patients described since the first description in 1787.¹ In most cases, agenesis is unilateral, with only 26 reported cases of bilateral agenesis. Most of the early cases were discovered by cadaver dissection. In 1972 Boudin reported the first living patient with bilateral internal carotid artery agenesis, based on an angiographical diagnosis.² There is no agreement on the development of the common carotid artery and its two branches, the internal carotid artery and the external carotid artery. The two theories for the embryogenesis of these arteries are that the common carotid artery and the proximal parts of the internal carotid artery and external carotid artery arise together from the third aortic arch; or that only the proximal part of the internal carotid artery arises from the third aortic arch, and the common carotid and external carotid arteries arise from the aortic sac.⁴

Agenesis and hypoplasia should be differentiated. Agenesis is the complete developmental failure of an organ and its primordium, whereas hypoplasia is the incomplete development of a structure. The primordial internal carotid artery is well defined by the fourth embryonic week, whereas the skull base does not form until the fifth to sixth weeks of fetal life. Therefore, if the embryonic primordium of the internal carotid artery fails to develop (agenesis), no internal carotid artery is present when the skull base is formed, and no carotid canal develops. By contrast, a relatively mild or relatively late insult occurring in the course of development of the skull base portion of the internal carotid artery will result in a hypoplastic internal carotid artery within a hypoplastic carotid canal.³ Therefore, agenesis and hypoplasia of the internal carotid artery can be differentiated by the demonstration of the carotid canal in the skull base. Some authors have confused agenesis with hypoplasia, and carotid canals or internal carotid arteries were found in their patients.

The anterior cerebral circulation is most commonly supplied through enlarged basilar and posterior communicating arteries in patients with agenesis of the internal carotid artery. Occasionally an abnormal trans-sellar anastomosis or an anastomosis between the external carotid and intracranial systems provide collateral flow. Brain CT or MRI can demonstrate the enlarged abnormal vessels. In our patient, MRI showed abnormal dilatation of the basilar artery and absence of the internal carotid arteries. Therefore, MRI is a useful diagnostic tool for this disease. Especially, MR angiography can show the further relation between anterior and posterior cerebral circulation clearly. This is the first report to describe the value of MR angiography.

Agenesis of the internal carotid artery may mainly cause cerebrovascular disease. Previous manifestations included subarachnoid haemorrhage in seven patients, cerebral ischaemia in five, seizure in three, brain tumour in two, intracerebral haemorrhage in one, chronic subdural haematoma in one, syncope in one, cancer in one, and cardiac anomaly in one. Ours is the first patient to present with intracerebellar haemorrhage. The haematoma was located in the subcortical portion of the cerebellar hemisphere, and there was no lesion near the haematoma. Spontaneous haemorrhage of the cerebellum usually occurs in the dentate nucleus region. In this case the location of the haematoma was unusual, suggesting that the haemor-

rhage might be caused by haemodynamic stress.

The prognosis for internal carotid artery agenesis is unknown, because of the lack of detail in previous reports. Our patient died of heart failure, but no necropsy was permitted. Her death may have been related to the recurrence of cerebrovascular disease.

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- 1 Tode. *Medizinisch chirurgische bibliothek (Kopenhagen)* 1787;10:408. Cited by: Fisher AGT. A case of complete absence of both internal carotid arteries, with a preliminary note on the developmental history of the stapodial artery. *J Anat* 1914;48:37-46.
- 2 Boudin G. Bilateral aplasia of the internal carotid artery. *Rev Neurol (Paris)* 1972;127:329-40.
- 3 Quint DJ, Silbergleit R, Young WC. Absence of the carotid canals at skull base CT. *Radiology* 1992;182:477-81.
- 4 Lie TA. *Congenital anomalies of the carotid arteries*. Amsterdam: Excerpta Medica, 1968: 44-9.

Possible distinct pathogenesis in low responder myasthenia gravis: association of soluble interleukin-2 receptor with acetylcholine receptor antibody titre or abnormal thymus

In myasthenia gravis there is an increase in soluble interleukin-2 receptor (sIL-2R), which is associated with cellular immunity. Confalonieri *et al*¹ showed that the concentration of sIL-2R correlated with the severity or the activity of the disease, and that there was no association of sIL-2R concentration with antibody to fetal calf acetylcholine receptor (AChR). On the other hand, Cohen-Kaminsky *et al*² reported a progressive decline of sIL-2R in myasthenia gravis after thymectomy which correlated with the clinical outcome. To elucidate the pathogenesis and cellular immunity in myasthenia gravis, we studied sIL-2R concentrations in 32 patients before immunosuppressive treatment.

