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Surgically Restored Sensation After Severe Brachial Plexus Injury in Neonates

ABSTRACT & COMMENTARY

Source: Anand P, Birch R. *Brain.* 2002;125:113-122.

DESPITE IMPROVEMENT IN PERINATAL CARE, THE INCIDENCE OF perinatal brachial plexus palsy (PBPP) has not declined in recent years (Dodds S, Wolfe S. *Curr Opin Pediatr.* 2000;12:40-47). The incidence of such injuries is approximately 0.1% in infants with birthweights < 4000 gm, but approximately 0.3% in infants weighing > 4500 gm at birth (Rouse DJ, et al. *JAMA.* 1996;276:1480-1486). Thus, a large hospital can expect to see several cases of PBPP annually. In addition to macrosomia, additional risk factors for PBPP include shoulder dystocia, forceps or vacuum- assisted delivery, breech delivery, prolonged labor, and a previous birth complicated by PBPP. Although the older literature uses the terms "Erb's palsy" and "Klumpke paralysis" to refer to upper and lower cervical PBPP, respectively, recent recommendations have suggested assessing PBPP on a 4-level scale of increasing severity (van Ouwerkerk, et al. *Childs Nerv Syst.* 2000;16:638-644).

Group 1 lesions involve lesions of the C5 or C6 roots or superior trunk with paralysis of shoulder abduction, elbow flexion, and forearm supination. Finger motion is normal. Spontaneous recovery rate is approximately 90%.

Group 2 lesions include Group 1 lesions with the additional involvement of C7 roots or medial trunk. In this case, there is paralysis of the extensors but not flexors of the fingers. Spontaneous recovery rate is approximately 65%.

Group 3 lesions add involvement of finger flexors, so that there is essentially no hand motion. Horner's sign is absent. Spontaneous recovery rate is probably somewhat less than 50%.

Group 4 lesions present as a flail arm with Horner's sign, indicating complete plexus lesion. There is no spontaneous recovery. This group also includes another variant ("dominant C7" paralysis) in which there is selective failure of shoulder adduction and elbow extension.

VOLUME 20 • NUMBER 9 • MAY 2002 • PAGES 65-72

Unless a Group 4 lesion is clearly present at birth, the natural history of high spontaneous recovery of the lower grade lesions mandates conservative follow-up for a period of time following birth. Several authors recommend that if no recovery has occurred spontaneously by 3 months, then electrophysiological evaluation should be performed and if avulsion is confirmed, surgical repair be considered. This surgical repair is complex but is discussed in detail in this article.

The long-term outcome of sensory function in severe brachial palsy is unknown. Anand and Birch examined 24 patients who sustained severe (defined as either Group 3 or Group 4) injury at birth. These patients were examined at age 3-23 years, and 20/24 patients surgically repaired, the majority before 1 year of age. Remarkably, and in contrast to adults, none of these patients reported limb pain. This was true even in patients that had not been surgically repaired. All 4 of the nonoperated patients had persistent anesthesia to all sensory modalities in the injuired arm and hand, but 18/20 (90%) of operated patients had at least some recovery of sensation, and in 3 it was complete. All patients could accurately localize pain, suggesting that plasticity had occurred, preserving original topographic organization. Interestingly, there was no clear correlation between interval between time of injury (birth) and the time of surgical repair, up to at least 35 months and return of sensory function; motor function is clearly better restored the earlier the operation is performed.

COMMENTARY

This paper beautifully illustrates the differences between nerve root avulsion in the developing and adult nervous systems. Whereas the recovery of sensory function is poor and persistence of chronic pain high in the adult, the situation is totally different in the young child. This paper also suggests that the nature of sensory nerve recovery changes after 3 years of age. Further studies are needed to define the temporal window where recovery begins to resemble the adult pattern. Presumably, molecular mechanisms underlie these dramatic differences. —ROSARIO TRIFILETTI

Efficacy and Safety of Modafinil (Provigil®) for the Treatment of Fatigue in MS

ABSTRACTS & COMMENTARY

Sources: Rammohan KW, et al. *J Neurol Neurosurg Psychiatry.* 2002;72:179-183; Willoughby E. *J Neurol Neurosurg Psychiatry.* 2002;72:150.

