Should psychosis be treated with tPA like a stroke? Evidence for pathological coagulopathy in psychosis

Kara B. Miecznikowski, BS[1], Henry A. Nasrallah, MD[2]
[1]University of Cincinnati College of Medicine, [2]Department of Psychiatry and Behavioral Neuroscience

University of CINCINNATI

Background

Schizophrenia and related psychosis spectrum disorders are heterogeneous illnesses with many proposed underlying genetic and environmental etiologies. Many published studies report that antipsychotic therapy is associated with a state of hypercoagulability. However, fewer studies have examined whether increased coagulability exists in unmedicated schizophrenia (SZ) or other psychoses. Some studies have reported a full remission of psychotic symptoms with warfarin, a well-known anticoagulant, raising the possibility that psychosis may be associated with coagulopathy.

Objective

The present review describes the available literature on biomarkers of coagulopathy in patients with SZ and other psychoses, raising the possibility that anticoagulant therapy may represent a novel therapeutic strategy in schizophrenia.

Methods

A PubMed search using the keywords “psychosis” OR “schizophrenia” AND (“coagulation” OR “tissue plasminogen activator” OR “thromboembolism”) for studies published between 2012 and 2023 yielded 290 results. Studies were included for final analysis if they were (1) controlled studies; (2) reported on individuals with a clinical diagnosis of schizophrenia or psychoses related to psychiatric illness; (3) in the English language. Studies were excluded from review if they (1) were review articles; (2) case reports; (3) animal studies; (4) focused on antipsychotics as a factor in coagulopathy.

Results

Seven studies met study criteria and were included for qualitative synthesis. Five included patients with SZ and related psychoses, while two also included patients with major depression and bipolar disorders. Numerous plasma proteins involved in regulating coagulation were identified as being low in patients with SZ, including thrombolytic agents such as tissue plasminogen activator (tPA), plasmin, protein S, and plasminogen, although one study found that tPA was reduced in chronic SZ but elevated in first-episode SZ (FES). Contributing to hypercoagulability, FES patients had elevated levels of plasminogen activator inhibitor-1 (PAI-1) and soluble P-selectin (sP-sel), as well as a higher PAI-1/tPA ratio. The risk of deep vein thrombosis and pulmonary embolism was found to be increased not only in SZ but depressive and bipolar disorders. SZ patients had a high prevalence of markers of low tPA/plasmin, including hyperinsulinemia, hypertriglyceridemia, hyperhomocysteinemia, and antiphospholipid antibodies, all of which decrease or increase tPA or PAI-1 activity, respectively. Patients with psychosis spectrum disorders presenting with acute psychosis had increased markers of thrombogenesis, including plasma levels of D-dimers, factor VIII, and sP-sel, which remained elevated one year after medication initiation.

Limitations

Most studies included some patients that were not antipsychotic naïve; most did not control for potential confounding factors (BMI, mobility, smoking status, etc.).

Study	Design, n	Results
Hsu et al., 2015	Population-based cohort SZ (n = 60,264) HC (n = 60,264)	The risk (aHR) of DVT (2.02) and PE (1.99) was relatively higher among SZ patients
Hoirisch-Clapauch & Nardi, 2014	Case-control SZ (n = 70) HC (n = 98)	SZ patients had an increased prevalence of markers of decreased tPA and/or plasmin activity, including hyperinsulinemia ($p < 0.001$), hypertriglyceridemia ($p = 0.005$), hyperhomocysteinemia ($p < 0.001$), medium or high antiphospholipid antibody titer ($p = 0.002$), and decreased free protein-S levels ($p = 0.005$)
Elmi et al., 2019	Prospective case-control PSD (n = 42) HC (n = 20)	tPA levels were decreased in PSD patients but did not reach statistical significance ($p = 0.35$); PAI-1 levels were lower ($p = 0.03$) in SZA patients
Lin et al., 2019	Population-based cohort SZ (n = 29,467) HC (n = 117,868)	Patients with concurrent MDD, BD, and SZ had an increased risk (aHR) of developing both DVT (2.995) and PE (2.591); this increased risk for DVT existed in patients with SZ (2.848), BD (3.049), and MDD (3.800) individually, as did increased risk for PE (2.245, 2.728, 3.464, respectively)
Santa Cruz et al., 2021	Case-control, cross sectional SZ (n = 10) BD (n = 10) HC (n = 14)	Patients with BD and SZ had an alteration of serum proteins ($p < 0.05$) that indicated differences in the complement and coagulation cascade pathways as compared to healthy controls; alpha-2-antiplasmin was decreased in BD ($\log2(FC) = -1.49$) and vitamin K-dependent protein S was increased in SZ ($\log2(FC) = 1.24$)
Masopust et al., 2013	Prospective case-control PSD (n = 36) HC (n = 37)	D-dimer ($p < 0.001$), factor VIII ($p = 0.02$) and sP-sel ($p < 0.001$) plasma levels were significantly increased in patients with acute psychosis prior to treatment compared to controls
Zheng et al., 2023	Case-control FES (n = 27) CS (n = 27) HC (n = 27)	FES patients had higher PAI-1 ($p = 0.006$), sP-sel ($p = 0.009$), TpP ($p < 0.001$), and PAI-1/tPA ($p = 0.002$) when compared to controls; PAI-1, tPA, TpP, and vWF in FES patients decreased after AP treatment but returned to pre-treatment levels

SZ, schizophrenia; HC, healthy controls; DVT, deep venous thrombosis; PE, pulmonary embolism; AP, antipsychotic; tPA, tissue plasminogen activator; BMI, body mass index; PSD, psychotis spectrum disorders; PAI-1, plasminogen activator inhibitor-1; MDD, major depressive disorder; BD, bipolar disorder; SZA, schizoaffective disorder; aHR, adjusted hazard ratio; FC, fold changes; sP-sel, soluble platelet selectin; FES, first episode schizophrenia; CS, chronic schizophrenia; vWF, von Willenbrand factor; tpP, thrombotic precursor protein

Discussion

Taken altogether, these findings suggest that the association between hypercoagulability and psychosis spectrum disorders may not be purely iatrogenic in nature but a persistent feature of the disease. Further studies are warranted to confirm this hypothesis.

References

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