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Journal of Neuroimmunology 179 (2006) 145–151

Journal of Neuroimmunology

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Association between microchimerism and multiple sclerosis in Canadian twins

Cristen J. Willer [a,1], Blanca M. Herrera [a], Katie M.E. Morrison [a], A.D. Sadovnick [c], George C. Ebers [a,b,*] for the Canadian Collaborative Study on Genetic Susceptibility to Multiple Sclerosis

[a] Department of Clinical Neurology, University of Oxford, Oxford, UK
[b] Wellcome Trust Center for Human Genetics, University of Oxford, Oxford, UK
[c] Department of Medical Genetics and Faculty of Medicine (Neurology), University of British Columbia, Vancouver, Canada

Received 7 August 2005; received in revised form 7 June 2006; accepted 13 June 2006

Abstract

Microchimerism, the persistence of foreign cells thought to derive from previous pregnancies, has been associated with autoimmune diseases. A maternal parent-of-origin effect in MS remains unexplained. We tested for microchimerism in monozygotic and dizygotic twin-pairs with MS. Microchimerism was associated with MS in affected females from monozygotic concordant pairs when compared to both affected ($p=0.020$) and unaffected ($p=0.025$) females in monozygotic discordant pairs. Microchimerism was increased in affected females of dizygotic discordant pairs ($p=0.059$). The rate of microchimerism was significantly higher in affected twins than in unaffected co-twins ($p=0.0059$). These observations show an association in twins between the presence of microchimerism and having MS.

Keywords: Multiple sclerosis; Microchimerism; Twins

1. Introduction

Microchimerism, the enduring presence of a small number of non-host cells, is associated with the development of some autoimmune disorders. The most common and plausible source of microchimerism is the presence of fetal stem cells from a previous pregnancy that persist in the maternal bone marrow or lymph nodes and continue to be tolerated by the mother's immune system. Stem cells may also be transferred between dizygotic (DZ) twins during pregnancy but this has not been proven in humans. However, transfer between monozygotic (MZ) twins in the twin–twin transfusion syndrome has been confirmed (Bourthoumieu et al., 2005) and transfer from mother to fetus has also been shown (Bianchi et al., 1996; Maloney et al., 1999). Other possible sources of microchimerism include transmission of cells from mother to fetus during pregnancy, from bone marrow or organ transplant, or blood transfusion. Most pregnant women and a large proportion of parous women are positive for microchimeric cells (Table 1) (Bianchi et al., 1996; Thomas et al., 1994).

The hypothesis that autoimmune diseases are associated with microchimerism was based in part on studies of the autoimmune disease scleroderma. The clinical features of scleroderma resemble those of graft-versus-host disease (GvHD) (Nelson, 1998), which can occur following transplantation if donor cells attack the cells of the host (Santos and Cole, 1958). This led to the hypothesis that a mechanism involving foreign cells (Nelson, 1996) transferred during a

* Corresponding author. Department of Clinical Neurology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, UK. Tel.: +44 1865 228579; fax: +44 1865 224757.
E-mail address: george.ebers@clneuro.ox.ac.uk (G.C. Ebers).
[1] Present address: Department of Biostatistics, University of Michigan, Ann Arbor, USA.

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doi:10.1016/j.jneuroim.2006.06.011

Table 1
Prevalence of microchimerism in peripheral blood of women from published studies

