Brachial amyotrophic diplegia associated with a novel *SOD1* mutation (L106P)

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Brachial amyotrophic diplegia (BAD) is a subtype of sporadic lower motor neuron disease (LMND) presenting with adult onset, mainly in men, and remaining largely restricted to proximal arm and shoulder girdle muscles without involvement of the lower limbs or appearance of pyramidal signs.[1,2] Mutations in the copper/zinc superoxide dismutase (*SOD1*) gene have been described in familial cases of ALS and occurring in sporadic cases of ALS,[3-4] but not in patients with BAD. We describe here a patient with BAD syndrome associated with a novel *SOD1* mutation.

Case report. A 77-year-old man was referred to our clinic for a 12-month history of bilateral painless arm weakness and wasting. The patient did not have a history of diabetes. Weakness began in the left arm and progressed to the proximal right arm 2 months later. Family history was unremarkable for neuromuscular disorders and entrapment neuropathies. There were no symptoms in the lower limbs or sphincter disturbances. Neurologic examination showed a peculiar posture of the "man in the barrel" with both hands hanging loosely at his sides (figure). Severe atrophy and weakness of both upper limb muscles were present, mainly in proximal areas (Medical Research Council score 1/5 for shoulder abductor and flexor muscles, supraspinatus, infraspinatus, deltoid, biceps brachii, and pectoralis major; 2/5 for elbow extensor, flexor, and wrist extensor muscles; 3/5 for wrist flexor and hand muscles). There was no atrophy or weakness in the bulbar or neck muscles or in the lower limbs and no scapular winging. Fasciculations were evident only in the upper limb muscles. Tendon reflexes were absent in the upper limbs and normal at the knees and ankles. Plantar responses were flexor. Sensory examination was normal, and no other neurologic signs were found. Needle electromyography showed denervation potentials with reduced recruitment in all upper limb muscles but normal facial, tongue, neck, and lower limb muscles. Nerve conduction studies in the upper limbs showed lower amplitude of compound muscle action potentials of the median, ulnar, and radial nerves, bilaterally, with normal motor and sensory nerve conduction velocities and without evident conduction blocks. Nerve conduction studies in the lower limbs were normal. A wide screening was otherwise normal, including brain and spinal cord MR images, CSF examination, and blood studies (cell counts, erythrocyte sedimentation rate, immunoelectrophoresis, creatine kinase, vitamin B_{12}, β-hexosaminidase, thyroid function, research for tumor markers, antinuclear antibodies, anti-GM1 and anti-asialo GM1 antibodies). Genetic testing for mutations in the survival motor neuron gene (exons 7 and 8) and for X-linked spinobulbar muscular atrophy was negative. Direct sequencing of the five exons of *SOD1* gene revealed a heterozygous substitution T to C in exon 4 at position 1,126 (see figure E-1 on the *Neurology* Web site at www.neurology.org) that caused an amino acid change at codon 106 (leucine to proline, L106P). This mutation was not found in 150 normal control subjects from southern Italy or in the patient's asymptomatic daughter, age 45. The clinical conditions of the patient remained stable over the following 18 months, and no

