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Update in Neurodegenerative Diseases Pathogenesis and Treatment: Alzheimer's Disease

ABSTRACTS & COMMENTARY

Sources: Gotz J, et al. *Science.* 2001;293:1491-1495; Gouras GK, Beal MF. *Neuron.* 2001;30:641-642; Nilsberth C, et al. *Nat Neurosci.* 2001;4:887-893; Lewis J, et al. *Science.* 2001;293:1487-1491.

Research in the field of neurodegenerative diseases is advancing rapidly. We are reaching the threshold where there appear to be novel insights into both disease mechanisms as well as new therapeutic approaches. There is accumulating evidence for roles of protein aggregation, metabolic dysfunction, and oxidative damage as being central to the pathogenesis of neurodegenerative diseases. In Alzheimer's disease (AD), there may be direct toxic effects of β-amyloid protofibrils. In the case of Huntington's disease (HD), there appears to be specific dysfunction of transcriptional regulation. In Parkinson's disease (PD), there appear to be accumulations of a-synuclein leading to aggregates and impairment of the ubiquitin proteasome system. The latter 2 diseases will be discussed in future issues. These findings provide a number of attractive targets for neuroprotective therapies. The development of transgenic mouse models of neurodegenerative diseases has rapidly accelerated the development of new therapeutic approaches.

In AD the focus has been on the role of beta amyloid (Aβ) in disease pathogenesis. This has been particularly strengthened by genetic studies that have demonstrated mutations in the amyloid precursor protein as well, as in the presenilin genes. These are associated with early life-onset familial AD and increased production of Aβ 1-42. A recent study, however, has demonstrated that certain mutations in the amyloid precursor protein associates with AD, but results in reduced production of Aβ. The latter instance appears to increase the generation of protofibrils. This reflects an intermediate stage of aggregation, which appears to be particularly toxic. These findings suggest that intracellular generation of Aβ may play a more direct role in disease pathogenesis, than the extracellular accumulations in senile plaques. Although Aβ deposits in senile plaques are closely linked to AD pathogenesis, neurofibril-

Volume 20 • Number 3 • November 2001 • Pages 17-24

INSIDE

lary tangles are a better pathologic correlate of dementia. Recent work shows that Aβ exacerbates neurofibrillary tangles. Administration of Aβ or increasing its production in mice with tau mutations, which are associated with frontotemporal degeneration, leads to an exacerbation of the development of neurofibrillary tangle formation.

Several new therapeutic approaches direct their efforts to treat Aβ deposition. These include Aβ immunization, β and γ-secretase inhibitors, modulators of inflammation, antioxidants, and cholesterol lowering drugs. Several groups of investigators have shown Aβ immunization to be efficacious. Not only does it reduce the deposition of Aβ plaques, it also improves cognitive deficits in transgenic mouse models. This approach has now entered clinical trials. A potential worry about γ-secretase inhibition was that it could inhibit notch signaling which could affect the bone marrow. Recent evidence, however, has shown that novel inhibitors can dissociate the 2 effects. Initial trials of γ-secretase inhibitors in man have commenced. Development of β-secretase inhibitors appears particularly promising, since β-secretase knockout mice show a normal phenotype, but no Aβ generation.

Two epidemiologic studies have shown that patients taking statin drugs have a lower incidence of AD. Studies in the transgenic mouse models of AD have clearly demonstrated that dietary manipulation of cholesterol or statin drugs can markedly reduce Aβ generation. Initial trials with statin drugs have started. Studies in the transgenic mice using ibuprofen, as an anti-inflammatory compound, or curcumurin, an antioxidant, have shown significant reductions in Aβ levels, development of senile plaques, and in behavioral deficits. A recent study examined the effects of clioquinol, a copper/zinc chelator which was able to solubilize Aβ from postmortem AD brain tissue. In transgenic mouse models of AD, administration of this compound is effective in reducing sedimentable Aβ as well as in reducing the numbers of amyloid plaques. There are concerns, however, that the compound produces subacute myelo-optic neuropathy, which may be due to vitamin B12 deficiency. Initial clinical trials with clioquinol in combination with vitamin B12 have been completed, and have now entered phase II with reportedly no encounter with myelo-optic neuropathy. A number of approaches for neuroprotection in AD have now entered the clinic, including a number of approaches which will test the primacy of Aβ in AD pathogenesis. In the meantime, the best presently available symptomatic therapy is with acetylcholinesterase inhibitors such as donepezil (Aricept), galantamine (Reminyl), and rivastigimine (Exelon). In addition, many practitioners recommend vitamin E, since 1 trial showed slowing of disease progression. **—flint beal**

