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Studies of associations between disability in multiple sclerosis, skin type, gender and ultraviolet radiation

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Recent studies suggest ultraviolet radiation (UVR)/vitamin D is protective against the development of multiple sclerosis (MS). We determined if outcome in MS is associated with the surrogate for host pigmentation, skin type, and parameters of UVR exposure. We used a validated questionnaire to determine skin type and UVR exposure during childhood (0–16 years), and early adult life (17–40 years), in 448 Caucasians with MS. Outcome was assessed using the Kurtzke Expanded Disability Status Score (EDSS) and Multiple Sclerosis Severity Scale (MSSS). We studied the association of skin type and exposure with dichotomized values of EDSS ($<$ and ≥ 6) and MSSS (continuous variable) using logistic and linear regression analyses, respectively. Sex, onset age and MS duration were significantly associated with outcome in all patients. In 169 females with established disease (≥ 10 years), sun sensitive skin types 1 and 2 were associated with reduced risk of EDSS ≥ 6 (odds ratio = 0.50; 95% CI = 0.26–0.97), and higher MSSS values (coefficient = -0.86; 95% CI = -1.67 to -0.05). Parameters of UVR exposure were not significantly associated with outcome. These preliminary data show an association between skin type and disability in female MS patients. They are compatible with independent studies suggesting that exposure mediates MS pathogenesis via vitamin D. Further studies are required to properly assess these potentially important findings. *Multiple Sclerosis* 2007; **13**: 369–375. http://msj.sagepub.com

Key words: disability evaluation; epidemiology; multiple sclerosis; sex factors; skin type; ultraviolet rays

Introduction

Multiple sclerosis (MS) is a chronic, demyelinating disease, with a clinical course mediated by poorly understood genetic–environmental interactions [1–3]. Data from a variety of studies have implicated the extent of exposure to ultraviolet radiation (UVR) as an environmental factor that mediates risk and outcome. Thus, the US Veterans study reported a negative correlation between MS rates and indices of annual and winter sunshine [4], and in Australia, the negative relationship between UVR and risk is stronger than the positive link with melanoma [5,6]. Exposure during childhood appeared particularly important, a finding compatible with migration studies [5–7]. MS mortality has been negatively associated with UVR exposure, and photochemotherapy with UVR-A and 1,25-dihydroxyvitamin D prevents progression in the experimental allergic encephalomyelitis (EAE) mouse model of MS [8–11]. In patients, vitamin D supplementation results in increased transforming growth factor-β [12], a cytokine linked with inhibition of MS-like effects in EAE mice. Further, a seasonal relationship between the number of active lesions found using gadolinium-enhancing

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magnetic resonance imaging (MRI) and serum 25-hydroxyvitamin D levels is reported [13]. The mechanism of these effects is unclear, though UVR directly or via vitamin D may mediate the Th1 and Th2 cell balance [10]. Interestingly, vitamin D deficiency, decreased bone density and increased fractures are common in MS patients [14]. There are no data examining the association between UVR exposure and disability in MS patients, though clearly, such a link would have public health implications.

Skin pigmentation is an important phenotype in the context of UVR and MS outcome; increased pigmentation results in reduced vitamin D synthesis [15]. The widely-used Fitzpatrick classification system [16], assesses the tanning and burning reaction of skin to UVR. Thus, skin type 1 describes Caucasians who cannot tan and whose skin burns easily, while type 4 describes easy tanning and rare burning. It might be hypothesized that subjects with sun sensitive skin types 1 and 2 are less likely to suffer severe disability, as their relative failure to pigment allows optimum vitamin D synthesis.

We have determined if MS patients with skin types 1 and 2 suffer less disability, assessed using the Kurtzke Expanded Disability Status Scale (EDSS) [17], and recently described Multiple Sclerosis Severity Score (MSSS) [18]. This approach corrects EDSS by comparing a patient's disability with the distribution of scores in cases with equivalent disease duration. We have also determined whether the extent and duration of exposure, particularly during childhood and early adult life, are associated with the extent of disability. Sex, age at onset and disease duration are strongly associated with the extent of disability and were included.

