

1.1. Overview of Dutch cases of narcolepsy associated with Pandemic influenza vaccine (Pandemrix®)

Introduction

In November 2009, a mass vaccination against Influenza A (H1N1) was performed in the Netherlands. Pandemrix® was used in healthy children aged 6 months to 5 years and in close relatives of children aged less than 6 months. The vaccine was administered two times with a three-week interval.

Pandemrix® contains a split, inactivated, influenza virus, containing antigen equivalent to A/California/7/2009 (H1N1)v-like strain (X-179A). AS03 is used as adjuvant, consisting of an oil and water emulsion with squalene and tocopherol [1].

In addition another H1N1 vaccine, Focetria®, was used in persons with risk factors, which also includes children.

Since autumn 2010 Pandemrix® has been linked to the presentation of narcolepsy. Narcolepsy is a chronic sleep disorder, in its full clinical presentation characterised by excessive daytime sleepiness, sleep attacks at inappropriate times and accompanied, when classically presenting by cataplexia, hypnagogic/hypnopompic hallucinations and sleep paralysis. Especially in the onset of this disorder the symptoms are often aspecific, consisting of sleepiness or behavioural changes. Narcolepsy is a multifactorial disorder, involving a genetic susceptibility, with a strong association with HLA-DBQ-1*602, in combination with environmental factors. The exact pathogenesis is not revealed at present however and an auto immune component is established by the detection of auto-antibodies against hypocretin, a neurotransmitter involved in the regulation of the sleep-wake-pattern [2]. Incidence rates average 0.74 to 1.37 cases per 100,000 person-years [3].

The association between Pandemrix® and narcolepsy has not been clarified at present. Elevated relative risk of narcolepsy in Pandemrix® vaccinees is confined to some of the Nordic countries, namely the Finnish, Icelandic and Swedish populations [4].

On April 15th, narcolepsy is reported to have been added in the Epar for Pandemrix® [5].

Due to differences in vaccination policies (vaccination of all children and adolescents in Sweden and Finland, instead of a population limited to children aged up to five years in the Netherlands and children with a medical indication), findings from these countries are not applicable to the Dutch situation, especially since narcolepsy has a peak incidence among teenagers.

The cases Lareb received are presented in order of presentation in brief in table 1 and discussed in more detail below, thus giving an overview of the Dutch cases of narcolepsy associated with Pandemrix® administration.

Reports

Table 1. Reports of narcolepsy associated with the use of Pandemrix[®] and Focetria[®]

| Patient, Number, Sex, Age, Source | Drug, daily dose Indication for use | Concomitant Medication | Suspected adverse drug reaction | Time to onset, Outcome, causality |
|--|--|------------------------|---------------------------------|-----------------------------------|
| A 112011 M, 2-4 years RIVM | pandemic influenza vaccine (Pandemrix) prophylaxis | | narcolepsy | 2 day not recovered unlikely |
| B 111048 M, 2-4 years RIVM/parents | pandemic influenza vaccine (Pandemrix) prophylaxis | DTP vaccination | narcolepsy | 4 months not recovered possible |
| C 117581 F, 11-20 years parents | pandemic influenza vaccine (Pandemrix)-prophylaxis | | narcolepsy | 2 months not recovered, possible |

The Netherlands Pharmacovigilance Centre Lareb has received three reports of diagnosed cases of narcolepsy associated in time to Pandemrix[®], without firm confirmation of a causal relationship. In two cases causality is possible (B and C). In one of the cases causality is implausible due to a latency of days at most (A). One case concerns a person aged 11-20 at presentation who was vaccinated according to the policy of the country she resided in. In one additional case narcolepsy is suspected, however not diagnosed in a patient vaccinated with Focetria[®].

Case A

This well documented serious spontaneous report from a physician concerns a male aged 2-4 years HLA-1DQB-1*0602 positive, with confirmed (observation and hypocretin) narcolepsy (sleep attacks, cataplexia, weight gain, no hypnagogic hallucination nor sleep paralysis) following two-times administration of pandemic influenza vaccine (Pandemrix[®], batch number A81CA160A) with an unknown latency, however days at most. The patient outcome has not recovered. Concomitant medication was not reported.

