Infantile onset myasthenia gravis with MuSK antibodies

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Approximately 80% of patients with myasthenia gravis (MG) show a high antibody (Ab) titer against acetylcholine receptor (AChR). Patients with MG who do not have high titer of anti-AChR are called seronegative MG (SNMG) and their clinical characteristics are shown to be rather different from anti-AChR positive MG in the literature.[1] It was recently reported that 70% of sera from generalized SNMG patients contained Ab to a muscle-specific receptor tyrosine kinase (MuSK).[2] The frequency of anti-MuSK Ab in generalized SNMG is reportedly from 38% to 47% of cases.[3-5] Anti-MuSK MG mainly affects young to middle-aged adults. We describe a case of late infantile onset MG with anti-MuSK Ab.

Case report. A 29-year-old man first experienced bilateral ptosis after febrile seizures when he was 2 years old. His parents soon noticed abnormal phonation. At age 3 years, the diagnosis of MG was made based on a positive edrophonium test. Treatment was initiated with oral prednisolone. His ocular symptoms responded well to the steroid therapy, but his bulbar symptoms persisted. At age 12 years, ptosis almost disappeared but nasal voice and dysphagia worsened. Along with 120 to 180 mg of pyridostigmine, the dose of prednisolone was increased to 40 mg/day, but the effect was limited. Symptoms were exacerbated when he worked hard or did not get enough sleep. Dyspnea never occurred. At age 26 years, the patient was referred to our hospital and we performed thymectomy, which did not produce a good result. Histology revealed normal thymus without thymoma or hyperplasia. Tacrolimus was initiated but then discontinued because of diarrhea. He was admitted to our hospital again at age 29 years because of exacerbation of bulbar symptoms.

On admission, his general condition was normal. Neurologically, there was no ptosis or diplopia. There was marked facial weakness. Nasal voice and dysphagia were present and he easily choked when drinking water. His tongue was atrophic and showed triple-furrowed appearance (figure). He showed moderate weakness in the neck and mild proximal muscle weakness at extremities. Tendon reflexes and sensory systems were normal. The patient did not have exaggerated fasciculations. Edrophonium infusion improved his speech and swallowing. Blood cell count and serum chemistry were normal. Antinuclear Ab was slightly elevated, but rheumatoid factor, anti-RNP, anti-SS-A, anti-SS-B, and anti-Sm Ab were all negative. Thyroid function was normal and there was no anti-thyroid Ab detected. Anti-AChR Ab was also negative. Anti-MuSK Ab measured by radioimmunoassay was 4.80 nmol/L (normal range <0.05). Repetitive nerve stimulation of the median nerve revealed decrement of compound muscle action potential. Spirometry and arterial blood gas were normal. We performed plasma exchange using Spectra (COBE) three times at 2- to 3-day intervals. After the treatment, dysphagia and nasal voice decreased and muscle strength of neck and extremities improved. MG-ADL score decreased from 7 to 4.

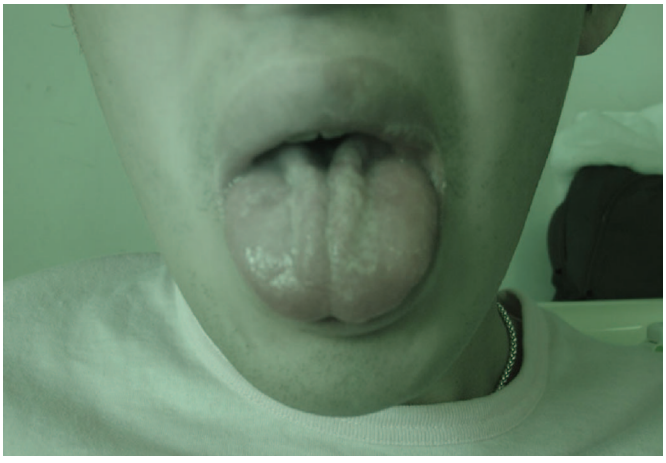

Figure. The patient's tongue was atrophic, showing so-called triple-furrowed tongue.

Discussion. This is a unique case of anti-MuSK MG presenting with late infantile onset. Congenital myasthenic syndrome was ruled out due to the reactivity to immunotherapies. Although clinical expression was slightly atypical at first, and we were unable to assess sera taken at disease onset, we believe that this disease has been affecting the patient for as long as 27 years. The reasons are as follows: 1) the patient has had variable dysarthria since the disease onset up to now, 2) although not specific to anti-MuSK MG, the atrophic tongue (triple-furrowed tongue), which is often observed in this disease, illustrates the chronic nature of the disease, and 3) there is no case report in the literature that has both anti-AChR Ab and anti-MuSK Ab simultaneously. The possibility that anti-MuSK Ab have developed during the disease course as a result of epitope spreading, the mechanism by which the immune system spreads its reactivity to MuSK protein, could not be completely excluded.

