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J. GORDON MILLICHAP, M.D., F.R.C.P., EDITOR

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SEIZURE DISORDERS

INTRAMUSCULAR VS INTRAVENOUS BENZODIAZEPINES FOR PREHOSPITAL TREATMENT OF STATUS EPILEPTICUS

Researchers at the Department of Emergency Medicine, University of Michigan, Ann Arbor, and other centers in the US, compared the efficacy of intramuscular (IM) midazolam with that of intravenous (IV) lorazepam for children and adults in status epilepticus treated by paramedics. This so-called RAMPART (Rapid Anticonvulsant Medications Prior to Arrival Trial) involved 79 hospitals and >4000 paramedics, and was funded by NIND & Stroke and others. The trial tested the hypothesis that IM midazolam was not inferior to IV lorazepam by 10% margin. Doses in children weighing 13-40 kg were 5 mg IM midazolam by autoinjector or 2 mg IV lorazepam; children >40 kg received 10 mg IM midazolam or 4 mg IV lorazepam. Subjects included had convulsions that persisted for >5 minutes and who were still convulsing after paramedics arrived. Primary outcome was absence of seizures at time of arrival in ED.

On arrival in the ED seizures were absent without rescue therapy in 329 of 448 subjects (73.4%) in the IM group and in 282 of 445 (63.4%) in the IV group (P<0.001). The treatment groups were similar in percent in need of endotracheal intubation (14.1% and 14.4%). Intubation was more commonly a sequela of continued seizures than an adverse effect of the benzodiazepine. In patients whose seizures ceased before arrival at ED, the median times to active treatment were 1.2 min in the IM-group and 4.8 min in the IV-group. Convulsions ceased in 3.3 min and 1.6 min after injection, respectively. Adverse-event rates were similar in the 2 groups. IM midazolam is at least as safe and effective as IV lorazepam for prehospital treatment of status epilepticus. (Silbergleit R, Durkalski V, Lowenstein D, et al. for the NETT investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus. **N Engl J Med** February 16, 2012;366:591-600). (Respond: Robert Silbergleit, MD, Dept Emergency Medicine, Ann Arbor, MI. E-mail: Robert.silbergleit@umich.edu).

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COMMENT. In an editorial, Hirsch LJ of Yale University Epilepsy Center notes that the mortality of status epilepticus is 15 to 22% and the outcome correlates with seizure duration. (**N Engl J Med** 2012;366:659-660). The definition of status has been shortened from 30 minutes to 5 to 10 minutes in recent studies. Seizures lasting > 5 minutes are likely to be self-sustained and require intervention. The RAMPAR Trial reported above found that the more rapid administration of the IM midazolam (1.2 min) than the IV lorazepam (4.8 min) outweighed the faster cessation of seizures with intravenous administration (1.6 min IV vs 3.3 min via IM route). The rate of hospitalization was lower in the IM-midazolam group, as compared with the IV-lorazepam group (57.6% vs 65.6%). Dr Hirsch comments that home treatment for status epilepticus may be found more satisfactory in the future, using the nasal or buccal routes for administering midazolam.

COMBINATION DRUG THERAPY IN REFRACTORY EPILEPSY

Researchers from University of Washington, Seattle, WA analyzed the treatment records from 148 developmentally disabled adults with refractory epilepsy cared for in 2 state-run institutions. Records charted monthly convulsive seizure occurrence and AED regimen over 30 years. Patients had a predominance of focal over generalized EEG abnormalities. The effects of 8 commonly used AEDs alone and in combination on seizure frequency were studied in within-patient comparisons. In decreasing order of frequency, the drugs compared were lamotrigine, valproate, carbamazepine, phenytoin, topiramate, levetiracetam, gabapentin, and zonisamide; phenobarbital and oxcarbazine were used at only one institution and were excluded from calculations. Individual AED combinations were first compared to an aggregate measure of all other combinations to which a patient had been exposed. This allowed greater statistical power to assess efficacy of individual combinations.