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The Genetics of Movement Disorders: Recent Developments

ABSTRACTS & COMMENTARY

Sources: Zimprich A, et al. *Nat Genet.* 2001;29:66-69; Zhou B, et al. *Nat Genet.* 2001;28:345-349; Rampoldi L, et al. *Nat Genet.* 2001;28:119-120.

In the last several months, the genetic mutations responsible for 3 rare neurologic conditions have been discovered: myoclonus-dystonia, Hallervorden-Spatz syndrome (HSS), and neuroacanthocytosis. These papers will alter the diagnosis of adult and pediatric patients with unusual movement disorders. More

importantly, they will provide important insights into the biologic mechanisms responsible for these unusual conditions.

Myoclonus-dystonia is a rare illness characterized by "lightning-like" myoclonic jerks affecting the proximal limbs and trunk. Symptoms typically begin in the first or second decade of life, and are often accompanied by focal dystonia manifesting as torticollis or writer's cramp. The disorder is autosomal dominant with incomplete penetrance, although some sporadic cases may occur. Affected patients in the same family may have myoclonus alone, myoclonus plus dystonia, or even dystonia in isolation. A pathognomonic feature of the disorder is the exquisite response of myoclonic jerks to alcohol. Psychiatric pathology is extremely common in affected patients, particularly obsessive-compulsive disorder and panic attacks.

The disease locus for myoclonus-dystonia was mapped to chromosome 7q21 by several groups. Using genomic sequence from the Human Genome Project, Zimprich and colleagues detected loss-of-function mutations in the e-sarcoglycan gene in all index patients with myoclonus-dystonia. Penetrance depends on the parental origin of the disease allele, as most patients inherit the diseased gene from their father. e-sarcoglycan is 1 of 5 members of the sarcoglycan family of proteins that code for the transmembrane component of the dystrophin-glycoprotein complex. Mutations in the other members of this family cause autosomal-recessive limb-girdle muscular dystrophy. e-sarcoglycan is broadly expressed in both non-neural and neural tissues. It is striking that alteration of a protein component of the cell membrane is responsible for myoclonus-dystonia and its associated psychiatric conditions. This suggests the possibility that alteration of neuronal wiring or connections may be responsible for both disorders.

HSS is a disease dreaded by pediatric neurologists. An autosomal recessive disorder, it typically begins within the first 2 decades of life, causing relentless, progressive dystonia, parkinsonism, and pigmentary retinopathy. HSS may begin in adulthood, with clinical presentations that include palilalia, facial tics, severe intermittent dystonia, or parkinsonism. All affected patients accumulate high levels of iron in the globus pallidus, producing the so-called "eye of the tiger" sign on MRI imaging. Zhou and colleagues first mapped the HSS locus to chromosome 20p13, and then identified the responsible gene, pantothenate kinase 2 (PANK2), in patients with classic early onset HSS and adults with HSS as well.

PANK2 is an essential enzyme in coenzyme A biosynthesis, catalyzing cytoplasmic phosphorylation of pantothenate (vitamin B5). The resulting product, phosphopantothenate, normally condenses with cysteine. PANK2 deficiency thus leads to an accumulation of cysteine which auto-oxidizes in the presence of iron, producing free radicals that may accelerate cell death. Nonheme iron is highest in globus pallidus and the pars reticulata of the substantia nigra, areas that are most severely affected in HSS. The discovery of PANK2 suggests a possible therapeutic approach for patients with HSS. Using antioxidants such as vitamin E and CoQ10 and supplemental pantothenate, it may be possible to prevent or slow cell death. The discovery also allows patients to be diagnosed definitively, as genetic testing for patients suspected of having HSS is currently available through the University of Chicago.

