Narcolepsy and (Pandemic) Influenza Vaccines

Hanna Nohynek
24.1.2013 WHO Integrated Influenza meeting
Hongkong
Narcolepsy-cataplexy
ICSD-2 2005, ICD-10 G47.4

A. Excessive day time sleepiness >3 mo, daily

B. Cataplexy (= abrupt temporary loss of muscle tension in association with emotional / tense situations)

C. Diagnosis confirmed with polysomnography and sleep latency test / alternatively Li-hypocretin (orexin) concentration ≤110 pg/mL

D. No other better explanation
# Forms of narcolepsy

<table>
<thead>
<tr>
<th></th>
<th>Prevalence among narcoleptic patients</th>
<th>HLA DQB1*0602 positive</th>
<th>Li-hypocretin (orexin) low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy - cataplexy</td>
<td>&gt;50 %</td>
<td>&gt; 90 %</td>
<td>&gt; 90 %</td>
</tr>
<tr>
<td>Narcolepsy without cataplexy</td>
<td>10-50 %</td>
<td>41 %</td>
<td>10-21 %</td>
</tr>
<tr>
<td>Symptomatic narcolepsy(^1)</td>
<td>116 patients (review)</td>
<td>17 %</td>
<td>most</td>
</tr>
<tr>
<td>Population</td>
<td>-</td>
<td>11-35 %</td>
<td>0</td>
</tr>
</tbody>
</table>

ICSD-2 2005; \(^1\)Nishino and Kanbayashi 2005; Knudsen et al. 2010; Ritchie et al. 2010

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**According to Hublin 2010**

Narcolepsy vs Pandemrix / Hanna Nohynek
Rare disease, incidence <1/100 000
Onset in prepandemic era

Age at onset

Number of patients

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20


median=18

Age at onset (years)
Sweden opens inquiry into suspect flu vaccine

AFP / STOCKHOLM — Sweden's Medical Products Agency opened an inquiry Wednesday into vaccinations for swine flu made by British pharmaceutical company GlaxoSmithKline, suspected of provoking narcolepsy.

"The MPA has received six reports from health care professionals regarding narcolepsy as suspected adverse drug reaction following Pandemrix flu vaccination," it said in a statement. "The agency will, in consultation with external experts, assess the possible relationship between the vaccination and the reported reactions."
Studies initiated to verify signal

- In Sweden
- In Finland
- The European Medical Agency EMA
  - ECDC contracted the VAESCO study in 8 European countries,
  - GSK contracted a study in Canada (Arepanrix)
GACVS statement in December 2010

- Safety of pandemic influenza A(H1N1) 2009 vaccines

GACVS reviewed data on the safety of pandemic influenza A (H1N1) 2009 vaccines. Overall, safety information for the pandemic influenza vaccines continues to be reassuring. Since the Committee’s earlier report in June 2010,\(^5\) data from passive surveillance from different countries has not generated any new safety concerns other than reports of narcolepsy from Finland and Sweden in August. These reports are being investigated by independent groups in Europe.

WHO Weekly Epidemiological Record on 28 January 2011
Figur 1. Incidenser, per 100 000 personår, kvartalsvis 2009-2010.
### Results of the Finnish retrospective cohort study

**RR in validated child-adolescent cases in Finland**

<table>
<thead>
<tr>
<th>Follow-up period</th>
<th>Narcolepsy cases</th>
<th>Follow-up years</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not vacc</td>
<td>Vacc</td>
<td>Not vacc</td>
</tr>
<tr>
<td><strong>First contact:</strong> 2009-01-01 to 2010-12-31</td>
<td>7</td>
<td>57</td>
<td>1069247</td>
</tr>
<tr>
<td><strong>First contact:</strong> 2009-01-01 to 2010-08-15</td>
<td>7</td>
<td>46</td>
<td>986195</td>
</tr>
</tbody>
</table>

Vaccine attributable risk for developing narcolepsy

\[
= \frac{6}{100\,000} \text{ among those vaccinated 4-19 years of age}
\]

\[
= \frac{1}{16\,000}
\]

Nohynek et al PLOS One 2012
A disease with usually an insidious start
How do you define the date of onset?

- Onset of EDS
  Estimate from medical records
  = information mainly obtained from parents
- First documented contact to health care
- Referral to specialist / neurologist
- Diagnosis G47.4
MPA Sweden press release on association

Excessive Daytime Sleepiness

1st contact to health care

Referral

Date of Diagnosis G47.4

Nohynek et al PLOSOne 2012
Those vaccinated in specific age groups as indicated

Laboratory confirmed A(H1N1) cases
European Medicines Agency recommends restricting use of Pandemrix

In persons under 20 years of age Pandemrix to be used only in the absence of seasonal trivalent influenza vaccines, following link to very rare cases of narcolepsy in young people. Overall benefit-risk remains positive.
Is the association seen in other than signaling countries Sweden and Finland?
### Key issues to critically appraise in signal verification

#### Doses given to susceptible age group

<table>
<thead>
<tr>
<th>Country</th>
<th>Doses Pandemrix(^R) to 4-19 yr olds</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>~1,000,000</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>668,000</td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>339,312</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>470,000</td>
<td>5-18 yr olds</td>
</tr>
<tr>
<td>France</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>~700,000</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>~295,000</td>
<td>5-16 year olds</td>
</tr>
<tr>
<td>Canada</td>
<td>793,448 Q ~ 1,200,000</td>
<td>Arepanrix(^R) 5-18 yr olds</td>
</tr>
</tbody>
</table>

*Kilpi et al. ESPID 2011*
Key issues to critically appraise in signal verification II