Out of the most frequently used AED combinations, only lamotrigine (LTG) and valproate (VPA) combination had superior efficacy; seizure frequency was reduced by 50% or more in comparison to other regimens. The LTG/VPA combination was superior to VPA or LTG monotherapy, and CBZ/VPA, VPA/GBP, or CBZ/VPA/PHT combinations. While 2 concurrent AEDs provided improved efficacy over monotherapy, use of 3 AEDs at a time provided no further benefit over two AEDs combined. AEDs should be used no more than 2 at a time for optimal response. (Poolos NP, Warner LN, Humphreys SZ, Williams S. Comparative efficacy of combination drug therapy in refractory epilepsy. **Neurology** Jan 3, 2012;78:62-68). (Response and reprints: Dr Poolos. E-mail: npoolos@uw.edu).

COMMENT. The superior efficacy of LTG/VPA combination compared to other AED combinations is reported previously (Brodie MJ et al. **Epilepsy Res** 1997;26:423-432)(Pisani F et al. **Epilepsia** 1999;40:1141-1146) (Refs cited by authors). Synergism between the 2 drugs may explain the improved seizure control by a valproate-induced reduction in hepatic clearance of lamotrigine. However, the present study found no VPA effect on LTG serum concentrations, and the mechanism of synergism is unexplained.

COMBINED EPILEPSY/ADHD AND WORKING MEMORY

Researchers at University Children's Hospital Basel, and other centers in Switzerland, Norway, and Germany studied behavioral differences in working memory performance, response to methylphenidate, and functional brain organization in 17 boys with combined epilepsy/ADHD, 15 boys with developmental ADHD, and 15 healthy controls (aged 8-14 years). Boys with epilepsy-associated ADHD and those with ADHD without epilepsy both performed poorly on psychological tests with high cognitive load when compared to healthy controls. Methylphenidate improved cognitive performance almost to normal levels in both ADHD groups. Functional MRI showed similar reductions of activation in both ADHD groups, using working memory tasks. Boys with epilepsy/ADHD and ADHD without epilepsy recruited less cortical regions involved with working memory. ADHD with or without epilepsy show a common aberrant network of working memory. Following intake of methylphenidate, working memory was improved without alteration in the functional MRI. Seizures or administration of antiepileptic drugs in the epilepsy/ADHD group were not considered a cause of the working memory deficits. (Bechtel N, Kobel M, Penner I-K, et al. Attention-deficit/hyperactivity disorder in childhood epilepsy: a neuropsychological and functional imaging study. **Epilepsia** February 2012;53(2):325-333). (Respond: Dr Nina Bechtel, University Children's Hospital Basel, Spitalstrasse 33, 4056 Basel, Switzerland. E-mail: nina.bechtel@unibas.ch).

COMMENT. The authors conclude and confirm reports that ADHD with and without epilepsy represent epiphenomena of a common underlying functional and neurobehavioral pathophysiology, and that methylphenidate shows equivalent efficacy in both patient groups. Approximately 20% children with epilepsy have ADHD (Gross-Tsur V, et al. **J Pediatr** 1997;130:670-674), and -25% of children with ADHD have epileptiform, sleep-deprived EEGs (Millichap JJ, Stack CV, et al. **J Child Neurol** 2011;26(1):6-11).

A longitudinal follow-up study correlating clinical, neuropsychological, and EEG features with AED therapy reveals a temporal relation between subclinical epileptiform discharges, cognitive dysfunction, and effectiveness of AEDs on ADHD and EEG discharges (Laporte N, et al. Cognitive epilepsy: ADHD related to focal EEG discharges. **Pediatr Neurol** 2002;27:307-311). The authors' recommendation of AEDs in children with ADHD and abnormal EEG remains controversial and not generally accepted in practice. However, more recent studies confirm the reversal of transient cognitive impairment (TCI) with epileptiform EEG in children with ADHD without clinical seizures. (Schubert R. **Pediatr Neurol** 2005;32:1-10) (Mintz M, et al. **J Child Neurol** 2009;24(7):807-815). The doctrine or admonition, "Treat the patient's seizures and not the EEG," may require modification.

