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Risk of Guillain-Barré syndrome after exposure to pandemic influenza A(H1N1)pdm09 vaccination or infection: a Norwegian population-based cohort study

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Abstract Vaccinations and infections are possible triggers of Guillain-Barré syndrome (GBS). However, studies on GBS after vaccinations during the influenza A(H1N1)pmd09 pandemic in 2009, show inconsistent results. Only few studies have addressed the role of influenza infection. We used information from national health databases with information on the total Norwegian population (N = 4,832,211). Cox regression analyses with time-varying covariates and self-controlled case series was applied. The risk of being hospitalized with GBS during the pandemic period, within 42 days after an influenza diagnosis or pandemic vaccination was estimated. There were 490 GBS cases during 2009–2012 of which 410 cases occurred after October 1, 2009 of which 46 new cases occurred during the peak period of the influenza pandemic. An influenza diagnosis was registered for 2.47 % of the population and the vaccination coverage was 39.25 %. The incidence rate ratio of GBS during the pandemic peak relative to other periods was 1.46 [95 % confidence interval (CI) 1.08–1.98]. The adjusted hazard ratio (HR) of GBS within 42 days after a diagnosis of pandemic influenza was 4.89 (95 % CI 1.17–20.36). After pandemic vaccination the adjusted HR was 1.11 (95 % CI 0.51–2.43). Our results indicated that there was a significantly increased risk of GBS during the pandemic season and after pandemic influenza infection. However, vaccination did not increase the risk of GBS. The small number of GBS cases in this study warrants caution in the interpretation of the findings.

Keywords Guillain-Barré syndrome · Pandemrix® · Vaccination · Influenza · Registry · Norway

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Introduction

Guillain-Barré syndrome (GBS) is a rare but serious disease in which the immune system attacks nerve cells, causing muscle weakness, paralysis, and in some cases, death [1]. The causal mechanisms of GBS are not fully known, but GBS may be triggered by infectious illnesses, and vaccinations and influenza have been suggested as potential triggers [2, 3]. However, studies on GBS after influenza infection or vaccination show contradictory results.

During the influenza outbreak in 1976–1977, an American study found an increased risk of GBS after influenza vaccination [4]. Also, after the influenza A(H1N1)pmd09 pandemic in 2009, have several studies reported an association between H1N1 immunizations and GBS [5–7], while other studies have not found any association [3, 8, 9]. Thus the role of vaccination as a possible trigger of GBS is unclear. Following the 2009 pandemic, two international collaborative efforts studied the role of vaccination on the GBS [10, 11]. Results from these international studies were also inconsistent; one study showed a significant association between influenza A(H1N1) vaccine (pH1N1) [10],

while the other study reported that relative incidence of GBS was not significantly elevated after pandemic vaccination [11].

To our knowledge, only a few other studies have investigated the role of influenza infection in GBS, and as a potential confounder of the association between vaccination and GBS [3, 12–14].

During the 2009 pandemic, an adjuvanted influenza A(H1N1)pdm09 vaccine (Pandemrix®) was offered to the Norwegian population, and approximately 1.9 million people (39.25 % of the population) were vaccinated. We used information on GBS, pandemic influenza infection and vaccination from nationwide health data-bases. The aim was to estimate the associations between pandemic influenza A(H1N1)pdm09 infection or vaccination and GBS including all residents in Norway in the study population.

Methods

Data sources

We linked data from several national registries and health data-bases by using the unique 11-digit personal identification number provided to all Norwegian residents.

Information on GBS diagnoses during the period 2009–2012 were obtained from the Norwegian Patient Register (NPR) [15]. This is an administrative database to which all Norwegian hospitals and outpatient clinics report to receive governmental reimbursement. Diagnoses are reported according to the World Health Organization's International Classification of Diseases, Version 10 (ICD-10). The first registration of GBS (ICD-10 code G61.0) in the NPR for each patient was used in the analyses.

Information on vaccinations was obtained from the Norwegian Immunisation Register [16]. In Norway, the Pandemrix® vaccine was offered to the whole population. Notification of pandemic influenza vaccinations was mandatory during the influenza pandemic in 2009.

The Norwegian Directorate of Health reimburses consultations in emergency outpatient clinics and general practice. We used information on dates of physician consultations for those receiving an influenza diagnoses in the International Classification of Primary Care, second edition (ICPC-2) code system.

We also obtained information on laboratory confirmed pandemic influenza infections from the Norwegian Surveillance System for Communicable Diseases [17]. This registry is a nationwide system for surveillance of infectious diseases.

