

Myasthenia Gravis, Schizophrenia, and Colorectal Cancer in A Patient: Long-Term Follow-Up with Medication Complexity

Haebin Kim^{1,2}, Minha Hong^{1,2} and Geon Ho Bahn¹ ✉

¹Department of Neuropsychiatry, Kyung Hee University School of Medicine, Seoul, Republic of Korea

²Graduate School, Kyung Hee University, Seoul, Republic of Korea

In a case of 46-year-old woman suffering from schizophrenia for over 20 years, she experienced frequent episodes of dyspnea and confirmed as superimposed with myasthenia gravis (MG). Throughout the seven-year follow-up period, after diagnosed as MG, she has been hospitalized 6 times and also diagnosed as colorectal cancer. Authors experienced various conditions associated with untoward effects of medication for myasthenia, schizophrenia, and colorectal cancer. Therefore, authors reported considerations for the pharmacotherapy of schizophrenia with myasthenia gravis.

Psychiatry Investig 2013;10:300-302

Key Words Cancer, Dyspnea, Myasthenia gravis, Schizophrenia, Steroid.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease characterized by muscle weakness due to acetylcholine receptor autoantibodies of the neuromuscular junction.¹ Although schizophrenia was associated with nearly 50% higher life-time prevalence of one or more autoimmune disorders,² it is very rare for patients with schizophrenia to develop MG. There have been 2 similar case reports;^{3,4} however, no previous reports contained detailed description of the long-term therapeutic courses as the following.

Based on 7 years of experience in treating a patient with both diseases, the authors intended to report considerations when choosing therapeutic drugs for various MG symptoms, including dyspnea and for coexisting schizophrenia.

CASE

Ms A, a 46-year-old woman, diagnosed as disorganized type

schizophrenia when she was 20 years old in 1985, was frequently hospitalized to the psychiatric ward and showed poor response to medication. At age 35, she was hospitalized for pneumonia and acute respiratory distress syndrome (ARDS), and at 38, she was hospitalized 2 times for dyspnea associated with pneumonia.

At 39, her fourth ARDS occurred after infectious symptoms of the upper respiratory track. Based on clinical symptoms, such as repetitive respiratory failure, ptosis, and dysphonia, MG was suspected and diagnosis was confirmed by tensilon tests, as well as detecting antibodies for acetylcholinesterase. In order to exclude MG with thymoma, mediastinal computerized tomography (CT) was taken and there were no sign of thymoma. Respiratory failure was improved by administering pyridostigmine and immunosuppressants after plasmapheresis, and afterwards, Ms A was transferred to a chronic mental hospital.

At 42, respiratory failure recurred. Despite additional 15 mg of prednisolone, symptom was aggravated and she was transferred to the department of psychiatry, Kyung Hee University Hospital (KHUH). After maintaining the additional dosage, respiratory symptom was relieved and she was transferred back to the chronic mental hospital.

In January, 2011, respiratory failure symptoms recurred, and the patient was hospitalized at the intensive care unit of KHUH. Along with the administration of additional 10 mg of prednisolone, plasmapheresis and high dosage steroid pulse therapy were carried out and dyspneic symptom was stabilized. Ar-

Received: October 2, 2012 Revised: February 19, 2013

Accepted: March 23, 2013 Available online: September 16, 2013

✉ Correspondence: Geon Ho Bahn, MD, PhD

Department of Neuropsychiatry, Kyung Hee University School of Medicine, 26 Kyungheedaero, Dongdaemun-gu, Seoul 130-701, Republic of Korea

