2. Poster SOMMNIA, présenté au Congrès IDWeek en octobre 2016



The SOMNIA Study: Assessment of the Risk of Narcolepsy following Adjuvanted 2009 H1N1 Pandemic Vaccines

Cincinnati Children's · CDC · SOMNIA

Steven Black (Cincinnati); Miriam Sturkenboom, Maria de Ridder, Caitlin Dodd & Daniel Weibel (Erasmus University); Jan Bonhoeffer (Brighton Collaboration); Tom Shimabukuro & Frank Destefano (CDC Immunization Safety Office); Angela Gentile and Norberto Giglio (Argentina); Larry Svenson (Alberta Canada); Monika Naus, Lauren MacDonald and Bruce Carlton (British Columbia Canada); Salah Mahmud (Manitoba Canada); Jeff Kwong, Brian Murray, Karen Cauch-Dudek (Ontario Canada); Lars Pedersen (Denmark); Gert Jan Lammers & Sebastiaan Overeem (Netherlands); Maria Giner-Soriano, Rosa Morros (Catalunya Spain); Silvia Perez-Vilar & Javier Diez-Domingo (Valencia Spain); Lisen Arnheim-Dahlström (Sweden); Alexandre N. Datta, Ulf Kallweit & Yolanda Brauchli (Switzerland); Wan-Ting Huang, Yu-Shu Huang, Chung-Yao Hsu, Hsi-Chung Chen (Taiwan)

Background

Narcolepsy is a chronic neurological disorder involving the loss of the brain's ability to regulate sleep-wake cycles. Symptoms include excessive daytime sleepiness and sudden onset of sleep and cataplexy. In 2009 monovalent adjuvanted and non-adjuvanted influenza A(H1N1) pdm09 vaccines were introduced globally as a response to the influenza A(H1N1) 2009 pandemic. In Europe, vaccination campaigns began in the Fall of 2009 and shortly thereafter there were reports on an increased risk of narcolepsy following receipt of the AS03 adjuvanted Pandemrix® vaccine initially in Finland and Sweden. Due to the high level of media attention in Europe, it was not possible to rule out bias as a source of these signals or in these or other European studies that followed. The US CDC funded the SOMNIA study to assess the risk of narcolepsy following adjuvanted 2009 pandemic vaccine in countries where media attention was low.

Methods

Incidence Rates Trends from Seven Countries

Design	Dynamic retrospective cohort study
Periods	Pre pandemic influenza During pandemic but pre-vaccination During/Post pandemic and vaccination
Population	30 databases in 7 countries (> 540 million person years)
Data Source	Electronic health care databases (GP, claims)
Analysis	By country, by age group, by period with Join point analyses & IRR between periods
Level of detail	Differences in the level of granularity that could be submitted due to privacy rules

Case Control Study in Six Countries

Design	Retrospective Case Control
Index Date	Primary: MLST referral Secondary: EDS or Cataplexy date
Case Definition	Children: Brighton levels 1-2 Adults: Brighton levels 1-4
Case Finding	Primarily through sleep center records
Case evaluation	Blinded review locally
Controls	Up to ten matched controls per case
Co-Variates	Infections, co-morbidities
Analyses	By country, by vaccine, pooled
Other data	Virus circulation

Case Control Two Stage Data Pooling

Results: Case Control/Cross-Over Analyses Overall Summary

Adults

Country	Total Cases	Number of Cases with Media Attention Censoring in Europe	Analysis with Censoring in Europe after Media Attention Odds Ratio (95% CI)			Analysis including all Follow Up Time from all Sites Odds Ratio (95% CI)		
			Arepanrix AS03	Focetria MF-59	Pandemrix AS03	Arepanrix AS03	Focetria MF-59	Pandemrix AS03
Netherlands	33	7	NU	NE	NE	NU	0.81 (0.07-22)	*
Switzerland	40	7	NU	NE	NE	NU	1.48 (0.13-8)	1.16 (0.03-8)
Spain Catalonia	13	8	NU	NE	NE	NU	*	*
Spain Valencia	36	8	NU	NE	NE	NU	*	2.82 (0.4-8)
Taiwan	88	88				NU	1.16 (0.19-8.4)	NU
Ontario	28	28				1.00 (0.13-6.42)	NU	NU
Argentina*	4	4				NU	0.41 (0.02-47)	NU
TOTAL	280	184						