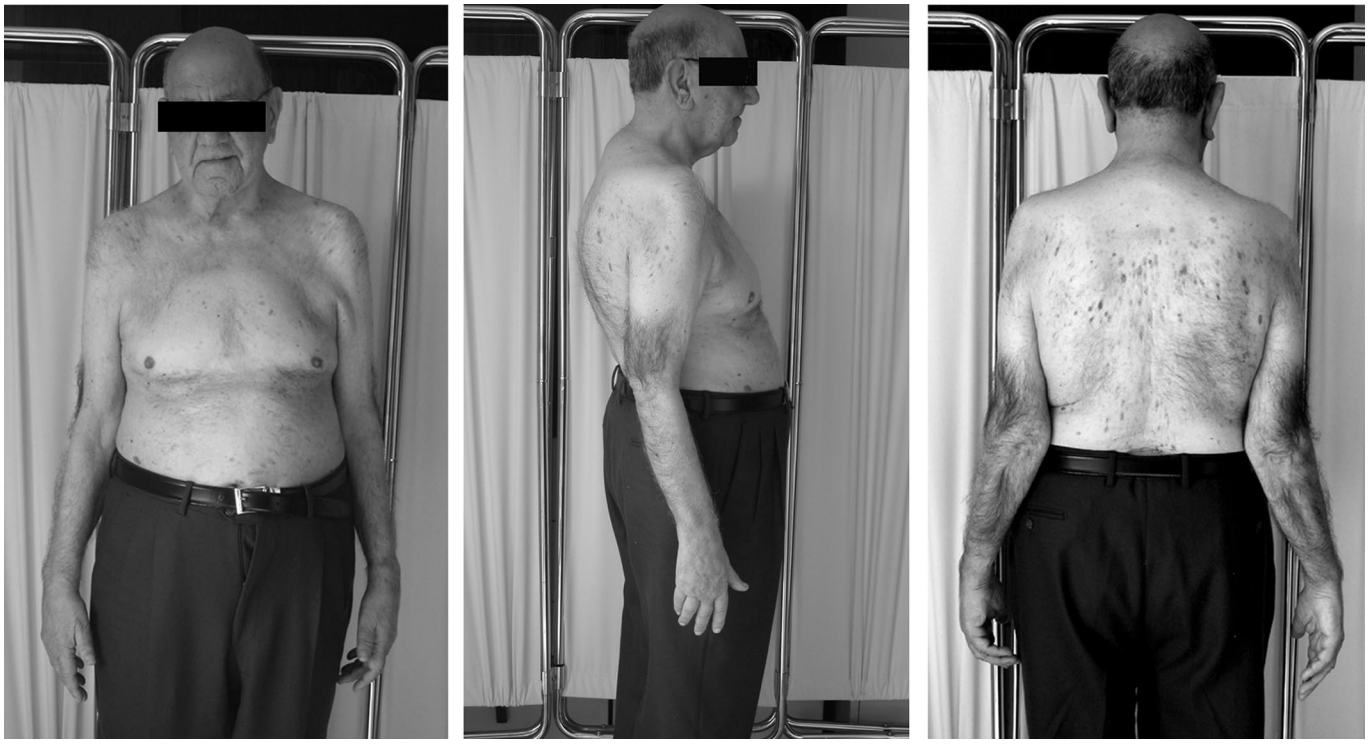

Figure. A 77-year-old man had a 12-month history of bilateral painless arm weakness and wasting. Neurologic examination showed a peculiar posture of the "man in the barrel" with both hands hanging loosely at his sides.

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further progression of the disease into areas other than the upper limbs was evident.

Discussion. BAD syndrome is a form of LMND without known genetic defects. Our patient had clinical and electrophysiologic findings of BAD and a mutation in the *SOD1* gene. Many *SOD1* mutations have been described in patients with both familial or sporadic ALS, spreading through the entire *SOD1* coding or noncoding regions.[3-5] Although we cannot exclude that our patient may further develop signs of ALS, our conclusion 30 months after the onset of the disease confirmed an involvement restricted to the upper limbs and without pyramidal tract dysfunction. The mutation L106P identified in our patient has not been previously described. A different amino acid substitution (leucine to valine) in the same codon (L106V) has been reported in two families with autosomal dominant ALS.[6] The clinical characteristics of these patients were similar to those reported in other cases of familial ALS with *SOD* mutations. Of note, the patients with Leu106Val substitution had an earlier age at onset than that observed in our case. L106, an evolutionarily conserved residue among different species, is the major hydrophobic plug for the end of the β barrel, and L106 changes are expected to destabilize the subunit fold.[7] Valine and proline mutants could have a different effect for maintaining the β-barrel fold. Although valine at codon 106 might be expected to alter hydrophobic packing interactions of the side chain into the end of the β barrel, proline at codon 106 might be expected to introduce restriction to the allowed backbone angles along the polypeptide chain turn at one pole of the β barrel and could also affect packing.

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References

1. Katz JS, Wolfe GI, Andersson PB, et al. Brachial amyotrophic diplegia. A slowly progressive motor neuron disorder. Neurology 1999;53:1071–1076.
2. Van den Berg-Vos RM, Visser J, Franssen H, et al. Sporadic lower motor neuron disease with adult onset: classification of subtypes. Brain 2003; 126:1036–1047.
3. Jones CT, Brock DJH, Challencellor AM, et al. Cu/Zn superoxide dismutase (SOD1) mutations and sporadic amyotrophic lateral sclerosis. Lancet 1993;342:1050–1051.
4. Shaw CE, Enayat ZE, Chioza BA, et al. Mutations in all five exons of SOD-1 may cause ALS. Ann Neurol 1998;43:390–394.
5. Conforti FL, Magariello A, Mazzei R, et al. Abnormally high levels of SOD1 mRNA in a patient with amyotrophic lateral sclerosis. Muscle Nerve 2004;29:610–611.
6. Cudkowicz ME, McKenn-Yasek D, Sapp PE, et al. Epidemiology of mutations in superoxide dismutase in amyotrophic lateral sclerosis. Ann Neurol 1997;41:210–221.
7. Deng HX, Hentati A, Tainer JA, et al. Amyotrophic lateral sclerosis and structural defects in Cu,Zn superoxide dismutase. Science 1993;261:1047–1051.

Hirayama disease associated with a severe rhythmic movement disorder involving neck flexions

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Hirayama disease is a cervical myelopathy with teenage onset of unilateral or asymmetric weakness and atrophy of intrinsic hand and forearm muscles. It is initially progressive for several years but eventually stabilizes.[1,2] Its pathophysiology is still debated: Most authors report evidence of dynamic cord compression during neck flexion,[1-4] but others disagree with this terminology.[5]

We report on a 10-year-old girl with Hirayama disease who, since infancy, had had a severe and persistent nocturnal rhythmic movement disorder with extreme repeated neck flexions caused by body and head rocking in a prone position.