Tel: +82-2-958-8556, Fax: +82-2-957-1997

E-mail: mompeian@hanmail.net

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ipiprazole 15 mg, paliperidone 6 mg and quetiapine 1200 mg was being administered for psychiatric symptom control from the transferred hospital. However, in order to avoid potential drug interactions, only quetiapine 1200 mg was administered through the nasogastric tube. Afterwards, psychotic symptoms aggravated. As persecutory and somatic delusions, as well as insomnia continued, the patient was moved to the psychiatric ward and haloperidol was added up to 10 mg. After increasing the dosage of haloperidol, lower extremity tremor, which seemed to be one of the symptoms of extrapyramidal syndrome (EPS), was observed, and procyclidine, an anticholinergic, was added. Three weeks later, the patient showed respiratory distress, with particular aggravation during night time. This was thought to be caused by exacerbation of myasthenia gravis due to administration of anticholinergics. Then, anticholinergics were stopped. Afterwards, dyspnea, somatic and persecutory delusions got worse at night and had trouble falling asleep. The patient's symptoms were suspected to be exacerbation of schizophrenia or sleep disorder due to respiratory muscle fatigue from MG. While the patient complained of insomnia, arterial blood gas analysis was tested and showed normal results. Chest X-rays were filmed because of frequent respiratory infections and atelectasis history and mild atelectasis was seen at the left lower lobe of the lung. Therapy with spirometer was considered, but postponed concerning respiratory muscle fatigue. MG exacerbation was suspected as ptosis and hoarseness symptoms worsened, and maintenance therapy with 10 mg prednisolone was carried out without dose reduction. For aggravated symptoms of schizophrenia, such as day time emotional fluctuation and aggravated persecutory delusions, haloperidol was increased to 20 mg and chlorpromazine 50 mg was added for sleep control. Overall symptoms improved after 130 days of hospitalization and Ms A was discharged.

Four months after discharge, in order to evaluate severe anemia, she was transferred to KHUH and underwent a colonoscopy. Biopsy specimen was diagnosed as colorectal cancer. After surgical resection in the colon, she was hospitalized to the psychiatric ward for 2 weeks, and afterwards, Ms A was discharged to a chronic mental hospital.

DISCUSSION

As schizophrenia is a chronic disorder, multiple drugs, like antipsychotics, mood-stabilizers, anticholinergics and beta-adrenergic receptor inhibiting medications are administered alone or mixed. In patients with schizophrenia superimposed with MG, neuronal stimulation is inhibited by these medications,⁵ and as a result MG symptoms could be exacerbated. The most recent case report of schizophrenia superimposed

with MG was by Shiao et al.⁴ As the case reported here, respiratory distress in patients with schizophrenia could be misinterpreted as severe anxiety. However, when respiratory distress occurs repeatedly and exacerbates after benzodiazepine administration, diagnosis of MG should be the one of the index of suspicion. In this case, respiratory distress occurred after 3 weeks with anticholinergics for EPS control. Authors thought that it was the exacerbation of MG due to anticholinergic medicine and stopped the medication.

Drug interaction between antipsychotics for schizophrenia and corticosteroid and azathioprine for MG is also an important consideration. Dexamethasone mildly inhibits antipsychotics, such as chlorpromazine, clozapine, haloperidol, and ziprasidone, which is metabolized by the cytochrome P450 CYP3A.⁶ In patients administered with clozapine, agranulocytosis could occur⁷ and concurrent use with azathioprine, a cytotoxic drug, should be avoided.⁶ In the case report by Rózsa et al.,³ 44-year-old man was diagnosed as schizophrenia in 1985 and was being treated by flupentixol depot medication. During his treatment, sarcoidosis was found from his CT scan and was diagnosed as MG. Remission of MG and sarcoidosis was achieved after administration of corticosteroids and azathioprine. Afterwards, schizophrenia recurred during steroid treatment, and symptoms were improved with additional haloperidol administration in addition to the flupentixol depot medication. Just like this case, 5.7% of patients taking steroids showed psychotic symptoms as side effects. These symptoms are dose-dependent and 93% of them improve after discontinuing steroids. If schizophrenic symptoms are severe and continuous, haloperidol is effective and tends to stabilize the patient's mood.⁸ Also, in the case we presented, psychotic symptoms were aggravated while using steroids for respiratory distress, and symptoms were controlled after adding haloperidol. In the case of Ms A, agranulocytosis previously occurred while using clozapine and the medication was stopped.