WITH ALL THEIR FUNCTIONAL NEUROLOGICAL impairments, patients with multiple sclerosis (MS) suffer from a potentially enormous, steadily rising risk of the vulnerable inflammatory and degenerative myelin of the brain. Many experienced observers say that 75-90% of MS patients are destined to suffer serious fatigue periods at one time or another during their lifetime. Experienced observers also state that 45-64% of all chronic MS patients will at least briefly express disabling fatigue at almost any given time or place. A number of drugs have attempted to relieve these sufferings. At present, however, neither the pharmaceutical industry nor experienced clinical neurologists have found effective ways to help MS patients overcome their progressive fatigue. However, a great deal of effort and, possibly, some success to the problem has now been applied recently. This relates to giving particular attention to a drug called modafinil and how it works for narcolepsy.

In 1998, 18 US narcolepsy centers reported on the efficacy and safety of modafinil, a promising new drug promoting daytime wakefulness (*Ann Neurol.* 1998;43: 88-97). The study analyzed 283 patients who all suffered from genetically engendered, pathological narcolepsy. Prior to

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Table 1

Exclusion Criteria for Testing Modafinil Effects

Narcolepsy
Sleep Apnea
Hypothyroidism
Blood pressure > 150/100 mm Hg
Severe depression
History of narcotics
Drug misuse
Excessive consumption of caffeine
Medications affecting fatigue

treatment, innate narcolepsy had forced the onset of irresistible sleep and cataplexy at random intervals throughout the day. Treatment with modafinil, however, has measurably and rapidly improved the daily, wakeful functions of active narcolepsy. For example, in a recent additional trial of 151 patients with genetic-based narcolepsy, modafinil significantly increased daytime wakefulness and improved individuals' states of fatigue at night. Because of the benefits of this narcolepsy program, the next step for modafinil is to bring patients with MS out of their fatigued state.

Modafinil is a drug somewhat like amphetamine, which stimulates wakefulness, but the 2 are not functionally identical to that sympathomimetic amine. Modafinil also does not bind to relevant receptors for sleep/wake regulation such as do the norephinephrins, serotinin, dopamine, GABA, benzodiazepam, or others.

Table 2

The Following Concomitant Medications that Affect Fatigue and Were Not Allowed During Modafinil Study

Amantadine
Methylphenidate
Antipsychotic agents
Amphetamines
Pemoline
Phenobarbital
Tizanidine
Monoamine oxidase inhibitors
Anticoagulant drugs
Barbiturates
Tricyclic antidepressant drugs
Benzodiazepines
Antihistamines other than astemizole
Fexfenadine
Loratadine

*Patients enrolled in study permitted to use:
*Interferon-ß
*glatiramer acetate

Modafinil does not reduce cataplexy, but if as noted, it could possibly reduce fatigue in patients with MS and in a single-blind study it would bring a great response.

In hoping to reduce fatigue in patients with MS, a single-blind study was conducted as follows.

The following protocol lasted 9 weeks without omissions, infections, or temporary absences.

- Phase 1. The first 2 weeks took only blinded placebos to test patients who might confound the protocol's excess of emotional improvement. Thenceforth:
- Phase 2. Gave 200 mg/d of modafinil for 2 weeks followed by placebos for 2 weeks;
- Phase 3. Gave 400 mg/d modafinil during subsequent 2 weeks followed by placebos for 2 weeks;
- Phase 4. Four matching subsequent daily placebos of pretended 200 or 400 modafinil for 2 weeks.

In this protocol, treatment with Phase 2 brought 200 mg/d of modafinil for 2 weeks and attained a modest, but significant, improvement in all 3 fatigue scales. This compares more favorably than to the parallel placebo as well as amantadine and pemoline. Later, however, this test slipped back to neutral and lost its favorable effect.