Case report. The girl had a 10-month history of difficulty using her left hand while playing the clarinet and performing gymnastics, increasing when her hand was cold. She had no history of trauma, pain, paresthesias, or symptoms referring to the lower extremities and no family history of neurologic disease. On examination, she was a prepubertal girl with height in the 75th percentile. She had atrophy and weakness (Medical Research Council grade 3 to 4/5) of the thenar, hypothenar, and interossei muscle groups of the left hand and mild weakness of finger extension on the same side. There was no weakness more proximally or in other limbs and no fasciculations. Sensory examination was normal, and all deep tendon reflexes were present and symmetric.

Nerve conduction study in the upper limbs showed normal motor nerve conduction velocity for ulnar (wrist to Erb point) and median (wrist to elbow) nerves. Compound muscle action potential amplitude was reduced on the left (right/left ulnar nerve = 13/0.7 mV, normal >5 mV; right/left median nerve = 9/2.5 mV, normal >5 mV). Ulnar nerve F waves were absent on the left and normal on the right. Orthodromic sensory nerve action potentials of the right and left ulnar nerves were of normal amplitude (>8 μV). Needle EMG showed a reduced interference pattern with polyphasic and high-amplitude motor unit potentials during voluntary activity and fasciculation potentials at rest in the left flexor carpi radialis and abductor pollicis brevis muscles. Standard cervical spine MRI with contrast material and routine blood studies were normal. MRI in neck flexion could not be obtained.

Several weeks later, the parents reported an unusual rocking habit during sleep since infancy. They made a videotape of the episodes showing the child in the prone position with knees flexed under her torso and head down in her pillow, rocking back and forth (one cycle lasting 1 to 2 seconds), flexing her neck violently and repeatedly for approximately 15 minutes (figure). This occurred every night, often several times in the same night. These episodes were consistent with a rhythmic movement disorder (RMD).[6] We encouraged the family to wake the child each time she started with the body rocking; the habit disappeared within 2 weeks and did not recur.

At the 3-year follow-up examination, there was no progression of hand weakness or atrophy and no other symptoms. Some left-hand atrophy persists with a mild improvement in strength.

Discussion. This case fulfills the requirements for the diagnosis of Hirayama disease.[2] Its association with a severe motor stereotypy affecting the neck suggests that the two are related. RMDs with head and body rocking are a known variety of childhood parasomnia.[6] However, the violent neck flexions and the late persistence of the movements are unique in this case.

If Hirayama disease and the RMD are indeed related and if the clinical syndrome is due to repeated microtraumas, why did our patient become symptomatic in early teenage years while the stereotypy had been present since infancy? The occurrence of her symptoms corresponds to the beginning of the growth spurt in girls. It has been hypothesized that a disproportionate shortening of the dorsal roots accentuated during the juvenile growth spurt might explain the timing of the onset of the condition.[7] Hirayama disease is much more frequent in males (17:1),[2] and it may be that very unusual conditions must occur for the disease to manifest in females.

This case is a striking "natural" model of the possible role of neck flexion as a pathogenic factor in Hirayama disease and argues for repeated neck flexions as a possible mechanical or traumatic origin of the disease.

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Figure. Instant photographs taken from parent's video recording from the nocturnal head and body rocking, showing the sequence of the stereotypy with extreme neck flexion. One full cycle of the rocking lasted 1 to 2 seconds. This was repeated for as long as 15 minutes, often several times per night.

References

1. Hirayama K, Tokumaru Y. Cervical dural sac and spinal cord in juvenile muscular atrophy of distal upper extremity. Neurology 2000;54:1922–1926.
2. Kikuchi S, Tashiro K. Juvenile muscular atrophy of distal upper extremity (Hirayama's disease). In: Jones HR, De Vivo DC, Darras BT, eds. Neuromuscular disorders of infancy, childhood, and adolescence: a clinician's approach. Philadelphia: Butterworth Heinemann, 2003:167–181.
3. Baba Y, Nakajima M, Utsunomiya H, et al. Magnetic resonance imaging of thoracic epidural venous dilation in Hirayama disease. Neurology 2004;62:1426–1428.
4. Restuccia D, Rubino M, Valeriani M, Mirabella M, Sabatelli M, Tonali P. Cervical cord dysfunction during neck flexion in Hirayama's disease. Neurology 2003;60:1980–1983.
5. Willeit J, Kiechl S, Kiechl-Kohlendorfer U, Golaszewski S, Peer S, Poewe W. Juvenile asymmetric segmental spinal muscular atrophy (Hirayama's disease): three cases without evidence of "flexion myelopathy." Acta Neurol Scand 2001;104:320–322.
6. Hoban TF. Rhythmic movement disorder in children. CNS Spectr 2003; 8:135–138.
7. Toma S, Shiozawa Z. Amyotrophic cervical myelopathy in adolescence. J Neurol Neurosurg Psychiatry 1995;58:56–64.

