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The Effect of Childhood Viral Infections on the Incidence of Multiple Sclerosis

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Abstract

***Background*:** In this study, the history of viral infections of measles, chickenpox and mumps in childhood was compared between the two groups of adults with multiple sclerosis (MS) and healthy people.

***Materials and Methods*:** In this case-control study, a group of 45 MS patients and a group of 135 healthy people who were similar based on some variables were invited. Patients had a definite diagnosis of MS and control group consisted of people accompanying MS patients. Data were collected by a trained expert in face-to-face interview sessions. For data analysis, odds ratio index was calculated and 95% confidence interval was also computed. The mean age of respondents at the time of viral infections was also compared between the two groups

***Results*:** The proportions of infected people by measles, chickenpox and mumps among MS patients were 58%, 56% and 40%, respectively. These proportions in healthy group were 68%, 52% and 44%, respectively. There was not any significant difference between these proportions in the two groups. Mean age of morbidity for measles, chickenpox and mumps among patients were 6.8±3.1, 8.7±2.98 and 10.6±4.7 years, and were significantly higher that these mean ages (4.1±2.1, 5.3±3.1 and 8.4±2.8, respectively) among healthy people (p<0.001).

***Conclusion*:** Although there was not any significant difference between the history of morbidity of measles, chickenpox and mumps in the two groups of MS patients and healthy people, the mean ages of these viral infections among MS patients were significantly higher than healthy people.

Introduction

Multiple Sclerosis (MS) as a progressive disease of Central Nervous System (CNS) is a result of interaction between some congenital and environmental factors [1, 2]. The effect of various environmental factors including infectious disease on the incidence of MS has been studied by many researchers [3-6]. Among infectious agents, viruses were more suspected and studied than other infectious disease agents of which Epstein Barr virus was the most frequently studied agent [7-10]. It has been well known that MS disease as an immunity system disorder is generated in a complicated process. However, some might play a trigger role such as stressors [11-14].

Wild spices of measles, mumps and rubella viruses are infectious agents of CNS [15]. Measles virus with high virulence and pathogenecity causes a permanent immunity in human body after the infection [16]. This can explain the probable association between viral infections and MS in adulthood.

Although the effect of infectious disease on MS has frequently, been confirmed, but the mechanism of this effect is not clear enough. Therefore investigations are still needed to clarify how infections, in particular, viral infections cause MS disease. Previous studies did not reject the association between the respondents' age at the time of viral infections and the risk of MS in adulthood as well as the effect of viral infections on the incidence of MS [17-18].

According to Shoenfeld et al. study there are three explanations for the effect of viral infections on such an autoimmune disorder (MS). First, infections agent become a substance similar to a familial antigen due to some molecular changes. Second explanation says that a mechanism is generated in immune system which activates B lymphocytes that in return is accounted for antibodies that destroy body tissues including CNS. The third explanation is called "innocent bystander" which says immune system is activated against other infection agents (such as viral agents) and generates T lymphocytes and also increases the level of cytokines which destroy myelin sheets in CNS [19].

In the present study, the history of viral infections of measles, chickenpox and mumps in childhood was compared between the two groups of adults with multiple sclerosis and healthy people. Further the age of respondents at the time of these infections was compared between the two groups.

Materials and Methods

In this case-control study, 45 MS patients and 135 healthy people who had not any history of CNS related disease were recruited. The two groups were matched based on some important factors including age, gender, social class, educational status and marital status. Patients were selected from the list of all MS patients who were registered as definite diagnosis of MS in the two neurologists' private offices in Tehran and Shiraz. Healthy people in the control group were invited from patients relatives and those who were accompanying patients. These people were similar to patients based on important factors listed above. Since most of accompany people were patients first degree relatives such as brother or sister, these people were similar to the patients group congenitally.

Data were collected using a checklist which was completed by trained expert in interview sessions. In order to protect interviewer bias, interviewer was not aware of the respondents' assignment to the two groups of case and control. If it was impossible to hide patients' disease from interviewer, data were collected from Patients relatives such as father, mother sister and brother. In cases that it was difficult for patients to remember the history of morbidity, the questions were asked from parents or other first degree relatives. Interviews were performed in the neurologists private offices and when patients and their accompanies were sitting in waiting room. Consent form was taken from respondents after they relieved in-detailed information about the objectives and the methods of the study.

There were two sections of questions in study checklist. Seven demographic items were asking about age, gender, annual family income, educational status, occupation, smoking, living place and comorbidity.

