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Prion Disease: Genetic and Infectious

ABSTRACTS & COMMENTARY

Sources: Prusiner SB. *N Engl J Med*. 2001;344:1516-1526; Roos RP. *N Engl J Med*. 2001;344:1548-1551; Lloyd SE, et al. *Proc Natl Acad Sci U S A*. 2001;98:6279-6283.

The normal human *PrP* gene (PrPc) maps to the short arm of chromosome 20 and is designated *PRNP*. Presently, 5 different pathological mutations of *PRNP* (PrP^{Sc}) have been linked to fatal familial prion diseases. Prion diseases need be not only poor genetics, however, they also can come in the form of infectious proteins transferred from the nervous systems of other animals. Prusiner points out that prion diseases naturally fall genetically into the category of one of the major, late life neurodegenerative illnesses. As is well known, genetic variability affects a number of the neurodegenerative disorders (eg, Alzheimer's, Parkinson's, Huntington's, ALS, etc), and, in many instances, reflects the abnormal effect of more than a single genetic abnormality. None of these more widespread illnesses, however, share the rapidly disastrous, functional abnormalities caused by pathological prions. What's different about pathological prions from other genetic diseases? The answer is that no other genetic abnormality can produce an infectious killer protein that is infectious. Nor can any family member, other than an identical twin, be likely to obtain the rare human killer protein unless they randomly cannibalize dying members of an infected tribe. The genetically inherited dominant genes that cause Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker (GSS) disease, and fatal familial insomnia are all rare, progress rapidly, and reflect inborn mutations in PrP proteins. They're not ordinarily infectious from person to person, but see below.

Abnormal (variant) PrP^{Sc} prions act as infections, but as noted above, unlike all other infectious agents, they fail to contain the nucleic acids DNA or RNA. Nevertheless, they possess infectious capacity. Once infected, the production of abnormal prions may be transferred from one animal to another of the same species as well as to other nonprimate mammals or even humans. This infectious aspect of the abnormal prion was first identified a little more than 40 years ago when an aboriginal, isolated New Guinea Kuru tribe was found to be indulging

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INSIDE

in cannibalism. A high, remarkable death rate in the tribe had developed gradually preceded by 14 advancing illnesses consisting of ataxia, tremor, dementia, and death. Death was followed by cannibalistic eating of the dead persons' brains and muscles. A few years later, extracts from Kuru brains injected into the brains of chimpanzees induced a behavioral disintegration as well as autopsied brain that resembled the sufferings of prion disease in New Guinea. Since that time, abnormal PrP prions have unfortunately been transferred into human brain from undiagnosed, contaminated brain electrodes, from application of similarly infected dura mater of patients dying from prion deaths, too close surgical operations, and from cadaveric growth hormone taken from women dying from prion disease.

PrP^{Sc} diseases can affect a variety of species: human (Kuru, variant CJD, FFI); sheep (scrapie); cattle, (Mad cow disease), bovine spongiform encephalopathy (BSE); mink (transmissible mink encephalopathy); mules, deer, and elk (chronic wasting disease); feline spongiform encephalopathy (FSE); and exotic ungulate encephalopathy (Kudu, nyala, oryx). The most dramatic disaster, however, relates to the tragedy that followed the rapid infection by pathological prions in English cattle that started early in 1980 and rose to a peak of danger in 1992.

Roos adds an important supplement to Prusiner's reports. Evidence indicates that from 1980 through 1982, cattle in South England were exposed in their diet to slaughtered feed of neural tissue taken from sheep or goats that died from scrapie, a well known disorder for centuries, but also a prion disease. Shortly after, for economic reasons, material from both cattle and sheep's nervous systems was ground up and used for cattle feed. The result was horrifying with an incidence of identified BSE in UK cattle in more than 37,000 cases in 1992. Stringent attention stopped the dangerous feedings and by 2000, English BSE incidence dropped to 1537. Much smaller numbers have turned up in Germany, Ireland, and France.

Mad cow disease due to transferred abnormal prions into humans was categorized as new variant CJD (vCJD) with the incident age of its human sufferers varying from 13 to 22 years at onset. At this writing, no explanation has been forthcoming of the age of this young cohort. As to the total incidence of new vCJD in the United Kingdom thus far, approximately 100 human cases have appeared. Presently, only 4 vCJD cases have been identified outside of England, 3 in France and 1 in Ireland.

