体陽性率を検討した．結果，psychosisを合併したNPSLE患者における同抗体の陽性率は5例中4例(80%)であり，psychosisを合併しない(神経症状のみ合併する) NPSLE患者では13例中0であった．精神神経症状を合併しないSLE患者では19例中1例(5.3%)であった．その他，多発性硬化症12例，感染性髄膜脳炎13例，多発性ニューロパチー10例，精神疾患10例および健常者12例では，いずれも陰性であった．以上の結果から抗αGDI抗体はNPSLE患者におけるpsychosisと何らかの関連性がある可能性が示唆されたが，未だ少数例の検討であり，特異性の確立には今後の多数例での検討が必要と考える[10]．

6. NPSLEと抗Hsp60抗体

多発単ニューロパチーで発症し，その後特徴的な大脳・小脳・脳幹に広範な白質病変を呈した69歳男性NPSLE患者を経験し，その血清中より上記システムを用い4つの抗神経抗体を検出し報告した[12]．その認識抗原蛋白は質量分析の結果，beta-actin，alpha-internexin，heat-shock protein 60(Hsp60)，glial fibrillary acidic protein (GFAP)であった．このうちのHsp60に関しては通常，ミトコンドリアのシャペロン蛋白として機能するが，ストレス下の血管内皮細胞膜表面に発現することが知られており，SLE患者において抗血管内皮細胞抗体の認識抗原として報告されている[13]．そこで我々は，各種神経疾患180例および健常者23例における血清中抗Hsp60抗体価をenzyme-linked immunosorbent assay (ELISA)法により測定した．結果，NPSLE患者および神経症状を合併したSjögren症候群患者で高値となる傾向がみられたが，健常者やその他神経疾患患者の抗体価との間に有意差は認められなかった．

7. 膠原病患者における抗神経抗体の役割

NPSLEの病態機序はその精神神経症状の多様性と同様，自己抗体が直接的に介在する神経障害のみならず血管障害，血液凝固異常といった多様な機序が想定されている．これまでに我々がNPSLE患者より同定した自己抗体の多くは，神経組織以外にも存在する細胞骨格関連蛋白や解糖系酵素などを認識抗原とする自己抗体であり，病態機序において直接的な役割は果たしている可能性は乏しいと思われる．これらの自己抗体が膠原病患者の共通した自己免疫異常を背景とした，神経障害の結果，二次的に産生された可能性もあるが，診断のバイオマーカーとしての価値を検討することはきわめて重要であると考える．なぜなら，膠原病では神経系の日和見感染や併存する神経疾患との鑑別がしばしば困難であるからである．

最後に本研究で紹介した，新たな抗神経抗体の同定のためのプロテオミクス解析法は，神経障害を合併した膠原病患者における新たなバイオマーカーの確立に極めて有効な研究手法であり，今後も新たな発展が望まれる．

謝辞：本研究にあたりLC-MS/MSシステムによる蛋白質同定にご協力いただきました岐阜大学大学院病態情報解析医学分野竹村正男先生，清島満先生，患者血清ならびに髄液を提供していただきました同内分泌代謝病態学分野加納克徳先生および同神経内科・老年学分野山田恵先生，香村彰宏先生，櫻井岳郎先生，林祐一先生，田中優司先生，保住功先生に深謝いたします．

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INTERNAL MEDICINE

□ PICTURES IN CLINICAL MEDICINE □

Markedly Ring-enhanced Optic Nerves Due to Metastasis of Signet-ring Cell Gastric Carcinoma

Yuichi Hayashi, Takehiro Kato, Yuji Tanaka, Megumi Yamada, Akihiro Koumura, Akio Kimura, Isao Hozumi and Takashi Inuzuka

Key words: MRI, signet-ring cell carcinoma, optic nerve, cerebrospinal fluid, optic neuropathy, leptomeningeal carcinomatosis

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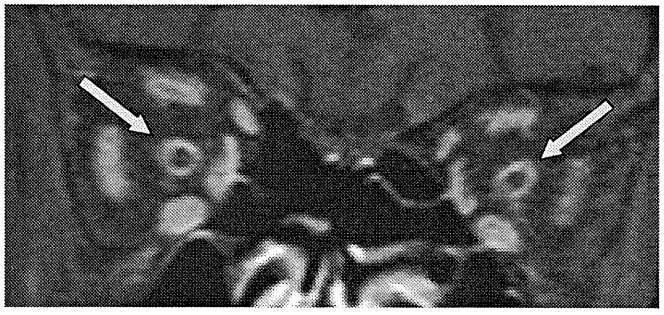

Picture 1. **Coronal fat-suppressed MRI with gadolinium showed a marked ring enhancement of the surrounding optic nerves (arrows).**

Signet-ring cell carcinoma frequently causes leptomeningeal carcinomatosis, one cause of optic neuropathy in elderly patients. A 77-year-old woman had shown progressive bilateral blindness for one month without any other symptoms. Coronal fat-suppressed MRI with gadolinium showed a marked ring enhancement of the surrounding optic nerves (Picture 1). CSF cytodiagnosis and histopathological examination of the gastric biopsy samples revealed signet-ring cell carcinoma. The patient was diagnosed with leptomeningeal carcinomatosis due to gastric cancer. She died 2 weeks after the diagnosis. Coronal fat-suppressed MRI with gadolinium is useful for the differential diagnosis of optic neuropathy, especially leptomeningeal carcinomatosis (1, 2).

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High Levels of Copper, Zinc, Iron and Magnesium, but not Calcium, in the Cerebrospinal Fluid of Patients with Fahr's Disease

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Kazunori Hashimoto[a] Megumi Yamada[a] Takeo Sakurai[a]
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Key Words
Fahr's disease · Calcification · Copper · Zinc · Dementia · Parkinsonism

Abstract
Patients with marked calcification of the basal ganglia and cerebellum have traditionally been referred to as having Fahr's disease, but the nomenclature has been criticized for including heterogeneous etiology. We describe 3 patients with idiopathic bilateral striatopallidodentate calcinosis (IBSPDC). The patients were a 24-year-old man with mental deterioration, a 57-year-old man with parkinsonism and dementia, and a 76-year-old woman with dementia and mild parkinsonism. The former 2 patients showed severe calcification of the basal ganglia and cerebellum, and the latter patient showed severe calcification of the cerebellum. We found significantly increased levels of copper (Cu), zinc (Zn), iron (Fe) and magnesium (Mg), using inductively coupled plasma mass spectrometry in the CSF of all these 3 patients. The increased levels of Cu, Zn, Fe and Mg reflect the involvement of metabolism of several metals and/or metal-binding proteins during the progression of IBSPDC. More numerous patients with IBSPDC should be examined in other races to clarify the common mechanism of the disease and to investigate the specific treatment.

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Introduction

Mild calcification of the basal ganglia is sometimes seen, especially in the elderly. Some patients with marked calcification of the basal ganglia and cerebellum have been reported to be associated with hypoparathyroidism. Most other idiopathic cases have traditionally been referred to as having Fahr's disease, but the nomenclature has been criticized for including a heterogeneous etiology and the disease has presented as a clinically complex syndrome. The patients have not been clearly demonstrated to exhibit any endocrine, metabolic or genetic disorder [1, 2]. The pathophysiological mechanism remains to be elucidated and there is no clue for the treatment. The disease is thus being referred to by some as idiopathic bilateral striatopallidodentate calcinosis (IBSPDC). Inductively coupled plasma mass spectrometry (ICP-MS) can measure the levels of several metals in a small amount of CSF [3]. We have measured those of Japanese patients with IBSPDC to clarify the pathophysiological features of the disease.

Case Reports

Patient 1

A 24-year-old man was hospitalized for gait and speech disturbance. He had been diagnosed with Fahr's disease when 15 years old in a hospital and his IQ was 79. On admission, neurological examination revealed mental deterioration (IQ 69), exaggerated deep tendon reflexes, mild rigidity on the right, and limb and truncal ataxia. CT showed a striking high density area in the basal ganglia and dentate nuclei and revealed progression with age (fig. 1a). No abnormal findings were detected in the blood tests including metals [calcium (Ca), iron (Fe), copper (Cu), zinc (Zn), magnesium (Mg) and manganese (Mn)], in Ca metabolism including parathyroid hormone and the Ellsworth-Howard test, and in routine CSF studies.

