Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19, hypercoagulation and what it could mean for patients with psychotic disorders

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It has been recently shown that COVID-19 is associated with a clinically significant coagulopathy. Several studies have indicated that elevated markers of fibrin degradation (D-dimers) in hospitalised patients are associated with poorer prognosis (death or ICU admission) (Fogarty et al., 2020; Connors and Levy, 2020). Coagulation test screening is suggested and routine thromboprophylaxis measures (including use of low molecular weight heparin) are recommended, although full anticoagulation is not yet advised in the management of such patients unless otherwise clinically indicated (Connors and Levy, 2020). We wish to draw attention to a potentially enhanced risk of thromboembolic complications in patients with psychotic disorders.

1. Coagulation and COVID-19

Virchow's triad describes three types of factors that contribute to development of thrombosis: stasis (abnormalities in blood flow); endothelial injury (abnormalities of the blood vessel wall; and a hypercoagulable state (abnormalities of the blood constituents). Patients with COVID-19 are likely to be less mobile in the context of their infection, especially in severe cases, increasing the risk of stasis. The SARS-CoV-2 virus is understood to become incorporated within host cells via binding to the angiotensin-converting enzyme 2 (ACE2) receptor. This receptor is expressed widely in endothelial cells, enabling the virus to contribute to endothelial injury. A hypercoagulable state may be induced as a result of the intense release of pro-inflammatory cytokines. These are key mediators of the immune response which can also activate the complement system, a key component of the innate immune system among the body's arsenal of early responses to infection. The complement system interacts closely with and can cause activation of the coagulation pathway (Oikonomopoulou et al., 2012). Activation of coagulation in COVID-19 is in keeping with observations of increased incidence of venous thromboembolism in critically ill patients (Klok et al., 2020).

2. Coagulation and psychotic disorders

Patients with psychotic disorders such as schizophrenia may have an approximately 2- to 3-fold increased risk of deep vein thrombosis or pulmonary embolism compared to controls (Lin et al., 2019). Several factors may underlie this association (see Fig. 1). Obesity, atherosclerosis and cardiovascular disease are common physical co-morbidities in people with schizophrenia which are associated with abnormalities of blood flow and thromboembolic risk. There is evidence that schizophrenia may be associated with endothelial dysfunction, as evidenced by elevated levels of plasma endothelial markers such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (Nguyen et al., 2018). These normally aid leukocyte adhesion to endothelium as part of the immune response, but if left unchecked may lead to endothelial damage as occurs in the development of atherosclerosis. There is well-described evidence for chronic, low-grade immune activation and inflammation in schizophrenia which may drive, or occur in association with, endothelial injury. There is also growing evidence that psychosis phenotypes are associated with abnormalities in blood constituents indicative of a hypercoagulable state (Chow et al., 2015; Hoirisch-Clapauch et al., 2016). Our proteomic studies we have implicated complement activation and hypercoagulation prior to the onset of subclinical psychotic experiences and psychotic disorder in the general population (English et al., 2018; Focking et al., 2019). These findings suggest that aberrations of the complement and coagulation systems are present early in the course of psychosis and may be part of the underlying associated pathophysiology. However, the influence of factors such as exposure to medication, chronic lifestyle factors or physical co-morbidity may increase with chronicity of the disorder. Antipsychotic therapy, for example, may be associated with an increased risk of thromboembolism (Barbui et al., 2014) although it is not clear whether this is as a direct result of their therapeutic pharmacological actions or secondary to other effects such as sedation or weight gain.

3. Implications

Patients with psychosis may be at increased thromboembolic risk in part due to lifestyle, medication and environmental factors, but the association may also be driven by biological dysregulation associated with the underlying disorder, acting in concert with these other factors. Given the accumulating evidence for coagulopathy associated with

