Reminder of important clinical lesson

Idiopathic pulmonary thromboembolism in the course of intensive psychiatric inpatient care: case report and treatment guidelines

Shane J McInerney,¹ Colm McDonald²¹Department of Psychiatry, University Hospital Galway, Galway, Ireland;²Department of Psychiatry, National University of Ireland Galway and West Galway Mental Health Services, HSE West, Galway, Ireland**Correspondence to** Dr Shane J McInerney, shane.mcinerney@nuigalway.ie**Summary**

Idiopathic thromboembolism can occur in psychiatric patients who have been inactive during a period of inpatient hospital treatment. These patients are usually treated with antipsychotic medication which has also been reported to increase risk for thromboembolic disease. Here the authors describe a patient with neither prior history of thromboembolism nor any medical risk factors for thromboembolic disease, who was admitted with an acute relapse of psychotic illness. During the course of her intensive psychiatric treatment, she had chest pain and CT-pulmonary arteriogram revealed bilateral lower lobe pulmonary embolism. She was anticoagulated and made a full medical recovery. Treatment with high dosages of typical and atypical antipsychotic medication and a lack of mobility related to intensive nursing care and sedation were likely risk factors in her development of pulmonary emboli.

BACKGROUND

Patients in acute psychiatric units are often prescribed high dosages of antipsychotic medication due to their level of distress and agitation during the course of a psychotic episode. Clinicians should be aware of the risk of pulmonary embolism in the context of acute psychiatric care and the indications for taking preventive measures.

CASE PRESENTATION

A 42-year-old lady with a long history of schizoaffective disorder and 11 previous involuntary admissions since the onset of her illness at age 30 was admitted involuntarily to the acute psychiatric unit of University Hospital Galway with a severe relapse of her psychotic illness. She had been non-compliant with oral psychotropic medication in the community. On admission, she displayed persecutory and grandiose delusions, agitation, disinhibition and markedly disorganised behaviour.

Before admission she had been prescribed flupenthixol decanoate 200 mg intramuscularly once weekly and amisulpride 400 mg twice daily. In order to manage her psychotic symptoms and disorganised behaviour, her oral medication was reinstituted and gradually increased until she was prescribed British National Formulary maximum doses of these antipsychotic medications, as well as benzodiazepine medication, aripiprazole and lithium. She had previously been prescribed numerous other antipsychotic medications including olanzapine and clozapine with variable response. She was also treated with eight administrations of electroconvulsive therapy which had been an effective treatment for her on eight previous occasions for relapse of her affective psychosis.

She received lengthy 1:1 special nursing care in a single room due to her level of agitation and her disinhibited and disruptive behaviour. While she was confined to her

room, she was also fearful of leaving the room due to her persecutory beliefs. She was intermittently agitated and made repeated attempts to abscond or set off emergency alarms, however she spent many daytime hours during this period in bed due to sedation and confinement to her room. Her response during this initial phase of treatment was poor with fluctuating psychotic beliefs and disorganised behaviour.

After 12 weeks in hospital she had stabbing chest pain. She had no shortness of breath, no radiating pain to her left arm or recent trauma. At this point she was being treated with flupenthixol decanoate 400 mg intramuscularly weekly, aripiprazole 30 mg at night, amisulpride 600 mg twice daily, lithium 600 mg at night and she was receiving a dose of 10 mg olanzapine each evening on an as required basis due to her level of distress and agitation over the previous fortnight. Despite these high doses of antipsychotic medication, she displayed minimal evidence of significant extra-pyramidal side effects other than occasional non-distressing akathisia. The patient had a normal body mass index and was a non-smoker and did not drink alcohol. She had no prior medical history of note and was not taking an oral contraceptive pill.

