Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Medicine

Psychosis and Venous Thromboembolism: A Clinical Analysis and Literature Review

Asmae Boukdir[1*], Hana Ballouk[1], Aouatef Khallouk[1], Aya Rhaouti[1], Sofia Bahetta[1], Jalal Toufiq[1]

[1]University Psychiatric Hospital Ar-razi in Sale, Faculty of Medicine and Pharmacy, Mohamed V University, Rabat, Morocco

DOI: https://doi.org/10.36347/sjmcr.2025.v13i01.024 | **Received:** 03.12.2024 | **Accepted:** 08.01.2025 | **Published:** 15.01.2025

***Corresponding author:** Asmae Boukdir
University psychiatric Hospital Ar-razi in Sale, Faculty of Medicine and Pharmacy, Mohamed V University, Rabat, Morocco

Abstract **Case Report**

Psychosis is an amalgamation of psychological symptoms resulting in a loss of contact with reality. Approximately 1.5% to 3.5% of the general population will meet the diagnostic criteria for a psychotic disorder, and around 3 in 100 individuals will experience isolated psychotic symptoms in their lifetime. On the other hand, venous thromboembolism (VTE) is a chronic condition that affects nearly 10 million people every year worldwide. The relationship between psychiatric disorders and thrombotic events has garnered increasing attention in recent years, with emerging evidence suggesting a bidirectional association. We present the case of a 38-year-old female who developed psychotic symptoms in 2019, twelve years after being diagnosed with portal vein thrombosis (PVT). Despite undergoing two psychiatric consultations in 2019 and 2020, formal antipsychotic treatment was not initiated until 2024 when she was prescribed Aripiprazole and Lorazepam, resulting in moderate improvement. The temporal sequence and clinical manifestations suggest potential pathophysiological connections between vascular pathology and the development of a psychotic disorder, warranting further investigation into this relationship. This case contributes to the limited literature on this association and highlights the importance of comprehensive evaluation and management approaches in such cases.

Keywords: Psychosis, Venous Thromboembolism (VTE), Portal Vein Thrombosis (PVT), Aripiprazole, Lorazepam.

INTRODUCTION

Venous thromboembolism (VTE) comprising both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially life-threatening condition. It represents the third most common cardiovascular disorder, affecting up to 5% of the population. (Duffet 2022). Portal vein thrombosis (PVT) is the narrowing or blocking of the portal vein by a blood clot, which can develop in the main body of the portal vein or its intrahepatic branches, or extend to the splenic or superior mesenteric veins. It can lead to portal hypertension and various complications. Portal vein thrombosis (PVT) frequently occurs with cirrhosis of the liver but may also be associated with various conditions such as systemic lupus erythematosus and hypercoagulable states. The lifetime risk of PVT in the general population is 1%. (Samant *et al*., 2024).

Psychosis is a common feature in many psychiatric, neuropsychiatric, neurologic, neurodevelopmental, and medical conditions. It is the hallmark feature of schizophrenia spectrum and other psychotic disorders, a co-occurring symptom in many mood and substance use disorders, as well as a challenging symptom in many neurologic and medical conditions. (Calabrese *et al*., 2023)

Research on psychosis has increased knowledge of the complexity of psychotic disorders and their pathogenesis. The dopamine hypothesis has significantly influenced the study of the neurochemistry of psychosis. However, it became evident early on that other factors also contribute to psychosis, including neurotransmitter dysregulation (dopamine, serotonin, glutamate, and γ-aminobutyric acid (GABA)), neuroinflammation, glial cells (microglia, astrocytes, and oligodendrocytes), the hypothalamic–pituitary–adrenal axis, the gut microbiome, oxidative stress, and mitochondrial dysfunction, all of which interact with one another. (Rawani *et al*., 2024)

Psychotic disorders and venous thromboembolism may be associated in observational studies. However, the causal relationship remains unclear. Various pathophysiological mechanisms could potentially link thrombotic events and psychotic symptoms.

Clinical Case: Patient and Observation

The patient is a 38-year-old single female, fourth among five siblings, with limited educational background, who previously worked for several years in a bakery. She lives with her parents and her sister, who describe her premorbid personality as calm and sociable.

