Clinical features of narcolepsy in children vaccinated with AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine in England

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ABBREVIATIONS

ICSD	International Classification of Sleep Disorders
HES	Hospital Episode Statistics
HLA	Human leukocyte antigen
NHS	National Health Service
VAESCO	Vaccine Adverse Event Surveillance and Communication

AIM The aim of this study was to investigate whether children in England with narcolepsy who received the ASO3 adjuvanted pandemic A/H1N1 2009 influenza vaccine (Pandemrix) differed clinically from unvaccinated patients.
METHOD A retrospective review was conducted in children with narcolepsy diagnosed by sleep centres and paediatric neurologists in 16 English hospitals. The inclusion criteria were patient age 4 to 18 years, onset of narcolepsy after January 2008, and diagnosis by the time of the key data-gathering visit in 2011. Clinical data came from hospital notes and general practitioner questionnaires. An expert panel validated the diagnoses.
RESULTS Seventy-five patients with narcolepsy were identified (43 males, 32 females; mean age at onset 10y 4mo, range 3–18y). Of these patients, 11 received the Pandemrix vaccine before narcolepsy onset. On first presentation, there were more frequent reports of cataplexy, among other features, in vaccinated than in unvaccinated patients (82% vs 55%), but only excessive weight gain (55% vs 20%) was significantly more frequent (p=0.03). Facial hypotonia (p=0.03) and tongue protrusion (p=0.01) were eventually seen more frequently in vaccinated children. When considering patients diagnosed within a year of onset, vaccinated children were not diagnosed more rapidly than unvaccinated children.
INTERPRETATION Some symptoms and signs of narcolepsy were more frequently reported in Pandemrix–vaccinated patients. There was no evidence of the more rapid diagnosis in vaccinated patients that has been reported in Finland and Sweden.

Narcolepsy is a rare, chronic, neurological disorder presenting with excessive daytime sleepiness, often associated with a transient loss of muscle tone triggered by strong emotion (cataplexy). In 2012, a study from Finland reported a 13-fold increased risk of narcolepsy after pandemic A/H1N1 2009 influenza vaccination in children and young people aged 4 to 19 years, in most of whom onset occurred abruptly within 3 months after vaccination.[1,2] Similarly, in 2013, a Swedish group reported that the pandemic A/H1N1 2009 influenza vaccination was a precipitating factor for childhood narcolepsy and that onset was more sudden in children in their postvaccination group than is generally the case.[3]

In England, a monovalent pandemic strain vaccine containing the oil-in-water adjuvant AS03 (Pandemrix) was introduced in October 2009 during the second wave of A/H1N1 influenza, or swine flu, infection, initially in people with high-risk clinical conditions[4,5] and then, from mid-December 2009, in healthy children aged less than 5 years.[6] By March 2010, around 37% of children in a risk group aged 2 to 15 years and 24% of healthy children aged under 5 years had been vaccinated in England.[7] A second pandemic vaccine, Celvapan (unadjuvanted), was used but accounted for less than 1% of doses.

We gathered data on children in England aged 18 years or less who developed narcolepsy and were diagnosed between January 2008 and July 2011. We found an increased risk of narcolepsy after vaccination with Pandemrix,[8] consistent with findings from Finland. Here we report on the clinical features of the patients with narcolepsy in England, exploring the possibility that the clinical presentation of the vaccinated patients was different from that of the unvaccinated patients, as described in Finland and Sweden.

METHOD

Patient ascertainment and validation

The study was conducted only in England, and not the whole UK, as the Health Protection Agency had approval for England from the National Information Governance Board for Health and Social Care (NIGB) (PIAG ref:

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PIAG 03-(c)/2001), which allowed us access to patient-identifiable information for purposes of monitoring vaccine safety, thereby avoiding any delays.

