Effect of 3,4-diaminopyridine on the gravity dependence of ocular drift in downbeat nystagmus

C. Helmchen, MD; A. Sprenger; H. Rambold, MD; T. Sander; D. Kömpf, MD; and D. Straumann, MD

The pathomechanism of downbeat nystagmus (DBN) remains controversial but each mechanism has to account for 1) its gaze-evoked vertical centripetal component which increases on down and lateral gaze,[1] and 2) the vertical bias component of the upward slow phase velocity (SPV) in gaze straight ahead. The vertical velocity bias of DBN has a gravity-dependent component which leads to maximal drift velocity when patients lie in prone position and minimal in supine position.[2] Recently, 3,4-diaminopyridine (3,4-DAP)[3] has been shown to be effective in reducing DBN in patients with their heads upright. However, DBN of several of those patients[3] showed only small changes. One reason might be that gravity-dependent mechanisms were not considered.

Patients and methods. A 63-year-old woman had a 4-year history of vertical oscillopsia, diplopia, blurred vision, and postural instability. Symptoms increased on downward gaze and considerably more when she bent her head forward. Clinically she showed DBN. In the head forward bending position there was a marked increase of DBN. Except for the tendency to fall backward, the neurologic examination was unremarkable. MRI, CSF, and blood screening were normal. Electronystagmography was normal except for mildly impaired horizontal smooth pursuit. DBN was superimposed on downward vertical smooth pursuit (gain: 0.54 at 0.3 Hz), upward pursuit was only slightly impaired (gain: 0.79). Saccades, subjective visual vertical, and funduscopy were normal.[4]

After the patient gave written consent DBN was recorded using the video-based Eyelink II system (SR Research, Toronto, Canada). Head-fixed LEDs attached to the headband of the Eyelink system were presented in front of the patient at a fixed distance (0.6 m) in gaze straight ahead and ± 10° up and down. Horizontal targets were presented at 40°. The head position was monitored by an inclinometer. The following five pitch positions of the head relative to the upright position were examined: head upright (0°), bending backward by 45° (−45°) and 90° (−90°), bending forward by 45° (+45°) and 90° (+90°). Eye position calibration was performed in vivo. Each eye movement channel was recorded with a sampling rate of 500 Hz and filtered using a Gaussian filter (50 Hz).

Recordings of DBN were performed 15, 45, and 90 minutes after 20 mg 3,4-DAP ingestion (university hospital pharmacy). Nystagmus was detected semiautomatically, using a velocity criteria of 30°/second.[4] Negative SPV indicates upbeating, positive downbeating nystagmus.

Results. Prior to 3,4-DAP ingestion, the SPV of DBN was small, ranging from 0.8 ± 0.3°/second in gaze straight ahead to 3.7 ± 0.93°/second on lateral gaze. SPV of ocular drift varied as a function of head position (figure, A), e.g., SPV in gaze straight ahead increased from 0.8 ± 0.3°/second in the upright head position to 12.6 ± 1.1°/second in the + 45° head position (anteflexion), and on lateral gaze from 3.7 ± 0.9°/second to 23.6 ± 1.7°/second (figure, B, baseline). In the −90° ("supine") head position, DBN changed into an upbeat nystagmus (UBN) of −8.43 ± 2.8°/second in gaze straight ahead. There were three main effects after 3,4-DAP ingestion.

First, SPV of DBN was hardly changed in the upright head position, either with gaze straight ahead (see figure, A) or in the lateral gaze position (see figure, B). Second, in the + 90° ("prone") head position SPV of DBN was reduced from 11.1 ± 1.3°/second to 3.2 ± 1.3°/second (>70%) (see figure, A). In lateral gaze, in the + 45° head position 15 minutes after ingestion, SPV was reduced from 23.6 ± 1.7°/second to 14.8 ± 2.8°/second (see figure, B). Third, SPV of UBN increased in the −90° head ("supine") position 90 minutes after ingestion from −8.4 ± 2.8°/second to −14.1 ± 1.3°/second in gaze straight ahead (see figure, A), whereas it did not change in lateral gaze. These effects on positional DBN started after 15 minutes and lasted for at least 1 hour (see figure, B).

In the + 45° and + 90° head position the patient noticed a strong improvement of blurred vision and oscillopsia disappeared. Thirty minutes after ingestion visual acuity was improved from 20/60 to 20/30. About 60 minutes after ingestion she noticed perioral and digital paresthesia for 10 minutes.

Discussion. We show that 3,4-DAP exerts a distinct influence on the gravity-dependent component of the vertical velocity bias of DBN.[2] This effect might account for why some DBN patients did not benefit from the therapy.[3] The spontaneous upward drift in DBN may be due to a vestibular tone imbalance,[5] an upward shift of the eyes' null position for vertical gaze holding,[6] or an asymmetry of vertical smooth pursuit signals.[7] The reduction of DBN in the prone pitch position after 3,4-DAP ingestion seems to occur at the cost of increasing UBN, i.e., the velocity bias is shifted in a downward direction. However, the curve relating SPV to head position (see figure, A) was not shifted since differences of DBN in gaze straight ahead between baseline and 3,4-DAP were only found for prone and supine head positions. This indicates specific but asymmetric effects of 3,4-DAP on the gravity-dependent component but only minor effects on the gravity-independent bias. 3,4-DAP seems to reduce DBN by influencing the vestibulocerebellar inhibition, not only of anterior semicircular canal afferents[3] but also of the physiologically overactive otolith-ocular reflex[2] in an asymmetric way.

From the Department of Neurology (Drs. Helmchen, Rambold, and Kömpf, and A. Sprenger and T. Sander), University of Lübeck, Germany; and Department of Neurology (Dr. Straumann), University of Zürich, Switzerland.

Supported by Deutsche Forschungsgemeinschaft (DFG).

Received March 18, 2004. Accepted in final form May 27, 2004.

Address correspondence and reprint requests to Prof. Dr. Christoph Helmchen, Department of Neurology, University Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany; e-mail: helmchen_ch@neuro.mu-luebeck.de

References

1. Zee DS, Yamazaki A, Butler PH, et al. Effects of ablation of flocculus and parafloccullus of eye movements in primate. J Neurophysiol 1981;46: 878–899.
2. Marti S, Palla A, Straumann D. Gravity dependence of ocular drift in patients with cerebellar downbeat nystagmus. Ann Neurol 2002;52:712–721.
3. Strupp M, Schüler O, Krafczyk S, et al. Treatment of downbeat nystagmus with 3,4-diaminopyridine: a placebo-controlled study. Neurology 2003;61:165–170.
4. Helmchen C, Rambold H, Kempermann U, Büttner-Ennever JA, Büttner U. Three-dimensional nystagmus components in mesencephalic lesions. Neurology 2002;59:1956–1965.
5. Baloh RW, Spooner JW. Downbeat nystagmus: a type of central vestibular nystagmus. Neurology 1981;31:304–310.
6. Glasauer S, Hoshi M, Kempermann U, Eggert T, Büttner U. Three-dimensional eye position and slow phase velocity in humans with downbeat nystagmus. J Neurophysiol 2003;89:338–354.
7. Zee DS, Friendlich AR, Robinson DA. The mechanism of downbeat nystagmus. Arch Neurol 1974;30:227–237.