A 35-year-old woman with uterine fibroids and multiple embolic strokes

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Paradoxical embolism remains an important cause of stroke in the young. If a patent foramen ovale (PFO) is present, an intensive search for the source of the thrombus is warranted. We report a 35-year-old woman with stroke, in whom the transesophageal echocardiogram showed a patent foramen ovale. Further investigation revealed thrombosis of the iliac veins adjacent to a massively enlarged fibroid uterus.

Case report. A previously healthy, right-handed, 35-year-old woman was admitted to the emergency department with weakness of her left arm and her left leg. These symptoms abruptly began 4 hours before admission while she was going about her usual daily activities. She had no sensory or visual changes, no cardiac or pulmonary symptoms, and was not hypertensive or diabetic. She denied cocaine use, trauma, prior deep vein thrombosis (DVT), or migraine. She had noted heavy menses for the past 12 years and had been diagnosed with a uterine fibroid 3 years previously. She had declined treatment for this. Examination revealed left sided hemiparesis with the leg more affected than the arm. There was slight left sided facial weakness. Cortical sensation and other cranial nerves were normal. There were no cerebellar signs, dysphasia, or neglect. There were no murmurs or bruits and the cardiac rhythm was regular. The uterus was palpable midway between the umbilicus and symphysis pubis.

DWI of the brain showed a hyperintense signal in the distribution of the right anterior cerebral artery with involvement of the ipsilateral middle cerebral territory as well (figure, A). The patient was started on aspirin and investigated for various causes of stroke. Complete blood count, ESR, platelet count, prothrombin time, and partial thromboplastin time were normal other than for evidence of mild iron deficiency anemia. Lipid profile, Sickle test, rapid plasma reagin for syphilis, lupus anticoagulant, urine drug screen, protein C and S levels, activated protein C resistance, antithrombin III, prothrombin gene, and factor V Leiden were all normal. ANA titers, rheumatoid factor, and homocysteine levels were normal. MRA of the cerebral and neck vessels and Doppler of the carotids were normal. The only abnormality on the transesophageal echocardiogram was a PFO with a maximum diameter of 6 mm with a right to left shunt during Valsalva maneuver. The atrial septum was aneurysmal. Doppler of the lower extremities revealed no thrombus in the leg veins. MR venography revealed bilateral internal iliac thrombi and compression of the common iliac and inferior vena cava (figure, B) by the large uterus. A heparin infusion was started and the patient was put on warfarin with a goal of maintaining INR between 2.0 and 3.0. A Greenfield filter was inserted in the inferior vena cava and catheter closure of

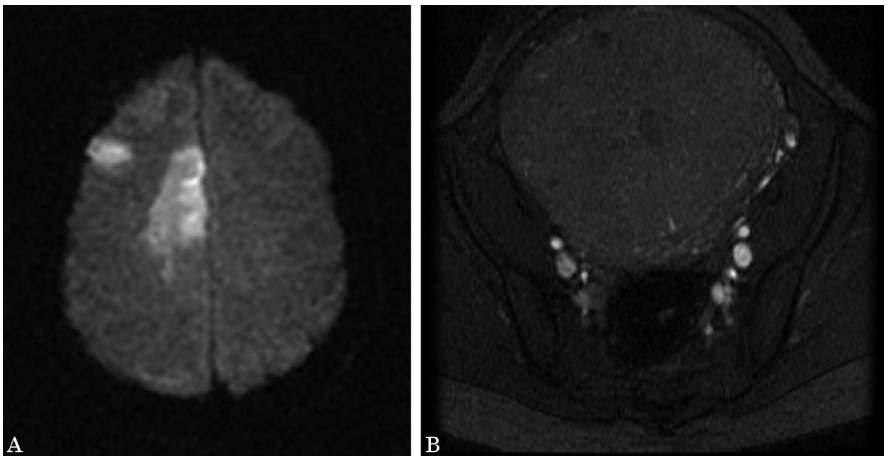

Figure. (A) Diffusion weighted imaging of the brain showing acute infarcts in the anterior and middle cerebral artery territories. (B) Magnetic resonance venogram of the pelvis showing thrombi in the right internal iliac vein. The large fibroid uterus compresses the veins.

the PFO was scheduled. At the time of this report, she is recovering well from her hemiparesis with regular occupational and physical therapy. She was started on GnRH analogues to decrease the severity of her menses while on aspirin and warfarin. Elective hysterectomy is planned after closure of the PFO.

Discussion. Principal causes of cerebral infarction in the young include extracranial arterial dissection, cardioembolism, inherited thrombophilic disorders, hematologic and immunologic disorders, migraine, drug abuse, premature atherosclerosis, pregnancy, and hormonal contraceptives.

However, extensive investigation for these conditions frequently fails to find a cause for stroke: cryptogenic stroke. Cryptogenic stroke is associated with PFO.[1] An extensive search for the source of embolus should be performed in a patient with a PFO.[2] This would include imaging for pelvic vein thrombi if there are no clots in the leg veins.