Roos emphasizes that safety of the blood supply for medical use has received special attention here in the United States. Up to the present, no human blood or blood fractions have given any evidence of carrying the new vCJD. No blood transfusion carrying vCJD has been found or mentioned in this country. Nevertheless, federal regulatory agents are making strong efforts to apply every possible prevention to keep blood free from CJD.

COMMENTARY

Despite the tragic epidemic of vCJD in the United Kingdom, France, and Ireland, *Neurology Alert* finds no record of vCJD disease appearing in the United States. *Weekly Report*, a contemporary American newsletter on blood collection and transfusion, indicates that no patient anywhere in the world has as yet received vCJD from blood, whether it be sporadic or from a human donor who later developed vCJD. The US Department of Agriculture has had a screening program for BSE and scrapie and stringent prophylactic attention has prevented any evidence carriers.

Just within the past month, Lloyd and colleagues report that in mice the first possible step in identifying genetic susceptibility to prion diseases may be "where a methionine (NM) or Valine (v) may be encoded in the prion protein." All diagnosed cases of vCJD to date have contained the NM genotype.

A final point to consider: despite the enormous biomedical research that has been given to the normal and variant prions, until recently no one has discovered the normal function of cellular prion protein (PrP^{C}). Without great shouting, a French group led by Mouillet-Richard has perhaps found the solution (Mouillet-Richard S, et al. *Science.* 2000;289:1925-1928). PrP^{C} is normally

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found on nerve cell surfaces and apparently may be a signal transduction protein. **—fred plum**

NCEP Guidelines: Implications for the Neurologist

ABSTRACT & COMMENTARY

Source: NCEP Expert Panel. *JAMA.* 2001;285:2486-2497.

The third report on the evaluation and treatment of elevated cholesterol in adults was released in May 2001. The Adult Treatment Panel III (ATPIII) promotes a much more aggressive stance than its predecessors, particularly with regard to statin therapy in patients with only mildly elevated lipids.

As with previous National Cholesterol Education Program (NCEP) reports, the key lipid component for prevention of atherosclerotic disease is the LDL subfraction. This emphasizes the importance of carrying lipid testing beyond total cholesterol alone. As shown in the Table, among patients with coronary artery disease (CAD), LDL cholesterol should be below 100 mg/dL. If this cannot easily be achieved with diet, then lipid-lowering therapy with a statin agent should be implemented. Patients with symptomatic carotid artery disease are also to be placed in this top category.

In contrast to prior NCEP guidelines, all patients with diabetes mellitus are considered to have a "coronary artery disease risk equivalent," placing them automatically in the top category. The ATPIII also puts increased emphasis on the effects of elevated cholesterol in women and the elderly. While the majority of early data on statin therapy focused on only middle-aged men, recent studies have indicated the benefit of these agents across a wider range of age and gender.

The ATPIII also argues that patients with a distinct "metabolic syndrome" may gain benefits from statin therapy beyond merely lower cholesterol. This syndrome encompasses a spectrum of abdominal obesity, insulin resistance, atherogenic dyslipidemia (elevated triglyceride, small LDL particles, and low HDL cholesterol) as well as prothrombotic or proinflammatory states. Regression of atherosclerosis in these patients may be promoted with statin therapy. Treatment for hyperglycemia and the use of aspirin may be complementary.

COMMENTARY

Perhaps the most striking aspect of the NCEP report is the unfortunate absence of any reference to stroke. Indeed, the NCEP panel does not include a neurologist and the Member Organization list does not include the American Stroke Association (ASA) or National Stroke Association (NSA).

This leaves neurologists who treat patients with stroke wondering: where does this leave me? If stroke is a vascular disease, can the recommendations as made here for heart disease be followed in parallel? How should prior stroke be factored in among other markers of atherosclerotic disease?

Most information regarding the use of statin therapy for patients with stroke derives from the cardiac literature (patients with CAD). Specific data regarding stroke patients are lacking. Certain forms of stroke, such as those caused by atrial fibrillation or cardiac embolism, may not bear a relation to cholesterol levels. The risk of other forms of stroke such as intracerebral hemorrhage may actually be magnified by low cholesterol.