See also pages 606 and 621

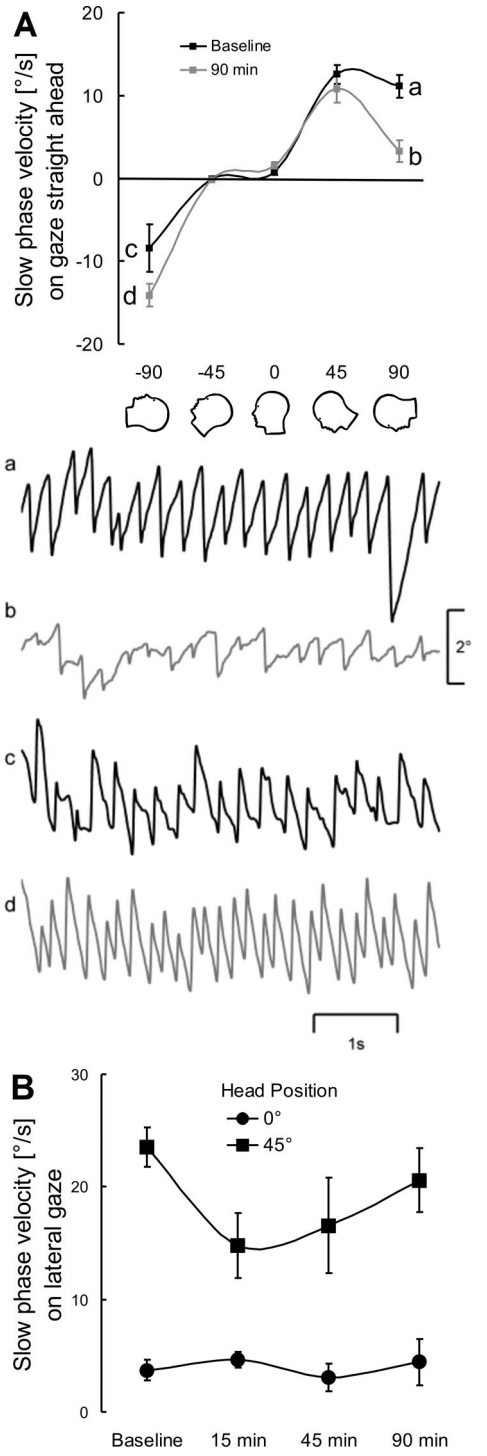

Figure. (A) Vertical ocular drift velocity (slow phase velocity [SPV] in °/second, ± SD) in gaze straight ahead is shown as a function of head position (abscissa) before (black trace) and 90 minutes after (gray trace) 3,4-DAP ingestion. Original recordings for baseline (a, c, black) and 3,4 DAP (b, d, gray) are shown as examples below. The drug hardly affects downbeat nystagmus (DBN) in the upright head position but reduces SPV in the + 90° (prone) and increases it in the −90° (supine) head position. (B) Time course of the SPV of DBN on lateral gaze in the head upright (filled circles) and the + 45° (prone) head position (squares).

Hallucinations during methylphenidate therapy

Varda Gross-Tsur, MD; Adina Joseph, MD; and Ruth S. Shalev, MD

Methylphenidate (MPH) is the medication of choice for attention deficit hyperactivity disorder (ADHD), administered to millions of children with minimal side effects.[1] The appearance of hallucinations at therapeutic doses of MPH has rarely been reported.[1,2] We describe three children with ADHD, who were treated with low doses of MPH and developed complex visual and haptic hallucinations. The causal role of MPH in the development of hallucinations was based on their appearance after ingestion of the drug, resolving after its withdrawal, and the absence of psychiatric comorbidity that could explain such phenomena. In one patient, the hallucinations reappeared after an inadvertent rechallenge.

Case reports. Case 1. A 7-year-old adopted boy with ADHD and oppositional defiant disorder was treated with MPH, 0.3 mg/kg (7.5 mg), once daily. After 1 year of treatment, he reported seeing and feeling snakes crawling on and around him starting ~1 hour after drug ingestion. The teaching staff assumed an emotional problem and used psychological interventions to free him of these behaviors. When these proved ineffective and to rule out drug-induced hallucinations, placebo was substituted for MPH with immediate cessation of hallucinations. Pemoline was begun, and no psychiatric symptoms reappeared during a follow-up period of >2 years.

Case 2. A 12-year-old boy with cerebral palsy, low normal intelligence, and ADHD, combined subtype, was treated with MPH, 0.3 mg/kg (10 mg), once daily with marked improvement in attention and hyperactivity. One morning, he was observed crawling on the floor complaining that roaches were surrounding him. This phenomenon appeared 2 hours after ingesting MPH, continuing for almost 2 hours, and disappeared without any specific intervention. MPH was withdrawn, and there was no recurrence. However, deterioration in school performance was so dramatic that rechallenge with MPH was attempted at his previous dose. Immediate recurrence of hallucinations necessitated stopping MPH. Three-year follow-up evaluation has been uneventful.

Case 3. A 7.5-year-old boy with normal intelligence was diagnosed with ADHD and mild learning disabilities. He had been treated successfully with 0.25 mg/kg MPH once daily (7.5 mg). Several months later, he became distressed, claiming that mosquitoes and other crawling creatures were in his bedroom and on him. He refused to sleep in his bed and would not enter his room. After several days, MPH was stopped, the visual and haptic sensations ceased, and within a week he returned to sleep in his room. During a follow-up period of 2 years, there was no recurrence of the hallucinations.

Discussion. We describe three patients who developed haptic and visual hallucinations at low therapeutic doses of MPH. Rechallenge in Patient 2 elicited hallucinations, and in Patient 1, use of placebo resulted in their cessation. The hallucinations appeared several hours after ingesting MPH. In Patient 2, the hallucinations began shortly after beginning use of MPH, but the other two had received MPH for longer periods. All hallucinatory phenomena resolved promptly after MPH was discontinued.

A previous report of MPH-induced visual and haptic hallucinations in two children is similar to ours; one, after several years of treatment, became fearful and had seen horseflies, whereas the other saw mosquitoes and other bugs on his face, accompanied by an itching sensation. Rechallenge caused reappearance of the hallucinations, and after MPH cessation, the hallucinations disappeared.[2] One additional case was reported of a patient who had been treated with OROS MPH (Concerta, McNeil Consumer & Specialty Pharmaceuticals, Fort Washington, PA).[1]

MPH is a phenylethylamine with structural and pharmacologic properties similar to those of amphetamine, and the effects of both are mediated via neurotransmitter systems, such as dopamine and norepinephrine.[3,4] Visual and auditory hallucinations are known to occur during amphetamine use[5] and are also seen in schizophrenia, a psychiatric illness in which dopamine overactivity is hypothesized to be pathophysiologically relevant.[6] We speculate that hallucinations associated with MPH and amphetamine use, as well as those appearing in schizophrenia, are mediated via dopaminergic pathways, although other neurotransmitter systems may also be involved.

In summary, we describe three children with ADHD who manifested hallucinations as a side effect of MPH at low therapeutic doses. These children were seen in our clinic during a 5-year period during which ~2,000 children with ADHD were diagnosed and treated. The prevalence of hallucinations in conjunction with MPH is rare, probably <0.2%.[1] However, the comorbidities in our patients may have rendered them more vulnerable to hallucinatory phenomena. Because MPH is a widely used, well-studied, and safe pharmacologic agent,[1] physicians who prescribe MPH should be aware of even rare adverse manifestations occurring at therapeutic doses.

From the Neuropediatric Unit, Shaare Zedek Medical Center, Jerusalem, Israel.

The authors received a 1-year research grant in excess of $10,000 from Novartis in 1997.

Received January 19, 2004. Accepted in final form March 26, 2004.