INVESTIGATIONS

Following medical review, she had an ECG and blood sampling which were normal apart from d-dimers (672 ng/l, normal range=0–200 ng/l) which were elevated. Subsequently a chest x-ray (reported as normal) and CT-pulmonary arteriogram was obtained which revealed bilateral lower lobe pulmonary embolism. A number of investigations were conducted to exclude causes for her pulmonary embolism including abdominal ultrasound and thrombophilia screen which were reported as normal. The thrombophilia screen was carried out following the acute event and before the

Box 1 Risk factors for venous thromboembolism or pulmonary embolism

Virchow's triad presents the three broad categories of factors that are thought to contribute to thrombosis:

- ▶ Alterations in normal blood flow (stasis)
- ▶ Increased clotting potential of the blood (hypercoagulability)
- ▶ Damage to the walls of the veins.
- ▶ Examples of these risk factors include:
- ▶ Prolonged immobilisation
- ▶ Extended travel (sitting in a car, airplane, train, etc.)
- ▶ Hospitalisation or prolonged bed rest
- ▶ Increased blood clotting potential
- ▶ Medications: birth control pills, oestrogen
- ▶ Smoking
- ▶ Genetic predisposition
- ▶ Polycythemia (increased number of red blood cells)
- ▶ Cancer
- ▶ Pregnancy, including 6–8 weeks postpartum
- ▶ Surgery
- ▶ Damage to vessel wall
- ▶ Prior deep venous thrombosis
- ▶ Trauma to the lower leg with or without surgery or casting

patient was being treated with warfarin. Mammography to outrule breast pathology was normal.

DIFFERENTIAL DIAGNOSIS

Myocardial infarction, thrombophilia, carcinoma.

TREATMENT

The patient subsequently received warfarin treatment. Her mental state eventually improved in the subsequent months after further medication alterations, which included a retriage of clozapine, and she was discharged on approved leave to a supervised community mental health facility after 36 weeks of involuntary admission.

OUTCOME AND FOLLOW-UP

Warfarin treatment reached therapeutic levels and she made a full medical recovery without medical complications. She remained insightful about her mental illness but her psychotic symptoms and disorganised behaviour abated. She was treated with warfarin for a 6-month period as per international guidelines for a patient with a first VTE episode.

DISCUSSION

Venous thromboembolism (VTE) has been associated with risk factors such as smoking, trauma, immobilisation, surgery, pregnancy, use of combined oral contraceptives, malignant disorders and certain cardiac and haemostatic disorders, including factor V Leiden mutation (box 1).¹

There have been reports that the risk of VTE is increased in psychiatric patients, especially those with schizophrenia or bipolar disorder. A case controlled study of nearly 30 000 UK residents attending general practitioners and receiving antipsychotic medication, found that current exposure to

Table 1 Score of risk factors for venous thromboembolism in hospitalised psychiatric patients with reduced mobility

Score 2 risk factors
History of deep-vein thrombosis or pulmonary embolism
Cancer (active/treated)
Age >75 years
Acute infections including sepsis or acute respiratory disease
Score 1 risk factors
Immobilisation (including paralysis of lower extremity, physical restraint >8 h, catatonia)
Hormone therapy (oral contraception, hormonal replacement therapy)
Obesity (body mass index >30)
Age 60–74 years
Varicose veins/venous insufficiency
Dehydration
Thrombophilia
Treatment with antipsychotics

conventional antipsychotic drugs was associated with a significantly increased risk of idiopathic VTE compared with non-use of antipsychotic medication. This study found that the risk for venous thrombosis was highest during the first few months of conventional antipsychotic drug use, with low potency antipsychotic drugs such as chlorpromazine being more strongly associated. Of note, this study excluded any patient who had suffered an acute psychotic episode within 2 months of the index date as this was considered to carry inherent risk for thrombotic events.²

A recent study by Parker *et al* found an association between use of antipsychotic drugs and risk of VTE in a large primary care population with those being prescribed in the previous 24 months with atypical, low potency drugs, while adjusting for potential risk factors.³

Thomassen *et al* reported from autopsy reports of ten psychiatric patients who had pulmonary embolism recorded as the cause of death. Five of these patients were taking antipsychotic medication and had no risk factors such as immobilisation. They concluded that antipsychotic drug use was associated with venous thrombosis.⁴

A number of possible explanations have been put forward to link thromboembolism with antipsychotic medication. One explanation is that conventional antipsychotic drugs are associated with enhanced aggregation of platelets.⁴ A second possible explanation is that anticardiolipin antibodies, which are associated with increased risk of venous or arterial thrombosis, are raised in some patients prescribed antipsychotic medication.^{5 6} It has been shown that non-medicated patients with psychosis are more likely to have IgG anticardiolipin antibodies and lupus anticoagulant than a group of normal controls and that the incidence of anticardiolipin antibodies and lupus anticoagulant in those with psychosis increased after treatment with medication.⁷