Prior to influenza vaccination the patient suffered from infections which were not responsive to multiple courses of antibiotic therapy. Fatigue was at latest mentioned by GP two days following the first pandemic vaccine administration. Behavioural symptoms existed since April 2009. Laboratory testing revealed mild hypothyroidism. Diagnostic testing for Niemann Pick C will be performed.

Causality: (due to maximal two days latency) unlikely.

Case B

This well documented serious spontaneous report concerns a male aged 2-4 years with sleepiness and fatigue, diagnosed as narcolepsy with cataplexia following administration of Infanrix IPV, a Diphtheria, Tetanus, acellular Pertussis, Poliomyelitis (inactivated) vaccine (Batch AC20B123AM) and Pandemrix[®] (A81CA049D), (November 2009 and December 2009). The vaccine (DTaP) was given in April 2010 and the first signs of fatigue occurred in the end of April. In July the patient was hospitalised in Italy because of somnolence, decreased muscle strength, dysarthria and decreased balance. Days later admission in a

tertiary centre followed due to worsening of condition. Initially, ataxia was diagnosed due to a suspected viral infection for which aciclovir was started. In July the patient was examined in the Netherlands with partially improvement however, later, narcolepsy with cataplexia was diagnosed.

Behavioural changes were also reported, starting in the autumn of 2009.
 Causality: possible

Case C

This well documented serious spontaneous report from a consumer concerns a female aged 11-20 years, with narcolepsy with cataplexia and deficient hypocretin following administration of pandemic influenza vaccine (Pandemrix[®], batch A81CA136A) for prophylaxis with a latency of 2 months before onset of symptoms. The clinical picture worsened gradually with manifestation of excessive daytime sleepiness, sleep attacks, however absent sleep paralysis and hypnopompic hallucinations with a progressively increased impact on daily life. Symptoms were treated with modafinil. The patient has recovered partially following treatment. Concomitant medication was not reported.

The patient has no known medical history. The patient has no known past drug therapy.

The vaccine was administered outside the Netherlands in an EU country with a general vaccination policy prior to the 2009 type A H1N1 pandemic.
 Causality: possible

Other sources of information

Databases

Eudravigilance database

On May 26th 2011, the Eudravigilance database contained in 281 reports of Pandemrix[®] associated narcolepsy. 185 originated from Sweden and Finland Sweden (101); Finland (84). More information on geographic distribution is shown in table 2.

Besides the Dutch reports, 36 cases concerned children aged 6 or years or younger. Ten cases concerned cases of children aged five years or younger.

Table 2. Reports of narcolepsy in the Eudravigilance database per country

| country | reports |
|----------------|----------------|
| Sweden | 101 |
| Finland | 84 |
| France | 31 |
| Norway | 17 |
| Germany | 26 |
| Switzerland | 3 |
| Ireland | 11 |
| Netherlands | 4* |
| United Kingdom | 3 |

| country | reports |
|----------|---------|
| Portugal | 1 |

* contains one duplicate report

WHO database

As of May 26th 2011, in addition to the Dutch cases, the WHO database contains 126 reports concerning narcolepsy associated with vaccination with Pandemrix[®]. All but 16 originate from Sweden and Finland. This database contains eleven Norwegian cases, two Swiss, two Irish cases and one case from Great Britain. No cases from other countries of particular interest like Denmark or Estonia are present in the WHO database. Thirteen cases concern children aged six year or younger, comparable to the population indicated for vaccinated with Pandemrix[®] in the Netherlands.

No cases concerning Focetria[®] associated narcolepsy are present in the Eudravigilance or WHO database.

Discussion

Lareb received three cases of diagnosed narcolepsy after vaccination with Pandemrix[®]. In two cases (B and C) no strong indications for a causative role of Pandemrix[®] exist, however causality cannot be excluded. Hence a possible causality is assigned to these cases. One of these cases concerns a patient vaccinated abroad. In one case (A) causality is unlikely due to symptoms dating back at latest days after vaccine administration but according to data retrieved from the general practitioner's documentation, most probably originating from a period prior to vaccine administration.

References

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3. ECDC. ECDC – VAESCO investigation into narcolepsy. (version date: 2-2-2011, access date: 29-3-2011 BC)
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This signal has been raised on July 2011. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmef.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).