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NEUROMUSCULAR DISORDERS

COLQ-MUTANT CONGENITAL MYASTHENIC SYNDROMES

The clinical and molecular genetic findings of 22 COLQ-mutant congenital myasthenic syndromes (CMS) are reported from 14 centers mainly in Europe. They represented 10% of the total CMS patients with a genetic diagnosis at these centers. The mutations in acetylcholinesterase (AChE) collagen-like tail subunit gene (COLQ) are associated with end-plate AChE deficiency. The disease presents at birth (in 11 patients) with hypotonia, ptosis, ophthalmoparesis, facial weakness, weak cry and suck, and respiratory insufficiency. In 4 patients, initial symptoms of muscle weakness and fatigability were delayed until 2 to 7 years of age. Respiratory crises occurred in 10 patients, precipitated by infections in 5. None had arthrogryposis; one had congenital clubfeet. Diurnal fluctuation of symptoms was noted in 8 patients, and disease progression occurred in 9 (41%). Repetitive nerve stimulation caused a decremental response in all but 2. Myopathic potentials were recorded on EMG in 15. A characteristic double CMAP was observed in more than half the patients. None of 8 tested showed AChR antibodies. Serum CK levels were normal. Muscle biopsy in 11 patients was unremarkable in 4 and showed myopathic changes in 4. AChE inhibitor treatment (pyridostigmine) was generally ineffective long-term or caused worsening of symptoms. A surprising short-term beneficial effect was observed in 4 patients. Tensilon test performed in 4 patients was positive in 2. Ephedrine had a beneficial effect in 5 cases treated. Genetic analysis of family members was compatible with a recessive inheritance, nine belonging to consanguineous marriages. Clinical phenotypes were variable. Some patients differed from the classical phenotype, having a mild course without progression. Others had limb-girdle proximal weakness reminiscent of CMS with DOK7 gene mutation, with sparing of eye muscle involvement. (Mihaylova V, Muller JS, Vilchez JJ et al. Clinical and molecular genetic findings in COLQ-mutant congenital myasthenic syndromes. **Brain**

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March 2008;131:747-759). (Respond: Hanns Lochmuller MD, Institute of Human Genetics, University of Newcastle upon Tyne, International Centre for Life, Central Parkway, Newcastle upon Tyne NE1 3BZ, UK).

COMMENT. Molecular genetic testing is important in diagnosis and therapy of infants with CMS. The administration of esterase inhibitors in patients with COLQ mutations can result in serious complications, and an initial short-term beneficial effect may be misleading. Ephedrine (2 to 3 mg/kg/day) was the most effective therapy in the above study. Most patients with COLQ mutations are disabled from infancy, and muscle weakness is progressive and complicated by ventilatory insufficiency and scoliosis. Clinical diagnosis is supported by repetitive CMAP, and increased muscle weakness following administration of pyridostigmine. COLQ gene mutations are the third most common cause of CMS, and occur as frequently as DOK7 mutation cases.

HISTOCHEMICAL ABNORMALITIES IN VARIOUS FORMS OF CONGENITAL MUSCULAR DYSTROPHY

A large Australasian cohort of patients with congenital muscular dystrophy (CMD) was screened to determine the frequency of various forms, in a study at Children's Hospital at Westmead; the University of Sydney; University of Melbourne, Australia; and University of Nevada, Reno; and University of Illinois, Chicago. Of 101 patients, 45% were screened by immunofluorescence and showed abnormal staining for glycosylated-a-dystroglycan (DG) in 25%. Half of these had reduced DG by Western Blot test. All patients with abnormal DG staining had DNA sequencing of the fukutin-related protein, fukutin, POMGnT1 and POMT1 genes, and mutations were identified in one patient for each of the genes. Abnormalities in collagen VI immunofluorescence were identified in 12% of CMD patients, COL6 mutations in 8 of 9 patients tested, and laminin a-2 deficiency occurred in 8% of cases. (Peat RA, Smith JM, Compton AG et al. The diagnosis and etiology of congenital muscular dystrophy. **Neurology** Dec 26, 2007 (Epub ahead of print)).