Uterine myomas can be associated with iliac vein thrombosis and pulmonary embolism.[3] In such cases, a large uterine myoma compresses veins in the pelvis, and causes venous stasis and clot formation. Previous patients were managed by anticoagulation with IV heparin and the insertion of a Greenfield filter to prevent the extension of the thrombus and further pulmonary embolism during and after hysterectomy.[3] GnRH analogues and progestins have been used prior to surgery in order to reduce bleeding and diminish the size of the fibroid.[4] Our case is unusual in that a uterine myoma caused multiple cerebral arterial territory infarcts due to pelvic vein thrombosis and subsequent embolism through a PFO. This emphasizes the need to consider pelvic processes in atypical embolic stroke circumstances.[5]

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References

1. Mas J-L, Arquizan C, Lamy C, et al, the Patent Foramen Ovale and Atrial Septal Aneurysm Study Group. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001;345:1740–1746.
2. Wu LA, Malouf JF, Dearani JA, et al. Patent foramen ovale in cryptogenic stroke: current understanding and management options. Arch Intern Med 2004;164:950–956.
3. Nishikawa H, Ideishi M, Nishimura T, et al. Deep venous thrombosis and pulmonary thromboembolism associated with a huge uterine myoma—a case report. Angiology 2000;51:161–166.
4. Stewart EA. Uterine fibroids. Lancet 2001;357:293–298.
5. Greer DM, Buonanno FS. Cerebral infarction in conjunction with patent foramen ovale and May-Thurner syndrome. J Neuroimaging 2001;11:432–434.

Reversal of warfarin-induced anticoagulation with factor VIIa prior to rt-PA in acute stroke

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Thrombolytics for stroke are contraindicated if a patient's prothrombin time (PT) is above 15. Recombinant factor VII (rVIIa) has been approved for the rapid reversal of warfarin-induced coagulopathy. Since rVIIa can reverse coagulopathy quickly, it might be useful to correct PT elevations in patients who are eligible for thrombolytics.

Case report. A 71-year-old, right-handed woman with a history of left hemispheric ischemic stroke presented to our emergency department with new onset of left arm and leg weakness, facial droop, visual field blurring, and dysarthria. The symptoms began initially at 9:15 AM and en route to the hospital, she became quadriplegic. Upon arrival, the patient was oriented and had mild dysarthria and bilateral facial droop, left greater than right. Strength was 0/5 in all extremities and deep tendon reflexes were 2+ in the right limbs and 1+ in the left. NIH Stroke Scale score was 20.

The patient's previous ischemic stroke resulted in residual right hemiparesis and mild facial drooping but she lived independently despite her deficits. She had non-insulin-dependent diabetes mellitus, congestive heart failure, and aortic and mitral valve replacements. She was taking sotalol, metolazone, hydrochlorothiazide, spironolactone, furosemide, potassium supplement, digoxin, isosorbide dinitrate, simvastatin, rosiglitazone, glyburide, and warfarin 5 mg daily.

Noncontrast brain CT revealed old left hemispheric infarcts. PT was 18.6 seconds (normal range 11.5 to 13.7), INR 2.2, and PTT 32 seconds (normal range 25 to 37). Carotid ultrasound, once the patient was stabilized, showed no significant stenosis.

Although the patient was within the temporal window for IV rt-PA use, her elevated PT/INR excluded her from treatment. The patient gave informed consent to reverse anticoagulation with rVIIa (1.2 mg), which would then be followed by IV rt-PA 15 minutes later. IV rt-PA was started 135 minutes after symptom onset and the patient was transferred to the neurology ICU. Within 1 hour her strength on the left side improved markedly and her speech was back to baseline. The NIH Stroke Scale score was back to the pre-admission level of 5 the next morning. Baseline and discharge modified Rankin scale was 2, whereas on admission it was 5. She was discharged home after 5 days once the INR was 2.3. Noncontrast CT scan 1 month later revealed no new infarcts and no evidence of intracranial hemorrhage.

Discussion. Recombinant FVIIa is used to treat bleeding diatheses, including hemophilia A and B, while also demonstrating very low thrombotic effects.[1] Factor VIIa forms a complex with tissue factor (TF) in areas of endothelial damage. This complex activates factor X (Xa), which catalyzes the formation of thrombin from prothrombin to form the hemostatic plug. Factor VIIa also functions independently of TF to stimulate the formation of factor Xa, potentiating thrombin formation.[2] To measure factor VII activity, the PT is most useful since it measures the activity of the vitamin K-dependent cofactors inhibited by warfarin. Recombinant VIIa directly stimulates the coagulation cascade and overcomes the inhibition caused by warfarin. The rapidity of INR reduction to < 1.5 has been reported to occur within 10 minutes.[1]

The conventional method of reversing warfarin anticoagulation has been with vitamin K supplementation and fresh-frozen plasma. In acute ischemic stroke, the major disadvantage of these agents is the time required to reverse the anticoagulant effect. In our case, we chose rVIIa for two major reasons. First, because of the rapid onset of action, we were able to quickly decrease the PT/INR to permit rt-PA administration. Secondly, the half-life of rVIIa has been measured to be less than 3 hours,[2] which is advantageous since potential prolonged activation of the coagulation cascade in ischemic stroke is unwanted.

