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Influence of Childhood Physical Neglect on Depression: Potential Moderation by a Polymorphism in the QKI Gene

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Abstract

Objective: Childhood physical neglect (CPN) is a common but often overlooked form of abuse that may contribute to depression. We aimed at examining the potential impact of CPN and its interactions with genes related to oligodendrocytes (ODCs) and myelin function on adult depressive symptoms and antidepressant treatment response.

Methods: A group of 209 Chinese Han patients with major depressive disorder (MDD) completed the Hamilton Depression Scale-17 (HAMD-17) at baseline and after 8 weeks antidepressant treatment. The Childhood Trauma Questionnaire was used to evaluate the occurrence of childhood physical neglect. Twelve single nucleotide polymorphisms (SNPs) in functional regions were successfully genotyped in seven genes associated with ODCs and myelin function.

Results: Childhood physical neglect is related to education and social support, especially the subjective social support of those who experience CPN. The GG genotype of the 3'UTR functional polymorphism rs715020 in the QKI gene showed significant association with diminished effects of childhood physical neglect on adult depressive symptoms(P=.003) even after the Bonferroni correction. No significant interactions between candidate genes and CPN on antidepressant response were observed.

Conclusion: These results indicate that CPN are potentially associated with ODCs and myelin-related gene QKI, and may influence adult depressive symptoms in major depression disorder (MDD) patients. This finding needs to be further replicated in a larger sample.

Keywords: Depression; Anti-depressive agents; Child abuse; Gene-environment interaction; Genetic polymorphism; Myelin sheath

Introduction

A large number of children today are at risk of a specific subtype of childhood maltreatment, physical neglect. The global prevalence of self-reported childhood physical neglect (CPN) was recently estimated to be 16.3% [1]. The adverse effects of CPN appear to be as severe as those observed in other subtypes of abuse. CPN is associated with an increase in the risk of substance abuse, risky sexual behavior, posttraumatic stress disorder and affective disorders [2-4]. However, few scientific studies have paid close attention to CPN.

Maternal separation is an accepted classical animal model that is used to examine the effects of early life stress, which may result in disturbances in normal brain development [5] and may impact both physical and mental health [6]. Maternal separation leads to a combination of physical changes, such as altered thermal, nutritive and tactile stimulatory needs of the pup from the mother [7]. This bears similarities to the content of childhood physical neglect in which "the failure of caretakers to provide for a child's basic physical needs, include in food, shelter, clothing, safety, and health care" is evident [8]. Kikusui et al. reported that early weaning, which is one of the most important events involved in maternal deprivation, induced developmental changes in myelin formation and led to anxiety-related behavioral effects in mice. Thus early physical neglect may influence myelin formation and potentially interact with the risk factors associated with mood and behavioral problems.

Furthermore, growing evidence from studies of postmortem human tissue microarrays [9,10], histopathology [11,12] and neuroimaging [9] suggests that oligodendrocytes (ODCs) and myelin dysfunction play an important role in the pathophysiology of depression and antidepressant treatment response [9]. Rajkowska et al. proposed that the combination of genetic and environmental factors (e.g., stress) could initially lead to glial cell pathology and consequently contribute to neuronal pathology later in life, as depressive illnesses progresses [13].

For these reasons, the present study sought to (i) examine the potential impact of CPN on general functioning, adult depressive symptoms and antidepressant treatment response, and (ii) test whether genetic polymorphisms related to ODC and myelin function interact with CPN to affect adult depressive symptoms and antidepressant response.

Methods

Study design and subjects

Subjects were Chinese Han individuals aged between 18 to 60 years, with a diagnosis of new or recently relapsed major depression disorder (MDD). The baseline scores on the 17-item Hamilton Depression Rating Scale (HAMD-17) were>17. Exclusion criteria used for this study have been previously reported [14]. All of the subjects were informed of the potential risks and benefits of the study and gave their informed consent prior to their participation in the study.