In the other section, there were 13 special items about the history of viral infections of measles, chickenpox and mumps in childhood. These items were asking about the viral infections occurrence history and the age of respondents at the time of infections as well as the history of vaccination against them. There was an additional item asking about the history of any other disease in childhood. There was not any question about the type of MS, because it was not important in our study.

Sample size was calculated based on the results derived from a pilot study by which the proportions needed were obtained. Regarding 99% confidence interval, test power of 90% and the least amount of difference predicted between the two groups, 45 people were calculated as the sample size for each group. We considered 45 patients in the case group and 135 healthy people as the control group. In order to eliminate the effect of confounding variables, the number of people in the control group was three times higher than this number in the case group. The history of viral infections and the age of respondents at the time of infections were the two main independent variables and the incidence of MS was dependent variable in our study. Variables such as age, gender, social class, educational status, and marital status were matched in the two groups of case and control. Data were analyzed in SPSS-14. Further to descriptive statistics methods that was used to present the results in tables and by numerical indices, parametric tests (such as *t*-test and proportion test) and non-parametric tests were used to compare groups. Odds ratio and its 95% confidence interval was also calculated to show the level of risks. Mean age of respondents at the time of viral infections was also compared between the two groups

Results

Information about some demographic variables in the two groups of case and control are presented in table 1. This table shows that the two groups were similar based on these variables and there is no significant difference between the two groups (Table 1).

Mean age in the two groups of case and control were 27.4±7.5 and 28.4±6.6 years, respectively. Three fifth (60%, N=27) of respondents in the case group were female. This proportion was identical to the proportion of female respondents in the control group (60%, N=80). Table 2 shows the number of respondents in case and control groups who reported the history of viral infections (measles, mumps and chickenpox) in their childhood.

As it is present in table 2, 58% (N=25) of MS patients reported Measles in their childhood, and this proportion among healthy group was 52% (N=68). The odds ratio among respondents who reported the history of measles in childhood to develop MS in their adulthood was 1.28 comparing to respondents who did not reported this history. The proportions of respondents in case group (MS patients) who reported the history of mumps and chickenpox in their childhood were 40% (N=16) and 56% (N=24), respectively. These proportions in control group (healthy people) were 36% (N=44) and 40% (N=52), respectively. Odds ratios calculated for mumps and chickenpox were 1.92 and 1.2. Our analysis showed that none of these three ORs were statistically significant. In the next step of analysis, the mean age of respondents at the time of their viral infections was compared in the two groups of case and control.

Table 3 shows the frequency distribution of respondents in the two groups based on their age at the time of their viral infections of measles, mumps and chickenpox. Although, our results did not show significant difference between the two groups of case and control based on the history of these viral infections in childhood but respondents mean age at the time of viral infections of measles and chickenpox was significantly different between the two groups. The findings showed that mean ages of respondents in the case group at the time of measles (6.8±3.1 years) and chickenpox (8.7±2.98 years) infections in childhood were significantly higher than these mean ages (4.1±2.1 and 5.3±3.1 years, respectively) among respondents in control group (t=4.8, p=0.0001 and t=4.6 p=0.0001, respectively). In case of mumps, mean age of morbidity in childhood among MS patients (10.6±4.7) was significantly higher than this mean age among healthy people (8.4±2.8), (t=2.3, p=0.05).

Table 1. Frequency distribution of respondents in the two groups of case and control based on some demographic variables.

Demographic variables		Case group N (%)	Control group N (%)	Total N(%)	*p*-Value
Age(yeai)	<19	7(15.5)	24(17.8)	31(17.2)	>0.05
	20-29	24(53.3)	74(54.8)	98(54.4)	
	>30	14(31.2)	37(37.4)	51(28.4)	
Gender	male	18(40)	54(40)	72(40)	0.79
	female	27(60)	81(60)	108(60)	
Marital status	single	21(46.7)	60(44.4)	81(45)	0.71
	married	24(53.3)	75(55.6)	99(55)	
Birth season	spring	13(31.7)	34(27.8)	47(28.0)	0.7
	summer	10(24.4)	36(28.3)	46(27.4)	
	autumn	12(29.3)	31(24.4)	43(25.6)	
	winter	6(14.6)	26(20.5)	32(19.0)	
Social class	low	10(23.8)	23(21.3)	33(22.0)	0.95
	moderate	20(47.6)	53(49.1)	73(48.7)	
	high	12(28.6)	32(29.6)	44(29.3)	
Educational status	illiterate	2(4.4)	4(3.0)	6(3.7)	0.68
	primary	2(4.4)	6(4.4)	8(5.0)	
	secondary	6(13.3)	20(14.8)	26(16.3)	
	high school	25(55.6)	67(49.6)	72(45.0)	
	higher	10(22.3)	38(28.2)	48(30.0)	