Address correspondence and reprint requests to Dr. Ruth Shalev, Neuropediatric Unit, Shaare Zedek Medical Center, POB 3235, Jerusalem 91031, Israel; e-mail: shalev@szmc.org.il

References

1. Wilens T, Pelham W, Stein M, et al. ADHD treatment with once-daily OROS methylphenidate: interim 12-month results from a long-term open-label study. J Am Acad Child Adolesc Psychiatry 2003;42:424–433.
2. Young JG. Methylphenidate-induced hallucinosis: case histories and possible mechanisms of action. J Dev Behav Pediatr 1981;2:35–38.
3. Klein-Schwartz W, McGrath J. Poison centers' experience with methylphenidate abuse in pre-teens and adolescents. J Am Acad Child Adolesc Psychiatry 2003;42:288–294.
4. Martinez D, Slifstein M, Broft A, et al. Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. J Cereb Blood Flow Metab 2003;23:285–300.
5. Hall W, Hando J, Darke S, Ross J. Psychological morbidity and route of administration among amphetamine users in Sydney, Australia. Addiction 1996;91:81–87.
6. McGowan S, Lawrence AD, Sales T, Quested D, Grasby P. Presynaptic dopaminergic dysfunction in schizophrenia: a positron emission tomographic [18F]fluorodopa study. Arch Gen Psychiatry 2004;61:134–142.

Myxedema, papilledema, and elevated CSF protein

Natasha Frost, MD; Michael S. Lee, MD; and Patrick Sweeney, MD

Elevated CSF protein has been well documented in patients with isolated clinical hypothyroidism and autoimmune thyroiditis-associated encephalopathy.[1-5] Researchers postulate this is caused by dysfunction of the blood-brain barrier (BBB) and protein exchange.[1,4] We report a patient with severe hypothyroidism associated with papilledema, elevated CSF protein, and elevated intracranial pressure (ICP). Her symptoms and signs improved with treatment of hypothyroidism.

Case report. A 45-year-old woman sought treatment for a 2-year history of progressive bilateral blurred vision. Vision did not correct with glasses but did not interfere with activity. Other history included an intermittent dull bilateral frontal headache, low energy, and irregular menses. Her family reported she slept nearly the entire day and was less active. She completed 3 months of acetazolamide therapy for presumed pseudotumor cerebri without improvement in her vision or headache. Her only medical history was pernicious anemia treated with monthly B12 supplementation.

Examination revealed a female with a height of 160 cm and weight of 88 kg. Her pulse was 60 beats/min, and blood pressure was 108/58 mm Hg. She had dry skin, acanthosis nigrans, and myxedematous facial features. There was no thyromegaly. She was cooperative but slow to reply. On Folstein Mini-Mental State Examination, she scored 18 of 30 points. She was not oriented to date, president, or hospital name. She refused to write, read, or copy. Neuro-ophthalmologic evaluation revealed visual acuities of 20/25 OD and 20/30 OS and normal pupillary and slit lamp examinations. She identified 10/10 Ishihara color plates OU. Funduscopic examination showed bilateral disc edema, right greater than left, without hemorrhages or exudates. Poor patient cooperation prevented formal perimetry. Reflexes were symmetric with slow relaxation. The remainder of her neurologic examination was normal.

Brain MRI with and without gadolinium demonstrated two areas of periventricular small vessel disease. MR venography was negative for thrombosis and stenosis. Supine fluoroscopic lumbar puncture revealed an opening pressure of 40 cm of water. The fluid was clear, colorless with 0 RBC, 0 WBC, glucose of 69 mg/dL (reference, 40 to 70), and protein of 192 mg/dL (reference, 15 to 45). Laboratory evaluation demonstrated markedly abnormal thyroid function studies: thyroid-stimulating hormone (TSH), 328.6 μU/mL (reference, 0.4 to 5.5); T4, 0.5 μg/dL (reference, 5.0 to 11.0); T3, < 20 ng/dL (reference, 94 to 170); T4 uptake, 1.31 (0.7 to 1.2); free thyroxine index, 0.4 μg/dL (reference, 6 to 11); thyroglobulin antibody, 401.1 IU/mL (reference, <10); and microsomal antibody, 497.7 IU/mL (reference, <5). With the exception of a hematocrit of 27.1%, mildly decreased response to adrenocorticotropic hormone stimulation, and elevated serum lipids, the remainder of her blood work was unremarkable.

The patient was diagnosed with Hashimoto hypothyroidism. She was prescribed levoxyl (King Pharmaceuticals, Bristol, TN), 100 μg daily. Acetazolamide was not restarted. Repeat lumbar puncture or other therapeutic procedures were not performed. After 6 weeks of treatment, TSH decreased to 10.07 μU/mL, T4 increased to 6.9 μg/dL, and T3 increased to 69 ng/dL. Her headaches, blurred vision, sleep cycle, and energy improved. Repeat ophthalmologic examination revealed acuities of 20/20 OD and 20/30 OS and marked improvement of her papilledema OD and resolution OS.

Discussion. As early as 1938, elevated CSF protein was reported in 25% of patients with myxedema.[1] Later studies documented elevated protein in clinical hypothyroidism but not in subclinical or effectively treated hypothyroidism.[4] The pathophysiology of elevated protein has not been fully elucidated but is postulated to be secondary to altered BBB permeability. This explanation is supported by research demonstrating increased BBB permeability in myxedematous rats.[1] The protein elevation appears unrelated to thyroid antibodies because these are present in clinical and subclinical hypothyroidism.[4]

Several other diagnostic possibilities were considered in this case. Intracranial hypertension has been reported in a number of cases of spinal tumors with elevated CSF protein. The most likely cause seems to be malabsorption of CSF from elevated protein clotting outflow channels.[6] Although a spine MRI was not performed in our patient, the resolution of her signs and symptoms after thyroid replacement argues against a spinal tumor. Whereas headache and papilledema are associated with severe iron deficiency anemia and idiopathic intracranial hypertension, abnormal CSF is an exclusion criteria for both.[1,7] Finally, although autoimmune thyroiditis-associated encephalopathy has elevated CSF protein and cognitive changes, the additional criteria of neuropsychiatric features, myoclonus, generalized tonic-clonic seizures, or focal neurologic deficits were not seen in our patient.[5]

Elevated CSF protein associated with hypothyroidism has been documented, but to our knowledge papilledema and increased ICP have not.[1-3] We suggest elevated CSF protein from hypothyroidism was the cause of our patient's symptoms and should be considered in the differential diagnosis of papilledema.

From the Departments of Neurology (Drs. Frost and Sweeney) and Neuroophthalmology (Dr. Lee), Cleveland Clinic, OH.

Received February 18, 2004. Accepted in final form March 31, 2004.

Address correspondence and reprint requests to Dr. Natasha Frost, Department of Neurology, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195; e-mail: frostn@ccf.org

References

1. Fishman RA. Cerebrospinal Fluid in Diseases of the Nervous System, 2nd ed. Philadelphia: WB Saunders, 1992.
2. Nickel SN, Frame B. Neurologic manifestations of myxedema. Neurology 1958;8:511–517.
3. Merritt HH, Fremont-Smith F. The Cerebrospinal Fluid. Philadelphia: WB Saunders, 1938.
4. Nystrom E, Hamberger A, Lindstedt G, Lundquist C, Wikkelso C. Cerebrospinal fluid proteins in subclinical and overt hypothyroidism. Acta Neurol Scand 1997;95:311–314.
5. Sawka AM, Fatourechi V, Boeve BF, Mokri B. Rarity of encephalopathy associated with autoimmune thyroiditis: a case series from Mayo Clinic from 1950–1996. Thyroid 2002;12:393–398.
6. Costello F, Kardon RH, Wall M, Kirby P, Ryken T, Lee AG. Papilledema as the presenting manifestation of spinal schwannoma. J Neuroophthalmol 2002;22:199–203.
7. Biousse V, Rucker JC, Vignal C, Crassard I, Katz BJ, Newman NJ. Anemia and papilledema. Am J Ophthalmol 2003;135:437–446.

