



Pulmonary thromboembolism and sudden death in psychiatric patients – Two cases report

Tromboembolija pluća i iznenadna smrt psihijatrijskih bolesnika

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Abstract

Introduction. Pulmonary thromboembolism occurs usually by running a thrombus from the deep veins of the legs rarely periprostatic or periuterine veins. Virchow's triad of necessary conditions for the occurrence of thrombosis involves disruption of blood flow, disruption of blood chemistry and damage to the vessel wall. Venous thrombosis is often associated with the implementation of antipsychotic therapy. **Case report.** We reported two cases of sudden death of psychiatric patients who were in both cases fixed during hospitalization. The first case was a 26-year-old woman treated a year with the diagnose of postpartum reactive psychosis. She was hospitalized because of mental state worsening with a dominant depressed mood, visual and auditory hallucinations. Her therapy was determined by diazepam, clozapine, haloperidol and lamotrigine. Suddenly, the patient died on the fifth day of hospitalization. The autopsy showed massive thromboembolism of the pulmonary artery branches. Toxicological analysis revealed the presence of therapeutic doses of antipsychotics. The second case was a 45-year-old man, a long-time alcoholic. On admission, the diagnosis of *delirium tremens* was established, and diazepam and haloperidol were administered. On the fifth day of hospitalization, he suddenly died. The autopsy showed thromboembolism of the branch of the pulmonary artery. Toxicological analysis established the presence of nordiazepam in urine (0.06 mg/L). Both patients were fixed during hospitalization. **Conclusion.** Both presented psychiatric patients were younger than 50 years, were not overweight, did not have changes of the venous blood vessels. Nowadays, when the issue of medical responsibility often arises in these and similar cases of sudden death in patients treated in psychiatric clinics, the questions on medical malpractice could be expected.

Key words:

psychotic disorders; antipsychotic agents; immobilization; time factors; venous thrombosis; pulmonary embolism.

Apstrakt

Uvod. Plućna tromboembolija najčešće nastaje pokretanjem tromba iz dubokih vena nogu, ređe iz periprostatickih ili periuterinskih vena. Virhovljevo trojstvo neophodnih uslova za nastanak tromboze podrazumeva poremećaj protoka krvi, poremećaj hemizma krvi i oštećenje zida krvnog suda. Venska tromboza se često dovodi u vezu sa primenom antipsihotične terapije. **Prikaz bolesnika.** Prikazali smo dve naprasne smrti psihijatrijskih bolesnika koji su bili fiksirani tokom hospitalizacije. Prvi bolesnik bila je žena, stara 26 godina, lečena godinu dana pod dijagnozom postpartalne psihotične reakcije. Hospitalizovana je zbog pogoršanja psihičkog stanja sa dominantnim depresivnim raspoloženjem, vizuelnim i akustičnim halucinacijama. Određena joj je terapija: diazepam, klozapin, haloperidol i lamotrigin. Naprasno, umrla je petog dana hospitalizacije. Obdukcijom je ustanovljena masivna tromboembolija grana plućne arterije. Toksikološkom analizom ustanovljeno je prisustvo terapijskih doza antipsihotika. Drugi bolesnik bio je muškarac, star 45 godina, dugogodišnji alkoholičar. Na prijemu je bila postavljena dijagnoza *delirium tremens* i ordinirana terapija: diazepam i haloperidol. Petog dana hospitalizacije umro je naprasno. Obdukcijom je ustanovljena tromboembolija grana plućne arterije. Toksikološkom analizom ustanovljeno je prisustvo nordiazepama u urinu (0,06 mg/L). **Zaključak.** U prikazanim slučajevima oba psihijatrijska bolesnika bila su mlađa od 50 godina, nisu bili gojazni, nisu imali promene na venskim krvnim sudovima, a umrli su zbog tromboembolije pluća. U ovom trenutku, kada se pitanje lekarske odgovornosti često postavlja, može se očekivati da se postavi pitanje načina lečenja u ovakvim i sličnim slučajevima iznenadne smrti kod bolesnika lečenih u psihijatrijskim klinikama.

Ključne reči:

psihotički poremećaji; antipsihotici; imobilizacija; vreme, faktor; tromboza, venska; pluća, embolija.

Introduction

Pulmonary thromboembolism occurs in 95% of cases by initiating thrombus from the deep veins in the legs, or less commonly from periprostatic or periuterine veins. Virchow's triad of necessary conditions for the occurrence of thrombosis involves disorder of blood flow, disruption of blood chemistry and damage to the vessel wall¹. Clinical practice shows that the thrombosis is often seen in obese, elderly people with disseminated malignant tumors or after surgery. Drugs that influence thrombosis are antipsychotics, usually the first generation, and also contraceptive therapy is mentioned². Based on analysis of autopsy materials, deaths from pulmonary thromboembolism in 31% states the history of psychiatric pathology³. Other authors state that pulmonary thromboembolism occurs in psychiatric patients as a cause of sudden death in 4%⁴. Some authors suggest that there may be additional factors along with antipsychotic drugs that cause thrombosis in psychiatric patients, like obesity, stillness, increased level of atiphospholipids, hyperhomocysteinemia, and hyperprolactinemia^{4,5}. We reported two sudden deaths in psychiatric patients, in whom the cause of death, massive pulmonary thromboembolism, was established by forensic autopsy.

