stem stroke, suggesting a prolonged atonic curve as a supranuclear type of parasympathetic pelvic nerve dysfunction.

Griffiths *et al* reported bilateral lesions of the pontine micturition centre leading to a period of urinary retention lasting from 2 to 9 weeks, whereas lesions located on only one side had no obvious specific effect on lower urinary tract function.[2] This may be accounted for by bilateral innervation of the spinal parasympathetic nucleus by the pontine micturition centre.[2] However, histology verified that only 15% of the right pontine micturition centre was destroyed.[2] A recent PET imaging study disclosed that cortical and pontine micturition sites in humans are predominantly on the right side.[6] It is therefore possible that extensive involvement of a unilateral pontine micturition centre, especially the right side, may cause transient urinary retention as found in our patient. Another possibility is that the amorphous lesions in the pons could have interrupted outflow pathways from the opposite pontine micturition centre.

ATSUSHI KOMIYAMA
Department of Neurology, Urafune Hospital of Yokohama City University, Yokohama, Japan

AKIHIKO KUBOTA
Department of Neurology, Yokohama City University School of Medicine, Yokohama, Japan

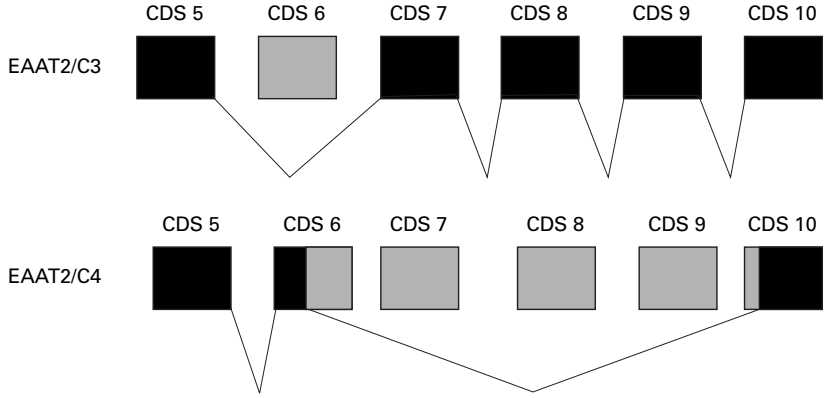
HIDEO HIDAI
Yokohama Dai-ichi Hospital, Yokohama, Japan

Correspondence to: Dr Atsushi Komiyama; Department of Neurology, Hiratsuka Kyousai Hospital, 9-11 Oiwake, Hiratsuka 254-0047, Japan. Telephone 0081 463 32 1950; fax: 0081 463 31 1865.

1 Barrington FJF. The effect of lesions of the hind- and mid-brain on micturition in the cat. *Q J Exp Physiol* 1925;**15**:81–102.
2 Griffiths D, Holstege G, Dalm E, *et al*. Control and coordination of bladder and urethral function in the brainstem of the cat. *Neurourol Urodynam* 1990;**9**:63–82.
3 Honda H. Clinico-pathological investigation on the urinary disturbance and lower brain stem lesions (in Japanese with an English abstract). *No To Shinkei* 1967;**19**:743–55.
4 Holman E. Difficult urination associated with intracranial tumors of the posterior fossa. *Arch Neurol Psychiatry* 1926;**15**:371–80.
5 Sakakibara R, Hattori T, Yasuda K, *et al*. Micturitional disturbance and the pontine tegmental lesion: urodyamic and MRI analyses of vascular cases. *J Neurol Sci* 1996;**141**:105–10.
6 Blok BFM, Willemsen ATM, Holstege G. A PET study on brain control of micturition in humans. *Brain* 1997;**120**:111–21.

Splicing of the glutamate transporter EAAT2: a candidate gene of amyotrophic lateral sclerosis

Defective glutamatergic neurotransmission may have a critical role in the pathogenesis of amyotrophic lateral sclerosis (ALS). A reduced synaptic glutamate reuptake has been found in the motor cortex and spinal cord of patients with sporadic ALS.[1] More recently, a selective loss of the glial glutamate transporter protein EAAT2 has been described.[2] Most recently aberrant splicing of the EAAT2 transcript was reported to be the cause for a reduced expression of the EAAT2 protein.[3] Several novel EAAT2 transcripts were cloned from patients with ALS and described as disease specific. In vitro expression studies suggested that proteins translated from these transcripts were rapidly degraded and show a dominant negative effect on normal EAAT2 protein which appears to be the predominat glutamate transporter in the CNS.[3] A loss of EAAT2 can lead to neuronal degeneration through abnormal accumulation of the potential neurotoxin glutamate and excitotoxic mechanisms. This pathogenetic concept was supported by the clinical efficacy of antiglutamatergic drugs in patients with ALS and transgenic models. One of the reported transcripts was characterised by the skipping of the protein coding exon 8 of the EAAT2 gene. This transcript was amplified by polymerase chain reaction from ALS-CSF and suggested as a diagnostic tool in ALS.[3] Interestingly, this transcript is identical to an alternative splicing product of the EAAT2 transcript which we have recently reported and named EAAT2/C1. This and another splice product, named EAAT2/C2, have been cloned from normal human brain RNA.[4]