Individuals with the ICPC-2 code R80 (influenza like illness) registered during the pandemic peak in Norway (October 1, 2009, through December 31, 2009) or registered with a positive laboratory test for pandemic influenza were considered as exposed to pandemic influenza infection.

Study population

The study population included the entire Norwegian residents as registered in the National Population Registry per October 1, 2009 (N = 4,832,211).

Statistical analysis

The pandemic peak in Norway occurred between October 1, and December 31, 2009 [18]. The vaccination campaign began on October 19, 2009, and about 97 % of the pandemic vaccinations were administered before December 31, 2009. Two approaches were used to assess the risk of GBS following pandemic influenza infection or vaccination. First, a Cox proportional-hazards regression was applied, with number of days since October 1, 2009 as the time metric. Vaccination status and influenza diagnosis were included as time-varying covariates. Crude and adjusted hazard ratios (HRs) of GBS, with 95 % confidence intervals (CIs) were estimated using a 42-day risk window after pandemic vaccination or influenza infection. Thus, patients were considered as exposed only during the first 42 days after vaccination or influenza infection. The risk window of 42-days was chosen to facilitate comparisons with other studies. Sex and year of birth (categorized as <1980 and ≥ 1980) were considered as potential confounders and were included in the adjusted analyses.

The population was followed until diagnosis of GBS, death, emigration or end of follow-up (December 31, 2012), whichever occurred first.

In addition to the Cox regression models, a self-controlled case series (SCCS) method was applied. In the SCCS model, cases serve as their own control by comparing the individual risk of disease within a defined exposure window, to the individual risk in other time periods [19]. An advantage with this method is that time-constant confounding is eliminated. Only information from exposed cases was used, and the applied observation time was the complete study period of 4 years; 2009–2012. The SCCS approach was applied in three separate models. In model I, we estimated the risk of being hospitalized with GBS during the pandemic peak (October 1, 2009 through December 31, 2009). The incidence rate ratios (IRRs) of GBS in the pandemic peak were compared with the risk of GBS outside this period. In model II and model III, we estimated IRR of GBS in a 42-day risk window following either a diagnosis of pandemic influenza or after vaccination. The IRRs were calculated using conditional Poisson regression.

All analyses were performed using the Stata 13 software (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.).

Results

During 2009–2012, 490 individuals were diagnosed with GBS in Norway (Fig. 1). There were 410 cases of GBS diagnosed on or after October 1, 2009 (Table 1), of which 46 cases occurred during the pandemic peak (October 1, 2009 through December 31, 2009). The incidence of GBS was 2.7 per 100,000 person-years. Figure 1 shows the observed number of GBS cases in 3-month intervals diagnosed between January 1, 2009 and December 31, 2012. The highest number of new cases occurred during the pandemic peak. Figure 2 shows the age distribution of patients registered with GBS. The mean age at diagnosis was 50.4 years with a standard deviation of 21.8 years. The majority of GBS cases (83.67 %) were observed among individuals born before 1980.

Two individuals were diagnosed with GBS within the 42-day risk window after a physician diagnosis of influenza, and eight individuals were hospitalized with GBS within 42 days after pandemic vaccination. Cox proportional-hazards regression analyses showed that influenza infection was associated with a higher risk of GBS in both the crude (HR 4.22, 95 % CI 1.01–17.59) and the adjusted analyses (HR 4.89, 95 % CI 1.17–20.36). The risk of GBS after influenza vaccination was neither statistically significant in the crude (HR 1.07, 95 % CI 0.49–2.35) nor the adjusted analyses (HR 1.11, 95 % CI 0.51–2.43) (Table 2).

The IRR of GBS during the pandemic peak (model I) was significantly elevated when compared with the other periods (IRR 1.46, 95 % CI 1.08–1.98) (Table 3). The IRR of GBS in a 42-day risk window following a diagnosis of influenza (model II) was also significantly elevated (IRR 6.54, 95 % CI 1.48–28.97), whereas the association between pandemic vaccination and risk of GBS (model III) was not statistically significant (IRR 1.12, 95 % CI 0.55–2.26).

