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Update in Neurodegenerative Diseases: Pathogenesis and Treatment

ABSTRACTS & COMMENTARY

Sources: Nucifora FC Jr, et al. Interference by huntingtin and atrophin-1 with CBP-mediated transcription leading to cellular toxicity. *Science.* 2001;291:2423-2428; Steffan JS, et al. Huntingtin inhibits acetyltransferases and histone deacetylase inhibitors suppress in vivo pathogenesis. *Nature.* 2001; in press; The Huntington Study Group. A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. *Neurology.* 2001;57:397-404.

Huntington's Disease

In huntington's disease (hd), recent work has focused on the interaction of huntingtin with transcription factors. The genetic abnormality called huntingtin in HD is a CAG repeat expansion of more than 39 CAGs. Expanded polyglutamine domains in the mutant protein result in protein interactions, with other polyglutamine containing proteins by facilitating a "polar zipper" mechanism. Recent studies demonstrated that mutant huntingtin can interact directly with several transcription factors including P53, P300, and the transcription factor coactivator CREB-binding protein (CBP). In the presence of mutant huntingtin in cell culture, in transgenic HD mice, as well as in human postmortem brain tissues, CBP is depleted from its normal nuclear localization, and sequestered into huntingtin containing aggregates. This effect depends on the length of the polyglutamine repeat stretch. Furthermore, transcription assays have shown that expression of the growth factor, BDNF, is regulated by CBP, and it is downregulated in HD brain tissue. This provides further evidence that mutant huntingtin expression is detrimental to gene transcription. The importance of these interactions is underscored by observations that CBP function is similarly modulated by mutant polyglutamine repeats in other CAG repeat-expansion diseases, including spinobulbar muscular atrophy, spinocerebellar ataxia-3, and dentatorubropallidoluysin atrophy (DRPLA).

One means by which CBP modulates gene transcription is by

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INSIDE

acting as a histone acetylase. Accordingly, it sequestrates CBP into huntingtin aggregates which decreases histone acetylation, and reduces gene transcription. The histone acetylase activity of CBP is directly inhibited by mutant huntingtin. This raises the novel possibility that a therapy for HD may be to increase histone acetylation to ameliorate the illness. A number of compounds have been developed that are histone deacetylase inhibitors. These agents were developed for the treatment of cancer, since they induce the differentiation of cancer cells, causing increased vulnerability to cancer chemotherapy. Initial studies have shown efficacy of these compounds in cell culture models of HD, as well as a drosophila model. A tantalizing approach, therefore, is to use these agents as a novel therapy for HD.

COMMENTARY

A downstream consequence of the impaired transcriptional regulation in HD may be defective energy metabolism. We and others used magnetic resonance spectroscopy to establish that there are elevations of lactate in the basal ganglia, and reductions in phosphocreatine and ATP levels in the skeletal muscle of Huntington's patients, including patients at risk. In view of this, we investigated whether agents that may modulate energy metabolism could have therapeutic efficacy. A recent trial studied the effects of coenzyme Q10, an energy modulator, and remacemide, an NMDA excitatory amino acid antagonist. The results showed that coenzyme Q10 administration slowed disease progression by 13%, while remacemide had no effects. Although remacemide provided efficacy in mice, the dose used was intolerable in humans. We also investigated whether oral administration of creatine, which can increase brain phosphocreatine levels, exerts neuroprotective effects. Our studies have shown significant neuroprotective effects in transgenic mouse models of both ALS and HD (Ferrante RJ, et al. *J Neurosci.* 2000;20:4389-4397). Clinical trials to determine whether these agents will have efficacy in man are either being planned or underway. Initial studies using neurotransplantation in HD have shown limited improvement and that the grafts survive. Although symptomatic treatment with dopamine receptor antagonists exerts some effects on chorea, most patients prefer to avoid the side effects of these medications. **—flint beal**

Parkinson's Disease

Sources: McNaught KSP, et al. Failure of the ubiquitin proteasome system in Parkinson's disease. *Nat Rev Neuroscience.* 2001;2:589-594; Shimura H, et al. Ubiquitination of a new form of alpha-synuclein by parkin from human brain: Implications for Parkinson's disease. *Science.* 2001;293:224-225; Beal MF. Experimental models of Parkinson's disease. *Nat Rev Neurosci.* 2001;2:325-334; Glasson BI, et al. Oxidative damage linked to neurodegeneration by selective alpha-synuclein nitration in synuclienopathy lesions. *Science.* 2001; 291:595-597.

