SHORT COMMUNICATION

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Fatal pulmonary thromboembolism after prolonged physical immobilization in hospitalized psychiatric patients

Fatalna plućna tromboembolija posle produžene fizičke imobilizacije kod hospitalizovanih psihijatrijskih bolesnika

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Abstract

Background/Aim. Pulmonary thromboembolism (PTE) may be one of the causes of sudden death in hospitalized psychiatric patients. The aim of our study was to investigate whether fatal PTE in these patients may be the result of their prolonged physical immobilization, particularly when there were associated risk factors, and to emphasize the importance of this problem. **Methods.** A retrospective analysis of medical records of psychiatric patients died suddenly at the Department of Intensive Care of the Clinic of Psychiatry "Dr Laza Lazarevic", Belgrade, in the period January 1, 2010 – December 31, 2011, was performed. Data of those for which the autopsy showed PTE as the immediate cause of death were extracted, and the presence of risk factors for the development of deep vein thrombosis analyzed. **Results.** In the observed period, out of 4,001 hospitalized psychiatric patients 53 died, and for 18 of them autopsy was required due to sudden death. In five patients, autopsy revealed PTE as a direct and sole cause of death. All the five patients were males, mean age 45.2 years, and during hospitalization all received strong antipsychotics and diazepam. Of the total duration of their hospital stay (mean 8.2 days), they were temporarily immobilized during an average 4.2 days. Four of them had acute infection, three were active smokers, and the two had a body mass index > 30 kg/m^2. **Conclusion.** Our results suggest a possible link between prolonged physical immobilization of psychiatric patients who also receive antipsychotic therapy, and total PTE.

Key words:
pulmonary embolism; psychiatry; patients; risk factors; immobilization.

Apstrakt

Uvod/Cilj. Plućna tromboembolija (PTE) može da bude jedan od uzroka iznenadne smrti kod hospitalizovanih psihijatrijskih bolesnika. Cilj našeg rada bio je da ispitamo da li fatalna PTE kod ovih bolesnika može da bude posledica njihove produžene nepokretnosti, posebno kada postoje i pridruženi faktori rizika, te da ukažemo na značaj ovog problema. **Metode.** Izvršena je retrospektivna analiza bolničke dokumentacije psihijatrijskih bolesnika koji su iznenada preminuli u Odeljenju za intenzivnu terapiju Klinike za psihijatriju "Dr Laza Lazarević" u Beogradu, u periodu 1. januar 2010 – 31. decembar 2011. i izdvojeni su podaci o onima za koje je autopsijom ustanovljeno da je neposredni uzrok smrti bila PTE. U njihovim istorijama bolesti analizirano je prisustvo faktora rizika od razvoja tromboze dubokih vena. **Rezultati.** U posmatranom periodu, od ukupno 4 001 hospitalizovanog psihijatrijskog bolesnika preminulo je 53, od kojih je za 18 tražena autopsija zbog iznedne smrti. Kod pet bolesnika autopsijski je utvrđeno da je neposredni i jedini uzrok smrti bila PTE. Svih pet bili su muškog pola, prosečne starosti 45,2 godine, i tokom hospitalizacije dobijali su snažne antipsihotike i diazepam. Od ukupnog trajanja njihove hospitalizacije (prosečno 8,2 dana), oni su bili privremeno imobilisani tokom prosečno 4,2 dana. Četvorica su imala akutnu infekciju, trojica su bili aktivni pušači, a dvojica su imali indeks telesne mase > 30 kg/m^2. **Zaključak.** Naši rezultati ukazuju na moguću povezanost produžene fizičke imobilizacije psihijatrijskih bolesnika, koji istovremenu primaju antipsihotičnu terapiju, i fatalne PTE.

Ključne reči:
pluća, embolija; psihijatrija; bolesnici; faktori rizika; imobilizacija.

Introduction

Deep vein thrombosis (DVT) is pointed out in the literature as one of the leading causes of morbidity and mortality in nonsurgical patients. Nowadays, this problem has not been enough considered in the population of hospitalized psychiatric patients [1]. According to the literary data, DVT frequency in the risky hospitalized patients without prophylactic therapy is 10–40%, where, 70–80% of such thrombosis are clinically silent -nor asymptomatic [2].

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Clinical manifestations of massive pulmonary thromboembolism (PTE) as the most serious DVT complication are regularly dramatic, but in some patients subtle or unspecific clinical symptoms can be seen. Then pulmonary embolism as the cause of sudden unexpected death appears as „unsuspected killer“ [2, 3].

