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Paresthesia and sensory disturbances associated with 2009 pandemic vaccine receipt: Clinical features and risk factors

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ABSTRACT

Background: Paresthesia was the third-most-common adverse event following immunization (AEFI) with 2009 monovalent AS03-adjuvanted A(H1N1)pdm09 vaccine in Quebec, Canada and was also frequently reported in Europe. This study assessed clinical features and risk factors associated with this unexpected AEFI.

Methods: Reports to the passive surveillance system were summarized. A case–control study was conducted to assess risk factors and additional investigations were undertaken among cases with symptoms persisting ≥12 months.

Results: There were 328 reports of paresthesia affecting the vaccinated arm (58%), but also face (45%), lower limbs (40%) and back/thorax (23%) with numbness but also muscle weakness (61%), motor impairment (61%), generalized myalgia (37%), visual (14%) and/or speech effects (15%). Reporting rate was highest in women of reproductive age, peaking at 30–39 years-old (28/100,000 doses administered) and exceeding that of men of the same age (7/100,000 doses) by 4-fold. Median time to onset was 2 h. Symptoms subsided within one week in 37% but lasted ≥6 months in 26%. No consistent or objective neurological findings were identified. Risk was increased with allergy history, respiratory illness the day of vaccination, depressive symptoms and family history of pulmonary disease, but decreased with physical activity the day of vaccination, and regular weekly alcohol consumption.

Conclusion: Paresthesia following 2009 pandemic vaccine receipt lasted several weeks and included other motor-sensory disturbances in an important subset of patients. Although it does not correspond with known neurological disease, and causality remains uncertain, further investigation is warranted to understand the nature and frequency of paresthesia as a possible AEFI with influenza vaccines.

1. Introduction

Several pandemic vaccines used in 2009 for the prevention and control of influenza during the A(H1N1)pdm09 epidemic have been associated with neurological concerns. An increased risk of the Guillain-Barré syndrome (GBS) has been observed with both adjuvanted and non-adjuvanted pandemic vaccines in some countries [1–4] but not others [5–7]. An increase in narcolepsy has been associated with AS03-adjuvanted pandemic vaccine [8–12] but not with non-adjuvanted vaccines [13,14]. There were also anecdotal reports of acute disseminated encephalomyelitis [15–20].

In Quebec, the second largest Canadian province (population: 8 million), 4.4 million people were vaccinated during the fall 2009 mass pandemic campaign, of whom 96% received a monovalent AS03-adjuvanted pandemic vaccine manufactured locally (Arepanrix®, GSK Canada). Between 26 October and 31 December, 2009 the Quebec passive Vaccine Adverse Event Reporting Surveillance (VAERS) system received 2229 reports of adverse events following immunization (AEFI), corresponding to a rate of 50.4 AEFI per 100,000 doses administered. After allergic-like symptoms (752 reports) [21] and local reactions (402 reports), the third-most-often

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reported AEFI was paresthesia. This unexpected adverse event was also frequently reported in Sweden and France but with no description of its associated clinical features [22–26]. This paper describes the clinical and epidemiological characteristics of this unexpected AEFI as reported to the Quebec VAERS system and further assessed in ensuing case–control study and clinical investigations.

2. Methods

2.1. Passive surveillance

In Quebec, the Public Health Act requires healthcare professionals to report to public health unusual clinical problems temporally associated with vaccination and suspected of being linked to the vaccine. To improve the sensitivity of the passive surveillance system, all physicians received a letter from their Medical Officer of Health just before the pandemic mass vaccination campaign underscoring the importance of AEFI reporting in the context of a new AS03-adjuvanted vaccine. The AEFI form includes tick boxes for adverse events of interest, one of which is anesthesia/paresthesia and has a free text zone for additional details. This study includes reports of paresthesia notified to VAERS for pandemic vaccines administered between 26 October and 31 December, 2009.

2.2. Case–control study

The case–control study included cases reported to VAERS aged 18–64 years-old, with onset of anesthesia/paresthesia ≤72 h after vaccination, excluding reports of Guillain-Barré Syndrome (GBS). Controls were randomly selected from the Quebec pandemic vaccination registry of all vaccinated individuals in the province. Since nearly three-quarters of the reported cases were female, controls were also frequency-matched 3:1 by gender. Identified controls who subsequently reported anesthesia/paresthesia within 72 h of pandemic vaccination were excluded. The chief Medical Officer of Health legally mandated this investigation that, under the Public Health Act, did not require Research Ethics Board approval.