COMMENT. Various histochemical and DNA sequencing abnormalities are identified in a large cohort of CMD cases. Patients with abnormal glycosylated a-dystroglycan immunofluorescence were most common in this cohort. Other studies have suggested that the cause of 50% of all CMDs is a primary deficiency in laminin a2, and Ullrich CMD is a second most common form. Molecular diagnostic testing is important for genetic counseling and an emerging new era of gene therapy (Rando TA. Get personal with gene therapy for muscular dystrophy. **Lancet Neurology** 2008;7:196-8).

MRI IN CONGENITAL FACIAL PALSY

Magnetic resonance (MR) findings in a 12-month-old boy with congenital unilateral facial palsy and a 9-month-old girl with atypical Moebius syndrome are reported from the National Center of Neurology and Psychiatry, Kodaira, Japan. In the boy with unilateral palsy, MRI showed an asymmetry of internal auditory channels with absence of the right facial nerve. MRI on the girl with Moebius syndrome showed a slightly hypoplastic

brainstem and lack of visualization of the proximal part of the facial nerves. 3D-constructive interference in steady state (3D-CISS) MRI sequences, with reconstructions perpendicular to the bilateral internal auditory channel, were required to demonstrate facial nerve anomalies. (Sasaki M, Imamura Y, Sato N. Magnetic resonance imaging in congenital facial palsy. **Brain Dev** Feb 2008;30:206-210).(Respond: Dr M Sasaki, E-mail: massaki@nc np.go.jp).

COMMENT. Three-dimensional constructive interference in steady state MRI sequence is useful in the differential diagnosis of congenital facial palsy. 3D-CISS MRI provides T2-weighted images with high spatial resolution.

MOVEMENT DISORDERS

GENETICS OF EARLY ONSET RESTLESS LEGS SYNDROME

Linkage analysis was performed in a four-generational German family with restless legs syndrome (RLS) affecting 15 of 37 family members, in a study at the University of Lubeck, Germany. Age at onset was in early childhood or adolescence in 9 (60%) cases. Clinical findings included a desire to move the legs, paresthesias, motor restlessness at night resulting in sleep disturbance and daytime fatigue. Several family members had severe psychiatric problems, including depression and personality disorder. The inheritance pattern was autosomal dominant. A new RLS gene locus (RLS3) was identified on chromosome 9 in all of 12 patients tested, and 11 of these carried an additional closely linked RLS locus. (Lohmann-Hedrich K, Neumann A, Kleensang A, et al. Evidence for linkage of restless legs syndrome to chromosome 9p. Are there two distinct loci? **Neurology** February 2008;70:686-694). (Reprints: Dr Christine Klein, Department of Neurology, University of Lubeck, 23538 Lubeck, Germany. E-mail: christine.klein@neuro.uni-luebeck.de).

COMMENT. A linkage to a new locus (RLS3) on chromosome 9p has been identified in a family with RLS of early onset. Five gene loci have previously been mapped in cases of primary RLS to chromosomes 12q, 14q, 9p, 2q, and 20p. To date, no gene mutation has been found. RLS is primary or secondary. The primary form is highly familial; secondary RLS is often associated with iron deficiency, renal disease, or pregnancy. The pathophysiology may be related to dopamine insufficiency and low iron storage in substantia nigra.

NEUROCUTANEOUS SYNDROMES

LINEAR NEVUS SEBACEUM SYNDROME AND INFANTILE SPASMS

Two infants with linear nevus sebaceum syndrome and infantile spasms are reported from Safra Childrens Hospital, Sheba Medical Center, Tel Hashomer, Israel; and Hospital for Sick Children, Toronto, Canada. Case 1 presented at age 4 months with focal motor and generalized convulsive seizures with low-grade fever. Family history was positive for febrile seizures in the mother. A 3-cm gray-yellow scaly patch was noted on the frontal-central scalp area that enlarged and turned red and thickened after discharge. Brain MRI showed bilateral

