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The role of past sun exposure in Multiple Sclerosis

by

Ingrid A.F. van der Mei

Doctorandus (Master's)

Environmental Health Sciences, Human Movement Sciences

A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy



University of Tasmania (September, 2004)

DECLARATION

This Thesis contains no material which has been accepted for any degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the Thesis, and to the best of my knowledge and belief no material previously published or written by another person, except where due acknowledgement is made in the text of the Thesis.

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SIGNATURE

Ingrid A.F. van der Mei

ABSTRACT

This epidemiological thesis firstly reviews the disease Multiple Sclerosis (MS): its history, pathology, clinical expression, and the current views on immunopathogenesis, aetiology and treatment. A separate review on ultraviolet radiation (UVR) and MS indicates that recent work in photoimmunology provides evidence that UVR can attenuate T helper 1 cell mediated processes through several mechanisms, and that epidemiological features of MS, such as the striking latitudinal gradient and seasonal variation in month of birth, MS onset and disease activity, are at least in part consistent with the hypothesis that UVR exposure may reduce the risk of MS. An ecological analysis was conducted as part of the PhD to demonstrate that regional variation in MS prevalence in the continent of Australia could be closely predicted by regional UVR levels, but analytical epidemiological studies are required to further investigate the UVR hypothesis.

The project central to this thesis was a population based case-control study on Multiple Sclerosis, conducted in Tasmania, Australia. It examined: (i) whether high past sun exposure was associated with a reduced risk of MS, (ii) whether sibship structure and past infections influenced the risk of MS and (iii) whether having had children and differences in prevalence and strength of MS risk factors between men and women could explain the sex difference in MS. Interviews were conducted with 136 cases with MS and 272 controls randomly drawn from the community and matched on sex and birth year. In one of the methodology chapters, a measure-retest and method comparison was conducted to examine aspects of reliability of the sun exposure measures used in the case-control study. A separate study on 104 healthy volunteers was carried out to examine the effect of seasonal variation and body hair on melanin density estimates based on skin reflectance.

The case-control study showed that higher past sun exposure, particularly during childhood and early adolescence, was associated with a reduced risk of MS, which is compatible with UVR having a protective role against MS. Having younger siblings, but not older siblings, was also associated with a reduced risk of MS, while having had glandular fever or having high antibody titers against the Epstein-Barr virus was associated with an increased risk of MS. Among women, a negative association was found between having had children and MS.

The finding of an inverse association between sun exposure during childhood and early adolescence and MS, if confirmed in future work, will have important public health implications.

ACKNOWLEDGEMENTS

In 1998, I joined the Menzies Centre for Population Health Research on a one year Australian-European Program Award to conduct epidemiological research and to bring back my newly acquired knowledge to the Netherlands. Rather than returning to the Netherlands, Professor Dwyer (director of the Menzies Centre) gave me the opportunity to conduct research on Multiple Sclerosis. There are a number of people I would like to acknowledge for their contributions they have made to the research I have conducted at the Menzies Centre.

Firstly, my supervisors, Professor Dwyer and Associate Professor Anne-Louise Ponsonby. Professor Dwyer has not only given me the opportunity to conduct my PhD at the Menzies Centre, but has also contributed greatly to my increased epidemiological knowledge as well as being central in providing feedback on statistical analyses, publications and thesis chapters.

Thanks must also go to my second supervisor, Anne-Louise Ponsonby. I am deeply grateful to Anne-Louise for the incredible amount of time devoted to supervising me. Her constructive criticism and eye for detail has resulted in high quality research, which is reflected in some excellent results in this thesis. I have benefited in areas such as research methods, publication writing and statistical analyses as well as the invaluable skill of improving efficiency when working part-time. With Anne-Louise located in Canberra, our contact was mostly by phone and email. This was refined to a fine art (with only the very occasional glitch in the system).

I would like to sincerely thank the research team involved in the fieldwork. High quality work can only be done with a high quality team. Trish Groom and Jane Pittaway conducted the interviews in a professional and personable manner. They made many evening phone calls and pursued every avenue to obtain high response rates. Thanks to Natasha Newton for her excellent data entry and both Natasha and Emma Stubbs for their administrative assistance. Tim Albion created a solid database for our complex work, which never failed.

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PUBLICATIONS AND PRESENTATIONS AT SCIENTIFIC MEETINGS

Publications

Ponsonby A-L, van der Mei IAF, Dwyer T, Blizzard, BV Taylor, Kemp A, Simmons RD, Kilpatrick T. High infant contact during early life is associated with a reduced risk of multiple sclerosis. Manuscript submitted to JAMA.