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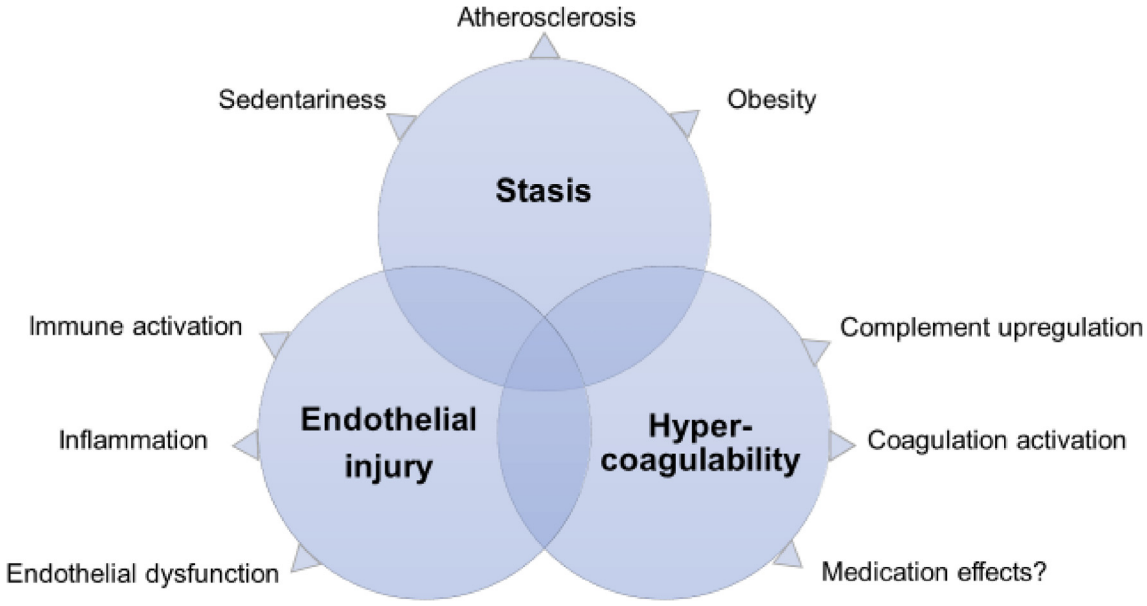

Fig. 1. Examples of factors that may underlie the association between psychotic disorders and thromboembolic risk according to Virchow's triad.

COVID-19, patients with psychosis who acquire COVID-19 may be at enhanced risk for thromboembolic complications While this potential link is informed by the risk factors and evidence for hypercoagulation associated with both conditions, in the absence of sufficient data it remains speculative. There is an urgent need for research to formally evaluate the risk of thromboembolic complications in patients with psychosis who develop infection with COVID-19 to guide clinical management decisions in this population. Clinicians in psychiatry, general medicine and intensive care should evaluate these factors with special consideration of the potential for increased risk of thromboembolic complications. Screening for coagulation abnormalities should be implemented in line with current (and rapidly developing) guidance.

Conflicts of interest

DM, MC and DRC report a patent pending (UK Patent Application No. 1919155.0, "Biomarkers to predict psychosis"). The authors otherwise report no conflicts of interest in relation to this work.

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References

Barbui, C., Conti, V., Cipriani, A., 2014. Antipsychotic drug exposure and risk of venous thromboembolism: a systematic review and meta-analysis of observational studies. Drug Saf. 37 (2), 79–90.
Chow, V., Reddel, C., Pennings, G., et al., 2015. Global hypercoagulability in patients with schizophrenia receiving long-term antipsychotic therapy. Schizophr. Res. 162 (1–3), 175–182.
Connors, J.M., Levy, J.H., 2020. COVID-19 and its implications for thrombosis and anticoagulation. Blood.
English, J.A., Lopez, L.M., O'Gorman, A., et al., 2018. Blood-based protein changes in childhood are associated with increased risk for later psychotic disorder: evidence from a nested case-control study of the ALSPAC longitudinal birth cohort. Schizophr Bull. 44 (2), 297–306.
Focking, M., Sabherwal, S., Cates, H.M., et al., 2019. Complement pathway changes at age 12 are associated with psychotic experiences at age 18 in a longitudinal population-based study: evidence for a role of stress. Mol. Psychiatry.
Fogarty, H., Townsend, L., Ni Cheallaigh, C., et al., 2020. COVID-19 Coagulopathy in Caucasian patients. Br. J. Haematol.
Hoirisch-Clapauch, S., Amaral, O.B., Mezzasalma, M.A., Panizzutti, R., Nardi, A.E., 2016. Dysfunction in the coagulation system and schizophrenia. Transl. Psychiatry 6, e704.
Klok, F.A., Kruip, M., van der Meer, N.J.M., et al., 2020. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb. Res.
Lin, C.E., Chung, C.H., Chen, L.F., Chien, W.C., 2019. Increased risk for venous thromboembolism among patients with concurrent depressive, bipolar, and schizophrenic disorders. Gen. Hosp. Psychiatry 61, 34–40.
Nguyen, T.T., Dev, S.I., Chen, G., et al., 2018. Abnormal levels of vascular endothelial biomarkers in schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 268 (8), 849–860.
Oikonomopoulou, K., Ricklin, D., Ward, P.A., Lambris, J.D., 2012. Interactions between coagulation and complement–their role in inflammation. Semin. Immunopathol. 34 (1), 151–165.