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A 15-year History of the Department of Neurology, Yamaguchi University School of Medicine

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Abstract This paper provides a brief 15-year history of the Department of Neurology, Yamaguchi University School of Medicine. The Department began as the Division of Neurology, Yamaguchi University Hospital, in 1988, and was recognized as the Department of Neurology in 1993. Although the official staffs numbered no more than 3, physicians who wanted to become neurologists came together, and the total number of alumni reached 40. In 2001, the Department of Neurology and the Department of Neurosurgery joined together to form the Department of Clinical Neuroscience based on a reorganization of the departments of Yamaguchi University School of Medicine. For the past 15 years, my colleagues and I have devoted ourselves to medical treatment and clinical research for both outpatients and inpatients. Sixteen physicians have obtained a doctorate and 19 have been certified as neurological specialists by the Japanese Neurological Society. Investigations of neurodegenerative diseases, especially of Parkinson-related disorders have been promoted to clarify their pathogenesis and symptomatology. This contributed much to recognition of corticobasal degeneration and progressive supranuclear palsy as "special diseases" by the National Health Insurance in 2003.

Key words: neurology, Yamaguchi University School of Medicine, headache, neurodegenerative disease, corticobasal degeneration

History

The Division of Neurology, Yamaguchi University Hospital, was started in 1988, and I began to work as the Director in February 1989. Four neurologists came to me from the Division of Psychiatry, then collaborating in treatment of outpatients and inpatients, education of medical students and neuroscience research. Eight beds were prepared initially for us in the ward. However, we suffered from lack of staff rooms, laboratories and assistants, equipments for research and clinical service and other essentials. Slow but steady progress was realized because an average of 2 new physicians joined us every year for these 15 years.

In 1993, the Ministry of Education approved establishment of the Department of Neurology at Yamaguchi University School of Medicine. The new department included only three staffs; a professor, an associate professor and an assistant professor. This new Department of Neurology annexed the Division of Neurology as a clinical service department. In 2001, Yamaguchi University School of Medicine reorganized its departments, and the Department of Neurology and the Department of Neurosurgery joined together to form the Department of Clinical Neuroscience. Now, in 2004, the number of physicians working in the neurological division of this Department was 18, with 40 as alumni, of whom 16 obtained a doctorate and 19 were certified as a neurological specialist by the Japanese Neurological Society.

Outpatient department

When the Division of Neurology was started in 1988, the outpatient department was a main part of the clinical practice because 8 inpatient beds limited patient care and clinical research. At first, there were about 700 new outpatients every year, gradually increasing in number and finally reaching more than 1,000 a year, with about 800 returning outpatients every month. Main maladies of outpatients did not change over the past 15 years; the most frequent was headache, followed in order by epilepsy, diseases of the peripheral nervous system (this was because electrophysiological evaluations of many diabetic patients were requested by the Third Department of Internal Medicine),vertigo and dizziness, various neurotic complaints and then by miscellaneous organic diseases such as cerebrovascular disease, Parkinson-related disorders, dementing disorders, myeloradiculopathy associated with spinal column diseases, multiple sclerosis and myopathy of various causes. Motor neuron diseases, memingitis/encephalitis and metabolic/toxic encephalopathy are important in the field of neurology, but there were relatively small number of such cases. In 2003, 44% of the total outpatients were referred from other clinical divisions in our hospital, and 23% from physicians outside the hospital; the remainder came to us of their own accord.

We had four special outpatient clinics in addition to clinics for ordinary neurological diseases. The four clinics were set up for headache disorders, dementing disorders, botulinum toxin therapy and follow-up of patients who had undergone DBS (deep brain stimulation) for Parkinson's disease (PD). The headache clinic was started in September 2000 because triptans specific for migraine therapy became available in Japan in April 2000. Opening of the headache clinic was announced to the community by mass media (local newspapers and televisions). Then, the number of outpatients with headache increased markedly. In August 2000, total number of new outpatients, regardless of the type of disorder, was 55. In September 2000, the number increased to 180, and nearly the entire increase was accounted for by patients with headache (Fig. 1).[1] The types of headache were compared for the 8 months before opening of the headache clinic, and the 8 months after its opening. Migraine, tension-type headache, and other headache disorders comprised 8%, 60% and 32%, respectively, of all headaches treated from September 2000 to

