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Breastfeeding is associated with lower risk for multiple sclerosis

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Abstract

Background: Multiple sclerosis (MS) is an autoimmune disease with known genetic and environmental susceptibility factors. Breastfeeding has been shown to be protective in other autoimmune diseases.

Objective: This case-control study analyzed the association of breastfeeding in infancy on the risk of developing MS.

Methods: A case-control study was performed in Berlin of 245 MS patients and 296 population-based controls, who completed a standardized questionnaire on their history and duration of breastfeeding in infancy and demographic characteristics. Univariable and multivariable logistic regression analysis was performed to investigate the association between breastfeeding and MS. The multivariate model was adjusted for age, gender, number of older siblings, number of inhabitants in place of domicile between ages 0 and 6 (categorized in each case), and daycare attendance between ages 0 and 3.

Results: In multivariable analysis, breastfeeding showed an independent association with MS (adjusted OR 0.58; $p = 0.028$). However, with no breastfeeding as reference, the protective effect only emerges after four months of breastfeeding (multivariable analysis for ≤ four months adjusted OR 0.87; $p = 0.614$ and for > four months OR 0.51; $p = 0.016$).

Conclusion: The results of this case-control study support the hypothesis that breastfeeding is associated with a lower risk of MS. These results are in line with findings of previous studies on other autoimmune diseases, in which breastfeeding was shown to have protective effects.

Keywords

Multiple sclerosis, risk factors, breastfeeding

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Introduction

Multiple sclerosis (MS) is an autoimmune disease with high and increasing prevalence in developed countries.[1] The prevalence of autoimmune conditions like allergic disease, Crohn's disease and type 1 diabetes is highest in Western countries, which may indicate a correlation with Western lifestyle.[2] Previous infection with Epstein-Barr virus, vitamin D insufficiency and smoking are established risk factors for developing MS.[3–7] Breastfeeding has been identified as protective for bronchial asthma, atopic dermatitis, type 1 diabetes mellitus and Crohn's disease in previous studies,[8–12] suggesting that human milk has immunomodulatory properties. In some diseases only a duration of breastfeeding > six months has a protective effect,[13] whereas in other cases, such as celiac disease and excess body fat, a gradual influence of breastfeeding duration has been shown.[14,15] For this reason, breastfeeding is

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recommended by the World Health Organization as the sole form of nutrition for six months after birth. The association between breastfeeding and MS has so far been investigated in two studies, which yielded contradictory results. Spencely and Dick found no association between breastfeeding and MS risk,[16] whereas in a study comparing patients with MS who were breastfed for 8.4 months with controls who were breastfed for 12.5 months, Pisacane et al. showed an association between prolonged breastfeeding and decreased risk of MS.[17]

We performed a case-control study in Germany to investigate a possible association between breastfeeding and occurrence of MS.

Methods

Participants

The design of the study has been reported previously.[18] Briefly, cases were recruited from patients with either clinically isolated syndrome (CIS) and definite MS, who met the 2005 revised McDonald's criteria for MS[19] and attended the MS ambulatory center in the Department of Neurology, Charité – Universitätsmedizin Berlin, at its two branches in Berlin-Mitte and Berlin-Steglitz between 2006 and 2009. We included patients with CIS, relapsing–remitting, secondary progressive and primary progressive MS at different stages of disease. A total of 429 MS patients meeting inclusion criteria were invited by letter to participate in the study; of these, 33 letters were returned as "address unknown"; 245 patients agreed to participate and returned standardized questionnaires, yielding a participation rate of 62%. Controls were selected from two general practitioners' (GP) practices in Berlin-Prenzlauer Berg and Berlin-Zehlendorf, which serve approximately the same catchment areas as those of the MS outpatient clinics. Here, patients without MS, CIS or any other inflammation of the central nervous system (CNS) were invited to participate in the study by the receptionist. If patients verbally agreed, the standardized questionnaire, which was identical to that sent to MS patients, was directly distributed to the patient during the GP visit by the GPs' medical staff between October and December 2009 (Prenzlauer Berg) and between March and May 2010 (Zehlendorf). Because of the method of recruiting controls, estimating a response rate is not possible. In total, questionnaires from 296 controls were returned. The study was approved by the local ethics committee of Charité – Universitätsmedizin Berlin (EA1/121/08), and all MS patients provided written informed consent.

Inclusion and exclusion criteria

Inclusion criteria for patients in this study comprised 1) the diagnosis of either definite MS according to the revised 2005 McDonald criteria or CIS, 2) an age of 18 to 80 years and 3) the ability to give signed, informed consent. Inclusion criteria for controls in this study comprised 1) no diagnosis of MS, CIS or any other inflammation of the CNS, 2) no other diagnosis of a severe medical or psychiatric disorder, 3) an age of 18 to 80 years and 4) the ability to give signed, informed consent.