The final report from Rampoldi and colleagues details the discovery of the gene for neuroacanthocytosis. This autosomal recessive disorder afflicts patients in late teens and adulthood. Affected patients develop chorea, psychiatric disturbances, epilepsy, oral self-mutilatory behavior, and peripheral neuropathy. Current diagnosis depends on the demonstration of acanthocytes in the peripheral blood smear.

The disorder was mapped to chromosome 9q21 in several Japanese families, and the responsible gene, chorein, was finally isolated. Chorein is expressed throughout the brain and is homologous to proteins that control cycling of transmembrane proteins of the trans-Golgi apparatus. This may explain the development of acanthocytes due to disruption of the plasma membrane structure.

COMMENTARY

These 3 discoveries demonstrate the power of genetics to expand our understanding of neurologic illness. In the short term, neurologists will be able to definitively diagnose diseases that were previously only recognized and suspected by clinical features alone. In the long term, the development of animal models of these disorders will allow for rationale drug design and new treatments. **—steven frucht**

Nonaccidental Head Injury in Children: New Clues from Neuropathology

ABSTRACTS & COMMENTARY

Sources: Geddes JF, et al. *Brain.* 2001;124:1290-1298, 1299-1306; Shannon P, Becker L. *Lancet.* 2001;358:686-687; Graham DI. *Brain.* 2001;124(Pt 7):1261-1262.

Nonaccidental trauma (largely related to child abuse) is an important cause of brain injury in

young infants. Head injury is the most common neurological cause of death and disability in young children. Some studies (Duhaime AC, et al. *Pediatrics.* 1992;90: 179-185) have suggested that approximately 25% of cases of head injury in children younger than age 2 are due to nonaccidental trauma. Due to sensitive medicolegal implications, reliable history is rarely available to help determine precisely what happened.

A prominent feature of nonaccidental head trauma, especially in younger children, is the presence of subdural hematoma, subarachnoid hemorrhage, and retinal hemorrhage in the face of minimal external evidence of trauma in many patients. This led to the concept of the "shaken-baby syndrome," brain injury related to repetitive whiplash motions at the relatively hyperextensible neck of the young child. More recent data (Duhaime AC, et al. *N Engl J Med.* 1998;338:1822-1829) suggest that some sort of impact was likely necessary to account for the spectrum of brain injury seen in these cases (so called "shaken impact syndrome").

Relatively little is known about the mechanisms of injury in these children. Two sequential papers by Geddes and colleagues make important new contributions to our understanding. Geddes et al performed detailed neuropathological studies on 53 infants with nonaccidental head trauma on whom complete autopsies were also performed. These patients were subdivided into 2 groups: 37 infants, age ranging from 20 days to 9 months, and 16 children ranging from 13 months to 8 years. Patterns of brain injury seemed to differ between the 2 groups. Whereas 75% of children had evidence of extracranial injury, only 41% of infants had such evidence. More than 50% of infants had no evidence of skull fracture and approximately a quarter had no evidence of subscalp bruising. In contrast, children always had evidence of subscalp bleeding. Microscopic neuropathology showed that diffuse axonal injury is rare in both infants and children (seen in about 5% of cases), but focal traumatic axonal injury was much more common, seen in about 40% of cases. Strikingly, traumatic axonal injury was present at the craniocervical junction in the majority of infants in which focal traumatic axonal injury was seen (11/16 cases), whereas no children had such injury but rather had injury to deep white matter.