Phase 3 raised the dose to 400 mg of modafinil per day for 14 days. This time, however, another question test indicated that greater fatigue followed the modafinil, particularly when taking the 400-mg dose.

The most general adverse symptoms included headache, nausea, and asthenia. Modafinil by and large was well tolerated in these patients.

Seventy-six percent of patients were taking interferons or glatiramer acetate with no interference. Rammohan and colleagues suggest that 200 mg/d modafinil significantly improves fatigue and is well tolerated in patients with MS. Sixty five (90%) patients completed the study.

Neurologists will appreciate the excellent up-to-minute essay about MS in a recent issue of *Lancet* (Compston A, Coles A. *Lancet.* 2002;359:1221-1231). **—FRED PLUM**

Electrical Stimulation Improves Repair of Nerve Injury

ABSTRACT & COMMENTARY

Source: Zealear DL, et al. *J Neurophysiol.* 2002;87:2195-2199.

AT PRESENT, MEDICAL INSURERS WILL NOT COVER facial nerve electrical stimulation for the treatment of

Bell's palsy. Recent evidence in rodents suggests it may be beneficial and, thus, warrants further attention. The evidence is not all in, especially in the facial nerve, and very little has been undertaken in the motor vagus nerve.

Both the posterior cricoarytenoid muscle (PCA), a vocal cord abductor, and the thyroarytenoid muscle (TA), a vocal cord adductor, are innervated by the recurrent laryngeal nerve. Injury to this nerve commonly results in aberrant reinnervation whereby adductor nerve fibers enter the abductor muscle, resulting in functional laryngeal paralysis. Might continuous electrical stimulation of either muscle enhance correct reinnervation by its native nerve fibers?

Eight canines underwent electrode implantation of their PCA muscles for continuous electrical stimulation and recording of the electromyographic (EMG) activity, both spontaneous and evoked. Resection and reanastomosis of the right recurrent laryngeal nerve was performed and continuous electrical stimulation over an 11-month period was administered to 4 dogs, with the 4 remaining animals serving as nonstimulated controls. Correct PCA reinnervation was assessed by measuring maximal vocal cord opening, both spontaneously and in response to CO_2 enhanced respiratory drive. Aberrant reinnervation was assessed by evaluating reflex vocal cord activity, both in response to saline application to the vocal cord mucosa, and by electrically stimulating the internal branch of the superior laryngeal nerve. Both of these normally reflexly close the glottis by stimulating the TA. Physiologic assessments were performed monthly. Two-tailed, unpaired Student's t-test provided statistical analysis.

Appropriate reinervation was significantly enhanced ($P < 0.0064$) and aberrant innervation inhibited ($P < 0.0084$) by continuous stimulation of the PCA muscle. A nonsignificant ($P < 0.113$) trend to increased magnitude of PCA reinnervation was also seen. Continuous stimulation, for reasons yet to be elucidated, appears to foster correct reconnection of nerve to muscle.

COMMENTARY

Brief electrical stimulation of injured motor nerves promotes their reinnervation into muscle (Al-Majed AA, et al. *J Neurosci.* 2000;20:2602-2608). Following resection and reanastomosis of rat femoral nerve, continuous electrical stimulation of injured nerve at 20 Hz, for 1 hour to 2 weeks, shortened the time necessary for motor reinnervation from 10 weeks (with no electrical stimulation) to 3 weeks. Although the mechanism of this benefit is uncertain, it may be via enhanced production of neurotrophic factors (Al-Majed AA, et al. *Eur J Neurosci.* 2000;12:4381-4390). Electrical stimulation was applied to the femoral nerve, again following unilateral femoral nerve resection and repair. Using semiquantitative in situ hybridization to measure mRNA expression of brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine kinase B (trkB), electrical stimulation for 1 hour increased BDNF and trkB mRNA by 3- and 2-fold, respectively, within 8 hours, and by 6- and 4-fold, respectively, by 2 days. Sham stimulation resulted in no such increase. Alternatively, protein absorption may be altered by a change in the electric field of extracellular matrix molecules engendered by the electric stimulation, thereby increasing neurite extension (Kotwal A, Schmidt CE. *Biomaterials.* 2001;22:1055-1064). —**MICHAEL RUBIN**

Spontaneous CSF Leaks and Connective Tissue Disorders: Is There a Connection?