Sleep centres and paediatric neurology centres in England that saw children were identified via the British Sleep Society and the British Paediatric Neurology Association. They were contacted in July 2011 to identify children aged 4 to 18 years living in England (referred to as 'English children' or 'English cases') diagnosed with narcolepsy with onset after January 2008. Out of the 23 centres contacted, 16 reported children who fulfilled the criteria. These centres reported most of the patients included in the study. As an alternative source of ascertainment, we also used the Hospital Episode Statistics (HES) database[9] of all patients admitted to National Health Service (NHS) hospitals in England. We identified, via their NHS number, all children in the same age group in the same time period with the International Statistical Classification of Diseases and Related Problems, 10th Revision (ICD-10)[10] diagnosis code G47.4 (narcolepsy and cataplexy).

The researchers visited the 16 study centres from August 2011 to February 2012 and obtained clinical details and investigation results from hospital notes in a key data-gathering visit. General practitioners were sent questionnaires to determine the patient's pandemic and seasonal influenza vaccination history, the date of onset of symptoms, the date of first health care consultation for a sleep problem, any underlying clinical condition for which the pandemic vaccine was indicated, and clinical or laboratory evidence of swine flu or influenza-like illnesses since 2007.

These data were reviewed by three narcolepsy experts (blinded to vaccination status) who confirmed the patients in which the diagnosis was definite according to the American Academy of Sleep Medicine's International Classification of Sleep Disorders (ICSD-2) criteria[11] (see Appendix SI, online supporting information). Patients not meeting these criteria but with a convincing clinical history were classified as having 'probable narcolepsy'. The remainder were excluded.

Index dates: definitions

The date of symptom onset was the earliest date of excessive daytime sleepiness or cataplexy as given by the general practitioner or recorded in the hospital notes. When the exact date was unavailable, the mid-point of the month was used. All patients known at each centre were systematically ascertained during the key centre visit. The date of diagnosis was the earliest date identified as to when the diagnosis was made.

Statistical analysis

The comparison of the speed of diagnosis in Pandemrix-vaccinated and unvaccinated patients had to allow for the longer time for those with onset in 2008 to be diagnosed compared with those in whom onset occurred later. We selected patients diagnosed within a year of onset and with onset more than a year before the key visit date and then compared the average time to diagnosis in vaccinated versus unvaccinated patients using the Kruskal–Wallis test.

When comparing symptoms in vaccinated and unvaccinated patients, Fisher's exact test was used. As a result of the large number of comparisons, significance (two-tailed test) at both the 5% level (some evidence) and 1% level (clearer evidence) was recorded.

What this paper adds

- The incidence of narcolepsy in children aged 4 to 18 years in 2008 was 0.42/100 000 in England.
- In England, 1 in 75 patients with narcolepsy had suspected swine flu infection.
- Weight gain, facial hypotonia, and tongue protrusion were significantly more frequent in Pandemrix-vaccinated patients.
- There was no evidence of quicker diagnosis in patients who were vaccinated.

RESULTS

Identification of study patients

We examined the clinical records of 245 patients who were identified by clinicians at the 16 applicable study centres, from the HES database search, or by both. The HES database identified 162 patients in England, with 130 matching data received from the 16 study centres. Only 25 other patients fitted our study definition and were, therefore, included in the analysis. The HES data also showed that no centre diagnosing more than four patients had been missed.[8] A total of 130 of the patients identified were excluded from the study because symptom onset was before January 2008, and 23 were excluded because study centres had excluded a diagnosis of narcolepsy by the time of data collection. The 92 remaining patients were reviewed by an independent narcolepsy expert panel: there was insufficient information for 10 patients to confirm the diagnosis; in three patients the date of diagnosis was after the key visit; three patients were outside the 4 to 18 years age range, and in one patient detailed symptom onset information was received late. Of the 75 patients included in this analysis, in 66 diagnosis was 'definite' according to the ICSD-2 criteria[11] (56 had narcolepsy with cataplexy and 10 had narcolepsy without cataplexy) and nine were classified as having 'probable narcolepsy'. Table I shows the demographic features.

Characteristics of the patients

Thirty-two patients in this study (43%) were female and 43 (57%) were male; of these, three females and eight males had received the Pandemrix vaccine. The mean age at onset of narcolepsy for all 75 patients was 10 years 4 months (range 3–18y); for unvaccinated patients, the mean age at onset was 10 years 7 months (range 3–18y), and for vaccinated patients it was 8 years 11 months (range 3–16y). Other details are given in Table I.