In a second paper, Geddes et al used immunohistochemical methods to study the mechanisms underlying the axonal injury they observed. In this study, only the infants considered in the prior paper (37 cases) were examined. Using beta-amyloid precursor protein (beta-APP) immunohistochemistry to detect axonal damage, they could document evidence of diffuse axonal injury in only 2 of 37 cases. This suggests that the "diffuse axonal shearing" seen in severe traumatic injury (ie, motor vehicle accidents) is not an important mechanism of nonaccidental traumatic injury in infants. Global hypoxic-ischemic injury was by far the most common finding, and evidence of vascular axonal injury in 12 of 37 cases. Global hypoxic-ischemic injury was a necessary concomitant to focal axonal injury in almost all cases (11/12) where focal axonal injury was seen.

COMMENTARY

The 2 sequential papers by Geddes et al appear to be a major landmark in the relatively sparse neurological literature on nonaccidental trauma in infants and children. These papers revise our current concept of "shaken-baby syndrome" in that it clearly demonstrates that the shaking does not produce sufficient force to produce diffuse axonal injury in the majority of cases. In infants, shaking of the highly hyperextensible neck may lead to, in many cases, focal axonal injury at the craniocervical junction, which then leads to apnea and global hypoxic-ischemic injury. We eagerly await a paper from this group regarding further studies on the 16 children who appear to have important differences from the 37 infants studied. Obviously, as an autopsy study, these papers shed the most light on the most severe cases, but one would presume similar mechanisms operative in survivors of such trauma.

One aspect of the nonaccidental trauma problem which the Geddes et al papers cannot yet address is causality. In the infants subjected to such trauma, which came first: the apnea or the shaking (which leads to brainstem injury and apnea)? In my experience, many parents will indicate that they shook their infants vigorously because they believed them to have stopped breathing, hardly a criminal act. Clearly these issues have major medicolegal implications. **—rosario trifiletti**

Migraine Diagnosis and Treatment: Results from the American Migraine Study II

ABSTRACTS & COMMENTARY

Sources: Lipton RB, et al. *Headache.* 2001;41:638-645; Lipton RB, et al. *Headache.* 2001;41:646-657.

As a 10-year follow-up to their landmark American Migraine Study I completed in 1989 (Stewart WF, et al. *JAMA.* 1992;267:64-69), Lipton and

colleagues now report on the results of another large population-based survey completed in 1999. The goal of the survey was again to identify patterns of migraine diagnosis, medication use, and migraine-associated disability. In the second report, Lipton et al report on the prevalence, sociodemographic profile, and overall "burden of migraine" in the United States.

A survey was mailed to 20,000 US households. The survey was designed to identify individuals with headaches, and determine headache severity, frequency, associated symptoms, and disability. Of the 43,527 people older than age 12, 29,727 responded giving a 68.3% response rate. A total of 3738 individuals could be diagnosed with migraine fulfilling International Headache Society (IHS) criteria. The total estimated prevalence in the United States was 27.9 million or 12.6% of the population. The prevalence of migraine by gender was 18.2% female, and 6.5% male. Migraine prevalence was 2-3% higher among whites than blacks and inversely related to household income. Prevalence increased from 12 years of age to 40 years of age. The most frequently reported migraine symptoms were "pulsatile" pain (85%), light sensitivity (80%), and nausea (73%). It was notable that only 59% complained of unilateral pain and 36% had migraine-associated aura.

Only 48% of individuals with survey-diagnosed migraine had ever been diagnosed by a physician. This compares to the 38% disparity described in the 1989 study. A total of 41% of migraineurs surveyed use prescription drugs for their migraine and this compares to 37% in 1989. There was roughly the same proportion of migraineurs using over-the-counter medications in 1999 (57%) and 1989 (59%). In terms of migraine-associated disability, the survey revealed that 57% of diagnosed and 45% of undiagnosed migraineurs experienced at least a 50% reduction in work/school productivity ($P > .001$).