ABSTRACT & COMMENTARY

Source: Mokri B, et al. *Neurology.* 2002;58:814-816.

One of the editors recently examined a tall and slender young woman with a spontaneous CSF leak and a history of a spontaneous internal carotid artery dissection 6 years before. An underlying connective tissue disorder was suspected but not proven. Mokri and associates have reported a series of patients with spontaneous intracranial hypotension due to a spontaneous CSF leak in whom there was clinical evidence of an underlying connective tissue disorder.

Of 58 consecutive patients seen at the Mayo Clinic with spontaneous CSF leaks, 9 exhibited clinical features of connective tissue disorder (*see Table*).

Connective tissue disorders such as Marfan syndrome, neurofibromatosis, autosomal dominant polycystic kidney disease, and familial osteosclerosis are associated with abnormalities of the meninges. Meningeal diverticula and ectasia of the dural sac are frequent MRI findings in Marfan patients (Fattori R, et al. *Lancet.* 1999;354:910-913). In Marfan syndrome, mutations of the gene for fibrillin-1 lead to defects in collagen and elastin, especially in the walls of blood vessels. Spontaneous retinal detachment and spontaneous arterial dissections occur in Marfan syndrome, Ehlers-Danlos syndrome, and osteogenesis imperfecta. Brandt et al have demonstrated ultrastructural abnormalities of collagen and elastin in patients

Table

Clinical Features of Nine Patients

Patient	Age in years/ Sex	HFJ	SL	Arachnodactly	Other
1	11/F	+	+	0	Dilated aortic root, family history of AAA
2	40/F	0	0	0	History of retinal detachment
3	24/M	+	0	+	Tall/Slender
4	47/M	0	0	0	History or retinal detachment
5	62F	+	+	+	Tall/slender
6	37/F	+	+	+	Tall/slender, pectus excavatum, MVP, dilated aortic root
7	29/F	+	0	0	Tall/slender
8	34/F	0	0	0	Bilateral internal carotid artery dissections
9	33/F	+	0	+	

HFJ = hyperflexible joints, SL = skin laxity

(modified from Mokri B, et al. *Neurology.* 2002;58:814-816.)

with carotid dissection (Brandt T, et al. *Ann Neurol.* 1998;44:281-285).

Mokri et al suggest that in some patients with spontaneous CSF leak, a disorder of connective tissue is present that leads to dural weakness and rupture.

COMMENTARY

Like Mokri et al, this editor believes that the occurrence of both an internal carotid artery dissection and a spontaneous CSF leak in the same patient is more than just a coincidence. Unfortunately, at present, in patients who do not have the clinical phenotype of a fibrillinopathy, the association between spontaneous CSF leak and connective tissue disorder is hypothetical and will remain so until ultrastructural studies of skin biopsies and analysis of cultured dermal fibroblasts become routinely available to clinicians. **—JOHN J. CARONNA**

Microsurgery for Spinal Stenosis

ABSTRACT & COMMENTARY

Source: Guiot BH, et al. *Spine.* 2002;27:432-438.

CAN MICROSURGERY SATISFACTORILY ADDRESS LUMbar spinal stenosis? Microendoscopic decompressive laminotomy (MEDL) was compared to standard procedures in this cadaver study to determine if MEDL provides comparable and adequate decompression.