Seroconversion of anti-GM1 antibodies in patients with amyotrophic lateral sclerosis

S. Haggiag, MD; B. Steiner-Birmanns, MD; I. Wirguin, MD; C. Sicsic, BSc; T. Brenner, PhD; and I. Steiner, MD

Elevated titers of anti-GM1 antibodies, particularly those of the IgM class that recognize the Gal β(1–3)Gal-NAc epitope (GM1), are occasionally detected in patients with pure motor syndromes including multifocal motor neuropathies and motor neuron diseases (MNDs).[1] Although circumstantial evidence might implicate these antibodies in MND pathogenesis,[2,3] the administration of immunomodulatory therapies in anecdotal cases of MND with anti-GM1 antibodies has produced controversial or disappointing results.[4,5] Thus, their presence in patients with ALS constitutes a clinical conundrum: Are they the outcome of initial damage to peripheral motor neurons? Do they contribute to the neuronal damage? Is their presence a marker for a small subpopulation of patients who present with motor neuron syndrome but actually do not have MND?

We have recently encountered an ALS patient who developed anti-GM1 antibodies during her disease course. This prompted us to retrospectively study all files of ALS patients hospitalized in our institute within the years 1989 to 2003 for the presence of examinations of anti-GM1 antibodies. Antibodies were measured using the ELISA method: Purified GM1, GD1a, and GO1b (Sigma, St. Louis, MO) in methanol was added to microtitration plates (Costar, New York, NY) until complete evaporation; plates were saturated with 1% bovine serum albumin (BSA; Sigma) in phosphate-buffered saline (pH 7.4) for 4 hours, and serum was added in duplicate to the wells at an initial dilution of 1:400 for anti-GM1 and GD1b and 1:100 for anti-GQ1a in saturating solution and incubated overnight. Sera were considered positive when the difference between GM1-, GD1b-, and BSA-coated wells exceeded 0.2. Positive sera were titrated by serial twofold dilutions until negative.

As such antibodies were not routinely measured in every ALS patient, nor were repeat determinations ordered for all patients who initially had a negative or a low titer (below 1:800), this study was by no means aimed to evaluate the incidence of this phenomenon. Within this period of time, 87 ALS patients were examined for anti-GM1 antibodies. In 20, repeated examinations were performed. In 13 of 20 they were always negative, in 4 of 20 they were always positive, and in 3 of 20 patients seroconversion was detected.

Case reports. A 56-year-old woman presented with a 1-year history of muscle cramps and 3 months of progressive left hand distal weakness. In recent weeks, her family noted a change in her speech and increased fatigability. Her father died at age 49 from ALS of 3 years' duration, and she reported that at age 7, she was hospitalized with the diagnosis of poliomyelitis but recovered completely. Examination revealed a slim woman with mild atrophy of the tongue and fasciculations, minimal distal left hand weakness, brisk deep tendon reflexes, and no pyramidal signs. The rest of the examination was normal. An electrodiagnostic study demonstrated normal conduction velocities with no conduction blocks and active denervation in both upper extremities. Initial titer of anti-GM1 antibodies was negative (below 1:800). The rest of the workup including CSF analysis and systemic immunogram (erythrocyte sedimentation rate, immunoglobulin electrophoresis, antinuclear factor, antibodies to myelin-associated glycoprotein) was normal. Half a year later, a repeated anti-GM1 IgM titer was 1:1,600, while anti-GM1 IgG, anti-GD1b, and anti-GQ1b were negative. A year later, the anti-GM1 IgM titer rose to 1:3,200. Her clinical condition continued to progress. Her speech deteriorated, the strength in both hands worsened, and she started to experience walking difficulties. A course of six plasma exchanges was given with no effect. Today, 3 years since the appearance of symptomatology, she is unable to speak, has a feeding gastrostomy, and is wheelchair bound.

Two additional patients who initially had negative anti-GM1 antibodies and a positive IgM follow-up study were identified (table). They, too, had a typical ALS course and died after 1.5 years of follow-up.

Discussion. These three anecdotal cases raise several questions that need to be addressed in a prospective study to evaluate the significance of our observation: 1) What is the incidence of seroconversion of anti-GM1 antibodies in ALS patients? Currently, we surmise that our observation might represent an underestimated phenomenon, as repeated anti-GM1 titers are measured only in a few ALS patients. 2) Are these antibodies part of the initial pathogenetic mechanism in these patients, or are they the outcome of a previous exposure of motor neuron antigens to the immune system, as has been suggested in postpolio syndrome[6] and other conditions[7]? 3) Do the antibodies contribute to the damage to the nervous system, as has been shown experimentally[3]? 4) Are they present at levels below detection at disease onset and might therefore cause the disease, or are they the outcome of motor neuron damage with exposure of autoantigen to the immune system? A prospective study on a large cohort of ALS patients that will measure the rate of seroconversion of anti-GM1 antibodies and examine the natural history and response to immunomodulatory therapy will enable us to provide answers to these questions.

From the Department of Neurology and Agnes Ginges Center for Human Neurogenetics (Drs. Haggiag, Steiner-Birmanns, Sicsic, Brenner, and Steiner), Hadassah University Hospital, Jerusalem, and Soroka Medical Center (Dr. Wirguin), Faculty of Health Sciences, Ben Gurion University, Beer Sheva, Israel.

Received February 5, 2004. Accepted in final form April 3, 2004.

Address correspondence and reprint requests to Dr. I. Steiner, Department of Neurology, Hadassah University Hospital, PO Box 12 000, Jerusalem, 91 120, Israel; e-mail: isteiner@md2.huji.ac.il

Table *Features of three motor neuron disease patients with seroconversion of anti-GM1 antibodies*

No.	Age, y/sex	Diagnosis	Follow-up period, y	First titer	Second titer	Therapy	Course
1	56/F	fALS	>2.5	Negative	1:1,600	Plasmapheresis	Typical for fALS
2	58/M	ALS	1.5	Negative	1:1,600	None	ALS, died
3	66/M	ALS	1	Negative	1:1,600	None	ALS, died

fALS = familial ALS.

References

1. van Schaik IN, Bossuyt PM, Brand A, Vermeulen M. Diagnostic value of GM1 antibodies in motor neuron disorders and neuropathies: a meta-analysis. Neurology 1995;45:1570–1577.
2. Pestronk A, Chaudhry V, Feldman EL, et al. Lower motor neuron syndromes defined by patterns of weakness, nerve conduction abnormalities, and high titers of antiglycolipid antibodies. Ann Neurol 1990;27:316–326.
3. Corbo M, Quattrini A, Lugaresi A, Santoro M, Latov N, Hays AP. Patterns of reactivity of human anti-GM1 antibodies with spinal cord and motor neurons. Ann Neurol 1992;32:487–493.
4. Dalakas MC, Stein DP, Otero C, Sekul E, Cupler EJ, McCrosky S. Effect of high-dose intravenous immunoglobulin on amyotrophic lateral sclerosis and multifocal motor neuropathy. Arch Neurol 1994;51:861–864.
5. van den Berg LH, Franssen H, Van Doorn PA, Wokke JH. Intravenous immunoglobulin treatment in lower motor neuron disease associated with highly raised anti-GM1 antibodies. J Neurol Neurosurg Psychiatry 1997;63:674–677.
6. Farbu E, Rekand T, Tysnes OB, Aarli JA, Gilhus NE, Vedeler CA. GM1 antibodies in post-polio syndrome and previous paralytic polio. J Neuroimmunol 2003;139:141–144.
7. Ravindranath RM, Ravindranath MH, Graves MC. Augmentation of natural antiganglioside IgM antibodies in lower motor neuron disease (LMND) and role of CD5+ B cells. Cell Mol Life Sci 1997;53:750–758.

