Acta Neurol Scand 2002: 105: 88–94
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ACTA NEUROLOGICA
SCANDINAVICA
ISSN 0001-6314

Varicella, ephemeral breastfeeding and eczema as risk factors for multiple sclerosis in Mexicans

Tarrats R, Ordoñez G, Rios C, Sotelo J. Varicella, ephemeral breastfeeding and eczema as risk factors for multiple sclerosis in Mexicans.
Acta Neurol Scand 2002: 105: 88–94. © Munksgaard 2002.

Objectives – It has been suggested that the incidence of multiple sclerosis (MS) in Mexico and other countries of Latin America has increased steadily for the last two decades. We made a thorough search of antecedents on MS patients that could be potential risk factors. *Methods* – A case–control study was conducted using a questionnaire that included demographic, nutritional, infectious and personal antecedents previously identified in other reports as possible risk factors for MS. *Results* – The frequency of varicella, ephemeral breastfeeding and eczema in the medical history of MS patients were significant when compared with controls; all appeared to be mutually additive. However, they were unrelated with clinical characteristics or disease severity. *Conclusion* – During the last decades, breastfeeding has been abandoned in large segments of society and the incidence of varicella and childhood eczema keeps a north–south gradient similar to that described for MS. These factors may participate in the sharp increase of MS in countries like Mexico traditionally considered as an area of very low incidence.

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Key words: multiple sclerosis; breastfeeding; varicella virus; eczema; multiple sclerosis in Latin America

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Accepted for publication July 16, 2001

Geographical areas where a given disease has either a low incidence or presents a recent increase constitute a valuable terrain for studies on etiology and pathogenesis (1). That is the case of multiple sclerosis (MS) in Mexico, where recent data indicate that its prevalence has been continuously increasing from the early 1980s, so much that at the end of the 1990s it became one of the most frequent causes of hospitalization in neurological wards (2–4). Although proper epidemiological studies are lacking, it seems that MS is having a sustained increase in Mexican subjects; the most important argument supporting this possibility is the fact that the great majority of MS patients in Mexico are young adults, chronic cases with more than 15 years of disease are rare (3).

Thirty years ago, Alter and Olivares (5) reported a very low incidence of MS in Mexico. Nonetheless, during the last two decades a progressive and sustained increase of MS cases has been observed in most medical centers throughout the country. It is a widespread opinion among neurologists that it represents a real increase, rather than this being due to better diagnostic capabilities or any other parallel explanation. Thus, if Mexico is a new epidemiological area for MS, important information on etiopathogenesis could be obtained. A research strategy is the analysis of similarities and differences between Mexico and countries where endemicity for MS has been stable.

Comparisons of clinical characteristics of MS between Mexican patients and patients from endemic countries have shown three main differences: (1) the onset of MS in Mexicans is observed at an earlier age, a mean of 27 years of age, about 3–5 years less than in most other studies (2). In one-third of cases, the initial neurological sign is optic neuritis progressing to MS, in contrast to about 10–15% in endemic countries; and (3) the severity of the disease is lower when compared by the long-term disability scale (3). An additional

finding has been that the mean sociocultural and economic strata of MS patients in Mexico are higher than that of the general population and of patients with other neurological disorders treated at the same institution (3). This difference has also been noted in MS patients from endemic countries (6).

For the last two decades there has been in Mexico an intricated social transformation resulting in large segments of society living under sociocultural and economical conditions similar to those of developed countries, whereas another large proportion keeps traditional ways of life that greatly differ from those of developed countries. The genetic nature of most Mexicans is a complex mixture of European and Asiatic genes which creates a unique breed, dissimilar from their original ancestors. About 5% of Mexicans are Indians with almost exclusively mongoloid genetic background, on the other side of the spectrum, another 5% has almost exclusively Caucasoid genetic background; whereas the great majority, around 90%, are Mestizos with a very complex mixture of European and Asiatic genes. We have speculated that European genes might be a predisposing factor for MS whereas Asiatic genes might be a protective factor (2). The clinical expression of MS in Mexicans could also be influenced by these genetic factors, making the clinical profile of many MS patients similar to that reported in Asian patients (2–4, 6).

