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Vascular endothelial growth factor in patients with schizophrenia: A systematic review and meta-analysis

Błażej Misiak[a,*], Filip Stramecki[b], Bartłomiej Stańczykiewicz[c], Dorota Frydecka[b], Alba Lubeiro[d]

[a] Department of Genetics, Wroclaw Medical University, Marcinkowskiego 1 Street, 50-368 Wroclaw, Poland
[b] Department of Psychiatry, Wroclaw Medical University, Pasteura 10 Street, 50-367 Wroclaw, Poland
[c] Department of Nervous System Diseases, Wroclaw Medical University, Bartla 5 Street, 51-618 Wroclaw, Poland
[d] Department of Psychiatry, School of Medicine, University of Valladolid, Av. Ramón y Cajal, 7, 47005 Valladolid, Spain

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ABSTRACT

Background: Accumulating evidence indicates that schizophrenia might be accompanied by abnormal vascularization. Vascular endothelial growth factor (VEGF) is one of key molecules involved in the development of vessels with vasodilatory activities.

Objectives: We aimed to perform a systematic review and meta-analysis of studies investigating serum or plasma levels of VEGF in patients with schizophrenia and first-episode psychosis (FEP).

Methods: Electronic databases were searched from their inception until 18th Apr 2018. Meta-analysis was performed using random-effects models with Hedges' g as the effect size estimate. Quality assessment was performed using the Newcastle-Ottawa Scale.

Results: We included 15 eligible studies, representing 982 patients and 791 healthy controls. Main analysis revealed no significant differences in VEGF levels between patients and controls ($g = 0.10$, 95%CI = −0.24–0.45, $p = .553$). Subgroup analysis demonstrated unaltered levels of VEGF in FEP patients ($g = 0.03$, 95%CI = −0.53–0.59, $p = .911$), including antipsychotic-naïve individuals ($g = 0.34$, 95%CI = −0.07–0.74, $p = .103$). However, the levels of VEGF were significantly higher in medicated multiple-episode schizophrenia (MES) patients ($g = 0.45$, 95%CI = 0.03–0.87, $p = .036$) compared to controls. Heterogeneity across studies was significant in the majority of analyses, except for the analysis of antipsychotic-naïve FEP patients. Tests of asymmetry were insignificant, indicating a lack of publication bias.

Limitations: Main limitations of our meta-analysis include inability to address medication effects exhaustively and relatively low number of studies in subgroup analyses.

Conclusions: Our results indicate elevated levels of VEGF in MES patients that are unaltered in FEP individuals. Longitudinal studies are required to disentangle whether elevated levels of VEGF in MES patients reflect illness progression, comorbid physical health impairments or appear due to medication effects.

1. Introduction

Schizophrenia is a heterogenous mental disorder with multiple genetic and environmental factors, involved in its pathophysiology. There is mounting evidence showing the association between brain structure abnormalities and schizophrenia. Neuroimaging studies have shown significant enlargement of lateral ventricles and smaller brain volumes in schizophrenia subjects (Shenton et al., 2001). Apart from neurostructural abnormalities, microvascular alterations in the brain have been also reported in patients with schizophrenia (Hanson and Gottesman, 2005). A recent study by Moises et al. (2015) revealed a significant over-representation of genes involved in vascular function, vasoregulation, shear stress, cerebral ischemia, neurodevelopment and post-ischemic repair among genes that might impact schizophrenia susceptibility. On the other hand, it has been proved that administration of recombinant human erythropoietin, which stimulates the process of angiogenesis, leads to significant improvement of cognitive functioning in schizophrenia patients (Chai et al., 2016; Ehrenreich et al., 2007).

There are two distinct processes responsible for the formation of new blood vessels. Vasculogenesis refers to a process of blood vessels development, which occurs as a de novo maturation of endothelial cells. Angiogenesis in turn involves the formation of new capillaries from pre-existing vessels. It is primarily engaged in neovascularization

* Corresponding author.
E-mail address: blazej_misiak@interia.pl (B. Misiak).

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during embryogenesis but also takes part in tissue response to brain injury and plays a pivotal role in connecting vascular endothelium with astrocytes and neurons (Katsel et al., 2017). Vascular endothelial growth factor (VEGF) is a signal protein that stimulates both vasculogenesis and angiogenesis. Its production can be induced in various cells ranging from endothelial cells to monocytes and ending up on ones which are not receiving enough oxygen (Ferrara et al., 2003; Holmes et al., 2007). Importantly, VEGF acts through its specific receptors expressed not solely by endothelium but also astroglial cells and neurons of any degree of maturity (Lee et al., 2015). It plays a relevant role in neuroprotection and regeneration of central nervous system cells, and stimulates axonal outgrowth and neuronal differentiation (Sun et al., 2003). Therefore, VEGF can be considered as a molecule responsible for neuronal regeneration after brain injuries. Additionally, VEGF is responsible for neurogenesis in the adult brain (Jin et al., 2002).

Decreased VEGF expression in the dorsolateral prefrontal cortex has been reported in patients suffering from schizophrenia (Fulzele and Pillai, 2009). In addition, several cytokines, which are believed to play a role in the pathophysiology of schizophrenia, might impact the production of VEGF (Stocks et al., 2005). Cytokine alterations in schizophrenia patients have been addressed in several meta-analyses (Miller et al., 2011; Potvin et al., 2008; Upthegrove et al., 2014). In the recent years, several studies have been carried out to find a relationship between peripheral blood levels of VEGF and schizophrenia. However, a quantitative and qualitative synthesis of these studies has not been performed so far. Therefore, in this study we aimed to perform a systematic review and meta-analysis of cross-sectional studies comparing serum or plasma levels of VEGF between patients with schizophrenia or first-episode psychosis (FEP) and healthy controls.