Materials and methods

Patients

Unrelated Northern European Caucasians, with clinically definite MS (Poser criteria), were recruited with written informed consent and Ethics Committee approval from the Neurology Departments in the University Hospital of North Staffordshire and Walton Centre in the neighbouring Mersey Region. We recruited 1075 cases into a study designed to identify genetic factors associated with MS risk and outcome, and distributed the UVR questionnaire for self-completion to 901 cases. We obtained a response from 474 patients and a complete response from 448 patients.

Assessment of disability

Clinical examinations were performed by a neurologist during a stable period of disease. At the time of EDSS assessments, none of the patients studied had received disease-modifying therapy. EDSS values were dichotomized into 0–5.5 (mild/moderate disability) versus 6–10 (severe disability). MSSS values were determined using the algorithm available on http://www-gene.cimr.cam.ac.uk/MSgenetics/GAMES/MSSS

UVR exposure and skin type

Cases completed a validated questionnaire [19] which recorded: (i) skin type – type 1 = always burn/never tan, type 2 = usually burn/tan with difficulty, type 3 = sometimes mild burn/average tanning ability, and type 4 = rarely burn/easily tan; (ii) cumulative exposure, determined by adding hours of exposure on each weekday and during weekends in categories – $\leq$16 and 16.1–40 years; (iii) sunburning during 0–16 years recorded as no/yes; and (iv) sunbathing assessed as never, rarely, occasionally and often, during $\leq$16 and 16.1–40 years.

Statistical analysis

Analyses were performed using Stata release 8 for Windows (Stata Corporation, College Station, TX, USA). We used logistic regression analysis to study the association between exposure parameters and EDSS ($<$6.0 versus $\geq$6.0) [20]. MS disability is significantly associated with disease duration, and as most cases entering into research studies have only a single EDSS measurement, measurements should be normalized for disease duration. This is problematic in a cross-sectional study. Accordingly, to lessen the impact of duration, we first studied the case group of 448 patients and secondly, a subgroup of 233 patients in whom the disease course was established, as they had suffered MS for at least 10 years [20]. The MSSS corrects EDSS by comparing disability with the distribution of scores in cases with equivalent duration [18]. This outcome measure should be less influenced by duration. We used linear regression analysis (with sex, onset age, but not duration) to study links with MSSS. As skin type 1 is relatively uncommon (5.4% cases), we combined cases with sun-sensitive types 1 and 2 and, examined their association with disability relative to types 3 and 4 combined as reference. We also combined sunbathing categories, never and rarely and, occasionally and often.

Results

MS patients

The characteristics of the patients studied ($n = 448$, mean onset age = 31.9 years, mean disease duration = 12.4 years, mean EDSS 4.4, 72.8% female), and patients not studied ($n = 453$, mean onset age = 30.5 years, mean disease duration = 12.8 years, mean EDSS 5.0, 70.4% female) were similar. Table 1 shows the characteristics of the total patient groups, female and male, as well as the number of cases with EDSS $<$ and ≥ 6. The risk of reaching EDSS ≥ 6 was positively associated with MS duration (odds ratio = 1.11/year; 95% CI = 1.07–1.14), onset age (MS duration-adjusted odds ratio = 1.07/year; 95% CI = 1.05–1.10) and male (MS duration-adjusted odds ratio = 2.07; 95% CI = 1.05–1.10). We used a 20-point moving average plot to demonstrate a clear linear relationship between EDSS and MS duration. The relationship of EDSS with onset age was linear, but much weaker. EDSS and MSSS values were significantly associated (Pearson's $P = 0.8140$). In individual linear regression models, male (coefficient = 0.84; 95% CI = 0.46–1.22), and increasing onset age (coefficient = 0.08; 95% CI = 0.06–0.10), were linked with increasing MSSS.

Skin type, EDSS and MSSS in the total case group

In 448 cases, we first determined that relative to skin types 3/4, types 1/2 were not significantly associated with reduced risk of worse outcome assessed using EDSS (MS duration, sex, age at onset included), or MSSS (sex, age at onset included) (Table 2). We investigated if an association of skin type with disability was mediated by sex; relative to females with skin types 3/4, those with types 1/2 appeared at reduced risk of EDSS ≥ 6, though the association was not significant. No association was found in males (Table 2). Similar results were obtained with MSSS as endpoint with a non-significant association in females observed (Table 2).