* Data collection ongoing
NU is vaccine not used in this country
NE is no cases with known exposure to vaccine (either no vaccination or vaccine brand not specified)

Children

Country	Total Cases	Number of Cases with Media Attention Censoring in Europe	Analysis with Censoring in Europe after Media Attention Odds Ratio (95% CI)			Analysis including all Follow Up Time from all Sites Odds Ratio (95% CI)		
			Arepanrix AS03	Focetria MF-59	Pandemrix AS03	Arepanrix AS03	Focetria MF-59	Pandemrix AS03
Netherlands	33	2	NU	NE	*	NU	0.84 (0.04-88)	1.44** (0.34-88)
Switzerland	33	1	NU	NE	NE	NU	0.72 (0.02-35)	NE
Spain Catalonia	8	0	NU	NE	NE	NU	*	*
Spain Valencia	11	2	NU	NE	NE	NU	2.81 (0.4)	NE
Taiwan	81	81				NU	2.84 (0.2-28.8)	NU
Ontario	28	28				0.84 (0.19-3.63)	NU	NU
Argentina*	11	11				NU	7.27 (0.83-413)	NU
TOTAL	193	86						

* Data collection ongoing
** Pandemrix data from a post hoc case-coverage study in the Netherlands with 758 cases exposed at AS prior to the SOT
NU is vaccine not used in this country
NE is no cases with known exposure to vaccine (either no vaccination or vaccine brand not specified)

Results: Case Control Analysis
With Censoring of Follow-up Time in Europe after Media Attention

Vaccine	Adults OR (95% CI)	Children OR (95% CI)
Pandemrix AS03	No Direct Estimate	No Direct Estimate
Arepanrix AS03	1.00 * (0.13-6.42)	0.80 * (0.15-3.82)
Focetria MF-59	0.71 (0.16-3.14)	5.32 (1.04-27.2)
Unadjuvanted	1.55 ** (0.77-3.11)	1.41** (0.73-2.72)

*Estimate from Ontario only
**Estimate from Taiwan Only

Results: Case Control Analysis
Including all Follow-up Time from all Participating Sites

Vaccine	Adults OR (95% CI)	Children OR (95% CI)
Pandemrix AS03	0.28 (0.03-2.36)	No Direct Estimate Possible
Arepanrix AS03	1.00 * (0.13-6.42)	0.80 * (0.15-3.82)
Focetria MF-59	0.28 (0.03-2.36)	1.42 (0.45-4.43)
Unadjuvanted	1.59** (0.81-3.10)	1.41** (0.73-2.72)

*Estimate from Ontario only
**Estimate from Taiwan Only

Incidence Rates

Incidence Rate Trend from Sweden (A signaling country)

Incidence Rates from Non-Signaling Countries: Spain, Netherlands, UK, Denmark, Canada[1], Taiwan

Conclusions

- Comparison of Incidence Rates before, during, and after the use of adjuvanted 2009 pandemic influenza vaccines provided no evidence outside of the signaling country Sweden for any vaccine effect.
- In the case control study, there was no evidence of an increased risk of narcolepsy following AS03 vaccines, although data for Pandemrix was limited.
- For Focetria, an elevated point estimate in children was observed in one analysis that was based upon a small number of cases. Further evaluation of this association is underway.

Support and COI

This study was supported through a research contract between the CDC and the Brighton Collaboration.
Steven Black has been a consultant for Novartis Vaccines and is currently a consultant for GSK, Protein Sciences, Merck and WHO as serves on DSMBs for GSK and Takeda.

1. Incidence rates from Canada do not include Ontario as these data were not available

3. Liens web fourni par le MSSS en lien avec des discussions sur la Narcolepsie au congrès IDWeek en octobre 2016 :

http://www.empr.com/idweek-2016--vaccines/questions-remain-about-possible-narcolepsy-risk-for-some-h1n1-vaccines/article/568831/

http://med.stanford.edu/news/all-news/2015/07/side-effect-of-flu-vaccine-yields-new-insights-into-narcolepsy.html

http://www.iflscience.com/health-and-medicine/we-may-finally-know-why-flu-vaccine-triggered-narcolepsy/

http://stm.sciencemag.org/content/7/294/294ra105

Articles scientifiques :

Risk of narcolepsy associated with inactivated adjuvanted (AS03) A/H1N1 (2009) pandemic influenza vaccine in Quebec.