CME

Volitional facial palsy after a vascular lesion of the supplementary motor area

Ralf Jox, MD; Roland Bruning, MD; Gerhard Hamann, MD; and Adrian Danek, MD

The concept of parallel cortical representation is well established in sensory systems and increasingly accepted for motor function.[1,2] Dissociation of voluntary and emotional facial movements serves as an excellent example. While the primary motor cortex in the precentral gyrus (M1) is active during voluntary movements, the supplementary motor area (SMA) has been thought essential for emotional innervation.[3] New anatomic studies in nonhuman primates, however, question the role of the SMA and attribute it to the cingulate cortex instead.[4] Whether this new concept holds true also for humans has not yet been addressed.

Case Report. A 62-year-old woman presented with a 2-week history of frontal headache, tingling of the right foot, and word finding difficulties. Upon examination, her face looked symmetric at rest (figure, A), but facial movements were reduced on the right side when she was asked to voluntarily show her teeth or quickly alternate between widening and pursing her lips (see figure, B). Yet, smiling and natural laughing were symmetric (see figure, C). There was some bucco-facial apraxia, but no aphasia on formal testing. In addition, there was a central sensorimotor deficit of the distal right leg with hypesthesia, mild paresis (Medical Research Council scale grade 4+), an increased ankle reflex, and extensor plantar response. MRI revealed a cerebral hemorrhage located in the left superior frontal gyrus and the adjoining medial wall (see figure, D through F). Venous thrombosis appeared to be the most likely cause, even though the superior sagittal sinus was patent both in venous magnetic resonance angiography and T2-weighted imaging. The patient improved considerably on IV heparin.

Discussion. One-sided volitional paresis of the face in the presence of spared emotional innervation has been reported with a variety of lesion sites, ranging from the primary motor cortex and the pyramidal tract down to the pons.[5] Conversely, impaired emotional innervation of the face has been associated with infratentorial lesions, but may also be found after thalamic or anterior capsular damage.[6] Anatomic tract-tracing experiments in nonhuman primates have demonstrated that corticofacial projections arise from six distinct cortical motor areas: M1 (Brodmann area 4/F1), SMA (M2/6m/F3), rostral and caudal cingulate motor cortices (M3 and M4/24c and 23c), and dorsal and ventral lateral premotor cortices (6d and 6v/F2 and F4).[4] These sites have counterparts in distinct cortical areas of the human brain with probably homologous functions.[1,2]

Our patient had a lesion that involved the cortical representation of the lower extremity, thus explaining her sensorimotor deficit of the right foot. Her facial palsy, however, is difficult to explain according to traditional concepts. The face representation of the precentral gyrus (M1) and its descending fibers were clearly spared, as was the lateral premotor cortex. Rather, the lesion was primarily located between the vertical lines through the anterior commissure (VCA) and posterior commissure (VCP), corresponding to the left SMA proper. This area contains a representation of the face.[1,2] We hypothesize that the left SMA lesion was responsible for the right-sided facial motor impairment. In contrast to earlier observations of an emotional facial palsy after SMA resections,[3] this lesion spared the patient's emotional expressions. This is in accordance with recent data demonstrating that the cingulate motor areas are crucially involved in laughter and other facial expression of emotions.[4,7] Our patient's lesion did not extend to the cingulate gyrus or sulcus (see figure E-F). Sparing of its motor areas (M3 and M4) may explain the patient's intact emotional facial innervation.

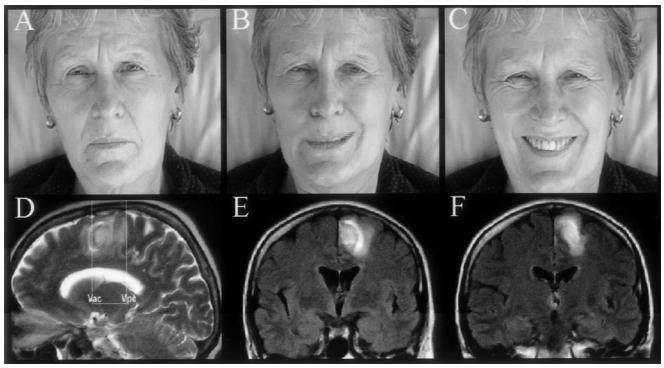

Figure. (A) Face at rest; (B) When pronouncing "x," right lower facial paresis becomes apparent; (C) A laugh produces symmetric facial contractions; (D) A cerebral hemorrhage is seen on the T2-weighted left parasagittal MRI (repetition time [TR] = 5,225 msec, echo time [TE] = 119 msec, slice thickness = 5 mm, distance from midline 14 mm). Damage to the supplementary motor area (SMA) can be inferred from the spatial relation to the vertical lines through the anterior and posterior commissures (VCA and VCP, Talairach stereotaxic system[1]); (E, F) The same lesion in coronal fluid-attenuated inversion recovery sequence images (TR = 5,000 msec, TE = 110 msec, slice thickness = 6 mm). The lesion does not extend to the cingulate sulcus and gyrus.

Clinico-radiologic observations of central facial palsy help to corroborate or refute experimental data concerning parallel motor pathways. Multiple representation is of major clinical interest because of the possible role of parallel motor areas for recovery of function after brain damage.

Acknowledgments

The authors thank Gisela Stenglein-Krapf and Susanne Stuiber for cognitive testing of the patient.

From the Department of Neurology (Drs. Jox, Hamann, and Danek) and the Division of Neuroradiology (Dr. Bruning), University Hospital Munich-Grosshadern, Ludwig-Maximilians-University Munich, Germany.

Received February 16, 2004. Accepted in final form April 12, 2004.

Address correspondence and reprint requests to Prof. Dr. Adrian Danek, Neurologische Klinik and Poliklinik, Ludwig-Maximilians-Universität München, Marchioninistrasse 15, D-81377 München, Germany; e-mail: danek@lmu.de

References

1. Picard N, Strick PL. Motor areas of the medial wall: a review of their location and functional activation. Cereb Cortex 1996;6:342–353.
2. Rizzolatti G, Luppino G, Matelli M. The organization of the cortical motor system: new concepts. Electroencephalogr Clin Neurophysiol 1998; 106:283–296.
3. Laplane D, Talairach J, Meininger V, Bancaud J, Orgogozo JM. Clinical consequences of corticectomies involving the supplementary motor area in man. J Neurol Sci 1977;34:301–314.
4. Morecraft RJ, Louie JL, Herrick JL, Stilwell-Morecraft KS. Cortical innervation of the facial nucleus in the non-human primate: a new interpretation of the effects of stroke and related subtotal brain trauma on the muscles of facial expression. Brain 2001;124:176–208.
5. Hopf HC, Muller-Forell W, Hopf NJ. Localization of emotional and volitional facial paresis. Neurology 1992;42:1918–1923.
6. Ross RT, Mathiesen R. Images in clinical medicine. Volitional and emotional supranuclear facial weakness. N Engl J Med 1998;338:1515.
7. Wild B, Rodden FA, Grodd W, Ruch W. Neural correlates of laughter and humour. Brain 2003;126:2121–2138.