Pandemic vaccination history

Eleven definite patients had received the Pandemrix vaccine before narcolepsy onset: six within 3 months of onset,

Table I: Demographic features of the 75 children with narcolepsy

	Never received Pandemrix vaccine or was vaccinated after first symptoms (*n*=64)	Received Pandemrix vaccine before first symptoms (*n*=11)	Total (*n*=75)
Sex			
Male	35	8	43
Female	29	3	32
Ethnicity			
White	22	6	28
Black	7	1	8
Mixed	5	0	5
Asian	1	0	1
Not known	29	4	33
Age at onset			
3–8y	25	7	32
9–13y	23	2	25
14–18y	16	2	18
Diagnostic category			
Narcolepsy with cataplexy	46	10	56
Narcolepsy without cataplexy	9	1	10
Probable narcolepsy	9	0	9

one between 4 and 6 months, and four between 7 and 14 months (range of age at vaccination 3–16y). The four children vaccinated after the onset of narcolepsy were grouped with the unvaccinated children.

Seasonal vaccination history

Seven children received seasonal vaccine between 2007 and 2011 inclusive. Three of them had seasonal vaccine within 3 months of the onset of narcolepsy (one in 2009, one in 2010, and one in 2011); one of these (the patient in 2010) was also given Pandemrix within 4 months of onset. The other four children had seasonal vaccine 10 months or more before onset, two of whom were also given Pandemrix before narcolepsy onset.

History of influenza-like illness

Of the 64 children who had not received Pandemrix before onset of narcolepsy, two had an influenza-like illness in the 6 months before the first symptoms. There was no history of an influenza-like illness in the 11 vaccinated patients. One child who did not receive Pandemrix had suspected swine flu infection in July 2009 and developed narcolepsy in 2011; however, no other child had clinical or laboratory evidence of swine flu infection before onset of narcolepsy.

Family history of narcolepsy

There were no English children with narcolepsy with first-degree relatives with confirmed narcolepsy, but two unvaccinated patients and one patient who received Pandemrix vaccine after narcolepsy onset had grandfathers with narcolepsy. In a further 13 children (two of whom were vaccinated with Pandemrix), there was a history of other sleep-related problems in close relatives. For 41 children (five vaccinated for A/H1N1) there was no history of sleep disorder and for 18 the information was unavailable. Two sets of twins were identified; one set was identical and in the other zygosity was unknown. In both cases only one twin developed narcolepsy.

Presenting symptoms

The presenting symptoms were those recorded by the general practitioner or by the sleep centre when the child was first seen with suspected narcolepsy (see Table II). The symptoms more frequently reported in patients who were Pandemrix vaccinated than in those unvaccinated were cataplexy (82% vs 55%), excessive weight gain (55% vs 20%), behavioural problems (36% vs 17%), tongue protrusion (27% vs 9%), facial hypotonia (27% vs 8%), slurred speech (27% vs 8%), and abnormal movements (27% vs 11%). None of these was significant at the 1% level and only excessive weight gain was significant at the 5% level. All 75 patients presented with excessive daytime sleepiness.

Symptoms reported at any time

Facial hypotonia and tongue protrusion were eventually more frequent in Pandemrix-vaccinated children (significant at the 5% level). Of the 11 vaccinated children, 10 (91%) eventually developed cataplexy, compared with 46 out of 64 (72%) of the unvaccinated children; this difference was not statistically significant and there were no other significant differences between the vaccinated and unvaccinated groups (see Table II).

Speed of diagnosis

Considering patients diagnosed within a year of onset and before 2011, there was no statistically significant difference in the speed of diagnosis of the six patients with pandemic vaccination before onset (median interval onset to diagnosis 199d) and the 23 unvaccinated patients (median interval 208d; Kruskal–Wallis test, p=0.71).