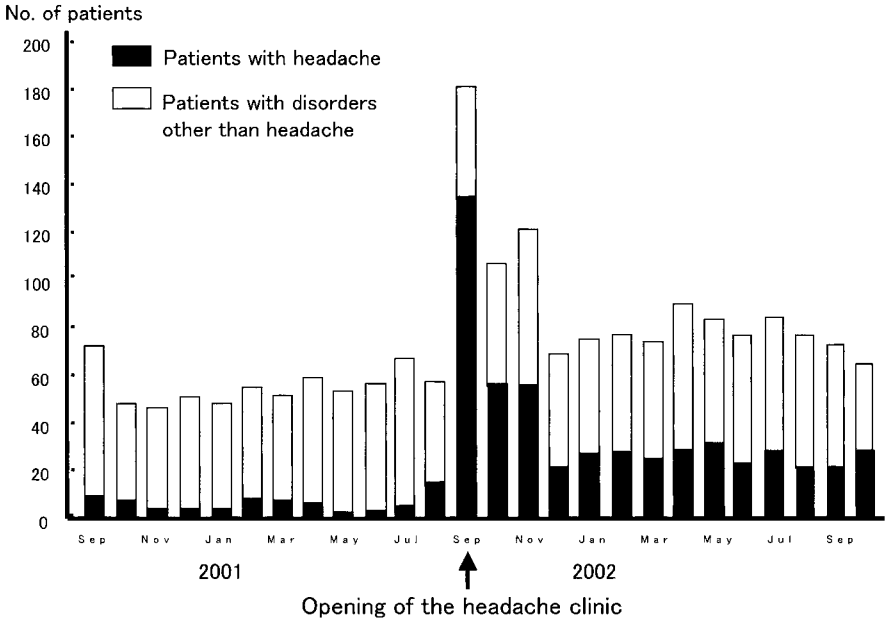

Fig. 1 Number of new outpatients who visited the Division of Neurology, Yamaguchi University Hospital, per month from September 2000 to October 2002. A marked increase is observed after opening of the headache clinic and is accounted for mainly by headache patients.

April 2001 (before opening of the clinic). Migraine, tension-type headache, and other headache disorders comprised 35%, 51% and 14%, respectively, from September 2001 to April 2002 (after opening of the clinic), with similar trends thereafter (Fig. 2).[2] Thus, after the clinic opened, many patients with migraine came asking for proper diagnosis and treatment. A questionnaire was sent to these 78 migraine patients before treatment; 50 (64%) were returned.[2] The responses were analyzed, and the following data were obtained. Sixteen percent of patients reported that they were unable to perform ADL (activities of daily living), and 66% reported the performance of ADL was difficult, percentages reflective of the severity of headaches. Thirty percent of patients reported "no treatment despite of consultation", and 26% reported "no consultations".[2] In such patients, migraine attacks can now be controlled well with triptans, NSAIDs and other prophylactic drugs, and thus, our headache clinic probably contributed much to alleviation of headaches in migraineurs in particular.

At "the dementia clinic" patients with dementia, especially with Alzheimer's disease, were examined and treated. This clinic was started because donepezyl hydrochloride, an anti-dementia agent was recognized in 1999 by the National Health Insurance and systematic assessment and treatment were needed for demented patients to qualify for coverage. Moreover, new anti-dementia agents including galantamine have been clinically tested under approval of the University Committee of Ethics.

"The botulinum toxin therapy clinic" was started for the treatment of patients with dystonia. Botulinum toxin A (Botox®) was initially recognized in 1996 in Japan for use only in patients with blepharospasm, later extended to hemifacial spasm and spasmodic torticollis, by the National Health Insurance. About 60 patients with such dystonia were treated over the past 7 years, with favorable effects in almost all patients. Many patients with other types of dystonia are eagerly awaiting treatment with Botox®.

A special clinic for patients with PD was started to follow up on patients who had undergone subthalamic nucleus (STN) DBS for refractory parkinsonism. A system was set up such that preoperative and postoperative assessments were done in our Division of Neurology but DBS itself was performed in the Division of Neurosurgery. This system is the rule in representative hospitals in the U.S.A. and Europe for assessment of the true efficacy of DBS. Indications for DBS followed strict criteria and were determined by cooperation between the Division of Neurology staff and

