Psychoses in Three Cases with Myasthenia Gravis and Thymoma —— Proposal of a Paraneoplastic Autoimmune Neuropsychiatric Syndrome

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Three patients with neuropsychiatric symptoms (NPSs) associated with thymoma, high serum titers of antiacetylcholine receptor (AchR) antibody and generalized myasthenia gravis (MG) are reported. The NPSs were homogeneous; (1) Altered consciousness as manifested by dreamy state with paramnesia, (2) psychosensory symptoms (the sudden change of senses of smell and taste with behavior abnormalities, auditory and visual hallucinations, déjà experiences, microteleopsia and derealization), (3) cognitive disturbances (recent memory loss with compulsive behaviors), (4) emotional disturbances (agitation, fear and anger), and (5) psychotic symptoms (secondary delusions and hallucinations) were characteristic. The NPSs preceded by several months to years the onset of MG, and thereafter they were closely related to worsening and relapse of MG. A typical patient showed repeatedly abnormal electroencephalograms (EEG) indicative of cerebral dysfunction. Another showed improvement of the NPSs after thymectomy and immunosuppressive therapy. The organicity of the phenomenology of psychoses with the same NPSs was suggested and it appears to comprise a unique paraneoplastic syndrome by central autoimmune mechanism. We proposed an autoimmune psychiatric syndrome and the genesis of psychosis due to the central cholinergic dysfunction in MG. —— myasthenia gravis; thymoma; psychosis; paraneoplastic syndrome; cholinergic system

Myasthenia gravis (MG) is the best known model of an autoimmune neurological disease and is classified as an organ-specific autoimmune disease. The typical symptoms of MG are due to the damage of the postsynaptic nicotinic acetylcholine receptor (AchR) of the neuromuscular junction.

However, patients with MG may have additional neurological impairments that are not explained by easy fatigability of the muscle; e.g. EEG abnormal-
Ities (Hokkanen and Toivakka 1969; Kazis et al. 1984), transient neurological
signs (Patten 1978; Shintani et al. 1989) and epilepsy (Hoefer et al. 1958; Snead
et al. 1980) have been reported, which suggest the involvement of the central
nervous system (CNS). However, psychiatric disturbances have been described
only in sporadic case reports (Oosterhuis and Wilde 1964; Gittleson and Richard-
neurological syndromes have been reported including psychic disturbances with
thymoma, with or without MG, which are suggestive of cholinergic dysfunction by
the autoimmune mechanism (Bogousslavsky et al. 1983; Hallbach et al. 1987;
McArdle and Millingen 1988). Thus, the question would arise as to whether there
is a specific type of psychic or neuropsychiatric symptoms (NPSs) that are
presumably due to the central cholinergic dysfunction in MG (Musha et al. 1981;

We have treated three patients with MG, that were associated with thymoma
(malignant in one patient), high titers of anti-AchR antibody in serum and rather
homogeneous NPSs. From their symptomatology we feel the CNS involvement
does occur in MG and propose a possibility of paraneoplastic autoimmune psychi-
atric syndrome (psychosyndrome) due to the cerebral cholinergic dysfunction.
Although MG patients are likely to have psychasthenic personality (Oosterhuis
and Wilde 1964) and emotional reactions (Magni et al. 1988), specific psychopath-
ology and behaviors as described in this paper are worth reporting.

SUBJECTS AND METHODS

As a part of investigations of NPSs in MG, we studied 66 consecutive patients having
well-established MG who were referred to the Department of Neuropsychiatry of Tohoku
University Hospital and the Division of Thoracic and Cardiovascular Surgery of National
Sendai Hospital for thymectomy and evaluation of the mental state. Among them we
found the three patients described in this paper. Titers of anti-AchR antibody in serum
were measured by the method of Ohta et al. (1980).

CASE REPORTS

The clinical data of the three patients are summarized in Table 1.

Patient 1 K.S. Female

In August of 1978 a 25-year-old single woman was referred to us because of her
psychotic state.