In parkinson's disease (pd), major advances have come from the finding of 2 associated separate genetic defects associated with the illness. Autosomal dominant inherited PD has been associated with mutations in the protein a-synuclein. Autosomal recessive early onset PD has been associated with mutations in a protein termed parkin. It has been demonstrated that a-synuclein is a major component of lewy bodies, the pathologic hallmark of PD. It is, therefore, theorized that abnormal aggregation of this protein may directly contribute to the disease pathogenesis. It is thought that aggregated protein may prevent normal degradation, thereby contributing to cellular stress. The parkin protein has been demonstrated to be a ubiquitin ligase (E3). Ubiquitin conjugation to damaged proteins is essential for their

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degradation by the proteasome. It is, therefore, theorized that the parkin mutation, which impairs the normal functioning of ubiquitin ligase enzymatic activity, may lead to accumulation of abnormal proteins. Recently it has been demonstrated that one of the substrates of parkin is a 22-kDa glycosylated form of a-synuclein referred to as a-SP22. It appears that the familial PD-related mutations in parkin reduce the polyubiquitination of proteins such as a-SP22, which has been shown to accumulate in a non-ubiqutinated form in dopamine neurons in the substantia nigra compacta of juvenile onset PD patients. In transgenic mouse models of ALS, there is also increasing evidence that aggregates of mutated Cu/Zn superoxide dismutase may play a critical role. Recent evidence suggests that abnormal catalytic activity of Cu/Zn superoxide dismutase is less likely to be important since removing the catalytic copper does not have an effect on disease progression.

COMMENTARY

Also, substantial evidence demonstrates impairments of mitochondrial complex I activity in the substantia nigra of PD. Interestingly, systemic administration of the specific complex I inhibitor rotenone produces selective degeneration of substantia nigra neurons. It produces cytoplasmic inclusions that have the characteristic appearance of lewy bodies, and stain with a-synuclein and ubiquitin. Other studies have shown that administration of the neurotoxin MPTP can also upregulate the expression of a-synuclein. Possibly, these metabolic defects could contribute to the generation of lewy bodies by upregulating a-synuclein expression, and also by inducing oxidative stress. Lewy bodies in human PD are oxidatively modified and stained with antibodies raised against nitrated a-synuclein. Nitration is a characteristic feature of oxidative damage mediated by peroxynitrite.

A major NIH funded initiative to investigate neuroprotective treatments in PD has recently been announced. Ongoing trials are evaluating neuroprotective effects of monoamine oxidase b inhibitors, riluzole, and coenzyme Q10. Many other agents targeted at oxidative damage, growth factors, or apoptotic cell death appear promising in animal studies. Lastly, both PD and ALS are primary targets for replacement therapy using neuronal stem cells. **—flint beal**

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Primary Lateral Sclerosis—An Uncommon, Midlife Cortico-Spinal System Disease

ABSTRACTS & COMMENTARY

Sources: Le Forestier NL, et al. Does primary lateral sclerosis exist? A study of 20 patients and review of literature. *Brain.* 2001;124:1989-1999; Kuipers-Upmeijer J, et al. Primary lateral sclerosis: Clinical, neurophysiological, and magnetic resonance findings. *J Neurol Neurosurg Psychiatry.* 2001;71:615-620.

Le forestier and colleagues annually treat and follow 450 patients in the Amyotrophic Lateral Sclerosis (ALS) Center of the Salpetriere Hospital, Paris. Among this large group of patients with corticospinal motor neuron disease, they identified and followed 20 sufferers of primary lateral sclerosis (PLS) for at least 3-5 years. The sufferers themselves already had an average of 8 years of illness before they came to the ALS Center. Mean follow-up amounted to an average of 43 months with a single duration of 14 years, but with no deaths. (Criteria for diagnosis were based on Pringle CE, et al. *Brain.* 1992;115:495-520). Given the probability that most of the remaining ± 430 patients at the Salpetriere had been accurately diagnosed and treated for classic ALS, one might suspect at least a 25% annual mortality in that group. It follows that PLS incidence should amount to much less than 1% of classic ALS.