Diagnostic investigations

Cerebrospinal fluid (CSF) hypocretin-1 levels were measured in 13 patients, two of whom had been Pandemrix vaccinated (both with low hypocretin-1 level) and 11 unvaccinated patients (nine with low hypocretin-1 level and two with normal levels). Of the 11 patients with low CSF hypocretin-1 levels, nine had cataplexy. The two with normal levels of hypocretin-1 both had cataplexy. Human leukocyte antigen (HLA) typing was carried out in 34 patients; 31 patients had the predisposing haplotype DQB1*0602 and 27 of those patients had cataplexy. The six vaccinated patients were all haplotype positive and all had cataplexy. Sleep studies were carried out in 46 patients who met ICSD-2 criteria confirming narcolepsy (of these seven were vaccinated). In two other patients, the sleep centre reported 'compatible with narcolepsy' (of whom one was vaccinated). The remainder did not meet full ICSD-2

Table II: Reported symptoms and signs in 75 children with narcolepsy, *n* (%)

	Presenting symptoms			Symptoms reported at any time		
Total children with narcolepsy (*n*=75)	Unvaccinated/ vaccinated[a] after onset (*n*=64)	Vaccinated[a] (*n*=11)	Exact *p* value for presenting symptoms	Unvaccinated/ vaccinated[a] after onset (*n*=64)	Vaccinated[a] (*n*=11)	Exact *p* value for symptoms at any time
Sleep disturbance						
Excessive daytime sleepiness	64 (100)	11 (100)	---	64 (100)	11 (100)	---
Sleep disturbance/ nightmares	34 (53)	4 (36)	0.35	41 (64)	7 (64)	1.00
Hypnagogic/ hypnopompic/ hallucinations	18 (28)	3 (27)	1.00	36 (56)	6 (55)	1.00
Sleep paralysis	6 (9)	1 (9)	1.00	14 (22)	2 (18)	1.00
Prolonged night-time sleep	6 (9)	1 (9)	1.00	6 (9)	1 (9)	1.00
Sleep automatisms	3 (5)	0 (0)	1.00	3 (5)	0 (0)	1.00
Movement disorder						
Abnormal movements	7 (11)	3 (27)	0.16	10 (16)	3 (27)	0.39
Tongue protrusion/ tongue lolling	6 (9)	3 (27)	0.12	7 (11)	5 (45)	**0.01**
Facial hypotonia	5 (8)	3 (27)	0.09	6 (9)	4 (36)	**0.03**
Ataxia	7 (11)	0 (0)	0.58	7 (11)	0 (0)	0.58
Ptosis	2 (3)	1 (9)	0.38	3 (5)	1 (9)	0.48
Behaviour and learning difficulties						
Affecting academic progress	14 (22)	3 (27)	0.70	22 (34)	3 (27)	0.74
Behaviour problems/ aggression/mood swings	11 (17)	4 (36)	0.22	19 (30)	6 (55)	0.16
Affecting memory	2 (3)	0 (0)	1.00	2 (3)	1 (9)	0.38
Other						
Cataplexy	35 (55)	9 (82)	0.11	46 (72)	10 (91)	0.27
Excessive weight gain	13 (20)	6 (55)	**0.03**	22 (34)	6 (55)	0.31
Restless legs syndrome/ painful legs/cramps in legs	6 (9)	1 (9)	1.00	12 (19)	2 (18)	1.00
Snoring	7 (11)	1 (9)	1.00	8 (13)	2 (18)	0.64
Slurred speech	5 (8)	3 (27)	0.09	5 (8)	3 (27)	0.09
Headaches	5 (8)	0 (0)	1.00	6 (9)	0 (0)	0.58
Incontinence	2 (3)	1 (9)	0.38	2 (3)	1 (9)	0.38

Bold type indicates significant values. [a]Vaccinated with Pandemrix vaccine.

criteria, and the investigations were not diagnostic, not available, or had not been performed (see Table III).