Clinical symptoms of the present case were similar to previously reported cases with marked facial weakness, bulbar palsy, and neck weakness. Response to treatment was also comparable. Steroids and cholinesterase inhibitors showed limited effect but thymectomy was not beneficial. We chose simple plasma exchange instead of immunoadsorption therapy based on previous results[4,5] and a reported case[6] which responded to plasma exchange but not to immunoadsorption therapy using a tryptophan column. Our case also confirms the efficacy of plasma exchange in anti-MuSK MG.

Anti-MuSK MG is found mainly in women ages 18 to 60 years with generalized SNMG. However, this apparently uniform disease entity seems to be expanding. Although it has been believed that anti-MuSK Ab are not detected in ocular MG, a case of anti-MuSK ocular MG was recently reported.[7] We have presented a late infantile onset anti-MuSK MG. This case suggests that the spectrum of this disease may be wider than previously suspected.

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Hypoglossal neuropathy in Lewis-Sumner syndrome masquerading as motor neuron disease

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Lewis-Sumner syndrome (LSS) is a peripheral neuropathy characterized by multifocal weakness and wasting and associated sensory impairment[1] considered to be a variant of chronic inflammatory polyneuropathy (CIDP). LSS is associated with multifocal persistent conduction block and other signs of demyelination.[1,2] We report a patient with probable LSS presenting with tongue hemiatrophy thought to have motor neuron disease.

Case report. A 56-year-old man with chronic alcoholism presented to the neuromuscular clinic with a 6-year history of progressive painless right arm weakness and right hand paresthesias and a 2-year history of left arm weakness, burning pain, and numbness in the feet, and falls. On evaluation by another neurologist immediately following symptom onset, he was found to have tongue atrophy and fasciculations, right arm weakness and wasting, and decreased sensation in the right hand. MRI of the brain and cervical spinal cord, anti-GM1 antibodies, and genetic testing for Kennedy's disease were unrevealing. Electrodiagnostic study, limited to sensory and motor nerve conduction study of the right median and ulnar nerves, demonstrated a mildly prolonged median distal motor latency and reduced median sensory nerve conduction velocity across the wrist suggesting carpal tunnel syndrome (table E-1 on the *Neurology* Web site at www.neurology.org). Needle EMG showed acute and chronic partial denervation in multiple muscles of both arms and the distal legs and was believed to be consistent with lower motor neuron disease.

His examination in neuromuscular clinic 6 years later revealed fasciculations and hemiatrophy of the left tongue (figure, A), with no weakness or other bulbar findings. He also demonstrated wasting and fasciculations of both arms and weakness of the intrinsic hand muscles, wrist, and long finger extensors of 2/5 (Medical Research Council) on the right and 3/5 on the left and of both deltoids 0/5, biceps 3/5, and triceps 4/5. He exhibited mild stocking sensory loss to all modalities and trace or absent deep tendon reflexes throughout. He had a normal lumbar puncture, including protein. Electrodiagnostic study of both upper and lower extremities (table E-1) revealed markedly reduced left median motor nerve conduction velocity (19 m/sec, normal >50 m/sec) and abnormal temporal dispersion of the left median motor compound muscle action potential in the forearm (figure, B). The left ulnar motor nerve also demonstrated a substantial reduction of conduction velocity (26 m/sec, normal >50 m/sec) in the forearm but no conduction block. Right motor nerve conduction showed mild prolongation of the median distal motor latency. Median, ulnar, and sural sensory nerve action potentials were absent bilaterally. Needle EMG demonstrated acute and chronic partial denervation and fasciculation potentials in multiple muscles of both arms and the distal legs. Though no partial motor conduction block was noted to secure a definite diagnosis,[1] the electrodiagnostic study was thought to be consistent with probable LSS. The patient declined needle EMG of the tongue and sural nerve biopsy. Treatment with IV immunoglobulin (IVIg) therapy was initiated at 2 g/kg of body weight. Within 3 weeks, he noted moderate improvement of arm strength but no change in tongue hemiatrophy. This improvement has been sustained with monthly IVIg infusions.