Control group	Tissue studied	Technique	Number positive for MC/total	% Positive for MC	Reference
Normal women, pregnancy history unknown	DNA from peripheral blood	PCR for Y-chromosome sequences	1/25	4	Artlett et al. (1998)
Scleroderma patients and controls	DNA from peripheral blood	PCR for HLA alleles	17/31	55	Maloney et al. (1999)
Healthy control women who have had sons	DNA from peripheral blood	PCR for Y-chromosome sequences	12/24	50	Nelson et al. (1998)
Japanese women with sons (2–18 years old)	DNA from peripheral blood	PCR for Y-chromosome sequences	6/12	50	Murata et al. (1999)
Women with sons and nulliparous women	DNA from peripheral blood, and CD34+ enriched fraction	PCR for Y-chromosome sequences	2/8	25	Toda et al. (2001)
Asian women with at least one son	DNA from peripheral blood	PCR for Y-chromosome sequences	8/41	20	Miyashita et al. (2000)
Women pregnant with female fetuses	Plasma and serum from peripheral blood	PCR for Y-chromosome sequences	0/23	0	Lo et al. (1998)
Normal women pregnant with male fetuses at time of study	DNA from peripheral blood	PCR for Y-chromosome sequences	13/19	68	Bianchi et al. (1996)
Women pregnant with female fetuses at time of study	DNA from peripheral blood	PCR for Y-chromosome sequences	4/13	31	Bianchi et al. (1996)

previous pregnancy may play a role in scleroderma (Famularo and De Simone, 1999). Samples of skin lesions and peripheral blood leukocytes from women with scleroderma were found to contain male cells more often than control women (Artlett et al., 1998; Miyashita et al., 2000; Nelson et al., 1998). Similarly, women with autoimmune Hashimoto's thyroiditis had higher rates of male microchimeric cells than controls with nodular goiter (Klintschar et al., 2001).

GvHD is said to be more common when the human leukocyte antigen (HLA) profile of the host matches the donor (Williamson and Warwick, 1995) since similar microchimeric cells presumably reside undetected in the bone marrow or liver (Artlett et al., 1997). Females with scleroderma are more likely to be HLA-compatible with their mothers or children compared to unaffected women (Maloney et al., 1999). We have previously found no evidence for increased HLA-compatibility between multiple sclerosis patients and their mothers (Willer et al., 2005); however, this does not exclude a role for microchimerism in multiple sclerosis, particularly if the primary source of microchimeric cells is from the offspring of affected individuals. HLA-compatibility and microchimerism might be incompletely correlated and therefore difficult to detect in a complex disease. Furthermore, the role of minor histocompatibility antigens was not examined.

Here we tested the hypothesis that microchimerism is associated with multiple sclerosis (Willer et al., 2002) by testing for microchimerism in twins diagnosed with MS and their co-twins. These studies were stimulated by the finding of a maternal parent of origin effect in half-suiblings (Ebers et al., 2004). We compared concordant MZ pairs to discordant MZ pairs to test whether concordance itself is associated with microchimerism. We compared the rates of microchimerism in affected members of discordant pairs, both MZ and DZ to their unaffected co-twins. We observed significantly higher rates of microchimerism in women affected with MS than in their unaffected co-twins, and significantly higher rates of microchimerism in concordant MZ pairs compared to discordant MZ pairs.

2. Methods

2.1. Ascertainment

All twin subjects were identified through the Canadian Collaborative Project on the Genetic Susceptibility to Multiple Sclerosis. Twins with MS, their co-twins, mothers, husbands and twins' husbands were asked to participate in the study. Written consent was obtained from all participants in the study and the research protocol was approved by local Institutional Review Boards at each clinic and research center. A diagnosis of multiple sclerosis was made according to Poser's guidelines (Poser et al., 1983). Probands with a diagnosis of possible MS and their co-twins were excluded from the analysis. If the twin proband was considered to meet the criteria for probable or definite MS and the co-twin had a diagnosis of possible MS then the twin pair was included in the study.

2.2. Study sample

There were a total of 190 samples collected under sterile conditions and tested for microchimerism at a minimum of one locus (Figs. 1 and 2). The characteristics of the twin sample from the Canadian Collaborative Study have been previously reported (Willer et al., 2003). Informativity at the beta-globin locus required homozygosity for the genomic DNA, and the Y-chromosome test was performed on females only. A detailed history of all previous pregnancies (if female), blood