Clinical Diagnosis

The applied minimal diagnosis of PLS includes the following qualities: 1) a progressive, uneven, uncommon, middle aged adult degenerative neurological disease damaging predominantly the corticospinal motor system. Presumably it reflects a genetic abnormality; 2) the disorder always lasts more than 3 years and the suffering patient usually proceeds to a relatively continuous degenerative death 15 years or more after onset; 3) the anatomic-functional abnormality of the disease consists predominantly of symmetrical, bilateral spastic damage to the lower spinal and bulbar pyramidal motor systems. The upper extremities usually become somewhat less spastic than the lower, and the hands often show moderate atrophy greater than the feet. By contrast, both feet and hands in PLS become much less withered than develop in ALS; and 4) a small fraction of bulbospinal and spinal motor neurons may degener-

ate over the years but they seldom create sufficient weakness to cause the specific cause of death. No clues so far exist to understand the specific cause and development of LSE by blood, CSF analysis, brain imaging, or any other laboratory tests. Diligent autopsies are extremely rare, but muscle biopsies are frequent.

Most PLS patients experienced muscle cramps (16/20) and muscle fasciculations (18/20) but, as mentioned, not primary muscle atrophy. Eight of Le Forestiers et al's patients developed moderate secondary muscle atrophy in the hands but severe spasticity impeded 10 patients, 2 of whom suffered sufficient stiffness to be motor dysfunctional. Standard, general, cognitive tests never reached a dementia pattern, although 16 patients displayed moderately impaired frontal lobe neuropsychological functions. Seven patients developed oculomotor defects. Two displayed typical, progressive supranuclear opthalmoplegia, while 5 additional patients developed errors in antisaccadic efforts.

Seventeen of the 20 PLS patients developed pseudobulbar palsy between years of 1-7 of their illness. This was characterized by emotional lability, difficult swallowing, slow monotonous speaking, and urinary urgency (the last symptom is rare in ALS).Ten patients became unable to take deep breaths voluntarily, but tracheostomy was seldom necessary as in ALS. Muscle strength in the limbs remained near normal in 6 patients, but in almost all others became either moderately or, in 2 patients, severely weak.

A number of electrophysiological tests were used but were not explicitly important.

EMG Studies

All patients had both EMG studies as well as muscle biopsies. Six EMGs early in PLS patients reflected an absence of ALS. Successive EMG tests over time and varying motor unit potentials (MUP) were conducted and indicated a pattern of partial motor neuronal denervation followed by patches of reinnervation. The same findings were substantiated by muscle biopsies. Others have argued that these changes were mirrors of spasticity, but the major evidence appears to be one of spontaneous neuronal disintegration and repair. Spinal motor cell losses in PLS were much fewer than one finds in ALS.

At the time of this writing, 6 patients retained almost normal muscular strength despite their spasticity. Ten more were weakened but not more seriously than grade 4-5 in the UK Medical Research Council scale. Weakness and spasticity mainly affected proximal hip muscles and distal muscles, ones in the upper extremities. Strength varied in several patients with loss during the relatively early years but regained strength later on. All patients developed at least mild pseudobulbar palsy. Dysfunction of noncorticospinal systems also appeared in random qualities such as abnormal VEPs and SEPs. Brain MRI demonstrated no abnormalities in 6 patients, temporobasal atrophy in 3, and mild atrophy of the primary motor area of 1.

COMMENTARY

As *Neurology Alert* went to press, the report of 10 PLS patients reported by Kuipers-Upmeijer and colleagues appeared. This verified the long survival and slow progression of PLS. It also indicates the inconsistent motor deficits described by Le Forestier et al and unknowingly supported almost all their observations. Kuipers-Upmeijer et al emphasize the indication that mild lower motor neuron defects appeared during maximal voluntary contractions and that 1 patient had a consistently reduced capacity in lower motor neuron efforts. As in Le Forestier et al's report, MRI atrophy affected the precentral cerebral gyrus but diffferently, the parietal-occipital regions. Both investigators conclude that PLS belongs to the relatively large corticobulbar-spinal family, the individual genes of which remain unsolved. **—fred plum**

Does the Cerebellum Have a Sense of Humor?