Skin type, EDSS and MSSS in cases with established disease

As the range of MS duration was wide ($<$1–34 years), we studied 233 patients with MS of ≥ 10 years duration. The characteristics of these cases are shown in Table 3, and in addition to the exposure

Table 1 Characteristics of male and female MS patients with EDSS values $<$ and ≥ 6

	Total	Females	Males	EDSS <6	EDSS ≥ 6
No.	448	326	122	265 (59.2%)	183 (40.8%)
Females/males				206/59	120/63
Onset age (years ± SD)	31.9 ± 9.4	30.9 ± 8.7	32.8 ± 9.0	30.7 ± 9.0	33.7 ± 9.7
MS duration (years ± SD)	12.4 ± 8.6	12.4 ± 8.5	12.4 ± 8.7	10.5 ± 7.4	15.1 ± 9.5
Mean EDSS (± SD)	4.4 ± 2.1	4.2 ± 2.1	4.9 ± 1.9	3.0 ± 1.3	6.6 ± 0.78
Mean MSSS (± SD)	5.6 ± 2.7	5.3 ± 2.7	6.3 ± 2.5	4.1 ± 2.3	7.7 ± 1.6
MSSS (range)	0.16–9.9	0.16–9.9	0.30–9.9	0.16–9.1	4.2–9.9
Skin type					
1	24 (5.4%)	21 (6.4%)	3 (2.5%)	12 (4.5%)	12 (6.6%)
2	150 (33.5%)	113 (34.7%)	37 (30.3%)	99 (37.4%)	51 (27.9%)
3	217 (48.4%)	158 (48.5%)	59 (48.4%)	124 (46.8%)	93 (50.8%)
4	57 (12.7%)	34 (10.4%)	23 (18.9%)	30 (11.3%)	27 (14.8%)
Exposure (weeks)/year of life	8.9 ± 4.7	8.2 ± 4.4	10.2 ± 5.0	8.6 ± 4.5	9.4 ± 4.9
Hours exposure/day					
0–16 years	4.8 ± 2.4	4.6 ± 2.4	5.4 ± 2.4	4.7 ± 2.3	5.0 ± 2.4
16–40 years	4.1 ± 2.6	3.6 ± 2.3	5.0 ± 3.0	3.8 ± 2.5	4.4 ± 2.7
Childhood sunburn (no/yes)	191/257	140/186	51/71	106/159	85/98
Sunbathe 0–16 years					
Never	59 (13.2%)	44 (13.5%)	15 (12.3%)	37 (14.0%)	23 (12.6%)
Rarely	152 (33.9%)	105 (32.2%)	47 (38.5%)	93 (35.1%)	59 (32.2%)
Occasional	164 (36.6%)	124 (38.0%)	40 (32.8%)	99 (37.4%)	64 (35.0%)
Often	73 (16.3%)	53 (16.3%)	20 (16.4%)	36 (13.6%)	37 (20.2%)
Sunbathe 16–40 years					
Never	29 (6.5%)	22 (6.7%)	7 (5.7%)	14 (5.3%)	16 (8.7%)
Rarely	103 (23.0%)	68 (20.9%)	35 (28.7%)	64 (24.2%)	38 (20.8%)
Occasional	209 (46.7%)	151 (46.3%)	58 (47.5%)	127 (47.9%)	82 (44.8%)
Often	107 (23.9%)	85 (26.1%)	22 (18%)	60 (22.6%)	47 (25.7%)