Schematic presentation of alternative splicing in EAAT2 and its relation to the protein coding exons of the human EAAT2 gene.[5] Alternatively spliced exon sequences are shown in grey. Exon and intron lengths are not to scale. CDS=coding sequence.

Here we report the cloning of two further EAAT2 transcripts, named EAAT2/C3 and EAAT2/C4. Based on the EAAT2 sequence information we designed specific primers for reverse transcription (RT) of the EAAT2-mRNA using control human brain poly-A+ RNA as template (Clontech, Palo Alto). RT and PCR amplification were performed as described before (RT primer: 5' CAGTTACCATAG-GATACGCTGG; PCR primers: 5' GATAGTTGCTGAAGAG-GAGGGG; 5' CATATC-CTTATTT CT-CACGTTTCC).[4] PCR cloning and DNA sequencing disclosed two novel EAAT2 transcripts which resulted from splicing of protein coding sequences. EAAT2/C3 orginated from a deletion of 234 nucleotides (891–1124; GenBank UO3505) corresponding to exon 6 of the EAAT2 gene which is coding for 78 amino acids in the central part of the putative EAAT2 polypeptide (figure).[5] The EAAT2/C4 transcript was characterised by the deletion of 702 nucleotides ranging from position 992 to 1693 (GenBank U03505). The splicing occurred at internal 5'- and 3'-splice sites which showed an uncomplete consensus sequence. EAAT2/C4 resulted from deletion of exons seven to nine and parts of exons six and 10 (figure) with the downstream sequence still in frame.[5] At the putative protein level EAAT2/C4 showed a loss of 234 amino acids located in the middle and C-terminal part of the polypeptide.

Our findings contribute to the notion that the EAAT2 transcript is highly variable. Splicing of the EAAT2 transcript is also found under normal conditions and may be part of post-transcriptional EAAT2 gene regulation. Furthermore, alternative EAAT2 transcripts were identified in other species. We conclude that splicing of the EAAT2 transcript is unlikely to be ALS specific. The EAAT2 gene regulation and its pathogenetic relevance are far from completely understood. The use of EAAT2 splicing products as diagnostic tools in ALS would be extremely valuable, but further evidence is necessary before concluding that these splice variants are specifically associated with ALS. However, the evolving knowledge on EAAT2 gene regulation will provide the basis for a comprehensive association study of EAAT2 splicing products in ALS and other neurodegenerative diseases.

THOMAS MEYER
CHRISTOPH MÜNCH
STEFAN LIEBAU
ANDREA FROMM
BIRGIT SCHWALENSTÖCKER
HELGE VÖLKEL
ALBERT C LUDOLPH
Department of Neurology, University of Ulm, Germany

Correspondence to: Dr Thomas Meyer, Department of Neurology, University of Ulm, Albert-Einstein-Allee 11/O25–5, 89081 Ulm, Germany. Telephone 0049 731 177 1200; fax 0049 731 177 1202.

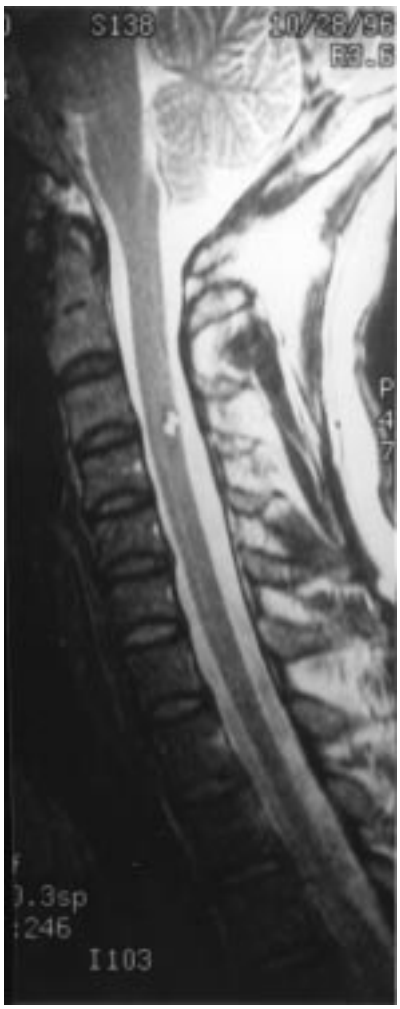
1 Rothstein JD, Martin LJ, Kuncl RW. Decreased glutamate transport by the brain and spinal cord in amyotrophic lateral sclerosis. *N Engl J Med* 1992;**326**:1464–8.
2 Rothstein JD, Van Kammen M, Levey AI, *et al*. Selective loss of glial glutamate transporter GLT-1 in amyotrophic lateral sclerosis. *Ann Neurol* 1995;**38**:73–84.
3 Lin CL, Bristol LA, Jin L, Dykes-Hoberg M, *et al*. Aberrant RNA processing in a neurodegenerative disease: the cause for absent EAAT2, a glutamate transporter, in amyotrophic lateral sclerosis. *Neuron* 1998;**20**:589–602.
4 Meyer T, Munch C, Knappenberger B, *et al*. Alternative splicing of the glutamate transporter EAAT2 (GLT-1). *Neurosci Lett* 1998; **241**:68–70.
5 Meyer T, Ludolph AC, Morkel M, *et al*. Genomic organization of the human excitatory amino acid transporter gene GLT-1. *Neuroreport* 1997;**8**:775–7.