In this study we described autopsy series of five patients with a period of prolonged physical immobilization that preceded PTE.

Methods

A retrospective analysis of medical records of psychiatric patients died suddenly at the Department for Intensive Care of the Clinic for Psychiatric Disorders “Dr Laza Lazarevic”, Belgrade, in the period January 1, 2010 – December 31, 2011, was performed, data of those for which the autopsy showed that PTE was the immediate cause of death were extracted, and the presence of risk factors for the development of deep vein thrombosis analyzed.

Results

We analysed retrospectively medical documentation of the Clinic for Psychiatric Disorders “Dr Laza Lazarevic”, Belgrade, as well as autopsy findings of the Institute for Pathology, Faculty of Medicine, Belgrade, during a period from January 1, 2010 – December 31 2011. The agitated psychotic patients, admitted to the Clinic were treated at the Department for Intensive Care. Out of 4,001 patients treated in this Department in the period observed, the number of dead persons was 53. Due to sudden, unexpected death, clinical autopsies were requested for 18 patients. Analyses of these autopsy reports revealed PTE as the leading and the only cause of death in five patients. Their clinical and demographic characteristics, as well as the potential risk factors for DVT (obesity, smoking and the acute infections) were noticed (Table 1).

On admission to the Clinic there were no data for existing malignant or previous surgical diseases, or diagnosed DVT in the patients. The average age of the examined pa-

Table 1

Autopsy series of 5 male patients with total pulmonary thromboembolism (PTE)

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Average value
Age (years)	59	43	50	25	50	45.40 ± 12.74
BMI > 30 kg/m^2	no	no	yes	yes	no	
Number of hospitalizations	first	multiple	multiple	first	multiple	
Psychiatric diagnosis	F10/F06.2*	F29	F20	F23	F 20.5	
Other somatic diseases	yes I 10	no	yes I 10	no	no	
Length of hospit.stays (days)	9	5	9	13	5	8.20 ± 3.45
Length of temp.restraint (days)	5	4	5	4	3	4.20 ± 0.84
Antibiotic therapy	Ceftriaxone 2 g i.v. 4 days		Ceftriaxone 2 g/day i.v. 4 days	Ceftriaxonum 2 g i.v. 2 days	no	
Convetional antipsychotic	Haloperidol 10 mg i.m. first 3 days	Haloperidol 15 mg i.m. First 3 days	Haloperidol 10 mg i.m. 1 day	Haloperidol 20 mg i.m. 8 days,4 mg per os 4 days	Haloperidol 15 mg/day i.m.,Chlorpromazine 100 mg/per os, 5 days	
Atipical antipsychotic	no	no	Rispolept 2 mg per os p.d. 8 days	no	no	
Anxiolytic	Diazepam 30 mg i.m. first 3 days	Diazepam 30 mg i.m. 4 days	Diazepam 30 mg i.m. 7 days	Diazepam 20 mg i.m. 4 days	Diazepam 30 mg i.m. 5 days	
Psychostabilizer	no	no	no	Carbamazepine 600 mg.per os p.d. 8 days,300 mg per os p.d.1 day,200 mg per os 4 days	no	
Acute infection/febrile state	yes	yes	yes	yes	no	
Antihypertensive th.	Hemopres© 2x1 tbl.	no	Captopril 25 mg per os Lisinopril 10 mg per os p.d.	no	no	
Smoking	yes	no	yes	no	yes	

F10 (Mental disorders and behavioural disorders caused by use of alcohol); *F06.2 (Organic delusional disorder similar to schizophrenia; F29 (Non-organic psychosis, non-specific; F20 (Schizophrenia; F23 (Acute and transient mental diseases); F20.5 (Residual schizophrenia); I 10 (Hypertensio arterialis); Hemopres® (hydrochlorothiazide, amiloride); BMI – body mass index

tients was 45.40 ± 12.74 years. By objective examination, none of the patients showed either signs of fresh traumatism or anamnestic data to inherited hematological diseasea. There was alcohol abuse in the anamnesis of only one patient. Two patients had hypertension controlled with antihypertensive drugs (Table 1). Routine laboratory examinations in all the patients were within limits of the referent values after admission to the Clinic, except signs of liver damage of etilic genesis in the patient No 1 (Table 2).

a clear indication for temporary two hours physical immobilization with intermittent periods of thirty minutes deliberation. Patients were under the intensive control of medical staff including follow-up of vital parameters, displaying of possible injuries, right belts setting [4–6]. According to data from the literature prolonged physical immobilization of three or more days with simultaneous appliciation of antipsychotics is a major risk factor for DVT appearance being in correlation with the data given in our study [7–9].