Her medical history became significant in 2007 with the onset of portal and mesenteric vein thrombosis, which eventually progressed to portal hypertension complicated by recurrent episodes of edematous-ascitic decompensation. This chronic condition has required long-term management with anticoagulation (Acenocoumarol) and diuretics (Spironolactone and Furosemide). No surgical history, toxic exposures, or allergies were reported.

The patient's psychiatric history began with initial consultations in March 2019, followed by another visit in early 2020. The onset of psychiatric symptoms emerged progressively from January 2020, marked by significant behavioral changes. She exhibited social withdrawal, increased irritability, and refusal to communicate with family members. The patient developed delusional beliefs, particularly regarding pregnancy and multiple miscarriages, accompanied by auditory and visual hallucinations, including seeing "Satan fleeing." During hospitalizations in internal medicine, she displayed peculiar behaviors, death-related anxieties, and made attempts to escape, which her family managed to tolerate.

By February 2024, the patient's condition had deteriorated to include insomnia, persistent delusions, bizarre behaviors such as inappropriate undressing and hair-pulling, self-destructive actions such as wandering and fire-setting tendencies. This prompted a psychiatric consultation, which led to the prescription of lorazepam and aripiprazole treatment, resulting in moderate and gradual improvement.

A biological workup revealed bicytopenia (anemia and thrombocytopenia), hepatic panel showed mild abnormalities, with normal ASAT and ALAT levels but slight elevations in GGT and alkaline phosphatase. The ionogram was unremarkable, and viral serologies for hepatitis B and C, and HIV were negative.

Abdominal CT showed chronic portal vein thrombosis with multiple porto-systemic collateral pathways and splenomegaly, while a brain CT scan revealed no abnormalities.

This case presents a diagnostic challenge. Given the patient's history of portal vein thrombosis and its complications, the differential diagnosis spans primary psychotic disorders, such as schizophrenia and secondary causes, particularly vascular-related psychotic manifestations. However, the primary focus should remain on elucidating the interplay between her medical and psychiatric conditions to refine the diagnosis and guide treatment. Through this case report and a review of the current literature, we will examine the links between the two phenomena.

Discussion

There is a lack of literature or documented cases directly connecting psychosis with portal vein thrombosis (PVT). Nonetheless, the correlation between psychosis and venous thromboembolism (VTE) has been extensively examined. Although there is substantial evidence linking an increased risk of VTE to individuals with psychosis, there has been significantly less focus on the potential mechanisms by which VTE might contribute to psychosis (Di *et al*., 2021). This suggests that the influence of vascular conditions like VTE on the development of psychotic symptoms is still not fully understood and deserves more research.

Masopust *et al*., (2011) investigated the relationship between venous thromboembolism (VTE) and acute psychosis specifically in unmedicated patients, by assessing markers of thrombogenesis and thrombocyte activation. The results showed that plasma levels of D-dimer and sP-selectin were significantly higher in patients with acute psychosis compared to healthy controls. Elevated levels of D-dimer indicate pathological blood clotting and fibrinolysis, which are consistent with previous findings linking D-dimer to deep vein thrombosis risk (Andreescu *et al*., 2002). Increased plasma levels of sP-selectin, a marker of inflammation and thrombogenesis, were also noted, linking thrombocyte activation to atherogenesis and endothelial dysfunction (Osinbowale *et al*., 2010). There was also a trend toward increased levels of factor VIII in patients with psychosis, especially among women, further supporting a hypercoagulable state that increases the risk of VTE (Morioka *et al*., 1997).

These findings align with previous studies that have shown elevated platelet activation and coagulation abnormalities in schizophrenia. For instance, Iwata *et al*., (1999) found elevated serum soluble L-selectin in unmedicated schizophrenia patients. Similarly, Walsh *et al*., (2000) demonstrated increased platelet receptor expression in schizophrenia patients. Additionally, Morioka *et al*., (1997) reported venous thrombosis in patients with psychiatric stupor, further supporting the link between mental illness and thrombosis. The discussion highlights that VTE may often go unrecognized in individuals with severe mental disorders due to asymptomatic presentations and limited knowledge of VTE diagnostics among psychiatrists (Osinbowale *et al*., 2010).

Overall, the study by Masopust *et al*., emphasizes that acute psychosis, even in the absence of antipsychotic medication - which has consistently been

linked to an increased risk of venous thromboembolism (VTE) in schizophrenia - is associated with pathological thrombogenesis and platelet activation, which may elevate the risk of venous thromboembolism (VTE) (Di *et al*., 2021).