Several epidemiological studies have suggested that exposure before the age of 15 years to one or various risk factors may increase the possibility of developing MS several years later (7–10). In Mexico, as one of the countries more clearly immersed in the so-called 'epidemiological transition' many socio-cultural, technological, economical and environmental changes have taken place during the last decades, they might be factors participating in the drastic variations, upwards or downwards, that have taken place during recent times in the incidence of various diseases (11), MS seems to be one of them.

The present study was conducted to investigate in Mexican patients demographic, nutritional, infectious and autoimmune antecedents that have been identified in other studies as possible risk factors associated with the development of MS.

Methods

A case–controlled study was conducted in 94 consecutive patients studied at the National Institute of Neurology and Neurosurgery of Mexico (NINNM) all had definitive diagnosis of MS (12) all were Mestizos and had always lived in the country. Similarly to that observed in other studies, MS patients from the NINNM have a mean socio-economic and educational level significantly higher than that found in patients with other neurological disorders (3). One of the drawbacks for case–controlled studies in MS is a possible selection bias when using controls who have a different social status because of the higher risk of MS found in affluent strata, the use of hospital controls having a lower socio-economic status can introduce a selection bias (6); to prevent this, the use of two or more control groups has been suggested (1). Therefore, we selected a control subgroup (C1) of 110 consecutive patients from the NINNM with a comprehensive variety of neurological diseases excluding demyelinating disorders and an additional control subgroup (C2) of 100 healthy workers from the NINNM. In this way, C1 was representative of the unselected population of neurological patients seen at the NINNM, while C2 was representative of the educational level of MS patients, together they made up the control group (C) of 210 subjects. Differences in age and gender between patients and controls were nonsignificant (Table 1).

A questionnaire containing 43 items was designed, it included age, gender, birthplace of parents and grandparents, residence during the first 15 years of life, duration of breastfeeding, economical status, schooling level, nutritional habits with special reference to ingestion of dairy

Table 1 Comparisons between multiple sclerosis (MS) patients and controls

	MS ($n = 94$)	C1 ($n = 110$)	P*	C2 ($n = 100$)	P	C ($n = 210$)	P	OR*	CI (95%)
Age (years)	36.4 ± 1.2	36.6 ± 1.1	0.92	34.2 ± 0.8	0.57	34 ± 0.7	0.08	–	–
Gender (M, %)	43	51.8	0.207	34	0.239	44	0.8	0.95	0.6–1.5
Schooling (years)	12 ± 0.4	9.9 ± 0.3	0.000	12.9 ± 0.3	0.116	11 ± 0.3	0.1	1.45	0.88–2.4
Breastfeeding (months)	8.2 ± 0.6	12.0 ± 1.0	0.001	12.4 ± 1.1	0.001	12 ± 0.7	0.001	0.58	0.35–0.95
Eczema (yes, %)	34	8	0.000	13	0.001	10	0.000	4.6	2.5–8.6
Varicella (yes, %)	79	36	0.000	45	0.000	42	0.000	5.2	2.9–9.3
Age/varicella (years)	8.3 ± 0.6	11.4 ± 1.4	0.024	8.6 ± 0.9	0.26	10 ± 0.8	0.02	0.67	0.33–1.3

* P was obtained by bivariate analyses of the respective control group against MS patients, together with unadjusted OR for the C group.

products (fresh milk or derivates) throughout their life since infancy, peculiar dietary predilections like ingestion of hot pepper and central nervous system products (in Mexico ingestion of brain and spinal cord from bovines and pork is common), pets (past or present), infections with detailed reference to viral disorders during childhood (measles, varicella, rubella, etc.), dermic or systemic allergies (past or present), habitation conditions, working conditions, etc. The whole questionnaire was individually administered to MS patients and controls by the same interviewer (RT); unanswered questions because of inaccurate recollection of childhood events were left to be answered by participants after the information was gathered through parents or family members; items that showed statistical significance in comparative analysis between MS and C subjects were compared again by bivariate and multivariate analysis between MS patients and C1 and C2 subgroups.

For statistical intragroup comparisons with regard to the risk factors detected, MS patients were separated according to three factors; age of onset, neurological sign at onset of MS and expanded disability status scale (EDSS) (13). These three characteristics have shown differences when MS in Mexicans has been compared with MS in patients from countries endemic for MS (3).