Stroke is, nevertheless, a vascular disease. For this reason, neurologists should err on the side of caution. Lowering of LDL cholesterol to Category I goals (< 100 mg/dL) or at least Category IIa (< 130 mg/dL) is recommended until more disease-specific data are available. **—alan z. segal**

Table

NCEP Cholesterol Management Guidelines

Risk Category	LDL Goal (mg/dL)	LDL Level— Lifestyle change needed	LDL Level— Drug therapy to be initiated
1) Coronary artery disease (or 10-year risk > 20%)*	< 100	≥ 100	≥ 130; (100-129, optional)
2) ≥ 2 risk factors** (10-year risk ≤ 20%)	< 130	≥ 130	a) 10-year CAD risk 10-20%; ≥ 130 b) 10-year CAD risk < 10%; ≥ 160
0-1 risk factors	< 160	≥ 160	≥ 190; (160-189, optional)

*10-year risk of coronary artery disease is determined using Framingham Point Scores (calculated on the basis of age, sex, blood pressure, tobacco use, and cholesterol levels)

**Major risk factors are: tobacco use, hypertension, low HDL-cholesterol levels (< 40 mg/dL), family history of premature CAD, and age (men ≥ 45, women ≥ 55)

Myasthenia Gravis, Steroids, and Osteoporosis Prevention

ABSTRACT & COMMENTARY

Source: Lewis SJ, Smith PE. *Acta Neurol Scand.* 2001;103: 320-322.

Guidelines for osteoporosis prevention during long-term steroid use often go unheeded. Two recommendations are offered: 1) bone density measurements using dual energy X-ray absorptiometry (DEXA) scanning every 1-3 years for patients on > 7.5 mg/d prednisolone for > 6 months; and 2) bisphosphonate treatment for patients on > 15 mg/d prednisolone (prednisolone is dose equivalent to prednisone) for > 6 months, regardless of DEXA result (Eastell R, et al. *J Intern Med.* 1998;244:271-292). Patients older than age 65, or demonstrating abnormal DEXA, existing osteoporotic fractures, premature menopause, or slender build, are also advised to take bisphosphonate. Remarkably, few neurologists appear to follow these suggestions.

Among 80 confirmed myasthenia gravis (MG) patients (47 male, mean age 63.3 years), followed by 5 consultant neurologists in a catchment area of 1.2 million, 34 (42.5%) were on corticosteroids for MG, all for longer than 6 months. Of these, 16 (47%) were on < 7.5 mg/d and 18 on > 7.5 mg/d. Only 4 patients from each group had undergone DEXA scanning (22% of those indicated). Of the 18 taking > 7.5 mg/d, 13 fulfilled bisphosphonate-recommended criteria but only 7 (54%) were so prescribed. Two each of the remaining 6 were taking calcium supplements, vitamin D, or no prophylaxis.

Neurologists prescribe steroid medication for MG moreso than for any other indication and should be attentive to osteoporosis prevention.

COMMENTARY

Osteoporotic fracture risk is best predicted by bone mineral density measurements. Each standard deviation of reduction in bone density augurs a > 2-fold increase in fracture (Marshall D, et al. *BMJ.* 1996;312: 1254-1259). For fracture prevention, hormone replacement—the gold standard for women—or bisphosphonates are indicated. Bisphosphonates, including alendronate (Fosamax) and risedronate (Actonel), block osteoclastic bone resorption, directly inhibit calcium-phosphate crystallization, and increase bone mass. Alendronate has been shown to reduce hip fractures by 50% and reduce hospitalizations and the need for prolonged bed rest due to back pain. Neurologists are in an ideal position to ensure that MG patients are given the full benefit of osteoporosis prophylaxis. **—michael rubin**

Antioxidant Treatment of Friedrich's Ataxia

ABSTRACT & COMMENTARY

Source: Lodi R, et al. *Ann Neurol.* 2001;49:590-596.

Patients with ataxia present a diagnostic and therapeutic challenge for the neurologist. It is helpful to divide the inherited ataxias into 2 groups, those that are autosomal recessive and those that are likely autosomal dominant (also known as the spinocerebellar ataxias or SCAs). Unlike the SCAs, symptoms of autosomal recessive ataxia typically begin within the first 2 decades of life. This group includes Friedrich's ataxia, ataxia from vitamin E deficiency, the Ramsay-Hunt syndrome, Unverricht-Lundborg disease, and Ataxia Telangiectasia.

Friedrich's ataxia is the most common form of inherited ataxia, with an incidence of 1 in 20,000. Starting before the age of 25, progressive limb ataxia, gait disturbance, and scoliosis usually bring the patient to medical attention. Friedrich's is a multisystem disorder, and cardiomyopathy and diabetes are frequent findings. Most patients have absent reflexes and up-going toes, and in nearly all cases a GAA repeat expansion in the first intron of the frataxin gene is found.