Table 2 Skin type, exposure and outcome in MS patients

	OR[a] (95% CI)	P	Coeff[b] (95% CI)	*P*
Total case group ($n=448$)				
Skin type				
1 and 2	0.68 (0.36–1.30)	0.24	−0.06 (−0.57 to 0.43)	0.80
3 and 4	Reference		Reference	
Total case group: females ($n=326$)				
Skin type				
1 and 2	0.64 (0.38–1.06)	0.09	−0.41 (−1.01 to 0.18)	0.17
3 and 4	Reference		Reference	
Total case group: males ($n=122$)				
Skin type				
1 and 2	1.51 (0.67–3.40)	0.32	0.58 (−0.31 to 1.47)	0.20
3 and 4	Reference		Reference	
Cases with MS ≥10 years ($n=233$)				
Skin type				
1 and 2	0.69 (0.39–1.22)	0.21	0.61 (−0.09 to 1.45)	0.08
3 and 4	Reference		Reference	
Cases with MS ≥10 years: females ($n=169$)				
Skin type				
1 and 2	0.50 (0.26–0.97)	0.04	−0.86 (−1.67 to −0.05)	0.04
3 and 4	Reference		Reference	
Cases with MS ≥10 years: males ($n=64$)				
Skin type				
1 and 2	2.10 (0.57–7.76)	0.27	0.30 (−1.03 to 1.62)	0.66
3 and 4	Reference		Reference	
Cases with MS ≥10 years ($n=233$)				
Total exposure (weeks)/year of life	2.28 (0.06–93.3)	0.66	1.78 (−3.36 to 5.92)	0.40
Mean hours exposure/day				
0–16 years	1.03 (0.90–1.16)	0.76	0.08 (−0.07 to 0.23)	0.33
16–40 years	1.04 (0.92–1.17)	0.55	0.03 (−0.12 to 0.18)	0.68
Childhood sunburning (no/yes)	1.46 (0.78–2.72)	0.23	0.12 (−0.59 to 0.82)	0.75
Sunbathing 0–16 years				
Never/rarely	Reference		Reference	
Occasional/often	1.00 (0.87–1.15)	0.99	0.03 (−0.67 to 0.73)	0.93
Sunbathing 16–40 years				
Never/rarely	Reference		Reference	
Occasional/often	1.00 (0.88–1.14)	0.96	0.10 (−0.67 to 0.86)	0.80

[a]Logistic regression analysis (gender, onset age, MS duration in models) of association of variables with EDSS < and ≥6. In individual models, MS duration (odds ratio = 1.04, 95% CI = 1.02–1.08, $P=0.003$; male sex (odds ratio = 1.60, 95% CI = 1.06–2.42, $P=0.026$) and onset age (odds ratio = 1.05, 95% CI = 1.02–1.08, $P=0.003$) were significantly associated with EDSS.
[b]Linear regression analysis (gender, age at onset in models) of association between variables and MSSS. In individual models, males (coefficient = 0.54, 95% CI = 0.02–1.07, $P=0.043$) and onset age (odds ratio = 0.09, 95% CI = 0.06–0.13, $P<0.001$) were significantly associated with MSSS.

parameters (not shown), are similar to those in Table 1. Relative to skin types 3/4, types 1/2 were not significantly associated with either EDSS or MSSS, though the link with MSSS approached significance. We stratified cases by gender and found that relative to females with skin types 3/4, those with types 1/2 were at significantly reduced risk of EDSS ≥6 or higher MSSS (Table 2). Skin types 1 and 2 were similarly associated (odds ratio = 0.50; 95% CI = 0.15–1.61 and odds ratio = 0.39; 95% CI = 0.07–2.16, respectively), with EDSS indicating the validity of combining cases with these phenotypes. A similar association was observed for MSSS (data not shown). No associations were observed in males for either EDSS or MSSS. Inclusion of the UVR exposure parameters, shown in Table 1, in models did not change the values of the odds ratios or coefficients shown in Table 2 (data not shown).

The association of EDSS with skin type was similar in patients stratified by the median onset age (29.0 years); <29 years odds ratio = 0.46, 95% CI = 0.14–1.52; >29 years odds ratio = 0.47, 95% CI = 0.21–0.95. Similar results were obtained for MSSS (data not shown).