ABSTRACT & COMMENTARY

Source: Parvizi J, et al. Pathological laughter and crying. A link to the cerebellum. *Brain*. 2001;124:1708-1719.

The term pathological laughter and crying (PLC) refers to uncontrollable episodes of laughter or crying that occur without apparent reason or with insufficient cause. PLC, therefore, is a disorder of emotional expression rather than a primary disturbance of mood. The most common cause of PLC is pseudobulbar palsy but it also has been reported in multiple sclerosis, gelastic epilepsy, and in association with infarcts and tumors of posterior fossa structures.

Parvizi and associates studied a 51-year-old righthanded man with PLC following a right cerebellar stroke. Pathological crying was noted by his family immediately after the stroke and pathological laughter soon afterwards. Acutely, the neurological evaluation was remarkable for gait ataxia and dysmetria of the right limbs. Cranial nerve examination was normal except for gaze-evoked nystagmus on rightward gaze.

Fourteen months later, ambulation and coordination had improved but PLC persisted unchanged. On cognitive testing, attention and recent memory were mildly impaired, executive function was more impaired. There were no depressive or anxiety-related symptoms.

On MRI there were 3 small infarcts in the right and left middle cerebellar peduncles and mid basis pontis, and 2 larger infarcts in the superior and inferior semilunar lobules of the right cerebellar hemisphere. No lesions were detected elsewhere in the brain.

Based on their evaluations, Parvizi and colleagues concluded that there was a partial deafferentation of the cerebellum from descending inputs of left telencephalic structures. Therefore, they postulate that PLC in this case was due to disruption of pathways between forebrain structures that process emotionally competent stimuli and their relevant context, and then signal this information to the cerebellum. The cerebellum in turn computes a certain profile and level of emotional response which it then communicates to cortical and subcortical motor areas involved in generating emotional responses.

The patient's PLC improved following administration of a selective serotonin reputake inhibitor (SSRI), in accord with previous reports that the condition is responsive to treatment with either SSRI or tricyclic antidepressants.

COMMENTARY

In times past, philosophers and psychologists pondered over the mechanism of laughter. Ever since the discovery of "laughing gas," or nitrous oxide anesthesia, in the last century, scientists have examined laughter as a chemical and physical phenomenon that is distinct from an emotional state of amusement.

PLC is an example of laughter divorced from emotion and context. The patient with PLC not only laughs or cries for no apparent reason, but also may both laugh and cry in response to the same stimulus. In other situations, a patient may laugh inappropriately in response to sad news. In patients with pseudo bulbar palsy, PLC has been explained as a result of disinhibition of subcortical "centers for laughing and crying," presumably located in the brainstem adjacent to the facial nerve nuclei and respiratory control nuclei. Disinhibition or mere loss of cortical control cannot explain the phenomena observed in patients with PLC.

Parvizi et al's alternative view of PLC helps to explain some of the clinical phenomenology in affected patients but it also raises questions that only further neuroanatomical and neurophysiological studies can answer. **—john j. caronna**

HDL Cholesterol and Alzheimer's Neuropathology

ABSTRACT & COMMENTARY

Source: Launer LJ, et al. Cholesterol and neuropathologic markers of AD: A population based autopsy study. *Neurology*. 2001;57:1447-1452.

There has been increasing interest in a possible link between Alzheimer's disease (AD) and elevated cholesterol following the reports that cholesterol-lowering medications such as the statins may reduce risk of dementia. Now, a new study has provided indirect evidence that components of HDL cholesterol may play a role in the development of the neuritic plaques and neurofibrillary tangles associated with AD.

Investigators at the NIH used information previously collected about circulating cholesterol levels and autopsy results from 218 Japanese-American men to carry out this study. They examined the correlation between plasma cholesterol levels at various stages of life and the appearance of plaques and neurofibrillary tangles in the brain after death. The study participants had been originally examined as part of the Honolulu Heart Program between 1965 and 1971. They were later re-examined between 1991 and 2001 as part of the Honolulu-Asia Aging Study. The investigators controled for a variety of possible confounding factors in their analysis, such as age at death, APOE genotype, midlife systolic blood pressure, as well as comorbid conditions such as stroke.