Discussion. Cranial neuropathies occur relatively frequently in LSS.[1-5] The incidence of cranial nerve involvement in LSS was recently reported to be approximately 15%[4] and is similar to that of CIDP.[6] A number of cranial nerve palsies have been seen in this disorder, including those involving cranial nerves II, III, IV, V, and VII, IX, and X.[4,6] However, reports of hypoglossal neuropathy occurring in LSS are rare. A MEDLINE search revealed only three cases,[4,7] two of which were in association with other cranial neuropathies and noted only after the disease relapsed and not as a presenting sign.[4]

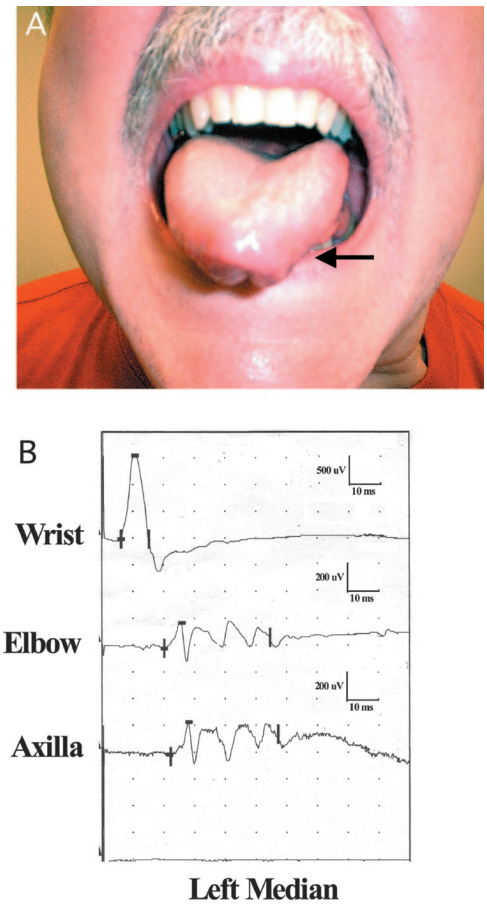

Figure. (A) There is significant hemiatrophy of the left side of the tongue (denoted by the arrow), consistent with a left hypoglossal neuropathy. (B) Left median motor nerve recordings from the abductor pollicis brevis muscle. The sites of stimulation are as indicated. Electrical stimulation was applied at a level 20% above that needed to produce a maximal compound muscle action potential (CMAP) amplitude. Note the >80% drop in the amplitude, >50% drop in the area, and >250% increase in duration of the median CMAP both at the elbow and axilla. The study is consistent with abnormal temporal dispersion in the left forearm.

LSS was initially diagnosed as motor neuron disease in our patient due to tongue hemiatrophy and fasciculations, restricted right hand numbness suggesting superimposed carpal tunnel syndrome, and nerve conduction study limited to one limb. Forms of mononeuropathy multiplex including LSS often require extensive electrodiagnostic testing to arrive at a diagnosis and to rule out other conditions such as motor neuron disease. Tests should include motor and sensory nerve conduction study of multiple limbs and proximal sites, to search for signs of sensory involvement or multifocal demyelination,[5] and comprehensive needle EMG to show a pattern of denervation more in keeping with involvement of individual nerves rather than myotomal regions. Motor neuron disease should not be assumed in patients presenting with clinical signs of a hypoglossal neuropathy, especially when unilateral, and extensive electrophysiologic evaluation is required to exclude other, potentially treatable, neuromuscular conditions.

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Identification of new serum autoantibodies in neuromyelitis optica using protein microarrays

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Neuromyelitis optica (NMO) or Devic's disease is a severe demyelinating disease of the CNS affecting primarily optic nerves and spinal cord, secondary to a B-cell- and Ab-mediated autoimmune condition.[1] This concept was recently bolstered by the demonstration of disease-specific NMO-Abs,[2] and the apparent beneficial effect of B-cell depletion.[3] Here, we used a protein microarray approach to profile the Ag reactivity of serum IgG from NMO patients.

Sera from five patients fulfilling NMO criteria (Cases 2 through 6 described elsewhere[3]) and five healthy controls were tested. Because patients experienced relapses and progressive clinical impairment despite therapy, they received rituximab as an off-label, innovative treatment.[3]

Case report. A 20-year-old woman with NMO associated with a high relapse rate (19 relapses within the last 6 years) was blind, wheelchair bound, and had a mid-thoracic sensory level and urinary and stool incontinence. Following treatment with rituximab, she experienced improved strength and sensation in her legs. She had an attack of myelitis approximately 1 month after her first course of rituximab from which she recovered spontaneously without additional treatment. At 1 year follow up, her vision remained impaired but she recovered full strength in her legs, normal sensation, both bowel and bladder control, and ambulates using a walker.