The necessity to rapidly decrease the PT/INR to permit thrombolytic use was the catalyst in our decision.[3] The outcome was optimal in regards to resolution of symptoms without any hemorrhagic or thrombotic complications. Once optimal usage guidelines are established, rVIIa may safely permit an increased number of patients to benefit from thrombolytic therapy that would otherwise be excluded due to elevated PT/INR. More data need to be collected to discern the interaction between rVIIa and rt-PA, especially in regards to a theoretical, counteractive, prothrombotic effect of rVIIa on rt-PA. Additionally, there is also the need to evaluate whether rVIIa may potentially reduce the hemorrhagic risk of rt-PA administration. Either prospective studies or case series involving the concomitant use of rVIIa and rt-PA should be undertaken.

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References

1. Sorensen B, Johansen P, Nielsen GL, Sorensen JC, Ingerslev J. Reversal of the international normalized ratio with recombinant activated factor VII in central nervous system bleeding during warfarin thromboprophylaxis: clinical and biochemical aspects. Blood Coag Fibrinol 2003;14:469–477.
2. Lindley CM, Sawyer WT, Macik BG, et al. Pharmacokinetics and pharmacodynamics of recombinant factor VIIa. Clin Pharmacol Ther 1994;55:638–648.
3. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581–1587.

Severe anaphylactic reaction to glatiramer acetate with specific IgE

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Glatiramer acetate (GA, Copaxone) is approved for the treatment of multiple sclerosis (MS). Given subcutaneously once daily it significantly reduces the relapse rate.[1] GA is a random mixture of synthetic polypeptides composed of L-glutamic acid, L-lysine, L-alanine, and L-tyrosine in a defined molar residue ratio of 0.14:0.34:0.43:0.09 with an average molecular mass of 4,700 to 11,000 Da. The induction of GA-reactive T-helper2 like regulatory cells seems to be relevant for the clinical effects of GA.[1] In addition to local adverse events at the injection site, systemic adverse reactions are common. An immediate post-injection systemic reaction (IPISR) is experienced at least once in about 10% of patients. IPISR is characterized by flushing, chest tightness, dyspnea, palpitations, and anxiety and always resolves spontaneously without sequels within a few minutes.[1] Although IPISR clinically resembles anaphylaxis, its unpredictable and sporadic nature does not suggest an allergic basis and the cause is unknown.[1] In contrast, true systemic anaphylactic reactions are rare.[2]

According to the manufacturer (Aventis, Austria), 66 nonfatal anaphylactic reactions in about 80,000 treated patients have been reported worldwide. We present here a patient with systemic anaphylactic reaction to GA, who shows a strong immunoglobulin (Ig) response to GA, including specific IgE.

Case report. A 31-year-old woman presented with double vision and brainstem signs. Medical history revealed optic neuritis at age 29. MRI showed numerous active as well as inactive supra- and infratentorial lesions and in the CSF oligoclonal bands were positive. MS was diagnosed and GA treatment was initiated. During the first 6 months, GA was combined with IVIg at a dose of 0.4 g/kg body weight once a month to bridge the delayed onset of immunomodulation with GA. Ten months after starting GA, the patient reported generalized flushing, itching urticarial lesions, dyspnea, abdominal cramps, and vomiting, starting 5 minutes after injection and lasting for 20 minutes. IPISR was suspected and GA therapy was continued. Three months later, the same symptoms happened 2 minutes after GA injection, but in addition, the patient collapsed and was unconscious for some minutes. Thirty minutes later the symptoms were only partly resolved and the emergency doctor measured a systolic blood pressure of 70 mm Hg. After administration of IV adrenalin and antihistamine, the symptoms resolved.

GA treatment was stopped and prick and intracutaneous tests with GA were performed, showing positive results with undiluted GA in solvent and at a dilution of 1:100. Total serum IgE was raised to 300 IU (normal < 100 IU). Medical history for previous atopic conditions revealed an exanthema following penicillin in childhood and elevated total serum IgE for years. Specific anti-GA serum antibodies were investigated.[3] High GA directed humoral reactivity was found that could be ascribed mainly to IgG1 and IgG4 antibodies; however, low levels of IgM, IgG2, and most importantly IgE were detectable (figure). No specific GA reactive IgG3 antibodies were found.