Montplaisir J[1], Petit D[2], Quinn MJ[2], Ouakki M[3], Deceuninck G[4], Desautels A[5], Mignot E[6], De Wals P[7].

PLoS One. 2014 Sep 29;9(9):e108489. doi: 10.1371/journal.pone.0108489. eCollection 2014.

https://www.ncbi.nlm.nih.gov/pubmed/25264897

Conclusions
We can cautiously conclude that our results are consistent with a risk of narcolepsy of small magnitude (approximately one case per million dose) following administration of the adjuvanted (AS03) A/H1N1 pandemic vaccine manufactured in Quebec, and that this risk occurred preferentially in people under 20 years of age with a short latency (#16 weeks between vaccine administration and disease onset) and with the presence of cataplexy. However, given the small numbers, the impossibility to completely exclude a confounding effect of A/H1N1 (2009) virus infection and/or a reporting bias, our results are to be considered as weak evidence of a causal relationship. We can, however, reasonably exclude the existence of an excess risk of much higher magnitude as reported in some European countries in which Pandemrix had been used. Further studies comparing influenza and autoimmune responses to Pandemrix versus Arepanrix will be needed to shed light on these differences.

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

Johansen K[1], Brasseur D[2], MacDonald N[3], Nohynek H[4], Vandeputte J[5], Wood D[6], Neels P[7]; Scientific Committee.

Biologicals. 2016 Jul;44(4):276-80. doi: 10.1016/j.biologicals.2016.04.007. Epub 2016 Jun 18.

https://www.ncbi.nlm.nih.gov/pubmed/27329008

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.

Extrait page 278 :

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 MF59adjuvanted 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.

Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination.

Partinen M[1], Kornum BR[2], Plazzi G[3], Jennum P[4], Julkunen I[5], Vaarala O[6].

Lancet Neurol. 2014 Jun;13(6):600-13. doi: 10.1016/S1474-4422(14)70075-4.

https://www.ncbi.nlm.nih.gov/pubmed/24849861

Abstract

Narcolepsy is a sleep disorder characterised by loss of hypothalamic hypocretin (orexin) neurons. The prevalence of narcolepsy is about 30 per 100 000 people, and typical age at onset is 12-16 years. Narcolepsy is strongly associated with the HLA-DQB1*06:02 genotype, and has been thought of as an immune-mediated disease. Other risk genes, such as T-cell-receptor α chain and purinergic receptor subtype 2Y11, are also implicated. Interest in narcolepsy has increased since the epidemiological observations that H1N1 infection and vaccination are potential triggering factors, and an increase in the incidence of narcolepsy after the pandemic AS03 adjuvanted H1N1 vaccination in 2010 from Sweden and Finland supports the immune-mediated pathogenesis. Epidemiological observations from studies in China also suggest a role for H1N1 virus infections as a trigger for narcolepsy. Although the pathological mechanisms are unknown, an H1N1 virus-derived antigen might be the trigger.

