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Original Article:

The Association of Breastfeeding and Multiple Sclerosis: Does Formula have any other Risks?

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Abstract

Introduction: Multiple sclerosis (MS) is a complex autoimmune disorder of the central nervous system that affects millions of individuals worldwide. While the etiology of MS remains multifactorial and incompletely understood, emerging evidence suggests that various environmental and lifestyle factors may influence its onset and progression. Among these factors, breastfeeding has gained attention as a potential protective mechanism against the development of MS. However, it is unclear whether breastfeeding, colostrum feeding, and formula or cow milk intake during infancy have any relationship with the development of MS, which type of MS would be influenced further, and if breastfeeding has any effect on the age of MS onset.

Materials and Methods: 100 MS patients and 100 healthy controls took part in this study. Male to female ratio was similar in both groups. Demographic characteristics and history of breastfeeding were collected via a questionnaire.

Results: The mean duration of breastfeeding was considerably lower in some MS patients who had onset of the disease before or at the age of 30 compared to those with onset after 30 years (15.2 $\pm$ 10.2 versus 19.5 $\pm$ 11.0 months, P = 0.09). Breastfeeding with a duration of more than 11 months was more frequent in the latter group (83% versus 60%, P = 0.044). Patients with age-onset before or at 30 also revealed a higher rate of feeding with formula or cow milk (56.5% versus 33% and P = 0.063). More frequent feeding with formula or cow milk among MS patients compared to healthy controls (51% versus 31%, P=0.006) was observed.

Conclusion: Formula or cow milk consumption during infancy may be a considerable risk factor for developing MS besides other etiologic factors.

Keywords: Breast-feeding, Colostrum, Formula feeding, Multiple sclerosis

1. Introduction

Multiple sclerosis (MS) is a demyelinating autoimmune disease with a worldwide distribution that is more frequent in Europe, Canada, the United States, New Zealand, and Southern Australia, but relatively rare in Asia [1-4].

The complex etiology with multifactorial causation regarding genetic and environmental factors has gained acceptance internationally [5-8]. However, geographical variability indicates that genetic characteristics influence familial risk while population risk appears to be strongly determined by environmental and lifestyle factors [8] Infections, cigarette smoking and vitamin D exposure are the

most substantiated environmental risk factors [9-12], but the question as to whether diet during infancy or childhood has any effects has been debated.

Feeding with breast milk during the first years of life has demonstrated to have great effects on protection against infections (like enterocolitis) or low prevalence of some diseases (e.g., insulin depended diabetes mellitus or cancer in breastfed [13-16] However, in MS which is proposed as an autoimmune disease triggered by viral infections, the role of breastfeeding during infancy is less considered [6]. Besides, the effects of breastfeeding attributed to the contents of immunoglobulin, its essential fatty acids may have a function in the building of myelin during the first years of life. Consequently, lack of breastfeeding and excessive consumption of cow milk during infancy could result in the formation of unstable myelin which is susceptible to injury [17].

On the other hand, colostrum, initial milk produced in the first days of post-partum has a different structure compared to the one produced on other days with higher levels of immunoglobulin, growth factor, and cytokines [18]. Despite valuable effects, some mothers do not feed their neonates with colostrum because of a cultural old belief in Iran. The current study is based on the hypothesis that lack of breastfeeding during infancy could be a risk factor for the appearance of MS later in life. Therefore, we assessed whether breastfeeding, colostrum feeding, and formula or cow milk intake during infancy have any relationship with the development of MS; which type of MS would be influenced further, and if breastfeeding has any effects on the age of MS onset.

2. Materials and Methods

Design

A case-control study was conducted to evaluate the possibility of feeding with formula in infancy as a potential risk factor for multiple sclerosis and if breastfeeding could have any protective effects.