Statistical analysis was performed by student's *t*-test for continuous variables and the χ^2 test for categorical variables in order to compare two-by-two the control groups with MS patients, crude prevalence ratios were also calculated with 95% confidence interval. Only those variables having statistical significance ($P < 0.05$) after these comparisons were included in a logistic regression model. Odds ratios derived from the Logistic Regression Analysis were adjusted before and after for possible confounders. All analyses were made using STATA software.

Results

Demographic characteristics and antecedents that were statistically significant in MS patients were compared with C1, C2 and C controls are shown in Table 1. To test the reliability of C1 and C2 for comparisons with MS patients the sociocultural level based on years of schooling was analysed; C1 subjects had a mean of 9.9 ± 0.3 years (SE), C2 subjects had 12.9 ± 0.3 years. When contrasted by bivariate analysis with that of MS patients (12 ± 0.4 years) the difference was significant for C1 subjects ($P < 0.001$) but lost significance for C2 subjects ($P < 0.116$) thus showing the suitability of controls for the intended comparisons.

From all factors studied, three antecedents were significant when MS patients were compared with all controls (C1, C2 and C): duration of breastfeeding ($P < 0.001$); eczema during childhood defined as chronic allergic reactions of the skin ($P < 0.001$, crude OR 4.6) and varicella ($P < 0.001$, crude OR 5.2) (Table 1). When all three variables were included in a logistic regression model the values were modified as observed in Table 2, but remained highly significant. From various possible confounders searched for logistic regression analysis, such as age, gender, place of birth, food intolerance, eruptive infections from childhood, etc. we found that only measles was a significant confounder for varicella ($P < 0.008$, OR 2.7, CI 1.3–5.5).

The percentages of subjects who were not breastfed were similar in all groups; 10% in MS; 13% in C; 15% in C1 and 10% in C2. Mean duration of breastfeeding was 8.2 ± 0.6 months for MS patients; 12 ± 0.7 months for C; 12.0 ± 1.0 months for C1 subjects and 12.4 ± 1.1 months for C2 subjects; the 'duration measure' included subjects who were never breastfed with a value of 0 months. Percentages of MS patients with antecedents of eczema or varicella were 34 and 79%, respectively; for C subjects were 10 and 42% ($P < 0.001$); for C1 subjects were 8 and 36% ($P < 0.001$); for C2 subjects were 13 and 45% ($P < 0.001$). The mean age of varicella infection in MS patients was 8.3 ± 0.6 years; in C subjects was 10 ± 0.8 years; in C1 subjects was 11.4 ± 1.4 years and in C2 subjects was 8.6 ± 0.9 years ($P < 0.26$). Eighty-eight per cent of MS patients had at least one of the three significant variables (<8 months of breastfeeding, eczema or varicella), 56% had at least two and 18% had all three; for C subjects the percentages were 66, 22 and 1%, respectively; for C1 subjects were 63, 18 and 1% and for C2 subjects were 69, 26 and 1%. Using the logistic regression model, we were able to estimate the proportion of subjects in the sample with defined characteristics of risk, for example, the proportion of subjects with MS having 0 months of breastfeeding, and positive antecedents of eczema and varicella would be 0.77, in contrast, the proportion of MS subjects

Table 2 Logistic regression analysis of significant risk factors for multiple sclerosis (MS)

	OR	CI (95%)	*P*
Breastfeeding (<8 months)	1.05	1.01–1.09	0.031
Eczema	4.10	1.95–8.62	0.000
Varicella	4.83	2.53–9.20	0.000

CI = Confidence interval; OR = odds ratio.

Table 3 Items addressed that did not show significant differences between multiple sclerosis (MS) patients and controls