Extratit pages 607-608

The role of AS03 as a bystander activator or a direct trigger of narcolepsy is not supported by epidemiological evidence from Canada, as the same AS03 adjuvant produced in the same Belgian factory that was used in Pandemrix was used in Canada for Arepanrix. No clear association with narcolepsy has been reported from Canada, despite many individuals being vaccinated with Arepanrix in 2009–10. Of the 7·8 million people in Quebec older than 6 months, 4·4 million were vaccinated (57% coverage) and two million of these were younger than 17 years. Only two cases of narcolepsy had been reported through pharmacovigilance by January, 2011, and by December, 2013, no new information about an association of Arepanrix with narcolepsy in Quebec had been reported. Therefore, the adjuvant alone seems not to be the trigger of narcolepsy. The role of the adjuvant might, however, be crucial as a booster of the narcolepsyrelated immunity triggered by the viral component of Pandemrix. This kind of dual effect of Pandemrix should be investigated because no reports exist of narcolepsy in association with other non-adjuvanted H1N1 viruscontaining vaccines such as seasonal influenza vaccines. Some diff erences existed in the production process between the two vaccines. In Pandemrix the viral suspension was produced in Dresden, Germany; in Arepanrix the viral suspension was produced in Quebec, Canada. The process of production diff ers in the factories, and the excipients diff er from each other. 22,128. Theoretically, the differences in the composition of H1N1 antigen could 22,128 at least partly explain why the association has been stronger with Pandemrix than with Arepanrix. The immunological diff erences in the H1N1 antigen between H1N1 infl uenza vaccinations could also explain why narcolepsy has not been associated with other H1N1 vaccines used on a large scale globally; these vaccines all contain the haemaglutinin epitope with cross-reactivity to hypocretin epitopes, and the amount of haemaglutinin is four times higher per dose in seasonal infl uenza vaccines than in adjuvanted vaccines.128 22.

Antigenic differences between AS03 adjuvanted influenza A (H1N1) pandemic vaccines: implications for pandemrix-associated narcolepsy risk.

Vaarala O[1], Vuorela A[1], Partinen M[2], Baumann M[3], Freitag TL[4], Meri S[4], Saavalainen P[4], Jauhiainen M[5], Soliymani R[3], Kirjavainen T[6], Olsen P[7], Saarenpää-Heikkilä O[8], Rouvinen J[9], Roivainen M[10], Nohynek H[1], Jokinen J[1], Julkunen I[11], Kilpi T[1].

PLoS One. 2014 Dec 15;9(12):e114361. doi: 10.1371/journal.pone.0114361. eCollection 2014.

https://www.ncbi.nlm.nih.gov/pubmed/25501681

Abstract

BACKGROUND:

Narcolepsy results from immune-mediated destruction of hypocretin secreting neurons in hypothalamus, however the triggers and disease mechanisms are poorly understood. Vaccine-attributable risk of narcolepsy reported so far with the AS03 adjuvanted H1N1 vaccination Pandemrix has been manifold compared to the AS03 adjuvanted Arepanrix, which contained differently produced H1N1 viral antigen preparation. Hence, antigenic differences and antibody response to these vaccines were investigated.

METHODS AND FINDINGS:

Increased circulating IgG-antibody levels to Pandemrix H1N1 antigen were found in 47 children with Pandemrix-associated narcolepsy when compared to 57 healthy children vaccinated with Pandemrix. H1N1 antigen of Arepanrix inhibited poorly these antibodies indicating antigenic difference between Arepanrix and Pandemrix. High-resolution gel electrophoresis quantitation and mass spectrometry identification analyses revealed higher amounts of structurally altered viral nucleoprotein (NP) in Pandemrix. Increased antibody levels to hemagglutinin (HA) and NP, particularly to detergent treated NP, was seen in narcolepsy. Higher levels of antibodies to NP were found in children with DQB1*06:02 risk allele and in DQB1*06:02 transgenic mice immunized with Pandemrix when compared to controls.

CONCLUSIONS:

This work identified 1) higher amounts of structurally altered viral NP in Pandemrix than in Arepanrix, 2) detergent-induced antigenic changes of viral NP, that are recognized by antibodies from children with narcolepsy, and 3) increased antibody response to NP in association of DQB1*06:02 risk allele of narcolepsy. These findings provide a link between Pandemrix and narcolepsy. Although detailed mechanisms of Pandemrix in narcolepsy remain elusive, our results move the focus from adjuvant(s) onto the H1N1 viral proteins

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Narcolepsy, 2009 A(H1N1) pandemic influenza, and pandemic influenza vaccinations: what is known and unknown about the neurological disorder, the role for autoimmunity, and vaccine adjuvants.

Ahmed SS[1], Schur PH[2], MacDonald NE[3], Steinman L[4].