Increasing evidence indicates that patients with Friedrich's ataxia have a heightened susceptibility to oxidative stress. Using phosphorus magnetic resonance spectroscopy, Lodi and colleagues previously measured phosphocreatine and ATP levels in living muscle. They demonstrated that patients with Friedrich's ataxia have defects in both cardiac and skeletal muscle metabolism.

The present study tested the hypothesis that treatment with high-dose antioxidants could improve measures of oxidative stress in these patients. Ten patients with genetically proven Friedrich's ataxia were treated with oral Coenzyme Q10 (400 mg/d) and vitamin E (2100 IU/d) for 6 months. Patients were evaluated by physical and neurological examination, echocardiography, and magnetic resonance spectroscopy of cardiac and skeletal muscle. All patients were able to tolerate CoQ10 and vitamin E. Echocardiographic measures of left ventricular hypertrophy did not change. Similarly, neurologic

examinations and clinical ratings on a standard ataxia scale did not change. In virtually all patients, however, a dramatic and statistically significant improvement in spectroscopic measures of energy metabolism occurred in both skeletal and cardiac muscle. The improvement was greatest in patients without left ventricular hypertrophy (ie, those treated earlier in their disease course), and greater in patients with longer GAA repeat length (ie, more severe disease).

COMMENTARY

This first study shows that high-dose oral antioxidant therapy improves cellular bioenergetics in Friedrich's ataxia. Improvements were sustained over 6 months of treatment, and the treatment was easy to tolerate. Patients who were treated earlier in the courses of their disease, and those with more severe metabolic deficits, were most likely to improve.

Skeptics might criticize this study because Lodi et al failed to demonstrate a clinically significant change with therapy. Although echocardiographic parameters and neurologic exams were unaffected by treatment, these are relatively insensitive measures of disease progression. The improvement in energy metabolism was robust and sustained, raising the possibility that long-term prophylactic treatment of presymptomatic patients might demonstrate an improvement in the forthcoming neurologic exams.

This study is important for patients with Friedrich's ataxia and also for patients with other neurodegenerative diseases. Based on the power of this study, on the lack of alternative treatments, and on the benign nature of oral antioxidants, it would seem reasonable to recommend high-dose antioxidant treatment for Friedrich's patients as well as those at risk for the disease. Whether these promising results can be extended to other disorders of oxidative stress (such as Parkinson's disease) remains to be seen. **—steven frucht**

Resective Epilepsy Surgery: The Case for Early Intervention

ABSTRACTS & COMMENTARY

Sources: Hennessy MJ, et al. *J Neurol Neurosurg Psychiatry*. 2001;70:450-458; Duncan JS. *J Neurol Neurosurg Psychiatry*. 2001;70:432.

Hennessy and colleagues retrospectively analyzed the outcome of en bloc temporal lobectomy in 80 epilepsy patients with focal lesions other than hippocampal sclerosis (HS). Using an actuarial approach, they found that the probability of achieving at least 1 year of seizure remission within 5 years of follow-up was 71%. This is comparable to the international experience for either temporal lobectomy or lesional epilepsy regardless of location. They also found that dysembryoplastic neuroepithelial tumors (DNET) were associated with favorable outcomes.

In an accompanying editorial, Duncan emphasizes the need for early evaluation of surgical candidacy. Comparing the finding of adverse outcome associated with long duration (> 10 years) of epilepsy, Duncan states that most surgical series have waited more than 15-20 years after the onset of seizures. In other words, most patients are referred for surgery too late for them to be in the best outcome group.

COMMENTARY

The analysis of epilepsy surgery outcome reported here is somewhat limited. Extratemporal resections were not included, and the inclusion criterion of a neuropathologically proven focal lesion other than HS only applied to one-third of 234 consecutive cases of en bloc temporal lobectomies. Nonetheless, the conclusions drawn are likely applicable to temporal lobe epilepsy that is nonlesional or associated with HS.

In terms of clinical parameters that may have had an effect on postoperative outcome, Hennessy et al round up the usual suspects. As in other studies (many cited by the authors), these included perinatal complications, family history of epilepsy, febrile convulsions, seizure type and EEG features, and results of neuropsychological testing.