All 32 patients (eight male and 24 female) participating in this study were older than 6 years (mean 31.7 (range 7 to 72) years at onset), because sIL-2R concentration has been reported to be higher in healthy infants under 6 years old than in adults.³ The number of patients with type I, IIa, IIb, or III myasthenia gravis, according to Osserman's classification, was 12, 10, five, and five respectively. The thymus was examined for abnormality by CT, and thymectomy was performed on 21 patients, including one whose thymus was atrophic. All thymuses were categorised histologically after removal, as thymoma, hyperplasia, atrophy, or normal. Patients' serum samples were frozen at -70°C until assayed for sIL-2R and antibody to AChR. The sIL-2R was measured by the cellfree interleukin-2 receptor bead-assay kit (T cell diagnosis C Ltd, Cambridge MA, USA) using two monoclonal antibodies directed against two different epitopes on IL-2R. The normal value of sIL-2R measured in serum samples obtained from 110 unrelated healthy controls was 390.7 (SD

101.7) U/ml. Samples were assayed in duplicate and the intra-assay coefficient of variance was 9.3%. Antibody to human AChR was measured by immunoprecipitation. The antigen used was human AChR purified from rhabdomyosarcoma cell line TE 671. The normal value (mean + 3SD) was 0.12 nM. Intra-assay coefficient of variance was 9.0%.

The sIL-2R correlated negatively with antibody titre to human AChR (figure; $r = 0.588$, $P < 0.01$). Thymic histology showed an association with sIL-2R concentration (one way ANOVA, $p < 0.025$), but the Osserman clinical type did not. The sIL-2R in patients with thymoma (317.2 (64.1) U/ml) was significantly lower than in the normal subjects, or patients with atrophic or normal thymus (535.7 (174.1) U/ml; Scheffe test, $P < 0.025$), but not significantly lower than in patients with hyperplasia (426.2 (126.6) U/ml). All four patients with a high concentration of sIL-2R (more than mean + 2SD) had a low AChR antibody titre (< 1 nM).

Some publications^{1,2} have shown a positive correlation between sIL-2R and disease activity in myasthenia gravis, which does not coincide with our result. It is also well established that patients with myasthenia gravis with thymic hyperplasia or thymoma have a higher titre of AChR antibody than patients with a normal thymus. According to our results of the negative correlation pattern of sIL-2R with AChR antibody titre and the association of sIL-2R with thymic abnormality in myasthenia gravis, it is not likely that sIL-2R is merely a T cell activation marker, because AChR antibody production is T cell dependent.

The problem is to decide what the pathogenic mechanism is in seronegative patients. Mossman *et al* showed that the immunoglobulin from seronegative patients with myasthenia gravis could induce impairment of chemical transmission at neuromuscular junctions in mice.⁴ Cohen-Kaminsky *et al* pointed out that the group of patients with myasthenia gravis with low AChR antibody titre seemed to represent a particular subgroup of the disease, which might be associated with a pathogenic mechanism involving AChR antibody produced in undetectable amounts but especially pathogenic antibody.² We previously reported that ocular myasthenia gravis had a different genetic background from generalised myasthenia gravis: the ocular type showed a low AChR antibody titre and no antinuclear antithy-

Correlation between sIL-2R and antibody titre to human AChR. Correlation was assessed in 28 patients in whom AChR antibody was detected. The concentrations of sIL-2R in four patients without AChR antibody were 475, 419, 785 and 516 U/ml.

roglobulin, antimicrosome, or antiskeletal muscle autoantibodies whereas the generalised type showed a high titre and incidence of autoantibodies including AChR antibody.⁵ Seronegative patients or those with low AChR antibody may form a low responder subgroup of myasthenia gravis distinct from the high responders, who show a high titre of AChR antibody.

Twelve patients (37.5%) were of the ocular type, which is higher than the incidence in the report of Confalonieri *et al.*¹ All subjects in Cohen-Kaminsky's report had generalised myasthenia gravis of type IIa or IIb.² Chiu *et al.*⁶ reported a difference in myasthenia gravis expression between Chinese and Caucasians. The characteristic population pattern in our study may be common to east Asians and may partly cause a different correlation between sIL-2R and disease activity.¹² The study of this characteristic population may lead to the elucidation of the pathogenesis of low responder myasthenia gravis.

We thank Ms Ichikawa (SRL, Tokyo, Japan) for technical assistance in detecting sIL-2R. The work was supported partly by Grant in Aid of Scientific Research No 04670604 from the Ministry of Education, Science, and Culture of Japan.

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- 1 Confalonieri P, Antozzi C, Cornelio F, *et al.* Immune activation in myasthenia gravis, soluble interleukin-2 receptor, interferon- γ and tumor necrosis factor- α levels in patients' serum. *J Neuroimmunol* 1993;48:33-6.
- 2 Cohen-Kaminsky S, Jacques Y, Aime C, *et al.* Follow-up of soluble interleukin-2 receptor levels after thymectomy in patients with myasthenia gravis. *Clin Immunol Immunopathol* 1992;62:190-8.
- 3 Komp DM, Shapiro E, McNamara J. Soluble interleukin-2 receptor in childhood non-Hodgkin's lymphoma. *Blood* 1988;71:1172-4.
- 4 Mossman S, Vincent A, Newsom-Davis A. Myasthenia gravis without acetylcholine-receptor antibody: a distinct disease entity. *Lancet* 1986;i:116-8.
- 5 Kida K, Hayashi M, Yamada I, *et al.* Heterogeneity in myasthenia gravis: HLA phenotypes and autoantibody responses in ocular and generalized types. *Ann Neurol* 1987;21:274-8.
- 6 Chiu H-C, Vincent A, Newsom-Davis J, *et al.* Myasthenia gravis: population differences in disease expression and acetylcholine receptor antibody titers between Chinese and Caucasians. *Neurology* 1987;37:1854-7.