polymicrogyria and subependymal heterotopia. At age 8 months, she developed infantile spasms and modified hypsarrhythmia on EEG. Seizures were controlled with vigabatrin. At age 2.5 years, she is seizure-free on topiramate and clobazam. Case 2 presented at age 3 months with generalized seizures and two 2.5 cm hyperpigmented nevi in the right parietal-temporal area. Eye exam revealed a right esotropia and coloboma. MRI showed right hemimegalencephaly. EEG recorded right hemisphere slowing and interictal spikes and slow waves. Seizures were controlled with phenobarbital. He was readmitted at age 11 months with infantile spasms and hypsarrhythmia, resistant to vigabatrin and controlled by ACTH. At age 3 years he presented with frequent generalized tonic-clonic and myoclonic seizures and developmental delay. The pigmented nevi had each enlarged to 5 cm in diameter. EEG showed a generalized slow-spike and wave pattern, consistent with Lennox-Gastaut syndrome. The literature on linear nevus sebaceous syndrome is reviewed. (Menascu S, Donner EJ. Linear nevus sebaceous syndrome: case reports and review of the literature. **Pediatr Neurol** March 2008;38:207-210). (Respond: Dr Menascu, Atad St, PO Box 69, Omer 84965, Israel).

COMMENT. The neurocutaneous linear nevus sebaceum syndrome is characterized by a triad of epidermal nevi, seizures, and mental retardation. A review of 60 cases by Solomon et al, in 1975, described the dermatologic lesions as epidermal nevi associated with neurologic, ophthalmic, skeletal, cardiovascular, and urological abnormalities. Children with a suspected linear nevus sebaceum syndrome should have EEG, MRI, and ophthalmology exams. Seizures occur in up to 75% cases, frequently infantile spasms, West syndrome and evolving into Lennox-Gastaut syndrome. The term linear nevus sebaceum syndrome is usually reserved for cases with midline nevi, while "epidermal nevus syndrome" is more inclusive for all varieties of epidermal nevi.

SEIZURE DISORDERS

HERBAL MEDICINE AND EPILEPSY

The potentially harmful effects of herbal remedies and herb-antiepileptic drug interactions in patients with epilepsy are reviewed by researchers at the Center for Integrative Complementary Medicine, and Division of Neurology and Toxicology, Shaare Zedek Medical Center, Jerusalem, Israel. In the US, the Dietary Supplement Health and Education Act of 1994 removed herbal preparations from the jurisdiction of the FDA. Physicians are unaware of the degree of usage of complementary and alternative medicine (CAM) by their patients. Less than 40% of patients using CAM share this information with their conventional physician. Case reports of herb-induced seizures published between 1993 and 2004 include 14 infants treated with gingko biloba, pennyroyal (in mint tea), or star anise (used for colic). Japanese star anise contains the neurotoxin anisatin, a potent GABA antagonist. Chinese star anise is a spice and tea, used as a sedative for infants with colic. It contains veanisatins that are epileptogenic. Seven infants with star anise-induced seizures were seen at the Miami Children's Hospital ED over a 2-year period (Ize-Ludlow D, et al. Pediatrics 2004;114:653-656). Pennyroyal contains seizure-inducing monoterpine R-(plus)-pulegone. Gingkotoxin, 4-O-methoxypyridoxine (MPN) is a vitamin B6 derivative that inhibits GABA synthesis from glutamate. The toxin is contained in either gingko seeds or

leaves. Herbal preparations may also be contaminated by heavy metals such as lead or arsenic that can induce seizures.

Gingko biloba and other herbs may also cause seizures by interference with the absorption and metabolism of antiepileptic drugs (AED). They inhibit cytochrome P450 enzymes (CYP) involved in AED metabolism and oxidation. Gingko induces CYP2C19, reducing serum levels of phenytoin and valproate. Grapefruit juice containing furanocoumarins inhibits the effect of CYP3A4 on AEDs. A large glass of fresh grapefruit juice can significantly increase bioavailability of carbamazepine and diazepam. Some herbal preparations (eg green tea) interfere with AED metabolism by inhibiting or activating P-glycoproteins (Pgps) that alter the absorption and transport of AEDs across the blood-brain barrier. Acetazolamide is a Pgp substrate, and other AEDs may have this property. Herbal formulas contain many herbs and several generic names, adding to the difficulty in predicting the likelihood of seizure induction. (Samuels N, Finkelstein Y, Singer SR, Oberbaum M. Herbal medicine and epilepsy: Proconvulsive effects and interactions with antiepileptic drugs. **Epilepsia** March 2008;49:373-380). (Respond: Dr Noah Samuels, The Center for Integrative Complementary Medicine, Shaare Zedek Medical Center, POB 3235, Jerusalem, Israel 91031. E-mail: refplus@netvision.net.il).