Questionnaire

The standardized questionnaire completed by cases and controls covered demographic characteristics (sex, year of birth), past medical history of asthma, type 1 diabetes and rheumatic diseases, and history and duration of breastfeeding. In all cases, mothers or relatives of patients and controls provided the information about breastfeeding.

Statistical analysis

In the case-control study, adjusted odds ratios (OR) were estimated from multivariable logistic regression analysis, in which MS was applied as the dependent variable. We defined a priori to adjust the effect of breastfeeding on the probability of MS for all the factors shown to be independent predictors for MS in Conradi et al.[18] by adjusting for the factors age, gender, number of older siblings, number of inhabitants for place of domicile between ages 0 and 6 (categorized in each case) and daycare attendance between ages 0 and 3. We also assessed the hypothesis that the significance and effect size of the factor breastfeeding depends on the duration of breastfeeding,[10,17] or more precisely, that a minimum of four months of breastfeeding is necessary for a protective influence. We divided duration of breastfeeding into three categories: no breastfeeding (reference category), breastfeeding $\leq$ four months and breastfeeding $>$ four months. To comply with the principle of parsimonious modeling, we used an automatic variable selection for model choice (stepwise backward selection method). The goodness of fit of each model was evaluated using the Hosmer and Lemeshow test. All p-values were two-sided. All univariate analysis was exploratory, no multiple hypothesis testing was performed and therefore we did not control the family-wise error rate. Data analysis was performed using SPSS PASW 18 for Windows. Analysis was restricted to patients who had submitted completed questionnaires. The percentage of missing values ranged from 0% in the variable age to 39.6% (patients) and 37.8% (controls) for duration of breastfeeding. Frequency of responses was similar between cases and controls.

Results

Questionnaires from 245 MS patients and 296 controls were evaluated. Descriptive demographic characteristics for cases and controls are shown in Table 1. Our control group included more men than in the MS group.

Table 1. Demographic data of all patients and controls.

Characteristic	Controls, *N*= 295	MS patients, *N*= 245
	n (%)	*n* (%)
Age, years		
Median (IQR)	40.0 (27–54)	46.0 (37–54)
Age group, (based on sample quartiles)		
<=31	107 (36.3)	29 (11.8)
32–43	63 (21.4)	73 (29.8)
44–54	52 (17.6)	84 (34.3)
>= 55	73 (24.7)	59 (24.1)
Female	182 (61.5)	181 (73.9)
Daycare attendance between ages 0 and 3	117 (40.3)	61 (25.4)
Medical history		
Asthma	24 (8.1)	6 (2.4)
Diabetes mellitus	4 (1.4)	5 (2.0)
Rheumatic diseases	6 (2.0)	3 (1.2)
Living in a city between ages 0 and 6 with inhabitants:		
< 10,000	24 (8.9)	42 (17.7)
10,000–100,000	68 (25.3)	61 (25.7)
> 100000	177 (65.8)	134 (56.5)
Number of older siblings		
0	135 (46.7)	125 (51.7)
1	76 (26.3)	82 (33.9)
2	49 (17.0)	31 (12.8)
>=3	29 (10.0)	4 (1.7)
Breastfed		
no	43 (18.9)	67 (31.2)
yes, <= four months	69 (30.4)	81 (37.7)
yes, > four months	115 (50.7)	67 (31.2)

MS: multiple sclerosis; IQR: interquartile range.

Table 2. Results of uni- and multivariate analysis for breastfeeding as a dichotomous risk factor for the probability of multiple sclerosis (MS) adjusted for the independent MS-predictors defined in Conradi et al.[18](age, gender, number of older siblings, number of inhabitants in place of domicile at age 0–6, and daycare attendance between ages 0 and 3) and as a categorical factor.

	Univariate			Multivariate§		
	OR	95% CI	*p*-value#	OR	95% CI	*p*-value
Breastfed	0.45	0.29–0.69	<0.0005	0.58	0.35–0.94	0.028
Breastfed no	1.00			1.00		
Breastfed ≤ four months	0.75	0.46–1.24	0.311	0.87	0.49–1.52	0.614
Breastfed > four month	0.37	0.23–0.61	<0.0005	0.51	0.29–0.88	0.016

§: stepwise backward selection; #: Fisher's exact test; OR: odds ratio; CI: confidence interval.

Multivariable logistic analysis revealed a significant negative association between breastfeeding and the development of MS (Table 2). The adjusted OR with 95% confidence interval (CI) was 0.58 (0.35–0.94). Duration of breastfeeding was also an independent factor for the risk for MS (Table 2). However, great discrepancy was found between the effects of breastfeeding ≤ four months and breastfeeding > four months. For this purpose we developed an alternative model with breastfeeding as a three-level categorical variable (with no breastfeeding as reference category). Overall breastfeeding proved to be a significant risk factor (p-value = 0.030). However, while breastfeeding ≤ four months did not significantly affect the risk for MS in comparison to no breastfeeding (adjusted OR with 95% CI 0.87 (0.49–1.52), p-value = 0.614), breastfeeding > four months did show a significant effect. Here, the adjusted OR, with no breastfeeding as reference, was 0.51 (0.29–0.88), p-value for the Wald statistic = 0.016. This suggests that rather than breastfeeding in general, only breastfeeding of more than four months has a protective effect against MS.