Decreased magnetisation transfer ratio due to demyelination: a case of central pontine myelinolysis

Conventional T2 weighted MRI has a high sensitivity for detecting multiple sclerosis lesions and is widely used for diagnosis and monitoring the efficacy of new treatments. An important limitation of T2 weighted images is their low pathological specificity: they do not identify the two pathological features that cause functional impairment in multiple sclerosis—namely, demyelination and axonal loss. This lack of pathological

specificity contributes to the weak relation between MRI abnormalities and disability in multiple sclerosis. Magnetisation transfer (MT) imaging indirectly visualises immobile water protons tightly bound to macromolecular structures that have very short T2 relaxation times and are invisible on conventional images. Measurement of MT ratio (MTR) in lesions provides information about structural integrity and by inference, myelin and axons. To explore the hypothesis that demyelination itself has an important effect on MTR, we performed MT imaging of a patient with central pontine myelinolysis—a condition in which demyelination is the predominant pathological feature.

A 50 year old woman presented with memory disturbance and poor balance. There was a long history of alcohol misuse leading to hospital admission with delirium tremens three months previously. There was no other history of note. Since then she had abstained from alcohol, after noticing residual poor balance and memory loss for recent events. Both problems worsened considerably in the weeks leading to her most recent admission. She also developed peripheral paraesthesiae, ankle swelling, and weight loss. Mental state examination showed a specific deficit in recent memory and formation of new memory, although registration was intact. On neurological examination she had a broad based ataxic gait and positive Romberg's test. Cranial nerve examination showed bilateral gaze-evoked non-sustained horizontal nystagmus, but no other abnormalities. Ataxia was present in upper and lower limbs, more pronounced in the legs. Tone was increased in the lower limbs. There was no left ankle reflex and plantar responses were extensor. Vibration sense was absent in both legs and joint position sense was decreased in the toes. Light touch and pinprick sensation were reduced in the hands.

T2 weighted MRI demonstrated a single high signal symmetric lesion confined to the basis pontis which appeared hypointense on T1 weighted images (fig 1). There was no enhancement after intravenous injection of gadolinium-DTPA. Mild cerebral atrophy was also noted. Further imaging was carried out on a 1.5 Tesla GE Signa MRI scanner

Figure 1 T2 weighted MRI showing high signal symmetric lesion in the centre of the pons, characteristic of central pontine myelinolysis.

with standard quadrature headcoil to obtain calculated MT images (fig 2). A dual spin echo sequence was used (TR 1730, TE 31/80, 28 contiguous 5 mm slices) both with and without presaturation pulses to saturate the broad resonance of immobile macromolecular protons. Results were analysed on a Sun workstation using image display software (Dispimage, DL Plummer, Department of Medical Physics, University College, London, UK). The MTR was greatly reduced in the centre of the pontine lesion with a value of 8.6%, compared with a normal value of 38.2% (obtained from the pons of five normal age matched female controls). Values for MTR in the surrounding rim of intact pontine tissue were normal. The greatest decrease in MTR was at the centre of the lesion, gradually increasing towards the outer edge.

The pathological findings associated with central pontine myelinolysis are remarkably homogeneous: a single large symmetric lesion is found in the basis pontis. There is usually a rim of intact pontine tissue. Microscopically the main abnormality is destruction of myelin, with relative neuronal preservation.¹ Myelin destruction is typically most severe at the centre of the lesion, becoming less pronounced towards the edge.¹ There are no inflammatory changes and oedema is absent.¹ In our patient we were confident that the lesion was due to central pontine myelinolysis, because of the clinical setting (alcoholism along with clinical features of Wernicke-Korsakoff syndrome) and the highly characteristic appearance of the MRI abnormality on the T2 and T1 weighted images. One notable feature was the lack of deficit related to the pontine lesion. Many patients with central pontine myelinolysis become profoundly disabled with bulbar palsy and tetraplegia during the acute phase of the illness. However, typical pathological changes of this condition have also been found at postmortem where there has been minimal neurological deficit referable to the pontine lesion. With the advent of MRI, patients like ours have been seen in whom the characteristic radiological abnormality has been identified in the presence of minimal clinical disability.

To identify specifically the structural

Figure 2 Calculated MTR image showing reduction of MTR in the pons, with preservation of signal in the surrounding rim.