RELATION OF COGNITIVE PROFICIENCY TO EPILEPSY FOCUS

Investigators at Children's Memorial Hospital/Northwestern University School of Medicine Epilepsy Center, Chicago, and Kangbuk Samsung Hospital, Seoul, Korea examined the relationship of cognitive proficiency (CP) to general intellectual ability

(GA) and seizure focus by retrospective chart review of 90 children (aged 6-18 years) with epilepsy, video-EEG recording, MRI, and neuropsychological testing (WISC-IV). Cognitive Proficiency Index (CPI) scores based on the WISC-IV Working Memory (WM) and Processing Speed (PS) indices were significantly lower than the General Ability Index (GAI) scores, comprising the WISC-IV Verbal Comprehension (VC) and Perceptual Reasoning (PR) indices. GAI>CPI differences were significantly greater in the right than left lateralized seizure group and also greater for the frontal than temporal group. CP was selectively compromised in those with seizures lateralized to the right hemisphere or localized to the frontal lobe. Right lateralization and frontal localization independently impact CP. GAI>CPI differences were significantly greater in the right-lateralized group than the generalized group and in the frontal-localized group than the generalized group. Deficits in CP are a defining neurocognitive characteristic of pediatric epilepsy in individuals with both focal and generalized onset, but especially when seizures originate from a primary epileptogenic focus within the right hemisphere or the frontal lobe. (Gottlieb L, Zelko FA, Kim DS, Nordli DR Jnr. Cognitive proficiency in pediatric epilepsy. **Epilepsy Behav** 2012;23:146-151). (Respond: Dr Frank A Zelko, Children's Memorial Hospital, #10, 2300 Children's Plaza, Chicago, IL 60614. E-mail: fzelko@childrensmemorial.org).

COMMENT. Children with epilepsy lateralized to the right hemisphere or localized to the right frontal lobe are at increased risk of cognitive deficits involving working memory and processing speed. Working memory maintains short-term information, and processing speed determines the amount of information that can be used and accommodated in working memory. Cognitive proficiency contributes to cognitive aptitude in learning and problem solving. A general availability of psychological services should add to the proficiency of epilepsy management in the clinic.

SHARED GENETIC BASIS OF EPILEPSY AND BEHAVIOR DISORDERS

Researchers from Columbia University, New York; UCLA; Northern Illinois University, DeKalb, IL; and Northwestern Children's Memorial Hospital, Chicago have examined whether the first-degree family history of unprovoked seizures in 308 probands with childhood onset epilepsy is associated with behavioral disorders. The association was assessed separately in uncomplicated and complicated epilepsy and for febrile seizures. Median age at onset was 4.2 years, and age at time of 9-year interview was 13.5 years. Epilepsy was uncomplicated in 213 (69.2%) and complicated in 95 (30.8%). Family history of unprovoked seizure was present in 24 probands with uncomplicated epilepsy (11.3%) and 9 probands with complicated epilepsy (9.5%). Family history of febrile seizures was present in 21 probands with uncomplicated (9.9%) and in 8 with complicated epilepsy (8.4%).

In probands with uncomplicated epilepsy, first-degree family history of unprovoked seizure was significantly associated with internalizing disorders, withdrawn/depressed, affective and anxiety disorders, aggressive and delinquent behavior, conduct disorder and oppositional defiant disorder. In probands with complicated epilepsy, family history of unprovoked seizure and behavioral problems

were not associated. Also, first-degree family history of febrile seizure was not associated with behavioral problems in probands with uncomplicated or in those with complicated epilepsy. The familial clustering of these disorders suggests that behavioral disorders may be another manifestation of the underlying pathophysiology involved in or related to epilepsy. (Hesdorffer DC, Caplan R, Berg AT. Familial clustering of epilepsy and behavioral disorders: evidence for a shared genetic basis. **Epilepsia** Feb 2012;53(2):301-307). (Respond: Dr Dale C Hesdorffer, GH Sergievsky Center, Columbia University, 610 West 168th St, P & S Unit 16, New York, NY 10032. E-mail: dch5@columbia.edu).