Patient 2

A 57-year-old man was hospitalized for dementia, bradykinesia, and gait disturbance. He showed parkinsonism at age 50 and mental deterioration since age 55. Neurological examination revealed dementia, slurred speech, limb ataxia, rigidity, bradykinesia and truncal ataxia. Interestingly, L-DOPA led to a slight improvement in symptoms. He showed similar CT findings as patient 1 (fig. 1b), diabetes mellitus, and no other abnormal findings either in the above-mentioned tests.

Patient 3

A 76-year-old woman came to our hospital for dementia. Neurological examination revealed dementia and mild parkisonism. CT showed a striking high density area in the dentate nuclei, and a moderate area in the basal ganglia and border of the cortex and white matter of the parietal lobe (fig. 1c). No abnormal findings were detected in the above-mentioned tests.

None of the 3 patients had a skeletal structural abnormality or a family history of IBSPDC. Analysis of the levels of Ca, Fe, Cu, Zn, Mg, and Mn in the scalp hair showed no specific findings in the 3 patients using a commercially-available ICP-MS method (La Belle Vie Inc., Tokyo, Japan).

Metals in CSF Analysis

CSF samples were obtained from 3 patients with IBSPDC and 15 controls (9 females and 6 males, age from 22 to 81 years with a mean of 52 years). CSF samples were nebulized with perhydroxyl-nitrate, and the levels of metals (Fe, Cu, Zn, Mg, and Mn) were measured using ICP-MS (HP4500, Agilent Technologies, Japan). Scandium (Sc), yttrium (Y) and thallium (Tl) were added to samples as internal standards. The concentrations of the elements were normalized by the internal standards. The level of

Ca in the CSF was measured by colorimetry using o-cresolphthalein-complexone (o-CPC) for appropriate means. This study was approved by the Ethics Committee of the Gifu University Graduate School of Medicine.

Results

The levels of Cu, Zn, Fe, and Mg were significantly increased by 3.7, 2.5, 1.9, and 1.6 times of control levels, respectively. Statistical analysis using Mann-Whitney U test showed significant difference ($p < 0.01$) in the levels of Cu, Fe and Mg, and significant difference ($p < 0.05$) in that of Zn, but the levels of Ca (1.1 times) and Mn (0.9 times) in the CSF of all 3 cases with IBSPDC were not significantly different from those of controls (table 1 and fig. 2)

Discussion

Chemical analyses of brain stones in the striopallidodental system has shown high levels of Ca and other metals, such as Fe, Mg, Cu, Zn, Mn, lead, and aluminium [4, 5]. However, there is no apparent explanation for the accumulation of calcium and other metals. The pathophysiological features of Fahr's disease thus remain to be elucidated. The term 'Fahr's disease' has various entities including familial and secondary cases. As the concept of Fahr's disease may encompass diseases derived from different genetic or environmental etiologies in the region, we prefer the term 'IBSPDC' to 'Fahr's disease'. In Japan, elderly patients with dementia and calcification of the basal ganglia were reported to show diffuse neurofibrillary tangles and absence of senile plaques in the pathology [6, 7]. Patients 2 and 3 are considered to be included in this category. We presented 3 clinically idiopathic cases of IBSPDC with variable clinical characteristics and ages.

ICP-MS can measure the level of several metals in a small amount of CSF (less than 1 ml). ICP-MS is more sensitive and accurate than traditional colorimetery and the atomic absorption spectrophotometry method for the measurement of several metals such as Cu, Zn, Mg, except for that of Ca.

Generally, the high density of the basal ganglia and cerebellum in CT images has been thought to be mainly associated with calcification. However, a disorder of Ca metabolism has not been demonstrated in IBSPDC. Only one preliminary study reported rather decreased levels of Ca in the CSF in Fahr's disease, contrary to our expectations [8]. Our 3 cases with IBSPDC showed various ages and clinical presentation, but a similar and significant increase in Cu, Zn, Fe and Mg. This suggests that some cases with IBSPDC are associated with a disorder including heavy metals, especially Cu, Zn, and Fe metabolism, and some metal-binding proteins. Even at low levels, Fe and Cu can catalyze a Fenton reaction, producing highly reactive hydroxyl radicals. Excessive amounts of Cu can be a directly neurotoxic factor and also damage neurons by producing reactive oxygen in neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis [9–11].

Pathological and biochemical analyses at autopsy are needed for further evaluation. In the study we could not recognize whether metals in the CSF are free or are derived from metal-binding proteins such as superoxide dismutase-1 and metallothioneins (MT). The high levels of metals in the CSF do not necessarily reflect correctly the pathophysiological mechanisms in the brain; however, this feature of the CSF provides some novel aspects of

the diseases. CSF of more numerous and clinically variable cases with IBSPDC should be examined in other races to clarify the common pathophysiological features.

We have detected high levels of Cu, Zn, Fe and Mg in the CSF of 3 patients with IBSPDC in Japan. There is no specific and effective treatment for IBSPDC at present, and the progression of the disease is accelerated with age. MT is a small (7 kDa), metal-binding (4 Cu and 3 Zn per molecule) protein that scavenges reactive oxygen species [10]. The study of CSF may provide a clue regarding a common pathway of IBSPDC including the metabolism of Cu, Zn, Fe and Mg and appropriate treatments including metal-chelating agents such as ammonium tetrathiomolybdate, a Cu-chelating agent [11], and metal-binding proteins such as MT [10].

Disclosure

Dr. Hozumi has received research support from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Basic Research (B) 19390151) and Mitsui Sumitomo Insurance Welfare Foundation, Japan.

Table 1. Levels of metals in CSF

	Age	Ca (mg/l)	Mg (mg/l)**	Fe (μg/l)**	Cu (μg/l)**	Zn (μg/l)*	Mn (μg/l)
Patient 1	26	45.0	49.1	418	33.9	8.00	2.10
Patient 2	58	42.0	47.3	461	38.0	10.0	1.00
Patient 3	76	49.0	48.2	458	40.1	22.2	2.10
Average ± SD	53.3 ± 25.3	45.3 ± 3.51	48.2 ± 0.90	446 ± 23.7	37.3 ± 3.15	13.4 ± 7.69	1.73 ± 0.635
Control (n = 15)							
Average ± SD	48.4 ± 22.2	41.1 ± 4.64	29.6 ± 6.52	238 ± 54.7	10.2 ± 2.07	5.30 ± 3.31	1.90 ± 0.971

The levels of Ca, Fe, Cu, Zn, Mg, and Mn in CSF of patients and controls (n = 13). Statistical analysis was performed using Mann-Whitney U test.

* Significant difference, $p < 0.05$. ** Significant difference, $p < 0.01$.

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Fig. 1. CT findings in patients. **a** CT findings in patient 1. A sagittal view shows a striking high density area in the basal ganglia and the dentate nuclei of the cerebellum. **b** CT findings in patient 2. An axial view shows a marked high density area in the basal ganglia and spots at various sites such as the pulvinar thalami, the subcortical area in the frontal lobe, and the border area of the cortex and white matter in the occipital lobe. **c** CT findings in patient 3. An axial view shows a striking high density area in the dentate nuclei of the cerebellum.