DISCUSSION

Epidemiology of narcolepsy

Based on the 29 incident English cases in 2008, we found that the annual incidence of narcolepsy before Pandemrix vaccination in 4- to 18-year-olds was 0.42 per 100 000.[8] This may underestimate the true incidence, as it is based on patients diagnosed by the end of this study, (mid-2011), and some patients may have been diagnosed after that time. The methods used to identify patients have differed between countries.[1–3,8,12–16] However, it is reassuring that several other studies found incidence rates of narcolepsy before the swine flu epidemic that were similar to our study's finding for England, suggesting that our patient ascertainment was satisfactory. For instance, Finland's average annual incidence in those younger than 17 years in 2002 to 2009 was 0.31/100 000,[2] Sweden's was 0.26/100 000,[3] and Norway's was estimated to be 0.5 to 1/100 000 per year.[13] The Vaccine Adverse Event Surveillance and Communication (VAESCO) Consortium study, undertaken in eight European countries, found that the pooled background incidence rate of diagnosed narcolepsy in children aged 5 to 19 years was 0.56/100 000.[16]

In Finland, only one child aged less than 11 years (a 9-year-old) had been diagnosed with narcolepsy in 2002 to 2009. The highest increase in diagnoses compared with previous years occurred in 2010 in children aged less than 11 years of age, a 177-fold increase in incidence.[2] The findings were different in England: the mean age of the 29 incident English children with narcolepsy in 2008 (i.e. before the Pandemrix vaccination) was 11 years 7 months, and 14 children were aged less than 11 years at diagnosis, with the youngest being 5 years old. The same ICSD-2 diagnostic criteria[11] were used in the two countries so this may reflect a real difference in the two populations rather than a difference in the ascertainment of patients.

Table III: Results of investigations

Investigation	Comments
CSF hypocretin-1 levels	CSF hypocretin-1 level was measured in 13 children. Of these, 11 had low levels (two were Pandemrix vaccinated) – in all cases below 50pg/ml – and two had normal levels. Hyprocretin-1 levels were not investigated in 62 patients or were not available by the end of the study period (nine of whom were Pandemrix vaccinated)
HLA-DQB1*0602	HLA-DQB1*0602 type was tested in 34 children. Of these, 31 were positive for HLA-DQB1*0602 (six of whom were Pandemrix vaccinated) and three were negative for HLA-DQB1*0602. In 41 patients, HLA-DQB1*0602 was not investigated or the result was not available by the end of the study period (five of whom were Pandemrix vaccinated)
Sleep studies	International Classification of Sleep Disorders Criteria for diagnosing narcolepsy: 1. Nocturnal polysomnography (minimum 6h); 2. Followed by an multiple sleep latency test with mean sleep latency of less than or equal to 8min; 3. Two or more sleep-onset rapid eye movement periods observed. In total, 46 patients met all three criteria (seven of whom were Pandemrix vaccinated). For seven patients, mean sleep latency test was not equal to or less than 8min. Two patients were reported as having symptoms 'compatible with narcolepsy' (one of whom was Pandemrix vaccinated). The test results were not diagnostic for 16 patients (three of whom were Pandemrix vaccinated), not available for one patient, and not done for three patients

Published values for cerebrospinal fluid hypocretin-1 levels: low, ≤110pg/ml; intermediate, >110pg/ml and ≤200pg/ml; normal, >200pg/ml.[22]
CSF, cerebrospinal fluid; HLA, human leukocyte antigen.

International differences in A/H1N1 2009 vaccination rates

In England, 11 children and adolescents who had received Pandemrix vaccination before the onset of narcolepsy symptoms were identified, a much smaller number than in Finland (50),[2] Sweden (28),[3] Ireland (28),[12] and Norway (58).[13] The French data are not directly comparable because 90% of French children aged 9 years or less were given Panenza – an unadjuvanted vaccine.[14] A possible explanation for the relatively small number of English cases is the low vaccine uptake (363 004 of 8 502 600 children aged 5–18y, i.e. 4.3%)[8] compared with the relatively high rates in Sweden (78% of children aged <18y)[3] and Finland (75% in the cohort age range 4–19y).[1]

Swine flu and other infections

In England, the general practitioner questionnaires reported an 'influenza-like illness' in two children and suspected swine flu in one child out of the 75 patients with narcolepsy. Similarly, Finland reported influenza-like illness in only four out of 50 vaccinated chidren.[2] In Sweden, eight out of 36 children had 'a previous infection' (one had an influenza-like illness),[3] and in Norway no previous infections were documented.[13] In Finland, a serological study found no evidence that influenza infection was a significant cause of childhood narcolepsy.[17] In France, there was no significant difference in the history of infection when children and adults with narcolepsy were matched with control subjects.[14] In contrast, an increase in narcolepsy was attributed to the 2009 H1N1 pandemic in a report from China.[18]