COMMENT. Epilepsy and behavioral disorders appear to have a common underlying genetic predisposition, whereas in the above study febrile seizure had no significant familial association with behavioral disorders. Previous reports of behavior disorder in children with febrile seizure have varied findings. Friderichsen C and Melchior J (**Acta Paediatr** 1954;43:307-317) found behavior disorders in 12 (4%) of 282 febrile seizure patients, and Millichap JG et al (**Neurology** 1960;10:643-653) in a prospective study of 110 febrile seizure patients reported recurrent episodes of aggressive behavior, temper tantrums, and hyperactivity in 35% patients. Patients with a history of birth trauma and those with cryptogenic epilepsies were excluded from the Friderichsen and Melchior series of febrile seizures but not from the study by Millichap and colleagues.

Risk of behavioral, developmental, and physical comorbidities with epilepsy/seizure disorder in a nationally representative sample of US children. (Russ SA, Larson K, Halfon N. **Pediatrics** February 2012;129(2):256-264). Estimated lifetime prevalence of epilepsy/seizure disorder was 1%, and of current epilepsy/seizure disorder was 6.3/1000. Children with current epilepsy/seizure disorder were significantly more likely than those never affected to have ADHD (23% vs 6%), developmental delay (51% vs 3%), autism (16% vs 1%), and headache (14% vs 5%). Those with prior but not current seizures had lesser risks.

NEUROMUSCULAR DISORDERS

SPINAL MUSCULAR ATROPHY II/III AND FEEDING PROBLEMS

Researchers at Kaohsiung Medical University Hospital, Taiwan studied the prevalence and risk factors of feeding and swallowing problems in 108 genetically confirmed patients with types II and III spinal muscular atrophy (SMA), age range 3-45 years, 60 with type II and 48 with type III. A questionnaire survey showed the 3 most common feeding and swallowing difficulties were choking (30.6%), difficulty conveying food to the mouth (20.4%), and difficulty chewing (20.4%). Motor function status (sitters vs walkers) was an independent risk factor for feeding and swallowing difficulties; 28 were walkers, 76 sitters, and 4 nonsitters. All 4 SMA II nonsitters had feeding and swallowing difficulties. Poor head control when feeding was a factor in 13 (12%) patients. Age was not an independent risk factor in this study; 10 patients, all with type II SMA and age <20 years (range 3-19 years), had feeding and swallowing difficulties and required respiratory management. Respiratory assistance or suction was required in 17

patients (15.8%). Patients with feeding and swallowing difficulties had higher rates of underweight and aspiration pneumonia than those without these problems. Individual treatment plans for SMA II/III patients should depend on motor function status. (Chen Y-S, Shih H-H, Chen T-H, Kuo C-H, Jong Y-J. Prevalence and risk factors for feeding and swallowing difficulties in spinal muscular atrophy types II and III. **J Pediatr** March 2012;160:447-451). (Response and reprints: Yuh-Jyh Jong MD, Department of Pediatrics, Kaohsiung Medical University Hospital, 100, Shih-Chuan 1st Road, Kaohsiung 80708, Taiwan. E-mail: yjjong2@gap.kmu.edu.tw)

COMMENT. Classification of SMA types I, II, III, and IV is based on age at onset and the highest function achieved. (Lunn MR, Wang CH. **Lancet** 2008;371:2120-2133). In a Hong Kong, China study (Chung BH et al. **Pediatrics** 2004;114(5):e548-e553) survival probabilities for type I SMA (n=22) at 1, 2, 4, 10, and 20 years were 50%, 40%, 30%, 30%, and 30%, respectively. For type II SMA (n=26), survival probabilities at 1, 2, 4, 10, and 20 years were 100%, 100%, 100%, 92%, and 92%, respectively. Sixteen of the SMA I patients and 4 of the SMA type II patients died of cardiorespiratory failure. All SMA III patients were surviving. The probability of remaining ambulatory at 20 years after onset of type IIIa (age of onset <3 years) was 50%, and for type IIIb (age of onset 3-30 years) it was 68%. Interval between disease onset and inability to walk was 15 years for type IIIa and 21.2 years for type IIIb patients. In the Taiwan study, feeding and swallowing difficulties, especially choking, in SMA types II and III patients were correlated with current motor function status.

