

Risk Factors for Poor Immune Response to Influenza Vaccination in Elderly People

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Influenza vaccination of elderly people is efficacious and cost effective for the prevention of influenza and its complications. Some studies have pointed out low immunogenicity in this group. Health status has been poorly investigated as a risk factor that may influence the immune response to influenza vaccine. We established an immunization response study of a highly-matched elderly population in a nursing home. One-hundred-twenty subjects of Ashkenazian origin had their vaccine-induced antibody response assessed. Good response was obtained in 30.8% (37/120), and 31.7% (38/120) did not react. A lack of good response was found to be associated with dementia (P=0.016) in a multivariate analysis. In addition to dementia, malnutrition was frequently observed among poor responders, suggesting that these factors should be considered in vaccination studies. Chemoprophylaxis in addition to vaccination for elderly presenting dementia should be considered, particularly for those people living nursing homes.

Key Words: Influenza, vaccination, immune response, risk factors, dementia.

Some groups of patients are at increased risk for severe complications and deaths due to pneumonia and influenza. These include people aged 65 and over, adults and children with chronic cardiopulmonary conditions, renal dysfunction, metabolic disorders, or immunosuppression, and pregnant women. During influenza epidemics, approximately 90% of the deaths attributed to pneumonia and influenza involve older people. Although mortality increases with age, the presence of one high-risk medical condition increases the death rate from pneumonia or influenza by 20-fold [1].

Vaccination is still one of the most important measures of control against influenza, and it is generally recommended for people with risk factors that predispose them to higher morbidity and mortality. Currently-licensed inactivated vaccines are safe and immunogenic, inducing immunity in 60-90% of healthy young adults. Strong evidence has demonstrated that influenza vaccination of persons over 65 years is efficacious and cost effective; it reduces the incidence of disease, hospitalizations and mortality by 50% [2,3]. However, some reports have pointed out that immunogenicity in older people is generally lower [4]. Few studies have assessed the influence of health status in the elderly as a risk factor for antibody response to influenza vaccination. Elderly persons with chronic lung disease have shown inadequate immune response rates [5]. Other underlying conditions, like chronic stress and functional disability, have been associated with poorer immune response to influenza vaccine [6; 7; 8].

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There is a lack of information about the influence of health status as a risk factor for antibody response to influenza vaccination in elderly Brazilians. Recently-approved neuraminidase inhibitors have come to the market and may be used for prophylaxis, combined with immunization, during outbreaks. We investigated risk factors that may influence the immune response in influenza-vaccinated elderly people living in a nursing home.

Material and Methods

Patients

Sera were obtained from 120 annually-vaccinated nursing home elderly residents, before and after vaccination (28-45 days), previous to the 1999 Brazilian influenza season. The medical ethics committee of the Sao Paulo Federal University approved the protocol and informed consent was obtained before enrollment.

Serology

All pre and post immunization sera obtained from the elderly group were tested by an enzyme linked immunoassay (ELISA) standardized in our laboratory, based on previous reports using the same technique. Control sera included in each run were obtained from the Adolfo Lutz Institute (the National Reference Laboratory) and the assays were performed as follows:

Hemagglutination-inhibition test (HI): samples of six subjects of the healthy control group were tested for influenza antibodies to each antigen separately (H1N1, H3N2 and B), before and after vaccination (30 days), according to procedures recommended by the Centers for Disease Control and Prevention (CDC, Atlanta) in a National Reference Laboratory for Influenza Surveillance (Instituto Adolfo Lutz, Sao Paulo). Results from these patients were used as reference values for the in-house ELISA.

Enzyme immunoassay (ELISA): samples were tested by a previously-standardized ELISA [9], as follows: polystyrene plates were coated with vaccine antigens – A/Sydney/5/97 (H3N2), A/Beijing/262/95 (H1N1), and B/Beijing/184/93 (Vaxgripe 1999, Paster Mérieux Connaught) - and incubated with diluted serum samples. After washing with six M Urea for selection of high avidity antibodies, anti-human IgG-HRP was added and optical densities (OD) read.

Patterns of antibody response were established using values of the reference sera as follows: 1) Determination of differences between OD values obtained for samples of pre and post vaccination tested by EIA; 2) Comparison between those values with HI titer results; 3) Discrimination of three levels of OD (ELISA) results based on the cutoffs that corresponded to three patterns of the HI test: no increase in titers (non reactive), fourfold or more increase (good response) and any increase lower than fourfold increase (intermediate response), at least for one virus subtype of the vaccine mix. 4- After this step, all 120 pre and post vaccination samples were tested by ELISA and classified according to these cutoffs.