The most significant positive predictive features were duration of epilepsy less than 10 years and age at operation younger than 30, certainly not independent variables. These results support 2 controversial pathophysiologic hypotheses: first, that the determinants of pharmacological resistance may be established early in the natural history of epilepsy, and, second, that secondary epileptogenesis accounts for surgical failure when epilepsy is long-standing (or, in Gower's words, "Seizures beget seizures"). Whatever pathophysiologic mechanisms are involved, a consensus is developing that epilepsy surgery should be offered early when appropriate.

In pursuing preoperative evaluation for surgery, one must first decide upon a definition of "medically intractable" epilepsy. This definition has become more critical in the last decade. Since 1993, 13 new antiepileptic drugs (AEDs) have been approved for use

in the United States. While 5 of these represent new formulations of older agents and are thus less relevant in expanding treatment options, the others represent truly novel AEDs. Some of the newer drugs may be more effective than others for specific seizure types; the empirical spectrum of action in humans is evolving as we gain more clinical experience. Nonetheless, if a neurologist were to perform serial trials of each of the new AEDs on a given patient prior to initiating a presurgical evaluation, surgery could potentially be postponed for years, and the current study demonstrates that such a delay can worsen surgical outcome. If "adequate" seizure control can be obtained in only 60-70% of patients in trials of 3 "older generation" AEDs (Smith DB, et al. *Epilepsia.* 1987;28[Suppl 3]:S50-58; Mattson RH, et al. *N Engl J Med.* 1992; 327:765-771), there is no reason to believe that the newer agents will increase the likelihood (probably less than 10%) of seizure freedom in any given patient who has failed 2 or more AEDs. Prior to the current boom in AED choices, an NIH Consensus Conference (Leppik IE. *Epilepsy Res.* 1992;5[Suppl]:7-11) proposed "that a person be defined as having intractable epilepsy if any seizures occur while the person is documented as having an AED concentration (or dosage) of at least one standard medication in the usually effective range at the time of the seizure within one year after the onset of epilepsy." This definition should set the standard for when a patient should first be considered for epilepsy surgery.

Vagus nerve stimulation, the only other nonpharmacologic treatment option (other than the ketogenic diet, which is useful in a select few), should also be considered early in the treatment algorithm (Benbadis SR, et al. *Neurology.* 2000;55:1780-1784). Its main advantage is to allow a lower degree of invasive treatment with its disadvantage being the low rate of achieving complete seizure remission, relative to temporal lobectomy. Finally, it is worth re-emphasizing a point previously discussed in *Neurology Alert*: epilepsy can be a fatal disorder and achieving seizure freedom reduces mortality as well as morbidity (Labar DR. *Neurology Alert* 1996;14:44-45). *Neurology Alert* suggests that more consideration be given to the appropriateness of early resective surgery for epilepsy patients. Such treatment may well be life preserving, in addition to health sustaining. **—andy dean**

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Practice Parameter: Bell's Palsy

ABSTRACT & COMMENTARY

Source: Grogan PM, Gronseth GS. *Neurology.* 2001;56: 830-836.

Various treatment options exist for bell's palsy, some undeniably useful, some unequivocally pointless. Artificial tears, lubricating ophthalmic ointment, and eyelid taping prevent corneal drying. Massage and facial nerve electrical stimulation provide psychological support, but little else. Within this spectrum, wither steroids, acyclovir, and facial nerve surgical decompression?

A special article by the Quality Standards Subcommittee of the American Academy of Neurology addresses this question. A MEDLINE search of the National Library of Medicine's database from 1966 to June 2000, and review of the references of these articles to identify other relevant reports on Bell's palsy, uncovered 230 articles examining steroids (only 9 were prospective), 92 addressing acyclovir (3 prospective), and 104 discussing surgical decompression (4 prospective). None were adequately powered class I studies, defined as a randomized, controlled trial with 1) clearly defined primary outcomes and exclusion and inclusion criteria; 2) equivalent baseline characteristics among treatment arms; and 3) satisfactory accounting of dropouts and crossovers. Results of class I and II (3 of 4 above criteria) were pooled where possible.

No definite benefit could be established for steroids, acyclovir, or surgical decompression. Probable benefit from steroids, with acyclovir possibly effective when combined with prednisone, was suggested by the available evidence. No recommendation could be made regarding surgical decompression. Bell's palsy remains a disease in search of a proven effective therapy.