Double-trouble: SMA type II and seropositive myasthenia gravis in a 51 yr old male. (Jokela M, Udd B, Paivarinta M. **Neuromuscular Disorders** Feb 2012;22:129-130). A case report from Finland concerned a patient with SMA type II living to age 51 years and then developing worsening of dysphagia and chewing over a few weeks. A mild respiratory infection led to rapid deterioration in ventilatory function and need for tracheostomy and permanent night-time ventilator support. Ptosis of left eye, ophthalmoplegia, myopathic face, and left hand weakness followed. Serum acetylcholine receptor antibodies were elevated (44 nmol/L; normal 0.25-0.40 nmol/L), and edrophonium testing for myasthenia gravis was positive. CT chest was negative for thymoma or thymus hyperplasia. Myasthenia responded to a course of iv immunoglobulin, oral prednisone, and pyridostigmine. Azathioprine was substituted for the prednisone. Ocular findings are very atypical for SMA and a diagnosis of MG was suspected as a chance association of two rare diseases.

TREATMENT AND OUTCOME OF STIFF-MAN SYNDROME

Neurologists at the Mayo Clinic, Rochester, MN extended their reports of patients with stiff-man syndrome (SMS), first reported there by Drs Moersch and Woltman in 1956. They describe the characteristics of a large cohort of 99 patients (67 female), their treatment and outcome. Median age at symptom onset was 40 years (range 5-70 years); 5 presented before 18 years of age. Mean follow-up from symptom onset was 5 years (range 0-23 years). Phenotypic symptoms included low back stiffness and spasms in all of 59 classic cases, exaggerated lumbar lordosis in 52, lower extremity stiffness and

spasms in 59, neck stiffness and spasms in 10, upper extremity stiffness and spasms in 4, abdominal wall stiffness and spasms in 26, respiratory symptoms with spasms in 6, and falls in 30. Symptoms were exacerbated by emotional stress, startle, cold, and movement. Seventy-nine were GAD65 antibody seropositive, and 53 (67%) had at least one coexisting autoimmune disease; 3 (4%) had cancer. GAD65 antibody values were significantly higher in patients with classic SMA than in those with partial or variant SMA. Treatment with diazepam (40 mg/day) provided sustained improvements. Immunotherapy gave additional improvements. Sixteen (64%) of 23 patients with extended follow-up remained ambulatory. (McKeon A, Robinson MT, McEvoy KM et al. Stiff-man syndrome and variants. Clinical course, treatments, and outcomes. **Arch Neurol** Feb 2012;69(2):230-238). (Respond: Andrew McKeon MD, Department of Neurology, Mayo Clinic. E-mail: mckeon.andrew@mayo.edu).

COMMENT. Stiff-man syndrome occurs mainly in adults but can occur in children. Diagnosis may be confirmed with EMG documentation of hyperexcitability of spinal motor neurons, GAD65 antibodies, and response to diazepam, first described by Howard FM Jr (**Proc Staff Meet Mayo Clin** 1963;38:203-212).

Several reports of stiff-child syndrome are uncovered by a PubMed search. The disorder must be distinguished from hyperexplexia or hereditary stiff-baby syndrome, an autosomal dominant disorder. The EMG shows persistent hyperexcitability at rest, abolished by diazepam. The hypertonia lessens during sleep and increases with the slightest startle or tactile stimulus. Nose tapping will elicit the hyperexplexic startle response in affected newborns. (Tohier C et al. **Arch Dis Child** 1991;66:460-461) (**Ped Neur Briefs** May 1991).