Case report 1

A woman, aged 26, with moderately developed musculoskeletal structure, nutritional status mediocre, gave birth to a healthy female child 14 months ago. Her psychological problems began two months following delivery. She was treated for the year as outpatient with antipsychotics (clozapine, lorazepam, lamotrigine, risperidone), diagnosed with *post-partum* reactive psychosis. She had postpartal amenorrhea, but values of hormones or cause of amenorrhea were not tested. Due to the deteriorating mental state and depressed mood dominant, visual and auditory hallucinations, she was hospitalized in a psychiatric institution. The patient was treated by diazepam, clozapine, haloperidol and lamotrigine. Standard blood biochemistry was performed and established elevated

sedimentation value of 14 mm/h (reference values: < 20 mm/h), S -glucose 6.4 mmol/L (reference values: 4.1–5.9 mmol/L), and S-cholesterol, 6.55 mmol/L (reference values: < 5.2 mmol/L) and other biochemical parameters were within the reference values. The results of blood tests showed $7.85 \times 10^9/L$ leukocytes [normal range (nr) $3.40\text{--}9.70 \times 10^9/L$] leukocyte counts without deviations, the number of red blood cells also in the reference values of $4.28 \times 10^{12}/L$ (nr $3.86\text{--}5.08 \times 10^{12}/L$). Other values, hemoglobin (HGB), hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDWC) were within the reference values, and mean corpuscular volume (MCV), the average volume of red blood cells was slightly elevated 99 fl (nr 83–97 fl). Platelet count was $267 \times 10^9/L$ (nr $158\text{--}424 \times 10^9/L$) and other platelet parameters (plateletcrit – PCT, mean platelet volume – MPV, platelet distribution width – PDWC) were without deviation. Laboratory tests of coagulation factors and D-dimer were not done. Examination by the psychiatrist showed her adequate response to the therapy. On the fifth day of hospitalization, the patient suddenly died. The autopsy showed massive thromboembolism of the pulmonary artery branches (Figure 1). By longitudinal cuts on the back of both legs, blood clots in the veins of both lower legs were observed. (Figure 2). Except cystic ovaries, no pathological changes in other organs were established. Toxicological analysis of blood samples showed the presence of diazepam (0.08 mg/L,) lamotrigine (0.10 mg/L) and temazepam (0,07 mg/L). Toxicological analysis of stomach contents, liver with gall bladder, kidney and brain showed the presence of therapeutic doses of antipsychotics. Mean values were established in these samples for clozapine (0.0526 mg/kg), N-desmethyl clozapine (0.0305 mg/kg), haloperidol (0.0055 mg/kg), lamotrigine (0.098 mg/kg) diazepam (0.0255 mg/kg) and temazepam (0.057 mg/kg).

Case report 2

We presented a 45-year-old man, with moderately developed musculoskeletal structure, nutritional status modera-



Fig. 1 – Embolus in the pulmonary artery.



Fig. 2 – Thrombosis of the veins of the lower extremities.

te, long-time alcoholic. The patient was occasionally and irregularly treated as outpatient, receiving diazepam. Due to the deterioration in his mental state, insane ideas, auditory and visual perceptual illusion, the patient was hospitalized in a psychiatric institution. On admission the diagnosis was *delirium tremens*, and administered therapy included diazepam, and haloperidol, and fixation in bed. Laboratory analysis showed elevated values of sedimentation 29 mm/h (reference values < 14 mm/h). Standard biochemical tests showed elevated values of S-AST 93 U/L (reference values < 40 U/L), S-ALT 61 U/L (reference values < 61 U/L) S-cholesterol 8.27 mmol/L (reference values < 5.20 mmol/L) and the other values within the reference range. Blood test showed red blood cells $4.11 \times 10^{12}/L$ (nr $3.7\text{--}5.8 \times 10^{12}/L$), hemoglobin and hematocrit were with no deviations, and the increased value of MCV 100 fl (nr 80–98 fl) and MCH 34.2 pg (nr 26–32 pg). Leukocyte count was $10.9 \times 10^9/L$ (nr $4.1\text{--}10.9 \times 10^9/L$), in the leukocyte formula granulocytes were increased, 86% (nr 45–70%), whereas the percentage of lymphocytes decreased, 7% (nr 20–40%). The platelet count was $319 \times 10^9/L$ (nr $150\text{--}400 \times 10^9/L$), and other parameters of platelets (PCT, MPW, PDWC) were without deviations. Laboratory tests of coagulation factors and D-dimer were not performed. On the fifth day of hospitalization the patient suddenly died. The autopsy showed massive thromboembolism of the pulmonary artery branches (Figure 3). The longitudinal incisions along the back of both legs revealed the presence of blood clots in the veins of both lower legs and thighs. Microscopic examination showed fatty alterations of the liver with focal inflammatory infiltration. Other organs showed no pathological changes. Toxicological analysis of urine revealed the presence of nordiazepam (0.06 mg/L).