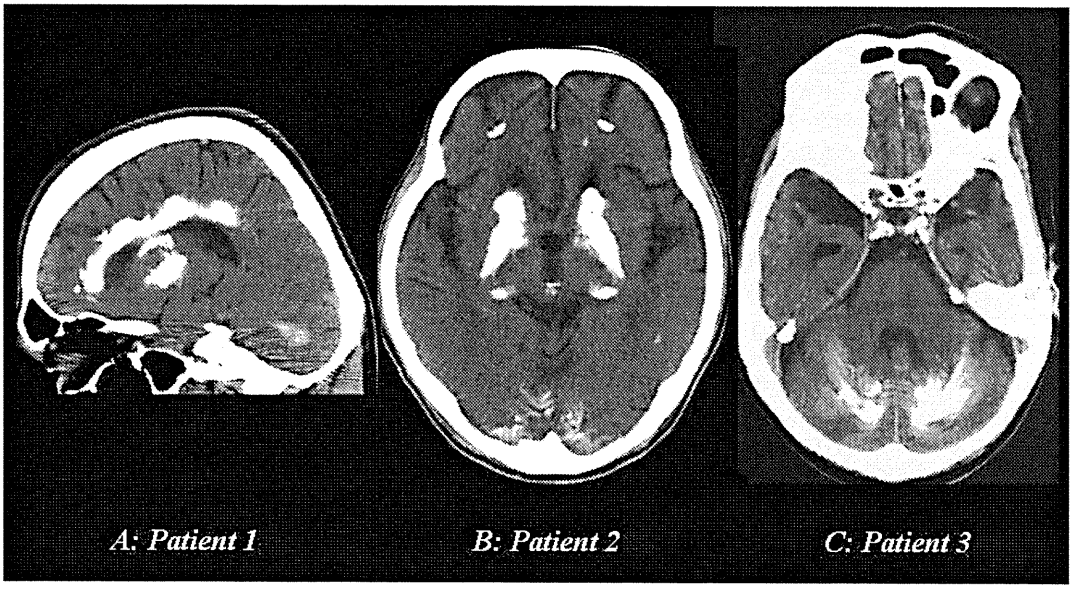
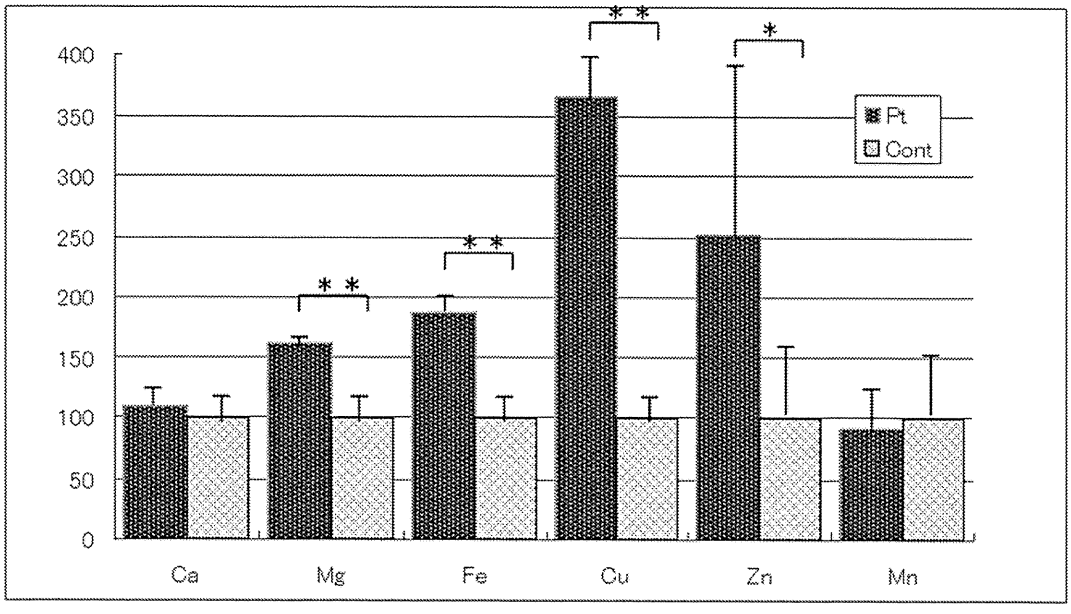


Fig. 2. Comparative values of metals in the CSF. The average levels of Ca, Fe, Cu, Zn, Mg, and Mn in the CSF of patients and controls are shown to be set at the value of 100 (%) in the figure. Especially the values of Cu and Zn in patients are markedly higher compared to those of controls. * Significant difference, $p < 0.05$. ** significant difference, $p < 0.01$.



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INTERNAL MEDICINE

□ CASE REPORT □

Serial Monitoring of Basal Metabolic Rate for Therapeutic Evaluation in an Isaacs' Syndrome Patient with Chronic Fluctuating Symptoms

Yuichi Hayashi, Akio Kimura, Norihito Watanabe, Megumi Yamada, Takeo Sakurai, Yuji Tanaka, Isao Hozumi and Takashi Inuzuka

Abstract

A 52-year-old man presented with hyperhydrosis, painful pseudomyotonia and gait disturbance. The condition was diagnosed as Isaacs' syndrome on the basis of characteristic findings noted on an electromyogram. Carbamazepine treatment was only partially and transiently effective. Intravenous immunoglobulin therapy was effective. The basal metabolic rate (BMR) was serially monitored using an automatic integrated system for breath analysis. Serial monitoring of the BMR facilitates therapeutic evaluation in an Isaacs' syndrome patient with chronic fluctuating symptoms.

Key words: Isaacs' syndrome, intravenous immunoglobulin, basal metabolic rate, automatic integrated system for breath analysis, carbamazepine

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Introduction

Isaacs' syndrome (IS) is characterized by spontaneous and continuous activity of muscle fibers (1). Most cases of IS occur sporadically, and only 38% of all patients with IS test positive for anti-voltage-gated potassium channel (VGKC) antibodies (2).

Isaacs reported that the basal metabolic rate (BMR) is elevated in patients with acute-phase IS, but is normalized with treatment (1). Studies involving the serial monitoring of the BMR of these patients have not been performed because of the complicated procedures involved. We present the case of a patient with sporadic IS without anti-VGKC antibodies over a chronic fluctuating course. We serially monitored the patient's BMR for therapeutic evaluation using an automatic integrated system for breath analysis.

Case Report

A 52-year-old man presented with gait disturbance, painful muscle cramps and hyperhydrosis and was admitted to our hospital in February 2008. He had no specific familial history of disease. He began to suffer from hyperhydrosis when he was in his 30s and from gait disturbance in May 2007. He occasionally experienced dysphagia but recovered from it naturally. His clinical course had fluctuated over several months.

Physical examination revealed that the patient was well nourished. He suffered from mild mental retardation. His blood pressure, heart rate and body temperature were all found to be normal. Neurological examination revealed myokimia, hyperhydrosis, and hypertrophy of the leg muscles. Furthermore, the patient experienced muscle cramps at various times during the day and night. Grip myotonia was not detected; however, the patient's fingers spontaneously flexed after they were extended. His reflexes were slightly exaggerated but the Babinski sign was absent. A photograph of the patient showed flexed upper-limbs, forward-bend posture, standing with legs bending outwards, and hypertrophy of the calf muscles (Fig. 1). He walked with such posture. Painful cramps often occurred during walking. His cranial nerves and sensory perception were normal. He had experienced no epilepsy, hallucination, or insomnia.

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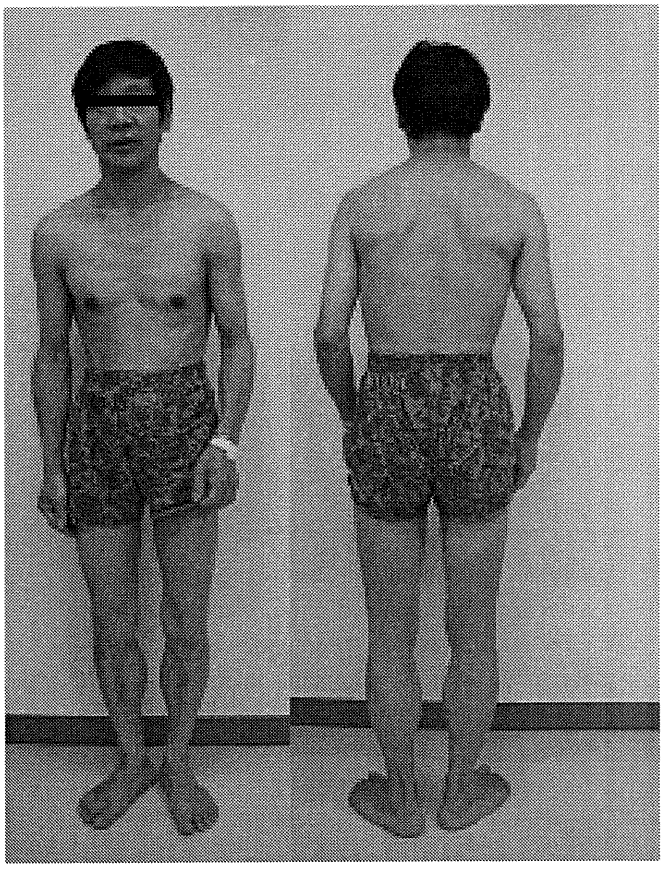

Figure 1. A photograph of the patient.