J Autoimmun. 2014 May;50:1-11. doi: 10.1016/j.jaut.2014.01.033. Epub 2014 Feb 19.

https://www.ncbi.nlm.nih.gov/pubmed/24559657

Abstract

The vaccine safety surveillance system effectively detected a very rare adverse event, narcolepsy, in subjects receiving AS03-adjuvanted A(H1N1) pandemic vaccine made using the European inactivation/purification protocol. The reports of increased cases of narcolepsy in non-vaccinated subjects infected with wild A(H1N1) pandemic influenza virus suggest a role for the viral antigen(s) in disease development. However, additional investigations are needed to better understand what factor(s) in wild influenza infection trigger(s) narcolepsy in susceptible hosts. An estimated 31 million doses of European AS03-adjuvanted A(H1N1) pandemic vaccine were used in more than 47 countries. The Canadian AS03-adjuvanted A(H1N1) pandemic vaccine was used with high coverage in Canada where an estimated 12 million doses were administered. As no similar narcolepsy association has been reported to date with the AS03-adjuvanted A(H1N1) pandemic vaccine made using the Canadian inactivation/purification protocol, this suggests that the AS03 adjuvant alone may not be responsible for the narcolepsy association. To date, no narcolepsy association has been reported with the MF59®-adjuvanted A(H1N1) pandemic vaccine. This review article provides a brief background on narcolepsy,

outlines the different types of vaccine preparations including the ones for influenza, reviews the accumulated evidence for the safety of adjuvants, and explores the association between autoimmune diseases and natural infections. It concludes by assimilating the historical observations and recent clinical studies to formulate a feasible hypothesis on why vaccine-associated narcolepsy may not be solely linked to the AS03 adjuvant but more likely be linked to how the specific influenza antigen component of the European AS03-adjuvanted pandemic vaccine was prepared. Careful and long-term epidemiological studies of subjects who developed narcolepsy in association with AS03-adjuvanted A(H1N1) pandemic vaccine prepared with the European inactivation/purification protocol are needed.

Extrait article :

To date, no increased-risk has been reported for the MF59adjuvanted A(H1N1)pdm09 vaccine, for which an estimated 6.5 million doses were distributed in EU/EEA and 25 million doses were used in Europe and Latin America. 19 In Canada, an estimated 12 million doses were administered of another AS03adjuvanted pandemic vaccine, Arepanrix, 20 and a lower association with narcolepsy 21 was observed with it compared to the European AS03-adjuvanted A(H1N1)pdm09 vaccine Pandemrix, used in Europe. These observations support the concept that vaccine-associated narcolepsy is not due solely to the characteristics of the adjuvant. The following sections will now provide additional clarifications/insights related to the published study and assumes that the reader has reviewed that study. Could differences in the adjuvanted A(H1N1)pdm09 vac 1 (…)
In Canada, why was the AS03-adjuvanted pandemic vaccine 20 associated with a lower risk of narcolepsy?
We believe that the low NP content in the vaccine explains the lack of disease development with the MF59-adjuvanted A (H1N1)pdm09 vaccine while the low projected population coverage for HLA DQB1 _ 06:02 in Canada (5.60 % based on linkage disequilibrium for DR-DQ) explains the lower incidence of narcolepsy in Canada with the Canadian AS03-adjuvanted A(H1N1)pdm09 vaccine compared to the European AS03- adjuvanted A(H1N1)pdm09 vaccine. Figure 1 is a world heat map indicating the projected population coverage for HLADQB1 _ 06:02 in the various countries. It is worth noting that the countries reporting vaccine-associated narcolepsy with the European AS03-adjuvanted A(H1N1)pdm09 vaccine also have a greater percentage of the population carrying the narcolepsy risk-allele, HLA-DQB1 _ 06:02, compared to countries not reporting A(H1N1)pdm09 vaccine-associated narcolepsy. Canada does not have a high percentage of the population carrying the narcolepsy risk-allele and would explain why the risk of narcolepsy was lower with the Canadian AS03-adjuvanted A (H1N1)pdm09 vaccine.

Comparison of Pandemrix and Arepanrix, two pH1N1 AS03-adjuvanted vaccines differentially associated with narcolepsy development.

Jacob L[1], Leib R[2], Ollila HM[1], Bonvalet M[1], Adams CM[2], Mignot E[3].