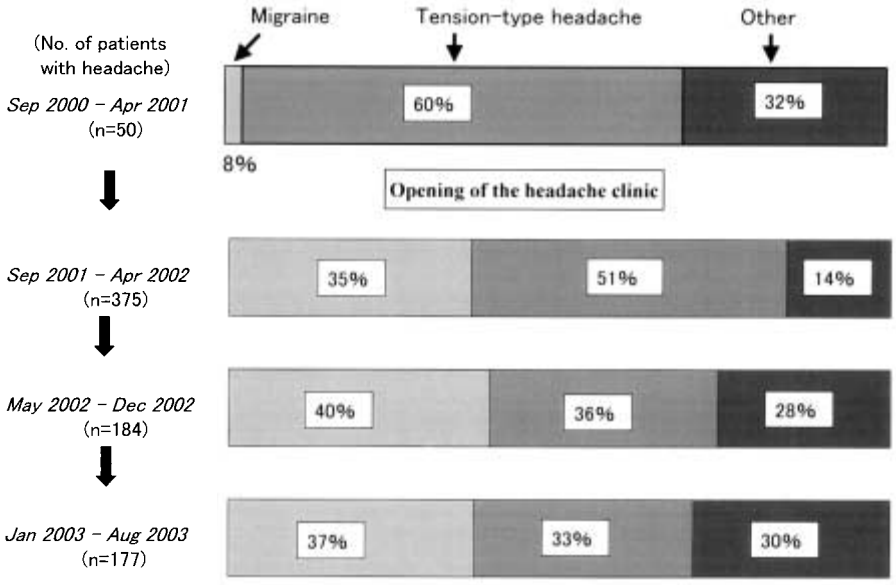

Fig. 2 Types of headache disorders treated before and after opening of the headache clinic. The proportion of patients with migraine increased remarkably.

the Division of Neurosurgery staff. Every patient considered a candidate for DBS was carefully evaluated. DBS was performed in more than 20 patients, and results were moderate to excellent, especially for patients with intractable wearing-off phenomena or levodopa-induced dyskinesia; there were no serious adverse effects.

Corticobasal degeneration (CBD): a clinical research

Parkinsonism from various causes was a main concern in our Department. We performed much clinical research on Parkinson's disease and allied disorders, out of which several doctoral theses were produced. I was a member of the Research Committee on the Neurodegenerative Diseases organized by the Ministry of Health, Labour and Welfare of Japan. Fellow Committee members and I conducted a survey of all patients with CBD treated in and before 2001 in the 29 institutions to which the members of the Committee belonged. Provisional diagnostic criteria for CBD were set by us on a clinical basis, consisting of "probable CBD" and "definite CBD".[3] "Probable CBD" comprises three clinical forms: (1) the classic form, consisting of progressive limb-kinetic apraxia and akinetic rigidity, predominantly on one side and associated with late dementia, (2) the quasi-classic form, showing progressive corticobasal signs other than limb-kinetic apraxia and/or akinetic rigidity, predominantly on one side and also associated with late dementia, and (3) the non-classic form, showing early aphasia, dementia, behavior disorder or other impairment of higher cortical functions, and associated with late lateralized limb-kinetic apraxia and akinetic rigidity. There was no "possible CBD" diagnosis. "Definite CBD" was pathologically confirmed CBD. According to the survey, there were 151 patients with "probable CBD", including 121 patients with the classic form, 17 with the quasi-classic form and 13 with the non-classic form. There were only 13 patients with "definite CBD" (Fig. 3).[4] The reason for the prevailing number of classic cases was probably that this form was most easily diagnosed clinically. The number of patients with progressive supranuclear palsy (PSP) was simultaneously examined in the same institutions. The ratio of the number of CBD patients to the number of PSP patients was 1/2.6 among clinical cases. The nationwide prevalence of CBD and of PSP has not yet been determined. Considering the prevalence of PSP (5.82 per 100,000 population) in 2001 in Yonago city recently reported by Nakashima et al.[4] and the CBD/PSP ratio 1/2.6 in our study, the prevalence of CBD was assumed to be 2.2 per 100,000 population, and the numbers of PSP and CBD patients in Japan in 2001 was estimated as 7,400 and 2,800, respectively.

In our Department over the past 15 years, we encountered 28 patients with "probable CBD", in whom clinical studies were made from