Melatonin, 3 mg, is effective for migraine prevention

M.F.P. Peres, MD, PhD; E. Zukerman, MD; F. da Cunha Tanuri, MD; F.R. Moreira, BS; and J. Cipolla-Neto, MD, PhD

There is increasing evidence that melatonin secretion and pineal function are related to headache disorders. Altered melatonin levels have been found in cluster headache, migraine with and without aura,[1] menstrual migraine,[2] and chronic migraine.[3]

A great variety of melatonin mechanisms may be linked to headache pathophysiology.[3] Melatonin may have anti-inflammatory effect, it scavenges toxic free radicals, reduces the up-regulation of proinflammatory cytokines, and inhibits nitric oxide synthase activity and dopamine release. It also interferes with membrane stabilization, γ-aminobutyric acid and opioid analgesia potentiation, protection from glutamate neurotoxicity, neurovascular regulation, and serotonin modulation. Melatonin and indomethacin share similar chemical structure.[4] Melatonin is then a possible candidate for migraine prevention. We tested the hypothesis of the potential effectiveness of melatonin for migraine prophylaxis.

Methods. We performed an open-label trial of melatonin, 3 mg, for migraine prevention. Forty patients with episodic migraine with or without aura according to the International Headache Society (IHS) diagnostic criteria were screened for the baseline period. Three patients did not have headaches during the baseline period; three patients were lost to follow-up evaluation. Thirty-four patients (29 women, 5 men) started prophylactic treatment with melatonin, 3 mg, 30 minutes before bedtime. Thirty-two patients completed the study. All patients signed an informed consent form. The local and federal ethics committees approved the study.

Study participants experienced between two and eight migraine attacks per month. Chronic daily headache patients were excluded. Patients on preventive therapy 3 months before recruitment for the trial were excluded. Patients were examined, and an adequate headache history was ascertained. Patients with insomnia or considerable sleep hygiene problems were excluded. The total study length was 4 months, with a 1-month baseline period and 3-month therapy phase. A study diary was provided to each study participant.

The primary endpoint was the percentage of patients with >50% reduction in headache frequency comparing baseline vs month 3 after treatment. Headache intensity, duration, and analgesic consumption were also ascertained. Analgesic units were considered according to the IHS classification. Triptans, ergots, nonsteroidal anti-inflammatory drugs, and analgesics were taken. An intention-to-treat analysis was done; all patients who returned for at least one follow-up visit were included (34 patients); and the mean values were carried to month 3.

One-way repeated-measures analysis of variance was used to compare values between the four periods. Tukey method was used for post hoc pairwise comparisons. All p values reported were two-tailed, and values <0.05 were considered significant.

Results. Thirty-two of 34 patients completed the study; 78.1% of patients (25/32) who completed the study had at least 50% reduction. No patients reported increase in headaches. Complete (100%) response was achieved in 8 patients (25%), >75% reduction was found in 7 patients (21.8%), and 50 to 75% reduction was seen in 10 patients (31.3%) after 3 months of therapy. Melatonin decreased headache frequency (7.6 ± 3.2 headaches/month at baseline, 4.4 ± 2.5 at month 1, and 3.0 ± 3.1 at month 3; $p < 0.001$), headache intensity on a 0 to 10 scale (7.4 ± 1.3 at baseline, 5.5 ± 1.9 at month 1, and 3.6 ± 2.7 at month 3; $p < 0.001$), and duration in hours (19.8 ± 19.8 at baseline, 10.2 ± 13.4 at month 1, and 8.8 ± 12.4 at month 3; $p < 0.001$). Significant clinical improvement was already achieved at month 1. Overall analgesic and triptan consumption also decreased ($p < 0.001$). Menstrually associated migraines equally decreased in frequency. Two patients withdrew from the study, one because of excessive sleepiness and the other because of alopecia. Three patients spontaneously reported increase in libido. No changes in body weight occurred (baseline 62.5 ± 10.0 kg vs month 3 62.5 ± 10.2 kg).

Discussion. Melatonin and migraine are linked in several ways. A circadian attack predilection has been reported in episodic (55%) and chronic (62.5%) migraineurs.[5] A distribution of attacks according to the estrous cycle is evident in menstrual migraine. True menstrual migraine occurs in 14%; menstrually associated migraine can occur in up to 55% of cases.[6] A circannual variation can be observed in cyclic migraine or in the cluster migraine association.

Only small studies reported benefit in migraine patients from melatonin treatment. One showed relief after melatonin infusion in status migrainous. A patient with delayed sleep phase syndrome and migraine had a dramatic decrease in headaches after beginning melatonin treatment.[7] This is the first study to assess melatonin efficacy in migraine prevention. In our small series of migraine patients, melatonin was effective in reducing the number of headache days per month. A controlled study may be worthwhile.

From the Hospital Israelita Albert Einstein (Drs. Peres, Zukerman, da Cunha Tanuri, and Moreira), São Paulo, Brazil; and Instituto de Ciências Biomédicas (Dr. Cipolla-Neto), Universidade de São Paulo, Brazil.

Received January 31, 2004. Accepted in final form April 14, 2004.

Address correspondence and reprint requests to Dr. Mario F.P. Peres, Al. Joaquim Eugenio de Lima, 881 cj 708, 01403-001 São Paulo SP, Brazil; e-mail: marioperes@yahoo.com

References

1. Claustrat B, Loisy C, Brun J, et al. Nocturnal plasma melatonin levels in migraine: a preliminary report. Headache 1989;29:242–245.
2. Murialdo G, Fonzi S, Costelli P, et al. Urinary melatonin excretion throughout the ovarian cycle in menstrually related migraine. Cephalalgia 1994;14:205–209.
3. Peres MF, Sanchez del Rio M, Seabra ML, et al. Hypothalamic involvement in chronic migraine. J Neurol Neurosurg Psychiatry 2001;71:747–751.
4. Peres MF, Stiles MA, Oshinsky M, Rozen TD. Remitting form of hemicrania continua with seasonal pattern. Headache 2001;41:592–594.
5. Galego JC, Cipullo JP, Cordeiro JA, Tognola WA. Clinical features of episodic migraine and transformed migraine: a comparative study. Arq Neuropsiquiatr 2002;60:912–916.
6. Silberstein SD. The role of sex hormones in headache. Neurology 1992; 42(suppl 2):37–42.
7. Claustrat B, Brun J, Geoffriau M, Zaidan R, Mallo C, Chazot G. Nocturnal plasma melatonin profile and melatonin kinetics during infusion in status migrainosus. Cephalalgia 1997;17:511–517.

HSV-2 sacral radiculitis (Elsberg syndrome)

O. Eberhardt, MD; W. Küker, MD; J. Dichgans, MD; and M. Weller, MD

A self-limiting syndrome of acute urinary retention in combination with variable other signs of spinal cord dysfunction and CSF pleocytosis was described by Elsberg >70 years ago.[1] In many instances, a viral etiology is found, and herpes simplex virus type 2 (HSV-2) reactivation from spinal ganglia is the most common associated infection. Lumbosacral involvement in neoplastic disease, as also reported by Elsberg, is rare. The clinical presentation of mostly younger patients with signs of acute radiculomyelitis, such as transient urinary retention and sensory lumbosacral symptoms, is thus referred to as Elsberg syndrome. Sexually active women are preferentially affected, adolescents only rarely.