IgG from patients with NMO and control sera were purified using NAb Protein G Spin column (Pierce Biotechnology) and applied (1 μg/mL) onto the protein microarray slides (Protoarray, Invitrogen). Significance for presence of IgG positivity against the target Ag was automatically determined (Protoarray Prospector-v2). Among the five NMO sera profiled, our case exhibited specific autoAbs, which were not found in either controls or the four other patients with NMO (figure, A through D). Ags recognized by these autoAbs are identified as 1) Cleavage and Polyadenylation Specificity Factor (CPSF-73) (see the figure, B), 2) Ring finger protein 141 (RNF141) (see the figure, C), 3) Myosin light chain 2, precursor lymphocyte-specific (see the figure, D). The serum IgG from the same patient was retested 6 months after treatment with rituximab (figure, E through G). Contrary to autoAbs directed against the two latest Ags (see the figure, F and G), the signal corresponding to anti-CPSF-73 was no longer present above the threshold of detection (see the figure, E).

Discussion. Using this protein microarray tool, we detected three new autoAbs. The first autoAb binds to the 73 kd-subunit CPSF. This protein belongs to a superfamily of zinc-dependent proteins consisting of four subunits, is required for mature mRNA, and has been located in rat hippocampal neurons. In addition, CPSF-73 closely interacts with CPSF-100, a protein involved in B cell development.[4] Therefore, it might be hypothesized that anti-CPSF-73 Abs could induce a translational imbalance leading to B-cell-mediated autoimmunity in the CNS. The two other autoAbs described are directed against newly discovered proteins that do not have defined function in humans yet. These three new Abs were only observed in one case, and thus are not diagnostic for NMO. Since they are not found

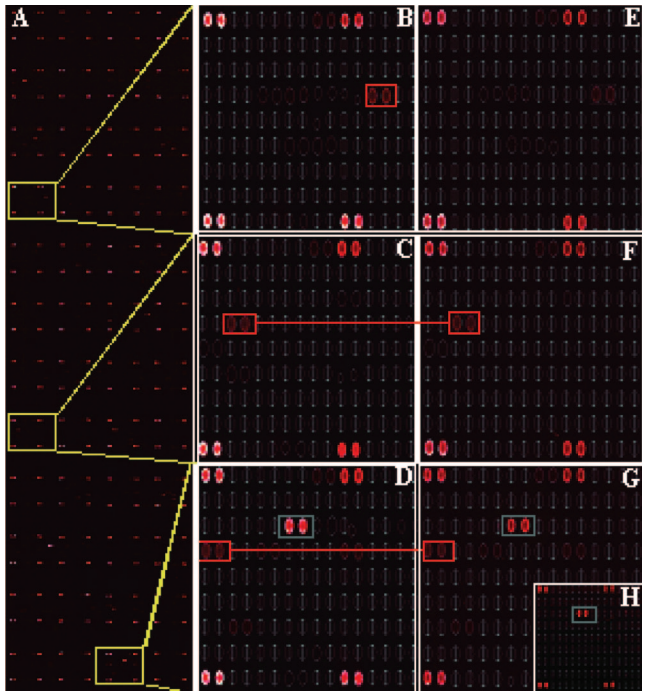

Figure. Protein microarray results for the case (A). (B through D) Serum IgG reactivity before rituximab. The red boxes highlight three doublets for positive reactivity (corrected for background and nonspecific binding as detected by the analysis software). These IgG autoAbs are directed against 1) Cleavage and Polyadenylation Specificity Factor (CPSF-73) (B), 2) Ring finger protein 141 (RNF141) (C), 3) Myosin light chain 2, precursor lymphocyte-specific (D). (E through G) Serum IgG reactivity 6 months after total B-cell depletion. The signal corresponding to anti-CPSF-73 IgG is abolished below detection threshold (E), contrary to that for anti-RNF141 IgG (F) and anti-Myosin light chain 2, precursor lymphocyte-specific IgG (G). The signal highlighted in a gray box in D and G (columns 7 through 8, row 3) is nonspecific as it is also present with secondary Ab only (H, negative control). Significant microarray signal is automatically determined by ≥3 SD over the median signal minus background value for all of the "target/non control" proteins on the array (Protoarray Prospector-v2).

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in healthy controls, these Abs may be indicative of disease-specific immune dysregulation. It will be important to test other inflammatory neurologic diseases, such as multiple sclerosis and CNS vasculitis.

Our patient presented with a somewhat unique phenotype—an unusually high relapse rate prior to rituximab despite PLEX and mitoxantrone and a relapse shortly after B-cell depletion. It is noteworthy that after B cell depletion, the serum anti-CPSF-73 became undetectable. Therefore, we speculate that in this patient with a particularly aggressive form of NMO, the concordance between decreasing level of serum anti-CPSF-73 and clinical improvement observed after rituximab may be linked to a functional role of this specific autoAb. Furthermore, only one of the three autoAbs was influenced by the B cell depletion procedure, which argues against a nonspecific effect of rituximab. These findings are in accordance with studies in other autoimmune diseases that report a positive correlation between clinical response following B cell depletion and decrease in serum levels of certain specific Ab.[5,6]

Our study does not contradict the relevance of the NMO/aquaporin-4-water-channel specific Abs since 1) 27 to 42% of patients with NMO were found negative for this marker,[2,7] and 2) our case report also tested positive for the NMO-IgG Ab. Thus, our results indicate that several Ags might be involved in NMO pathogenesis, as it is frequently seen in other autoimmune diseases like myasthenia gravis.