Laminae 1 through 4 of 4 cadavers were subjected to 4 surgical procedures, totaling 16 operations. Each level underwent each procedure. These included a) unilateral MEDL, with angulation of the endoscope to achieve contralateral decompression; b) bilateral MEDL, with 2 separate paramedian incisions; c) unilateral open laminotomy, ipsilateral medial facetectomy, and foraminotomy, with a midline incision for bilateral decompression; and d) bilateral open laminotomy, similar to (c) but with bilateral laminotomy. Computerized tomographic imaging of the spine was performed before and after each procedure and measurements of midsagittal diameters, interpedicular distances, and decompression diameters were taken for comparison. Student's t test and 2 × 2 analysis of variance provided statistical analysis.

All 4 procedures were comparable in achieving satisfactory decompression and all techniques visualized exiting nerve roots equally well. Complications included ipsilateral facet complex disruption (n = 2) and dural tear (n = 1) and were independent of the approach used. Although technically demanding for the surgeon, MEDL appears promising and clinical trials are required (and underway) to determine its true benefit.

COMMENTARY

Rarely, spinal stenosis may involve the thoracic spine. Among 28 such consecutive cases seen over 10 years, most (86%) presented with paraparesis and most (61%) were of insidious onset (Chang UK, et al. *Spinal Cord.* 2001;39:362-369). Lower thoracic segments (T9-T12) were most often involved (54%), followed by middle (25%) and upper (21%) segments. Ligamentum flavum ossification (64%), facet hypertrophy (46%), posterior longitudinal ligament hypertrophy (22%), and ventral spur or disc protrusion (14%) were causative. Surgery, either anterior or posterior decompression, or both, was

beneficial in 79%. Two patients with longstanding deficits did not change, with 4 patients deteriorating following surgery. Thoracic spinal stenosis with myelopathy responds to decompression, with results conditional on symptom duration, adequate decompression, and presence of additional proximal stenosis. Microendoscopic decompressive laminotomy may be applicable to this situation as well. **—MICHAEL RUBIN**

The Genetics of Primary Dystonias and Related Disorders

ABSTRACT & COMMENTARY

Source: Nemeth AH. *Brain.* 2002;125:695-721.

A RECENT REVIEW IN *Brain* AFFORDS *Neurology Alert* readers the opportunity to review a complicated area of movement disorders, the genetics of dystonia. Dystonias may be classified by their distribution (focal, segmental, multifocal, generalized), by age of onset, and by etiology. Primary dystonia refers to dystonia occurring without other neurologic findings, while "dystonia-plus" disorders include conditions in which dystonia is accompanied by myoclonus or parkinsonism. Secondary, or symptomatic dystonias, occur after stroke or drug exposure and are not considered further in this review. The final category, heredodegenerative dystonia, encompasses a wide variety of inherited neurodegenerative conditions where dystonia is accompanied by cognitive decline and pyramidal dysfunction. As a rule, primary dystonias are autosomal dominant while heredodegenerative dystonias are autosomal recessive.

COMMENTARY

Primary dystonias, originally described as idiopathic, are now recognized to be genetic in origin. They are classified by their date of discovery, and movement disorder neurologists refer to them by the designation DYT followed by a number. DYT1 dystonia, also known as Opphenheim's dystonia, is the most common genetic form; their symptoms typically begin in an arm or leg in childhood or early adulthood. DYT1 dystonia is 5-10 times more prevalent in the Ashkenazic Jewish population, and the penetrance is 30-40%. All cases of DYT1 dystonia arise from a single in-frame deletion of a GAG trinucleotide in the protein torsin A, a member of the heat-shock protein family. Torsin A is highly expressed in the substantia nigra and basal ganglia. Mutant torsin A forms inclusions around the cell nucleus suggesting that it may act as a chaperone in the folding of secreted proteins. Genetic testing for the DYT1 mutation is commercially available, and is most helpful in individuals with onset of dystonia in a limb before age 26. Other forms of primary dystonia include DYT6 and DYT7. DYT6 dystonia was described in 2 Menonite families, with autosomal dominant inheritance and incomplete penetrance. The clinical features of DYT6 are similar to DYT1, except that dystonia began in cranial or cervical regions in half the patients and symptoms typically began slightly later. DYT7 dystonia was described in a large German family with autosomal dominant adult-onset torticollis. DYT7 has been linked to chromosome 18, and DYT6 to chromosome 8.

