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ORIGINAL INVESTIGATION

Seasonality and BDNF polymorphism influences depression outcome in patients with atopic dermatitis and psoriasis

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ABSTRACT

Objectives: To examine the effect of seasonality and rs6265 genotype on depression outcome and brain-derived neurotrophic factor (BDNF) level with dermatitis patients from onset through remission.

Methods: Atopic dermatitis (AD, 56) and psoriasis (PS, 33) patients and healthy controls (HC, 49) were recruited over the 2014 calendar year. Patients were subdivided by immunoglobulin E (IgE) sensitivity (AD only), season and rs6265 genotype. Assessments were performed at onset and week 10 (Hamilton Depression Rating Scale [HAM-D], SCORAD/PASI, IgE, BDNF). Patients received standard corticosteroid and antihistamine interventions.

Results: All patients responded to corticosteroid treatment. Seasonally differential outcomes were observed in all groups. HAM-D was elevated at onset and improved over 10 weeks: AD cohort 1 (autumn/winter, AD-1) patients improved and AD cohort 2 (spring/summer, AD-2) patients remained elevated. BDNF levels were elevated in AD and seasonal differential: AD-2 declined at 10 weeks, whereas AD-1 remained high (intrinsic AD) or elevated further (extrinsic AD). PS cohort 2 declined to below control at 10 weeks. AD Val/Val had persistently elevated HAM-D and AD Val/Met were either normal (AD-1) or persistently elevated (AD-2).

Conclusions: Findings presented here suggest a strong influence of seasonality on depression outcome and BDNF expression in AD and PS and likely reflect separate patient populations which differentially respond to environment-based stressors.

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Atopic dermatitis; psoriasis; brain-derived neurotrophic factor; depression; seasonal variation

Introduction

Atopic dermatitis (AD) and psoriasis (PS) are chronic relapsing inflammatory skin diseases (Capon et al. 2004; Gupta et al. 2014; Mu et al. 2014; Harden et al. 2015) with prevalence worldwide ranging from 0.73 to 23.0% (Levy et al. 2003) and 0.91 to 8.5% (Parisi et al. 2013), respectively. High prevalence variability likely results from various factors including climate, ethnicity, genetic and socioeconomic causes as well methods of diagnosis and case definition (Ryan et al. 2014; Peng and Novak 2015). Seasonally related climate factors have traditionally been presumed to exacerbate dermatological diseases; however, few studies have directly addressed factors of climate in assessment of clinical outcomes.

Seasonal changes in mood and behaviour are considered to be common in the general population and are more pronounced in patients with psychiatric disorders (Winthorst et al. 2014). It is well known that seasonality exacerbates both skin diseases and

affective disorders (Teng et al. 1995; Whitney et al. 1999; Weiss et al. 2008), presumably through different mechanisms. Some common factors relating to development of depression have been proposed (e.g., social stress, low sunlight, dietary deficiencies, hormonal imbalances, etc.). A link between psychiatric pathologies and dermatological disorders has been the subject of extensive research (Calikusu et al. 2002; Chrostowska-Plak et al. 2013; Cheng et al. 2015). Several studies have demonstrated a possible connection between psychodermatological disorders and brain-derived neurotrophic factor (BDNF), a neurotrophin extensively studied in relation to psychiatric disorders (Namura et al. 2007; Hoffman et al. 2009; Ma et al. 2009; Bus et al. 2014).

Elevated serum BDNF has been observed concurrent with AD dermatological symptom presentation (Raap et al. 2006). In one study of intrinsic (IgE non-sensitive) AD patients, elevated serum BDNF and specific BDNF isoforms were found to strongly associate

with presence of disease and familial inheritance of tendency to develop dermatitis (Ma et al. 2009). Reduction of serum BDNF also correlates well with remission of AD symptoms (Namura et al. 2007). Further, BDNF gene polymorphisms have also been demonstrated to predispose individuals to depression (Ribeiro et al. 2007; Chagnon et al. 2015) and some evidence exists that patients with different BDNF polymorphic genotypes are more sensitive to seasonal triggers of depressive episodes (Comasco et al. 2011). Exacerbation of atopic disorders may increase the risk of suicide in winter and spring months (Timonen et al. 2004), and several studies have reported that suicidal and depressed patients have subnormal BDNF serum levels (Dawood et al. 2007; Deveci et al. 2007; Kim et al. 2007; Lee et al. 2007; Lee and Kim 2009; Molendijk et al. 2011).

In the present study, we examined the association of seasonally variable climate factors on depression and BDNF level from dermatological symptom onset to remission in atopic dermatitis and PS patients. Additionally, the effect of BDNF rs6265 single-nucleotide polymorphism (SNP) genotype on depression was also assessed. We report here distinct, seasonally dependent differences in dermatitis patient depression outcomes and related changes in serum BDNF expression which appear to describe separate, unique patient populations.

Methods

Study population

A 10-week, case-control, single-centre study was conducted with 138 volunteers (56 AD, 33 PS and 49 healthy controls [HC]). AD patients were divided by IgE sensitisation: EAD (extrinsic atopic dermatitis, IgE sensitive; $n=33$) and IAD (intrinsic atopic dermatitis, IgE non-sensitive; $n=23$). In addition, AD patients were assessed according to seasonal cohorts (AD-1, $n=37$; AD-2, $n=19$). The following subgroups for analysis were formed: EAD-1 ($n=22$), EAD-2 ($n=11$), IAD-1 ($n=15$) and IAD-2 ($n=8$). Gender ratio (m/f: HC, 0.88; AD, 0.93; PS, 1.1) and mean age (Mean $\pm$ SEM: HC, 34.9 ± 1.3 ; AD, 41.6 ± 2.3 ; PS, 35.1 ± 2.3) of patient groups were similar. Dropout numbers were as follows: HC, none; AD, 10; PS, 9. Patient inclusion criteria: no unstable non-dermatological medical conditions or pregnancy, no psychotropic medications within the previous month, no oral glucocorticoids or topical corticosteroids within 5 days prior to blood sampling, no history of mental or dermatological disorders, and good general physical health. Antidepressants were

indicated for one patient initially recruited for the study, who was excluded. Cooperating psychiatrists indicated that no study patients required antidepressant medications.