Table 2

Routine blood and serum laboratory analysis on the first day after patients admission to the Clinic

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Reference values
WBC ($x10^9$/L)	5.7	8.6	9.7	10.0	4.0	3.5–10
RBC ($x10^{12}$/L)	4.78	5.14	5.42	4.96	5.18	3.80–5.80
HGB (g/L)	114	146	149	141	154	110–165
HCT (g/L)	0.365	0.453	0.454	0.43	0.472	0.350–0.500
PLT ($x10^9$/L)	231	170	237	375	218	150–390
LYM (%)	26.4	20.2	9.9	24.7	37.5	17.0–78.0
MON (%)	4.8	5.8	3.1	3.1	6.7	4.3–10.0
GRA (%)	68.8	74	76	72.2	55.8	43.0–76.0
Acid uric (umol/L)	396	380	368	351		208–430
Glucose (mmol/L)	4.1	4	6.7	4.7	5.1	3.9–5.8
Urea (mmol/L)	7.4	2.8	6.8	2.9	3.8	2.5–8.3
Creatinine (umol/L)	83	102	92	104	102	53–106
Cholesterol (mmol/L)	3.3	4.7	5.2	3.4	–	3.6–5.7
Triglycerides (mmol/L)	0.69	2	1.22	2.24	–	0.4–2.26
HDL- C	–	–	–	1.19	–	0.78–1.94
LDL- C	–	–	-79	1.9	–	2–5.7
Total bilirubin (umol/L)	69.5	8.7	14.8	5.5	7.7	5.1–20.5
Total protein (g/L)	67	71	79	65	66	64–83
Iron (mmol/L)	5.4	15.6	14.1	19	18.4	11.3–31.3
AST (U/L)	88	25	32	39	33	3.0–37.0
ALT (U/L)	113	39	27	79	40	3.0-41.0
Gamma GT DRY (U/L)	135	36	28	62	45	9.0–55
CK (U/L)	24	101	272	130	140	38.0–171
CRP (ng/L)	–		3.5	2.6	4.3	0–5
Potassium (mmol/L)	3.9	3.53	3.52	4.61	3.73	3.5–5.3
Sodium (mmol/L)	130.6	139.8	145.9	142.7	135.9	135–148
Sedimentation (mm/h)	12	2	10	10	3	2.0–12
Fibrinogen (g/L)	–	2	2	2	2	2.0–4

WBC – leukocytes; RBC – erythrocytes; HGB – hemoglobin; HCT – hematocrit; PLT – platelets; LYM – lymphocytes; MON –monocytes; GRA – granulocytes; HDL-C. – high density cholesterol; LDL-C. – low density cholesterol; AST – aspartate aminotransferase; ALT – alanine aminotransferase; Gamma GT – gamma-glutamyl transpeptidase; CK – creatine kinase; CRP – C-reactive protein.

Neurological examinations excluded neurological diseases. Except the reduction of psychotic anxiety and the introduction of behavioral control no important progress of psychotic phase was noticed in all 5 patients.

Average hospital stay of the presented patients lasted 8.2 ± 3.45 days, and their temporarily physical immobilisation was 4.2 ± 0.84 days (Table 1).

Discussion

A true pathophysiological mechanism of DVT occurrence still remains insufficiently clear, so its multifactorial origin is probably in question [1]. There are a great number of risk factors for DVT occurrence classified in major (reduced mobility, surgical interventions, malignancy etc.) and minor ones (obesity, cardiovascular disorders, estrogen hormone therapy, etc. [4].

In all five presented patients signs of psychomotoric agitation and behavioral discontrol were present, so they were dangers *per se* and for the others. Due to this, there was

Temporary immobilization of the presented patients lasted averagely 4.20 ± 0.84 days. Hemodynamic changes in blood circulation as a result of prolonged physical immobolization increase risk of vein thromboembolism leading to vein stasis that, with a possible existence of vascular endotelial damages and dehydration-hipovolemy, is an increasing risk for thrombembolism (Virhovljev`s triad) [10].

During and after the period of prolonged immobilization performed by physical examination, none of the patients presented clinical symptoms and DVT signs. Formation of microembolus is often asymptomatic and means the first step in PTE pathonegesis. Sudden unexpected death may happen in physical mobilization, i.e. by activating these "silent thrombs" [11].