Clinical course of MG. In the spring of 1970, at age 17, her myasthenic symptoms
began with diplopia and gradually deteriorated into a generalized form. Six months later
thymoma was discovered and a thymectomy was performed. At age 19, a transient
myasthenic aggravation occurred. However, after ACTH treatment she improved and
could return to her daily life with only a small dose of anticholinesterase (anti-ChE).

Clinical course of NPSs. Since her early teens she had often felt déjà experiences,
derealization and microteleopsia. When 25 years old, without clear somatic and psychologi-
cal stress her myasthenic condition and mental state began to deteriorate. She gradually
developed a confusional state, in which she experienced many hallucinatory and illusional
phenomena. She was admitted to a regional hospital in June of 1978, and for two months
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was treated with anti-ChE and antianxiety drugs. During this time she showed no improvement either of the myasthenic or psychiatric spheres. When she was referred to us two months later, she still showed numerous psychosensory and psychotic symptoms. She complained about recent memory loss and we observed compulsive writing behaviors to help her memory. Although her orientation was normal, she showed in dreamy consciousness, temporal disintegration of time and misidentification of persons. She also experienced vivid déjà vu, olfactory and gustatory hallucinations. She would suddenly smell a curious odor with a feeling of familiarity or she would hear voices commenting on her acts and in addition hallucinated the faces of known persons. She had bizarre somatic hallucinations and illusions with erotic tendency. Considering her psychopathology we suspected her having organic brain syndrome or toxic state, but could not detect any causative factors from clinical laboratory findings except for well-established MG and diffuse slow EEGs. She was transferred to our psychiatric ward on July 30 of 1979. Because of associated strong déjà feelings and feelings of reliving previous experiences, she gradually developed paranoid attitude toward her surroundings. She could not distinguish her illusional and hallucinatory experiences from the reality in the dreamy state. She also misinterpreted her myasthenic condition as if she had been influenced by attending doctors and their treatment. Her mood swung from dysphoria to agitation with guilt feelings for her poor compliance to prescribed drugs. During the admission she consistently had borderline to abnormal EEGs with slow α rhythms and 4–5 Hz activities, that were sometimes more over anterior regions and with δ activities, but with no paroxysmal, focal or epileptic discharges. A brain CT scan was normal. Her anti-AChR antibody titer was not tested during this admission. After five months' admission she was discharged with her mental state in full remission, however, her daily life was confined to her house. Furthermore, over the course of the next 8 years she had three additional psychotic episodes similar to the previous ones, that were initiated with the aggravation of MG. Each time a low dosage of haloperidol with

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aMG, myasthenia gravis; NPSs, neuropsychiatric symptoms; AchR, acetylcholine receptor; anti-ChE, anticholinesterase, Positive > 0.6 pmol/ml serum, Date examined (Year/month/day).
prednisolone was effective since the psychotic state was not improved by anti-ChE alone. The last psychotic episode was from April to September in 1987.

Postoperative state. In July of 1989, after a common cold she suffered two myasthenic crises for the first time. Although her anti-AchR antibody titerers declined to 14.3 pmole/ml after the plasmapheresis in 1982, the titer very much increased to 57.3 pmole/ml immediately before her final admission. Suspecting the presence of a thymic remnant, thymectomy was performed. However, the thymus gland and its dissemination were not found. The day after this operation she wrote her wish to die. On the third day she attempted suicide by pulling out the tube of her respirator and died.

Patient 2 Y.T. Male

In October of 1982 a 62-year-10-month-old retired railroad chief worker was referred to us for his dreamy state 25 days after a thymectomy.

Clinical course of MG. His MG started with bulbar symptoms at age 59 years and 9 months old. He was treated with anti-ChE and the symptoms soon disappeared. About one year later, his myasthenic symptoms recurred and the same medication restored him within 2 months. Nine months after this, he again experienced dyspnea and difficulty in swallowing, and a malignant thymoma was discovered and surgically removed. His serum anti-AchR antibody titer at the consultation was very high (26.0 pmol/ml).

