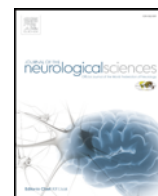




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Childhood cow's milk allergy and the risk of multiple sclerosis: A population based study

Sreeram V. Ramagopalan^{a,b}, David A. Dymnt^{a,b}, Colleen Guimond^c, Sarah-Michelle Orton^{a,b}, Irene M. Yee^c, George C. Ebers^{a,b}, A. Dossa Sadovnick^{c,d,*}

^a Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK

^b Department of Clinical Neurology, University of Oxford, Oxford, UK

^c Department of Medical Genetics, University of British Columbia, Vancouver, Canada

^d Faculty of Medicine, Division of Neurology, University of British Columbia, Vancouver, Canada

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ABSTRACT

Autoimmune mechanisms are thought to have a major role in the pathogenesis of multiple sclerosis (MS) and vitamin D is hypothesised to contribute to disease susceptibility. Cow's milk allergy (CMA) is a common childhood allergy arising from an immune system imbalance and can also lead to vitamin D deficiency due to dairy food avoidance. Here, we investigated whether or not CMA influences the subsequent risk to develop MS in a population-based cohort. We identified 6638 MS index cases and 2509 spousal controls with CMA information from the Canadian Collaborative Project on Genetic Susceptibility to MS (CCPGSMS). Frequency of CMA was compared between index cases and controls. No significant differences were found. Childhood CMA thus does not appear to be a risk factor for MS.

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1. Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterized by myelin loss, varying degrees of axonal pathology, and progressive neurological dysfunction [1]. MS is thought to be mediated by autoimmune processes, which may arise from defects in regulatory lymphocytes (CD4⁺CD25⁺ T cells) in individuals failing to suppress auto-reactive CD4⁺ and CD8⁺ cells [2].

Cow's milk allergy (CMA) is a common allergy in early childhood, with a prevalence of 2–6% [3]. CMA frequency decreases with age; adulthood incidence is only 0.1–0.5% [3]. The long-term prognosis for the majority of infants with CMS is good, with 90% naturally acquiring tolerance to cow's milk by the age 5 [3]. This induction of tolerance to dietary antigens has been shown to be associated with the development of regulatory CD4⁺CD25⁺ T lymphocytes [4]. It is thus plausible that delayed development of regulatory lymphocytes in individuals with CMA could permit auto-reactive cells relevant to MS to escape suppression or deletion, thereby enabling them to initiate or propagate the disease later in life.

CMA also carries nutritional implications as affected individuals tend to avoid dairy products and have been shown to be deficient in

25-hydroxyvitamin D [5]. Vitamin D has been implicated as being a risk factor in MS through an increasing number of epidemiological, immunological and genetic studies [6–8]. For example, decreased levels of 25-hydroxyvitamin D are associated with an increased risk to develop MS [9]. Thus, we hypothesize that CMA is a good candidate to be a risk factor for MS susceptibility.

The Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis (CCPGSMS) has collected information, including data on childhood CMA, on a cohort of more than 30,000 families in which at least one member has MS, as well as on spouse controls. We used this large sample to conduct the first investigation, to our knowledge, on whether or not CMA in childhood affects MS susceptibility.

2. Subjects and methods

The CCPGSMS is a unique, longitudinal, population-based MS study and the methodology has been previously described [10,11]. Briefly, MS clinics across Canada used standardised, personally administered questionnaires to screen individuals with MS and to collect data about themselves and their families.

Specific to this study, with appropriate consent, CMA data was collected by telephone interview from mothers of MS index cases and spouse controls (the term “spouse” is used generically to refer to legal spouse, common law partner, or same-sex partner). Mothers of cases and controls were asked if their child suffered from CMA and if so at

* Corresponding author. G920, Detwiller Pavilion, VCHA - UBC Hospital, University of British Columbia, 2211 Wesbrook Mall, Vancouver, British Columbia, V6T 2B5, Canada. Tel.: +1 604 822 5670; fax: +1 604 822 7362.