The study was approved by the Astana Medical University Health Ethical Review Boards within guidelines established by the 1964 Declaration of Helsinki. Patients were enrolled in the study after written informed consent. After first blood sample, patients were provided conventional treatments. For atopic dermatitis patients, this included antihistamines (e.g., diphenhydramine, desloratadine), topical corticosteroids (e.g., betamethasone, mometasone) up to 3 weeks and emollients up to 2 months. Psoriasis patients received antihistamines (e.g., diphenhydramine, desloratadine), topical corticosteroids (e.g., betamethasone, mometasone) up to 3 weeks and keratolytics (2% salicylic ointment) up to 2 weeks. Patients did not receive antidepressants and other psychotropic agents. Within 10 weeks of initial presentation, remission of dermatological symptoms was observed in all patients treated.

Patient dermatological and psychological scoring

Dermatological and psychological status of the patients was assessed twice: at entry point in the exacerbation of the disease (week 0) and after treatment initiation in the remission stage (week 10). Psychological assessments were performed by a dermatologist with a psychometrician certificate under the supervision of a board-certified psychiatrist. AD patients were assessed using the scoring of atopic dermatitis (SCORAD) index, which included objective (extent and intensity) and subjective (daytime pruritus and sleep loss) criteria (Oranje et al. 2007). PS patients were evaluated using the Psoriasis Area and Severity Index (PASI) that included objective (extent and intensity) criteria (Iltatho et al. 2007). Depression was assessed according to Diagnostic and Statistical Manual (DSM-IV) criteria and with Hamilton Depression Rating Scale (HAM-D) using the following ranges: absence, ≤ 7 ; mild, 8–16; moderate, 17–27; severe, ≥ 28 .

AD and PS seasonal division criteria

Dermatitis patients were subdivided into two cohorts by seasonal criteria based on temperature, humidity and dew point measures. Winter and summer type exacerbation in AD is known to be influenced by climate factors (Kramer et al. 2005; Silcocks and Williams 2005; Engebretsen et al. 2016) and general climatic seasonal associations (Timonen et al. 2004;

Weiss et al. 2008). PS incidence has also shown seasonality, with greatest exacerbations in spring and autumn months (Hancox et al. 2004). Sensitivity to irritation and mechanical damage in skin is dependent on stratum corneum-bound water and the rate of evaporative water loss is inversely related to temperature, humidity (Agner and Serup 1989; Engebretsen et al. 2016) and dew point (Gaul and Underwood 1952; Engebretsen et al. 2016), all of which vary seasonally. Therefore, we chose the following criteria for seasonal division of AD and PS groups based on 2014 climate data for Astana, Kazakhstan: cohort 1 (October–March): mean daily temperature $<5^{\circ}\text{C}$, relative humidity low $>60\%$, mean daily dew point $<-5^{\circ}\text{C}$. cohort 2 (April–June): mean daily temperature $>5^{\circ}\text{C}$, relative humidity low $<60\%$, mean daily dew point $>-5^{\circ}\text{C}$.

Sample collection and processing

Blood was taken between 08:00 and 10:00 h to prevent daily variations on weeks 0 and 10 and collected to serum separation tubes and EDTA tubes (for DNA extraction). Samples were cooled (1 h, 4°C) and centrifuged ($2000 \times g$, 10 min, 25°C). Serum was stored at -20°C before analysis. DNA extraction from whole blood was performed ≤ 3 days from collection and stored (-70°C).

DNA extraction and genotyping of BDNF variants

DNA was extracted using Wizard Genomic DNA purification (Promega, USA, A1120) and measured using NanoDrop 8000 (Thermo Fisher Scientific, USA). Amplification of rs6265 allelic variants was performed in a Stratagene Mx 3000P (Agilent Technologies, USA)

with TaqMan SNP Genotyping Assay (Thermo Fisher Scientific).

Analysis of serum BDNF and IgE levels

BDNF assay was performed using a solid-phase, sandwich, two-site, ELISA (Promega, G7610). The total IgE was detected using solid-phase, chemiluminescent immunometric assay in an IMMULITE 1000 (Siemens, Germany).

Statistics

Two-sample comparisons were performed by unpaired *t*-test or paired *t*-test where appropriate (week 0: week 10 comparisons, verified by Pearson's correlation). Unpaired, one-way analysis of variance and Bonferroni means separation test was used for multiple group comparisons. Data are presented as mean $\pm$ SEM.