Table 2. Frequency distribution of respondents in the two groups of case and control based on the history of measles, mumps and chickenpox infections in their childhood

Viral Infections		Case group N(%)	Control group N(%)	Odds Ratios	CI 95%
Measles	Yes	25(58)	68(52)	1.28	0.64-2.57
	No	18(42)	63(48)		
Chickenpox	Yes	24(56)	52(40)	1.92	0.96-3.85
	No	19(44)	79(60)		
Mumps	Yes	16(40)	44(36)	1.2	0.58-2.49
	No	24(60)	79(64)		

Table 3. Frequency distribution of respondents in the two groups of case and control based on their age at the time of measles, mumps and chickenpox infections in childhood

Respondents Age at childhood		Case group N(%)	Control group N(%)	Odds Ratios	CI 95%
Measles	0-7	15(60)	64(94)	2.8	1.2–6.5
	>8	10(40)	4(6)		
Chickenpox	0-7	9(37)	43(83)	2.2	1.3–3.7
	>8	15(63)	9(7)		
Mumps	0-6	4(25)	13(24)	1	0.48–9.0
	7-11	7(44)	36(68)	2.1	0.85–2.75
	>12	5(31)	4(8)	1.5	

Discussion

Comparing demographic variables of age, gender, social class, marital status and educational status in the two groups of case and control showed that respondents in these two groups were well-matched based on these variables. Eliminating the effect of these variables on the association between viral infections history in childhood and MS morbidity in adulthood increases the validity of this association as a causal relationship. Our findings showed that the history of viral infections of measles, mumps and chickenpox in childhood has no effect on the probability of MS morbidity in adulthood as there was no significant difference between the history of these viral infections in childhood among MS patients and healthy people who were matched based on some demographic variables.

According to these results, it is impossible to conclude that the history of viral infections of measles, mumps and chickenpox in childhood would increase or even decrease the level of risk for MS morbidity in adulthood. This result is in concordance on Bager et al. findings which is conducted on a big population of MS patients and their controls. Bager et al. concluded that the proportions of MS patients with the history of measles and mumps in their childhood were not significantly higher than proportions of healthy people with the history of these infections in their childhood [20]. In contrast, Zaadstra et al. concluded from their results that the proportions of respondents with the history of measles and mumps in their childhood among MS patients were significantly higher than these proportions in the control group [21]. Overall, the research studies which reject the association between these viral infections history in childhood and MS morbidity in adulthood were more frequent than investigations in which this association was confirmed.

Many studies, however, confirmed the association between Epstein-Barr virus infection in childhood and MS morbidity in adulthood. In these investigations, similar immune system reaction was observed between this viral infection and body reactions in which myelin is destroyed in CNS [22]. However, Lindsey and colleagues studied these similar reactions and concluded that immune system response against this viral infection in MS patients neither increase nor decrease [23].

Our findings showed important difference between the two groups of case and control. Mean ages of MS patients at the time of measles, mumps and chickenpox in their childhood were significantly higher than these mean ages among respondents in control group. In other words, there is a causal relation between the age of respondents at the time of these viral infections (measles, mumps and chickenpox) in childhood and the risk of MS disease in adulthood. This result is confirmed by other researchers [24-26]. However, some other rejected this relationship [27]. This relation could be interpreted in different ways. For instance, the difference between mean ages of MS patients and healthy people at the time of the viral infections might be due to a third variable that affect both the age of respondents at the time of the viral infections and the incidence of MS in forthcoming years. More serologic and immunologic studies would shed light on the process of this relation.

Overall, we concluded from our findings that although the history of viral infections of measles, mumps and chickenpox in childhood has no association with the incidence of MS disease in adulthood, but there could be a relation between the age of respondents at the time of these infections in childhood and the level of risk for MS morbidity in adulthood. There were some limitations in our study of which despite the blinding method used in this study, in some cases when interviewer was recorded respondents explanations to the queries, he/she mentioned

to his/her situation as being suffered from MS, and interviewer became aware of their assignment to the groups. Nevertheless, interviewers were well educated in orderm to minimize both the interviewer and interviewee bias when collecting and recording the data.

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Authors' Contributions
All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest
The authors declare no conflict of interest.

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