To check these associations were not dependent on the EDSS cut-off < and ≥6.0, we performed

Table 3 MS patients with EDSS $<$ and ≥ 6 and duration ≥ 10 years

	Total	Females	Males	EDSS <6	EDSS ≥ 6
No.	233	169	64	114 (48.9%)	119 (51.1%)
Females/males				90/24	79/40
Onset age (years $\pm$ SD)	29.4 $\pm$ 8.6	28.9 $\pm$ 8.2	31.7 $\pm$ 8.2	27.4 $\pm$ 7.8	31.3 $\pm$ 8.9
MS duration (years $\pm$ SD)	18.9 $\pm$ 6.8	18.8 $\pm$ 6.8	18.9 $\pm$ 6.9	17.3 $\pm$ 5.7	20.4 $\pm$ 7.5
Mean EDSS ($\pm$ SD)	4.9 $\pm$ 2.1	4.6 $\pm$ 2.2	5.4 $\pm$ 1.8	3.1 $\pm$ 1.4	6.7 $\pm$ 0.81
Mean MSSS ($\pm$ SD)[a]	4.9 $\pm$ 2.6	4.7 $\pm$ 2.7	5.5 $\pm$ 2.4	2.7 $\pm$ 1.6	6.7 $\pm$ 1.6
Skin type					
1	12 (5.2%)	10 (5.9%)	2 (3.1%)	6 (5.3%)	6 (5.0%)
2	69 (29.6%)	57 (33.7%)	12 (18.8%)	39 (34.2%)	30 (25.2%)
3	120 (51.5%)	86 (50.9%)	34 (53.1%)	55 (48.3%)	65 (54.6%)
4	32 (13.7%)	16 (9.5%)	16 (25.0%)	14 (12.3%)	18 (15.1%)

[a]Spearman $p = 0.7973$ for correlation between EDSS and MSSS.

secondary analyses to demonstrate that skin types 1/2 were associated with better outcome in females, with at least 10 years MS duration, dichotomized by EDSS <5.0 versus ≥ 5.0 (odds ratio = 0.53; 95% CI = 0.29–0.98) and <7.0 and ≥ 7.0 (odds ratio = 0.45; 95% CI = 0.18–1.08). These associations were not observed in male cases.

UVR exposure, EDSS and MSSS

Studied individually, parameters of exposure during ≤ 16 and 16.1–40 years of age, hours of exposure/day, childhood sunburning and sunbathing history were not significantly associated with EDSS or MSSS in either the 448 or 233 patients with MS of ≥ 10 years duration.

Relationship between UVR and skin type

In the 448 MS cases, increasing levels of exposure were associated with increasing skin type. Thus, testing for trend for the linear regression of sunbathing (all $P = 0.001$), hours exposure/day ($P = 0.048$, $P = 0.022$, respectively) and weeks exposure/year of life ($P = 0.003$) regressed over skin type, gave significant increases between ≤ 16 and 16.1–40 years. Childhood sunburning showed a significant negative trend with skin type ($P < 0.001$) in a logistic regression.

Discussion

MS is a leading cause of disability in Caucasians, though few factors are known to influence disease course. The possibility that UVR is protective of disease pathogenesis is suggested by various studies.

Identifying factors associated with disability in MS is problematic, as this endpoint is difficult to define. EDSS is widely-used, with low values reflecting multi-domain impairment, and middle and high values reflecting mobility. The correlation between EDSS and MRI indices of cerebral disease burden is not strong, implying that not all biological disease activity is assessed by this measure. However, EDSS does convey useful clinical information about disability and progression. Thus, a score of 3.5 indicates combinations of mild/moderate impairments in different domains, a score of 6 indicates a requirement for unilateral assistance to walk only 100 m, and a score of 8 indicates restriction to a wheelchair. Our main analysis was based on dichotomizing cases to good (EDSS <6.0) or bad (EDSS ≥ 6.0) outcomes. This point is defined with little inter-observer variability and has been previously used by us [20].

EDSS was associated with MS duration, indicating that assessing the impact of variables on outcome is best studied using a prospective approach. However, the rate of accumulation of disability is relatively slow (median time to EDSS = 6 is about 15 years) [2], and it is reasonable to first assess factors in a cross-sectional study. This requires that EDSS is normalized for MS duration. As EDSS is ordinal, the ratio EDSS/time from onset is not valid. We previously studied cases with a duration of ≥ 10 years, in whom MS course is more established. While this cut-off is somewhat arbitrary, it has been used with an EDSS ≤ 3.0 to define benign MS. Importantly, duration is significantly associated with EDSS, even in cases with MS for at least 10 years (Table 2). MSSS is also useful. Patients are stratified by the number of years from first symptoms until EDSS assessment, and a score is generated for each value of EDSS and MS duration. Thus, an MSSS of 5.0 describes severity progression at the median rate [18].

