Association of sFlt-1 and worsening psychopathology in relatives at high risk for psychosis: A longitudinal study

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Abstract

Background: Angiogenic dysfunction and abnormalities in psychopathology and brain structure have been reported in schizophrenia, but their relationships are mostly unknown. We recently demonstrated that sFlt-1, an anti-angiogenic factor, was significantly elevated in patients at familial high-risk for psychosis (FHR). We hypothesized that elevated sFlt-1 correlates with baseline and longitudinal changes in psychopathology, cognition, and brain structure.

Methods: Plasma sFlt-1 in FHR (n = 35) and HC (n = 39) was obtained at baseline. Schizotypal, cognitive, soft neurologic signs, and structural brain imaging (1.5 T T1-weighted MRI, FreeSurfer software) measures were obtained in both groups. Longitudinal clinical and brain structural measures were obtained in a subgroup of FHR patients. Baseline data analysis used correlations between sFlt-1 and clinical/imaging measures and adjusted for multiple corrections. Linear mixed-effects models described differences in trajectories between high sFlt-1 and low sFlt-1.

Results: Baseline sFlt-1 was significantly correlated with soft neurologic signs (r = 0.27, p = 0.02) and right entorhinal volume (r = 0.50, p = 0.02), but not other baseline clinical/brain structural measures. Longitudinal examination of the FHR group (sFlt-1 high, n = 14; sFlt-1 low, n = 14) demonstrated that high sFlt-1 was significantly associated with worsening schizotypal symptoms (t = 2.4, p = 0.018). Reduced right hippocampal/parahippocampal volume/thickness trajectories were observed in high versus low sFlt-1 groups.

Conclusions: The findings from this FHR study demonstrate that peripheral markers of angiogenic dysfunction can predict longitudinal clinical and brain structural changes. Also, these findings further support the hypothesis of altered microvascular circulation in schizophrenia and those at risk.

Published by Elsevier B.V.

1. Introduction

The neurobiological basis of schizophrenia (SZ) has several proposed hypotheses implicating mechanisms (Schizophrenia Working Group of the Psychiatric Genomics, C, 2014), but its pathophysiology remains to be elucidated. Microvascular abnormality may contribute to the pathophysiology of psychotic disorders, as evidenced by capillary ultra-structural damage, reduced blood flow, altered glucose metabolism, retinal microvascular abnormalities, uncoupling of cerebral blood flow/volume, and arterioscleral cerebral blood volume reductions in SZ (Hua et al., 2016; Meier et al., 2013; Talati et al., 2015; Uranova et al., 2010; Uranova et al., 2013), and investigating angiogenic pathways may provide a novel biological framework for understanding these phenotypes (Lopes et al., 2015). Angiogenesis involves a balance between pro- and anti-angiogenic factors and can result in various pathological conditions (Lopes et al., 2015). 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sFlt-1 is a splice variant of the vascular endothelial growth factor (VEGF) receptor with two proposed mechanisms; 1) VEGF trapping and 2) hetero-dimerization with the VEGF receptor (Kendall et al., 1996), altering VEGF receptor mediated signaling (Cindrova-Davies et al., 2011). Little is known about sFlt-1 in SZ, but much is known about VEGF in SZ and neurodevelopment (Erskine et al., 2011). For instance, a VEGF knockout model resulted in growth-cone path-finding errors and altered optic chiasm development (Erskine et al., 2011). In SZ, post-mortem brain analyses demonstrated reduced VEGF in the prefrontal cortex (PFC) (Fulzele and Pillai, 2009), thalamic VEGF dysregulation (Chu et al., 2009), and increased circulatory VEGF (Pillai et al., 2015). Medications targeting VEGF signaling (sorafenib, sunitinib, and pazopanib) have shown to result in psychosis (Demirici et al., 2015; Kunene and Porfirii, 2011; Kuo et al., 2014) and cognitive (Cao et al., 2004) symptoms, domains affected in psychotic disorders (Tamminga et al., 2014).

In FHR, abnormalities affecting brain structure and function have been identified. A review showed that accelerated volume reductions over time were associated with symptom and cognitive deficits (Thermenos et al., 2013). Also, PFC and hippocampal volume alterations were consistently reported in FHR neuroimaging studies (Thermenos et al., 2013). Investigations correlating angiogenesis biomarkers to brain structure and cognition have been described. VEGF polymorphisms in healthy patients have been associated with hippocampal volume (Blumberg et al., 2008). Elevations in serum VEGF levels were associated with decreased PFC volume (Pillai et al., 2015). An animal model investigating offspring from pre-eclamptic mothers, demonstrated that elevated sFlt-1 had a reduction in brain volume that was prevented with prenatal pravastatin treatment (Carver et al., 2014). Taken together, these findings point to the importance of examining the role of sFlt-1 on psychosis risk.

The current study assessed the impact of circulating sFlt-1 levels in antipsychotic-naïve FHR patients on baseline and longitudinal measures of psychopathology, cognition, and brain structure. We hypothesized that elevated sFlt-1 correlates with baseline and longitudinal changes in psychopathology, cognition, neurological function, and brain structure.