Family history of narcolepsy

There were no English children with narcolepsy with first-degree relatives with a history of narcolepsy. Two out of 37 Swedish children had a familial predisposition to narcolepsy and, similar to the findings in England, only one out of a pair of identical twins developed narcolepsy after Pandemrix vaccination.[3] In France, there was no reported difference in family history between vaccinated and unvaccinated patients.[14] Several studies have shown that in familial narcolepsy cases are the exception, with monozygotic twins showing only partial concordance.[19-21]

Symptoms and signs of narcolepsy

In Finland[1,2] and Norway,[13] the onset was described as 'abrupt'. In Sweden,[3] 19 of the 28 vaccinated patients developed symptoms within 12 weeks of vaccination; in the prevaccination group, the date of clinical onset was subtle with no obvious trigger factors, and in only one child could the clinical onset be dated to within 12 weeks.

Earlier onset of cataplexy after the onset of excessive daytime sleepiness in vaccinated compared with unvaccinated patients was reported in Finland,[2] Ireland,[12] and France.[14]

In Finland, 47 (94%) vaccinated patients had cataplexy at onset or soon after the children started to sleep excessively,[2] and in Norway[13] it was reported that cataplexy occurred within a few weeks of or at the same time as excessive daytime sleepiness in most of the vaccinated patients. In England, more vaccinated than unvaccinated patients had cataplexy at first presentation, but this difference did not reach statistical significance.

In Finland, it was reported that there was 'rapid weight gain in the beginning' in 63.4% (26 out of 41) of vaccinated children;[2] in Sweden, the corresponding figure was 61% (17 out of 28),[3] in Norway it was 35% (22 out of 58),[13] and in England excessive weight gain at onset was reported in 55% of vaccinated children, a significantly higher proportion than in unvaccinated children. However, as shown in Table I, the proportion of English children with narcolepsy in the youngest age group (3–8y) was higher in the group vaccinated with Pandemrix (7 out of 11, 64%) than in the group who did not receive Pandemrix (25 out of 64, 40%). Thus, younger age could be a confounding factor, as in Finland[2] and Sweden,[3] where the Pandemrix-vaccinated patients were also younger than the unvaccinated patients.

When considering symptoms reported at any time, facial hypotonia and tongue protrusion/lolling, as described by Plazzi et al.,[22] were more frequently seen in English children. The French study found 'almost no difference' in characteristics of vaccinated and unvaccinated patients of all ages.[14] The VAESCO study found that the prevalence of cataplexy was equally high in exposed and non-exposed children or adolescents (≤18y) with narcolepsy.[16]

Speed of diagnosis

In England, there was no difference in the speed of diagnosis between Pandemrix-vaccinated patients and unvaccinated patients, but, for valid comparison of vaccinated and unvaccinated patients (see 'Method'), the analysis was restricted to those diagnosed within a year of onset. In contrast, in France,[14] vaccinated patients (children and adults) were diagnosed more quickly than unvaccinated patients. Finland[2] also reported accelerated diagnosis of vaccinated patients; although the data analysis did not allow for vaccinated patients who might be diagnosed after the study finished, any such patients would result in smaller differences between vaccinated and unvaccinated patients. However, the mean age at diagnosis in Finnish cases with onset in 2009 or 2010 was 12 years 1 month (95% confidence interval [CI] 11.2–13.0y), which is significantly lower (p=0.027) than the mean age of 15 years 4 months (95% CI 11.8–18.7y) in those with onset before 2009. This supports evidence for more rapid diagnosis, as age at onset of symptoms was not significantly different between the groups. In Sweden,[3] the median duration from onset to diagnosis was 1 year (range 3mo–2y) in the postvaccination group and 5 years (range 1–8y) in the prevaccination group. The mean age at onset was 10 years in the postvaccination group and 12 years 6 months in the prevaccination group.