Hong-Yan *et al*., (2024) examined the bidirectional relationship between major depressive disorder (MDD) and venous thromboembolism (VTE). The study observed no association between VTE and MDD risk, which differed from the results of previous studies. However, it highlights shared pathways that could connect these conditions, including systemic inflammation, endothelial dysfunction, and hypercoagulability. Elevated levels of pro-inflammatory markers (e.g., cytokines) and associated behavioral changes, such as reduced physical activity and increased stress, are proposed as key mediators. These factors may amplify the risk of thrombotic events in individuals with depression (Gold *et al*., 2015).

Makivic *et al*., (2021) described a case of acute psychosis following a pulmonary embolism (PE) in a 46-year-old previously healthy patient with mild COVID-19, attributing the psychiatric symptoms to systemic inflammation, central nervous system hypoxia, and stress responses. This aligns with the hypothesis that thrombotic events, including portal venous thrombosis, can lead to neuropsychiatric symptoms via shared mechanisms of inflammation and hypoperfusion affecting brain function.

Additionally, ongoing studies and research aim to understand the pathogenesis of psychosis, with schizophrenia in particular, and mental disorders in general. There is a growing interest in this field, potentially exploring the mechanisms related to venous thromboembolism pathology.

Hoirisch *et al*., (2016) examined the potential link between the coagulation system and schizophrenia. They noted that five psychotic patients on chronic warfarin therapy for deep-vein thrombosis experienced long-term remission of psychotic symptoms. This observation led to the hypothesis that abnormalities in the coagulation pathway, specifically low tissue plasminogen activator (tPA) activity, might be a contributing factor (Hoirisch *et al*., 2013). Their hypothesis is further supported by the high prevalence of conditions affecting tPA activity in drug-naïve schizophrenia patients, such as antiphospholipid antibodies, elevated cytokine levels, hyperinsulinemia, and hyperhomocysteinemia (Delluc *et al*., 2014; Gris *et al*., 2015; Halacheva *et al*., 2009; Song *et al*., 2014).

Upon screening a group of schizophrenia patients and controls, they found that free-protein S deficiency was common among patients but absent in controls. Both free-protein S and functional protein C are natural anticoagulants that inhibit tPA inhibitors. Since all participants had normal protein C levels, this suggests an independent role of protein S in schizophrenia. Chronic patients and those in acute episodes showed multiple conditions affecting tPA and/or protein S activity, while patients in remission had fewer such conditions. (Hoirisch *et al*., 2013; Hoirisch *et al*., 2014)

Heurich *et al*., (2022) presented an in-depth exploration of the role of dysregulation in the complement and coagulation pathways in the development of psychosis, concluding by asserting that alterations in these pathways are significant risk factors for psychosis. They suggest that early identification and intervention can improve outcomes for individuals at high risk of developing psychotic disorders, emphasizing the need for biomarkers to predict psychosis risk (Yung *et al*., 2005).

Heurich *et al*., (2022) reviewed the evidence linking immune and coagulation dysfunction with psychosis, emphasizing genetic associations and changes in plasma proteins observed prior to the onset of psychotic symptoms. Supporting this, Sekar *et al*., (2016) demonstrated that schizophrenia is associated with varying levels of C4A and C4B expression in the brain, with higher C4A levels linked to an increased risk of schizophrenia. Their study found C4 proteins in various neuronal structures, and in mice, these proteins mediated synapse elimination during postnatal development. These findings suggest that excessive complement activity contributes to schizophrenia, potentially explaining the reduction of synapses observed in affected individuals.

Based on the findings of Mongan *et al*., (2021), plasma proteomic biomarkers, primarily components of the complement and coagulation pathways, have been shown to accurately differentiate individuals at clinical high risk for developping psychosis who go on to develop a first psychotic episode from those who do not. These results suggest that early dysregulation of the complement and coagulation cascades may play a crucial role in the development of psychosis, offering potential biomarkers for individualized prognosis and stratification strategies in at-risk populations.

In their article, Heurich *et al*., (2022) refine the prevailing two-hit hypothesis by integrating novel findings. They suggest that the "first hit" - early genetic and/or environmental disruptions to the developing central nervous system - creates an increased vulnerability to later environmental disruptions, or the "second-hit," ultimately leading to central nervous system manifestations of psychotic disorders (Bayer *et al*., 1999; Maynard *et al*., 2001; Feigenson *et al*., 2014). This theory is further expanded to include complement and coagulation dysregulation, which can trigger immune activation and contribute to the development of psychotic disorders.