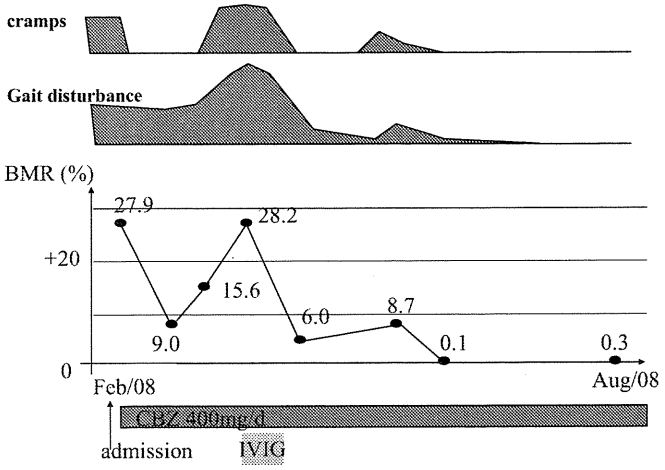

Figure 2. Serial monitoring of basal metabolic rates. We serially monitored the patient's basal metabolic rate (BMR) using an automatic integrated system for breath analysis (FUDAC-77), and found that the clinical symptoms fluctuated in tandem with the BMR. BMR: basal metabolic rate, CBZ: carbamazepine, IVIG: intravenous immunoglobulin (0.4 g/kg/d for 5 d)

Laboratory tests revealed that all the parameters, including the serum creatine kinase (CK) level and the thyroid hormone levels, were within the normal limits. Antibodies against VGKC and glutamic acid decarboxylase antibody were not detected in the serum.

An electromyogram (EMG) of the right biceps brachii, quadriceps and tibialis anterior muscles did not show myotonic discharge. Randomized doublet or triplet muscle waves were observed in the myokimic muscles of the left calf. A surface EMG study showed spontaneous and continuous motor-unit activity in the right biceps and the rectal abdominal muscles and the presence of M-wave afterdischarges in the upper extremities. Nerve conduction study was normal in the upper extremities, but it could not be assessed in the tibial nerves because of muscle cramps. Brain MRI and electroencephalography (EEG) showed no obvious abnormal findings. CT of the muscles showed hypertrophy of the calf muscles.

The BMR was measured at 9 a.m. while the patient was at rest and before breakfast, using an automatic integrated system for breath analysis (FUDAC-77, Fukuda Denshi, Tokyo, Japan). The BMR was 27.9% higher than the upper limit of the normal range for men in their 50s.

IS was diagnosed on the basis of the characteristic findings noted on the EMG, and the patient was administered oral carbamazepine (CBZ: 400 mg/d). The frequency of muscle cramps was reduced with the treatment. Furthermore, the BMR was reduced to 9.0% higher than the upper limit of the normal range. However, the gait disturbance did not improve. Shortly thereafter, the patient's symptoms deteriorated once again, and despite CBZ treatment, he frequently experienced muscle cramps all over his body, both during the day and at night. As was expected with the exacerbation of the symptoms, the BMR was increased to 28.2% higher than the upper limit of the normal range.

We initiated intravenous immunoglobulin (IVIG) therapy (0.4 g/kg/d for 5d). The patient's symptoms improved with IVIG, and the BMR was normalized and maintained for at least 6 months (Fig. 2).

Discussion

We present the case of a patient with chronic fluctuating symptoms of IS, not accompanied by any hormonal disease. The BMR was serially assessed, and it was found that the patient's clinical symptoms fluctuated in tandem with the BMR (Fig. 2).

The BMR is associated with many factors: age, sex, race, and thyroid hormone level (3). The major factors causing an increase in the BMR are hormonal disease and physiological factors; pregnancy, diet, a high environmental temperature, exercise, or a state of excitement (3). When we measure the BMR, the observed value reflects the result of total oxygen consumption of the whole body. The oxygen consumption of the brain and muscles at rest is estimated to be 23 and 20% of that of the whole body, respectively. The oxygen consumption of muscles at exercise reaches maximally 60 times that at rest (4). In general, the BMR test is not used as an indicator of chronic muscle activity; however, secondary chronic muscle activity due to an underlying disease may cause fluctuation in the BMR.

It is reported that IS is sometimes accompanied with dis-

turbance of the central nervous system (CNS), such as Morvan syndrome (5) or limbic encephalitis (6). However, the findings of brain MRI and EEG in the present case suggested no accompaniment of such a CNS disease. The increasing value of BMR in our case mainly reflected the oxygen consumption of muscles, not that of the brain.

In 1961, Isaacs first reported the cases of patients with acute-phase IS, whose BMR was elevated because of continuous or spontaneous muscle fiber activity, but was normalized with treatment (1). However, at that time, serial monitoring of the BMR was not performed because the methods available were complicated.

A closed-circuit respiratory device has been used to calculate the BMR (3). In the method that has traditionally been used to determine the BMR, the patient is required to breathe through the mouth into the analyzer for 6 minutes while at rest and before breakfast, and a skilled medical technologist analyzes the resting end-respiratory volumes for 6 minutes and manually draws a straight line to calculate the BMR.

Recently, an automatic integrated system for breath analysis (FUDAC-77) has been developed; this device automatically calculates the correct BMR by application of the method of least squares (a straight line experiment) (7), and remarkably facilitates its monitoring.

Anti-convulsion drug treatment (1), IVIG therapy (8), and plasma exchange (9) are reported to be effective modalities for IS patients; however, no study thus far has performed an objective therapeutic evaluation of the parameters that reflect the symptoms, such as the BMR. The condition of IS patients is reflected in real time in the BMR.

In the present case, CBZ treatment reduced spontaneous muscle activities, i.e., painful cramps. The BMR was reduced in tandem. However, the gait disturbance and posture did not improve because of completely uncontrolled continuous muscle fiber activities. Spontaneous and continuous muscle fiber activities were finally controlled by IVIG treatment.

Improvement shown by patients treated with immunomodulatory treatments is observed neurophysiologically, but quantitative assessment is also necessary. Serial BMR monitoring is a well-tolerated, quantitative assessment for IS patients with such a fluctuating course.

Acknowledgement

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症例報告
Case Report

特発性中脳水道狭窄症による閉塞性水頭症に対するV-Pシャント術の1年後から急速に進行するparkinsonismを呈した1例

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Rapidly Progressive Parkinsonism that Developed One Year after Ventriculoperitoneal Shunting for Idiopathic Aqueductal Stenosis: A Case Report

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Yuji Tanaka*, Isao Hozumi*, Takashi Inuzuka*

Abstract

A 46-year-old woman was diagnosed with having idiopathic aqueductal stenosis for which she underwent ventriculoperitoneal (V-P) shunting. One year after the surgery, she developed acute parkinsonism and sylvian aqueduct syndrome. Brain magnetic resonance imaging (MRI) did not reveal any signs of hydrocephalus and fluorodopa positron emission tomography (PET) did not reveal any decrease in accumulation of fluorodopa at the striatum. On admission, the Unified Parkinson Disease Rating Scale (UPDRS) (Part III) score was 30 points. The preliminary diagnosis was parkinsonism associated with V-P shunting: therefore, the levodopa dosage was increased from 200mg/day to 600mg/day. Thereafter, the symptoms of parkinsonism and the sylvian aqueduct syndrome markedly improved, and the UPDRS (Part III) score decreased. If such a patient presents without signs of hydrocephalus or shunt malfunction, dopaminergic medication should be used as the initial treatment.