Cases

Patients included in the study met all of the following inclusion criteria: (1) age from 20 to 45 years, (2) definite diagnosis of multiple sclerosis according to McDonald criteria[19], (3) Persian ethnicity, (4) living in Iran in the first fifteen years of life. Exclusion criteria were: (1) a better explanation for the patient's symptoms and signs in laboratory tests including autoimmune and vasculitis markers, (2) an ethnicity other than Persian, (3) another accompanying medical disease. All patients attended the neurological outpatient department of Shariati General Hospital.

Control group

One of the frequent selection biases in case-control studies about multiple sclerosis is different socioeconomic levels because some studies support the association between high socioeconomic status and MS [20-21]. To prevent this, we selected the control group from healthy persons who came to the same hospital as a patient (other than MS) family member. They matched the cases in terms of sex and age (plus or minus 2 years standard deviation).

Study procedure

All enrolled subjects including 100 cases and 100 controls gave written informed consent prior to participation and after discussing the aims and effects of the study. A questionnaire was designed containing information about age, gender, birthplace, residence in the first 1.5 years of life, educational level, marital status, type of birth, breastfeeding during infancy and its months, feeding with colostrum at birth, exclusive feeding with formula or combined with cow milk during infancy, family history of MS and smoking in patient or his/her roommates. The questionnaire was administered to all subjects by the same interviewer who was a neurologist. For missing data and if the subject did not know the answer, the interviewer phoned them as soon as possible after providing the information from their mothers. The clinical type of MS was denoted by the neurologist. For intragroup comparison, patients were classified as relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP), or progressive relapsing (PR).

Statistical analysis

Cases and controls were compared by the t-test, Fishers exact, or Chi-square test where appropriate. The backward stepwise (Likelihood Ratio) binary logistic regression analysis was performed to calculate the Odds Ratio adjusted for potential confounders related to the MS (including a family history of MS, smoking, and educational level) at the $p < 0.2$ level in the univariate analysis. All analyses were done using the Software Package for the Social Sciences (SPSS, version 21). P-value less than 0.05 was considered statically significant.

3. Results

Subjects disposition

One hundred MS patients and the same number of healthy controls took part in this study. Male to female ratio was similar in both groups (12/28).

Demographic characteristics and comparison of cases and controls are presented in Table 1. Despite considering selection bias in the context of socioeconomic state, the two groups differed significantly in terms of educational levels (p: 0.002).

Table 1. Characteristic comparison of multiple sclerosis (MS) patients and controls

Characteristic	MS N=100	Control N=100	PV
Age, mean (SD), years	30.9 (7.1)	31.0 (7.3)	0.969
Educational status:			0.002
(diploma or lower/academic education)	48/51	70/30	
Smoker%	13	4	0.022
Passive smoker in childhood%	44	34	0.147
History of Stress%	51	26	<0.001
Family history of MS%	14	2	0.002
Type of birth (vaginal/cesarean section)	94/6	96/4	0.743

Association between MS and breastfeeding

The mean duration of breastfeeding was 16.2 ± 10.5 (with a median of 20.5) months in MS patients and 17.8 ± 10.2 (with a median of 24) months in controls which reflects a slightly lower duration of breastfeeding in the MS group, but t-test analysis revealed no significant difference. (P = 0.267). Breast feeding for more than 6 months was 71% in MS patients and 78% in the control group and subsequent analysis yielded similar findings in both groups (P=0.256). After adjustment for matching factors, the odds ratio (OR) of MS related to a different cutoff of breastfeeding months was about 1.5 (with 95% CI: 0.8 – 2.9) (Table 2).

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Association of Colostrum and MS

A total number of 76 people in the MS patient group had been fed with colostrum during the first days after birth. In controls, which contained 77 people chi-square test was used to determine if there is lower total colostrum feeding among MS patients which reached no significant differences between the two groups (P=0.863).

Formula or cow milk and MS

There was a piece of strong evidence for more frequent feeding with formula or cow milk among MS patients compared to healthy controls (51% versus 31%, P=0.006) Ten cases and 6 controls had missing information on feeding with formula or cow milk which were excluded from the analysis.