Brain Behav Immun. 2015 Jul;47:44-57. doi: 10.1016/j.bbi.2014.11.004. Epub 2014 Nov 15.

https://www.ncbi.nlm.nih.gov/pubmed/?term=25452148

Abstract

Narcolepsy onset in children has been associated with the 2009 influenza A H1N1 pandemic and vaccination with Pandemrix. However it was not clearly observed with other adjuvanted pH1N1 vaccines such as Arepanrix or Focetria. Our aim was to characterize the differences between Pandemrix and Arepanrix that might explain the risk for narcolepsy after Pandemrix vaccination using 2D-DIGE and mass spectrometry (MS). We found that Pandemrix (2009 batch) and Arepanrix (2010 batch) showed 5 main viral proteins: hemagglutinin HA1 and HA2 subunits, neuraminidase NA, nucleoprotein NP, and matrix protein MA1 and non-viral proteins from the Gallus gallus growth matrix used in the manufacturing of the vaccines. Latticed patterns of HA1, HA2 and NA indicated charge and molecular weight heterogeneity, a phenomenon likely caused by glycosylation and sulfation. Overall, Pandemrix contained more NP and NA, while Arepanrix displayed a larger diversity of viral and chicken proteins, with the exception of five chicken proteins (PDCD6IP, TSPAN8, H-FABP, HSP and TUB proteins) that were relatively more abundant in Pandemrix. Glycosylation patterns were similar in both vaccines. A higher degree of deamidation and dioxidation was found in Pandemrix, probably reflecting differential degradation across batches. Interestingly, HA1 146N (residue 129N in the mature protein) displayed a 10-fold higher deamidation in Arepanrix versus Pandemrix. In recent vaccine strains and Focetria, 146N is mutated to D which is associated with increased production yields suggesting that 146N deamidation may have also occurred during the manufacturing of Arepanrix. The presence of 146N in large relative amounts in Pandemrix and the wild type virus and in lower relative quantities in Arepanrix or other H1N1 vaccines may have affected predisposition to narcolepsy.

(article qui vient de sortir dans ma veille, mais qui semble être juste sur le Pandemrix);

Risk of Narcolepsy after AS03 Adjuvanted Pandemic A/H1N1 2009 Influenza Vaccine in Adults: A Case-Coverage Study in England.

Stowe J[1], Andrews N[2], Kosky C[3], Dennis G[4], Eriksson S[5], Hall A[6], Leschziner G[7], Reading P[8], Shneerson JM[9], Donegan K[10], Miller E[11].

Sleep. 2016 May 1;39(5):1051-7. doi: 10.5665/sleep.5752.

https://www.ncbi.nlm.nih.gov/pubmed/26856903

Abstract

STUDY OBJECTIVES:

An increased risk of narcolepsy has been observed in children following ASO3-adjuvanted pandemic A/H1N1 2009 (Pandemrix) vaccine. We investigated whether this risk extends to adults in England.

METHODS:

Six adult sleep centers in England were visited between November 2012 and February 2014 and vaccination/clinical histories obtained from general practitioners. Suspected narcolepsy cases aged older than 17 y were selected. The risk of narcolepsy following Pandemrix was calculated using cases diagnosed by the time of the center visits and those with a diagnosis by November 30, 2011 after which

there was increased awareness of the risk in children. The odds of vaccination in cases and in matched population data were compared using a case-coverage design.

RESULTS:

Of 1,446 possible cases identified, most had onset before 2009 or were clearly not narcolepsy. Of the 60 remaining cases, 20 were excluded after expert review, leaving 40 cases with narcolepsy; 5 had received Pandemrix between 3 and 18 mo before onset. All the vaccinated cases had cataplexy, two received a diagnosis by November 2011 and two were aged 40 y or older. The odds ratio for vaccination in cases compared to the population was 4.24 (95% confidence interval 1.45-12.38) using all cases and 9.06 (1.90-43.17) using cases with a diagnosis by November 2011, giving an attributable risk of 0.59 cases per 100,000 doses.

CONCLUSIONS:

We found a significantly increased risk of narcolepsy in adults following Pandemrix vaccination in England. The risk was lower than that seen in children using a similar study design.