The subset of patients from the Honolulu-Asia Aging Study that underwent autopsy were found to be slightly older than the rest of the study population and had a greater representation of subjects affected by dementia. Of the 218 patients who underwent autopsies, 36 were found to have AD, 32 had vascular dementia, and 10 suffered from other dementias. A strong association was found between high late-life HDL cholesterol levels and increased numbers of neuritic plaques and tangles in the brain. Conversely, low levels of total cholesterol in midlife were associated with a lower number of neuritic plaques and neurofibrillary tangles. There was no such correlation found for diffuse and other non-neuritic plaques. It should be noted that there was no observed association between late life HDL cholesterol levels as a function of dementia diagnosis, such that similar findings were made in the pathologically confirmed cases of AD and vascular dementia.

COMMENTARY

This study found a dose response relationship

between the number of neuritic plaques and tangles in autopsy cases of dementia and late life HDL cholesterol levels. The observed association was based upon a trend in the number of plaques and tangles in comparing patients with the lowest cholesterol levels to those with progressively higher HDL values. It is notable that this trend was observed based on the study of both demented and normal subjects. Therefore, this study provides no additional evidence that elevated serum cholesterol levels affect the risk of dementia. Nevertheless, the possibility that subtypes of cholesterol play a role in the development of selected elements of Alzheimer's pathology is both biologically feasible and worthy of further study. **—norman r. relkin**

Effects of Steroids on MS Disease Progression

ABSTRACT & COMMENTARY

Source: Zivadinov R, et al. Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. *Neurology*. 2001; 57:1239-1247.

In this randomized 5-year study, 88 patients with relapsing-remitting multiple sclerosis (MS) were assigned to either regular pulses of IV methylprednisolone (IVMP) 1000 mg/d for 5 d every 4 months for 3 years, and then every 6 months for 2 years, vs. the same dose schedule only for relapses. MRI and clinical disability measures were performed in a blinded fashion. Patients on the regular pulse treatment received approximately 3 times the total amount of steroids than the relapse group over 5 years. The regular pulse IVMP group had less progression of disability than the relapse treated group (EDSS 1.7 vs 3.4, or a 32% reduction, $P < 0.0001$). Similarly, on brain MRI there was significantly less T1 black hole volume formation and less brain atrophy in the regular pulse IVMP group. There was no significant difference between treatment arms at 5 years, however, in the annualized relapse rate (0.6 vs 0.6) or T2 lesion volume on brain MRI (21.4 vs 27.8).

COMMENTARY

While corticosteroid therapy has been a mainstay in the treatment of acute relapses of MS to reduce the severity and duration of an attack, the benefits in changing the ultimate outcome of disease have been somewhat unclear. Also controversial is the use of regular pulses of IVMP in a "preventative" fashion to modify disease progression. This prospective study that combined standardized clinical assessments with highly quantitative brain MRI measures demonstrates a benefit of prophylactic pulse IVMP in slowing disease progression above that achieved by random treatment of relapses only. A larger multicenter trial, probably in combination with the interferon-beta or glatiramer acetate, will be required to more definitively establish a role of pulse IVMP therapy. **—brian r. apatoff**

Intensive Voice Treatment Helps Patients with PD

ABSTRACT & COMMENTARY

Source: Ramig LO, et al. Intensive voice treatment (LSVT) for patients with Parkinson's disease: A 2 year follow up. *J Neurol Neurosurg Psychiatry*. 2001;71:493-498.

Among the difficulties facing parkinson patients, speech disorders are particularly vexing. Unlike bradykinesia and rigidity, parkinsonism affecting the voice usually only partially responds to treatment with dopaminergic agents. Hoarseness, hypophonia, impaired articulation, tachyphemia, and vocal freezing can markedly impair patients' personal and professional lives, and are not uncommonly a major source of disability. The standard approach used by most neurologists is to refer these patients for speech therapy. However, once the treating neurologist writes the prescription for speech therapy, he or she usually has no way of knowing whether the therapy worked or whether benefits were maintained. In the current era of evidence-based medicine, neurologists need to know that the nonpharmacologic treatments they recommend are effective.