Results

Dermatological scoring

Dermatological scoring of patients yielded expected results, with both AD and PS patients responding favourably to corticosteroid and antihistamine treatment (Figure 1(a,b)). SCORAD rating of AD patients diminished by 46.3% (week 0: 37.5 ± 2.2 , $n = 56$; week 10: 20.1 ± 1.9 , $n = 46$; $P < 0.01$) and PASI scores of PS patients diminished by 57.0% (week 0: 17.9 ± 1.6 , $n = 33$; week 10: 7.7 ± 1.6 , $n = 24$; $P < 0.01$) by week 10 compared with symptom onset (study week 0). Measurement of serum IgE titres indicated the presence of two distinct subgroups of AD patients,

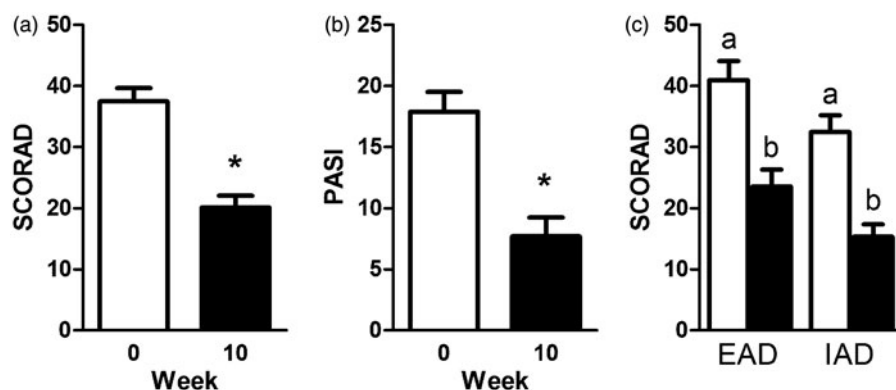


Figure 1. Scoring for disease activity in patients. (a) Mean SCORAD rating ($\pm$ SEM) of AD patients, (b) mean PASI rating ($\pm$ SEM) of PS patients at weeks 0 and 10. Asterisks denote differences ($P < 0.01$) between weeks 0 and 10 scores. (c) Mean SCORAD ($\pm$ SEM) of AD patients by IgE-sensitivity subtype. White bars: week 0; black bars, week 10. Letters of above bars denote results of a Bonferroni means separation test analysed within study week (one-way analysis of variance [ANOVA], $P < 0.001$). HC, healthy controls; EAD, extrinsic atopic dermatitis patients; IAD, intrinsic atopic dermatitis patients.

reflecting whether patients could be categorised as IgE sensitive (EAD) or IgE non-sensitive (IAD; Figure 1(c)). IgE titre in EAD (1133.0 ± 40.2 UI/ml, $n=33$) differed from that of IAD (47.5 ± 5.7 UI/ml, $n=23$; data not shown, $P < 0.0001$) at weeks 0 and 10 (EAD: 1165.0 ± 157.8 UI/ml, $n=27$; IAD: 43.3 ± 5.6 UI/ml, $n=19$; data not shown, $P < 0.0001$). No differences in IgE levels were observed in either AD group over the course of treatment. Examination of SCORAD ratings considered by AD subgroup did not reveal any differences in overall trend from that observed using pooled AD SCORAD data.

Elevated depression in dermatitis patients at symptom onset improves by week 10 in PS but remains elevated in AD

HAM-D scores indicated mild depression in dermatological patients (AD: 14.3 ± 0.9 , $n=56$; PS: 13.0 ± 1.1 , $n=33$) compared with HC (7.9 ± 0.9 , $n=52$; $P < 0.001$; Figure 2(a)). PS showed improvement to a level comparable to HC at 10 weeks (8.1 ± 1.1 , $n=24$), which differed from baseline ($P < 0.001$). In AD, however, HAM-D scores remained elevated compared with HC at week 10, but did constitute a reduction from baseline HAM-D scores at dermatitis onset (10.8 ± 0.7 , $n=46$; $P < 0.001$). AD patient HAM-D by IgE subtype indicated improvement at week 10 (EAD, $P < 0.001$; IAD, $P < 0.05$; Figure 2(b)); however, depression scores remained significantly elevated compared with HC ($P < 0.05$). Segregation of AD HAM-D data by IgE subtype did not indicate any difference in trend between extrinsic and intrinsic groups.

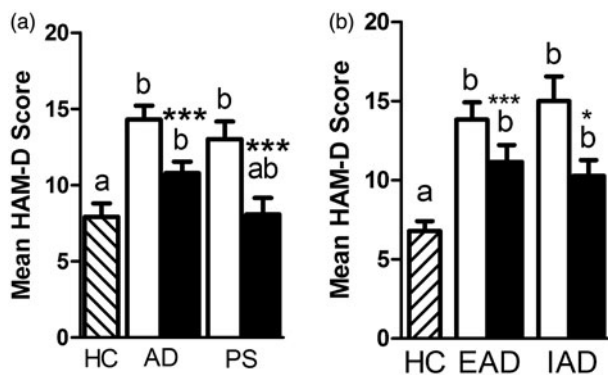


Figure 2. Depression scores in dermatological patients. (a) HAM-D scores in AD and PS patients. (b) HAM-D scores in AD patients by IgE subtype. Bars represent mean ($\pm$ SEM). Letters above bars are results of a Bonferroni means separation test analysed within study week (one-way ANOVA, $P < 0.05$). Asterisks above bars represent difference between weeks 0 and 10 means (* $P < 0.05$; *** $P < 0.001$). White bars: week 0; black bars: week 10. AD, atopic dermatitis patients (all).

Serum BDNF in AD at onset and week 10 were elevated compared with controls

Serum BDNF levels were distinctly elevated in AD (week 0: 49.74 ± 1.55 ng/ml, $n=56$; week 10: 50.69 ± 2.49 ng/ml, $n=46$) compared with both HC and PS at symptom onset ($P < 0.0001$; Figure 3). PS serum BDNF levels were not different from HC (40.49 ± 0.45 ng/ml, $n=49$) at either symptom onset (week 0: 40.12 ± 1.61 ng/ml, $n=33$) or week 10 (week 10: 38.64 ± 1.85 ng/ml, $n=24$). At week 10, no significant change in serum BDNF from week 0 baseline of AD patients was observed. Subdivision of AD into EAD (week 0: 48.54 ± 1.76 ng/ml, $n=33$; week 10: 52.30 ± 3.82 ng/ml, $n=27$) and IAD (51.47 ± 2.83 ng/ml, $n=23$; 48.40 ± 2.66 ng/ml, $n=19$) groups did not indicate any differences in serum BDNF level at either week 0 or week 10. However, both groups were different from HC ($P < 0.0001$, data not shown) at both weeks 0 and 10 and a reduction in IAD BDNF was observed at week 10 compared with week 0 ($P < 0.01$, data not shown).