Risk factors

Data from multidisciplinary patient files were obtained, including demographic information, nutritional status, cardiovascular, pulmonary, neurological, metabolic and hormonal disturbances, other illnesses and drug treatment. Any episode of respiratory infections during six months after immunization was assessed. The diagnosis of neurological disturbances was based on neurologist evaluation. These variables were further analyzed together with the antibody response patterns.

Statistical analysis

Influence of risk factors were subjected to univariate and multivariate analysis and considered statistically significant at $P < 0.05$. The statistical analyses were performing in SPSS version 10.0 software. For analysis of risk factors for no antibody response to vaccine, we initially grouped all subjects with good response and intermediate response together.

Results

Study subjects were predominantly female (90%), with a median age of 84.7 years (range 65 to 100 years), almost all Ashkenazian Jews, vaccinated yearly and living in a nursing home for 8.4 years (median). There were some differences in the number of previous immunizations among patients, but all subjects were immunized the year before the study.

A fourfold antibody increase in HI titres is the conventional standard for determining a significant response to viral vaccine. Comparison between EIA and HI from the control group showed great correspondence and allowed us to define three patterns of response according to the OD levels obtained from differences between paired samples (pre and post vaccination). According to the methodology, it was

established that those EIA values below the cutoff (unchanged HI titres) were considered non-reactive ($n = 38$, 31.7%); values above 0.4 (a fourfold or greater increase in HI) were considered highly reactive ($n = 37$, 30.8%), being considered as good responders. An intermediate pattern was obtained for 45 out of 120 participants (37.5%).

Characteristics of the study group and risk factors for non-response to influenza antigen vaccine are shown in Table 1. Among the 120 patients, 63 (52.5%) were considered to have progressive dementia. The criterion of this diagnosis was based on neurologist evaluation and included minimal signs of mental deterioration as discrete memory alterations. However, the great majority of the subjects presented other impairments of neurological function. A lack of response to influenza vaccine in this study was associated with dementia in univariate analysis (odds ratio, OR = 0.5, 95% CI 0.2–0.9, $P = 0.02$ by the Fisher exact test) and in the multivariate analysis ($P = 0.016$) as well. In fact, 26 out of 38 (68.4%) of the non-responder patients had dementia and 45 of 57 (78.9%) subjects without dementia showed antibody response (data not show).

Based on a univariate analysis, the nutritional status was apparently a risk factor for poor immune response to influenza vaccine. Malnutrition gave a nearly significant value of $P = 0.067$, but probably since most of the demented presented with malnutrition a non-significant P value was found in the multivariate analysis. Investigating the elderly that presented malnutrition, only two subjects showed a good response, while eight had an intermediate pattern and 10 were non-responders. There was a strong correlation between malnutrition and the three patterns of response to vaccination ($r = 0.923$).

Absence of antibody response to influenza vaccine showed no correlation with respiratory infections. Indeed, no statistical significance was demonstrated for the use of immunomodulatory drugs (corticosteroids) or history of infections caused by herpes virus or candidiasis. The study population had a high incidence of chronic heart disease, but there was no association with a failure in the immune response to influenza vaccine, even in those elderly with another comorbidity, such as lung disease.

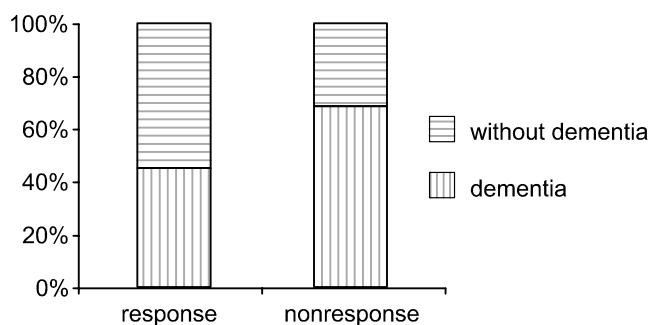
Discussion

Several reports have demonstrated low effectiveness of standard influenza vaccination in conferring adequate antibody response against influenza viral antigens in elderly people. Some authors report seroconversion rates of around 30% in elderly individuals [10,11]. Seroresponse measured by ELISA in this population showed similar results (highly reactive in 30.8%). An intermediate pattern, which was found in 31.7% of the aged people, had no strong association with optimal seroconversion, as defined for this study. Nevertheless, this intermediate response group expressed

Table 1. Clinical status of 120 aged subjects and influenza vaccine immune response