Case report. We report a 40-year-old woman who developed sensory loss in a lower sacral dermatome distribution, dull pain in the buttock region, and acute urinary retention. There were no motor symptoms, no obstipation, no fever, and no rash. CSF showed lymphocytic pleocytosis (162/μL) with elevated albumin (690 mg/dL). Serum HSV-2 immunoglobulin (Ig) M and IgG titers and the CSF/serum IgG index for herpes virus (3.7) were elevated, and HSV-2 PCR in the CSF was positive. Proctoscopy and gynecologic examination were normal. A diagnosis of HSV-2-related Elsberg syndrome was made. IV acyclovir for 2 weeks led to an almost complete resolution of pain and sensory loss.

Discussion. HSV-2 lies dormant in ~40% of sacral dorsal root ganglia, and newly replicated virus can spread axonally into the spinal cord. Alternatively, primary genital infection is assumed to cause neurologic dysfunction in younger patients. The presence of serum IgM antibodies does not prove primary infection but also can occur in reactivation. Urinary retention is found in ~5% of anogenital herpetic infections.[2] Associated neurologic dysfunction can be missed if subtle or can be lacking. Only a preceding anogenital rash or enlarged inguinal lymph nodes may suggest herpetic infection. In other cases, there is no exanthemic or enanthemic rash, or rash follows neurologic symptoms.[3] Herpetic proctitis with urinary retention is found in infection related to anal sexual intercourse.

Apart from urinary retention, constipation, erectile dysfunction, dull pain in the anogenital region, paresthesias, loss of sensation, or flaccid paresis of leg muscles in various combinations can be found.[2] Consistent with the lumbosacral origin of infection, the conus medullaris and lower thoracic cord are predominantly affected.[4] An ascending myelitis with often fatal outcome within weeks has been observed especially in immunosuppressed patients. Diabetes, HIV infection, and neoplasm seem to predispose to cervicothoracic ascension of necrotizing myelitis.[5] More recently, fatal cases of HSV-2 myelitis in immunocompetent patients and cases with midthoracic lesions have been reported.[4,6] HSV-2 infection can also cause isolated aseptic meningitis or encephalitis.

Other viruses implicated in lumbosacral radiculomyelitis include HSV-1, cytomegalovirus, Epstein–Barr virus, varicella-zoster virus, and enteric cytopathogenic human orphan virus.[3] The diagnosis of herpes infection is based on PCR technology and can be complemented by culture from vesicular fluid or less successfully from CSF, or by increasing antibody titers.[6] The CSF in symptomatic cases shows mild to moderate lymphocytic pleocytosis with minor elevation of CSF protein.

MRI in viral radiculomyelitis shows varying degrees of root or lower spinal cord edema with enlargement and hyperintensity on T2-weighted images, accompanied by contrast enhancement in acute infection but may be normal in other cases.[4] MRI reports of HSV sacral radiculitis or radiculomyelitis are sparse.[3,4] In our patient, there were enlarged and contrast-enhancing sacral radicular fibers without affection of the conus medullaris. These changes resolved after antiviral treatment (figure).

Remission is mostly complete in milder cases after one to several weeks. Antiviral treatment may shorten the symptomatic period if HSV infection is confirmed, although no evidence for neurologic improvement in herpetic radiculomyelitis from controlled trials is available. IV acyclovir for 10 to 14 days is the treatment of choice for immunocompromised patients or patients with severe or progressive disease. Severe myelitic deficits often persist despite antiviral treatment.[6] Vidarabine or corticosteroids have been claimed to speed improvement in single cases. Symptomatic treatment consists of analgesics, cholinergic drugs against detrusor areflexia, or intermittent catheterization. A recurrence of symptoms occurs in up to 30% of patients during the first year after herpetic meningitis or radiculomyelitis.[7] Thus, in a case of acute urinary retention with sacral sensory symptoms, an anogenital rash or mucosal lesion has to be looked for, and MRI and CSF examination may be necessary to exclude demyelinating disease and to establish the diagnosis of a potentially serious, but treatable, infectious disease.

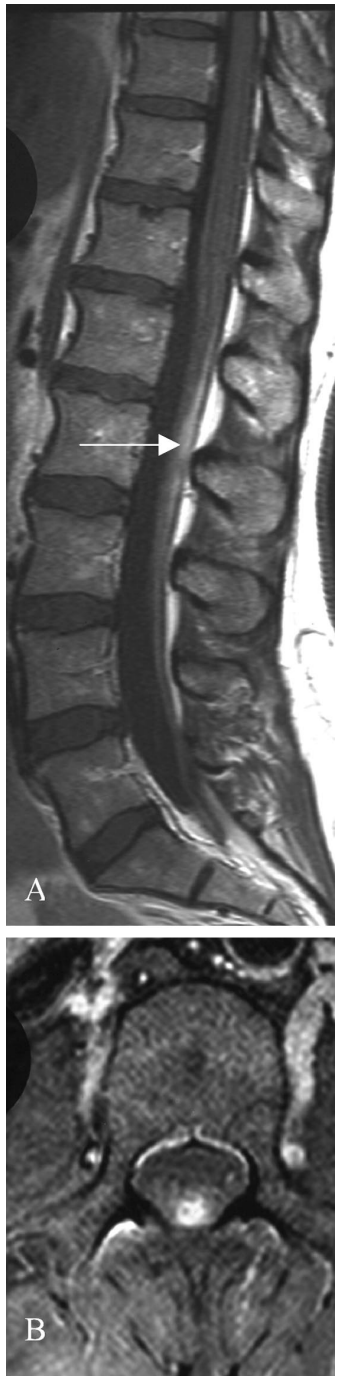

Figure. MRI documentation of herpes simplex virus type 2 (HSV-2)-induced Elsberg syndrome. Sagittal contrast-enhanced T1-weighted image (A) and transverse T1-weighted contrast-enhanced imaging at the level of the second lumbar vertebral body (fat suppression; B) show swollen radicular fibers in the upper lumbar spinal canal (A, arrow). The conus medullaris is not affected.

From the University of Tubingen Medical School, Germany.

Received February 3, 2004. Accepted in final form April 19, 2004.

Address correspondence and reprint requests to Dr. Michael Weller, University of Tubingen Medical School, Hoppe-Seyle-Strasse 3, Tubingen, D-72076 Germany; e-mail: Michael.weller@uni-tuebingen.de

References

1. Elsberg CA. Experiences in spinal surgery. Observation upon 60 laminectomies for spinal disease. Surg Gynecol Obstet 1931;16:117–135.
2. Oates JK, Greenhouse PRDH. Retention of urine in anogenital herpetic infection. Lancet 1978;I:691–692.
3. Küker W, Schaade L, Ritter K, Nacimiento W. MRI follow-up of herpes simplex virus (type 1) radiculomyelitis. Neurology 1999;52:1102–1103.
4. Ellie E, Rozenberg F, Dousset V, Beylot-Barry M. Herpes simplex virus type 2 ascending myeloradiculitis: MRI findings and rapid diagnosis by the polymerase chain method. J Neurol Neurosurg Psychiatry 1994;57:869–870.
5. Wiley CA, Van Patten PD, Carpenter PM, Powell HC, Thal LJ. Acute ascending necrotizing myelopathy caused by herpes simplex virus type 2. Neurology 1987;37:1791–1794.
6. Nakajima H, Furutama D, Kimura F, et al. Herpes simplex virus myelitis: clinical manifestations and diagnosis by the polymerase chain method. Eur Neurol 1998;39:163–167.
7. Aurelius E, Forsgren M, Gille E, Skoldenberg B. Neurologic morbidity after herpes simplex type 2 meningitis: a retrospective study of 40 patients. Scand J Infect Dis 2002;34:278–283.