COMMENTARY

The American Migraine Study II represents another pivotal neuro-epidemiological study. Lipton et al have shown that the prevalence of migraine has remained stable over the past decade. Gender differences, socioeconomic variables, and migraine characteristics have not changed as well. The increase in estimated total migraine from 23.6 million in 1989 to 27.9 million in 1999 is commensurate with the increase in total population and does not reflect some fundamental change in the disease state. Several methodological factors may have led to an underestimation or overestimation of migraine and are pointed out by Lipton et al. Since only "severe" headaches were counted as migraine, a large number of individuals with moderate headache could still fulfill IHS criteria but were excluded. Similarly, people on the other end of the spectrum with severe daily headaches were excluded by IHS definition of this being an episodic disorder. Nonetheless, meaningful conclusions can still be taken from this follow-up study. Despite the increase in awareness of migraine and the usefulness of the triptan class of drugs for acute migraine treatment, the burden of migraine remains significant. As it was 10 years ago, up to 50% of migraineurs are undiagnosed and even the ones who are diagnosed most are not given effective prescription medication. Lipton et al have demonstrated that the disability of migraine remains substantial. Primary care physicians are clearly not getting the message about the importance of migraine in their patients and this leaves the responsibility to neurologists to lead the way. **—jeffrey reich**

Ocular Myasthenia and Thymectomy

ABSTRACT & COMMENTARY

Source: Roberts PF, et al. *J Thorac Cardiovasc Surg.* 2001; 122:562-568.

Is thymectomy beneficial for ocular myasthenia gravis (OMG)? Between 1970 and 1998, 61 OMG patients, aged 14-73 years, underwent thymectomy at the University of California (Davis) Medical Center (n = 7) or the University of Rome (n = 54), and were followed up for a mean of 9 years. Diagnosis was made on the basis of a combination of symptoms, acetylcholine receptor antibody titer, repetitive nerve stimulation studies, or single fiber electromyography. Thymoma was present in 12. Transsternal thymectomy was performed in 55, transcervical in 6. Response to thymectomy was characterized as cured, improved, unchanged, or worse, depending on whether the patient was, respectively, symptom free and off medication, symptomatically improved and on less medication, symptomatically unchanged and on the same medication, or, lastly, symptomatically worse, on more medication, or dead. Overall, 71% were cured (n = 31, 51%) or improved (n = 12, 20%) by thymectomy, with 16 patients (26%) unchanged, 1 worsening, and 1 dying in the postoperative period. Improvement or cure was seen in 67% of the thymoma subgroup. Thymectomy, Roberts and col-

leagues conclude, is safe and effective in OMG.

COMMENTARY

Thymectomy is an accepted indication for thymoma. Given surgical expertise and ICU care in the 21st century, it is safe. What remains unproven is whether, absent thymoma or thymectomy is more efficacious than optimal medical management in myasthenia, ocular or generalized.

Based on an exhaustive literature review, the Quality Standards Subcommittee of the American Academy of Neurology concluded that thymectomy is a therapeutic option for nonthymomatous myasthenia gravis, but that its benefit has not yet been conclusively established (Gronseth GS, Barohn RJ. *Neurology.* 2000:55:7-15, Rubin M. *Neurology Alert.* 2000;19:1-2). The evidence for thymectomy in OMG is even weaker. Assuming it has a therapeutic benefit for OMG, deciding whether it should be performed comes down to the following. If the morbidity and mortality of thymectomy are greater than those of OMG becoming generalized, with its attendant consequences, thymectomy is contraindicated. Can this question be accurately answered?

From 20-50% of OMG cases go into remission without thymectomy. No controlled studies compare this to a surgical group. If OMG remains so for a year, it will become generalized in only 15%. Symptoms are in most instances easily treated with a combination of pyridostigmine and prednisone, the latter often inducing remission. The argument for thymectomy in OMG remains unconvincing and will remain so unless a prospective trial comparing thymectomy to best medical management is undertaken. **—michael rubin**

Dopamine in Stroke

ABSTRACT & COMMENTARY

Source: Scheidtmann K, et al. *Lancet.* 2001;358:787-790.