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Key words：parkinsonism, ventriculoperitoneal shunt, idiopathic aqueductal stenosis, fluorodopa-positron emission tomography, levodopa

はじめに

水頭症治療のV-Pシャントによる稀な合併症として，parkinsonismが報告されている[1-15]。V-Pシャントによってparkinsonismをきたす原因としては，シャント機能不全による頭蓋内圧上昇[16]のほかに，頭蓋内圧の変動が原因として推測されている[1,9,12]。治療に関しては，既報告例の多くでlevodopaが有効であり，症状改善後にはlevodopaの漸減中止が可能になることが多い[1-5,7-10,13-15]。今回われわれは，特発性中脳水道狭窄症による閉塞性水頭症に対しV-Pシャント術を施行した1年後から急速に進行するparkinsonismを呈し，levodopaが奏功した症例を経験したので報告する。

Ⅰ．症　例

〈患　者〉46歳，女性

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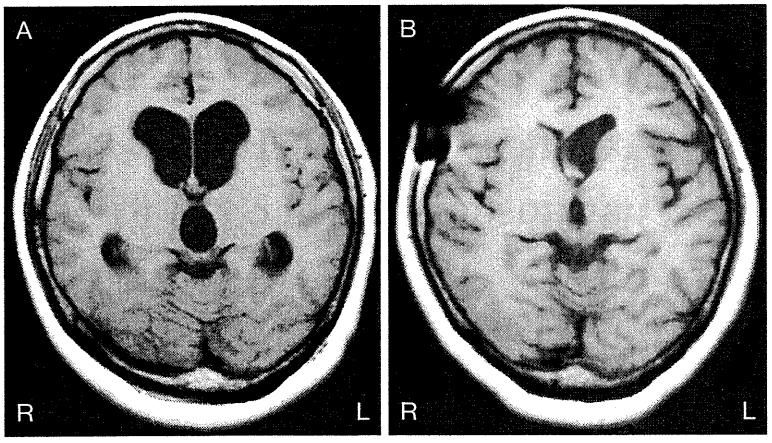

Fig. 1
A: Brain T_1-weighted axial magnetic resonance (MR) image (repetition time [TR], 400 ms; echo time [TE], 13 ms) obtained before V-P shunting shows obstructive hydrocephalus caused by idiopathic aqueductal stenosis. **B**: Brain T_1-weighted MR image (TR 405 ms, TE 15 ms) after V-P shunting for obstructive hydrocephalus.

主　訴　全身が動かしにくい，立てない，歩けない

既往歴　片頭痛（10歳時から）

家族歴　特記すべきことなし

現病歴　200X年11月初旬から，頭痛が出現し徐々に増強したため某病院脳神経外科を受診した。頭部MRIで両側側脳室～第3脳室の拡大を認め（**Fig. 1 A**），特発性中脳水道狭窄症と診断，当時同院での第1選択治療法であったV-Pシャント術を施行された。術後，症状，画像所見は改善し（**Fig. 1 B**），その後シャント圧は16 cmH_2Oで変更なく，日常生活や仕事を問題なく行っていた。

200X＋1年11月頃から，めまい，複視が出現し，徐々に悪化した。また，表情が乏しく，上肢の振戦，下肢の動かしにくさなどが出現し，起立歩行が困難となった。自分で食事がとれず，ほとんどしゃべれない状態となり，同年12月28日同院に入院した。頭部MRIで脳室の拡大は認めなかったためV-Pシャントの閉塞はないと考えられた。しかしその後も症状が続くため，精査加療目的で200X＋2年6月9日，当科に転院した。

入院時現症　身長158 cm，体重52 kg，体温36.8°C，血圧109/72 mmHg，脈拍79/min。表在リンパ節腫大は認めず，扁桃腺部に発赤・腫張は認めなかった。心音，呼吸音に異常なく，腹部は平坦かつ軟であった。皮疹は認めなかった。

神経学的所見では，意識は清明で，顔貌は仮面様で膏顔であった。脳神経領域では，両側眼球が間欠的に輻輳・開散を繰り返すいわゆる輻輳痙攣を認め，両側眼球の外転および上転制限がみられた。また，上眼瞼後退（Collier徴候）があり，Myerson徴候，単調なしゃべり，小声を認めた。運動系では，頸部・四肢筋力の軽度低下（徒手筋力テスト4レベル，び漫性），筋トーヌスは頸部・四肢に強剛，両下肢に痙性を認めた。また，右上下肢の安静時振戦があり，両側膝関節と足関節には廃用性変化と思われる拘縮を認めた。動作は緩慢で，起立・歩行，寝がえりは困難であった。深部腱反射は両上肢で亢進しており，右上肢病的反射を認めた。感覚系，自律神経系に明らかな異常は認めなかった。以上の所見から，中脳水道症候群としての眼症状，parkinsonism，錐体路徴候と考えられた。

入院時検査所見　検血・一般生化学検査では，明らかな異常は認めなかった。髄液検査では，蛋白の軽度上昇〔64 mg/dL（正常：＜45 mg/dL）〕を認めたが，培養検査，細胞診などで感染や腫瘍を示唆する異常所見は認めなかった。頭部MRIでは，右前頭部から右側脳室へのシャントがあり，右側脳室の狭小化，中脳水道の高度狭窄を認めた（**Fig. 2**）。拡散強調画像，T_1強調画像，T_2強調画像ではどこにも萎縮性変化や異常信号域はなく，造影効果は認めなかった。

シャント機能不全を疑い，シャント造影検査を施行した。まず，透視下でシャントバルブから脳室や腹腔へ造影剤を注入したが，抵抗なく投与することができた。次に，シャントバルブから脳室に造影剤を注入し頭部CTで経過を観察したが，造影剤はシャントを経由して腹腔へ流出した。これらの所見から，造影剤注入時に閉塞が解除された可能性は否定できないものの，明らかなシャント閉塞は認めず，中脳水道への造影剤の流出はないことから水頭症はシャント依存性であったと考えられた。シャントのflushing deviceからの髄液の戻りは不良であった。

Fluorodopa-PET画像では，両側基底核，黒質にfluorodopaの集積を認め，明らかな集積低下，左右差は認めなかった（**Fig. 3**）。MIBG（metaiodobenzylguanidine）心筋シンチグラフィでは集積低下を軽度に認めた［H/M（E）2.17，H/M（D）1.81〔基準値：H/M（E）2.34±0.36，H/M（D）2.49±0.40〕］。

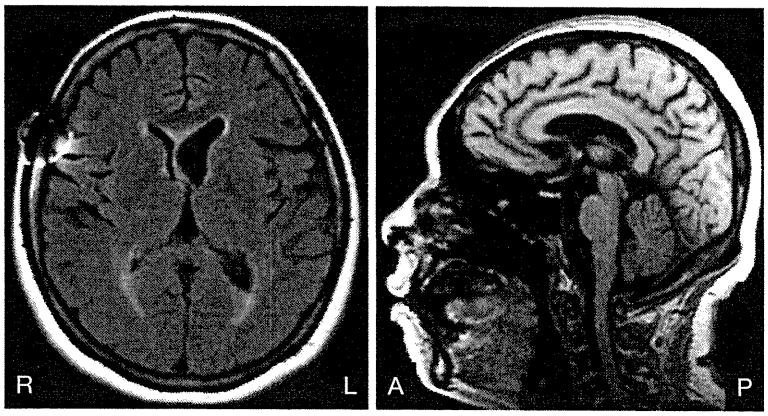

Fig. 2
Brain magnetic resonance (MR) image shows the V-P shunt via the anterior horn of the right ventricle, and fluid-attenuated inversion recovery (FLAIR) axial image (repetition time〔TR〕, 6,000 ms; echo time〔TE〕, 120 ms) shows the right slit ventricle. The aqueductal stenosis is evident on the T_1-weighted sagittal image (TR 9 ms, TE 4 ms).

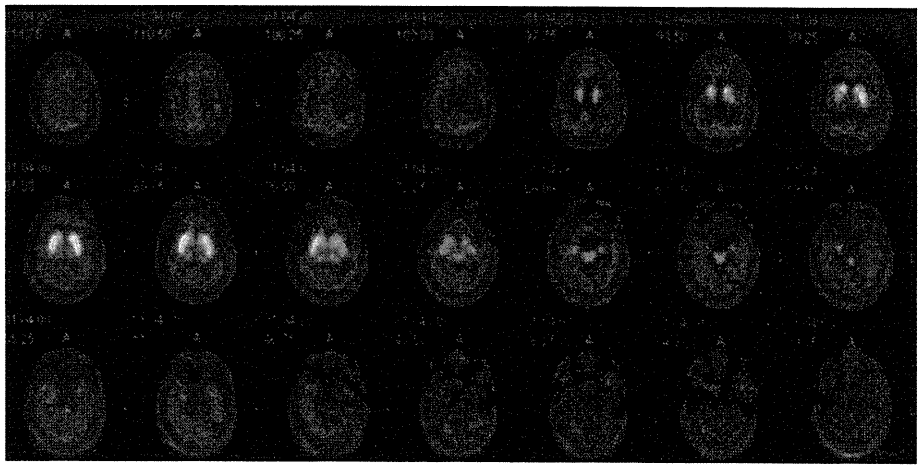

Fig. 3
Fluorodopa-PET did not show any specific decrease in accumulation at the striatum.