Fig. 3 – Bilateral massive pulmonary thromboembolism.

Discussion

In addition to standard Virchow's triade there are numerous other factors that promote the formation of venous thrombosis. They can be divided into several groups, but the most common is a division of the genetic, acquired diseases and external factors, and combined^{4,5}. Risk factors of veno-

us thromboembolic diseases in psychiatric patients are long-term hospitalization, catatonic conditions, neuroleptic malignant syndrome, limitation of mobility, dehydration, obesity, administration of antipsychotics, hyperprolactinemia, hyperhomocysteinemia, diagnosis of schizophrenia and bipolar affective disorder⁵. The score of risk factor for venous thromboembolism in hospitalized psychiatric patients with reduced mobility gives 2 points for personal history of venous thromboembolism, malignancy, age ≥ 75 years and acute infection, and 1 point to immobilization, physical restraint ≥ 8 h, estrogen therapy, obesity, age 60–74 years, varicose veins, dehydration, thrombophilia and treatment with antipsychotics. In patients with a score of ≤ 3 (low risk) or ≥ 4 (high risk) it is necessary to apply lower extremity exercises, adequate hydration, compressive antithrombotic stocking and in high-risk also heparin therapy⁵. Numerous papers report a connection between treatment with neuroleptics and venous thrombosis, but the exact mechanism of this association is not known. The level of prolactin in plasma was increased in the case shown as thromboembolism in a patient treated with amisulpiride⁶. Antipsychotics are generally dopaminergic antagonists resulting in the increased level of prolactin⁷. The first presented case had amenorrhea for more than a year. The patient was not submitted to hormone testing, nor determining the value of prolactin. Increased risk of venous thrombosis in fixed patients, has already been described, usually after a period of 3–5 days fixation, which corresponds to our cases in who the period of fixation was 5 days^{8,9}. Some authors suggest high doses of antipsychotics and quiescence as a cause of pulmonary thromboembolism in psychiatric patients in the intensive care unit¹⁰. *In vitro* experiments show that the second generation antipsychotics (olanzapine, clozapine) compared to haloperidol, inhibit platelet aggregation mostly clozapine (21%) and olanzapine (18%)¹¹. Statins, postmenopausal hormone replacement, antagonist of vitamin K and oral contraceptives given with antipsychotics, are most often mentioned drugs associated with venous thrombosis¹². The reported patients did not receive other therapy than antipsychotics. In patients with the diagnosis of schizophrenia on treatment with clozapine and olanzapine, secondary obesity occurs, which can help the development of thrombosis. But obesity, which is not induced by neuroleptics and psychiatric illness is also cited as a predisposing factor for the occurrence of thrombosis¹³. Body mass index (BMI) ≥ 30 kg/m² increases the risk of venous thrombosis 2–5 times¹⁴. Elevated total serum cholesterol and triglyceride levels were found in patients with thromboembolism as compared to the control group. One explanation of the mechanism is the influence on blood viscosity and erythrocyte aggregation¹⁴. The presented cases were not obese, but had elevated total cholesterol. As a side effect of antipsychotic drugs, agranulocytosis and leukopenia, were not present in the presented patients¹⁵. In both presented cases, higher values of MCV and elevated sedimentation value occurred. Some authors state that D-dimer and the factor VIII are increased in patients with psychosis without treatment compared to the normal control group¹⁶. These analyses in our cases were not performed.

Conclusion

Based on the two presented cases of venous thromboembolism in hospitalized psychiatric patients, the potential impact of antipsychotic treatment, given in therapeutic doses, on the occurrence of fatal pulmonary thromboembolism was confirmed, combined with risk factors such as fixing the patient and hypercholesterolemia, even in cases without other well-known risk factors (obesity, older age, changes in veins). In cases with

indicated administration of antipsychotic therapy, it is important to reduce the potential impact of other risk factors such as dehydration, elevated cholesterol levels and fixing to the bed, through its reduction to the shortest possible period, exercises of the lower limbs and wearing of elastic bandages. Nowadays, when the issue of medical responsibility often arises, the questions about medical negligence and malpractice can be expected in these and similar cases of sudden death in patients treated in psychiatric clinics.

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