MOVEMENT DISORDERS

BENIGN HEREDITARY CHOREA: RESPONSE TO LEVODOPA

A case of sporadic non-progressive chorea is reported in a 6 year-old girl from Hospital Sant Joan de Deu, Barcelona University and other centers in Spain and The Netherlands. At age 21 months she was diagnosed with severe motor delay and gait disorder. Birth and perinatal history including screening test for hypothyroidism were normal. A diagnosis of subclinical hypothyroidism was made at 2 years of age and she was treated with oral L-thyroxine. Language and learning skills have been age appropriate. At 3 years of age she was hypotonic, reflexes were normal, but her gait was unstable, clumsy, and wide-based, with frequent, sudden falls. Choreiform movements were generalized, affecting the mouth, limbs, and trunk, and were not progressive. A *TITF-1* de novo gene mutation test was positive. Levodopa therapy started at age 3 years 6 months controlled the chorea. When therapy was temporarily interrupted after 1 year, symptoms recurred with frequent falls and clumsy gait. Discontinuation of therapy slowly after 3 years of treatment was successful without relapse. (Fons C, Rizzu P, Garcia-Cazorla A, et al. TITF-1 gene mutation in a case of sporadic non-progressive chorea. Response to levodopa treatment. **Brain Dev** 2012;34:255-257). (Respond. Dr Carmen Fons, Department of Pediatric Neurology, Hospital Sant Joan de Deu, Barcelona, Spain. E-mail: cfons@hsjdbcn.org).

COMMENT. A novel nonsense mutation in the *TITF-1* gene is published simultaneously with the above case report in a Japanese family with benign hereditary chorea (Nakamura K et al. **J Neurol Sci** Feb 15, 2012;313(1-2):189-192). The proband showed severe generalized chorea, delayed motor development, subnormal intelligence, congenital hypothyroidism, bronchial asthma, and a history of pulmonary infection. These characteristics are features of *Brain-Thyroid-Lung syndrome*. Her brother and mother showed a mild benign hereditary chorea phenotype with congenital hypothyroidism. It is suggested that therapy with levodopa may compensate for underdeveloped dopaminergic pathways in this disorder.

Pathological findings in an autopsied Japanese adult with benign hereditary chorea 2 and hypotonia that presented at age 40 years showed mild degeneration of the striatum and cerebral white matter with astrocytosis. Non-progressive symptoms of chorea and hypotonia had persisted until the patient's death at 83 years. (Yoshida Y et al. **Neuropathology** Jan 12, 2012 [Epub ahead of print]).

INFECTIOUS DISORDERS

MANAGEMENT STRATEGY FOR CHILDHOOD ENCEPHALITIS

Researchers at the Children's Hospital, University of Oxford, and Alder Hey Children's NHS Foundation Trust, Liverpool, UK review the literature on encephalitis and suggest a management strategy. Encephalitis, defined as inflammation of brain parenchyma, is associated directly or indirectly with infectious agents (viruses or other microorganisms, fungi, parasites, rickettsiae) or caused by other inflammatory or immune-mediated pathologies (eg. ADEM, paraneoplastic, NMDAR encephalitis, voltage gated K channel limbic encephalitis). Herpes simplex virus (HSV) type 1 is the most common cause of sporadic encephalitis, either primary infection or via reactivation of virus in the trigeminal ganglion. Enteroviruses such as polio and arboviruses (Japanese encephalitis virus and West Nile virus) enter the brain across the blood-brain barrier. Etiology is undefined in 60% cases of encephalitis.

CSF should be sent: 1) to microbiology lab for microscopy, culture and sensitivity analysis; 2) to virology lab for PCR for HSV types 1 and 2, VZV, HHV-6 and -7, CMV, EBV, enteroviruses, respiratory viruses, HIV and C pneumonia; 3) to biochemistry for glucose (with paired plasma sample), lactate and oligoclonal bands; and 4) stored sample for future tests. Up to 10% of patients with viral encephalitis have a normal CSF. Some patients have a mononuclear pleocytosis and moderately elevated protein in the CSF, or raised red blood cell count (hemorrhagic encephalitis). Eosinophils suggest infection with helminthes, toxoplasma, Rickettsiae, or M pneumonia. Low CSF glucose suggests a bacterial, fungal or protozoal etiology. PCR may be negative early and after acyclovir. (Thompson C, Kneen R, Riordan A, Kelly D, Pollard AJ. Encephalitis in children. **Arch Dis Child** Feb 2012;97:150-161). (Respond: Dr Clara Thompson, C/o Professor AJ Pollard, Children's Hospital, Oxford, UK. E-mail: clara.thompson@doctors.org.uk).

COMMENT. This excellent review also refers to the value and indications for EEG and MRI in diagnosis of encephalitis, treatment including acyclovir, and prognosis.