After obtaining verbal consent, a standardized questionnaire was completed by trained personnel during phone interviews conducted between May and August 2010, 6–8 months following vaccination. The questionnaire systematically assessed clinical presentation among cases. The likelihood of neuropathic pain was assessed using the ID Pain questionnaire [27] in each affected limb, yielding a maximum of four evaluations per case. The highest ID Pain score was kept and categorized as: unlikely (<2), likely (2–3), or very likely (4–5) to be neuropathic pain [28]. Patients were sent a standardized diagram of the human body by mail to show affected areas. Written consent was requested to access medical records of cases who had sought health care.

Risk factors evaluated in both cases and controls included health status at vaccination, past personal and family medical history, prescribed medications and over-the-counter products used within 48 h before vaccination, past influenza vaccination history and occurrence of AEFIs with any previous vaccine, smoking, alcohol consumption, physical activity and employment.

Numbness may be a symptom of anxiety, depression, somatization or psychosomatic disorders. Accordingly these were assessed with four validated psychometric tools, including: (1) the Beck's Anxiety Inventory short form (BAI-S) which includes 13 questions [29]; (2) the Patient Health Questionnaire 9 (PHQ-9), a 10-item questionnaire adapted for the assessment of depression from the Primary Care Evaluation of Mental Disorders (PRIME-MD) [30]; (3) the Somatosensory Amplification Scale (SSAS), a 10-item questionnaire to evaluate individual sensitivity to normal physical, social, and bodily cues and sensations (hunger, ecchymosis, pollutants) [31]; and finally (4) the Forced Choice Symptom Interpretation Scale to assess individual attributional style, or preferential interpretation of symptoms within three scales (normalizing, psychologizing, or somatizing) with scores ranging 0–13 [32]. For example, palpitations can be normalized (interpreted as a sign of fatigue or excessive caffeine intake), psychologized (sign of nervousness or anxiety) or somatized (sign of serious heart condition).

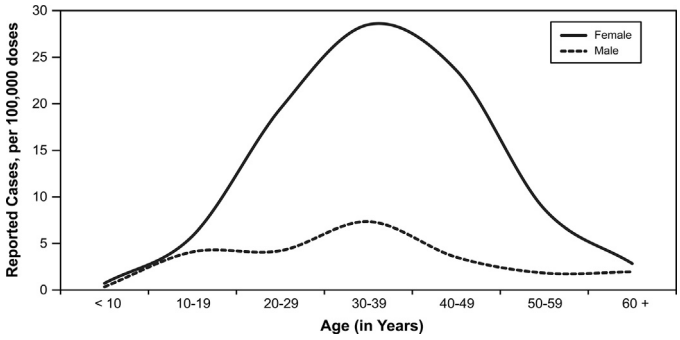

Fig. 1. Reported rate of paresthesia per 100,000 doses of AS03-adjuvanted pandemic vaccine by age and gender.

2.3. Clinical evaluation of persistent cases

Cases with persisting symptoms at the time of the case–control study were re-contacted in December 2010 (≈12 months post-vaccination) for participation in further clinical investigation approved by the institutional research ethics board. After written informed consent, a neurologist (KL) conducted physical and neurological examinations and 3-Tesla cerebral magnetic resonance imaging (MRI) scan.

2.4. Statistical analysis

AEFI rates were calculated using denominator data extracted from the provincial vaccination electronic registry. Proportions were compared with χ^2 or Fisher's exact test and means with the Kruskal–Wallis test. A Poisson distribution was used to calculate exact confidence intervals (CIs) and compare rates.

Odds ratios for risk factors and their CIs were estimated by unconditional logistic regression. The model initially included factors reaching threshold statistical significance ($p < 0.15$) in univariate analyses. Absence of collinearity was verified and model fit was assessed by the explained deviance and the Hosmer and Lemeshow test.

3. Results

3.1. Passive surveillance

A total of 328 paresthesia cases (15% of all reported AEFI) not attributable to GBS were reported through the VAERS system. Females accounted for 81% (267) and mean age was 39 years (Table 1). The overall paresthesia rate was 7.5 cases per 100,000 doses administered but varied significantly by sex and age (Fig. 1), lowest in children <10 years-old (0.5/100,000), increasing through adolescence, and peaking at 30–39 years (19.5/100,000), then decreasing. After 10 years-of-age, women were more affected than men (12.8 vs 3.4/100,000, $p < 0.001$; RR = 3.8, 95%CI: 2.8–5.1) although after 60 years-of-age, rates were similar between men and women (2.5/100,000) (Fig. 1). The reporting rate was highest in women 30–39 years-old (28/100,000 doses administered) in whom it exceeded that of men of the same age (7/100,000 doses administered) by