To investigate the association of feeding with formula or cow milk with MS, we constructed a Logistic Regression model with this variable instead of the breastfeeding variable and thus observed that feeding with formula or cow milk was associated with a higher risk of MS (Table 2). In order to adjust the potential risk factors that were elicited in the univariate analysis including educational level, smoking status, history of stress, and family history of MS, a multivariate analysis was performed. This analysis yielded the attenuation of crude OR in the assessment of the relationship between different types of milk feeding during infancy and MS

Association between breastfeeding and onset age or type of MS

The median age for the onset of MS symptoms was 25 years with the range of 12 – 45. In 23% symptoms had begun after the age of 30. Pearson correlation analysis revealed no linear correlation between the duration of breastfeeding and the age of beginning the disease (r = 0.108, P= 0.283), but the mean duration of breastfeeding was considerably lower in some MS patients who had onset of the disease before or at the age of 30 compared to those with onset after 30-year-old (15.2 ± 10.2 versus 19.5 ± 11.0 months, P = 0.09). Breastfeeding with a

duration of more than 11 months was more frequent in the latter group (83% versus 60%, P = 0.044). Patients with age-onset before or at 30 also revealed a higher rate of feeding with formula or cow (56.5% versus 33% and P = 0.063). The majority of cases (87%) had relapsing-remitting (RR) type of MS. 5 and 8 cases had primary (PP) and secondary progressive (SP) forms of MS, respectively. Intragroup comparison of patient's characteristics according to the type of disease is presented in Table 3.

Patients with PPMS had relatively higher median months of breastfeeding (24 months, range: 6-24) than SP (16.5 months, range: 0-24) or RR type (21months, range: 0-48), but this difference was not statistically significant (P= 0.598). Only one case (20%) with PPMS had a history of feeding with formula or cow milk, in comparison with 57% and 53% in patients with SP and RR MS, respectively. (P=0.296).

Table 2. Association of feeding with formula or cow's milk with higher risk of MS

	OR (95% CI)*	PV	OR (95% CI)**	PV
Breast feeding (months):				
>6	Reference	0.257	reference	0.904
=<6	1.5 (0.8 – 2.7)		1.0 (0.5 – 2.0)	
>8	Reference	0.156	reference	0.888
=<8	1.6 (0.8 – 2.9)		1.1 (0.5 – 2.1)	
>11	Reference	0.168	reference	
=<11	1.5 (0.8 – 2.8)		1.0 (0.5 – 2.0)	0.998
Formula or cow milk				
no	Reference		reference	
yes	2.3 (1.3 – 4.3)	0.006	1.7 (0.8 – 3.3)	0.145

* Adjusted for matching factors (age, sex)

** Further Adjusted for the following potential risk factors: educational level, smoking status, history of stress and family history of MS

Table 3. Comparison of cases according to the type of disease

	Relapsing remitting N=87	Primary progressive N=5	Secondary progressive N=8	PV
Age, median (range), years	30 (20-45)	40 (23-45)	28 (22-39)	0.129
Onset disease >30 years	20 (23)	3 (60)	0	0.028
Colostrum used (%)	67 (78)	3 (75)	6 (75)	0.862
Breast feeding months:				
>6(%)	62 (71)	4 (80)	5 (62.5)	0.689
>8(%)	59 (68)	4 (80)	5 (62.5)	0.801
>11(%)	56 (64)	4 (80)	5 (62.5)	0.767
Feeding with Formula or cow milk	41 (53)	1 (20)	4 (57)	0.296

4. Discussion

Human milk and colostrum are rich sources of proteins and polypeptides including lactoferrin, casein, proline-riched polypeptide, and lactoperoxidase having antiviral, antibacterial, and antitumor functions and accelerated immunomodulation [18]. As a result, lack of breastfeeding during infancy could be an important risk factor in the development of MS [22]. On the other hand, irregular distribution of MS with more prevalence in industrialized countries may reflect their different social attitudes to dairy diets [4,23] and breastfeeding, while in these countries there is a high intake of animal fats. Although the possible effect of decreased breastfeeding as a risk factor for MS has been suggested in several studies [24], it has remained controversial.