BDNF Val/Val genotype: elevated depression at symptom onset and week 10 in AD, elevated depression at symptom onset with recovery at week 10 in PS

Genotyping results for BDNF rs6265 (Val66Met) polymorphism indicated allelic frequencies for patient groups were as follows: HC (Val: 0.816, Met: 0.184), AD (Val: 0.786, Met: 0.214), PS (Val: 0.712, Met: 0.288). Genotypic distributions for patient groups were as follows (Val/Val:Val/Met:Met/Met): HC (0.653:0.327:0.020), AD (0.643:0.286:0.071), PS (0.485:0.455:0.061).

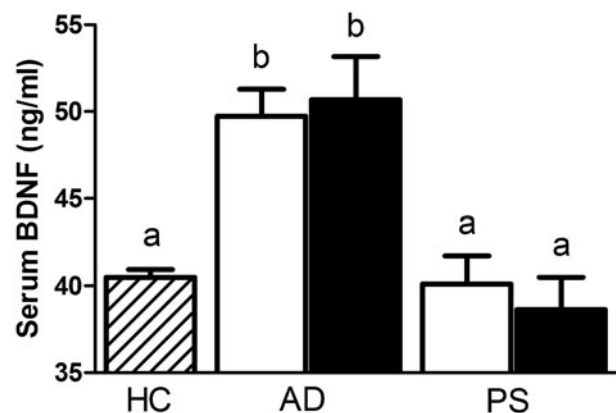


Figure 3. Serum BDNF levels in dermatitis patients. Comparison by study week with pooled atopic dermatitis patient data. Bars represent means ($\pm$ SEM) of serum BDNF levels (ng/ml) at week 0 (white bars) and week 10 (black bars). Letters above bars are results of a Bonferroni means separation test analysed within study week (one-way ANOVA; week 0: $P < 0.0001$, week 10: $P < 0.0001$).

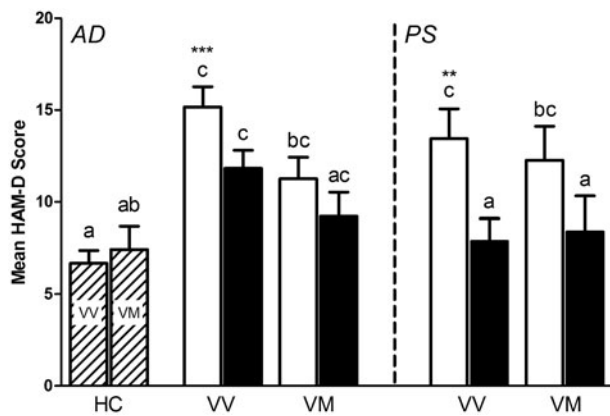


Figure 4. HAM-D scores of AD and PS patients compared by rs6265 BDNF polymorphism. Bars represent mean ($\pm$ SEM). Letters above bars are results of a Bonferroni means separation test compared within study week (one-way ANOVA, $P < 0.001$). Asterisks represent differences between weeks 0 and 10 means (** $P < 0.01$; *** $P < 0.001$). VV, rs6265 Val/Val genotype; VM, rs6265 Val/Met genotype.

BDNF Met/Met genotype data was not analysed for effects on depression or serum BDNF level due to small sample size.

HAM-D results by rs6265 polymorphism in AD and PS suggested existence of genotype-specific changes in depression over the course of the study. AD patients with Val/Val presented with mild depression at symptom onset (15.2 ± 1.1 , $n = 36$) and improved by week 10 (11.8 ± 1.0 , $n = 28$; $P < 0.001$), but remained mildly depressed compared with HC (Val/Val: 6.7 ± 0.7 , $n = 32$; Val/Met: 7.4 ± 1.3 , $n = 16$; $P < 0.001$; Figure 4). Val/Met patients presented with mild depression at week 0 (11.3 ± 1.2 , $n = 16$) and week 10 (9.2 ± 1.3 , $n = 14$) compared with HC, without significant improvement. Specifically, Val/Met patient HAM-D did not differ from the corresponding Val/Met HC at either week 0 or week 10, which suggests depression scores of this AD group represent intermediate values between the Val/Val AD and HC groups.

Val/Val PS patients were mildly depressed at symptom onset (13.4 ± 1.6 , $n = 16$) but improved to HC levels by week 10 (7.9 ± 1.2 , $n = 11$; $P < 0.01$). Val/Met PS patients presented with elevated depression scores at week 0 (12.3 ± 1.9 , $n = 15$); however, this elevation was not different from Val/Met HC scores and decrease in HAM-D at week 10 (8.4 ± 1.9 , $n = 12$) was also not significant. Noting that week 0 scores did not differ from week 0 Val/Val scores, these Val/Met PS results were interpreted to represent intermediate score values. Separation of genotypic groups by seasonal cohort revealed AD-1 Val/Met patients did not differ from HC (data not shown), whereas AD-1 Val/Val patients displayed a pattern similar to pooled Val/Val data

(elevated HAM-D at week 0: 13.8 ± 1.3 , $n = 25$ and week 10: 10.2 ± 1.1 , $n = 18$; $P < 0.001$, data not shown). AD-2 Val/Met patient HAM-D scores were consistently elevated over HC at both week 0 (16.5 ± 1.5 , $n = 8$) and 10 (13.3 ± 1.9 , $n = 6$; $P < 0.001$, data not shown).