	MS (%)	C (%)	OR (95% CI)	*P*
Country of birth of mother	100	99	0.99 (0.98–1.01)	0.54
Country of birth of father	97	99	1.0 (0.97–1.06)	0.39
Country of birth of maternal grandparents	92	99	1.07 (0.99–1.15)	0.06
Country of birth of paternal grandparents	93	97	1.04 (0.97–1.1)	0.18
Residence during the first 15 years of life (Mexico)	100	100	1.12 (0.93–1.36)	–
Economical status during childhood (floor of house made of cement)	82	86	0.75 (0.35–1.6)	0.28
Sewage inside home	82	86	0.75 (0.35–1.6)	0.28
Daily ingestion of milk during childhood	90	96	0.35 (0.10–0.16)	0.07
Milk intolerance during childhood	1.0	0	1.0 (0.98–1.0)	0.34
Pets during childhood	49	77	0.28 (0.15–0.52)	0.001
Pets were dogs or cats	89	95	2.5 (0.63–10.0)	0.16
One or two pets	69	74	1.3 (0.55–2.9)	0.34
Pets slept outside the house	77	88	4.7 (1.5–14.9)	0.21
Childhood measles	63	52	1.7 (0.99–3.1)	0.10
Age at measles	6.2 ± 3	6.4 ± 3.7	–	0.75
Childhood rubella	32	25	1.36 (0.72–2.5)	0.20
Age at rubella	7.6 ± 6.4	10.3 ± 7.9	–	0.22
Change of geographical area of residence from childhood to adulthood	31	29	1.12 (0.59–2.10)	0.41
Current economical status (floor of house made of cement)	97	100	1.02 (0.98–10)	0.12
Sewage inside current home	97	100	1.02 (0.98–10)	0.12
Currents pets	49	46	1.14 (0.64–2.0)	0.37
Pets are dogs or cats	85	95	3.3 (0.75–15.2)	0.10
One or two	76	75	0.96 (0.35–2.5)	0.57
Pets sleep outside of the house	79	88	2.03 (0.64–2.0)	0.17
Ingestion of bovine or pork brain	28	22	1.37 (0.71–2.6)	0.21
Ingestion of bovine or pork spinal cord	27	16	1.8 (0.93–3.7)	0.05
Daily ingestion of hot pepper	87	95	0.15 (0.41–0.59)	0.2
Current milk intolerance	21	16	2.1 (0.9–4.7)	0.35
Daily ingestion of milk	93	94	0.81 (0.25–2.6)	0.47
Daily ingestion of butter	67	74	0.7 (0.38–1.34)	0.18
Daily ingestion of milk cream	77	87	0.51 (0.24–1.0)	0.06
Daily ingestion of cheese	97	98	0.77 (0.12–4.7)	0.55
Daily ingestion of dairy products	84	88	0.72 (0.31–1.6)	0.27

with 12 months of breastfeeding and negative antecedents of eczema and varicella would be 0.01.

When intragroup comparisons of each of the three significant antecedents were made among MS patients according to the age at the clinical debut of MS, the initial MS symptoms and the EDSS score no significant differences were observed. The items addressed that did not show significant differences between MS patients and controls are shown in Table 3.

Conclusion

Epidemiological studies have consistently pointed out that exposure during the first 15 years of life to some still not clearly identified events may act as risk factors for the development of MS several years later; we elaborated a questionnaire that explored in MS patients events during childhood and throughout their lives that might participate in the etiopathogenesis of MS. From that exhaustive inquiry, only three antecedents, all of them from childhood, remained statistically significant in MS patients when compared with controls: duration of breastfeeding, eczema and varicella. The most significant was varicella, the less significant was eczema. All three seemed to be mutually additive in the risk for MS development in Mexican Mestizos later in life. However, they did not appear to influence the clinical course or the severity of the disease. Interestingly, all three have a north–south gradient of frequency similar to that described for MS; chickenpox, ephemeral breastfeeding and eczema are more frequent in industrialized countries (14–18).

In an attempt to construct a viable explanation for these findings some interesting features emerged: chickenpox, is caused by the varicella zoster virus (VZV), a complex DNA agent from the family herpes virus, which clearly exemplifies the concept of 'multiple viral pathogenicity' (19), the same VZV causes at least two different diseases,