Bilateral extraocular muscle atrophy in myotonic dystrophy type 1

T. Yamashita, MD; E. Matsubara, MD, PhD; I. Nagano, MD, PhD; M. Shoji, MD, PhD; and K. Abe, MD, PhD

External ophthalmoplegia is a rare sign in myotonic dystrophy type 1 (DM1). DM1 is caused by the expansion of an unstable CTG repeat in the *DMPK* gene on chromosome 19q13.3. Herein we report on a 31-year-old man with DM1 who developed unusual clinical symptoms: external ophthalmoplegia, upper limb-girdle muscle atrophy, and talipes equinovarus. Subsequent MRI revealed extremely atrophic extraocular muscles as compared with an age-matched healthy individual, indicating that this MRI finding confirms the pathologic relevance of extraocular muscle atrophy for ophthalmoplegia found in this DM1 patient.

Case report. A 31-year-old man was referred with dysarthria, diplopia, and dyspnea. A peculiar cry and difficulty in feeding were present from birth. At age 5 years, he was unable to run fast, and his voice sounded nasal. At age 9 years, bilateral talipes equinovarus and ophthalmoplegia were recognized. He noted a dyspnea at age 20 years and a progressive dysarthria since age 25 years. These symptoms have progressed slowly, and he had cardiac failure and pneumonia at age 31 years; thereafter, he was admitted to our hospital. His mother showed dysarthria, dysphasia, external ophthalmoplegia, and talipes equinovarus with childhood onset, which is almost identical to his clinical symptoms. On neurologic examination, he showed marked impairment of vertical and horizontal gazes of both eyes. Blepharoptosis was not evident, but bilateral weakness of facial muscles resulted in lagophthalmos and a small mouth unable to open wide. In addition to the small nasal voice, he was unable to keep talking long. Weakness was found in upper limbs, more marked proximally than distally, but sternocleidomastoid muscles were well preserved. He clearly had grip and percussion myotonia, but cataract, frontal baldness, and endocrine abnormality were absent. He also showed the congenital features: bilateral talipes equinovarus and high arched palate. There was no evidence of cognitive impairment or abnormalities in sensory, cerebellar, or autonomic nervous system function. EMG revealed typical myotonic changes such as dive bomber sound and myotonic discharge. No rapid reduction in the amplitude of compound muscle action potentials was evoked during repetitive nerve stimulation. The muscle biopsy also revealed chronic dystrophic features, but the ragged-red fibers, rimmed vacuole, and spheroid body were negative. The diagnosis for DM1 was confirmed by the presence of 60 CTG triplet expansion in the *DMPK* gene on chromosome 19q13.3. No examination of his mother with a clinical feature of myotonia could be made because she died of heart failure at age 43 years. Her younger twin had feeding difficulty from birth and died of respiratory failure at 4 months. The maternal grandaunt had diabetes, and the maternal granduncle had diabetes and frontal baldness. The inheritance appears to be compatible with a dominant trait.

Discussion. Control image of the patient (figure, A) showed small, atrophic extraocular muscles as compared with that obtained from the age-matched healthy volunteer (see figure, B). The sections compared represent the largest area, corresponding to the center of the muscle. The relative sparing of extraocular muscles is well known in myotonic dystrophy;[1,2] only slow saccades are observed in its mildest form, whereas external ophthalmoplegia is present in some severe cases.[1-6] In the latter, ophthalmoplegia is unequivocally associated with ptosis, which was not the case in our patient.[3-6] From this point of view, our patient also differed strikingly from chronic progressive external ophthalmoplegia, oculopharyngeal muscular dystrophy, and myasthenia gravis. There were no ragged red fibers and rimmed vacuole on muscle biopsy and no significant response to edrophonium chloride, making the aforementioned disorders unlikely. The common feature, extraocular muscle atrophy, may support the evidence that progressive external ophthalmoplegia was caused by myogenic muscular atrophy.

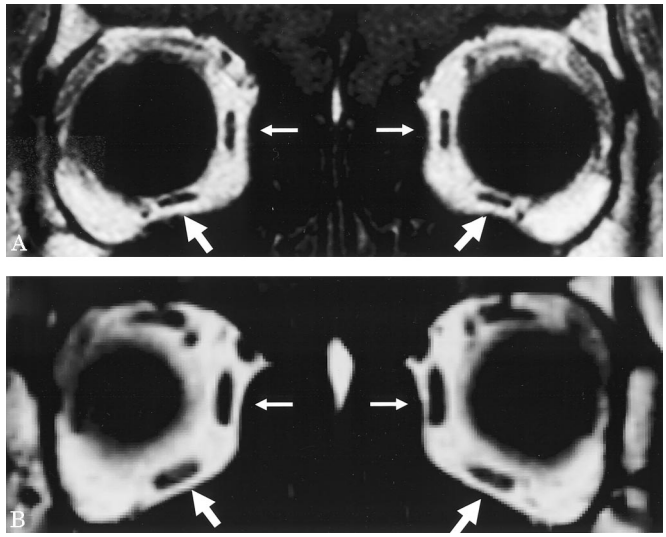

Figure. MRI for extraocular muscles in (A) patient with myotonic dystrophy (DM1) and (B) healthy control subject with coronal T1-weighted orbital image. Note the small and thin extraocular muscles bilaterally (thin arrows indicate medial recti; thick arrows, inferior recti).

It is relevant to note that our patient appears to have a congenital form of DM1, given its onset and severity. Usually a large CTG expansion is evident in the congenital form of DM1, but this is not the case in our patient. The lack of typical features, such as preserved sternocleidomastoid muscles, cataract, frontal baldness, and endocrine abnormality, is also characteristic in this case. It is possible that genotype may not always predict phenotype and that some other genetic and epigenetic factors may be operative. Although this is a unique case of the congenital form of DM1, further examination is necessary to determine whether our patient has a possible unique phenotype of myotonic dystrophy carrying an additional gene abnormality.

From the Department of Neurology, Graduate School of Medicine and Dentistry, Okayama University, Japan.

Received November 19, 2003. Accepted March 26, 2004.

Address correspondence and reprint requests to Dr. Koji Abe, Department of Neurology, Graduate School of Medicine and Dentistry, Okayama University, 2-5-1 Shikata-cho, Okayama 700-8558, Japan; e-mail: abek@cc.okayama-u.ac.jp

References

1. Di Costanzo A, Toriello A, Mottola A, Di Iorio G, Bonavita V, Tedeschi G. Relative sparing of extraocular muscles in myotonic dystrophy: an electrooculographic study. Acta Neurol Scand 1997;95:158–163.
2. Jones KJ, North KN. External ophthalmoplegia in neuromuscular disorders: case report and review of the literature. Neuromusc Disord 1997;7: 143–151.
3. Verry F. Myotonie dystrophique (maladie de Steinert) avec alteration masculaire degenerative. Ophthalmoplegia (Basel) 1947;114:281–284.
4. Walton JN, Nattrass FJ. On the classification, natural history, and treatment of the myopathies. Brain 1954;77:169–231.
5. Davidson SI. The eye in dystophia myotonia with a report on electromyography of the extra-ocular muscles. Br J Ophthalmol 1961;45:183–196.
6. Lessell S, Coppeto J, Samet S. Ophthalmoplegia in myotonic dystrophy. Am J Ophthalmol 1971;71:1231–1235.