Sleep problems in schizophrenia and MG could be explained by different mechanisms. In patients with both diseases, an integrated understanding in controlling sleep difficulties is needed. While sleep symptoms could simply be the symptoms of schizophrenia, it could also be an early sign of respiratory distress in patients superimposed with MG.⁹ Therefore, rather than sleep inducers, such as benzodiazepines or zolpidem, considering haloperidol administration might increase both total sleep time and sleep efficiency.¹⁰ Ms A improved in both psychotic and sleep problems when haloperidol was used for those symptoms.

Are there any specific relations between schizophrenia and autoimmune disorders like MG? Musha et al.¹¹ proposed 'paraneoplastic autoimmune neuropsychiatric syndrome' based on 3 cases of MG with thymoma, presenting psychotic

symptoms. Based on the Danish Psychiatric Register, a history of any autoimmune disease was associated with a 45% increase in risk for schizophrenia.⁶ Leykin et al.⁷ reported that the long-term immune suppression induced by neuroleptic treatment, such as haloperidol and clozapine, may inhibit putative autoimmune responses against the neurological sites, and could thus, act synergistically with the direct antagonistic action on the brain receptors for the overt amelioration of psychotic behavior. In our case, immune controllers, such as prednisolone and azathioprine, to prevent exacerbation of MG could also contribute to the amelioration of psychotic symptoms.

Finally, we have to consider the relationship among schizophrenia, MG and cancer. Ms A was diagnosed with colorectal cancer, and treated surgically. As we know, there are not any similar cases and make any conclusions whether it is related or not. Hemminki et al.¹² suggested the feasibility of the association with the use of immune modulating agents in patients with MG and with many kinds of cancers. In general, the findings from several countries support that excess mortality of patients with schizophrenia and cancer may be attributable to inequitable access to health screening and medical procedures, not simply higher incidence of cancer.¹³

It is highly possible for both schizophrenia and MG to be a lifetime disorder. As two diseases take place together, physicians do not have enough knowledge on how both symptom progression and therapeutic means proceed or interact. From that point, this case is significant for describing 7 years of experience and matters that require attention.

REFERENCES

1. Gold R, Hohlfeld R, Toyka KV. Progress in the treatment of myasthenia gravis. *Ther Adv Neurol Disord* 2008;1:36-51.
2. Eaton WW, Byrne M, Ewald H, Mors O, Chen CY, Agerbo E, et al. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. *Am J Psychiatry* 2006;163:521-528.
3. Rózsa C, Kis G, Komoly S, Anselmo V, Esik O, Láng I, et al. Myasthenia in a patient with sarcoidosis and schizophrenia. *Ideggyogy Sz* 2004;57:242-244.
4. Shiao WK, Bai YM, Su TP. Myasthenia gravis and respiratory failure in a patient with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;34:548-549.
5. Wittbrodt ET. Drugs and myasthenia gravis. An update. *Arch Intern Med* 1997;157:399-408.
6. Knight JG, Menkes DB, Highton J, Adams DD. Rationale for a trial of immunosuppressive therapy in acute schizophrenia. *Mol Psychiatry* 2007;12:424-431.
7. Leykin I, Mayer R, Shinitzky M. Short and long-term immunosuppressive effects of clozapine and haloperidol. *Immunopharmacology* 1997;37:75-86.
8. Bell G. Steroid-induced psychiatric disorders. *Nord Psykiatr Tidsskr* 1991;45:437-441.
9. Quera-Salva MA, Guilleminault C, Chevret S, Troche G, Fromageot C, Crowe McCann C, et al. Breathing disorders during sleep in myasthenia gravis. *Ann Neurol* 1992;31:86-92.
10. Monti JM, Monti D. Sleep in schizophrenia patients and the effects of antipsychotic drugs. *Sleep Med Rev* 2004;8:133-148.
11. Musha M, Tanaka F, Ohuti M. Psychoses in three cases with myasthenia gravis and thymoma--proposal of a paraneoplastic autoimmune neuropsychiatric syndrome. *Tohoku J Exp Med* 1993;169:335-344.
12. Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Autoimmune disease and subsequent digestive tract cancer by histology. *Ann Oncol* 2012;23:927-933.
13. Kisely S, Sadek J, MacKenzie A, Lawrence D, Campbell LA. Excess cancer mortality in psychiatric patients. *Can J Psychiatry* 2008;53:753-761.