COMMENT. The public demand and interest among physicians regarding the practice of complementary and alternative medicine are expanding. Physicians need to be aware of a potential link between herbal medicine and epilepsy in their patients. Parents of infants and children with refractory or unexplained seizures should be asked about possible use of star anise tea, gingko biloba, or pennyroyal, among other alternative preparations. The FDA cautions the public against the consumption of teas containing star anise. Herbal supplements are considered "natural," and their presumed safety and lack of side effects are rarely questioned. The benefits claimed are generally unsupported by scientific trials. Further research is needed to examine the role of herbal medicine in refractory epilepsy management and the interactions between herbal and conventional therapies.

A review of the literature on PubMed found 118 entries for epilepsy and herbal medicines, 11 involving gingko biloba, 8 ephedra-induced seizures, 6 Chinese and Japanese star anise cases, 2 for pennyroyal, and 2 for eucalyptus-induced seizures. Infants especially are involved.

THE EEG PHOTOPAROXYSMAL RESPONSE

Types of photosensitivity, prevalence and other characteristics of the photoparoxysmal response (PPR), associated seizures, effect of video games, and drug therapy are reviewed by the director of electroencephalography at the University of Illinois, Chicago. Photosensitivity has been graded according to the spread of epileptiform activity: occipital, parietal-occipital, also involving frontal areas, and generalized spike and wave complexes. The majority (65%) of PPR patients have had spontaneous epileptiform abnormalities, generalized spike and wave or partial, temporal lobe, or central rolandic multifocal sharp waves. The prevalence of PPR has diminished over time; in the 1960s it was 3% of all patients having an EEG in this laboratory, whereas now it is a rare occurrence. Studies after 2000 find a prevalence of 0.8%, 1.7% in children, and 1.8% in patients with clinical seizures. PPR is more common in Caucasians and females. Mean age is 12 years.

PPR occurs at the moment of eye opening or closing, and predominantly at a flicker frequency of 15-16 Hz and wavelength of 700nm. Inheritance is autosomal dominant. Luminance studies with sunglasses show variable results in the suppression of PPR. A deep red color is required for induction of PPR. In the prevention of the video game Pokemon effect, blue lenses inhibit the PPR by the short wave length and diminished illumination. Seizures evoked by video games are a manifestation of photosensitive epilepsy. During the PPR 75% patients experience impaired consciousness, opening of eyes or jerking, and pain in the eyes. Persistence of PPR after stimulation is ended is not associated with a higher risk of seizures. Other abnormalities in the EEG, not the PPR are significant in the cause of post-PPR seizures. Prognosis is generally good, especially after age 20 years. Valproic acid and levetiracetam are effective in eliminating PPR. (Hughes JR. The photoparoxysmal response: The probable cause of attacks during video games. **Clin EEG and Neurosci** Jan 2008;39(1):1-7). (Reprints: John R Hughes, MD PhD, University of Illinois Medical Center (M/C 796), 912 S Wood Street, Chicago, IL 60612).

COMMENT. Spikes confined to the occipital region and time-linked with photic stimulation may be a normal finding. Seizures evoked by photic stimulation are usually primary generalized: generalized tonic–clonic, absence, or myoclonic. Photosensitive seizures are classified as pure, occurring only during exposure to photic stimulation, or complicated by spontaneous seizures in addition. Some patients derive a pleasurable response to a self-induced seizure by waving their hands in front of their eyes.