Further studies are needed to assess the role of the specific autoAbs as potential biomarkers and to elucidate their function in demyelinating diseases.

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Gradual hearing loss with bilateral labyrinthine hemorrhage in chronic myelogenous leukemia

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Abrupt onset of hearing loss in chronic myelogenous leukemia has been reported. We report a patient in whom hearing loss and dizziness developed subacutely, and MRI revealed bilateral labyrinthine hemorrhage.

Case report. A previously healthy 55-year-old woman experienced 6 weeks of fatigue and headache. She was treated with two courses of oral antibiotics for a presumed sinus infection without improvement. She then developed progressive left-sided hearing loss over 4 days followed by progressive right-sided hearing loss, resulting in complete bilateral deafness. The hearing loss was associated with increasing dizziness that prompted hospitalization. On admission she had a white blood cell count of 800,000/μL with myelocytes, promyelocytes, and mature neutrophilic predominance. The diagnosis of chronic myelogenous leukemia in chronic phase was confirmed by the cytogenetic studies and reverse transcription PCR specific for the BCR-ABL fusion transcript (confirming the presence of the Philadelphia chromosome [a t(9;22) translocation containing the BCR-AL fusion gene which encodes a 210-kd protein with deregulated tyrosine kinase activity]). Brain MRI at 10 days after the onset of hearing loss revealed abnormal hyperintense signal on precontrast T1-weighted images within the semicircular canals, vestibules and cochleae bilaterally consistent with hemorrhage (figure, A). The T2-weighted images of the labyrinths were unremarkable (figure, B). No appreciable enhancement was found on the postgadolinium T1-weighted sequence. No abnormalities were seen in the brain parenchyma, but there was diffusely abnormal low signal on the T1-weighted images in the bone marrow, consistent with leukemic infiltration. Audiogram on admission revealed no response to air or bone conduction. The patient was initially treated with leukapheresis and hydroxyurea, and then imatinib. None of these treatments resulted in significant clinical improvement of her hearing. Audiogram at 4 weeks demonstrated some tone recognition at 250, 500, and 750 Hz in the right ear but no change when repeated 2 weeks later. By 8 weeks her balance and gait had improved significantly. An MRI done 10 weeks after the onset of hearing loss showed resolution of the abnormal high T1

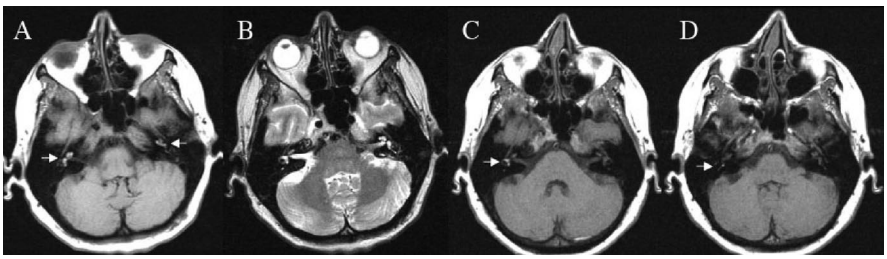

Figure. (A) Precontrast axial T1-weighted MRI (spin echo 635/15 milliseconds) at 10 days after the onset of hearing loss reveals hyperintense signal bilaterally in the cochleae and vestibules (arrows). (B) Axial T2-weighted MRI (fast spin echo 6080/104 milliseconds) at 10 days after the onset of hearing loss is unremarkable. (C, D) Follow-up noncontrast axial T1-weighted MRI (spin echo 450/12 milliseconds) at 10 weeks after the onset of hearing loss reveals interval resolution of bilateral labyrinthine T1 hyperintensity except for a small area of residual hyperintensity in the right vestibule and right semicircular canals (arrows).

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signal previously present in the left cochlea, left vestibule, and right cochlea; a small amount of abnormal T1 hyperintensity was present in the right vestibule and superior semicircular canal (figure, C and D).