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All patients were treated with single antidepressant drugs (SSRI or SNRI) according to current clinical practice. Only a low dose of a benzodiazepine anxiolytic, for the alleviation of insomnia, was used concomitantly. An initial comprehensive psychiatric and medical assessment was conducted by two independent senior psychiatrists for each patient. Using a standardized protocol with an interclass correlation of at least 0.9, the HAMD-17 was used to assess the severity of the depressive symptoms at baseline and after 2, 4, 6 and 8 weeks of treatment. The changes of HAMD score after 8 weeks of treatment which defined as (HAMD0w- HAMD8w) was used as continuous outcome variables to provide antidepressant treatment response. This study was approved by the Ethical Committee of the ZhongDa Hospital of Southeast University. All data included in this manuscript was obtained in compliance with the Helsinki Declaration.

Assessment of childhood trauma

Childhood physical neglect was assessed in 209 patients using the Childhood Trauma Questionnaire (28-item short form, CTQ-SF) [8], in which CPN comprises 5 items generating a range of scores from 5 to 25 points. The CPN score was treated as a dichotomous variable. According to the cutoff point postulated by Bernstein et al., a CPN score of ≥10 was designated as "severe" adversity (n=103), whereas a CPN score<10 was designated as "mild" adversity (n=106) [15,16].

Gene selection, genotyping methods and quality control

Seven candidate genes related to ODC and myelin function were selected for analysis. Four of these 7 genes encode various structural components of myelin (CNP, MAG, MOG, and MBP). The 3 remaining genes are essential in regulating myelin formation (NRG1, QKI, and TF). The HapMap data and SNP Tagger program on the Chinese Han, Beijing (CHB) population were used to select tagging SNPs in promoter and exonic regions with a minor allele frequency (MAF) ≥10% or more with a pair-wise r^2>0.80 in the Chinese Han, Beijing, (CHB) population. The Multiplex SNaPshot System using an ABI fluorescence-based assay discrimination method (Applied Biosystems, Foster City, CA, USA) was used to genotype the SNPs. Negative controls and 5% duplicated samples were genotyped for quality control. No discordance between samples was recorded.

Using Haploview 4.0 [17], 12 SNPs exhibiting a call rate >97%, and a Hardy–Weinberg equilibrium P>0.001 [18] were included in the analyses. Details of the SNPs are provided in Table 1.

Statistical analysis

Differences in the clinical variables between mild and severe CPN groups were evaluated using Pearson's $\chi 2$ test or Student's t-test with SPSS 13.0 (SPSS Inc., Chicago, IL, USA). The mean ± standard deviation was used to describe the values relating to patient demographic characteristics. Possible confounding effects of sex and age on patients' HAMD-17 scores were investigated by stepwise linear regression.

First, Student's t-test or analysis of variance (ANOVA) was used to investigate the influence of SNP genotypes on depression scores and antidepressant treatment response. Then, the general linear model was used to assess whether SNPs related to ODCs and myelin interacted with CPN to influence baseline HAMD-17scores and the changes in HAMD scores after 8 weeks of treatment. We considered SNP analyses that evaluated the continuous baseline HAMD-17 scores and changed HAMD scores based on genotype, CPN (mild vs. severe), and the two-way interaction between genotype and CPN. The sample had 87% power to detect a risk allele more than 20% frequency and a relative risk of 2.0at the 0.05 significance level with Power/Sample Size Calculator (http://stat.ubc.ca/~rollin/stats/ssize/caco.html). As we were testing multiple genetic variants, the Bonferroni correction was applied to adjust the nominal significance level within all of the SNPs tested in this study and α=0.0042 was determined to provide an appropriate threshold to detect a significant effect.

Gene	SNP ID	Location	%gene	HWpval	MAF	Alleles
CNP	rs11079028	3'UTR	100	0.175	0.116	G>A
	rs2070106	cds-synon	99.6	0.4541	0.386	G>A
MAG	rs2301600	cds-synon	99.3	0.629	0.4	G>A
MBP	rs470797	stop-gain	98.6	0.46	0.318	G>A
	rs9966986	5'gene	99.6	0.9032	0.364	A>G
MOG	rs2857766	3'UTR	100	0.7377	0.283	C>G
	rs29254	5'gene	100	0.0689	0.142	A>G
NRG1	rs6994992	5'gene	100	0.8701	0.45	A>G
	rs3924999	missense	100	0.3517	0.222	A>G
QKI	rs715020	3'UTR	99.6	0.8204	0.286	G>A
TF	rs8177181	5'gene	99.6	0.7206	0.312	A>T
	rs1049296	missense	100	0.0113	0.279	G>A

Note: HWpval: the Hardy–Weinberg equilibrium p value; %gen: the percentage non-missing for the specified marker; MAF: the minor allele frequency for the specified marker; Alleles: the major and minor alleles for the specified marker.

