

Overview of reports of long-lasting fatigue following immunisation with Cervarix[®]

Introduction

Since 2009, vaccination against the human papillomavirus (HPV), which can cause cervical cancer, has been a part of the National Immunisation Programme. Girls receive a total of three immunisations, starting in the year they will become 13 years, with the second and third immunisation given after 1 month and 6 months respectively. Currently, the vaccine used is Cervarix[®] (human papillomavirus1 type 16 L1 protein / human papillomavirus type 18 L1 protein).

Last year an increasing number of reports of girls experiencing long episodes of fatigue following immunisation with Cervarix[®] were received by Lareb. This increase in reports was seen after an article in a national newspaper which featured an article about the vaccine and fatigue. Currently, the SmPC of Cervarix[®] mentions fatigue (no duration specified) as a possible ADR occurring in more than 10% of the girls receiving the vaccination [1]. However, this ADR most likely refers to fatigue of limited duration occurring after vaccination. Long-lasting fatigue or chronic fatigue is not mentioned in this document.

In the literature, one of the criteria described for chronic fatigue is a duration of fatigue complaints of 6 months or longer [2]. Although in most cases chronic fatigue was not diagnosed, striking number of reports mentioned fatigue for a long period. Lareb provides an overview of reports of long-lasting fatigue following immunization with Cervarix[®].

With this overview Lareb wishes to inform to Medicines Evaluation Board and the National Institute for Public Health and the Environment about the reports received by Lareb concerning long-lasting fatigue after immunisation with Cervarix[®].

Reports

Lareb received a total of 51 reports of fatigue after immunisation with Cervarix[®]. Most reports were received in the first weeks after the publication in the national newspaper (46 reports in six weeks). Of these reports 30 were related to a vaccination in previous years.

In 31 cases, the fatigue lasted more than six months. In six cases the report was classified as serious because the girl had been admitted to the hospital for observation and additional testing.

The time to onset (latency) of the complaints after vaccination was diverse, ranging from less than 3 days to more than 3 months. The former was reported most often, but latencies of more than 3 months were also common. In addition to the latency, there was also a large range in duration of the complaints, which varied from less than 1 week to several years. A duration of more than 2 years was reported in 12 cases and in 7 of them the complaints lasted for more than 3 years. With regard to duration of the complaints it should be noted that in some cases the complaints were still present at the time of reporting. Therefore no accurate duration could be calculated in these cases. Details regarding latency and duration of the complaints are presented in table 1.

Table 1: Duration of fatigue in relation to latency (w=weeks, m=months)

Latency in days	duration <1w	duration 2-4w	duration 5w - 3m	duration 4-6m	duration >6m	total
existing prior to vaccination	0	0	0	0	2	2
0-3	7	6	1	2	6	22
4-7	0	0	0	0	2	2
8-28	0	0	0	1	6	7
29-91	0	0	1	0	7	8
≥92	0	0	1	1	8	10
Total	7	6	3	4	31	51

The outcome of the events in relation to their duration is presented in table 2. These data show that in approximately half of the cases, the patient recovered or was recovering from the event. Additionally, it seems that a duration of fatigue longer than 6 months was associated with a lower percentage of recovery.

Table 2: Outcome of fatigue in relation to the duration of the complaints (w=weeks, m=months)

Outcome	<1w	2-4w	5w-3m	4-6 m	>6m			totaal
					6-12m	13- 24m	>25m	
Recovered	7	5	0	1	3	1	0	17
Recovering	0	0	0	0	4	3	1	8
Not recovered	0	1	3	3	5	2	12	26
Total	7	6	3	4	12	6	13	51

In many cases additional diagnostic tests were performed, including laboratory tests for Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV) infections. In nine cases one of these infections was found (based on positive IgG antibodies), but the relationship with the experienced fatigue remains unclear in most of these cases. In six other cases laboratory tests were performed but no abnormalities could be found.

With regard to the severity of the complaints and their effects on everyday life, there was a distinct diversity. In a lot of cases, girls were able to return to a normal daily life after a period of fatigue, but there are also cases in which there was substantial non-attendance at school, sometimes leading to the repeating of a class. In addition, a lot of girls could spend less time practicing sports or other hobbies.

Other sources of information

Literature

In general, fatigue after vaccination is a well-known ADR for Cervarix® [1]. According to the SmPC the frequency of occurrence is more than 10% and this is confirmed by publications from RIVM [3-5], Lareb [6-8], and others [9,10].

Considering the design of these studies, this mainly concerns short term fatigue, which generally is related to local injection site inflammations. In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) received a total of 378 reports of fatigue and 499 reports of malaise in relation to immunisation with Cervarix[®], including several reports of chronic fatigue syndrome and post-viral fatigue. They concluded that the number of reports received was not higher than was to be expected on the basis of coincidence. They used the Maximised Sequential Probability Ratio Test (MaxSPRT) to perform an 'observed versus expected' analysis. This method adjusts for various levels of possible under-reporting, which is a well-known issue in spontaneous reporting systems. According to the authors, there was no indication of a causal relationship between the occurrence of fatigue and the administration of Cervarix[®] [11].

Discussion and conclusion

In 2012, after a publication about Cervarix[®] in a national newspaper, there was a sudden increase of reports of fatigue after immunisation with Cervarix[®]. These reports were related to immunisations that had occurred in the previous years and there was an equal distributions over those years.

The reports were remarkable, both in terms of duration and severity of the complaints, but in most cases no cause for the complaints could be found.

A possible explanation for the long duration of the complaints could be that the short-term fatigue that is well known after immunisation with Cervarix[®], develops into long-term fatigue due to the presence other factors.

One of the important confounders to take into account is the age of the girls that were vaccinated. At the age of 12-13 years, long-lasting fatigue is not uncommon, and occurs in considerable percentages of girls [12]. However, formally the numbers of reports of fatigue and the published background prevalence figures cannot be compared. In order to confirm or reject a causal relationship of long-lasting fatigue after immunization with Cervarix[®], additional epidemiological research is needed.

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This overview was published in October 2013. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbqmeb.nl/cbq/en/default.htm