Twenty or more years ago, laboratory investigators found that rats suffering severe cerebral damage rapidly improved their motor behavior in response to systemically applied amphetamine. These findings led to human pharmacological trials incorporating amphetamine or methylphenidate along with vigorous physiotherapy, the latter factor being imperative. Each study up to now followed a different, institution-developed pattern. Crisostomo and colleagues (*Ann Neurol.* 1988;23:94-97) used only 1 oral dose of 10 mg amphetamine in 4 patients, 2 of whom increased arm and leg function moderately well and the other 2 only minimally. The 4 who did not take amphetamine developed essentially no improvement.

Walker-Batson and colleagues treated 10 hemiplegics with 10 mg amphetamine started between 16 and 30 days after stroke onset and repeated the agent every 4 days thenceforth (*Stroke.* 1995;26:2254-2259). Ten other hemiplegics received placebos in the same order. In the case of complications or a necessity to remove a person by either arm of the study, a substitute was obtained to replace the subject. Each person in each of the 2 groups was tested 1 week and evaluated again 1 year following the end of amphetamine treatment. At the end of 1 week and 1 year later the amphetamine group reported significant, permanent improvement ($P = .047$). The contribution appears to have provided the first good effort to facilitate specific, intentional skeletal motor activities beyond standard physiotherapy.

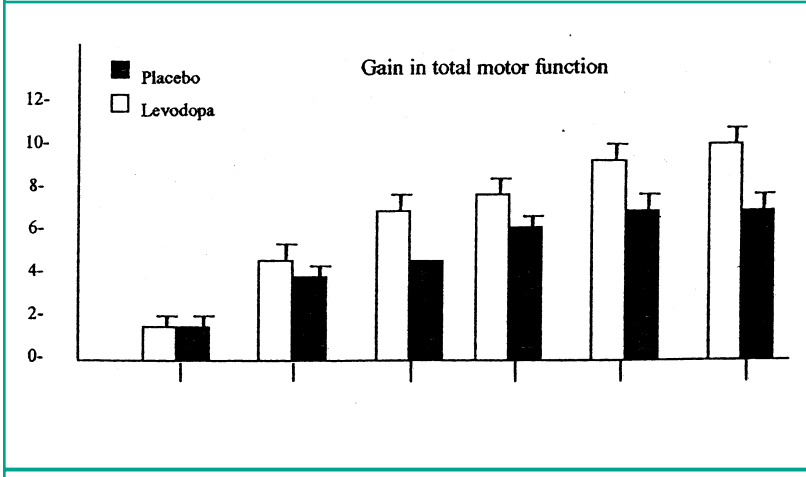
Grade and colleagues conducted a study similar to the above, blindly using methylphenidate for 3 weeks compared to a standard, double-blinded placebo (*Arch Phys Med Rehabil.* 1998;79:1047-1050). Five patients out of 11 finished methylphenidate 15 mg daily with the others tapering or on nonsurpassing lower amounts. Patients receiving methylphenidate showed less depression, more success in activity of daily life, and improved motor recovery. Compared to all caregivers, however, only the therapists directly identified particular patient's singular improvement.

Scheidtmann and colleagues chose to use dopamine to ameliorate the degree of motor paralysis following severe cerebral infarction. Patients with aphasia were not chosen for this first effort.

Out of 53 randomized patients with severe dysfunctional cerebral hemispheric motor strokes, 22 were started and finished on levodopa/carbidopa. At the same time, 27 similar patients received placebos from the start. Each hemiplegic patient started with 1 week free of all drugs related to norepinephrine. For the next 3 weeks, 22 patients took levodopa-carbidopa 100 mg daily at least 30 minutes before physiotherapy. In the second week and onward, both groups received 1 hour of physiotherapy, 5 each week, but took no more levodopa. Among the stroke cohort, 39 of the 47 patients had either middle or (1) middle-anterior cerebral artery infarctions, and the remainder were strictocapsular or lacunar strokes. Following the seventh week, mean Rivermead motor assessment (RMA) indicated that the levodopa group both walked independently and had significant improvement of arm function compared to the nontreated patients. Almost all patients in