Table 1: General characteristics of genotyped polymorphisms.

	Mild CPN (n=106)	Severe CPN (n=103)	χ2/t	*P*
Sex (male/female)	44/62	43/60	0.001	0.972
Age (mean ± S.D)	36.38 ± 13.52	38.71 ± 12.60	-1.288	0.199
Years of education (mean ± S.D.)	12.55 ± 3.85	10.90 ± 3.83	3.089	0.002
Family history of MDD (yes/no)	16/90	16/87	0.008	0.930
Episodes	2.08 ± 1.60	1.86 ± 1.24	1.110	0.268
Baseline HAMD-17 score (mean ± S.D.)	27.35 ± 5.39	28.13 ± 5.96	-0.988	0.324
Changes of HAMD-17 score (mean ± S.D.)	19.34 ± 7.10	19.68 ± 7.75	-0.331	0.741

Note: CPN: Childhood Physical Neglect; MDD: Major Depressive Disorder; HAMD-17: Hamilton Rating Scale for Depression.

Table 2: Demographic and clinical characteristics of mild and severe CPN patients.

Results

A total of 209 patients were successfully genotyped. There were no significant differences between the mild and severe CPN subgroups with regard to sex, age, family history of MDD, MDD episodes, HAMD-17scores or antidepressant response. However, for severe CPN patients, the years of education were significantly less than those of mild CPN patients (t=3.089, P=0.002). The demographic and clinical characteristics of the patients in both groups are shown in Table 2.

Stepwise linear regression showed that age but not sex was a significant correlate (F=16.535, P<.001) of HAMD-17 scores and was included as a covariate in further analysis.

There was no significant association of any SNP investigated with depression scores or with antidepressant treatment response (Supplementary Tables 1 and 2). A significant interaction effect was observed before the Bonferroni correction between CPN and rs715020 in the QKI(quaking) gene, but in no other SNPs (Supplementary Table 3), here a genotype effect was apparent only in the severe CPN group (F=4.469, P=0.013, Table 3). In a two-genotype analysis comparing A allele carriers with GG homozygotes, results show that GG homozygotes

Genotype	Mild CPN (n=106)	Severe CPN (n=102)
AA	27.17 ± 5.39(n=12)	31.00 ± 5.35(n=4)
AG	26.74 ± 5.17(n=34)	29.62 ± 5.41(n=55)
GG	27.73 ± 5.72(n=60)	26.05 ± 6.17(n=43)
Note: CPN: Childhood Physical Neglect.		

Table 3: Effects of childhood physical neglect and rs715020 on adult depressive symptoms.

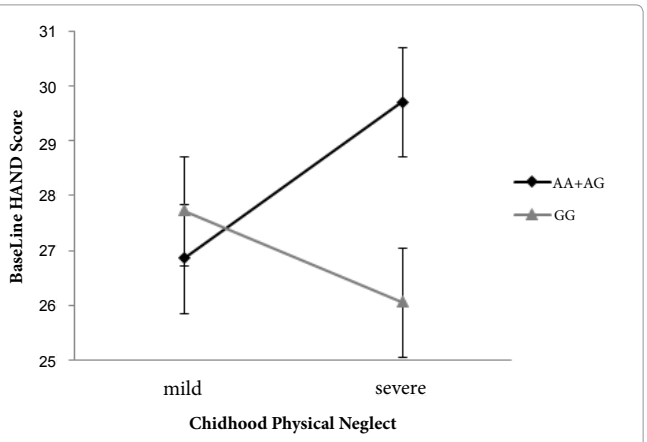

Figure 1: Effect of QKI gene rs715020 genotypes and childhood physical neglect on adult depression symptoms. Error bars indicate SEM.

have significantly lower HAMD-17 scores (F=8.985, P=0.003, Figure 1), a significant effect after Bonferroni correction.

In the analysis of SNP x CPN interactions with antidepressant treatment response, no significant interactions were found (P>0.05), including rs715020 in QKI (Supplementary Table 3).