HLA DQB1*06:02 prevalence globally
<table>
<thead>
<tr>
<th>Country</th>
<th>Study design</th>
<th>Primary outcome</th>
<th>Primary follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>Case inventory</td>
<td>Date of diagnosis G47.4</td>
<td>1.10.2009 - 31.12.2010</td>
</tr>
<tr>
<td></td>
<td>Population based</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>Retrospective cohort</td>
<td>First contact to health care for EDS</td>
<td>1.1.2009 - 15.8.2010</td>
</tr>
<tr>
<td></td>
<td>Population based</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>Retrospective cohort</td>
<td>First contact to health care for EDS</td>
<td>1.4.2009 - 15.8.2010</td>
</tr>
<tr>
<td></td>
<td>Population based</td>
<td>Date of onset of EDS as recalled patient / parent</td>
<td>120 weeks postvacc</td>
</tr>
<tr>
<td>Norway</td>
<td>Retrospective cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Case control***</td>
<td>Date of referral to multiple sleep latency test</td>
<td>1.10.2009 - 30.4.2011</td>
</tr>
<tr>
<td>Germany</td>
<td>Case control</td>
<td></td>
<td>Study discontinued</td>
</tr>
<tr>
<td>UK</td>
<td>Self ControlledCaseSeries</td>
<td></td>
<td>Study in press</td>
</tr>
<tr>
<td>Canada</td>
<td>Retrospective cohort</td>
<td></td>
<td>Study completed</td>
</tr>
</tbody>
</table>

*5-18-year-olds  **5-16-year-olds  ***children and adults

Narcolepsy vs Pandemrix / Hanna Nohynek
Association significant in all European countries where large numbers of Pandemrix doses were used in susceptible age group

<table>
<thead>
<tr>
<th>Country</th>
<th>Age group yrs</th>
<th>Study design</th>
<th>Definition of onset</th>
<th>Follow up period</th>
<th>Risk (RR/OR)</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>4-19</td>
<td>RC</td>
<td>1. contact with HC</td>
<td>1.1.2009-15.8.2010</td>
<td>12.7</td>
<td>6.1 - 30.8</td>
</tr>
<tr>
<td>Sweden</td>
<td>≤19</td>
<td>RC</td>
<td>Date of dg G47.4</td>
<td>1.10.2009-31.12.2010</td>
<td>4.06</td>
<td>2.87 - 5.58</td>
</tr>
<tr>
<td>Ireland</td>
<td>5-19</td>
<td>RC</td>
<td>1. contact with HC</td>
<td>1.4.2009-31.12.2010</td>
<td>13.0</td>
<td>4.6 - 34.7</td>
</tr>
<tr>
<td>France</td>
<td>all</td>
<td>C-C</td>
<td>Date of referral MSLT</td>
<td>1.4.2009-30.4.2011</td>
<td>5.09</td>
<td>2.11 -12.26</td>
</tr>
<tr>
<td>Norway</td>
<td>4-19</td>
<td>RC C-C</td>
<td>Date of EDS by patient</td>
<td>1.10.2009-30.6.2010</td>
<td>14.5</td>
<td>In press</td>
</tr>
<tr>
<td>UK</td>
<td>4-19</td>
<td>SCCS CaseC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RC = retrospective cohort; C-C = case control; SCCS = self-controlled case series; CaseC = case-cohort

MSLT = multiple sleep latency test
Conclusions from the epidemiological studies

• Pandemrix vaccination is significantly associated with an abrupt increase in narcolepsy-cataplexy among children and teens, and possibly also in adults

• The relative risk varies between 3 to 14 / 100 000 in the susceptible age group

• The vaccine attributable absolute risk is small (<7 /100 000 vaccinated) but consistently seen in different populations where Pandemrix was used in large numbers in susceptible age group

• In most countries, the postlicensure safety surveillance did not pick up the signal

• Most likely such a rare event would not have been picked up even in large prelicensure trials
If the association is causal, what could the biological mechanism be?
Suggested biological mechanism: immune mediated.

Pandemrix as an accelerator of narcolepsy: rapid disease development after vaccination

Hypocretin / Orexin producing neurons in hypothalamus

HLADQB1*0602

0

5

8

10 years

Immune response

Against neurons

Day time sleepiness

Diagnosis

By-stander effect and/or a booster of autoimmunity

Narcolepsy vs Pandemrix / Hanna Nohynek

@Outi Vaarala
The association of the HLA DR and DQ gene region alleles with autoimmune diseases

- Diabetes mellitus, type 1
  - HLA DQB1*0302 ja HLA DQB*02 ↑

- MS-disease
  - HLA DRB1*1501 ↑

- Coeliac disease
  - HLA-DQA1*05 ja HLA-DQB1*02 ↑

- Narcolepsy-cataplexy
  - HLA DQB1*0602 ↑
Conclusions from the immunological and virological studies in Finland on Pandemrix and narcolepsy

• Children who developed narcolepsy after Pandemrix vaccination
  1) Show similar HLA related susceptibility as earlier reported for narcolepsy without Pandemrix association
  2) Did not show clinical or immunological evidence of H1N1 infection (NS1 protein assay)
  3) Reacted abnormally to Pandemrix vaccination:
     • Developed narcolepsy with cataplexy
     • Developed increased levels of antibodies binding to AS03 and to H1N1 antigen suspension of Pandemrix

Vaarala O, Julkunen I unpublished
Gaps in knowledge – significance to vaccine development and NVPs

- What is the biologically plausible mechanism?
- Would the affected patients become narcoleptic later on in their life anyhow; i.e. did vaccine trigger the disease in advance?
- What does this incident mean to the future development of adjuvanted influenza / pandemic vaccines?
- What does the finding mean to the future seasonal influenza vaccination of those Pandemrix exposed?
- How to contain the negative safety messages and impact to influenza vaccination / vaccinations in general?