Discussion. In normal cochleae and vestibules, the endolymphatic fluid and perilymphatic fluid generate the same MR signals as CSF.[1] High signal seen on the precontrast T1-weighted images in our case helps to exclude an inflammatory process as the sole cause. The strategy of obtaining only enhanced images in the evaluation of sudden hearing loss may be misleading because without precontrast imaging, contrast enhancement related to inflammatory cochleitis and high T1 signal related to intracochlear hemorrhage cannot be easily distinguished.[2] Hyperintense T1 signal on precontrast scans can be caused by methemoglobin due to hemorrhage or elevated protein levels or both.[3] Hyperintense T1 signal has been shown to persist for up to 6 months after the onset of symptoms, due to the extended lifespan of erythrocytes in perilymphatic fluid.[1] In the acute phase, T2-weighted images demonstrate hypointense signal due to the accumulation of deoxyhemoglobin and methemoglobin within intact erythrocytes, although this was not seen in our case.

Bilateral hearing loss, an uncommon manifestation of leukemia, has been reported in patients with acute and, rarely, chronic myeloid forms.[4] Proposed etiologies include hyperleukocytosis, causing leukostasis and abnormal microvascular perfusion, leukemic infiltration, and infection.[5] Autopsy cases from patients with acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphocytic leukemia, and chronic lymphocytic leukemia demonstrated hemorrhage, leukemic infiltration, infection,[6] and reduced hair cells. The inner ear is supplied by the labyrinthine artery (a branch of the anterior inferior cerebellar artery), whose small caliber and tortuosity predispose it to effects of hyperviscosity.[4] Most reports are of acute hearing loss,[4,5,7] which is more suggestive of infarction or hemorrhage rather than leukemic infiltration.[4,5] In our patient, the improvement on MRI is likely due to resolution of blood products. Whether the initial hemorrhage was due to leukemic infiltration or infarct is not clear, but the persistence of hearing loss suggests the latter.

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Hemangioblastoma of the obex mimicking anorexia nervosa

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Hemangioblastomas are benign vascular tumors that may affect CNS sporadically or as part of von Hippel–Lindau syndrome. The natural history of hemangioblastomas, which are characterized by a progressive and unpredictable rate of growth, has been well studied for the patients with VHL because they commonly need a long follow-up.[1,2]

Posterior fossa and spine are the most frequent localizations. The dorsal pontomedullary junction, at the obex, is a common site for posterior fossa hemangioblastomas, producing mainly symptoms related to impairment of lower cranial nerves. Obstructive hydrocephalus may also occur when the lesion blocks CSF circulation. In the current study on two VHL patients with such lesions but no hydrocephalus, aversion to food, which especially in young females may frequently have a psychological origin, was the common presenting clinical feature.

Case reports. Case 1. An 18-year-old woman presented to our hospital with a 4-year history of eating disorders, initially suggesting anorexia nervosa, with a recent worsening of her condition leading to a 37% weight loss in a few months. She had hypoesthesia and hyposthenia in the upper limbs, nausea, dizziness, and cervical pain and presented with a progressive dysphagia, which caused an aspiration pneumonia accompanied by deterioration of consciousness. No other symptoms of brainstem damage were detected. CT showed a large solid hemangioblastoma displacing the IV ventricle and involving the obex area (figure, A). These radiologic findings and family history suggested a diagnosis of VHL, which was confirmed by a VHL gene mutation analysis. Following surgical removal of the tumor and rehabilitation, the patient underwent a very good recovery, including a full normalization of her feeding habits.

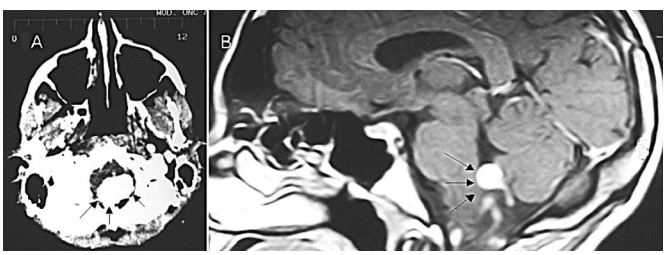

Figure. Contrast CT of Case 1 (A) and MRI of Case 2 (B), showing both the hemangioblastomas (arrows) growing in the obex area of the medulla oblongata.

Case 2. A 27-year-old woman affected by VHL disease was periodically monitored with MRI for multiple CNS localizations, including a small solid nodule at the caudal end of the fourth ventricle floor associated with a syrinx of the medulla oblongata. Aversion to food intake had started 4 years before admission, resulting in a progressive weight loss from 55 to 37 kg (32%), for which she was undergoing psychotherapy. During the last months, she had mild ataxia, fatigue, palpitations, headache, vomiting, and sporadic opistotonic fits. No other signs of brainstem dysfunction were observed. MRI showed a mild increase in size of the lesion in the fourth ventricle (figure, B). A surgical removal of the obex lesion and three small satellite nodules at the cervicobulbar junction resulted in an immediate relief of her eating disorder and a rapid return of her body weight to normal.