入院後経過 (Fig. 4)　前医で levodopa 200 mg/day を投与したが，明らかな効果は認めなかった。また，シャント機能不全が疑われたためシャント圧を 12〜18 cmH_2O で調整したが，症状の改善は認めなかった。

当科転院時，起立・歩行，寝がえりは困難な状態で，UPDRS（Unified Parkinson's Disease Rating Scale）(part Ⅲ) は 30 点であった。中脳水道狭窄症による閉塞性水頭症に対する V-P シャントに伴う parkinsonism と考え，既報告例では levodopa が奏功することから levodopa を 200 mg/day から 600 mg/day に増量した。その後，眼球運動障害，輻輳痙攣などの中脳水道症候群や，仮面様顔貌，小声，頸部・四肢の強剛，右上下肢の振戦などの parkinsonism は軽快し，UPDRS (part Ⅲ) は 18〜19 点に減少した。さらなる改善を期待し levodopa を 900 mg/day に増量したが，副作用の嘔気が出現したため 600 mg/day に戻した。寝がえり，座位が自分でできるようになったが，両下肢の関節拘縮のため歩行は困難であった。症状は改善したため，リハビリテーションを目的として前医に転院した。その後，他院で V-P シャ

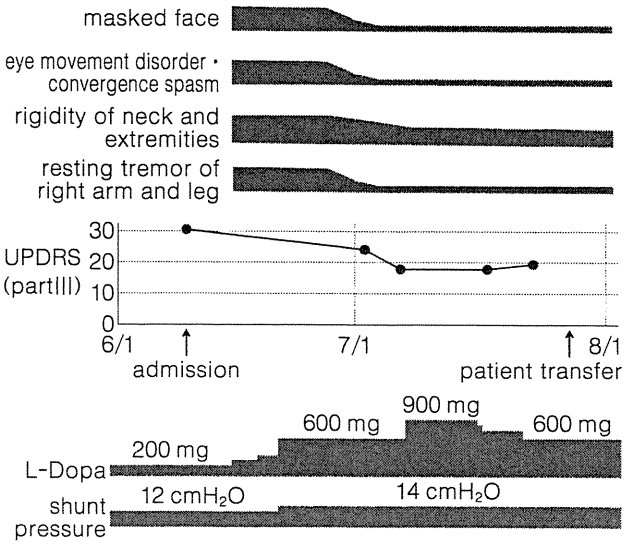

Fig. 4　Clinical course
On admission, the patient presented with a masked face, ocular motor dysfunction, convergence spasms, rigidity, and tremors. The UPDRS (Unified Parkinson Disease Rating Scale) score (Part III) was 30. After the levodopa dosage was increased to 600 mg/day, symptoms of parkinsonism and sylvian aqueduct syndrome markedly improved, and the UPDRS score (Part III) decreased.

ントに関連したparkinsonismの再発予防を目的に，より生理的な髄液循環を保つことができる第3脳室底開窓術を受け，200X＋3年5月にはlevodopaを300 mg/dayまで減量しているが，症状の再燃はみられない。

Ⅱ．考　　察

中脳水道狭窄症に対する治療としてV-Pシャント術が行われ，合併症としてparkinsonismを呈することが稀に報告されている。中脳水道狭窄症による閉塞性水頭症に対するV-Pシャントに関連したparkinsonismに関する報告は，今までに本例を含めて29例ある[1-15]。中脳水道狭窄症の原因の多くは特発性であるが，腫瘍による報告もある[16-18]。

中脳水道狭窄症による閉塞性水頭症に対するV-Pシャントに関連したparkinsonismに伴う神経症状には特徴があり，中脳水道症候群などを含む中脳障害による症状を伴うことが多い。Cinalliら[11]によるとV-Pシャントの機能不全によって，動作緩慢，構音障害，振戦，無動無言などの錐体外路症状（28.6%）のほかに，眼症状（100%）として上方注視麻痺，輻輳麻痺，眼球運動障害，上眼瞼後退など，錐体路症状（32.1%）として深部腱反射亢進，筋トーヌス亢進などを認め，そのほかに記憶障害（17.9%），意識障害（57.1%）を伴うことがある。本例でも，錐体外路症状に加え，中脳水道症候群としての眼症状，錐体路徴候を伴っていた。同疾患では振戦，固縮などの典型的なparkinsonismが出現する[12]ため，Parkinson病との鑑別が重要である。本例では，発症から1年以上にもわたりlevodopaを継続していることや，MIBG心筋シンチグラフィで軽度の集積低下を示したこと，明らかなシャント不全をとらえられていない点において，Parkinson病の可能性も疑われる。しかし一方で，発症から症状の進行が急速であることや，輻輳痙攣・眼球運動障害などの中脳水道症候群を伴っていること，fluorodopa-PETで正常を示したことから，Parkinson病の可能性はむしろ低いと考えられた。

Zeidlerら[8]の9例の報告によると，parkinsonismの発症年齢は7～57歳，parkinsonism発症までにシャントを留置・交換した回数は0～多数回，水頭症診断からparkinsonism発症までの期間は9カ月～24年，parkinsonism発症時の水頭症の有無に関しては9例中4例で水頭症は認めないという結果であった。症状出現時に画像上水頭症を認めないことやシャント留置後あるいは交換後しばらく経過した後に出現することがあるため，診断には同疾患を積極的に疑う必要があると考えられた。

中脳水道狭窄症による閉塞性水頭症に対するV-Pシャントに関連したparkinsonismの発症機序として，いくつかの説が存在している。1つには，シャント閉塞などのシャント機能不全による頭蓋内圧の亢進である。頭蓋内圧が上昇することによって中脳の圧迫，虚血をきたし，可逆性に黒質線条体路を含む中脳の障害をきたすとされている[16]。あるいは，黒質線条体路が第3脳室近傍を走行していることから，第3脳室の拡大によって圧迫や虚血をきたしparkinsonismを呈すると考えられている[9]。一方で，シャント機能不全に対してシャントを交換した後にparkinsonismが出現し，水頭症を伴わない症例も散見される[8,15,17-19]。そのため，頭蓋内圧上昇以外の要因として，頭蓋内圧の変動がもたらす神経路の圧迫と解放によって，特に第3脳室近傍での黒質線条体路に可逆性の障害が生じるのではないかと推察されている[1,9,12]。本例では，水頭症を画像的に認めずシャント閉塞もなかったことから，なんらかの原因によって頭蓋内圧の変動があり，第3脳室周囲で障害をきたしたのではないかと推測する。

頭蓋内圧が変動した原因に関しては，推測にすぎないが，右側脳室の狭小化を認めることからslit like ventricle syndrome（SVS）をきたしていたからかもしれない。SVSでは，縮小した脳室壁によってシャントの先端がtrapされて閉塞し，さらにシャント閉塞による脳室内圧の上昇によって脳室腔が拡大しtrapされたシャント先端が開放される，いわゆるon-off mechanismによって頭蓋内圧が間欠的に変動すると考えられている[19]。また，SVSにおいて長期のシャント留置に起因する脳組織側のcomplianceの低下によって脳室拡大がみられないこともあるため，注意が必要である[19]。

同疾患におけるfluorodopa-PET所見に関しては1例で報告があり，尾状核，被殻の血流の低下を定量的に認めたというものである[3]。本例において定性的には明らかな集積低下は認めなかったが，今後の症例の蓄積が必要と考えられる。本例ではlevodopa治療が有効であったにもかかわらず，fluorodopa-PETで線条体のドパミン神経終末の取り込みに異常を認めなかった。このことは，本例でのparkinsonismの原因が，神経終末の芳香族アミノ酸脱炭酸酵素活性やドパミン保持能の異常ではなく，シャント不全によって生じた黒質線条体路への機械的機序を原因とするドパミン欠乏にあることを示唆する所見かもしれない。