Discussion

The present study was conducted to explore childhood physical neglect and its interactions with genes related to ODCs and myelin in adult depressive symptoms and antidepressant treatment response. The results suggest that polymorphisms in the QKI gene may moderate the effects of CPN in adult depressive symptoms in Chinese MDD patients. The GG genotype of the 3'UTR functional polymorphisms 715020 in the QKI gene associated with the diminished effects of childhood physical neglect on adult depressive symptoms. However, we failed to find any gene–CPN interactions on antidepressant remission in the subjects.

Childhood physical neglect has been reported to be the most common form of child abuse [19]. However, it seems to be historically overlooked in the field of child abuse research [1]. Our study showed that subjects who experienced severe CPN were more likely to have lower education levels in adulthood. Although the mean baseline HAMD-17 scores in the severe CPN subjects were slightly higher than those obtained in the mild CPN group, we were unable to detect a significant and direct relationship between CPN and the severity of adult depressive symptoms or antidepressant treatment response. Several studies have focused on the influence of CPN on MDD, but the results were inconsistent. Kounou et al. showed that MDD patients reported more frequent physical neglect than health controls [20]. However, Gulec et al. failed to find a relationship between CPN and depression [21]. Moreover, Grassi-Oliveira et al. also failed to find an effect of CPN on the severity of depressive symptom, which is consistent with the present finding [22]. No published studies have examined the association between CPN and the response to antidepressants in MDD. Such a relationship must be verified in larger independent samples in the future.

In the present study, we identified specific interactions between CPN and genetic polymorphisms in the QKI gene in adult depressive symptoms. A two-genotype "recessive" modelforrs 715020 showed significant interaction after applying a highly conservative Bonferroni correction for multiple testing. Recently, an animal model of maternal separation with early weaning (MSEW) was used to simulate early life neglect. George et al. [9] showed that MSEW mice exhibited increased and persistent anxiety, hyperactivity, and behavioral despair. Further molecular studies by Bordner et al. [23] found that, in addition to behavioral changes, MSEW also leads to dysregulation of markers of mature ODCs. These findings provide useful information that elucidates the combined action of CPN and abnormal ODCs in inducing behavioral and mood disorders.

The quaking gene is designated as a quaking homologue of KH domain RNA binding (mouse) (QKI) [24]. It is a member of the signal transduction and activation of the RNA (STAR) protein family, which is located in the 6q26 chromosome region and spans approximately 159,000 base pairs. Using an autosomal recessive mutant (qkv) model, the dysfunction of the mouse QKI gene has been well described as related to body tremor and the severe demyelination of the central nervous system [25]. To date, an increasing number of studies have confirmed that the human QKI gene in the brain plays a fundamental role in myelination and ODC differentiation [26,27]. Abnormal QKI expression may be critical in influencing other myelin-associated gene expression abnormalities in psychiatric disorders, such as schizophrenia and MDD. In postmortem human brain studies, Haroutunian et al. demonstrated that the expression of QKI mRNA was reduced in seven cortical regions and the hippocampus in schizophrenia patients [28]. Aberg et al. found that, mRNA levels of several myelin-related genes were reduced in schizophrenic patients compared to control subjects. Meanwhile, potential QKI-binding sites in the 3'UTR region of these genes may explain the mechanisms underlying the effect of QKI on the inter-individual variation of expression in these myelin-related genes [29]. Klempan et al. revealed that multiple transcripts of QKI mRNA resulted in significant reductions of expression in cortical regions, the hippocampus and amygdala in suicidal MDD patients compared with control subjects [30]. All of these studies support a specific role of QKI in myelination-related deficits.

There are several limitations to our investigation. First, because there is a restricted number of SNPs, we only selected the polymorphisms of coding and promoter regions in a limited number of ODC and myelin-related genes. This limited selection could lead to the incomplete capture the overall genetic variation naturally observed in these systems. Second, multiple removal criteria were applied to ensure sample quality, which reduced the sample size of the study. The reported findings should be viewed as preliminary results that must be replicated in larger independent samples.

Conclusion

In conclusion, our results indicate that the QKI gene is a potential moderator of the effects of childhood physical neglect on adult depressive symptoms in MDD patients. Further work is necessary to confirm these preliminary results across independent populations, and further laboratory-based functional genomic studies are needed to understand the mechanisms underlying these epidemiological observations.

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