2. Methods and materials

2.1. Participants

The study protocol, consent form, and in the case of minors, assent, with a guardian providing informed consent, were reviewed and approved by the IRB at the University of Pittsburgh and VA Pittsburgh Healthcare System (VAPHS). The FHR participants had either a first- or second-degree relative diagnosed with schizophrenia or schizoaffective disorder. The parental diagnosis was confirmed by Structural Clinical Interview for DSM-IV Axis I (SCID) interviews (First et al., 2012). Healthy controls (HC) were recruited by advertisements in the same geographic area. The FHR and HC participants were evaluated using the Schedule for Affective Disorders and Schizophrenia for Children (K-SADS), diagnoses were confirmed by consensus (Chambers et al., 1985; First et al., 2012); participants diagnosed with DSM-IV mental retardation, lifetime psychotic disorder, prior antipsychotic exposure, significant neurological/medical conditions, or IQ <75 were excluded (Keshavan et al., 2008).

Clinical assessments and MRI scans were conducted at several time points. The planned follow-up time was 1, 2 and 3 years, unless onset of psychosis occurred earlier, at which point assessments were conducted soon after transition. Thirty-five FHR participants had plasma sFlt-1 collected at baseline. Three of 35 participants converted to psychosis (schizophrenia, n = 1; schizoaffective, n = 2) during the 3 year follow up period. At follow-up, non-converters had either no psychiatric diagnosis (n = 9) or non-psychotic psychiatric disorder (n = 23). For the longitudinal examination of clinical and imaging measures, we median split sFlt-1 in the FHR group.

2.2. Clinical assessments

Outcome was assessed by interim medical/psychiatric histories and annual interviews by the same clinicians who assessed the participant at baseline. The Structured Interview for Prodromal Symptoms (SIPS) and the Chapman Schizotypy Scales (CHAP) were obtained at baseline and follow up. (Chapman et al., 1994). The SIPS scale evaluates positive, negative, disorganized, and general symptoms and rates severity on the Scale of Prodromal Symptoms (SOPS). The CHAP scale includes true/false self-report questions that measure positive (magical ideation and perceptual aberration) and negative schizotypy (Chapman et al., 1994), and the former is predictive for future conversion to psychosis (Diwadkar et al., 2006; Keshavan et al., 2008). The modified neurological evaluation scale (NES) was performed by trained raters and yields two subscale scores (repetitive motor and cognitive-perceptual) (Heinrichs and Buchanan, 1988; Keshavan et al., 2003). Percentage of perseverative errors (PERSERR) committed on the Wisconsin Card Sort Test (WCST) was used to assess executive function (Robinson et al., 1980). In the longitudinal analysis, the FHR group had 28 patients with one or more follow up clinical measures. We performed a median split by sFlt-1 level to create two groups with 14 participants in each group.

2.3. Image processing, quality assurance, and reliability

All magnetic resonance imaging (MRI) scans were conducted at the University of Pittsburgh Medical Center (1.5 T Signa Whole Body Scanner, GE Medical Systems, Milwaukee, WI). At baseline there were 23 FHR and 12 healthy comparison patients with available MRI data. For the longitudinal analysis the FHR group had 13 patients with one or more MRI scans. We performed a median split by sFlt-1 level to create two groups with 7 participants in the high sFlt-1 and 6 in the low sFlt-1 group. All images underwent rigorous quality control, checked for scanner artifacts, and performed blind to participant identity. Images were converted to Neuroimaging Informatics Technology Initiative format and checked for scanner artifacts by trained raters. Images were run through a first-level auto-reconstruction in Free-Surfer 5.1 software. The skull-stripped brains were checked for remaining dura or sinuses that could interfere with accurate segmentation. When non-brain tissue was found, trained raters edited images manually. All raters had inter-rater reliabilities and intra-rater reliability >95%. When deemed sufficiently clean for segmentation by an independent rater, images were run through second- and third-level auto-reconstruction, during which grey matter thickness and volume measures were extracted.

2.4. sFlt-1 assay

Plasma samples were collected at baseline after overnight fasting from a total of 74 patients (39 controls, 35 FHR). Samples were de-identified and plasma aliquots frozen at −80 °C until use to avoid freeze/thaw cycles. Laboratory analysis was conducted in Dr. Yao’s laboratory at VAPHS. Plasma samples were processed with Meso Scale Discovery’s Multi-ARRAY® Technology (Maryland, DE). The MSD human growth factor panel 1 assay kit provided quantifications for sFlt-1. MSD is a multiplex immunoassay system with specific capture antibodies for analytes that are coated in arrays, within each well of a 96-well carbon electrode plate. The detection system uses patented SULFO-TAG labels. The electrical stimulation is decoupled from the output signal, which is light, to generate the assays with minimal background. MSD labels can be conveniently conjugated to biological molecules, are stable and non-radioactive. Assays were developed, validated, and raw intensities converted to absolute concentrations after
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