Figure 1

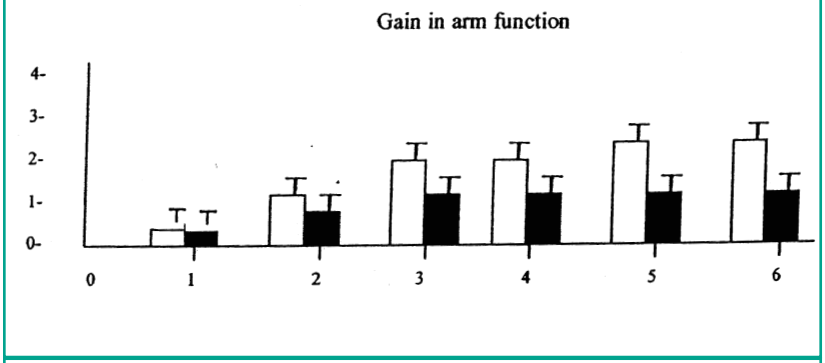
Rivermead Motor Assessment Scores



Overall gain in motor function: 3 weeks ($P < 0.004$) and 6 weeks ($P < 0.02$).
Adapted from Figure 2 in Scheidtmann K, et al. *Lancet.* 2001;358:787-790.

Figure 2

Rivermead Motor Assessment Scores



Arm gain in motor function: 3 weeks ($P < 0.015$) and 6 weeks ($P < 0.008$).
Adapted from Figure 2 in Scheidtmann K, et al. *Lancet.* 2001;358:787-790.

both groups continued to improve after the sixth week. Also, the difference between the levodopa and nonlevodopa patients continued to remain more functional than the nonlevodopa patients (*see Figures 1 and 2*).

COMMENTARY

Considerable differences mark levodopa compared to the amphetamines, which exert their energy on behavioral activity and, sometimes, accentuate athletic function. Dopamine, however, has cofunctions with the basal ganglia as well as using about 1% of its function on neosynephrine receptors. This novel report shows a promising improvement for levodopa in cerebral function due to large strokes. The program needs to be duplicated but would seem to have a promising future in neuro-rehabilitation. **—fred plum**

Brief Alerts

Practice Parameter: Repetitive Nerve Stimulation and Single Fiber EMG

Sources: AAEM Quality Assurance Committee. *Muscle Nerve.* 2001;24:1236-1238; *Muscle Nerve.* 2001;24:1239-1247.

What electrodiagnostic study protocol is recommended to confirm the presence of neuromuscular junctionopathy? Searching the Medline English database through 1998 using keywords including myasthenia gravis, Lambert Eaton myasthenic syndrome, botulism, and neuromuscular transmission and junction, 545 relevant articles were identified. Review of these articles and their references revealed 34 articles which met more than 2 of 6 criteria. Specifically, 1) the study was prospective; 2) a clinical diagnosis was made independent of the electrodiagnostic evaluation; 3) had detailed descriptions of the electrodiagnostic evaluation and 4) temperature were stated; and 5) proper reference values; and 6) criteria for abnormal findings were clearly noted. Based on these reports, the following recommendations are offered.

Repetitive nerve stimulation (RNS) recording from an affected muscle is the first step. For myasthenia, ensure that anticholinesterase medication has not been taken for at least 12 hours, stimulate at 2-5 Hz, perform baseline and immediate postexercise repetitive stimulation and repeat at 1 minute intervals up to 5 minutes. Maintain skin at 35°C and look for a reproducible decrement of 10% comparing first to fourth or fifth response in at least 1 muscle. For Lambert Eaton myasthenic syndrome, although there is no agreement on the minimum degree of increment needed, 100% increase in amplitude following exercise or tetanic stimulation is preferred.

If RNS is normal, perform single fiber EMG (SFEMG) in at least 1 affected muscle. If normal, repeat in a second affected muscle. SFEMG is abnormal if more than 10% of fiber pairs have abnormal jitter or blocking, or if mean jitter exceeds published norms.

In purely ocular myasthenia where RNS will likely be normal, SFEMG may be the initial study performed. **—michael rubin**

Predicting Nonrecovery in Traumatic Sixth Nerve Palsy

Source: Holmes JM, et al. *Ophthalmology*. 2001;108: 1457-1460.