Lhermitte's sign in cavernous angioma of the cervical spinal cord

The sudden feeling of "painless but unpleasant electric shock-like discharges" originating in the neck or upper back and spreading down the spine into the limbs on flexion of the head was first described in 1917 by Marie and Chatelin and later by Lhermitte in his seminal paper of 1924.[1] It is not a specific symptom but is most commonly encountered in cervical spinal cord demyelination caused by multiple sclerosis.[2 3] The sign has been found in many other conditions that cause a traumatic or compressive cervical myelopa-

thy, such as cervical spondylosis and epidural, subdural, and intraparenchymatous tumours. It has also been reported infrequently in radiation myelitis, pernicious anaemia (subacute combined degeneration), pyridoxine toxicity, nitrous oxide misuse, cisplatin and docetaxel neuropathies, cervical herpes zoster myelitis, paroxetine withdrawal, Behçet's disease, and systemic lupus erythematosus. Vascular disease of the cervical spine or intraspinal cord has never been noted to produce Lhermitte's sign.

A 48 year old left handed man presented with a history of a "burst, very brief electrical tingling" in the left forearm, hand, and lower leg for almost 2 years. The symptom occurred only on flexion of the neck and abated even when the neck was kept flexed. No other neck movements caused this symptom. A year later, the patient noted mild dysaesthesia in the left arm and leg. A sagittal heavily T2 weighted fast spin echo MR image of the cervical spine showed a small ovoid area of T2 hyperintensity within the posterior cervical spinal cord at the cervical 3–4 level with minimal mass effect. Subtle low signal intensity about its rim suggested hemosiderin deposition (figure). A few weeks later, after raking his yard, the patient experienced acute neck pain. A day later, he noticed diminished coordination of the left arm and leg. A sagittal T2 weighted fast spin echo MRI of the cervical spine obtained a few days later showed an extensive intramedullary low signal intensity area in the midposterior spinal cord compatible with interval haemorrhage, spinal cord expansion, and oedema. Results of spinal angiography were normal. The pain resolved in 10 days, and only mild numbness in the left hand and to lesser degree in the foot persisted. At operation, the lesion was found to be a cavernous angioma. After resection of the malformation, sensory deficits in the left hand and foot worsened, and discomfort with an unpleasant sensation of swelling developed in the hand. For 1 month after the operation, the patient also complained of spontaneous "electrical bursts" in the right arm and both legs. Neurological examination 6 months after the operation disclosed mild weakness of the left arm and hand with diminished stretch reflexes and equivocal plantar response in the left foot. Abnormalities elicited in the sensory examination were decreased pain sensation in the left hand, mild attenuation of two point discrimination, and dysgraphaesthesia in the left fingertips. Mild sensory ataxia on finger to nose testing and mild pseudoathetotic movements of the left hand were also noted.



Sagittal T2 weighted MRI (TR 3800/TE 96 ms) of the cervical spine shows a small ovoid area of T2 hyperintensity within the posterior cervical spinal cord at the cervical 3–4 level with minimal mass effect. Subtle low signal intensity about its rim suggests haemosiderin deposition.