The current paper describes a longitudinal study of Parkinson patients treated with 1 of 2 forms of speech therapy, with follow-up over 2 years. The study asked 2 questions: is the Lee Silverman vocal technique (LSVT) superior to Respiratory Therapy (RET), and are benefits sustained over a 2-year period? RET therapy targets increased inspiratory and expiratory muscle activity as a way of increasing speech volume. LSVT targets only the volume of speech, asking patients to produce a loud voice with maximum effort. Thirty-three patients were randomly assigned to receive either RET or LSVT therapy, each of which was performed 4 times per week for 4 weeks. Patients were then expected to continue practicing the exercises on their own. They were assessed immediately after completing the therapy, and again at the end of 2 years using a standard set of speech tests

(phonation, repetition, recitation of a passage). An examiner blinded to the patients' therapeutic assignment scored them at 4 weeks and 2 years.

The LSVT significantly improved measures of vocal loudness and inflection immediately after treatment, and benefits were maintained (with slight drop-off) at 24 months. By contrast, RET therapy did not significantly improve either measure of vocal function immediately after treatment or at 2-year follow-up.

COMMENTARY

Ramig and colleagues propose that the LSVT improves speech in Parkinson's disease by rendering speech production more efficient. Another possibility is that in addition to an underlying tendency to be hypophonic, Parkinson patients may underestimate the volume of speech that they produce. Proprioceptive and motor learning deficits are well described in Parkinson's disease, and it is possible that the effectiveness of the LSVT results from the continuous reinforcement of the need to overcompensate for perceived softness. Whatever the mechanism, this study (and others as well) shows that the LSVT is an effective treatment for speech disorders in Parkinson patients. Neurologists who refer Parkinson patients for speech therapy are encouraged to specify LSVT on the prescription in order to maximize their patients' outcomes. **—steven frucht**

Brief Alerts

Neuropathy News: CANOMAD

Source: Willison HJ, et al. The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies. *Brain*. 2001;124:1968-1977.

With fewer than 10 cases reported in the literature, this descriptive paper characterizes 16 new (plus 2 previously reported) patients with partial or complete chronic ataxic neuropathy, ophthalmoplegia, M protein, agglutination, and disialosyl antibodies (CANOMAD). Another in the group of paraproteinemic neuropathies, CANOMAD is associated with IgM antibodies directed against disialosyl epitopes of several gangliosides, including GD1b, GD3, GT1b, and GQ1b. All patients have slowly progressive sensory ataxia and areflexia with significant limb weakness in a minority (4/18). Only 2 of 18 noted significant sensory symptoms, but 8 noted perioral or acral paresthesiae. Men predominate (14/18) with a mean age of onset of 53 years, and most (16/18) demonstrate oculomotor (n = 9) or bulbar (n = 8) weakness, reminiscent of Miller Fisher syndrome (itself associated with anti-disialosyl IgG antibodies against GQ1b and GT1a). Significant disability is the rule, with only 3 of 18 able to walk unaided, and 5 of 18 wheelchair bound. High titer IgM antibodies, generally monoclonal with either kappa (8/16 tested by ELISA) or lambda (4/16), light chains are present, but occasionally (4/16) both kappa and lambda light chains coexist, implicating 2 distinct antibody clones. Eight of 17 demonstrated cold agglutination. Nerve conduction studies generally demonstrate demyelination with a minority showing axonopathy (n = 3). Cerebrospinal fluid (CSF) protein is usually elevated but may be normal (n = 5). CSF lymphocytic pleocytosis was seen in 3 but oligoclonal bands were absent in all. Of 8 patients who underwent brain MRI, 2 showed findings consistent with white matter demyelination. Three sural nerve biopsies were performed, one each demonstrating small onion bulb formations, nonspecific axonal degeneration, and large myelinated fiber dropout. No inflammatory cells or immunoglobulin deposits were seen. Patients with ataxic neuropathy and oculobulbar weakness should be screened for disialosyl IgM antibodies. No clinical treatment trials have yet been performed but intravenous immune globulin (IVIG) or plasma exchange may be beneficial. **—michael rubin**

IVIG and CIDP

Source: Hughes R, et al. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol.* 2001;50:195-201.