Clinical status	Total (%)	Response (n)*	Non response(n)
Malnutrition	20 (16.7)	10	10
Diabetes	12 (10.0)	10	2
Dementia	63 (52.5)	37	26
Anemia	37 (30.8)	23	14
Chronic cardiac disease	47 (39.2)	33	14
Chronic lung disease	16 (13.3)	13	3
Lung and cardiac disease	57 (47.5)	41	16
Smoking	29 (24.2)	22	7
Low thyroid hormone	15 (12.5)	12	3
Respiratory infections	40 (33.3)	27	13
Herpes virus infections	3 (2.5)	2	1
Corticoids use	13 (10.8)	9	4
Candidiasis	9 (7.5)	5	4

* Response considered any increase in antibody titers (good response plus intermediate response).

Figure 1. Influenza vaccine immune response and dementia.

* Difference significant (P=0.020).

some immune response, but it is not clear if this indicates protection against influenza infection. Those antibody titers could represent previous exposure to natural influenza virus, previous vaccination, or both [12]. The design of this study did not allow us to characterize subjects in terms of immune protection for those individuals that showed some antibody response. In addition, there was a low activity of influenza during the study period. This may explain the similar rates of respiratory infections among subjects with different antibody responses.

Protective efficacy of the influenza vaccine in the elderly depends on a sufficient antigenic match between the vaccine and epidemic viruses, on the immunogenicity of the vaccine (viral strain) and on the health status of the vaccine recipient [13,14]. In this study a patient group matched by age, previous vaccination status, ethnicity (Ashkenazian Jews) and time living in a nursing home was analyzed, and health status became the single important variable for seroresponse of the influenza vaccine.

Dementia was strongly correlated with poor immune response in vaccine recipients among all the risk factors that we analyzed. Evolution to a demential status may be the result of multiple mechanisms occurring at the same time, and some degenerative processes may affect the immune system. The degenerative cortical alteration is still poorly understood and is usually linked to functional mechanisms involving disability in activities of daily living. These conditions provoke a frequent need for care support for daily activities, which result in additional frustration, depression and chronic stress. The association between poor immune response and chronic stress has already been described [6]. Disability in older people has also been associated with lower immune response to influenza vaccine [7]. Similarly, depressed older people were reported to get cold more easily [15], and disabled depressed elderly show reduced immunoreactivity to influenza vaccine [16]. In addition, influenza outbreaks among nursing home residents with disabilities could lead to important morbidity and mortality [17]. Hence disabled and demented elderly are at higher risk for non-response to influenza vaccine, probably for influenza disease and influenza-related complications as well.

We did not find an increased risk for failed influenza vaccine response among those subjects with a history of conditions that might point to an immune depression status, such as corticosteroid use or infections due to herpes virus and candidiasis. All those risk factors are referred by physicians at a very low frequency to allow assessing differences among groups.

Nutritional deficiency and impaired immune function have been reported in aged people, often simultaneously [18,19]. However, the relationship between these conditions is still controversial and independence of the two phenomena has also been reported [20]. Factors that may contribute to these conflicting results are the several parameters proposed for nutritional status assessment, including biochemical, hematological, and protein markers. Some previous reports

have demonstrated the beneficial influence of nutritional support for antibody response after influenza vaccination in the elderly [21,22]. Indeed, others have suggested the effects of trace elements and vitamin supplementation for increasing antibody titers and reducing influenza infections [23,24]. In our study, malnutrition did not reach significance as a risk factor for non-response against influenza vaccine antigen. However, antibody pattern analysis of each group by itself suggested that nutritional status could influence progression of impaired immune response, expressed by an increased rate of failure in antibody response to influenza vaccine. These results confirm previous studies that indicate a higher frequency of influenza vaccine response among institutionalized elderly with a eutrophic status [25].

Specific anti-influenza therapy has been used to control outbreaks of influenza in older nursing home residents [13,26]. Since vaccine efficacy may be reduced because of impaired immune response, the risk of influenza disease increases in nursing homes during an epidemic season. Thus, identification of risk factors that contribute to failed vaccine immune response, such as dementia and malnutrition, are important in considering prophylactic administration of antiviral agents that can provide protection additional to that provided by vaccination [27].

In summary, we found that the frequency of non-reactivity to influenza vaccine antigens was consistent with published reports on elderly populations. Although the increase in antibody titers was not optimal among subjects with dementia and/or malnutrition, this should not be a reason for not vaccinating them. Indeed, elderly people in a nursing home with malnutrition and/or dementia should be considered for antiviral chemoprophylaxis, besides immunization, during epidemic influenza outbreaks.

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