The dystonia-plus syndromes include 3 major entities: dopa-responsive dystonia (DYT5), myoclonus-dystonia (DYT11), and rapid-onset dystonia-parkinsonism (DYT12). DYT5 is an autosomal dominant disorder that typically begins in the child's first decade. Dystonia, parkinsonism (particularly affecting the legs), and diurnal worsening of symptoms are the rule, and the disorder is much more common in women. DYT5 may mimic atypical cerebral palsy. Since it is exquisitely responsive to levodopa or anticholinergics, all children presenting with a motor disorder not attributable to hypoxia should be given a trial of levodopa. DYT5 is linked to mutations in the gene encoding GTP cyclohydrolase I, the rate-limiting enzyme in the synthesis of tetrahydrobiopterin, which is an essential cofactor for the synthesis of tyrosine, levodopa, and serotonin. DYT11 is an autosomal dominant disorder with markedly reduced penetrance in offspring of affected females. Proximal myoclonus usually begins in the first or second decade, with or without dystonia. The condition is slowly progressive and is almost always alcohol responsive. Numerous families with myoclonus-dystonia have been linked to mutations in a gene encoding epsilon-sarcoglycan (chromosome 7), although other families are not linked to chromosome 7. DYT12 is a rare autosomal dominant disorder characterized by onset of dystonic spasms and generalized parkinsonism from hours to weeks. Symptoms may begin in childhood or adulthood and are typically resistant to treatment with levodopa. The disorder has been linked to chromosome 19 in 3 families.

The heredodegenerative dystonias are a group of disorders linked by their inheritance pattern (autosomal recessive) and the fact that dystonia occurs in the company of cognitive and pyramidal dysfunction. Included in this group are Fahr's disease, pantothen-

ate kinase-associated neurodegeneration, X-linked dystonia-parkinsonism (DYT3) and chorea-acanthocytosis. Fahr's disease, idiopathic basal ganglia calcification, typically begins between ages 30 and 60 and presents with slowly progressive dystonia, parkinsonism, dysphagia, and psychiatric disturbances. Linkage to chromosome 14 has been reported in one family. Pantothenate kinase-associated neurodegeneration (previously known as Hallervorden-Spatz) is an autosomal recessive disorder typically presenting in childhood or adolescence with dystonia, parkinsonism, chorea, dementia, and pigmentary retinopathy. The "eye of the tiger sign" on MRI is a typical finding in childhood cases, due to deposition of iron in the medial pallidum and hyperintensity in the internal pallidum. The disorder is linked to a deficiency in pathothenate kinase, important in the synthesis of coenzyme A. DYT3 is limited to the Phillipine population where it is known as lubag. Symptoms begin in the fourth decade, usually with focal dystonia that generalizes within 5 years. Parkinsonism is also extremely common, and the illness usually progresses slowly and is unresponsive to levodopa. Chorea-acanthocytosis is an autosomal dominant disorder with onset in the 20s and 30s. Chorea, dystonia, parkinsonism, and dementia are common, as are mutilating orofacial dyskinesias. The responsible gene (chorein) is located on chromosome 9, and may be involved in the trans-Golgi network. **—STEVEN FRUCHT**

Drug Resistance Proteins: A Potential Mechanism for Medically Refractory Epilepsy

ABSTRACT & COMMENTARY

Source: Sisodiya SM, et al. *Brain.* 2002;125:22-31.