EYELID MYOCLONIA WITH ABSENCES (JEAVONS SYNDROME)

An open-label trial of levetiracetam in 35 patients (23 girls) with eyelid myoclonia (EM) was conducted at the Epilepsy Center, Federico II University, Napoli, and several additional epilepsy centers in Italy. Levetiracetam dosage was 10 mg/kg/day up to 50-60 mg/kg/day in 2 doses in a 12-18 week titration and evaluation phase. Mean dose was 1985 mg/day. Patients' mean age was 19 +/- 6 yrs. Of 28 (80%) patient responders, 6 were seizure-free, 15 had a >75% and 7 a >50% seizure reduction. Associated generalized tonic clonic seizures (GTCS) in 21 patients were controlled in 14 (66%). The number of days with EM and GTCS was significantly reduced compared to baseline. Paroxysmal abnormalities at eye closure and photoparoxysmal response disappeared or were reduced in 20 responders. Mean follow-up was 24 months. (Striano P, Sofia V, Capovilla G et al. A pilot trial of levetiracetam in eyelid myoclonia with absences (Jeavons syndrome). **Epilepsia** March 2008;49:425-430). (Respond: Dr Pasquale Striano MD PhD, Epilepsy Center, Frederico II University, Napoli, Italy. E-mail: pstriano@email.it).

COMMENT. Eyelid myoclonia with absences (Jeavons syndrome, 1977) is characterized by the triad of eyelid myoclonia with or without absences (EMA), seizures and EEG paroxysms induced by eye closure, and photosensitivity (Panayiotopoulos 1996, and others), Onset is in childhood, 2-14 years (mean 8 yrs), especially in girls. Marked intermittent jerking of eyelids after eye closure is associated with jerky upward deviation of eyeballs and retropulsion of the head. Generalized tonic clonic seizures are often associated. AED therapy is usually disappointing, and levetiracetam is the most promising. EMA is not yet recognized as a definite epileptic syndrome by the ILAE.

BUMETANIDE-ENHANCED PHENOBARBITAL IN NEONATAL SEIZURE MODEL

Anticonvulsant efficacy of phenobarbital, bumetanide, and a combination of these drugs was studied in an in vitro hippocampal rat pup (4-7 days) preparation, with recurrent seizures induced by exposure to low-Mg solution, at the Department of Neurology, Massachusetts General Hospital, Boston. The combination of phenobarbital and bumetanide abolished these experimental seizures in 70% of hippocampi and reduced their frequency and duration in the remaining 30%. The GABA-mediated outward flow of Cl in immature neurons is excitatory, contributing to a poor response to GABAergic anticonvulsants such as phenobarbital and benzodiazepines. The diuretic bumetanide blocks the Na K Cl transporter system and prevents the outward flow of Cl ions. Alteration of Cl ion transport by bumetanide facilitates the anticonvulsant action of phenobarbital in immature animal brain, providing a potential effective therapy for neonatal seizures. (Dzhala VI, Brumback AC, Staley KJ. Bumetanide enhances phenobarbital efficacy in a neonatal seizure model. **Ann Neurol** February 2008;63:222-235). (Respond: Dr Kevin J Staley, MD, Department of Neurology, Massachusetts General Hospital, 55 Fruit Street, VBK 910, Boston, MA 02114. E-mail: kstaley@partners.org).

COMMENT. The authors propose a clinical trial of bumetanide in combination with phenobarbital in the treatment of neonates with seizures. Previous studies cited have demonstrated a low risk of side effects with bumetanide in sick infants (Sullivan JE et al. 1996). The above laboratory study and others by my colleague, Dr Sookyong Koh, recipient of the Dreiffus-Penry Epilepsy Award at the AAN meeting, April 15, have advanced our understanding of seizure mechanisms and control of epilepsy-associated behavioral changes in the young.