The inclusion of the factor breastfeeding in modeling the logit of MS did not significantly alter the relevance and significance of the other predictors. Discrimination (AUCROC 0.752 resp. 0.738) and calibration (Nagelkerke R^2 0.261 and 0.236 for cases and controls, respectively) of the two models were satisfactory.

Discussion

Our results show that breastfeeding is inversely associated with the occurrence of MS, and breastfeeding might be a possible protective factor against MS. However, further analysis showed that the protective influence is established only after at least four months of breastfeeding.

Our findings are in line with previous studies for asthma, atopic dermatitis and Crohn's disease,[8–10] in which breastfeeding was also shown to be protective. However, in particular for asthma and atopic dermatitis, studies to date have been prospective and focused on outcome in early childhood. Furthermore, some of these studies actually showed higher incidence of these diseases in breastfed children; however, this is arguably the result of the study designs in question, which included no randomization, no blinding and exhibited confounding factors.[20,21] Usually mothers with a history of asthma and or atopic dermatitis prefer to breastfeed to prevent these diseases in their children, which results in a higher genetic risk in breastfed children.[22] Studies investigating the effect of breastfeeding on inflammatory bowel diseases have focused on adults using a case-control study design, but in most cases were not able to achieve statistically significant results demonstrating protective effects. The low quality of studies and biased results have been discussed as possible explanations for the lack of significance. A systemic review using meta-analysis, which factored in the varying quality of studies, found a protective role of breastfeeding against ulcerative colitis and inflammatory bowel disease.[23]

As mentioned above, only two studies, both with a case-control design, have investigated the link between breastfeeding and MS. While Spencely and Dick could not find an association, Pisacane et al. showed that controls are likely to have been breastfed for a longer period of time than MS patients.[16,17] This observation fits with our data to show for the first time in a larger population and considering other environmental factors that breastfeeding has an independent association with the occurrence of MS. Duration of breastfeeding was also demonstrated as playing a crucial role.

As this was a retrospective case-control study, we have to bear in mind possible limitations and misclassification as a result of recall and selection bias: 39.6% patients and 37.8% controls were not able to answer questions on the duration of breastfeeding. This may introduce a bias regarding association between breastfeeding and MS risk, limiting the validity of our results. Furthermore, the controls were significantly younger than the average age of patients, which may influence the recall bias as well. Our study included MS patients with different disease types and duration of disease, recruited from our outpatient clinics. While breastfeeding may also influence clinical aspects of MS, subgroup analysis and correlation with course or onset of disease was not possible due to the small number of cases. Future studies of larger groups could answer these questions. A further possible limitation could have resulted from the difference between the recruitment strategies for MS patients and controls and the missing matching that can introduce selection bias. On the other hand, it is difficult to recruit healthy controls with an age distribution similar to that of patients using the same recruitment strategies. The fact that our control subjects were recruited from patients visiting GPs increases the possibility that they may exhibit a higher prevalence of other diseases, in particular autoimmune diseases, than healthy controls. As mentioned above, other known environmental risk factors for MS exist that were not included in our questionnaire. Some of these may be confounders. For example, perhaps women who breastfeed are less likely to smoke or prefer a healthier lifestyle. Unfortunately, we do not have data for social economic status or age of the mother at birth; both may be associated with breastfeeding, and if different in MS cases and controls, may explain the reported finding. To overcome these limitations, a prospective population-based study should be performed. Because MS is quite a rare disease with a manifestation in young adults, such a project is nearly impossible to realize.

The underlying mechanism of breastfeeding's protective effect against MS has not yet been elucidated. However, human milk has been shown to influence the immune system of offspring by means of various mechanisms, including immunomodulatory effects by interleukin (IL)-10 production and the anti-inflammatory properties of transforming growth factor (TGF)-β.[24–26] On the other hand, several studies on environmental risk factors for MS also show the importance of environmental influences in infancy and youth. This evidence is supported by well-known migration studies and more recent findings that the month of birth can influence the risk of developing MS.[27–30] Correlation and interaction between these different factors in early life have not yet been investigated. Clearly, the increasing incidence of MS is to some extent explained by the Western lifestyle, which incorporates several risk factors, including low rates of breastfeeding.

In conclusion, this study indicates that breastfeeding for more than four months may be protective against MS. These results are in line with findings of previous studies of other autoimmune diseases where breastfeeding was shown to have protective effects and, as such, lack of breastfeeding may identify an additional environmental risk factor for MS. Although the study was subject to some limitations, it has implications for mothers wanting to protect their

offspring from MS. Our data should be confirmed in larger studies with matched controls, a different geographical recruitment area and that take into account known environmental and social risk factors.

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Conflict of interest statements

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