Clinical course of NPSs. Two years before the onset of MG at age 57, he sometimes experienced muscle cramps in his lower legs and excessive sweating. Also his olfactory and gustatory sensations markedly changed. He would suddenly smell an unpleasant and nasty odor and was unable to distinguish sweet and salt tastes. Thus, he strangely used to take a meal with red peppers and a mass of salt. His mental state also changed. He was observed to be persecutory and delusional against his colleagues, and became paramnestic. At work he often had feelings of reliving previous experiences, and he felt strong déjà feelings in his daily routine. He thought his ideas related to work were stolen by his colleagues, and had a tendency to get angry about that. His wife observed that he was often dreamy at home. These NPSs worsened with the three aggravations of MG.

Postoperative state. When we examined him, his orientation was normal. He had a good understanding of the surgery performed and of the need for taking medication. However, he sometimes said he was not able to see the differences between the dream and the real world. At that time visual hallucinations were vividly described as if being in almost full insight. Therefore, his consciousness was thought to be in neither a cloudy nor a delirious state, but in a dreamy one. Although this mental condition gradually subsided with a small amount of haloperidol, he died from respiratory crisis of MG one month later.

Patient 3 S.M. Male

In March of 1986, a 64-year-old retired city officer, was referred to us for a dreamy state two weeks after a thymectomy.

Clinical course of MG. At age 63 years and 6 months old, while on a trip, he suddenly became unable to chew his food well or carry his baggage. Two weeks after this his right eyelid ptosis began, and weakness of extremities, dysphagia and disturbance of gait followed. Treatment was started, but he responded poorly to anti-ChE. At age 64, thymoma (60 g) was found and removed by an extended thymectomy. His serum anti-AchR antibody titer was high (16.2 pmol/ml) at the admission.

Clinical course of NPSs. At age 58, about five years before the onset of MG, he gradually developed a nervous condition and lost interest in his surroundings. His wife reported that he had become dysphoric, short-tempered and oversuspicious, which caused him problems related to his family members. Thus his wife felt his personality had changed. He also often noticed that his recent memory was failing. He became compulsive, and repeatedly counted an amount of money and numbers, and he often made memoranda of trivial things. At this same time his gustatory and olfactory senses changed.
He began to put a large amount of salt into soup, and nightly ate sweet cakes in the kitchen, something he had never eaten before. He could not often take even a freshly prepared meal as he would suddenly smell rotten unpleasant odors. In addition he had frequent déjà experiences in which he felt his daily routine was reproduced as having been previously experienced, and as a result he became slightly confused. He often said he felt as if he had been in a dream, and could not distinguish the dreamy experiences from the real acts. Sometimes he heard voices calling his name or commenting on his behaviors. He often experienced these psychopathological phenomena still at the onset of MG at age 63.

Postoperative state. Two weeks after the operation when we were consulted, he was in the dreamy state in which he had visual hallucinations like a motion picture. Although he said he felt as if he had been in a dream world and seemed unable to discriminate reality from his dream, his orientation was normal. He acted in the correct and polite ways to his attending doctors and nurses. He received medication and the treatment in good manners and without help. He was given a small dose of haloperidol (up to 3 mg/day) orally. It took about two months to make a full recovery from this mental state.

Six years after the thymectomy he was well on a regimen of 30 mg of prednisolone every other day, and 30 mg/day of ambenonium chloride. He did not experience the NPSs any longer.

**DISCUSSION**

The patients described here have two common features: (1) They had MG, thymoma and high titers of anti-AchR antibody; (2) The NPSs were rather homogeneous (i.e. a syndrome), which preceded by several months to years the onset of MG and reached the psychotic state in the culminating period. These NPSs subsided with steroids and antipsychotics, but worsened or reappeared with relapses of MG. Therefore, it is clear that these NPSs have a strong relationship with MG.

