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Chronic thromboembolic pulmonary hypertension and schizophrenia

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Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by persistent thromboemboli in the pulmonary arteries, which cause pulmonary hypertension and result in right heart failure and death [1]. CTEPH occurs in 2–4% of patients with acute pulmonary embolism (PE) [2], indicating a pathological relationship between the two diseases. Several common risk factors for CTEPH and PE have been reported, such as certain medical therapies, thrombophilia, and a genetic predisposition [1,3,4]. However, no report has addressed the association between CTEPH and schizophrenia, although an association between PE and schizophrenia has been suggested due to enhanced blood clotting from the long-term administration of antipsychotic drugs and immobility syndrome [5]. We report a significantly higher prevalence of schizophrenia in patients with CTEPH than in those with pulmonary arterial hypertension (PAH) and the general population.

We treated 110 patients with CTEPH (63.1 ± 1.3 years, 86 women) and 150 patients with PAH (48.7 ± 1.4 years, 110 women) diagnosed at our hospital between December 1992 and June 2015. The diagnosis of CTEPH and PAH, and schizophrenia was based on the current CTEPH guideline [6] and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, respectively. The mean pulmonary arterial pressure was comparable between the two groups (CTEPH 42.0 ± 0.9 mm Hg, PAH 43.7 ± 1.5 mm Hg, $P = 0.353$). The prevalence of schizophrenia was compared between patients with CTEPH and PAH, and the general Japanese population in 2008 according to the Japanese government's statistics [7,8] using Fisher's exact test with a significance level of $P < 0.016$ for Bonferroni correction. The prevalence of schizophrenia was 8/110 patients with CTEPH, 1/150 patients with PAH, and 795,000/127,692,000 people in the general population; thus, it was significantly higher in patients with CTEPH than in the other two groups (both $P < 0.01$) (Fig. 1). The characteristics of patients with CTEPH and schizophrenia are shown in Table 1. The period between the onset of CTEPH and that of schizophrenia and antipsychotic medications was valuable in each case.

This is the first report of such an association between CTEPH and schizophrenia. The diagnosis of schizophrenia preceded the onset of CTEPH in all cases. There are three possible reasons why schizophrenia increased the prevalence of CTEPH. First, CTEPH is directly induced by the activation of blood coagulation and enhanced blood clotting. Schizophrenia and/or antipsychotics induce an increased release of adrenaline, increased activation of the markers of thrombogenesis, increased level of the antiphospholipid antibody, and changes in serotonin metabolism in the platelets [5], all of which may cause CTEPH. Second, schizophrenia and/or antipsychotics predispose individuals with PE to CTEPH. Three of 8 patients had a history of PE, which may have been underdiagnosed in the other patients. Residual emboli and abnormalities on lung perfusion scans are observed in 52% and 37% of patients, respectively, 1 year after acute PE [9,10]. Therefore, antipsychotics may prevent thrombolysis and anticoagulation of PE, and lead to CTEPH. Third, venous thromboembolism may have been underdiagnosed and suboptimally treated among patients with schizophrenia [5], which increased PE and CTEPH. Although this needs confirmed in future studies with a large

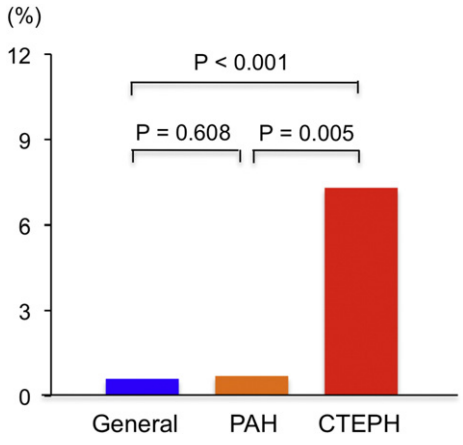

Fig. 1. Prevalence of schizophrenia in the general Japanese population, patients with PAH, and patients with CTEPH. CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension.

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Table 1
Characteristics of patients with CTEPH and schizophrenia.

Case no.	Age at onset (years)	Sex	Onset of CTEPH after the diagnosis of schizophrenia (years)	Medication	Complication
1	40	F	7	Risperidone	–
2	61	M	2	Zotepine, lithium	Hyperthyroidism
3	34	F	5	Quetiapine, haloperidol	PE
4	47	F	10	Levomepromazine, valproate, lithium	–
5	56	F	24	Risperidone, valproate, lithium	PE
6	49	M	14	Paliperidone	–
7	65	F	7	Haloperidol	PE
8	72	M	35	Haloperidol, Chlorpromazine	APS

APS, Antiphospholipid syndrome; CTEPH, chronic thromboembolic pulmonary hypertension; F, female; M, male; PE, pulmonary embolism; no., number.

sample, our finding suggests the importance of medical attention to the pulmonary circulation of patients with schizophrenia.

Conflicts of interest

The authors declare no conflicts of interest.

References

[1] G. Piazza, S.Z. Goldhaber, Chronic thromboembolic pulmonary hypertension, N. Engl. J. Med. 364 (2011) 351–360.
[2] V. Pengo, A.W. Lensing, M.H. Prins, et al., Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism, N. Engl. J. Med. 350 (2004) 2257–2264.
[3] G. Piazza, S.Z. Goldhaber, Acute pulmonary embolism: part I: epidemiology and diagnosis, Circulation 114 (2006) e28–e32.
[4] D. Bonderman, H. Wilkens, S. Wakounig, et al., Risk factors for chronic thromboembolic pulmonary hypertension, Eur. Respir. J. 33 (2009) 325–331.
[5] J. Masopust, R. Malý, M. Vališ, Risk of venous thromboembolism during treatment with antipsychotic agents, Psychiatry Clin. Neurosci. 66 (2012) 541–552.
[6] N. Galiè, M.M. Hoeper, M. Humbert, et al., Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT), Eur. Heart J. 30 (2009) 2493–2537.
[7] Current population estimates as of October 1, 2008, Ministry of Internal Affairs and Communication, Japan (http://www.stat.go.jp/english/data/jinsui/2008np/index.htm).
[8] Patient Survey in 2008 (in Japanese), Ministry of Health, Labour and Welfare, Japan (http://www.mhlw.go.jp/toukei/saikin/hw/kanja/10syoubyo/dl/h23syobyo.pdf).
[9] M. Nijkeuter, M.M.C. Hovens, B.L. Davidson, et al., Resolution of thromboemboli in patients with acute pulmonary embolism, Chest 129 (2006) 192–197.
[10] M. Miniati, S. Monti, M. Bottai, et al., Survival and restoration of pulmonary perfusion in a long-term follow-up of patients after pulmonary embolism, Medicine 85 (2006) 253–262.