Discussion. Anti GA-antibodies develop in most patients treated with GA and do not induce anaphylactic reactions or compromise treatment benefit, although the latter has been questioned recently.[4,5] GA reactive IgM, IgG1, and IgG2 may be present also in untreated individuals.[3] Typical for GA treatment is the induction of anti GA IgG4 antibodies, whereas specific IgE has hitherto not been found in treated patients, which is in accordance with the low rate of anaphylaxis.[3,4] Our case demonstrates that anti-GA IgE can occur in GA-treated patients. In addition, when compared to other patients evaluated in the same laboratory, the GA-specific IgG4 titer is exceedingly high.[3] It is known that the GA-induced T-helper2 like cell population produces anti-inflammatory cytokines such as IL4 and IL10, which regulate isotype switching to IgG4 and IgE in B cells.[6,7] One might speculate that an extraordinarily strong GA-specific immunostimulation in our patient caused interleukin-4 mediated isotype switching not only to IgG4, which is suggested to offer protection against type I immune reactivity, but also to proanaphylactic IgE.[7]

Due to the common occurrence of harmless IPISR, the development of anaphylaxis may initially be missed, as our case demonstrates. Especially in patients with MS with a history of an atopic condition, patient reports of systemic reactions during GA treatment should be analyzed especially regarding anaphylaxis.

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References

1. Ziemssen T, Neuhaus O, Hohlfeld R. Risk-benefit assessment of glatiramer acetate in multiple sclerosis. Drug Saf 2001;24:979–990.
2. Bayerl C, Bohland P, Jung EG. Systemic reaction to glatiramer acetate. Contact Dermatitis 2000;43:62–63.
3. Farina C, Vargas V, Heydari N, Kümpfel T, Meinl E, Hohlfeld R. Treatment with glatiramer acetate induces specific IgG4 antibodies in multiple sclerosis patients. J Neuroimmunol 2002;123:188–192.

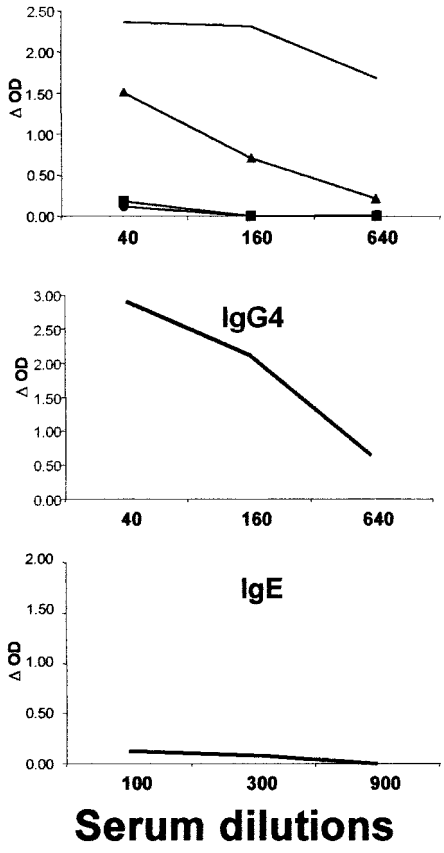

Figure. Glatiramer acetate (GA) reactive immunoglobulin (Ig) repertoire. OD = difference in the mean adsorbence between the GA-coated and uncoated wells, which is expressing the specific GA antibody level; line = total Ig; square = IgM; triangle = IgG1; circle = IgG2.

4. Brenner T, Arnon R, Sela M, et al. Humoral and cellular immune response to copolymer 1 in multiple sclerosis patients treated with Copaxone. J Neuroimmunol 2001;115:152–160.
5. Salama HH, Hong J, Zang YC, El-Mongui A, Zhang J. Blocking effects of serum reactive antibodies induced by glatiramer acetate treatment in multiple sclerosis. Brain 2003;126:2638–2647.
6. Farina C, Then Bergh F, Albrecht H, et al. Treatment of multiple sclerosis with Copaxone (COP): ELISPOT assay detects COP-induced interleukin-4 and interferon-gamma response in blood cells. Brain 2001;124:705–719.
7. Jeannin P, Lecoanet S, Delneste Y, Gauchat JF, Bonnefoy JY. IgE versus IgG4 production can be differentially regulated by IL-10. J Immunol 1998;160:3555–3561.

The effect of entacapone on homocysteine levels in Parkinson disease

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Elevated plasma homocysteine (Hcy) has been reported in patients with Parkinson disease (PD) treated with levodopa (LD) and is a risk factor for vascular disease and dementia.[1] Plasma Hcy levels in patients with PD treated with LD are thought to be elevated by increased synthesis from the metabolism of LD by catechol-O-methyltransferase (COMT). An animal study has demonstrated that pretreatment with a COMT inhibitor can block the elevation of plasma Hcy levels when LD is given.[2] These findings suggest that a COMT inhibitor, such as entacapone, may be able to block the elevation of plasma Hcy levels in patients with PD treated with LD. In the current study, we assessed the influence of entacapone on plasma Hcy levels in patients previously treated with LD alone.