“What affects your MS? – Responses to an anonymous, Internet-based epidemiological survey.” Simmons RD, Ponsonby AL, van der Mei IAF, Sheridan P. Multiple Sclerosis 2004;10:202-211

van der Mei IAF, Ponsonby A-L, Dwyer T, Blizzard L, Simmons R, Taylor BV, Butzkueven H, Kilpatrick T. Past sun exposure, skin phenotype and risk of multiple sclerosis: a case-control study. BMJ 2003;327:316-320

Ponsonby A-L, McMichael A, van der Mei IAF. Ultraviolet radiation and autoimmune disease: insights from epidemiological research. Toxicology 2002;181-182:71-78

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Rubio JP, Bahlo M, Butzkueven H, van der Mei IAF, Sale MM, Dickinson JL, Groom P, Johnson LJ, Simmons RD, Tait B, Varney M, Taylor B, Dwyer T, Williamson R, Gough NM, Kilpatrick TJ, Speed TP Foote SJ. Genetic dissection of the HLA region using haplotypes of Tasmanians with Multiple Sclerosis. Am J Hum Genet 2002;70:1125-1137

van der Mei IAF, Ponsonby AL, Blizzard L, Dwyer T. Regional variation in Multiple Sclerosis prevalence in Australia and its association with ambient Ultraviolet radiation. Neuroepidemiology 2001;20:168-174.

Scientific presentations

van der Mei IAF, Ponsonby AL, Dwyer T, Blizzard L, Simmons R, Taylor BV, Butzkueven H, Kilpatrick T. Past sun exposure, skin phenotype and risk of multiple sclerosis: a case-control study. The Royal Australian College of General Practitioners 46th National convention & Annual General Meeting Balance, Hobart, October 2003 (Oral presentation)

van der Mei IAF, Ponsonby AL, Dwyer T, Blizzard L, Simmons R, Taylor BV, Butzkueven H, Kilpatrick T. Past sun exposure, skin phenotype and risk of multiple sclerosis: a case-control study. Australasian Epidemiological Association Annual Meeting, Perth, September 2003 (Oral presentation, Awarded with travel bursary)

van der Mei IAF, Ponsonby AL, Dwyer T, Blizzard L, Simmons R, Taylor BV, Butzkueven H, Kilpatrick T. Past sun exposure, skin phenotype and risk of multiple sclerosis: a case-control study. International Society for Environmental Epidemiology, Perth, September 2003 (Poster

presentation)

van der Mei IAF, Ponsonby A-L Current epidemiological research in Australia to assess the role of exposure of ultraviolet radiation and other environmental factors on Multiple Sclerosis. Scientific meeting on "Progress in Multiple Sclerosis Research", Sydney, October 2002 (Oral presentation)

van der Mei IAF, Stankovich J, Ponsonby A-L, Dwyer T. An approach to study gene-environment interactions in the Tasmanian Multiple Sclerosis Research Program. Australasian Epidemiological Association Annual Meeting, Canberra, November 2000 (Oral presentation)

van der Mei IAF, Ponsonby A-L, Blizzard L, Dwyer T. Regional variation in Multiple Sclerosis prevalence in Australia and its association with ambient Ultraviolet radiation. Scientific meeting on 'Progress in Multiple Sclerosis Research', Melbourne, November 2000 (Oral presentation)

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Travel bursary for Australasian Epidemiological Association Annual Meeting, Perth, September 2003 for oral presentation: Past sun exposure, skin phenotype and risk of multiple sclerosis: a case-control study.

Travel bursary for Australasian Epidemiological Association Annual Meeting, Canberra, November 2000 for oral presentation: An approach to study gene-environment interactions in the Tasmanian Multiple Sclerosis Research Program.

ABBREVIATIONS

AF	Attributable fraction
CGRP	calcitonin gene related peptide
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
DSS	Disability Status Scale
EAE	experimental allergic encephalomyelitis
EA-R	early antigen complex (restricted), viral protein of Epstein-Barr virus
EA-D	early antigen complex (diffuse), viral protein of Epstein-Barr virus
EBNA	Epstein-Barr nuclear antigen, viral protein of Epstein-Barr virus
EBV	Epstein-Barr virus
EDSS	Expanded Disability Status Scale
HHV	human herpes virus
HLA	human leukocyte antigen
HSV	herpes simplex virus
ICC	intraclass correlation coefficient
IDDM	type 1 diabetes mellitus
Ig	immunoglobulin
IL	interleukin
IM	infectious mononucleosis
INF	interferon
κ	kappa statistic
MBP	myelin basic protein
MED	mean erythematous dose
MHC	major histocompatibility complex
MOG	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
MS	Multiple Sclerosis
ON	optic neuritis
OR	odds ratio
PLP	proteolipid protein
RR	rate ratio
SD	standard deviation
SE	standard error
Th	T helper
TNF	tumour necrosis factor
TGF	transforming growth factor
UVR	ultraviolet radiation
VCA	viral capsid antigen, viral protein of Epstein-Barr virus
VZV	varicella zoster virus