Another hypothesis is that the acute psychotic phase is associated with an increase in adrenaline secretion, which may enhance the coagulation mechanism. The metabolic syndrome produced from second generation antipsychotic drugs with resultant obesity and hyperprolactinaemia have also been implicated in the development of VTE.⁸ A case report on four cases of VTE associated with olanzapine proposed that the metabolic and sedating effects

Table 2 Recommended prevention of venous thromboembolism based on risk level

Low risk 0–3 points
Regular physical exercise of lower extremities
Sufficient hydration
Graduated compression stockings
Medium risk 4–7 points
Regular physical exercise of lower extremities
Sufficient hydration
Graduated compression stockings
LMWH <3400 units daily s.c.
High risk 8 points
Regular physical exercise of lower extremities
Sufficient hydration
Graduated compression stockings
LMWH >3400 units daily s.c.
LMWH, low molecular weight heparin.

of olanzapine along with its hypercoagulability effect via affinity for 5-HT_{2A} receptors may be involved in its aetiology.⁹

A further explanation for the association between VTE and psychiatric patients is that venous stasis is exacerbated by sedation and/or reduced mobilisation commonly found in patients treated with low-potency antipsychotic drugs, and this contributes to the risk of thrombosis.¹ Additional risk factors for VTE inherent to specific psychiatric conditions include physical restraint, catatonia and neuroleptic syndrome with the common underlying factor in these conditions being immobility.¹⁰

Lack of physical activity has also been identified as an important factor in the development of VTE. A large prospective cohort study on female nurses found that the risk of pulmonary embolism was more than twofold in women who spend most time sitting compared with those who spent the least time sitting.¹¹ A serious complication of long-distance travel by flight is thromboembolism with a direct relation between VTE incidence and long-distance flights has been documented.¹²

The mechanisms proposed to explain this occurrence include that lack of muscular activity in the lower extremities results in venous stasis and thrombosis. Lower levels of circulating factors such as tissue plasminogen activator, platelets and fibrinogen may increase thrombosis and plasma viscosity.¹³

Maly *et al* have proposed an algorithm of prevention of VTE in hospitalised psychiatric patients, suggesting a risk factor scoring system to guide management and reduce risk of thromboembolic events (table 1).¹⁴

In these guidelines, risk factors are graded according to whether there is an evidence base for their aetiology in thromboembolic disease (score of two) or consensus base (score of one). The total number of risk factors is then added and from this the appropriate treatment is recommended (table 2). A total score of equal to or less than four would lead to low-molecular weight heparin being administered unless this is contraindicated. An editorial in the BMJ has advised that clinicians be aware of the possible vascular effects of antipsychotic medications and to develop a treatment strategy based on the individual's vascular risk factors.¹⁵

Learning points

- ▶ High dose long-term antipsychotic medication may be independently associated with increased risk of thromboembolic events, although more research is required to establish this conclusively.
- ▶ Inactivity among acutely unwell psychiatric patients even without other known risk factors should be recognised by clinicians as a risk factor for VTE.
- ▶ Clinicians caring for such patients should be vigilant for the occurrence of VTE and consider implementing prophylactic measures such as graduated compression stockings, exercise and low-molecular weight heparin in acutely unwell patients with restricted mobility, in particular if they carry other risk factors for VTE.
- ▶ Simple measures such as maintaining adequate hydration, avoidance of strict bedrest and an increased level of exercise may be sufficient in most cases to prevent VTE in low risk cases.
- ▶ If patients have any physical complaints such as pain or swelling to their legs, this should be thoroughly investigated.

Acknowledgements The authors would like to thank the medical and nursing staff of Acute Psychiatric Unit of University Hospital Galway.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

McInerney SJ, McDonald C. Idiopathic pulmonary thromboembolism in the course of intensive psychiatric inpatient care: case report and treatment guidelines. *BMJ Case Reports* 2012;10.1136/bcr.12.2011.5285, Published XXX

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