Multiple drug resistance (MDR) has been recognized as an obstacle to cancer treatment for at least two decades. Tumor cells may demonstrate intrinsic or acquired resistance to diverse chemotherapeutic agents. This could be effected by various mechanisms, but one of the best studied involves cellular drug transporters. Sisodiya and colleagues explored the possibility that a similar mechanism may be involved in focal epilepsies that are resistant to anticonvulsant drug (ACD) treatment.

Sisodiya et al performed immunohistochemistry for 2 MDR proteins (multidrug-resistance gene 1 P-glycoprotein, MDR1, and multidrug resistance-associated protein 1, MRP1) on pathological specimens of dysembryoplastic neuroepithelial tumors (DNET, 8 cases), focal cortical dysplasia (FCD, 14 cases), and hippocampal sclerosis (HS, 8 cases). MDR1 can transport phenytoin, phenobarbital, and other planar lipophilic molecules. MRP1 transports epoxides and glucurides, such as metabolites of carbamazepine and lamotrigine. The tissue was acquired during resective surgery from patients with medically refractory epilepsy. Neurons and astrocytes do not normally express these MDRs. The lesional tissue was compared to histologically normal adjacent tissue. All DNET and FCD cases showed increased expression of both MDRs in reactive astrocytes. Five FCD patients had MRP1 expression in dysplastic neurons as well. Five HS specimens expressed both MDRs in astrocytes in the gliotic hippocampus. Interestingly, immunohistochemically detectable overexpression of MDRs did not extend into normal adjacent tissue.

COMMENTARY

Epidemiologic studies demonstrate that 60-70% of patients with epilepsy can achieve seizure freedom on ACDs. Why do the remainder of patients have medically intractable epilepsy? Clearly, there is no single answer to this question. Seizure disorders are heterogeneous in their pathophysiology, as are the patients who suffer from them. Nevertheless, one must try.

There are at least 3 intriguing features of the theory that MDRs may be involved in refractory epilepsy. The first is that the hypothesis does not appeal to any of the conventional theories of epileptogenesis (ie, excess cortical excitation, reduced inhibition, or aberrant cortical-cortical or cortical-subcortical networks). Intraoperative microdialysis for ACDs performed immediately prior to resection might help to confirm that there are lower ACD levels in tissue subsequently shown to have increased MDR expression.

Second, potentially important diagnostic tools may become available to identify patients who are destined to develop intractable seizures. For example, Rao et al (Rao VV, et al. *Proc Natl Acad Sci U S A.* 1999;96:3900-3905) have used noninvasive single-photon-emission computed tomography (SPECT) with a membrane permeant radiopharmaceutical whose transport is mediated by MDR1 and MRP1 to obtain images indirectly reflecting the contribution of these MDRs to the blood-CSF barrier. Further studies should address whether SPECT or a similar technique has sufficient resolution

to detect changes in MDR-mediated transport that would predict intractable epilepsy.

Finally, MDR-reversing agents are currently undergoing clinical trials in cancer chemotherapy (Tan B, et al. *Curr Opin Oncol.* 2000;12:450-458). Might some of these agents be useful adjuncts to ACD treatment in patients now categorized as medically refractory? *Neurology Alert* recognizes that this commentary is more speculative than usual, but believes that this unconventional hypothesis may have important implications for a medically and psychosocially devastating disorder. **—ANDY DEAN**

Dr. Dean is Assistant Professor of Neurology and Neuroscience, Director of the Epilepsy Monitoring Unit, Department of Neurology, New York Presbyterian Hospital—Cornell Campus.