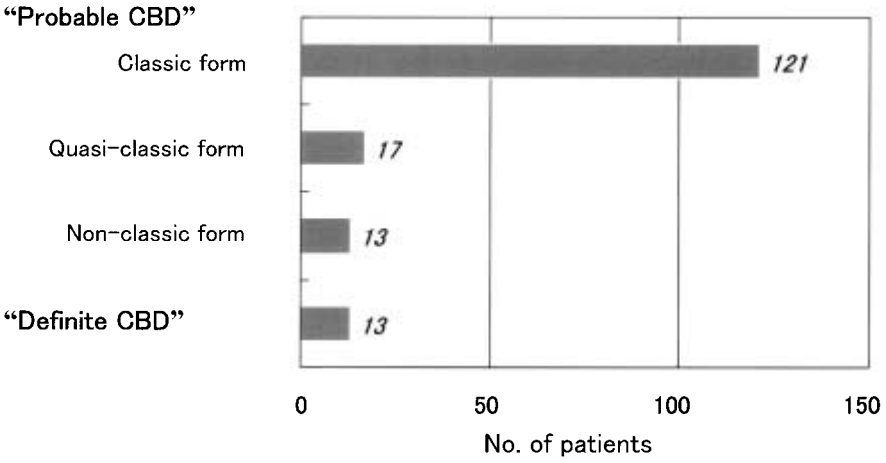

Fig. 3 One hundred and sixty-four patients (73 males, 91 females) with CBD who were detected by a survey of 29 neurological institutions in Japan in 2001. The classic form of "probable CBD" accounts for the greatest.

many viewpoints. Based on the inclusion criteria, limb-kinetic apraxia and akinetic rigidity, both predominant on one side, were mandatory, whether they occurred early or late. Additional common symptoms in the 28 patients were unstable gait (89%), dysarthria (89%), increased deep tendon reflex (82%), supranuclear vertical gaze palsy (75%), grasp reflex (71%), limb dystonia (68%), Babinski (or Chaddock) sign (61%), dementia (50%), cortical sensory disturbance (50%) and tremor (43%). Well-known symptoms, such as alien limb(39%) and reflex myoclonus (25%), were not so frequent, nor aphasia (14%). The prevalence of these symptoms nearly matched the prevalence in the series (64 cases of CBD) reported by Rinne et al.[5] (Table 1).

The physicians of our Department conducted

Table 1 Comparison of clinical features of CBD patients between our series and the series of Rinne et al.[5] The incidences of each sign are almost similar except for a few signs.

	Our series (2004; n=28)		Rinne et al.[5] (1994; n=64)
		%	%
1. Motor signs			
1) Akinetic rigidity	28	(100)	100
2) Dysequilibrium(unstable gait)	25	(89)	73
3) Tremor	12	(43)	48
4) Limb dystonia	19	(68)	67
5) Reflex myoclonus	7	(25)	67
2. Cortical signs			
1) Cortical sensory disturbance	14	(50)	45
2) Motor apraxia	28	(100)	84
3) Alien limb sign	11	(39)	47
4) Grasp reflex	20	(71)	48
5) Dementia	14	(50)	31
6) Aphasia	4	(14)	16
3. Others			
1) Accelerated tendon reflex	23	(82)	70
2) Babinski sign	17	(61)	48
3) Supranuclear gaze palsy	21	(75)	59
4) Blepharospasm	2	(7)	20
5) Dysarthria	25	(89)	53

a number of clinical investigations into CBD, comparing the features between CBD, PSP and PD. Negoro et al.[6] compared the number of nerve cells in the basal ganglia and frontal lobe between normal control subjects, patients with CBD and patients with PSP using 1H-MRS (magnetic resonance spectroscopy). The NAA (N-acetyl aspartate)/choline (or creatine) ratio showed the number of nerve cells in the basal ganglia to be significantly less in both CBD and PSP patients than in normal controls. The number of nerve cells in the frontal lobe was significantly less in CBD patients than in PSP patients and normal controls, and it did not differ between PSP patients and normal controls. This means that the actual loss of nerve cells in the frontal lobe is not so marked in PSP as in CBD, although both CBD and PSP patients are known to show frontal lobe signs and fronto-subcortical dementia.

Ogasawara et al.[7] studied activation of the sensory cortex following tactile stimulation of hand using functional MRI. The palm of the hand of patients with CBD, patients with PSP, and normal controls was stimulated with a wooden stick regularly at 2 Hz, and the number of significantly activated voxels of the contralateral sensory cortex was counted on MR images. In patients with CBD, the stimuli were given to the more disabled hand. In all patients, including those with CBD, the contralateral sensory cortex was well activated following the tactile stimulation, and the number of activated voxels did not significantly differ between patients with CBD, those with PSP and normal controls. This means that although peri-rolandic lesions are essential to CBD, activation of the primary senso-

ry cortex occurs normally, as in PSP. It is hypothesized that in CBD a higher discriminating ability linked to the parietal cortex is lost.