Lhermitte's sign is a common symptom in neurological practice. However, the pathophysiology of the sign is not well known. Because flexion of the neck causes the dysaesthetic symptoms, it has been suggested that an increased mechanical sensitivity of these damaged myelinated axons causes an abnormal origin or transmission of sensory information. In the cat model, deformation of experimentally demyelinated dorsal columns by <1 mm increased the frequency of action potentials in both spontaneously active and previously silent fibres.[4] Routine flexion of the neck can lengthen and deform the cervical cord slightly and provide synchronisation of a volley of aberrant activity in damaged dorsal column myelinated axons. Nordin *et al*[5] reported activation of multiple units in the neurogram of the median nerve, presumably arising from activated sensory fibres in the dorsal columns of a patient with Lhermitte's sign on flexion of the neck. As expected, multiple sclerosis is the most common cause of Lhermitte's sign, occurring in about one third of patients.[2] The sign, however, is not specific and may be present in other clinical conditions that compress or damage myelinated sensory axons of the dorsal columns of the cervical cord. Occasionally, Lhermitte's sign is the presenting complaint of the underlying medical cause.

To our knowledge, this is the first reported case of Lhermitte's sign caused by a vascular disease in the cervical spinal cord. It was, in fact, the presenting symptom in our patient. The pathological findings confirmed the MRI diagnosis as a cavernous angioma. It is probable that the underlying lesion acted by producing compression or ischaemia on the dorsal columns of the cervical spinal cord.

D KEVIN MURPHY
JOSÉ A GUTRECHT
Department of Neurology, Lahey Clinic Medical Center, Burlington, Massachusetts

Correspondence to: José A. Gutrecht, MD, Department of Neurology, Lahey Clinic Medical Center, 41 Mall Road, Burlington, MA 01805, USA. Telephone 781 744 8631; fax 781 744 5243.

1 Lhermitte J, Bollack J, Nicolas M. Les douleurs à type de décharge électrique consécutives à la flexion céphalique dans la sclérose en plaques: un case de forme sensitive de la sclérose multiple. *Rev Neurol* 1924;39:56–62.
2 Kanchandani R, Howe JG. Lhermitte's sign in multiple sclerosis: a clinical survey and review of the literature. *J Neurol Neurosurg Psychiatry* 1982;**45**:308–12.
3 Gutrecht JA, Zamani AA, Salgado ED. Anatomic-radiologic basis of Lhermitte's sign in multiple sclerosis. *Arch Neurol* 1993;**50**:849–51.
4 Smith KJ, McDonald WI. Spontaneous and mechanically evoked activity due to central demyelinating lesion. *Nature* 1980;**286**:154—5.
5 Nordin M, Nyström B, Wallin U, *et al*. Ectopic sensory discharges and paresthesiae in patients with disorders of peripheral nerves, dorsal roots and dorsal columns. *Pain* 1984;**20**:231–45.

Autosomal dominant paroxysmal kinesigenic choreoathetosis: a clinical and genetic study of two families

Paroxysmal kinesigenic choreoathetosis (PKC), characterised by brief attacks of abnormal involuntary movements induced by sudden voluntary movements, is either idiopathic (familial or sporadic) or symptomatic. A total of about 20 families with PKC have been reported, with autosomal dominant inheritance in most of them. No genetic study has been reported in familial PKC up to now.

We report two unrelated families with autosomal dominant PKC, in which we performed linkage analyses with loci involved in other paroxysmal movement disorders: (1) the locus for paroxysmal dystonic choreoathetosis (PDC), also known as paroxysmal nonkinesigenic dyskinesia, on chromosome 2q33–35,[1] (2) the locus for AD paroxysmal choreoathetosis/spasticity (CSE), classified as "complicated" PDC, on chromosome 1p,[2] and (3) the locus for episodic ataxia/myokymia (EA-1) on chromosome 12p13.[3]

Family A was Portuguese and family B was French. They contained a total of 10 affected and nine unaffected family members, who were all interviewed and examined by the same physician. There was no family history of epilepsy. In one family, three of the five affected members also had migraine with visual aura. Except for one patient, who had had a parkinsonian resting tremor since the age of 52, neurological examination was normal. The phenotypes of the 10 patients were very homogeneous. Age at onset of PKC attacks ranged from 1.5 to 13 years (median 6.5 years). Attacks occurred five to 20 times daily in nine patients and once a year in the other. Attacks were always triggered by a sudden movement of a lower limb (rising from a sitting position, running) that often occurred in response to an unexpected stimulus after sustained immobility. Embarrassment and stress were precipitating factors. In a few patients, fatigue, cold, or menstruation also favoured attacks. The latency between the triggering factor and dyskinesia was 0–2 seconds. Dyskinesias were usually preceded by a short aura (paraesthesias, n=4; muscular tension, n=5) in the affected hemibody. Duration of attacks was 3 to 40 seconds. Involuntary movements involved one side of the body, but sometimes extended rapidly to the whole body, with preservation of consciousness. During attacks, the intensity of the dyskinesias increased and decreased progressively. In addition to frequent dysarthria (n=7) related to orofacial dyskinesia, breathing problems (n=1) and falls (n=5) sometimes occurred during violent