Late Breakers

Move Over Avonex®. The 48-week EVIDENCE trial data were released by the FDA on March 7. EVIDENCE was a randomized, head-to-head, open-label/blinded-examiner, parallel-groups design trial comparing "standard" dose beta interferon(INF)-1α (Avonex® 30 µg 1 × week) to a higher/more frequent dose of beta INF-1α (Rebif® 44 µg 3 × weeks). Inclusion criteria were INF-naïve patients with relapsing remitting MS and EDSS -5.5. The primary end point was the proportion of relapse free at 24 and 48 weeks. MRI lesion data were secondary end points. The 24-week data had been presented at the XVII World Congress of Neurology in London in June 2001. The full data set was presented at the American Academy of Neurology 2002 meeting in Denver in April. However, the FDA has made available topline results. To review at 24 weeks 74.9% of patients on Rebif® were exacerbation free vs. 63.3% taking Avonex® (P = 0.0005). Later at 48 weeks, 62% of patients taking Rebif® were exacerbation free compared to 52% on Avonex® (P = 0.006). The results were compelling enough for the FDA to break the Orphan Drug Status (ODS) for Avonex® and allow Rebif® on the US market a full year ahead of Avonex's ODS exclusivity. Rebif® was launced in the United States 4 days later. There now appears to be a sufficient body of clinical evidence that higher and more frequent dosing of beta-INF is more effective in reducing MS relapses. Issues that remain to be resolved are whether higher/more frequent dosing actually improves disability outcome and whether neutralizing antibodies increase with Rebif® and become clinically meaningful. For now, we welcome the addition of Rebif® to the MS armamentarium. **—JEFFREY REICH**

CME Questions

19. Regarding functional recovery after perinatal brachial plexus injury (PRPP):
a. spontaneous recovery rates are high in Grade 1 and Grade 2 injuries.
b. sensory function may recover in infants with high-grade avulsions only if surgery is performed by age 3 months.
c. following surgery, there is substantial loss of topographic localization of stimuli.
d. a substantial number of children report pain several years following severe perinatal brachial plexus injury.
e. only nonoperated patients describe severe pain years after perinatal brachial plexus injury.

20. Electrical stimulation following nerve injury:
a. depresses BDNF levels in regenerating nerve.
b. enhances nerve growth factor (NGF) levels.
c. increases trkB mRNA expression in the injured nerve.
d. All of the above
e. None of the above

21. In patients with a spontaneous CSF leak, all of the following suggest an underlying connective tissue disorder *except*:
a. hyperflexible joints.
b. laxity of joints
c. history of a carotid artery dissection.
d. retinal detachment at a young age.
e. mental retardation.

22. Microendoscopic decompressive laminotomy:
a. is the procedure of choice for lumbar spinal stenosis.
b. is associated with an increased incidence of dural tears.
c. may be as effective for spinal stenosis as unilateral open laminotomy.
d. is associated with a decreased incidence of injury to the exiting nerve roots.
e. None of the above

23. In the treatment of fatigue in MS, Rammohan et al found that:
a. modafinil was well tolerated in patients.
b. 200 mg/d of modafinil significantly improves fatigue.
c. 400 mg/d did not significantly improve fatigue.
d. None of the above
e. All of the above

In Future Issues: **Orthostatic Intolerance After Space Flight**

American Health Consultants
Building Six, Suite 400
3525 Piedmont Road NE
Atlanta, Georgia 30305-1515
Tel (404) 262-7436 Fax (404) 262-7837
www.ahcpub.com

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May 1, 2002

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.

During this year, here are some of the special features we will include in *Neurology Alert*:

- *Late Breakers*. A monthly column featuring short reviews of current therapeutics in both early and pivotal stage development in the field of neurology.

- *Pharmacology Watch*. A monthly supplement featuring up-to-date news and reviews of the leading pharmaceutical companies, the latest clinical tests and approvals, and drug updates.

- www.neurologyalert.com. Coming soon! Subscribers will have free access to this web site, which will offer online versions of the newsletter, access to other Thomson publications, a reader's forum, and up-to-date news and events in the field of neurology.

As we progress through 2002, you can look forward to another year 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.

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,

The *Neurology Alert* staff

Donald R. Johnston, VP/Group Publisher
Glen Harris, Editorial Group Head
Robin S. Mason, Managing Editor
Neill Larmore, Associate Managing Editor
Robert Kimball, Senior Copy Editor
Schandale Kornegay, Marketing Product Manager