治療に関しては，水頭症がある場合はその治療をまず行い，症状が遷延する場合にlevodopaが有効であるとする報告が多い[1-5,7-10,13-15]。多くの症例でlevodopa投

与後に症状は改善し，その後漸減中止することができる。本例でも levodopa を増量後，明らかに parkinsonism の改善を認めた。ただ，輻輳痙攣や眼球運動障害に対して levodopa が有効であるという報告は今までになく，本症例で改善した機序や原因に関しては明らかでない。

ま と め

特発性中脳水道狭窄症による閉塞性水頭症に対する V-P シャント術から 1 年後に，急速に進行する parkinsonism を呈した 1 例を経験した。levodopa 投与によって parkinsonism は改善した。画像上水頭症を認めない場合でも同疾患を疑い，levodopa の投与を考慮する必要がある。

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Antibodies to the $GABA_B$ receptor in limbic encephalitis with seizures: case series and characterisation of the antigen

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Summary

Background Some encephalitides or seizure disorders once thought idiopathic now seem to be immune mediated. We aimed to describe the clinical features of one such disorder and to identify the autoantigen involved.

Methods 15 patients who were suspected to have paraneoplastic or immune-mediated limbic encephalitis were clinically assessed. Confocal microscopy, immunoprecipitation, and mass spectrometry were used to characterise the autoantigen. An assay of HEK293 cells transfected with rodent $GABA_{B1}$ or $GABA_{B2}$ receptor subunits was used as a serological test. 91 patients with encephalitis suspected to be paraneoplastic or immune mediated and 13 individuals with syndromes associated with antibodies to glutamic acid decarboxylase 65 were used as controls.

Findings All patients presented with early or prominent seizures; other symptoms, MRI, and electroencephalography findings were consistent with predominant limbic dysfunction. All patients had antibodies (mainly IgG1) against a neuronal cell-surface antigen; in three patients antibodies were detected only in CSF. Immunoprecipitation and mass spectrometry showed that the antibodies recognise the B1 subunit of the $GABA_B$ receptor, an inhibitory receptor that has been associated with seizures and memory dysfunction when disrupted. Confocal microscopy showed colocalisation of the antibody with $GABA_B$ receptors. Seven of 15 patients had tumours, five of which were small-cell lung cancer, and seven patients had non-neuronal autoantibodies. Although nine of ten patients who received immunotherapy and cancer treatment (when a tumour was found) showed neurological improvement, none of the four patients who were not similarly treated improved ($p=0\cdot005$). Low levels of $GABA_{B1}$ receptor antibodies were identified in two of 104 controls ($p<0\cdot0001$).

Interpretation $GABA_B$ receptor autoimmune encephalitis is a potentially treatable disorder characterised by seizures and, in some patients, associated with small-cell lung cancer and with other autoantibodies.

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Introduction

Synaptic plasticity is an essential property of neurons that is involved in memory, learning, and cognition. Plasticity depends on the interactions of ion channels and synaptic receptors, including excitatory glutamate NMDA receptors and AMPA receptors, and inhibitory $GABA_B$ receptors.[1,2] In animal models, pharmacological or genetic disruption of these receptors result in seizures and changes in memory, learning, and behaviour.[3–6] Immune responses against these receptors would therefore be expected to result in similar symptoms. Indeed, two disorders, one associated with antibodies to extracellular epitopes of the NR1 subunit of NMDA receptors[7] and the other associated with antibodies to GluR1/2 subunits of AMPA receptors,[8] have recently been identified. These disorders result in encephalitis with prominent psychiatric, behavioural, and memory problems, often accompanied by seizures. The antibodies implicated in these two autoimmune disorders cause a decrease in the amounts of the target receptor in cultured neurons, suggesting the antibodies are pathogenic. Patients with these syndromes often respond to treatment, and in some patients the immune response occurs as a paraneoplastic event. These findings, as well as the prevalence of some of these disorders (eg, anti-NMDA receptor encephalitis[7,9,10]), have raised the possibility that other syndromes in which memory and behaviour are impaired and seizures are common could also be immune mediated. In some of these syndromes an immune-mediated pathogenesis is suggested by the clinical response to immunotherapy, the CSF and MRI findings suggesting limbic encephalitis, and the detection of antibodies to unknown neuronal cell-surface antigens. We aimed to identify the autoantigen involved in a new disorder that has most of these suggestive features.

Methods

Study population

Between January, 2006, and June, 2009, we studied 410 patients with encephalitis suspected to be paraneoplastic or immune mediated. These patients were seen by the authors or by clinicians at other institutions and the patients' sera and CSF were sent for analysis of novel autoantibodies to the Center for Paraneoplastic Disorders at the University of Pennsylvania (PA, USA). We identified autoantibodies in the serum or CSF of 357 patients, including 275 patients with antibodies to NMDA receptors (including 75 patients previously reported[7]), 27 with antibodies to voltage-gated potassium

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channels, 19 with antibodies to glutamic acid decarboxylase 65 (GAD65), 15 with antibodies to AMPA receptors (including ten patients previously reported[8]), 11 with anti-Ma2 antibodies, eight with anti-HuD antibodies, and two with anti-CRMP5 antibodies (patients each had only one of these antibodies). Of the remaining 53 patients, 15 had serum or CSF antibodies with reactivity against neuronal cell-surface antigens predominantly in the neuropil of sectioned rat brain. Because of the serum and CSF findings and the response to immunotherapy and cancer treatment of the first of these patients to be clinically and immunologically studied (the index patient), we focused on these 15 patients. Clinical information about the patients was obtained by the investigators or provided by referring physicians. Patients were said to have neurologically improved if they were able to function independently or with little assistance when they returned home. Control samples were CSF or serum from 104 patients, including 91 randomly selected by use of an online random integer generator from the 410 individuals with encephalitis and 13 who had syndromes associated with GAD65 antibodies and who were not included in the group of 410 patients. These 13 patients were seen either by the study investigators or their serum, CSF, and clinical information were sent from other institutions to the primary investigator (JD) for study of disorders of unknown cause.

For the **random integer generator** see http://www.random.org/integers/

Studies were approved by the University of Pennsylvania Institutional Review Board, and written informed consent was obtained from all patients or their representatives.

Procedures

To establish whether serum or CSF contained antibodies to neural tissue, sagittal sections were taken from the brains of adult female Wistar rats; brains had been immersed in 4% paraformaldehyde at 4°C for 2 h, cryoprotected with 40% sucrose for 24 h, and snap frozen in chilled isopentane. Paraffin-embedded tumour tissue from patients was deparaffinised and the antigens retrieved.[11] 7 μm thick frozen (or 4 μm paraffin) tissue sections were incubated with 0·3% hydrogen peroxide for 20 min, with 10% goat serum in PBS for 1 h, and with patients' or control individuals' serum (1:250) or CSF (1:10) or a guineapig polyclonal antibody against an intracellular epitope of the $GABA_{B1}$ receptor (1:200; AB2256, Millipore, Billerica, MA, USA) at 4°C overnight. After using the appropriate secondary antibodies (all 1:2000, diluted in PBS with 5% goat serum), labelling was developed with the avidin–biotin–peroxidase method. Results were photographed under a fluorescence microscope using Zeiss Axiovision software (Zeiss, Thornwood, NY, USA).

Immunohistochemistry with human tissue (small-cell lung cancer) was done by use of IgG purified from patients' or control individuals' sera and labelled with biotin.[12] No secondary antibody was needed, thus avoiding background labelling caused by other human IgG in the tissue.

To identify the antigen and its localisation on cells in vitro, rat hippocampal neuronal cultures were prepared as reported previously.[13] Live neurons grown on coverslips were incubated for 1 h at 37°C with patient or control serum (final dilution 1:200) or CSF (1:10). After removing the media and washing with PBS, neurons were fixed with 4% paraformaldehyde and were made permeable with 0·1% Triton X-100 (Sigma-Aldrich, St Louis, MO, USA). Neurons were single or double immunolabelled with a guineapig polyclonal $GABA_{B1}$ receptor antibody (1:200), followed by the corresponding Alexa Fluor secondary antibodies (1:2000; Molecular Probes, Invitrogen, Eugene, OR, USA). Results were photographed as detailed above.