Examination of serum BDNF level by rs6265 genotype did not indicate any differences between genotypic groups in either AD (EAD and IAD) or PS. AD serum BDNF remained significantly elevated compared with HC regardless of rs6265 genotype (week 0: Val/Val, 49.0 ± 2.3 , $n = 36$; Val/Met, 51.4 ± 1.8 , $n = 28$. Week 10: Val/Val, 49.5 ± 3.0 , $n = 28$; Val/Met, 53.3 ± 5.7 , $n = 14$; $P < 0.0001$, data not shown). Finally, separation of AD patients by cohort and rs6265 genotype indicated that AD-1 was persistently elevated over HC at week 0 ($P < 0.0001$, data not shown) and week 10 ($P < 0.0001$, data not shown), whereas AD-2 was elevated over HC at week 0 (Val/Val, 46.7 ± 1.0 , $n = 11$; Val/Met, 49.6 ± 1.8 , $n = 7$; $P = 0.0003$, data not shown) and declined to HC levels by week 10 (data not shown). Cohort analysis of PS genotype data was not performed due to small sample size.

Season of dermatosis onset has a primary influence on resolution of depression

HAM-D scores in all dermatitis patients were elevated at symptom onset (AD-1: 12.5 ± 1.1 , $n = 37$; AD-2: 17.7 ± 1.5 , $n = 19$; PS-1: 11.2 ± 1.8 , $n = 18$, PS-2: 15.2 ± 1.0 , $n = 15$) compared with HC when divided by seasonal cohort with AD-2 patients presenting with scores significantly higher than other patient groups ($P < 0.0001$, Figure 5(a)). Improvement in depression by week 10 to scores indistinguishable from HC was observed in all dermatitis patient groups (AD-1: 9.2 ± 0.8 , $n = 29$; PS-1: 7.7 ± 1.4 , $n = 14$; PS-2: 8.6 ± 1.7 , $n = 10$), with the exception of AD-2 (13.5 ± 1.2 , $n = 17$), which remained significantly elevated ($P < 0.0001$). Examination of AD HAM-D scores by seasonal cohort and IgE sensitivity indicated no differences in trend between IgE subtypes (Figure 5(b,c)), which suggested that differences among patient group HAM-D scores were mainly attributed to season of onset. Ratio of rs6265 genotypes represented in each cohort were found to be similar ($P > 0.5$, data not shown).

Cohort 1 AD patients display elevated serum BDNF at dermatological symptom onset and further increase at week 10

Serum BDNF titre when examined by pooled data indicated a simple relationship between disease and BDNF level (Figure 3), whereas subdivision of data by

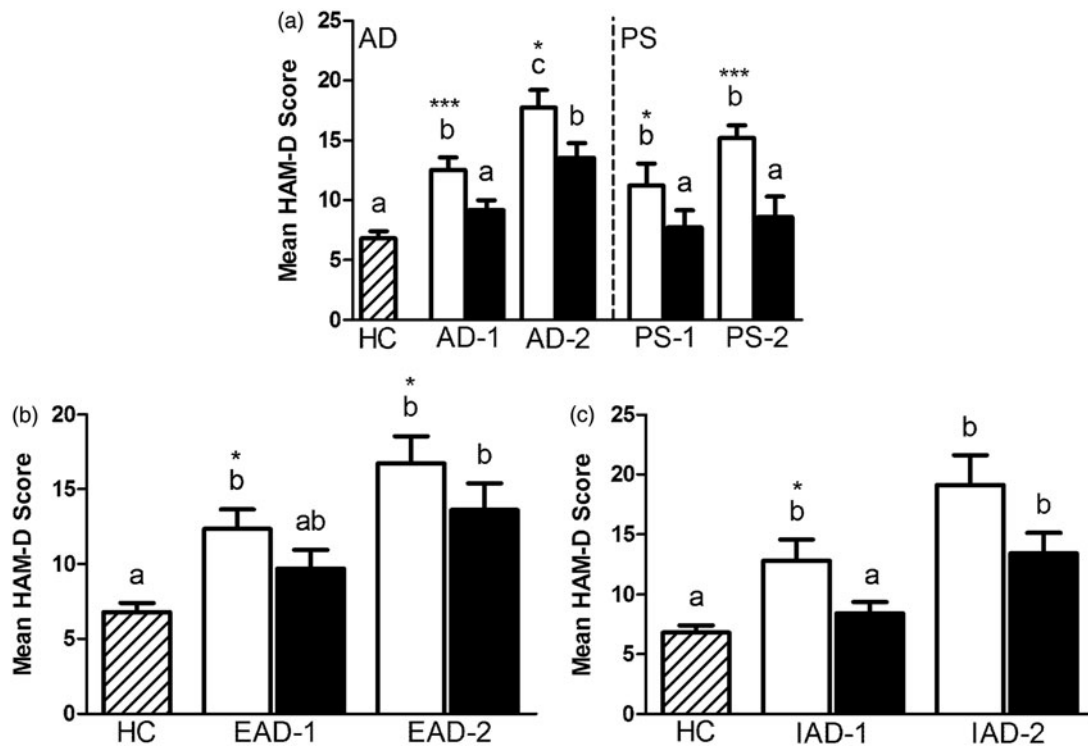


Figure 5. Seasonal depression scores in AD and PS patients. (a) Pooled data by cohort, (b) EAD patients by cohort and (c) IAD patients by cohort at week 0 (white bars) and week 10 (black bars). Bars represent mean scores ($\pm$ SEM). Letters above bars are results of a Bonferroni means separation test analysed within study week (one-way ANOVA, $P < 0.0001$). Asterisks denote results of a comparison between weeks 0 and 10 within patient groups (* $P < 0.05$; *** $P < 0.001$). AD-1, AD patient cohort 1; AD-2, AD patient cohort 2; PS-1, PS patient cohort 1; PS-2, PS patient cohort 2; EAD-1, extrinsic AD patient cohort 1; EAD-2, extrinsic AD patient cohort 2; IAD-1, intrinsic AD patient cohort 1; IAD-2, intrinsic AD patient cohort 2.