In the period of 4.0 ± 3.08 days following measures of temporary physical immobilization, the presented patients experienced sudden unexpected death, so clinical autopsy was requested. Although physical immobilization still con-

tinues to be the subject of converse discussions including ethic aspects, taking into consideration that it is realized against the patients` will, sometimes it is necessary because a recommended medical therapy for treatment of aggressive patients is not sufficient to attain a so-called "chemical immobilization" of these patients [4, 5].

Therefore, many authors think about the application of mechanical prophylaxis, special exercises for the lower limbs, as well as introduction of low molecular heparin during physical immobilization.

All the five presented patients were treated by psychopharmacotherapy including an incisive antipsychotic, haloperidol, as well as anxiolytic diazepam, in two patients adding atypical (case 3) and sedative antipsychotic (case 5). Only one patient received psychostabilizer (case 4).

World multilateral studies connect the increased risk for DVT with application of antipsychotic therapy (32% higher risk in relation to patients without antipsychotics in therapy) [9, 12]. Especially, it is very important to point out the role of low potent antipsychotics of the first generation (chlorpromazine, thioridazine) but also clozapine and antipsychotics of the second generation (risperidone, olanzapine) [13, 14]. Certainly, there is some risk, but it is considerably lower when incisive antipsychotics (haloperidol) are in question and in relation to atypical antipsychotics it is 28% and 73%, respectively. Also, two patients receiving simultaneously two or more antipsychotics had the increased risk in relation to those being on monotherapy. Namely, it has been shown that this risk is significantly higher already in the first three months after drug introduction [9].

Biological mechanisms` link of antipsychotic therapy and DVT remains unknown although many hypotheses point out that increased risk might be the result of sedative effects of drugs, as well as obesity, decreased fibrinolytic activity as a part of metabolic syndrome, hyperleptinemy, circulating antiphospholipid antibodies, hyperhomocisteinemy, increased platelet aggregation and so on [1, 10]. There are no relevant studies connecting the use of anxiolytics and psychostabilizer and DVT [11].

Increased platelets aggregation as well as increased secretion of adrenaline in acute psychotic excitation patients lead to increased blood coagulation making us to conclude that psychosis can also be „procoagulating phase". The mentioned study [15] confirms the presence of higher markers of thrombogenesis in plasma of acute psychotic patients compared to healthy persons (D-dimer, factor VIII as well as soluble P-selectin).

Three of five our patients were smokers while two of them were obese (BMI > 30 kg/m^2). According to data from the literature, either smoking or obesity are very important factors of risk for DVT appearance. They are brought to the link with increased fibrinogen, factor VIII and factor IX in the plasma as well as fibrinolysis decrease. Also, it is mentioned that the level of interleukin (IL) 6, as the main procoagulating cytokin in humans, as well as the level of C-reactive protein are increased in smokers` [16].

In four of five presented patients, following measures of prolonged immobilization, high febrility, sedimentation rebounds and leukocytosis were developed, so parenteral antibiotic therapy was included because of confirmed respiratory infection in these patients.

Recent studies bring respiratory infection (but also urinary system and skin infection) to the link with up to two times increased risk for DVT, especially in the first two weeks after the beginning of infection, setting the same aside as a factor of risk for DVT [17].

Many psychotic patients are not able to show symptoms adequately which could point out to DVT, as pain in legs, swelling, red coloring and so on, owing to psychic functions disorders in relation to qualitative consciosness changes and damaged cognition. Sometimes such symptoms can be wrongly interpreted by clinicians as oedema owing to cardial decompensation, cellulitis, rheumatic swellings.

Also, symptoms as feeling pressure in chest heart palpitation, heavy breathing are attributed to psychotic anxiousness, they experience horrible perceptive illusions and so on, but in reality they can be symptoms of unrecognized submassive pulmonary embolism.

Limits of our study are related to the *post mortem* diagnose of PTE, so it does not include patients with DVT and PTE diagnosed and adequately treated during hospitalization. It is possible that in some cases of fatal PTE sudden unexpected heart death is pronounced on the basis of clinical parameters.

Conclusion

Following previous learnings from the literature, the results of our study suggest that it would be useful to give special attention to immobilized psychotic patients taking into consideration potential risk factors for DVT and PTE. Failure of standardized protocols for DVT prevention with possible fatal outcome in hospitalized psychiatric patients underlines the need for further prospective research in this direction.

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