Discussion. The results reinforce the notion that clinical conditions initially interpretable as psychiatric eating disorders can be caused by focal brain lesions. Whereas there is considerable evidence that eating disorders can occur following hypothalamic or right frontal and temporal lobe damage,[3,4] cases of anorexia possibly resulting from brainstem lesions have seldom been reported.[5,6] The two cases described here are interesting because their eating disorders were undoubtedly caused by treatable brainstem tumors, as shown by the complete recovery of normal eating habits following the surgical removal of such tumors. Both patients had a VHL disease initially presenting with persistent food refusal, followed by the appearance of clear-cut neurologic

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symptoms in about 4 years. An organic basis for an apparently functional anorexic condition should be suspected when chronic food aversion is associated with symptoms such as occasional fainting, palpitations, dyspepsia, and vomiting, all of which are often neglected in a typical focal sign–seeking neurologic exam. With regard to pathophysiology, the most likely cause of the current eating disorders and associated symptoms was an encroachment of the lesions on the region of the nuclei of the lower cranial nerves, especially the vagus nerve and the nucleus of the solitary tract. The vagus nerve plays a major role in the regulation of alimentary canal functions from pharynx to colon, and the nucleus of the solitary tract has recently been shown to be a key relay of satiety signals conveyed by afferent vagal fibers,[7] so that disturbances in appetite regulation can be expected to occur after lesions of these structures. On the other hand, observations of eating disorders in cases with lesions involving the brainstem at the medulla oblongata are rare.[3]

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Passive smoking and Parkinson disease

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Cigarette smoking is consistently associated with a reduced risk of Parkinson disease (PD), having been reported in prospective studies,[1] retrospective case-control studies,[2] twin studies,[3] and studies of case-sibling pairs.[4] Conjecture remains as to whether this association reflects a true biologic neuroprotection from tobacco smoking or whether shared genetic and behavioral factors influence both smoking propensity and PD risk.

Although genetic and behavioral factors may have less influence on an individual's exposure to passive tobacco smoke, there are no previous reports on the effects of passive smoking on the risk for PD. Here we provide evidence that passive exposure to cigarette smoke might also be less common in PD.

We recruited 163 patients with PD. Inclusion criteria were community-dwelling patients who had consulted the clinic of one of the authors between October 2003 and October 2004 and received a diagnosis of definite idiopathic PD[5]; assessed at >27 on the Mini-Mental State Examination (MMSE); capable of completing the risk factor questionnaire; and currently listed in the Australian Commonwealth Electoral Roll (voting is compulsory in Australia). Exclusion criteria were a diagnosis of dementia or symptoms suggestive of an alternative form of parkinsonism. Each of 151 patients was individually matched to a control (free of parkinsonism and screening >27 MMSE) selected by random sampling from all enrolled voters of the same sex, age (±2 years), and residential suburb.

Questions were asked regarding history of tobacco smoking. Information about initiation, cessation, frequency, and quantities smoked was collected. Regular smoking was defined as having smoked "as often as once/week regularly for 6 months or more." In addition, several questions assessed exposure to passive smoke. These assessed whether and for how long: 1) participants had lived with a smoker (and how often the smoker smoked in the participant's vicinity) and 2) participants had worked in workplaces with substantial tobacco smoke. The relevant section of our structured questionnaire is presented in table E-1 on the *Neurology* Web site (go to www.neurology.org). The development and establishment of test–retest repeatability of the study instrument is described elsewhere.[6]

Relative odds of passive smoking exposure (PD cases to controls) and 95% CIs were estimated using conditional logistic regression for matched sets in SAS version 9.1. The multivariable model included consumptions of coffee (average cups per day), alcohol (average drinks per day), and tea (regular), family history of PD (first- or second-degree relative), hobby gardening, and tobacco smoking (pack-years) as potential confounding variables. Exposures for active smoking, coffee, tea, and alcohol were considered up to age at diagnosis in cases; for control subjects, truncation occurred at age at diagnosis of their matched case. No truncation was applied to the passive smoking data.

Eighty-six percent of eligible patients and 69% of invited control subjects participated. Sixty-three percent of participants were men; mean age was 67 years (SD 9 years). Median years since diagnosis of PD for cases was 6 years (range 0 to 33 years).