Investigations

CSF hypocretin-1 levels were measured in 13 of the English children, in 11 of whom levels were abnormally low (two were Pandemrix vaccinated). Hypocretin-1 levels were normal in two children with cataplexy. In Finland, CSF hypocretin-1 was measured in 13 out of 50 patients and was low in all cases.[2] CSF hypocretin-1 was measured in 21 out of 36 patients in Sweden (and was low in 20)[3] and in 41 out of 58 patients in Norway (low in all).[13] According to a recent review, 90% of patients with narcolepsy with cataplexy have low CSF hypocretin-1 levels, but the test is less sensitive in narcolepsy patients without cataplexy, with up to 20% of such individuals being identified as hypocretin-1 deficient.[23]

HLA typing was performed in 34 English children: 31 had the DQB1*0602 haplotype, and all six who were Pandemrix vaccinated were positive. In Finland, 32 out of 50 were haplotyped and all were positive[2], in Sweden 21 out of 36 were tested and 20 were positive, including the 17 vaccinated patients,[3] and in Norway 37 out of 58 were tested and all were positive.[13] The DQB1*0602 haplotype is found with much the same frequency in England (14.4%) as in Sweden (14.1%), with a slightly higher rate in Finland (17.1%).[24]

The association of narcolepsy with HLA haplotype and the association with low or undetectable CSF hypocretin-1 levels have been recognized previously and suggest that narcolepsy is an autoimmune disorder, the target cell population being the hypocretin-producing cells in the hypothalamus.[25–28]

Strengths and limitations of the study

Limitations

Only 11 of the English children with narcolepsy had received Pandemrix vaccine, a relatively small number, explained by the relatively low vaccine uptake in England. This small number reduces the likelihood of finding statistically significant differences between vaccinated and unvaccinated patients. The symptom history was taken from hospital notes so there was no systematic questioning of all patients. It is possible that this led to bias, although the Finnish study also depended on histories taken by the local clinician. To make a valid comparison between the speed of diagnosis in vaccinated and unvaccinated groups of children we limited the analysis to those who had been diagnosed within a year – a relatively rapidly diagnosed subgroup – which limited our ability to detect an overall difference between the groups. Finally, sleep studies were not carried out in all of the children in this study; however, the ICSD-2 diagnostic criteria of narcolepsy[11] used by the independent expert panel in our study (also used by the Finnish[2] and Swedish[3] studies) allows for the diagnosis of narcolepsy without sleep studies in children who have cataplexy (see Appendix SI). Other investigators[12,14,16] have used the Brighton Collaboration criteria,[23] which do not allow for the diagnosis of narcolepsy without supporting investigations (e.g. CSF hypocretin-1 measurement or sleep studies).

Strengths

The strengths of this study are that children had been seen and diagnosed in recognized sleep centres and the diagnoses were validated by three independent experts blinded to the child's vaccination status. Independent ascertainment via national Hospital Episode Statistics confirmed that we had not missed any major centres that diagnose narcolepsy in children. The vaccination history was obtained directly from the general practitioners who provided the primary care of the children and who kept records of vaccines administered to the children.

CONCLUSION

Recent publications have reported that Pandemrix vaccination is associated with abrupt onset of narcolepsy[1–3,13] and an earlier onset of cataplexy[2,12,14] than is seen in unvaccinated children. We found that some narcolepsy symptoms, including cataplexy at presentation, were more commonly described in vaccinated than unvaccinated patients. We did

not find evidence of the abrupt onset and more rapid diagnosis of vaccinated patients that has been reported in Finland[2] and Sweden.[3] It is possible that pandemic H1N1 vaccination accelerated the onset of narcolepsy in children who would have developed it later anyway. If this was the case, a smaller than expected number of children will present with narcolepsy in the future. Only long-term studies in countries such as Finland and Sweden, with high pandemic H1N1 vaccination rates, would be able to demonstrate this.

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SUPPORTING INFORMATION

The following additional material may be found online:

Appendix SI: ICSD-2 diagnostic criteria of narcolepsy with cataplexy.[11]

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