The NPSs are classified as follows: (1) consciousness disturbances such as dreamy state with paramnesia (all patients); (2) psychosensory symptoms such as the sudden change of senses of smell and taste (all patients), visual hallucinations (Patient 1), microteleopsia (Patient 1), auditory hallucinations (Patient 1 & 3), derealization (Patient 1) and déjà experiences (all patients); (3) cognitive disturbances such as recent memory impairment with resultant compulsive writing (Patient 1 & 3); (4) emotional disturbances with psychomotoric excitement such as agitation, fear and anger (all patients); (5) psychotic symptoms such as secondary delusions and hallucinations (Patient 1 & 2 and probably Patient 3).

Only a few reports have described the alteration of the senses of smell and taste in association with MG. Alajouanine et al. (1957) reported two patients with MG who lost the sense of taste and could not distinguish particularly the salt and sweet taste. In one case, similar to our patients, a change of taste preceded the onset of MG by six weeks. The other case noted a rotten-egg like odor for three days. The autopsy revealed no morphological changes in the brain. Interestingly, the symptoms in both their and our patients were severe enough for them to alter their daily behaviors. Therefore, these subjective symptoms may have supplemental value in making an early diagnosis, and as a prodromal sign of
worsening MG.

Clinically, it is difficult to differentiate whether these are due to neurological symptoms or psychopathological ones. These symptoms have both the paroxysmal quality of hallucination and that of illusion. The sudden changes of smell and taste, including other perceptual changes, are designated as psychosensory symptoms, which can be regarded as bridging symptoms in the borderland between neurological and psychiatric disorders. (Stevens 1966; Musha and Tanaka 1985; Silberman et al. 1985).

There are some lines of work suggesting an important role for Ach transmission in the olfactory system. Several reports suggested a relationship between the function of the cholinergic and the olfactory system in Alzheimer type dementia (Simpson et al. 1984; Serby et al. 1985). Although the cause and the significance of the symptoms of smell and taste in our cases are not understood, olfactory and gustatory transmission may be involved in terms of the cholinergic blockade by the autoimmune mechanism.

The other prominent symptoms frequently seen are déjà experiences and dreamy consciousness with paramnesia. In this condition the patients fell into a psychotic decompensation, where they were first in confusion and finally misinterpreted their experiences in a paranoid manner. This type of phenomenology is clearly attributable to an organic cerebral dysfunction.

In the literature there are some reports on EEG abnormalities ranging from diffuse slowing to focal discharges with or without epileptic discharges, which, however, have no relationship with duration of MG, and even severity of MG (Hokkanen and Toivakka 1969; Kazis et al. 1984). MG patients (even juvenile MG) have an increased incidence of seizures relative to the normal population (Hokkanen and Toivakka 1969; Snead et al. 1980) and we also found 4 epileptics among 66 MG patients. However, a specific type of EEG abnormality and that of seizure pattern have not been reported in the literature. Hokkanen (1969) found two psychotics and thirty six milder psychic disorders out of 179 MG in Finland. However, no mention was made of a specific type of psychopathology.

Patient 1 repeatedly showed abnormal EEGs with no focal or epileptic discharges. This is of importance because it clearly indicates the organic CNS dysfunction. The other two patients could not have tested for EEG. Although the profiles of the NPSs in our patients seem to resemble those of the temporal lobe epilepsy and its interictal phenomena (Stevens 1966), the patients did not have epileptic seizures before the onset of MG. Involvements of temporolimbic areas should be considered in the NPSs, but more data will be needed for the clarification of cerebral lesion in relationship to this particular syndrome.

Along this line, there is another source of evidence suggesting the CNS involvement. Lefvert and Pirskanen (1977) reported that eight of 12 MG patients had AchR antibody in serum and cerebrospinal fluid. A more direct evidence for the CNS involvement in MG came from the finding of EEG abnor-
malities in animals by immunization with AchR and injection of human MG serum (Fulpius et al. 1977).

During the postoperative psychoses the patients behaved lucidly to their situation and physical state with good orientation and almost full insight. Thus, we consider that they were not in cloudy state, but in prolonged dreamy state. Considering this state and their easily falling into the dreamy state before onset of MG, it seems that our patients have an increased susceptibility to alteration of consciousness.