COMMENTARY

Herpes simplex virus (HSV) type 1 is reportedly the major cause of Bell's palsy (*Curr Treat Options Neurol.* 2000;2:407-416), but HSV type 6 is also a common culprit. Using polymerase chain reaction (PCR), type 6 HSV DNA was detected in the tear fluid of 35% of patients (7 of 20) with Bell's palsy (*J Clin Microbiol.* 2000;38:2753-2755). Varicella zoster virus (VZV) reactivation (Ramsay Hunt syndrome), which may appear without skin lesions and mimic Bell's palsy, was found in 10% (2 of 20). VZV is more resistant to acyclovir,

and may be responsible for some treatment failures. If suspected, higher doses of acyclovir are recommended.

Transmastoid decompression may benefit severe Bell's palsy. Among 101 adults with significant denervation following prednisone therapy for Bell's palsy, defined as > 95% amplitude drop in compound muscle action potential on facial motor nerve stimulation, 58 underwent decompression and 43 were followed conservatively. Two months following surgery, the operated group demonstrated a significantly better House-Brackmann grade than the nonsurgical group (*Otolaryngol Head Neck Surg.* 2001;124:282-286). Further studies are warranted, however, before recommendation of this procedure is justified. **—michael rubin**

Chelation Therapy and Cognitive Outcome in Children Exposed to Lead

ABSTRACT & COMMENTARY

Source: Rogan WJ, et al. *N Engl J Med.* 2001;344:1421-1426.

Many children in the united states are exposed to lead levels that appear to be associated with impaired cognitive performance. Several studies (eg, *Pediatrics.* 1991;87:219-227; *Pediatrics.* 1992;90: 855-861) suggest that exposure to lead levels as low as 20 mcg/dL before 2 years of age are associated with impaired performance on developmental tests performed some 2-8 years after exposure. It is not known if these cognitive impairments are lifelong.

The medical treatment of lead neurotoxicity in children has focused upon chelation therapy. Chelating agents such as succimer (dimercaptosuccinic acid) bind lead ion and form a complex that is much more readily excreted from the body. The Centers for Disease Control (CDC) has set guidelines, based on blood lead levels, for appropriateness of initiation of chelation therapy. Such therapy is recommended for children whose blood lead levels are > 44 mcg/dL, a level associated with other symptoms of lead poisoning besides cognitive impairment. The CDC has made no definite recommendations for children whose blood lead levels fall in the 20-45 mcg/dL range; these children might be expected to have cognitive impairment as their only symptom, and clearly there are far greater numbers of children with these levels of exposure than those with overt (> 44 mcg/dL) lead toxicity.

Rogan and colleagues performed a randomized, double-blind, placebo-controlled trial of orally-administered succimer to children aged 12-33 months, whose blood lead levels were within the range 20-44 mcg/dL. Cognitive, motor, behavioral, and neuropsychological performance in these children was then monitored over the next 3 years. The study was statistically designed to detect as little as a 3-point difference in mean IQ at a 3-year follow-up. As might be expected, the study population was largely comprised of inner-city poor, with approximately 75% of the study patients African-American and approximately 35% with an annual family income of < $10,000. A total of 780 were randomized to receive from 1 to 3 26-day oral courses of either succimer or placebo. The mean blood levels in both treatment groups were approximately 26 mcg/dL, and succimer therapy led to a mean reduction of blood lead levels lower than 20 mcg/dL sustained for 1 year. Thus, patients in the succimer-treated group had their blood lead level reduced below the presumed "neurotoxicity threshold" of 20 mcg/L whereas placebo-treated patients had mean blood levels well above the "neurotoxicity threshold" for the next year.

Rogan et al then examined multiple neuropsychological measures 36 months after treatment. They found no statistically significant differences between either group with respect to performance, verbal or full-scale IQ, as determined using a modified Wechsler Scale. Assessment of attention, language, sensorimotor, visuospatial, and memory function in the 2 groups was performed using the Developmental Neuropsychological Assessment subscales (NEPSY). Also, a revised version of the widely used Conner's parental rating scale found no differences in the incident of measures of hyperactive or oppositional behavior in the 2 groups.

