The Call of the Brain

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Eye drop test for diagnosis of Parkinson disease (PD)

Recent studies have shown that cardiac sympathetic innervation is reduced in patients with PD.[1,2] Sawada et al[3] postulated that sympathetic innervation to the pupillary dilator muscle in PD may be reduced because it is innervated by the cervical sympathetic ganglia. They studied sympathetic dysfunction in the pupils as a possible diagnostic marker of PD by comparing responses to cocaine eye drops and phenylephrine eye drops. Cocaine blocks norepinephrine uptake, and cocaine-induced mydriasis is dependent on the sympathetic nerve terminal density. In contrast, phenylephrine acts directly on the adrenergic receptor to cause mydriasis.

Thirty eight patients with PD, 20 age-matched controls (with no evidence of neurologic disease) and 10 patients with multisystem atrophy (MSA) were enrolled. Cocaine-induced mydriasis in patients with PD was significantly less than that in the control and MSA groups while there was no significant difference between the control and MSA groups. The three groups did not differ in phenylephrine-induced mydriasis. The mean difference between phenylephrine- and cocaine-induced mydriasis was significantly greater in the PD group than in the control and MSA groups. Using a cutoff point of 1.0 mm, the sensitivity and specificity of phenylephrine- and cocaine-induced mydriasis difference for the diagnosis of PD were 0.80 (95% CI, 0.65-0.94) and 0.79 (95% CI, 0.67-0.94), respectively (3).

Although eye drop tests can be affected by several factors, including corneal permeability and age, these variations are consistent within an individual patient, and the difference between phenylephrine- and cocaine-induced mydriasis can be a good measure of pupillary sympathetic innervation. However, these results need to be replicated before this simple test can be touted as the first diagnostic test for PD.

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Early-onset Multiple Sclerosis (MS): to treat or not to treat

No disease-modifying drugs are approved for children with early-onset multiple sclerosis (EOMS). They have marked disability at a younger age than patients with adult-onset MS.[1,2] Moreover, cerebral proton magnetic resonance spectroscopy of patients with EOMS reveals metabolic alterations indicating early axonal damage.[3] Pohl et al[4] analyzed the safety and tolerability of subcutaneous IFNbeta-1a in 51 patients with EOMS and propose that treatment of pediatric MS should be considered.

A retrospective analysis of clinical and laboratory data of 36 girls and 15 boys with definite relapsing/remitting MS according to established criteria[5] and a disease manifestation before age 16 years was conducted. Treatment was started at a mean age of about 15 years after a mean disease duration of 2 years.

In 46 patients, treatment was initiated with 22 ug IFNß-1a (Rebif) three times weekly. In 5 patients with highly active disease, treatment was started with 44ug IFNß-1a three times weekly. Patients receiving the low dose were switched to the high dose in the presence of disease activity (relapses, new or contrast-enhancing MRI lesions). Treatment was started with the complete dosage from the first injection onward without gradual increase and maintained for a mean duration of 1.8 years.

In the patients with EOMS treated with IFNß-1a, yearly relapse rates decreased from a mean pretreatment value of 1.9 to 0.8. Twenty one patients were relapse free during treatment; the mean treatment duration in this group was 1.5 years. At the end of the treatment observation period, the median Expanded Standard Disability Status Scale (EDSS) score was 1.5 (range 0-5). EDSS scores remained stable in 48 of the 51 treated patients.

The most frequent systemic adverse effects were flu-like symptoms in 65% patients. Blood count abnormalities were seen in 39% and liver enzyme abnormalities in 35%. All laboratory abnormalities were clinically asymptomatic, and the majority were transient with a WHO grade 1 severity.Two patients developed serious systemic symptoms within weeks of starting therapy but their symptoms resolved in 2-4 weeks following termination of IFNß-1a. All but one of the patients could be treated with the application frequency and doses recommended for adults; only the

youngest patient with an age of 8 years and a very low body weight of 22 kg was switched to twice-weekly application of 22 ug IFNß-1a due to liver enzyme elevations.

Pohl et al therefore recommend that juvenile patients with EOMS be treated with IFNß-1a as approved in adult-onset MS with regular monitoring of blood count and liver enzymes. However, in children younger than age 10 years or with a body weight of less than 30 kg, a reduction in the cumulative weekly dose should be considered. Phase II clinical trials are warranted to assess the efficacy of IFNß-1a in childhood and juvenile MS.