seasonal cohort revealed several striking differences in outcome among dermatitis patients (Figure 6(a)). Among AD patients, there were marked differences in trend at week 10. In AD-1 (58.86 ± 2.95 , $n = 29$), BDNF level increased significantly compared with HC (40.49 ± 0.45 , $n = 49$) and week 0 levels (50.84 ± 13.95 , $n = 37$), whereas in AD-2 (week 0: 47.62 ± 0.92 , $n = 19$), BDNF level at week 10 decreased to control levels (36.74 ± 1.14 , $n = 17$; $P < 0.001$). In PS, serum BDNF levels of PS-1 patients were nearly identical with pooled PS data values (<3% increase); however, week 10 BDNF levels in PS-2 patients were depressed below HC levels (35.04 ± 1.56 , $n = 10$; $P < 0.002$).

Subdivision of AD cohorts by IgE sensitivity revealed different trends in both seasonal cohorts (Figure 6(b,c)). Week 0 BDNF levels of AD-1 (EAD-1: 48.88 ± 2.54 , $n = 22$; IAD-1: 53.72 ± 4.25 , $n = 15$) patients were elevated ($P < 0.0001$), but similar among IgE subtypes ($P > 0.05$, data not shown). Week 10 IAD-1 was unchanged (54.21 ± 2.79 , $n = 12$), whereas EAD-1 levels were markedly increased (62.15 ± 4.53 , $n = 17$; $P < 0.01$). This latter result accounted for the trending effect of week 10 BDNF increase observed in the pooled data. In AD-2 (EAD-2: 47.87 ± 1.49 , $n = 11$; IAD-2: 47.25 ± 0.91 , $n = 8$), EAD-2 was elevated compared

with HC, yet IAD-2 was not different from either HC or IAD-1 titres, likely resulting from a smaller sample size. AD-2 Patients in both IgE subgroups (EAD-2: 35.55 ± 1.52 , $n = 10$; IAD-2: 38.44 ± 2.68 , $n = 7$) showed decrease in serum BDNF at week 10 ($P < 0.01$ and $P < 0.05$, respectively), reflecting the trend observed in the pooled AD-2 data.

Pearson correlation of individual HAM-D scores with BDNF levels at week 0 ($r = 0.166$, $P = 0.050$), week 10 ($r = 0.019$, $P = 0.838$) and with pooled data ($r = 0.094$, $P = 0.130$) did not indicate a strong association between depression measured by HAM-D and serum BDNF level. In addition, no Pearson's correlation was observed between dermatological score and BDNF of AD patients at week 0 (AD: $r = 0.006$, $P = 0.967$; PS: $r = -0.157$, $P = 0.384$) or week 10 (AD: $r = 0.088$, $P = 0.561$). In PS, however, a slight correlation at week 10 was observed between dermatological score and BDNF blood levels (PS: $r = 0.045$, $P = 0.027$).

Discussion

In the present study we demonstrate that seasonality of dermatitis symptom onset differentially affects depression outcome and serum BDNF levels during