While portal vein thrombosis is not directly addressed in the literature recent findings on the pathogenesis of psychosis align with our exploration of how systemic inflammation, along with immune and coagulation dysregulation, might bridge the gap between psychosis and venous thromboembolism (VTE) in general. Understanding the genetic and molecular mechanisms involved could help elucidate the potential pathophysiological connections underpinning both conditions.

CONCLUSION

This clinical analysis underscores the importance of a comprehensive evaluation in patients with complex medical and psychiatric histories. It highlights the diagnostic and therapeutic challenges encountered when managing patients with co-occurring thrombotic and psychotic disorders. Although the direct link between portal vein thrombosis (PVT) and psychosis is rarely documented, the extensive literature on venous thromboembolism (VTE) and psychosis indicates a heightened risk of thrombotic events in patients with psychotic disorders. Current evidence suggests that pathophysiological mechanisms including coagulation abnormalities, immune responses, and systemic inflammation may serve as common pathways linking psychosis and VTE. Future research should focus on identifying potential biomarkers and elucidating molecular mechanisms that could clarify the connection between psychosis and VTE, thereby paving the way for more targeted interventions and improved patient outcomes.

REFERENCES

- Andreescu, A. C., Cushman, M., & Rosendaal, F. R. (2002). D-dimer as a risk factor for deep vein thrombosis: The Leiden Thrombophilia Study. *Thrombosis and haemostasis*, *87*(1), 47–51.
- Bayer, T. A., Falkai, P., & Maier, W. (1999). Genetic and non-genetic vulnerability factors in schizophrenia: The basis of the "two-hit hypothesis". *Journal of psychiatric research*, *33*(6), 543–548.
- Calabrese, J., & Al Khalili, Y. (2023). Psychosis. In StatPearls. StatPearls Publishing.
- Delluc, A., Rousseau, A., Le Galudec, M., Canceil, O., Woodhams, B., Etienne, S., Walter, M., Mottier, D., Van Dreden, P., & Lacut, K. (2014). Prevalence of antiphospholipid antibodies in psychiatric patients users and non-users of antipsychotics. *British journal of haematology*, *164*(2), 272–279.
- Di, X., Chen, M., Shen, S., & Cui, X. (2021). Antipsychotic use and Risk of Venous Thromboembolism: A Meta-Analysis. *Psychiatry research*, *296*, 113691.
- Duffett, L. (2022). Deep venous thrombosis. *Annals of internal medicine*, *175*(9), ITC129–ITC144.
- Feigenson, K. A., Kusnecov, A. W., & Silverstein, S. M. (2014). Inflammation and the two-hit hypothesis of schizophrenia. *Neuroscience and biobehavioral reviews*, *38*, 72–93.
- Gold, P. W. (2015). The organization of the stress system and its dysregulation in depressive illness. *Molecular psychiatry*, *20*(1), 32–47.
- Gris, J. C., Nobile, B., & Bouvier, S. (2015). Neuropsychiatric presentations of antiphospholipid antibodies. *Thrombosis research*, *135*(Suppl 1), S56–S59.
- Halacheva, K., Dimova, S., Tolev, T., Dimov, D., & Nikolova, M. (2009). Elevated anticardiolipin antibodies in schizophrenic patients before and during neuroleptic medication. *Psychiatry research*, *169*(1), 51–55.
- Heurich, M., Föcking, M., Mongan, D., Cagney, G., & Cotter, D. R. (2022). Dysregulation of complement and coagulation pathways: Emerging mechanisms in the development of psychosis. *Molecular psychiatry*, *27*(1), 127–140.
- Hoirisch-Clapauch, S., & Nardi, A. E. (2013). Multiple roles of tissue plasminogen activator in schizophrenia pathophysiology. *Seminars in thrombosis and hemostasis*, *39*(8), 950–954.
- Hoirisch-Clapauch, S., & Nardi, A. E. (2013). Psychiatric remission with warfarin: Should psychosis be addressed as plasminogen activator imbalance?. *Medical hypotheses*, *80*(2), 137–141.
- Hoirisch-Clapauch, S., & Nardi, A. E. (2014). Markers of low activity of tissue plasminogen activator/plasmin are prevalent in schizophrenia patients. *Schizophrenia research*, *159*(1), 118–123.
- Hoirisch-Clapauch, S., Amaral, O. B., Mezzasalma, M. A., Panizzutti, R., & Nardi, A. E. (2016). Dysfunction in the coagulation system and schizophrenia. *Translational Psychiatry*, *6*(1), e704.
- Makivic, N., Stöllberger, C., Schauer, D., Bernhofer, L., Pawelka, E., Erfurth, A., & Weidinger, F. (2021). Pulmonary embolism and acute psychosis, a case report of an outpatient with a mild course of COVID-19. *SN Comprehensive Clinical Medicine*, *3*(6), 1434–1439.
- Masopust, J., Malý, R., Andrýs, C., Vališ, M., Bažant, J., & Hosák, L. (2011). Markers of thrombogenesis are activated in unmedicated patients with acute psychosis: A matched case control study. *BMC Psychiatry*, *11*, 2.
- Maynard, T. M., Sikich, L., Lieberman, J. A., & LaMantia, A. S. (2001). Neural development, cell-cell signaling, and the "two-hit" hypothesis of schizophrenia. *Schizophrenia bulletin*, *27*(3), 457–476.
- Mongan, D., Föcking, M., Healy, C., Susai, S. R., Heurich, M., Wynne, K., Nelson, B., McGorry, P. D., Amminger, G. P., Nordentoft, M., Krebs, M. O., Riecher-Rössler, A., Bressan, R. A., Barrantes-Vidal, N., Borgwardt, S., Ruhrmann, S., Sachs, G., Pantelis, C., van der Gaag, M., de Haan, L., …