Exposure data were obtained using a questionnaire previously validated for use in skin cancer patients, and used by us to demonstrate a significant inverse association between UVR and prostate cancer risk in a smaller group than the current

study investigated [19]. Various questionnaires have been used to assess UVR exposure, but none has gained universal acceptance. All suffer from recall bias. A further complicating factor is that the extent of exposure to UVR may be substantially determined by host characteristics, such as skin type. We considered exposure before and after 16 years as migration age affects MS risk, though the UVR effect may occur *in utero* [21]. The UVR questionnaire has not been validated in MS patients, though in previous studies in 419 hospital clinic-recruited MS cases [20], patient assignments of their skin type agreed with that of the interviewing neurologist (unpublished data). Importantly, the expected relationship between skin type and extent of exposure was observed.

The ability to tan is central to the UVR/MS outcome hypothesis. Previous studies in patients with various diseases have shown that classifying subjects as skin types 1 or 4 is straightforward, though differentiating subjects with type 2 and 3 may be more problematic [22]. While we report an association between disability and skin type, this link was strongly determined by disease duration and gender. Thus, no significant association was observed in the total group of 448 male and female patients. Importantly, disease duration in these subjects varied from less than one year to more than 40 years, with about 20% patients having less than five years duration. Accordingly, we studied cases with MS duration of at least 10 years. The association of skin type with disability was gender-dependent. Thus, the association between skin types 1/2 and reduced risk of EDSS ≥ 6, that was not significant in the total group of 326 females, achieved significance in 169 females with a duration ≥ 10 years. The data indicate that skin type does not mediate disability in males. However, the numbers of males was relatively small and a larger group is needed to confirm this suggestion.

No significant associations between the various exposure parameters and disability were observed in females or males.

Our data are preliminary and require cautious interpretation and independent replication because of the difficulties in assessing previous exposure to UVR, skin type, and the relationship between duration and disability. The study was relatively small because final analysis was based on cases with MS ≥ 10 years duration. Even in these cases, duration was linked with disability, though we found similar links between skin type and EDSS in females with MS durations of up to 22 years (fourth quartile) (odds ratio = 0.31; 95% CI = 0.09–1.09). Even using MSSS as endpoint, identification of significant associations was dependent on the study of cases with established disease. Most studies show that gender exerts a significant effect on disability [23–26]. Thus, accumulation of disability is faster in males [23], and beta interferon may delay progression in females but not males [24]. Further, 1,25-dihydroxyvitamin D is protective in female but not male EAE mice [25]. In humans, females have higher skin reflectance (lighter skin) than males, though males are more sensitive to UVR, having a significantly lower mean minimal erythemal dose [27]. It is possible that females are more efficient at synthesizing vitamin D than males, and use the vitamin more effectively.

The mechanism for the observed association is unclear, though it could be based on skin type-mediated effects on the impact of UVR on the immune system or, on synthesis of vitamin D. Our data have replicated findings in skin and prostate cancer cases that skin type 1 individuals have lower levels of exposure to UVR than those with other types, presumably because of sun avoidance to reduce skin burning [28]. Some skin type 1 subjects may be hypovitaminotic because of low exposure and therefore, at increased risk of diseases putatively associated with chronically low vitamin D levels, though we did not observe this possibility in prostate cancer patients; skin type 1 was protective, implying that males with skin type 1 synthesized adequate amounts of vitamin D even though they had lower levels of exposure [28]. The relationship between skin type, extent/pattern of exposure, vitamin D synthesis and disease risk is poorly understood and may differ between case groups. Thus, low pigment skin type has been linked with increased risk of Type 1 diabetes, and it has been argued that polymorphic variants in pigmentation-associated genes associated with skin type 1 may be linked with increased MS risk [29,30]. While some data are conflicting, it is also noteworthy that there are reports that African-Americans patients (ie, skin types 5/6) with MS suffer worse outcomes than Caucasians [31]. Thus, while the concept that exposure to UVR may mediate clinical phenotype in a variety of diseases has potentially important public health implications, available data do not allow conclusions to be drawn.

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