2. Material and methods

2.1. Search strategy

Following the PRISMA guidelines (Moher et al., 2009), we performed a comprehensive search in the following databases: CINAHL Complete; Academic Search Complete; ERIC; Health Source: Nursing/Academic Edition and Medline. Independent online search was performed by two reviewers (BS and AL) from database inception until 18th April 2018. We used the following combination of keywords: "(immunity OR vascular endothelial growth factor OR VEGF) AND (psychosis OR schizophr* OR psychotic)". Furthermore, we reviewed reference lists of eligible publications. Studies were included if they met the following criteria: 1) VEGF concentrations measured in plasma or serum; 2) necessary data available in the article or upon request (via contacting corresponding authors); 3) studies comparing the levels of VEGF in patients with schizophrenia, schizoaffective disorder or FEP and healthy controls and 4) articles written in the English language. We excluded 1) animal model studies; 2) studies without a control group and 3) studies without data necessary to perform meta-analysis. The protocol of our systematic review and meta-analysis was not registered. The PRISMA checklist has been provided in Supplementary Table 1.

2.2. Data analysis

The following data was extracted from eligible publications (mean ± SD or the number of cases) by one author (BM): 1) age; 2) sex; 3) body-mass index (BMI); 4) the levels of VEGF; 5) the number of smokers; 6) the Positive and Negative Syndrome Scale (PANSS) scores and 7) illness duration. In case of one study (Balõtšev et al., 2017), mean and SD for the levels of VEGF was calculated from median, sample size and range as described previously (Hozo et al., 2005). Quality of studies was evaluated using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2000).

Principal summary measures included differences in mean levels of VEGF. Data analysis was performed under random-effects models due to expected heterogeneity and effect size (ES) estimates were calculated as Hedges' g. Heterogeneity across studies was assessed using the Cochran Q test and I^2 estimates. Publication bias was evaluated using the Begg-Mazumdar's test and the Egger's test. Subgroup analyses were performed to investigate the levels of VEGF in distinct groups of patients, including those with first-episode psychosis (FEP) and multi-episode schizophrenia (MES) patients, and to check the effects of medication status (antipsychotic-naïve or antipsychotic-free patients vs. medicated patients). In case of categorical variables, meta-regression analysis was performed if each subgroup had at least 4 studies (Fu et al., 2011). In turn, meta-regression of continuous moderators was performed if a particular variable was assessed in at least 6 studies (Fu et al., 2011). Following this rule, we were able to test the effects of the following variables: age, sex, BMI, cigarette smoking, PANSS scores and illness duration on the ES estimates. Results of meta-analysis and meta-regression were considered statistically significant if the p-value was < 0.05. Statistical analysis was performed using the STATISTICA software, version 12.5.

3. Results

Out of 1394 records identified, 15 studies were finally included in our systematic review and meta-analysis (Fig. 1). There were 9 studies of FEP patients and 9 studies of MES patients (Table 1). These studies recruited a total of 982 patients (524 males and 458 females, mean age: 35.3 years) and 791 healthy controls (417 males and 374 females, mean age, 34.2 years). Sample size of patients varied between 13 (Kim et al., 2007) and 211 (Bocchio-Chiavetto et al., 2018), while the number of controls was between 13 and 148 (Balõtšev et al., 2017). The NOS score ranged between 4 and 7.

Patients and controls were matched for age and sex in the majority of studies. In two studies, patients were significantly older than controls (Dimitrov et al., 2013; Pillai et al., 2016). In some studies, authors also controlled for the effects of BMI and/or cigarette smoking status (Frydecka et al., 2018; Haring et al., 2015; Lee et al., 2015; Mäntylä et al., 2015; Nguyen et al., 2017; Bocchio-Chiavetto et al., 2018; Lin et al., 2018; Xiao et al., 2018). In two studies (Nguyen et al., 2017; Xiao et al., 2018), patients had significantly higher BMI than controls. In two studies (Mäntylä et al., 2015; Nguyen et al., 2017), cigarette smoking rates were significantly higher in the group of patients compared to controls. In six studies, healthy controls were recruited from the same community as patients (Balõtšev et al., 2017; Dimitrov et al., 2013; Haring et al., 2015; Lin et al., 2018; Lizano et al., 2016; Mäntylä et al., 2015).

In the majority of studies, patients were diagnosed according to the DSM-IV criteria, except for five studies that used the ICD-10 criteria (Balõtšev et al., 2017; Haring et al., 2015; Bocchio-Chiavetto et al., 2018; Lin et al., 2018; Xiao et al., 2018). In two studies of MES patients, individuals with schizoaffective disorder have been also included (Nguyen et al., 2017; Pillai et al., 2016). Patients with affective psychosis have been included in the majority of studies that measured the levels of VEGF in subjects with FEP. In one study (Lizano et al., 2016), all patients with FEP had a diagnosis of schizophrenia-spectrum disorders. All patients were antipsychotic-naïve or antipsychotic-free in six studies (Haring et al., 2015; Lee et al., 2015; Lizano et al., 2016; Mäntylä et al., 2015; Lin et al., 2018; Xiao et al., 2018).

There were no significant differences in the levels of VEGF between patients and controls in pooled analysis (Table 2). The levels of VEGF were also similar in FEP patients, including antipsychotic-naïve patients, and healthy controls. Similar results were obtained in FEP and MES patients, who were antipsychotic-naïve or antipsychotic-free (Fig. 2, Table 2). However, there were significantly higher levels of VEGF in medicated MES patients compared to controls (Fig. 2, Table 2). Heterogeneity was significant in almost all analyses except for the analysis of antipsychotic-naive FEP patients. Meta-regression analysis revealed that age, sex, type of assay (ELISA vs. CBA), cigarette smoking