In terms of thymoma, all patients had a histologically-proved thymoma (malignant thymoma in one case). Ananth et al. (1984) reported a 19-year-old woman, who experienced sudden psychotic hyper-religiosity six days preceding MG. They suggested an organic etiology of the psychosis associated with thymoma. Bogousslavsky et al. (1983) described a 54-year-old man who suffered from multiple neurologic disturbances (polyneuropathy, encephalopathy, dysautonomia) associated with MG and a malignant thymoma. In addition, during the hospitalization he suffered a convulsion, hallucinations and episodes of coma. EEGs showed a diffuse \( \theta \) to \( \delta \) dysrhythmias without epileptic features. Anti-AchR antibody was found in serum and cerebrospinal fluid. The authors suggested that the clinical picture is related to a generalized cholinergic dysfunction by the autoimmune mechanism.

Hallbach et al. (1987) reported two cases of a neuromuscular hyperactivity syndrome associated with a thymoma and high serum titer of anti-AchR antibody without MG. Besides myokimia and excessive sweating the patients showed intermittent psychosis with hallucinations, illusions, insomnia and delusions. Peripheral nerves showed signs of axonal sensory-motor neuropathy, but there was no evidence of central lesions. The authors suggested that this syndrome represents a unique type of autoimmune disease, which indicates cholinergic hyperactivity in the neuromuscular junction, autonomic nervous system and also in the CNS. Although our Patient 2 had MG, he had a similar symptomatology in terms of malignant thymoma, high titer of anti-AchR antibody, muscle cramps, excessive sweating and psychosis.

Furthermore, McArdle and Millingen (1988) reported a case of limbic encephalitis associated with recurrent malignant thymoma and MG, which showed confusion, loss of memory, hallucinations, abnormal behaviors, tachycardia, profuse sweating and elevated anti-AchR antibody titers. Autopsy revealed bilateral extensive neuronal loss with reactive gliosis, confined to the medial temporal cortex and Ammon's horn. Aarli et al. (1989) reported a 47-year-old woman with MG and a thymoma, who developed amnesia for recent events. Plasma exchange performed 9 months later, followed a dramatic improvement of the mnemonic dysfunction. They suggested that nicotinic AchR antibody binding to the CNS will lead to a functional loss of nicotinic AchR. Tucker et al. (1988) also reported the memory dysfunction in MG on the neuropsychological
tests. In one case, a patient's memory impairment significantly improved after plasma exchange. The authors suggested that MG has central cholinergic effects manifested by cognitive dysfunction. In terms of the cognitive function of our patients, Patients 1 and 3 had clearly noticed the subjective memory dysfunction with objective behavioral disturbances preceding the onset of MG. Because the NPSs including the cognitive dysfunction of Patient 3 were reversible after thymectomy and with immunosuppressive therapy, the same autoimmune pathomechanism may be involved in this etiology.

In our earlier report Musha (1989) reported a possibility of an autoimmune basis for the perceptual phenomena in MG because of close relationship to thymoma. Therefore, this is our impression that both the neurological symptoms related to MG and the accompanying psychiatric symptoms are a group of symptoms (i.e. a syndrome), which have a common immunological basis. We already proposed a possibility of neurological approach to psychosis in MG (Musha et al. 1981; Musha and Tanaka 1982, 1985), and the current study has delineated the clinical pictures and the genesis of the psychosis of MG in a more distinct form, that is, central cholinergic dysfunction.

Since patients with MG (Michaelson et al. 1982) and with paraneoplastic neurological syndromes (Anderson and Posner 1988) may have some antineural autoantibodies cross-reacting with neurons in their serum, there may be a possibility that the autoantibodies affect the different systems of the neuronal pathways. Although we did not have the direct evidence of central autoimmune cholinergic dysfunction, the clinical features of our patients are distinct enough to form a constellation of neuropsychiatric symptomatologies, that might be called autoimmune neuropsychiatric syndrome. Accumulation of similar cases and demonstration of central autoimmune mechanism by laboratory means would further support our notion that the psychoses with MG and thymoma are a unique type of autoimmune neuropsychiatric syndrome.

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**References**


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