Rat hippocampal neurons were grown in 100 mm wells (10^6 neurons per well) and incubated at 37°C with filtered serum (1:500) for 1 h. Neurons were then washed with PBS, lysed with buffer (sodium chloride 150 mM, EDTA [edetic acid] 1 mM, tris(hydroxymethyl) aminomethane [Tris]-hydrochloric acid 100 mM, deoxycholate acid 0·5%, 1% Triton X-100, pH 7·5) containing protease inhibitors (P8340; Sigma-Aldrich), and centrifuged at $16·1 \times 10^3$ gravities for 20 min at 4°C. The supernatant was retained and incubated with protein A/G agarose beads (20423; Pierce, Rockford, IL, USA) overnight at 4°C, centrifuged, and the pellet containing the beads with patients' antibodies bound to the target cell-surface antigen was washed with PBS, aliquoted, and kept at −80°C. A 25 μL aliquot of this pellet was resuspended in Laemmli buffer, boiled for 10 min, separated in 4–15% sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE), and the proteins visualised with EZBlue gel staining (G1041; Sigma-Aldrich). Protein bands from the gels were cut and sent for mass spectrometry to the Proteomics Core Facility of the Genomics Institute at the Abramson Cancer Center (University of Pennsylvania, PA, USA). Protein bands were trypsin digested and analysed with a nanoLC/nanospray/LTQ mass spectrometer (Thermo Electron Corporation, San Jose, CA, USA) as reported previously.[14] Briefly, a 3 μL trypsin-digested sample was injected with autosampler (Eksigent, Dublin, CA, USA). The digested samples were separated on a 10 cm C18 column, using nanoLC (Eksigent) with a 200 μL/min flow rate, and a 45 min gradient. Online nanospray was used to spray the separated peptides into a linear trap quadrupole, and raw data were obtained with Xcalibur software (Thermo Scientific, Waltham, MA, USA). The raw data files were searched against the National Center for Biotechnology Information and Swiss-Prot (Swiss Institute of Bioinformatics, Basel, Switzerland) databases with Mascot (Matrix Science, Boston, MA, USA). The cutoff score for definite protein identification was 70 or more.

After characterisation of the antigen, frozen samples of the pellets were separated in SDS-PAGE, transferred to nitrocellulose (162-0115; Bio-Rad, Hercules, CA, USA),

and blotted with the polyclonal antibodies against $GABA_{B1}$ (1:2000) or $GABA_{B2}$ (1:1000) receptor subunits. The reactivity was developed by use of biotinylated anti-guineapig IgG made in goat (1:2000; Vector Laboratories, Burlingame, CA, USA) and the avidin–biotin–peroxidase diaminobenzidine method.

To determine the sensitivity and specificity of patients' antibodies for the $GABA_B$ receptor, we used a semi-quantitative confocal microscopy analysis similar to that used for other synaptic receptors.[7,8] Live rat hippocampal neurons cultured for 14–21 days in vitro were incubated with patients' CSF (1:30 dilution in Neurobasal B27 medium; GIBCO, Invitrogen, Carlsbad, CA, USA) for 24 h, washed in PBS, fixed in paraformaldehyde (4% paraformaldehyde, 4% sucrose in PBS) for 5 min, made permeable with 0·25% Triton X-100 for 10 min, and blocked with 5% normal goat serum for 1 h. Neurons were incubated with a guineapig polyclonal antibody against an intracellular epitope of the $GABA_B$ receptor (1:1000; Invitrogen) and a mouse monoclonal antibody against the presynaptic marker Bassoon (1:200; Stressgen, Victoria, BC, Canada), washed, and incubated with the appropriate fluorescent-conjugated secondary antibodies (1:1000, Molecular Probes).

A laser-scanning confocal microscope (Leica TCS SP2; Leica, Deerfield, IL, USA) was used to obtain images. For each image, laser light levels and detector gain and offset were adjusted so that no pixel values were saturated. Images were automatically segmented with an iterative thresholding approach that finds maxima of fluorescence intensity,[15] and areas of interest containing dendrites were selected, and the number of individual clusters along dendrites was quantified by use of ImageJ interactive software (Research Services Branch, National Institute of Mental Health, Bethesda, MD, USA) as described previously.[7,8] The colocalisation of clusters

	Sex	Age (years)	Tumour by imaging or pathology	Presenting symptoms	Other clinical and immunological features
Patient					
1	Female	60	SCLC	Subacute onset of complex partial seizures, confusion, memory impairment	SIADH
2	Male	66	SCLC	Subacute onset of seizures, confusion, memory deficit, behavioural problems	N-type VGCC antibodies
3	Female	53	SCLC	Rapidly progressive memory deficits, abnormal sleeping habits, followed by frequent seizures (focal, secondarily generalised), confusion, decline in mental status leading to coma	Pruritic rash with initial weakness
4	Male	75	Mediastinal adenopathy	Subacute onset of seizures, confusion, memory deficit, psychosis, encephalitis; died soon after presentation, before definitive diagnosis or treatment	Poor respiratory status, refused intubation
5	Male	68	Neuroendocrine tumour of the lung	Subacute onset of seizures, status epilepticus, confusion, memory deficit	..
6	Female	43	CT and FDG/PET negative	Subacute onset of secondarily generalised tonic-clonic seizures, confusion, bizarre behaviours, delusions, paranoia, memory impairment	N-type VGCC antibodies
7	Male	69	CT and FDG/PET negative	Subacute onset of seizures, status epilepticus, severe encephalopathy, severe memory deficit, confusion	History of bipolar disorder
8	Female	24	CT and FDG/PET negative	Subacute onset of seizures, status epilepticus, confusion, memory deficit, fever; required intubation and ventilation owing to poor level of consciousness and airway protection	N-type VGCC antibodies
9	Male	63	CT and FDG/PET negative	Subacute onset of seizures, confusion, memory deficit, paranoia, psychosis, gustatory hallucinations	TPO and GAD65 antibodies; hypothyroidism and type 2 diabetes mellitus
10	Female	45	Benign ovarian mass	Subacute onset of complex partial and generalised seizures, confusion, short-term memory deficits	TPO and thyroglobulin antibodies in serum (not in CSF); no endocrinopathy
11	Female	62	CT chest, abdomen, pelvis negative	Subacute onset of generalised seizures, confusion, memory deficit, decreased level of consciousness, fluent aphasia, abnormal orolingual movements	..
12	Male	29	CT and FDG/PET negative	Subacute onset of temporal lobe and generalised tonic-clonic seizures, confusion, memory deficits; no cognitive deterioration	Childhood seizures
13	Female	30	CT and FDG/PET negative	3-month history of severe memory deficit, confusion, followed by seizures (generalised, subclinical)	GAD65 antibodies without endocrinopathy
14	Male	69	SCLC	Subacute onset of generalised tonic-clonic seizures, worsened short-term memory deficit, confusion	Mild short-term memory deficit from past history of subarachnoid haemorrhage
15	Male	70	SCLC	Subacute onset of seizures (partial motor and generalised); severe short-term memory loss, confusion, confabulation, visual hallucinations, disorientation, agitation	GAD65, TPO, and SOX1 antibodies; no endocrinopathy
Control					
1	Female	63	CT and FDG/PET negative	1 year progression of cerebellar ataxia; normal mental status, no seizures, no muscle spasms or stiffness	GAD65 antibodies, adult-onset insulin-dependent diabetes mellitus
2	Female	61	CT and FDG/PET negative	6 week history of gait disturbance, lower extremity myoclonus and stiffness; dysphagia, dysarthria, nystagmus, left gaze palsy. No seizures or cognitive symptoms	GAD65, TPO, and thyroglobulin antibodies (mild thyroid dysfunction)

SCLC=small-cell lung cancer. SIADH=syndrome of inappropriate antidiuretic hormone. VGCC=voltage-gated calcium channel. FDG=fluorodeoxyglucose. TPO=thyroid peroxidase. GAD65=glutamic acid decarboxylase 65. SOX1=sex determining region Y-box 1.

Table 1: **Demographic features and symptoms**