COMMENTARY

This study demonstrated that a reduction of blood lead levels below the CDC-accepted threshold of 20 mcg/dL during the third year of life in children with "moderate" lead exposure did not result in a significant difference in cognitive outcome, as assessed 3 years later. This suggests that, if there is significant neurotoxicity caused by lead levels between 20-44 mcg/dL (and much evidence suggests that there is), such toxicity must be essentially irreversible after 2 years of age, and perhaps sooner. This study is a potential death-blow to aggressive chelation of children with lead levels of 20-44 mcg/dL. Instead, efforts should be made to reduce the number of children exposed to lead levels > 20 mcg/dL. Thus, significant progress in this area is more likely to occur by means of social science and public policy than by postexposure medical treatment. **—rosario r. trifiletti**

Brief Alerts

Prepare Against Poliomyelitis

Source: Schrope M. *Nature News.* 2001;411:405.

Neurology Alert readers may remember our report earlier this year in April 2001, of young persons in the Dominican Republic who developed acute poliomyelitis in 2000 (*Neurology Alert* 2001;19:59-60). Presumably, the acute disease was due to a rare breakthrough of a virus strain used in oral vaccination. This new report, however, cites 2 cases of poliomyelitis paralysis in Bulgaria caused by a wild virus (not partially inhibited) which matched a strain from India. Both cases came from peripatetic gypsies. Health workers estimated that each clinical case of the disease implied that at least 100 asymptomatic persons had been infected by the virus and engendered the antibodies. Nevertheless, each of the 100 asymptomatic cases could have passed the virus to 100 more possible persons in their environments. Prompt vaccination in all Bulgarian children is in progress. *Neurology Alert* again warns our readers to advise their families and patients to be promptly vaccinated for poliomyelitis or, if already vaccinated, to acquire a booster if they anticipate traveling anywhere but First World countries. **—fred plum**

Diathermy Plus Deep Brain Stimulation can Destroy Brain Regions

Source: Nutt JG, et al. *Neurology.* 2001;56:1384-1386.

A 70-year-old man developed severe parkinson's disease (PD) at age 50 and at age 68 had quadripolar activating electrodes placed in the subthalamic nucleus. Moderate improvement in his PD ensued and he reduced his dopaminergic drugs 19 months following the implantation. Subsequently, he had his maxillary teeth extracted because of chronic alveolar osteonecrosis. The following day a diatherm induction coil was applied successively for 30 minutes on each cheek in an effort to accelerate gum repair. Coils were set at 95-µ pulses at 4000 Hz and a power setting of 10. After the first 39 minutes he became drowsy and after the second segment coma reigned. Clinical findings included small pupils, roving eye movements, and decrebrate posturing. MRI scanning 3 days later indicated T_2 segmental abnormalities said to affect the pointine and mid brain areas plus the cerebral peduncles. An MRI obtained 32 days after the catastrophe indicated a reduction of the T_2 lesions to the area of the electrodes in the subthalamic nucleus. The previously identified mesencephalic and pontine abnormalities had disappeared, which is to be expected since those areas directly regulate eye movements, a function the patient had never lost. At 50 days after onset, he appeared to possess only unchanging minimal awareness.

Nutt and associates believe that the patient's catastrophe may have developed due to heated electrodes from the maxillary placement of the diathermy. They suggest that the RF current transpassed through the base of the skull into the brain and may have been the accident that produced this distressing result. Whatever the mechanisms of this focal heat stroke, diathermy neighboring near steel electrodes is dangerous therapy. **—fred plum**

CME Questions

1. **For the treatment of Bell's palsy:**
   a. prednisolone is of proven benefit.
   b. acyclovir is of proven benefit.
   c. combining prednisolone with acyclovir is of proven benefit, moreso than individually.
   d. surgical decompression is of proven benefit.
   e. prednisolone and acyclovir may help, but controlled trials are still needed to prove this conclusively.

2. **Recent studies of lead neurotoxicity in children suggest that:**
   a. levels > 20 mcg/dL are not associated with neurotoxicity.
   b. lead neurotoxicity is always reversible.
   c. oral chelation therapy is not effective in reducing blood lead levels below safe thresholds.
   d. oral chelation therapy reduces blood lead levels but does not improve neuropsychological outcome.
   e. None of the above

3. **In the study of Friedrich's ataxia, Lodi et al found that:**
   a. high-dose oral antioxidant therapy improves cellular bioenergetics in Friedrich's ataxia.
   b. the high-dose oral antioxidant treatment was easy to tolerate.
   c. improvements were sustained over 6 months of antioxidant therapy .
   d. All of the above

In Future Issues:

Hysterical Sensory Symptoms Functionally Associated with Subcortical Nuclei