INFECTIOUS DISORDERS

VARICELLA ZOSTER VIRUS VASCULOPATHIES

The clinical, CSF, imaging, and virological features of varicella zoster virus (VZV) vasculopathies in 30 patients (7 children) are reviewed by researchers at various centers in the US and internationally. The data obtained on the 7 children, ages 1-7 and 18, show rash in 5, CSF pleocytosis in 6, focal lesions on MRI/CT in 7, focal vascular abnormalities by angiography or MRA in 3 of 4 tested, small vessel involvement in 2 and mixed in 5, CSF VZV DNA in 2, and IgG in 5, and reduced serum/CSF ratio of VZV IgG in 5, confirmation of intrathecal synthesis. Average time from rash to neurologic symptoms and signs and virologic analysis was 4.1 months. In children it varied from 1-2 days to 3 months. Detection of anti-VZV IgG antibody in CSF is a more sensitive indicator of VZV vasculopathy than VZV DNA ($p<0.001$). Of 15 patients (13 adults and 2 children) treated with IV acyclovir alone for 10-28 days, 66% improved or stabilized compared to 75% of 12 patients (9 adults and 3 children) who received both IV acyclovir and steroids. Of 2 children not treated, 1 stabilized and the other improved slowly. (Nagel MA, Cohrs RJ, Mahalingam R et al. The

varicella zoster virus vasculopathies. Clinical, CSF, imaging, and virologic features. **Neurology** March 11, 2008;70:853-860). (Reprints: Dr DH Gilden, Department of Neurology, Mail Stop B182, University of Colorado Health Sciences Center, 4200 E 9th Ave, Denver, CO 80262).

COMMENT. VZV is a possible cause of stroke in children and adults, even without a history of rash. Prior rash was absent in 29% of children and in 40% of the total group. Symptoms of vasculopathy can be delayed up to 3 months after the rash in children, 4 months in adults. CSF pleocytosis was present in the majority (86%) of children, but absent in 33% of the total group.

Acute infection, viral or bacterial, is a risk factor for cerebral infarction and stroke in all age groups. The reported prevalence of infection in the week preceding ischemic stroke ranges from 10% to 35%. Influenza vaccination has been correlated with a lower risk of stroke. (Emsley HCA, Hopkins SJ. **Lancet Neurology** April 2008;7:341-353).

Herpes zoster live-attenuated vaccine in elderly subjects was effective and increased VZV-T cell-mediated immunity within 6 weeks after vaccination. Boosting immunity by vaccination should protect older adults against herpes zoster and postherpetic neuralgia, at least 4 years or longer. (Levin MJ et al. **J Infect Dis** March 15, 2008;197:825-835).

BRAIN MALFORMATIONS

CLASSIFICATION OF CORTICAL BRAIN MALFORMATIONS

Clinical, radiological, and genetic classifications of 113 cases of malformations of cortical development (MCD) were evaluated at the Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands. Diagnosis was confirmed retrospectively in 48 patients during a 10-year period, and prospectively in 65 during only 4 years. Increased alertness or improved brain imaging might have accounted for the more recent higher prevalence of diagnosis of MCD. Disorders of proliferation (eg. congenital microcephalies) occurred in 11, disorders of migration (lissencephaly/heterotopia) in 51, disorders of cortical organization (eg schizencephaly) in 49, and MCD secondary to inborn errors of metabolism in 2. An etiologic diagnosis was established in 45 (40%) cases. In 21 patients (19%) molecular and/or genetic confirmation was established (eg. Miller-Dieker syndrome, inborn error of metabolism). Genetic defect was unknown in 17 (15%). A gestational insult had occurred in 7 (6%). In 34 of the remaining 68 patients, a genetic disorder was suspected based on multiple anomalies, family history, or consanguinity. More definitive diagnosis of MCD would lead to improved patient care and genetic counseling. (de Wit MCY, Lequin MH, de Coo IFM et al. Cortical brain malformations. Effect of clinical, neuroradiological, and modern genetic classification. **Arch Neurol** Mar 2008;65:358-366). (Respond: Grazia MS Mancini MD PhD, Department of Clinical Genetics, Erasmus Medical Center, PO Box 1738, 3000 DR Rotterdam, the Netherlands. E-mail: mancini@erasmusmc.nl).

COMMENT. See Sarnat HB. In **Progress in Pediatric Neurology III,** Chicago, PNB, 1997;365-9; and Norman MG et al. **Congenital Malformations of the Brain.** New York, Oxford University Press, 1995;452 pages, for excellent reviews of MCD advances.