Ogasawara et al.[8] then studied regional cerebral blood flow (rCBF) of the cerebral cortex in CBD, PSP and PD patients using a 3D-SSP (three dimensional surface stereotactic projection) method. 3D-SSP is useful for comparing rCBF between two patient groups based on 99mTc-HMPAO SPECT (single photon emission CT). rCBF was shown to be decreased in CBD patients compared to that in PD patients in the frontal and parietal cortices, especially in the upper peri-rolandic areas and the medial frontal areas. However, rCBF in PSP patients was decreased in the frontal cortex, especially in the lower peri-rolandic areas compared to that in PD patients. Therefore, a decrease in rCBF in the upper peri-rolandic areas and medial frontal areas is important in CBD, implying that in CBD patients, the lesions in these areas may cause such specific symptoms as limb-kinetic apraxia, cortical sensory loss and alien limb sign.

These findings were published as a series in some neurological journals and in official reports from the Research Group of the Ministry of Health, Labour and Welfare of Japan. As of October 2003, CBD and PSP were recognized as "special diseases" covered by the National Health Insurance. Now, the medical expenditures of patients with CBD, PSP or PD are covered by the National Health Insurance.

Doctoral theses

When they started their doctoral studies, the physicians of our Department were advised to conduct on a neurological issue in which they were deeply interested. For the selection of the subjects, appropriate advice was given, including a stay at another university or research institution. It was my opinion that every student who was seeking a doctorate should be involved in the forefront scientific fields. The resulting doctoral theses in our Department covered many fields: (1) dementia (provoked abnormal EEG activity in demented patients); (2) PD (correlation between rCBF and cognitive function in PD patients, kinesiology in PD, functional MRI in PD patients following standardized tasks); (3) multiple system atrophy (SPECT study); (4) CBD (change in evoked action potentials of the hand muscle following magnetic stimulation of the motor cortex); (5) rehabilitation medicine (neuropsychological factors interfering with the rehabilitation of stroke patients); (6) anti-ganglioside antibodies in Guillain-Barré syndrome; (7) Creutzfeldt-Jakob disease (CJD) (histopathology of prion protein in the brain of patients with CJD); (8) cytokines in a mouse model of experimental herpes simplex encephalitis ; (9) histochemical immunological change in the muscles in experimental graft-versus-host disease of mice; (10) identification of tetrodotoxin genes; (11) toxicity of VLDL (very-low-density lipoprotein) on cultured nerve cells (electrophoretic analysis); and (12) molecular analysis of aprataxin (the causative protein for early-onset ataxia with ocular motor apraxia and hypoalbuminemia).

Social endeavors

I joined the Research Committee on SMON (subacute myelo-optico-neuropathy) of the Ministry of Health, Labour and Welfare of Japan. SMON is a serious drug-induced disease caused by clioquinol (chinoform), which was previously marketed as a gastrointestinal drug in Japan. About 3,000 patients with SMON are still alive in Japan and follow-up and scientific studies have been conducted over 40 years by the Research Committee. In Yamaguchi Prefecture, there are about 20 SMON patients still living. These patients range in age from 64 to 90 years and we examined 12 to 16 of them every year at hospitals or by visiting their homes.[9] Reports on these SMON patients were presented at annual meetings of the Research Committee. Although these patients are well supported economically by the government, their handicaps increase with age.

Authorities of Yamaguchi Prefecture put together an official council to manage and support patients with advanced amyotrophic lateral sclerosis (ALS). The council consists of members from a representative hospital (Yamaguchi University Hospital), 10 core hospitals, and 17 alliance hospitals, 14 prefec-

tural health centers and an association of ALS patients. I and Dr. Negoro, associate professor of our Department worked as a chairman and a member, respectively, in this council. The welfare of patients with ALS in Yamaguchi Prefecture has been promoted through discussions and decisions of the council, aimed particularly at solving the problems associated with home care and hospitalization. The prefectural administration has provided financial support to ALS patients in hospitals and at home for the many necessary devices and instruments, including respirators and communication tools.

Conclusion

A 15-year history of the Department of Neurology, Yamaguchi University School of Medicine, was reviewed briefly with special reference to medical practice and researches. For outpatients, in addition to ordinary clinics, four special clinics were set up, bringing the advantages to patients with such special disorders. In neurology, specialization in respective specific fields is progressing, and thus, special clinics will be valuable for treatment and clinical study. Clinical investigations of neurodegenerative diseases, especially of CBD and PSP, were promoted, contributing to recognition of these two diseases as "special diseases" by the National Health Insurance. Patients with neurodegenerative diseases are now increasing in number and the need of study of their pathogenesis and treatment can not be overestimated. Basic researches were performed mainly by students who sought a doctorate, and many original papers were produced. From now on, more progress will be expected in both clinical and basic fields in the Department of Clinical Neuroscience under the leadership of a new professor.

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