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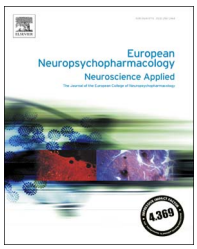

Serotonin transporter gene expression predicts the worsening of suicidal ideation and suicide attempts along a long-term follow-up of a Major Depressive Episode

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Abstract
The quest for biomarkers in suicidal behaviors has been elusive so far, despite their potential utility in clinical practice. One of the most robust biological findings in suicidal behaviors is the alteration of the serotonin transporter function in suicidal individuals. Our main objective was to investigate the predictive value of the serotonin transporter gene expression (*SLC6A4*) for suicidal ideation and as secondary, for suicide attempts in individuals with a major depressive episode (MDE). A 30-week prospective study was conducted on 148 patients with a MDE and 100 healthy controls including 4 evaluation times (0, 2, 8 and 30 weeks). Blood samples and clinical data were collected and *SLC6A4* mRNA levels were measured from peripheral blood mononuclear cells using RT-qPCR. We first demonstrated the stability and reproducibility of *SLC6A4* mRNA expression measures over time in healthy controls ($F=0.658$; $p=0.579$; $\eta^2=0.008$; $ICC=0.91$, 95% CI [0.87-0.94]). Baseline *SLC6A4* expression level (OR=0.563 [0.340-0.932], $p=0.026$) as well as early changes in *SLC6A4* expression between baseline and the 2nd week ($\beta=0.200$, $p=0.042$) predicted the worsening of suicidal ideation (WSI) in the following 8 weeks. Moreover, changes in *SLC6A4* expression between the 2nd and 8th weeks predicted the occurrence of a suicide attempt within 30 weeks (OR=10.976 [1.438-83.768], $p=0.021$). Altogether, the baseline level and the changes in *SLC6A4* mRNA expression during a MDE might predict the WSI and the occurrence of suicidal attempts and could be a useful biomarker in clinical practice.

1. Introduction

Suicide is a major cause of premature death worldwide and a serious public health issue. Suicidal behaviors are the most serious complications of mood disorders. Almost 90% of suicide completers suffer from a psychiatric disorder, mainly from a major depressive episode (MDE) (Arsenault-Lapierre et al., 2004). Although efficient treatment of mood disorders is an effective prevention strategy (Zalsman et al., 2017), a worsening of suicidal ideation (WSI) occurs in up to 30% of patients with a MDE during antidepressant treatment (Perroud et al., 2009; Zisook et al., 2009).

Many researches, over the past decades, focused on identifying subgroups of patients with a higher risk of suicidal ideation or behaviors, to predict and to prevent these complications in the context of clinical care. Suicidal behaviors have been associated with several risk factors such as a previous psychiatric disorder, single marital status, unemployment, childhood maltreatments, family history of suicidal behaviors or previous suicide attempts, impulsivity and alcohol use disorder (Fawcett et al., 1990; Fergusson et al., 2000; Mann, 1998; McCauley et al., 1997; Tidemalm et al., 2011). Moreover, depression severity, previous suicide attempts, retirement, weight loss, vascular or neurological diseases and being widowed have also been identified as risk factors for WSI during antidepressant treatment (Brent, 2016; Coughlin et al., 2016; Perroud et al., 2009). We notably reported that emergence or WSI in the first weeks after initiating an antidepressant treatment was mainly related to the worsening of depressive symptoms (with a attributable risk of 67.5%) (Courtet et al., 2014). Pharmacogenomics studies of antidepressant treatment-emergent suicidal events have been performed in large cohorts of depressed patients (reviewed in (Brent et al., 2010)). Associations with polymorphisms in genes involved in different systems have been reported but rarely replicated. Despite all of these findings, to date, no specific clinical or genetic markers or any combination has allowed to effectively predict the WSI in the context of clinical care.

In such a context, biomarkers could help clinicians to identify specific subpopulations at high risk for suicidality. Based on the assumption that suicidality is a phenomenon resulting from a complex interaction of genetic background, early environmental stress and proximal biological variation (Mann and Currier, 2010; Turecki, 2014), changes in gene expression offer a good opportunity to capture biological dysregulation associated with suicide risk. Several studies examined gene expression differences in peripheral blood in an attempt to describe biomarkers of MDE and antidepressant response (Iga et al., 2008) but few of them regarding suicide risk in depressed individuals (Chang et al., 2016). Two types of methodology are used in this research area, the hypothesis-free and candidate gene approaches. Interestingly, three studies of the same team described changes in blood expression levels that could predict suicidal ideations states and future hospitalizations due to suicidal behaviors using a hypothesis-free approach and different cohorts of males and females patients independently with heterogeneous psychiatric disorders (Le-Niculescu et al., 2013; Levey et al., 2016; Niculescu et al., 2015b). Of note, Mullins et al. did not replicate the results of one of these previous studies (Mullins et al., 2014). Moreover, a cross-sectional study that used a candidate gene-based approach including mRNA expression of *BDNF*, *FKBP5* and *NR3C1* genes in peripheral blood, did not find any differences between depressed patients with and without suicidal ideation (Roy et al., 2017).

To the best of our knowledge, no previous study focused on the serotonin transporter gene expression variation. This