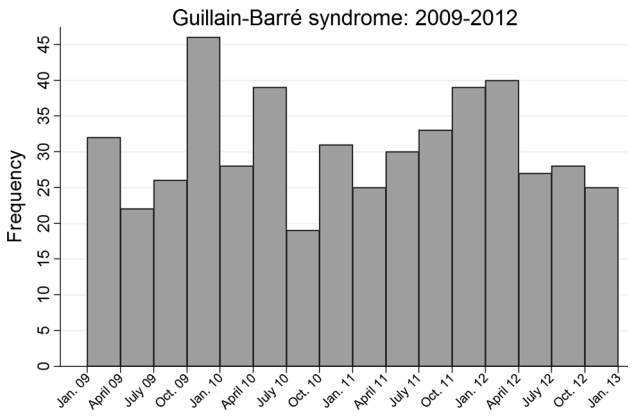

Fig. 1 Observed number of Guillain-Barré syndrome (GBS) cases per 3 month intervals from January 1, 2009 through December 31, 2012

Discussion

In this population-based study of GBS in Norway, we found an incidence rate of 2.7 per 100,000 person-years. By using national data-bases, we found an increased risk of GBS during the pandemic peak, supported by an increased risk of GBS in those diagnosed with influenza infection. Vaccination was not significantly associated with an increased risk of GBS.

Strengths and weaknesses

A major strength of the current study was the availability of national health data from the whole Norwegian population of more than 4.8 million individuals. By using data bases from primary care and emergency outpatient visits for the whole country, we had the unique opportunity to study not only the impact of pandemic vaccination, but also pandemic influenza infection. To our knowledge, few other studies have addressed risk of GBS according to both exposures [3, 12–14].

The Norwegian health care system is financed through governmental funding. All hospitalizations are free of charge while primary care consultations and emergency outpatient visits for persons aged 16 years or older are charged a minor fee and physicians are reimbursed by the government. We believe that registration of new cases of GBS is likely to be complete. However, GBS is a rare disease and consequently challenging to study its associations with rare exposures.

The vaccination register in Norway is one of very few that contains nationwide data on pandemic vaccinations. Notifications of all administered doses were mandatory during the pandemic, and registrations are nearly complete. As Norway had relatively high vaccination coverage in the general population (39.25 %), we had the opportunity to study a rare outcome, such as GBS, after vaccination.

Previous studies on GBS following the 2009 pandemic were mainly based on case–centre designs (collaborations between various health centres) [3], records collected from selected hospitals [6, 20, 21], or a case–control design [14]. These studies are therefore prone to biases from selection of participants, the methods of collecting information and recall bias. Many studies have been limited to a few counties or states [21, 22].

Table 1 Characteristics of the study population, all residents in Norway as of October 1, 2009

	Nr. of individuals (%)	Nr. of individuals vaccinated with Pandemrix® (%)	Nr. of individuals with an influenza diagnosis (%)	Nr. of Guillain-Barré syndrome cases (per 100,000 individuals)
Total	4,832,211 (100)	1,896,455 (39.25)	119,291 (2.47)[a]	410 (8.49)
Sex				
Male	2,412,286 (49.92)	864,727 (35.85)	54,285 (2.25)	226 (9.37)
Female	2,419,925 (50.08)	1,031,728 (42.63)	65,006 (2.69)	184 (7.60)
Year of birth				
<1980	3,007,831 (62.24)	1,155,428 (38.41)	54,999 (1.83)	331 (11.01)
≥1980	1,824,380 (37.76)	741,027 (40.62)	64,292 (3.52)	79 (4.33)

Nr Number

[a] Of which 10.2 % had a positive laboratory test for pandemic influenza

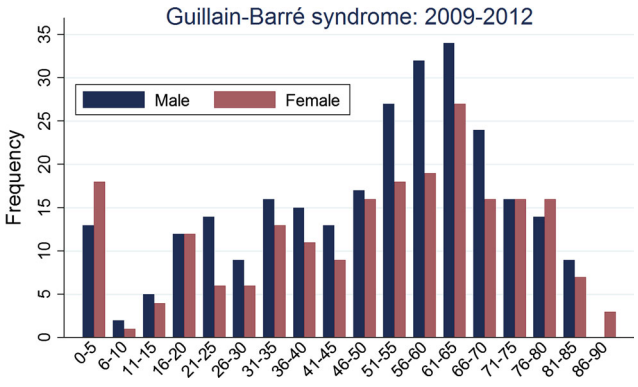

Fig. 2 Observed number of patients with Guillain-Barré syndrome (GBS) during the time period 2009–2012 by age at diagnosis in 5-year categories

A major strength of the current study is that our data was collected from the entire population prospectively and recorded independently of each other, eliminating differential reporting and selection bias. Although GBS is a rare disease and the number of GBS cases after pandemic vaccination in Norway was low, it is however comparable to previous studies [8, 9].