Thirty-two patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) were randomized in a multicenter, double-blind, crossover trial to receive either intravenous immunoglobulin (IVIG) 2.0 g/kg over 1-2 days or oral prednisolone tapering over 6 weeks from 60 mg/d to 10 mg/d. Diagnosis of CIDP was based on a progressive or relapsing course of sensorimotor dysfunction over > 2 months, with hypo- or areflexia, cerebrospinal fluid with < 10 white cells/uL, and nerve conduction studies demonstrating demyelinating polyneuropathy. Exclusionary criteria included other diseases associated with neuropathy, pregnancy, recent (within 6 weeks) treatment with IVIG, steroids, or plasmapheresis, a history of nonresponse to IVIG or prednisolone, or a diagnosis of multifocal motor neuropathy with conduction block. Assessment of efficacy included a disability rating, timed 10-meter walk, 9-hole pegboard

test, Medical Research Council (MRC) sum score, maximal grip strength, Rankin scale, and the short-form 36 (SF-36) quality-of-life scale.

COMMENTARY

Twenty-four patients completed the trial. Neither treatment demonstrated superiority over the other. Two weeks following randomization both produced significant improvement in the disability scale and in time to walk 10 meters. Disability grade was significantly diminished in both groups after 6 weeks. Treatment was generally well tolerated. Psychosis occurred in 1 prednisolone-treated patient. He was withdrawn. No serious adverse events were seen in the IVIG group. Both groups experienced equal incidences of headache (approximately 30%), indigestion (20%), fever, rash, and hypotension. Prednisolone and IVIG are equally efficacious for the treatment of CIDP. Although the former is inexpensive in the short term, long-term side effects of steroid treatment favor IVIG as the first-line therapy. **—michael rubin**

P0 and CIDP

Source: Yan WX, et al. P0 protein is a target antigen in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol.* 2001;50:286-292.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is the earliest described and best known form of a growing number of chronic acquired demyelinating polyneuropathies, including monoclonal gammopathy of undetermined significance (MGUS), polyneuropathy, organomegaly, endocrinopathy, M spike, skin changes (POEMS syndrome), multifocal motor neuropathy with conduction block (MMNCB), distal acquired demyelinating symmetric neuropathy (DADS), and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM). All share the commonality of demyelination but their mechanisms remain unclear. Certain demyelinating neuropathies demonstrate an association with various antibodies, offering a clue to their pathogenesis. These include Miller Fisher syndrome with GQ1b ganglioside antibodies, acute motor axonal neuropathy with GD1a ganglioside antibodies, and MMNCB with GM1 ganglioside antibodies. CIDP has resisted any such association but new evidence points to protein zero (P0), the major (80%) integral membrane protein of peripheral nerve myelin, as the target antigen.

Immunofluorescence and Western blotting of 21 CIDP patients' sera demonstrated 6 (28%) containing IgG antibodies directed against P0. Four of these were able to produce demyelination and partial conduction block following injection into rat sciatic nerve, while removal of P0 antigen by antigen absorption eliminated the demyelinative activity. P0 antibodies are present in a significant minority of CIDP patients and may play a role in its immunopathogenesis. **—michael rubin**

CME Questions

20. Pathological laughing and crying has been associated with which one of the following?

a. Epilepsy
b. Multiple sclerosis
c. Pontine infarction
d. Cerebellopontine angle tumor
e. All of the above

21. Elevated late life serum HDL cholesterol levels have been found to correlate with all of the following *except*:

a. increased numbers of neuritic plaques
b. increased numbers of neurofibrillary tangles.
c. increased numbers of diffuse plaques.

Editor's Note

Dear Readers:

Neurology is expanding its reports in mostly long-lived journals, and only few focus most of their contents on particular ideas and technologies. These latter more concentrated journals often teach approaches that discuss diseases, which have limited incidence. *Neurology Alert* has tried to concentrate on publications that affect relatively large numbers of patients. I would appreciate, however, your input about other kinds of neurological illness and therapy than what we concentrate on today. You would help me greatly to indicate subjects that either address small numbers of diseases or have the possibility of improving illnesses that present things that we are overlooking. Please feel free to send me an e-mail at frp2005@med.cornell.edu. **—fred plum**

In Future Issues: Is Schizophrenia a Degenerative Disease?