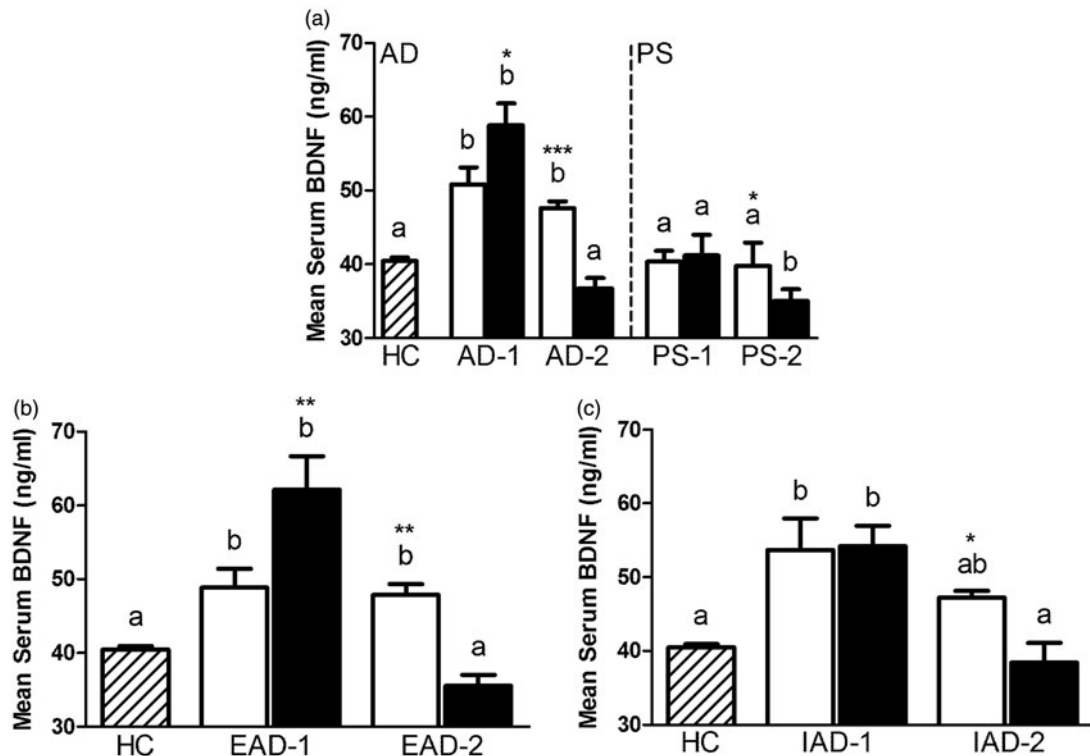


Figure 6. Seasonal-dependence of serum BDNF levels. AD and PS patients by seasonal cohort (a), AD patients by seasonal cohort and EAD subtype (b), and AD patients by seasonal cohort and IAD subtype (c) at week 0 (white bars) and week 10 (black bars). Bars represent mean serum titres (ng/ml; $\pm$ SEM). Letters above bars are results of a Bonferroni means separation test analysed within study week (one-way ANOVA, $P < 0.002$). Asterisks denote results of a comparison between weeks 0 and 10 within patient groups (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$).

disease exacerbation. All dermatological patients presented initially with relatively similar levels of depressive symptoms as measured by HAM-D. We found that depressive symptoms in AD patients with spring/early summer exacerbation (cohort 2, Figure 5(a)) was more pronounced and that spring/early summer AD patients remained depressed after improvement of dermatological symptoms, whereas winter/late autumn AD patients (cohort 1) were depressed at dermatitis onset but were no longer depressed by week 10 after the beginning of treatment. Seasonality of depressive symptoms would lead one initially to associate these symptoms with seasonal affective disorder (SAD); however, spring AD patients (cohort 2) display the poorest depressive symptom improvement among AD patients examined. Cohort 2 patients in Astana would experience 12.6–16.3 h of daylight, which produces a risk of SAD onset (now known as “depressive disorder with seasonal pattern” under DSM-V) of 0–0.15 based on a study of day length and risk of SAD onset by Young et al. (1997). This argues against a simple association with SAD as the underlying cause of depression since that disorder nearly exclusively manifests in autumn and winter months and tends to remit in spring (Young et al. 1997), which appears to be unrelated to

the pattern observed here. The present work, therefore, provides additional evidence supporting the *psychodermatosis* hypothesis (Gupta and Gupta 2003; Smulevich et al. 2004; Brzoza et al. 2005; Korabel et al. 2008; Chrostowska-Plak et al. 2013; Lugovic-Mihic et al. 2013; Senra and Wollenberg 2014; Cheng et al. 2015) and suggests that seasonally related mechanisms are active in the depression-related comorbidity of AD.

Precipitating climatological factors of dermatitis

Seasonal effects on dermatoses are considered common knowledge, albeit anecdotal, yet previous work by several authors have attempted to formally establish the role of season and/or climate conditions as instigating factors in dermatitis (Capon et al. 2004; Gupta et al. 2014; Peng and Novak 2015; Sabounchi et al. 2015). Seasonal presentation patterns in AD patients have been observed as noted in other studies (Timonen et al. 2004; Kramer et al. 2005; Silcocks and Williams 2005; Weiss et al. 2008) and resulted in apparently conflicting patterns of factor association. A comprehensive review by Engebretsen et al. (2016) has attempted to consolidate the disparate sea of literature reports and determine a set of primary factors

which influence dermatitis onset. Their primary conclusions were that low humidity, low temperature or high-to-low dew point with low-to-high barometric pressure transitions are the three primary triggers of dermatitis, contributing to increased rates of trans-epidermal evaporation. We specifically selected two separate temperature and humidity regimes, denoting also the corresponding dew point measures, as criteria for environmental triggers of dermatoses examined here: low temperature (cohort 1) and low relative humidity (cohort 2). Indeed, our results indicate that the course of resolution of depressive symptoms is specific to season of onset in AD and suggests that patients responding to differing environmental triggers may be considered as different patient populations.

Serum BDNF level and depressive symptoms in psychodermatoses

The “neurotrophic hypothesis” of mood disorders postulates that depression arises from lack of trophic support to the hippocampus based on functions of BDNF and states that depression results from stress-induced decreases in BDNF expression (Duman et al. 1997; Nestler et al. 2002; Shneider et al. 2010; Pinhasov et al. 2011). Under this model, antidepressant efficacy is associated with increased BDNF levels (Duman et al. 1997; Lauterborn et al. 2003; Reichenstein et al. 2008; Kreinin et al. 2015). Results inconsistent with the neurotrophin hypothesis also have been reported (Groves 2007). There are, for example, studies that did not detect increases in BDNF in depressed persons over the course of treatment with an antidepressant (Matrisciano et al. 2009). Further, data presented here appear superficially to corroborate the neurotrophic hypothesis of depression since patient groups with elevated BDNF have relatively low HAM-D scores (AD-1; Figures 5(a) and 6(a)) compared with groups presenting with lower BDNF levels and higher HAM-D scores (AD-2); however, analysis of BDNF titre and HAM-D of individuals with the pooled data set did not result in strong correlation (0.9% variation in HAM-D is explained by variation in BDNF). In addition, we found elevated HAM-D scores at onset and improvement to control score levels in the PS patient population examined (Figures 2(a) and 5(a)) without any elevation of BDNF level (Figures 3 and 6(a)).