Ninety-nine patients with head trauma followed by diplopia and sixth nerve palsy, in the absence of oculomotor weakness, were enrolled in this study to determine which factors predicted persistence of diplopia in primary gaze at 6 months. Fifteen patients did not complete the follow-up period. Among the remaining 84, failure to recover was associated with bilaterality, complete paralysis (inability to abduct past the midline on initial examination), and female gender. Though the last may be chance, the former appear biologically plausible. **—michael rubin**

CME Questions

18. Which one of the following statements is *false*?

a. Hallervorden-Spatz syndrome is caused by a defect in an enzyme involved in vitamin B6 metabolism.
b. Myoclonus-dystonia is an autosomal dominant syndrome, with a high incidence of psychiatric disorders.
c. The genetic defect in neuroacanthocytosis may affect the stability of cell membranes.
d. Oxidative stress may be important in Hallervorden-Spatz syndrome.

19. Regarding nonaccidental head injury in infants and children:

a. young infants (< 1 yr) probably have similar mechanisms of injury as compared to children (> 1 yr).
b. nonaccidental head injury is not an important cause of morbidity and mortality.
c. diffuse axonal injury, similar to that seen in high-velocity motor vehicle accidents, is a common finding.
d. hypoxic-ischemic injury seems to play an important role in these injuries.
e. focal axonal injury at the craniocervical junction appears to be an important finding in infants (< 1 yr) but not children (> 1 yr).

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American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Medical Economics Data, Inc.	Five Paragon Drive Montvale, NJ 07645

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name: Neurology Alert — 14. Issue Date for Circulation Data Below: November 2001

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			2267	2168
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	2042	1968
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	0	0
	(4)	Other Classes Mailed Through the USPS	0	0
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			2042	1968
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	0	0
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			14	14
f. Total Free Distribution *(Sum of 15d and 15e)*			14	14
g. Total Distribution *(Sum of 15c and 15f)*			2056	1982
h. Copies Not Distributed			211	186
i. Total *(Sum of 15g, and h.*			2267	2168
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			99	99

16. Publication of Statement of Ownership: Publication required. Will be printed in the November issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 9/27/01

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

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1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
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3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
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PS Form **3526**, September 1999 *(Reverse)*

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November 1, 2001

Dear Readers:

We at *Neurology Alert* would like to take the time to thank you for your support in the last year. We, along with Dr. Fred Plum and the excellent team of physicians on our editorial advisory board, strive to bring you the best, most useful newsletter each month that we possibly can.

Over the last year, here are some of the special features we have included in *Neurology Alert*:

- *Update on Neurogenetic Testing*. A review of several new genetic tests including hereditary neuropathies, hereditary ataxias, prion disease, and Rett syndrome written by Dr. Thomas D. Bird. This annual review helps neurologists keep up with the rapidly expanding field of molecular genetics.
- *NCEP Guidelines*. The National Cholesterol Education Program released its third report on the evaluation and treatment of elevated cholesterol in adults and *Neurology Alert* explains the implications for the neurologist.
- *Narcolepsy*. In one of the most exciting developments in neurology in the past few years, *Neurology Alert* reported on the recent findings regarding the pathophysiology of narcolepsy.

As we approach 2002, you can look forward to 12 more issues of incisive, up-to-date commentary on developments in the field of neurology. We will continue to add "extras" that make your newsletter subscription an even greater value. And, especially for 2002, look for the introduction of a *Neurology Alert* web site exclusive to newsletter subscribers.

Our most important tool in keeping *Neurology Alert* relevant to your needs, as always, is the feedback that you give to us. Thank you to all who filled out and returned to us a reader survey or CME survey. This helps us a great deal. We'd like to hear about the issues that are important to you so that we can provide the most relevant information to help you, as a clinician, do a better job. Please direct your comments to Neill Larmore, Associate Managing Editor, at neill.larmore@ahcpub.com, or call her directly at (404) 262-5480.

Thank you again for your support.

Sincerely,

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