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Beta Lactam antibiotics for ALS

Glutamate is the principal excitatory neurotransmitter in the nervous system. Inactivation of synaptic glutamate is handled by the glutamate transporter GLT1 (also known as EEAT2). Animal studies show that this transporter is important for normal excitatory synaptic transmission, while its dysfunction is implicated in acute and chronic neurological disorders, including ALS[1], stroke[2], brain tumors[3] and epilepsy.[4] Glutamate transporters in particular are important in preventing glutamate neurotoxicity.[5-8]

Using a blinded screen of over 1000 FDA-approved drugs and nutritionals, Rothstein et al[9] discovered that many beta-lactam antibiotics are potent stimulators of GLT1 expression and that this action appears to be mediated through increased transcription of the GLT1 gene. When delivered to animals, the beta-lactam ceftriaxone increased both brain expression of GLT1 and its biochemical and functional activity. It was also found to be neuroprotective in vitro when used in models of ischemic injury and motor neuron degeneration, both based in part on glutamate toxicity.[8] When used in an animal model of the fatal disease ALS, the drug delayed loss of neurons and muscle strength, and increased mouse survival. Thus these studies provide a class of potential neurotherapeutics that act to modulate the expression of glutamate neurotransmitter transporters via gene activation.

Additionally, the beta-lactam antibiotics, ceftriaxone in particular, were found to be neuroprotective when tested in a series of in vitro and in vivo. Ceftriaxone treatment also prevented motor neuron loss in a dose-dependent manner. Similar neuroprotective effects were seen with penicillin. Ceftriaxone was also seen to alter neurodegeneration in a disease model of ALS (G93A SOD1 mice) that involves altered expression of glutamate transporters. Studies have documented a contributory role for excess glutamate in this model, including neuroprotection by glutamate receptor blockade[8,10-12] Moreover, modest GLT1 overexpression can alter disease progression.[13] Rothstein et al treated G93A SOD1 mice with ceftriaxone. This treatment significantly delayed loss of muscle strength and body weight. This effect was observed within 7 days of treatment, and persisted for 4-6 weeks. By 19 weeks of age, the strength preservation was lost. In a similar manner, the drug also increased overall survival of the mice by 10 days. Two weeks of drug therapy, when started at 70 days of age, in these mice led to a significant prevention of motor neuron loss and reduction of hypercellular gliosis compared to saline-treated control G93A mice. It also increased GLT1 expression significantly in spinal cords in the chronically treated mice.

This study indicates that ceftriaxone may exert important effects on the central nervous system that are independent of its role as an antibiotic. The remaining link in the ceftriaxone-discovery cycle is a clinical trial. The National Institutes of Health has approved funding for a multicenter trial of ceftriaxone in patients with ALS; pending final assessment of safety issues, the study will begin in mid-2005.[14]

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'Sighting Genes'

Age-related macular degeneration (AMD) is the most common cause of blindness in the West after age 60 years. It is a progressive disease that destroys the center of the retina, or macula. Environmental factors, including smoking, obesity, and fat intake, contribute to disease progression. Over time, individuals with the disease may lose their central field of vision. Currently, there are no treatments available to reverse the progression of the AMD. April 15, 2005 issue of Science was laden with three back-to-back high profile papers elaborating the discovery of a major gene for AMD.[1-3] Each group employed a novel genetic model to tease out the genetic effect of this complex disease. Jonathan Haines and Margaret Pericak-Vance, who are the giants in the field of genetics of complex disorders and to whom the world owes several tools to tease genetic complexity and discoveries such as APOE e4 polymorphism increasing the risk of Alzheimer's disease[4], led one of these papers.[2] All groups homed onto a tyrosine to histidine polymorphism in exon 9 of complement factor H (CFH) gene and showed that it accounts for at least 40% of the risk for AMD.[1-3] CFH regulates complement activation by inhibiting the alternate complement cascade.[5] Complement has been shown to be deposited in Brusch's membrane and drusen in AMD.[6] The polymorphism is located in a region of CFH that binds to both heparin and C-reactive protein (CRP). It has been suggested that this binding could be altered by the replacement of a neutral tyrosine with a positively charged histidine[5], thus also suggesting that inflammation plays an important role in the etiology of the disease. Further work elucidating the actual biological significance of this genetic polymorphism is awaited.

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Shredding Alzheimer's

A large family-based genetic association study pointed to Ubiquilin 1 (UBQLN1) as another risk gene for Alzheimer's disease (AD).[1] UBQLN1 is involved in inhibiting degradation of several ubiquitin-dependent substrates.[2] Bertram et al conducted a candidate-gene association study on three genes located on chromosome 9q22, a region shown to harbour a risk gene for AD. They identified a genetic variant in UBQLN1, which led to alternate splicing of exon 8, thus resulting in a short and a long transcript of the gene. They showed that brains from autopsies of patients with AD had a predominance of the short transcript (with exon 8 spliced out) compared to the control brains (with absence of AD). They suggest that this alternately spliced form may affect the function of UBQLN1 leading to excess degradation of useful proteins in the proteosome.

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