This study showed that patients who were breastfed for six months or less had 1.5 times the risk of MS, compared to those who were breastfed for more than 6 months (95%CI: 0.8 – 2.9), although we could not prove it to be statistically significant due to lack of sufficient power. Colostrum feeding had no relationship with developing MS. Additional comparisons in different types of MS demonstrated no association between forms of milk feeding and developing a certain type of the disease. This study was performed in Iran, a country with social support for breastfeeding by the government. In a

study of 150 mothers living in California, but immigrated from Iran, Afghanistan, Vietnam, Cambodia, or Laos, Iranian mothers were the ones who exclusively breastfed their infants in the United States [25]. Hence, this should be considered in the interpretation of these results.

Bottle-feeding with formula or cow milk may substitute for breastfeeding because of convenience and an increase in the number of employed mothers [26]. Furthermore, a worldwide decline in breastfeeding occurred in the early 1960s whereas MS began to increase during the 1980s [27]. Taken together, the above-mentioned findings could justify the significantly higher consumption of cow milk or formula in MS group in comparison with that in the healthy control. Importantly, despite the attenuation of OR after further adjustment for potential risk factors, the confidence interval suggests this variable could be a considerable risk factor. In contrast with other nongenetic factors affecting the prevalence of MS, the relationship between formula or cow milk and MS is rarely considered in the literature.

Studies suggest that factors in cow milk influence the clinical presentation of MS; the patient with MS should avoid the intake of whole cow's milk and prefer skimmed milk, which has no animal fat [28]. Although the increase in the risk of diseases with moderate consumption of milk fat has not been substantiated, in modern countries during several processes like heating some potentially unsafe components may be produced which has concerned dairy industries to develop new nonthermal technologies [29]. Furthermore, high protein intake in formula-fed infants could result in the production of excessive urea and nitrogen beyond the capacity of the body's metabolizing systems causing subsequent outcomes [30,31]. Additionally, cow milk allergy with an estimated prevalence of 2-5% in children [32] as a possible challenge for immune system during childhood should not be overlooked. These findings enforce the hypothesis about the contributing effect of bottle feeding in the development of MS.

For evaluating whether breastfeeding has any effects on the age of MS presentation, we considered the mean months of breastfeeding and breastfeeding for more than 11 months.

The analysis interestingly revealed that MS patients with the presentation before the age of 30 had considerably (but not significantly) lower months of breastfeeding, yet higher frequency of cow milk or formula feeding during infancy. Specifically, breastfeeding for at least one year significantly correlated with the onset of disease after 30 years of age.

Epidemiological evidence supports the association between Ebstein-Barr virus infection and the onset of MS in childhood[12,33]. Manouchehrini and colleagues also reported varicella infection in childhood and throughout life as a risk factor for MS [33]. Thus, the advantage of breastfeeding in the protection of infections early in life [34] could diminish the role of certain infections in the development of later MS or at least delay the underlying pathophysiology.

5. Conclusion

Formula or cow milk consumption during infancy may be a considerable risk factor for developing MS in addition to other etiologic factors. This hypothesis along with the immunologic basis of MS could be further supported by future cohort studies. Although the kind of feeding did not vary among different types of MS, that long-time breastfeeding correlated with delayed presentation of MS may be due to its preventive effects against infections.

Ethical Considerations

Compliance with ethical guidelines

Approval was obtained from the local ethics committee of Imam Khomeini Hospital.

A consent form was signed by the patients for use in their case.

The datasets used during the current study are available from the corresponding author upon reasonable request.

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Author's contributions

Conceptualization: all authors; Methodology: F Esfahani; Investigation: RH Naeeni. Writing – Original Draft: S Yadegari, Writing – Review & Editing: M Mohammadi Lapevandani; Funding Acquisition: none; Resources: A Soltanzade, S Nafisi; Supervision: RH Naeeni.

Conflict of interest

The authors declare that they have no competing interests.

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