E-mail address: sadovnik@infinet.net (A.D. Sadovnick).

what categorical age. Categorical age at CMA (perinatal, early childhood (up to age 3) and late childhood (up to age 11)) was collected for index cases and spouse controls.

3. Statistical analyses

The Chi squared test was used to assess significance when comparing frequency of CMA in index cases and controls. The effect of CMA and sex on the risk of MS was assessed by logistic regression using the R statistical package.

4. Results

Complete information on CMA was available for 6638 index cases and 2509 spousal controls. The clinical and demographic details of the index cases and controls are shown in Table 1.

The frequencies of perinatal, early childhood and late childhood CMA were compared between index cases and controls. No significant differences were found either before or after stratification by sex (Table 2). Perinatal CMA was present in 4.3% of female MS cases and 3.9% of female controls ($p=0.61$) and 3.5% of male MS cases and 3.4% of male controls ($p=0.83$). Early childhood (up to age 3) CMA was present in 2.3% of female MS cases and 2.1% of female controls ($p=0.82$) and 1.8% of male MS cases and 1.4% of male controls ($p=0.30$). Late childhood (up to age 11) CMA was present in 2.1% of female MS cases and 1.7% of female controls ($p=0.51$) and 1.3% of male MS cases and 1.0% of male controls ($p=0.32$). This was confirmed by logistic regression analysis, which showed an effect of sex on the risk of MS ($p<1\times 10^{-16}$) but no effect of CMA ($p>0.6$) for each categorical age.

5. Discussion

The association of MS with extended MHC haplotypes [12], the female preponderance of the disease [13], a reduced number of relapses during pregnancy [14] and the presence of T cells that are reactive to myelin antigens all support the hypothesis that MS has an autoimmune aetiology [15], which may arise from an immune system imbalance [16]. The striking geographical distribution of the disease implicates a role for vitamin D in MS pathogenesis [17]. Migration and epidemiological studies suggest that the action of vitamin D is likely to be important during childhood [9,18]. CMA is a disorder thought to result from a late development of the immune system and consequent immune imbalance. CMA also has an indirect potential to cause vitamin D deficiency from avoidance of cow's milk products [5]. Thus, in early life, CMA is a highly plausible risk factor for MS. However, in this study, we found no effect of CMA on disease susceptibility.

There are limitations to this study. Maternal recall of CMA many years later may not be as accurate as data from clinical records etc. Furthermore, we are not sure if the reported CMA is self or physician diagnosed. Self/family diagnosis of CMA provides substantially inflated CMA prevalence figures [3]. There are also two major immunological mechanisms of CMA–IgE-mediated and non-IgE-

Table 2

Frequency of CMA in sex-stratified MS Index Cases and Spouse Controls.

	Perinatal CMA n (%)	Early life CMA n (%)	Later life CMA n (%)
Female Index Cases	216 (4.3)	111 (2.3)	103 (2.1)
Female Spouse Controls	30 (3.9)	16 (2.1)	13 (1.7)
p value	0.61	0.82	0.51
Male Index Cases	58 (3.5)	30 (1.8)	22 (1.3)
Male Spouse Controls	59 (3.4)	24 (1.4)	17 (1.0)
p value	0.83	0.3	0.32

mediated. In this study, we were unable to distinguish between these [3]. It may be that only one of these CMA forms are associated with subsequent risk of MS. Data was available for only 763 female spousal controls which may be underpowered to detect effects although this is compensated somewhat by having information on over 4900 female index cases.

In conclusion, we were unable to find an association between CMA and MS, suggesting that CMA is not a significant risk factor for MS.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Table 1

Clinical and demographic details of MS index cases and controls.

	MS Index Cases	Spouse Controls
n	6638	2509
Mean age in year (SD)	49.7(9.7)	51.8(9.2)
n (females)	4987	763
n (males)	1651	1746
Sex Ratio (f:m)	3:1	0.4:1
% Relapsing Remitting MS	71.9	/

SD = standard deviation, (f:m) = female to male sex ratio.

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