European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) High Risk Study Group (2021). Development of proteomic prediction models for transition to psychotic disorder in the clinical high-risk state and psychotic experiences in adolescence. *JAMA psychiatry*, *78*(1), 77–90.

- Morioka, H., Nagatomo, I., Yamada, K., Horikiri, Y., Okamura, H., & Takigawa, M. (1997). Deep venous thrombosis of the leg due to psychiatric stupor. *Psychiatry and clinical neurosciences*, *51*(5), 323–326.
- Osinbowale, O., Ali, L., & Chi, Y. W. (2010). Venous thromboembolism: A clinical review. *Postgraduate medicine*, *122*(2), 54–65.
- Rawani, N. S., Chan, A. W., Dursun, S. M., & Baker, G. B. (2024). The Underlying Neurobiological Mechanisms of Psychosis: Focus on Neurotransmission Dysregulation, Neuroinflammation, Oxidative Stress, and Mitochondrial Dysfunction. *Antioxidants (Basel, Switzerland)*, *13*(6), 709.
- Samant, H., Asafo-Agyei, K. O., Kimyaghalam, A., & Garfield, K. (2024). Portal vein thrombosis. In StatPearls. StatPearls Publishing.
- Sekar, A., Bialas, A. R., de Rivera, H., Davis, A., Hammond, T. R., Kamitaki, N., Tooley, K., Presumey, J., Baum, M., Van Doren, V., Genovese, G., Rose, S. A., Handsaker, R. E., Schizophrenia Working Group of the Psychiatric Genomics Consortium, Daly, M. J., Carroll, M. C., Stevens, B., & McCarroll, S. A. (2016). Schizophrenia risk from complex variation of complement component 4. *Nature*, *530*(7589), 177–183.
- Song, X., Fan, X., Li, X., Kennedy, D., Pang, L., Quan, M., Chen, X., Gao, J., Zhang, W., Zhang, J., & Lv, L. (2014). Serum levels of BDNF, folate and homocysteine: In relation to hippocampal volume and psychopathology in drug naïve, first episode schizophrenia. *Schizophrenia research*, *159*(1), 51–55.
- Yung, A. R., Yuen, H. P., McGorry, P. D., Phillips, L. J., Kelly, D., Dell'Olio, M., Francey, S. M., Cosgrave, E. M., Killackey, E., Stanford, C., Godfrey, K., & Buckby, J. (2005). Mapping the onset of psychosis: The Comprehensive Assessment of At-Risk Mental States. *The Australian and New Zealand journal of psychiatry*, *39*(11-12), 964–971.