One weakness in this study is the under-reporting of influenza infections. It has been estimated that around 30 % of the Norwegian population had clinical influenza during the pandemic [23], while less than 3 % of the population were diagnosed with influenza by a primary care physician. The low number of consultations can be explained by public recommendations during pandemic peak. Due to high demands on health clinics during the pandemic peak, people were advised not to seek medical help for influenza symptoms if they were not in need of urgent care or were at high risk of complications. Consequently, many people with influenza were regarded as unexposed which may have led to an underestimation of the association between influenza infection and GBS. Therefore, we estimated the risk of GBS during the period of pandemic peak, in addition to estimating the risk after receiving a physician diagnosis of influenza. Risk of GBS was significantly elevated during the pandemic peak relative to other time periods and supported by the elevated

Table 2 Hazard ratio (HR) of Guillain-Barré syndrome (GBS) for the period October 1, 2009 through December 31, 2012, with associated 95 % confidence interval (CI) within a 42-day risk window after an influenza diagnosis or vaccination; estimated by Cox proportional-hazards regression, using the resident Norwegian population as of October 1, 2009 (n = 4,832,211) as study population

		Nr. of GBS cases[a]	Person-year	Incidence rate per 1000 person-year	Crude HR (95 % CI)	Adjusted[b] HR (95 % CI)
Influenza diagnosis	No	407	5,621,223,110	0.03 (0.02–0.03)	1	1
	Yes	2	5,234,754	0.14 (0.04–0.56)	4.21 (1.01–17.59)	4.89 (1.17–20.36)
Vaccination	No	401	5,546,081,387	0.03 (0.02–0.03)	1	1
	Yes	8	80,376,477	0.04 (0.02–0.07)	1.07 (0.49–2.35)	1.11 (0.51–2.43)

Nr number

[a] Follow-up of one subject ended on October 1, 2009, giving a follow-up time of 0 days. Hence, he/she was excluded from the Cox regression analysis

[b] The model is adjusted for sex and year of birth. Influenza diagnosis and vaccination were simultaneously included in the adjusted model

Table 3 Incidence rate ratio (IRR) of Guillain-Barré syndrome (GBS) for the period January 1, 2009 through December 31, 2012, with associated 95 % confidence interval (CI); estimated by the self-controlled case series method

	Nr. of GBS cases	IRR (95 % CI)
Model I[a]		
Pandemic peak period	46	1.46 (1.08–1.98)
Model II[b]		
Influenza diagnosis	2	8.45 (1.79–39.77)
Model III[c]		
Vaccination	8	1.31 (0.65–2.66)

Nr number

[a] Includes all cases of GBS occurring between October 1, 2009 through December 1, 2009 as exposed. The IRR of GBS in the pandemic peak was compared with the risk of GBS outside this period

[b] The IRR of GBS was calculated in a 42-day risk window following influenza A(H1N1)pdm09 infection

[c] The IRR of GBS was calculated in a 42-day risk window following vaccination with Pandemrix

risk found in those diagnosed with influenza by a physician.

Comparison to the literature

In accordance with results from several other studies [3, 8, 9, 14, 20], we did not find an increased risk of GBS after vaccination against pandemic influenza in Norway. While some studies show a lack of association between GBS following influenza A (H1N1) vaccination [3, 8, 9, 14, 20], an increased risk of GBS following pandemic vaccination has been reported in other studies [5, 6, 21, 22]. Many of these studies, however, did not address influenza infection as a risk factor for GBS.

One American study reported no significant increase in risk of GBS within a risk period of 6 weeks after influenza vaccine; however, a statistically significant association between risk of GBS and antecedent infection was found [3]. Similar lack of associations with vaccinations was reported from an Australian study [20], British studies [8, 9] and from a European multinational case–control study [14]. In the latter study, the analyses were adjusted for influenza-like illness/upper respiratory tract infection and seasonal influenza vaccine.

In contrast, a meta-analysis study from the USA reported a modest increased risk of GBS after 2009 influenza A (H1N1) vaccination [5]. A Canadian study showed a small but significant increase in the number of GBS cases after mass influenza vaccination in Quebec [21] and a study from Germany on the Pandemrix vaccine reported a statistically significant association between GBS and vaccination in a 5–42 days risk window [6]. Unlike other studies, an American study by Vellozzi et al. [22] suggested a protective effect of influenza A (H1N1) vaccination. Vellozzi et al. showed that at the end of the influenza season, the cumulative risk of GBS was lower among vaccinated than among unvaccinated individuals.

Conclusion

This population-based study confirmed that GBS is a rare disease. Risk of GBS was significantly higher during the pandemic season relative to other time periods. Our results support that pandemic influenza increased the risk of GBS. Pandemic vaccination was not associated with an increased risk of GBS. In our study, a small number of individuals were diagnosed with GBS after a diagnosis with pandemic influenza infection or vaccinations and the results should be interpreted with caution.

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Conflict of interest The authors have no conflict of interest.

Ethical standard The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Region, Norway.

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