Caution should be exercised regarding these results as conclusive with respect to the neurotrophic hypothesis of depression in that emotional states are the resulting behavioural output of a myriad of internal signals and do not result from a single factor. Molendijk et al. (2012) reported seasonal variation in

serum BDNF in a study in The Netherlands of nearly 3,000 subjects with depression and no substance-abuse problems or psychotic or bipolar disorders. Their results show elevated serum BDNF in autumn and winter months with an annual nadir in March and subsequent rise to plateau levels by June, corresponding to cohorts 1 and 2 presented here, respectively. Further, BDNF reduction in depression could be masked by confounding seasonal BDNF elevation and increased immune activation. It is known that the expression of neurotrophins is strongly upregulated during allergic inflammation (Nockher and Renz 2005, 2006). Neurotrophins act as inflammatory cytokines, delivering activation and survival signals to effector cells of the allergic response and are also increased in allergic diseases (Nockher and Renz 2006), dramatically enhancing inflammation induced by immune cells (Kimata 2005; Roguedas-Contios and Misery 2011). Noting that AD belongs to Th2-regulated dermatoses (Ricci et al. 1994) and that central mechanisms in PS involve NF- κ B, INF- γ and IL-23 (Boehncke 2015), BDNF level changes may be secondary associated effects to comorbidity with depressive symptoms. As an additional note, the PS-2 population examined here presented with significantly reduced BDNF upon reduction of depressive symptoms reflected by HAM-D scores (86.5% of HC) and a similar outcome approaching significance was observed in AD-2 (90.7% of HC, $P=0.16$), suggesting the presence of antagonistic processes related to depression and immune activation on BDNF expression.

IgE titre does not relate to dermatological or depressive symptom presentation

Examination of other factors such as IgE sensitivity in AD patients did not suggest that AD disease subtype had any strong influence on development of SCORAD or depression, in agreement with other studies (Raap et al. 2006; Ma et al. 2009). Patterns of change in HAM-D scoring were similar between pooled data (Figure 2), pooled cohort data (in AD and PS; Figure 5(a)) and IgE subtype examined by cohort (in AD; Figure 5(b,c)). Differences in outcome of depression measures in AD were primarily seasonal cohort-based, as noted above. In contrast, strong IgE subtype-associated changes in serum BDNF level were measured which were additionally cohort-dependent as well (Figure 6(b,c)). Whereas other studies reported elevated BDNF at onset of dermatological symptoms in AD (Raap et al. 2006; Ma et al. 2009), we are not familiar with studies that followed changes in BDNF level over the time course of symptom onset and

resolution. Indeed, our pooled BDNF data for AD patients mirrors reported results of other studies (Figure 3), but when examined by IgE subtype and cohort, different patterns emerge (Figure 6(b,c)). AD-2 patients present with elevated BDNF that returns to control levels by week 10 after symptom onset and does not appear to be IgE dependent. AD-1 patients, however, show a further increase in BDNF level at week 10, with the majority of this effect contributed by EAD patient data. In contrast, IAD BDNF levels remaining relatively unchanged (Figure 6(c)). Further, we report for the first time here a seasonally dependent difference in serum BDNF among PS patients, with PS-2 patients showing significantly reduced BDNF at week 10, whereas PS-1 patient BDNF levels are unchanged and similar to that of controls (Figure 6(a)). Brunoni et al. (2015) reported that PS patients had below-normal levels of BDNF, but did not characterise patients by seasonal incidence. Noting that PS dermatological symptoms and inflammation are known to improve in months with longer day length and higher solar intensity (Park and Youn 1998; Youn et al. 1999), we speculate that immune-dependent BDNF reductions in this group at symptom resolution may relate to sunlight factors. Collectively, these results suggest the existence of different AD and PS patient populations that can be segregated by season of symptom onset.

Depression outcome in AD affected by BDNF rs6265 genotype

We report here a difference in improvement of HAM-D scores from dermatological symptom onset to 10 weeks later between patients with BDNF rs6265 G allele only (Val/Val genotype) and G and A alleles (Val/Met genotype; Figure 4). Val/Val patient depression scores were consistently elevated, whereas Val/Met patient depression scores were not elevated compared with their associated Val/Met HC. Val/Met patients were further characterised by seasonal cohort grouping and revealed that AD-1 patients were similar to control depression scores, yet AD-2 patients were elevated consistently over the course of study, again revealing a pronounced effect of seasonality in patient outcome with respect to depression.

BDNF rs6265 polymorphism has been linked in several studies of depression. Ribeiro et al. (2007) in a study of 284 depressed patients and age-matched controls reported that patients with Val/Val genotype were more susceptible to depression, as we state here. A potential stress-induced mechanism relating to our data comes from a study by Chagnon et al. (2015),

which reports that depression increases BDNF gene methylation and that depressed Val/Met patients had higher levels of methylation than Val/Val patients; however, they found that BDNF levels of both groups were still significantly elevated over controls. A study by Comasco et al. (2011) on development of postpartum depression reported that women with rs6265 Val/Val genotype were more susceptible to development of depression, specifically in autumn and winter months. Subdivision of Val/Met patients by seasonal cohort in our data revealed two subsets of patients with different manifestation of depressive symptoms (as seen in Comasco et al. 2011), which may account for the apparent contradiction between the Ribiero and Chagnon studies in that neither study appeared to account for season of onset when patients were examined.

Here, we report seasonality- and BDNF polymorphism-dependent differences in AD and PS patient outcomes for depression. Tentatively, the results appear to characterise different patient populations, although the sample size in our study was small. Whereas the role of BDNF with respect to signs of depression in patients examined here is unclear, marked differences have been observed in psychometric measures and may well describe patient populations with different prognoses requiring more focussed psychiatric care.

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Statement of interest

None to declare.

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