Methods. Subjects were selected from a group of patients participating in the Stalevo (carbidopa/levodopa/entacapone) Study (CELC200US02) designed to assess the tolerability of switching from LD to carbidopa/levodopa/entacapone. The study was a multicenter, open label, single arm study in which patients with PD were directly switched from baseline LD dose to an equivalent carbidopa/levodopa/entacapone dose and treated for 4 weeks.[3]

Results. The study cohort comprised 169 subjects from 22 US centers. Of these subjects, 33 had plasma Hcy levels measured at baseline and repeated after entacapone treatment (table). The low percentage of subjects with Hcy levels was due to the fact that only some centers were able to obtain IRB approval for the additional blood test. No correlation was found between plasma Hcy levels and baseline LD dosage ($p = 0.79$) or duration of LD therapy ($p = 0.93$). Our study failed to show a difference in plasma Hcy levels before and after initiation of entacapone therapy (baseline mean = 14.72, day 28 = 14.51, $p = 0.582$, paired two-tailed t test). When only the patients with the highest baseline Hcy levels were analyzed (top 30%), there was still no difference ($p = 0.46$, paired two-tailed t test). In addition, no correlation was found between changes in Hcy levels and the amount of entacapone taken during the 4-week period (400 to 1,000 mg/day; mean = 748.5, $p = 0.187$).

Discussion. This study failed to show any significant effect of entacapone on plasma Hcy levels in patients with PD treated with LD. In agreement with the results of previous studies,[1] Hcy levels were elevated in LD-treated patients with PD relative to historical controls (10 μM/L).[4,5] Our findings are also in agreement with a study of 15 subjects that found no effect of entacapone on Hcy levels.[6] Conversely, another study reported that subjects on entacapone and LD had a 19% lower Hcy level vs subjects on LD alone.[4] One explanation for the discrepancy is that the latter study compared Hcy levels between two different groups of patients while a within-subject comparison was used in our study and the former study. Thus, several potential confounding variables, such as B12 and folate levels, LD dose, duration of PD, and LD exposure are controlled for with a within-subject design whereas all these variables except B12 levels were found to be different in the two groups in the later study.

Table *Patient characteristics*

Characteristics	Values
Mean age, y (range)	69.6 y (50–89)
M/F	22/11
Levodopa daily dose, mg/day (mean)	150–750 (395.5)
Duration of levodopa therapy, mo (mean)	1–230 (49.4)
Baseline plasma Hcy level, μmol/L (mean)	6.3–125 (14.7)
Entacapone daily dose, mg/day (mean)	400–1,000 (748)
Plasma Hcy level 4 weeks after addition of entacapone, μmol/L (mean)	6.6–116 (14.5)

We were surprised by the lack of effect of entacapone on Hcy levels given the biochemical basis of our study and the animal data. There were limitations in study design, which may account for the lack of effect including a relatively small sample size and the relatively low daily doses of LD and entacapone used. An animal study using a COMT inhibitor after LD injections, which showed a reduction in Hcy levels, used a LD dose approximately 10-fold higher than dosages used in this trial.[2] Additionally, the COMT inhibitor used in that study was administered at a dose that was higher than used in our study. Thus, higher doses of LD and entacapone may be necessary to see an effect of COMT inhibition on Hcy levels.

Another limitation of this study was that the subjects' vitamins B6, B12, folate, and methylenetetrahydrofolate reductase genotype status were not measured. Since we made comparisons of Hcy within subjects before and after introduction of entacapone, none of these variables was likely to have changed significantly. We do not believe the time of the day or the time since subjects' last meal in relationship to blood collection are important considerations since a recent study reported no effect of fasting or time of day on blood Hcy levels.[5]

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References

1. Postume R, Lang A. Homocysteine and levodopa. Should Parkinson disease patients receive preventive therapy? Neurology 2004;63:886–891.
2. Miller JW, Shukitt-Hale B, Villalobos-Molina R, Nadeau MR, Selhub J, Joseph JA. Effect of L-dopa and the catechol-O-methyltransferase inhibitor Ro 41–0960 on sulfur amino acid metabolites in rats. Clin Neuropharmacol 1997;20:55–66.
3. Koller W, Guarnieri M, Hubble J, Rabinowicz AL, DS, Group atS-T. An open-label evaluation of the tolerability and safety of Stalevo (carbidopa, levodopa and entacapone) in Parkinson's disease patients experiencing wearing-off. J Neural Transm 2005;112:221–230. Epub 2004 Oct 22.
4. Lamberti P, Zoccolella S, Iliceto G, et al. Effects of levodopa and COMT inhibitors on plasma homocysteine in Parkinson's disease patients. Mov Disord 2004 (early view).
5. Guttormsen AB, Solheim E, Refsum H. Variation in plasma cystathionine and its relation to changes in plasma concentrations of homocysteine and methionine in healthy subjects during a 24-h observation period. Am J Clin Nutr 2004;79:76–79.
6. O'Suilleabhain PE, Bottiglieri T, Dewey RB Jr, Sharma S, Diaz-Arrastia R. Modest increase in plasma homocysteine follows levodopa initiation in Parkinson's disease. Mov Disord 2004 (early view).