one of them, chickenpox is more frequent during childhood, whereas the other, herpes zoster, is more frequent in adults (20). In both cases, the virus may become neurotrophic and remain latent within the nerve roots for long time. It is interesting to note that the geographical epidemiology of MS and varicella show striking similarities (15, 21) both maintaining a north–south gradient of incidence similar to that described for MS 50 years ago. Almost all people living in industrialized countries within the temperate climate contract varicella, whereas in tropical countries its frequency is less than 50% (14, 15, 20), the annual rate of varicella in Mexico in 1999 was 289/100,000 one-third of them occurred in subjects between the ages of 15 and 44 years (22). In industrialized temperate countries varicella is mostly a disease of childhood, whereas in the tropics it is mostly a disease of young adults (14, 22); in Mexico, there is evidence of a recent trend of a higher than expected risk for VZV infection in adolescents and young adults (23). Bachmann and Kesselring (24) have pointed out the possible association between infectious childhood diseases acquired at a later stage and the development of MS, in the case of varicella the highest age group at risk was found in subjects that acquired the infection between 5 and 11 years of age, similar to the mean age of varicella infection in our patients (8.3 ± 0.6 years). It has been postulated in several studies that some herpes virus, such as VZV virus, Epstein–Barr virus (EBV), herpes 6 virus or another still unrecognized agent from the herpes family could be involved in the ethiopathogenesis of MS (25–28). Although herpes viruses have not been found in MS plaques by *in situ* hybridization (29) and polymerase chain reaction (30), lymphocytes from MS patients express EBV proteins (27, 31) and VZV replicate in circulating mononuclear phagocytes (15), a fact that might facilitate its dissemination to distant sites such as the brain. In a recent study, vaccination of MS patients with VZV produced favorable, albeit preliminary, therapeutic results (32). An intriguing circumstance is that the administration of interferon improves the course of MS, nowadays interferons are considered an effective therapeutic measure in a substantial number of MS cases, however, the mechanisms are poorly understood. Coincidentally, interferon also reduces morbidity in herpes zoster infection and *in vitro* the VZV is sensitive to interferon (20). Slow infection with remissions and relapses is a common feature of herpes viruses (19). Occasionally, EBV and VZV are able to induce in human cases a demyelinating disease similar to that produced by MS (33). Also, antibodies to nuclear antigens of EBV cross-react with myelin basic protein (34) strengthening the possibility of an autoimmune etiology of MS triggered through a 'hit and run' mechanism of molecular mimicry (19) caused by an immune response originally directed against viral antigens, where the virus acts only as initiating factor (15, 19, 35, 36). Seropositivity for EBV is almost universal in MS patients (21, 25, 36, 37) but cross-reactive antibodies with another herpes virus, because of common viral antigens is a possibility, these cross-reactive antibodies are frequent in EBV infection (20). Currently, we are investigating the possible presence of viral particles from various herpes virus as well as antibodies against this virus in serum and CSF of MS patients.

Mexico has been considered as one of the countries more traditionally attached to the practice of breastfeeding, old studies have shown that until the late 1960s, more than 90% of mothers breastfed their infants. This is still so in large segments of society (17, 18), however, since the inception of maternalized milk early substitution to formulas with shorter periods of breastfeeding has been a growing phenomenon; it has been more notorious in working mothers and in the groups from higher socio-economic background (38). The possibility of diminished breastfeeding as a risk factor for MS has already been described (8) although the issue remains controversial (39, 40). If related with MS, the change in sequence of breastfeeding habits coincides in time with the increase of MS that started to take place, according to our studies, during the early 1980s (2, 3), about 20 years after the beginning of changes in breastfeeding practices. Considering the mean age of our MS patients, their time of birth (the late 1960s and early 1970s) coincided with a sharp decline of breastfeeding and early substitution by formulas; this change was far more evident among the urban groups in comparison with rural populations. Interestingly, the great majority of MS patients in Mexico belong to urban groups (3). The differences have been so drastic that duration of breastfeeding for more than 6 months was 98% in 1960; in 1982 the percentage had dropped to 28% in some rural areas and to 18% in most urban areas, similar to the percentage observed in industrialized countries (41–43); from 1982 to 1991 the figures were not modified substantially (41–43). The decline in breastfeeding during the early 1960s was a worldwide phenomenon, including Mexico (44–46). While the tendency has been recently reversed in most developed countries (42, 47, 48) it has been difficult to reverse in the urban sectors of developing countries, Mexico among them (18, 46, 49–51), although it seems to be a recent positive trend (41).

Ezcema, the third potential risk factor for MS in Mexicans, is defined as a generic term for chronic inflammatory atopic conditions of the skin (Stedman's medical dictionary) which are more frequent in developed than in developing countries (16); interestingly, breastfeeding is prophylactic against eczema, this protection extends throughout childhood and adolescence (16, 43).

The potential risk factors found indicate association rather than causality. However, speculating about our findings and the recent increase of MS in Mexico it could be hypothesized that the immunological handicap produced by insufficient period of breastfeeding (52–55) may render the child prone either to immune disbalance and autoimmunity or to a slow viral infection resulting in MS later in life.

Acknowledgement

This work was partly supported by the National Council of Science and Technology of Mexico (CONACyT) grant L0001-M9608.

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