Smoking prevalence in PD cases and effect size for ever smoking (odds ratio [OR] = 0.66) are consistent with Australian data[7]; a significant dose–response relationship was observed (pack-years OR = 0.98, 95% CI = 0.97 to 0.99). Interestingly, we observed that all variables assessing passive smoking exposure were also consistently less common in the PD vs control group (table). Whereas the 95% CIs for most of these observations span unity, these data provide preliminary evidence that passive smoking is, independently of active smoking, associated with a reduced risk for PD. Moreover, the passive smoking effect was statistically dose dependent, with increased exposure associated with reduced risk. Further evidence in support of this observation comes from our analysis of the sample stratified for regular/never active smoking status. This revealed similar trends in the passive smoking variables for both groups; the effect of exposure of passive tobacco smoke is independent of active smoking.

It has been argued that the association between smoking and PD is related to common genetic variables predisposing to both PD and an aversion to cigarette smoking. Whereas aversion to cigarette smoking may also influence an individual's preference for "smoke-free" environments, one might speculate that, compared with active smoking, passive smoking is less dependent upon genetic predilection. Alternatively, the association could result from the presence of neuroprotective constituents of cigarette smoke (e.g., nicotine or monoamine oxidase inhibitors). In this exploratory study, we did not examine more quantitative measures of passive smoking exposure; repeatability of these estimates was poor. Nor did we examine the specific sources and chronology of the exposures. Our data are also limited by power constraints and other potential biases inherent in case-control study design. Nonetheless, our results implicate passive smoking as another factor influencing PD risk.

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Table *Independent influences of active and passive tobacco smoking exposures on the risk for PD*

	PD cases, n (%)	Controls, n (%)	Adjusted OR (95% CI)*
Ever lived with a smoker			
All subjects	122 (75.8)	113 (76.4)	0.58 (0.29–1.17)
Ever smokers	50 (83.3)	59 (81.9)	0.75 (0.18–3.17)
Never smokers	72 (71.3)	54 (71.1)	0.52 (0.19–1.38)
Years lived with a smoker			
All subjects			
Nil	28 (20.1)	44 (29.5)	1.00 (referent)
1–15	38 (25.5)	28 (20.1)	0.69 (0.23–2.04)
15–25	42 (28.2)	44 (31.7)	0.35 (0.12–0.96)
26+	31 (20.8)	33 (23.7)	0.42 (0.15–1.19)
Dose-response			0.98 (0.96–1.00)
Ever smokers			
Nil	6 (10.7)	13 (18.8)	1.00 (referent)
1–15	11 (19.6)	13 (18.8)	0.68 (0.04–10.87)
15–25	21 (37.5)	19 (27.5)	0.19 (0.02–1.94)
26+	14 (25.0)	24 (34.8)	0.48 (0.08–2.74)
Missing data	4 (6.7)	4 (5.5)	
Dose-response			0.96 (0.91–1.02)
Never smokers			
Nil	28 (30.1)	21 (30.0)	1.00 (referent)
1–15	27 (29.0)	15 (21.4)	0.67 (0.15–2.97)
15–25	21 (22.6)	25 (35.7)	0.71 (0.18–2.81)
26+	17 (18.3)	9 (12.9)	0.51 (0.07–3.67)
Missing data	9 (8.8)	5 (6.7)	
Dose-response			0.98 (0.94–1.03)
Ever worked in a smoky workplace			
All subjects	39 (25.2)	49 (33.6)	0.65 (0.35–1.20)
Ever smokers	17 (29.3)	25 (35.7)	0.59 (0.20–1.71)
Never smokers	22 (22.9)	24 (31.6)	0.80 (0.31–2.07)
Years worked in a smoky workplace			
All subjects			
Nil	104 (74.8)	108 (72.0)	1.00 (referent)
1–10	16 (10.7)	23 (16.6)	0.69 (0.29–1.62)
>10	19 (12.7)	19 (13.7)	0.62 (0.25–1.56)
Dose-response			0.98 (0.95–1.02)
Ever smokers			
Nil	41 (73.2)	36 (56.3)	1.00 (referent)
1–10	9 (16.1)	8 (12.5)	0.89 (0.16–4.87)
>10	6 (10.7)	11 (17.2)	0.37 (0.07–2.07)
Missing data	4 (6.7)	9 (12.3)	
Dose-response			0.96 (0.91–1.02)
Never smokers			
Nil	71 (76.3)	52 (69.3)	1.00 (referent)
1–10	10 (10.8)	11 (14.7)	0.91 (0.24–3.48)
>10	10 (10.6)	12 (16.0)	0.66 (0.18–2.33)
Missing data			
Dose-response			0.97 (0.93–1.02)

*Conditional logistic regression model analyzing sex-, age-, and residence-matched cases and controls, adjusting for smoking (pack-years), coffee (average number of cups per day), alcohol (number of standard drinks per day), and tea consumption (regular or not), first- or second-degree family history of PD (yes or no), and a history of hobby gardening (yes or no).

PD = Parkinson disease; OR = odds ratio.

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