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SEIZURE DISORDERS

LORAZEPAM VS DIAZEPAM FOR STATUS EPILEPTICUS

Investigators at the Division of Emergency Medicine, Children's National Medical Center, Washington, DC, and ten additional US centers in the Pediatric Emergency Care Applied Research Network (PECARN), conducted a double-blind, randomized clinical trial comparing the efficacy and safety of lorazepam and diazepam in the treatment of generalized convulsive status epilepticus (SE) in children aged 3 months to younger than 18 years. Of a total of 273 patients presenting with SE from 2008-2012, 140 randomized to diazepam (0.2 mg/kg) and 133 to lorazepam (0.1 mg/kg) administered intravenously. Half this dose was repeated at 5 min if necessary, and fosphenytoin was administered if SE continued at 12 minutes.

SE was controlled for 10 min without recurrence within 30 min in 101 of 140 (72.1%) in the diazepam-treated group and 97 of 133 (72.9%) in the lorazepam group. The median time to termination of SE was 2.5 min in the diazepam group and 2 min in the lorazepam group (p=0.80). Assisted-ventilation (bag-valve-mask ventilation or endotracheal intubation) was administered in 26 patients in each group (16.0% given diazepam and 17.6% given lorazepam). There were no statistically significant differences in efficacy or safety outcomes in the two groups, except that lorazepam patients were more likely to be sedated (66.9% vs 50%, respectively). There was a significant difference favoring diazepam in time to return to baseline mental status (p=0.0004). The estimate for efficacy for febrile SE was lower than for other etiologies (65.2% vs 76.1%, respectively). (Chamberlain JM, Okada P, Holsti M, et al. Lorazepam vs diazepam for pediatric status epilepticus. A randomized clinical trial. **JAMA** 2014 Apr 23-30;311(16): 1652-60).

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COMMENTARY. Diazepam is FDA approved for the treatment of pediatric status epilepticus but lorazepam is not approved. Several reports of treatment with lorazepam have suggested superior effectiveness, longer duration of action, and lower incidence of respiratory depression when compared to diazepam, but the evidence to support lorazepam superiority is inconclusive. In one study, intravenously administered lorazepam was compared to rectal diazepam [1]. In a Cochrane Database Review [2], intravenous lorazepam is as effective as intravenous diazepam, has fewer adverse events, and rectal lorazepam may be more effective than rectal diazepam. Where intravenous access is unavailable, buccal midazolam is recommended as the treatment of choice and intranasal lorazepam is as effective as intravenous diazepam. In contrast to these positive lorazepam responses, the results of the present study do not support the preferred use of lorazepam vs diazepam in the treatment of pediatric convulsive status epilepticus [3]. Neither agent is optimal since SE is uncontrolled in 1 in 4 children and severe respiratory depression occurs in approximately 1 in 6.

The FEBSTAT study of the emergency management of febrile status epilepticus finds that the earlier the onset of treatment, the shorter the total seizure duration and better the outcome [4]. A comparison of buccal or intranasal midazolam vs intravenous or rectal diazepam found that non-IV midazolam was as effective as IV diazepam, and buccal midazolam was superior to rectal diazepam in achieving seizure control; and respiratory complications requiring intervention were similar, regardless of administration route [5]. A comparison of midazolam nasal spray and rectal diazepam solution for residential treatment of seizure exacerbations found midazolam was equal in efficacy to diazepam, and drowsiness occurred in more than 50% of administrations for both drugs. The majority of patients and caregivers preferred the nasal spray to rectal formulation [6]. In the UK, an epidemiological study strongly supports prehospital treatment with buccal midazolam as a widely used but unlicensed option in the community [1].

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PYRIDOXINE RESPONSIVENESS AND PNPO GENE MUTATIONS

Investigators at University Hospital, Zurich, Switzerland, and multiple centers in Europe and Canada, sequenced the pyridoxal 5-phosphate oxidase (PNPO) gene in 31 patients with pyridoxine-responsive seizures but normal biomarkers for antiquitin deficiency and normal sequencing of the ALDH7A1 gene. Eleven patients from 7 families carried 3 novel mutations of the PNPO gene. Response to pyridoxine was prompt in 4 patients, delayed in 2, on EEG only in 2, and initially absent in another 2 patients. Earlier and continuous pyridoxine therapy was related to a better prognosis. Two unrelated patients homozygous for the pArg225His mutation developed status epilepticus when switched to pyridoxal 5-phosphate (PLP).

The findings shift the paradigm of exclusive PLP responsiveness of patients with PNPO deficiency and contradict the strategy of using PLP instead of pyridoxine as the first-line vitamin to test for all inborn errors with vitamin B6-responsive seizures. Testing for PNPO mutations is important in pyridoxine-responsive patients with normal biomarkers for antiquitin deficiency or other B6-dependent neonatal epilepsies. A sequential trial with pyridoxine and PLP should be performed routinely in neonates with AED-resistant seizures, irrespective of a history of birth asphyxia. The challenge of recognizing a delayed pyridoxine effect and lack of specific biomarkers caries a risk of misdiagnosis. (Plecko B, Paul K, Mills P, et al. Pyridoxine responsiveness in novel mutations of the PNPO gene. **Neurology** 2014 Apr 22;82(16):1425-33).

COMMENTARY. In an editorial [1], the clinical characteristics of pyridoxine dependent epilepsy (PDE) and PLP-dependent cases are differentiated by their presentation with full-term and premature birth, respectively. The EEG of PDE has a classic burst-suppression pattern, whereas the PNPO deficiency is associated with a nonspecific and less paroxysmal pattern. Cases of partial pyridoxine responsiveness have PNPO mutations.

Congenital brain malformations and pyridoxine dependent epilepsy. Several cases of brain malformation are reported in association with pyridoxine dependent epilepsy (PDE), and a current case-report concerns an infant with seizures at 7 days, initially responsive to phenobarbital, later diagnosed with PDE caused by ALDH7A1 genetic defect. Brain sonography on day 1 and MRI on day 5 confirmed bilateral asymmetric ventriculomegaly caused by bilateral subependymal cysts. At age 7 months he was seizure free on pyridoxine 200 mg/day (29 mg/kg per day), neurological examination was unremarkable, EEG was normal, and ventriculomegaly was resolved. Despite the structural brain malformation, PDE should always be considered in the differential diagnosis of neonatal seizures refractory to treatment with AEDs [2].

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ETHOSUXIMIDE VS VALPROATE LONG-TERM REMISSION OF ABSENCE EPILEPSY

Investigators from the Epilepsy Center, Lurie Children's Hospital of Chicago, and Yale School of Medicine, New Haven, CT, examined the possible association between long-term seizure outcome of childhood absence epilepsy (CAE) and the initial treatment with ethosuximide (ESM) or valproic acid (VPA). Newly diagnosed patients throughout the State of Connecticut from 1993 to 1997 were identified through the offices of 16 of 17 child neurologists and data were also reviewed by three pediatric epileptologists. Initial success rates were 59% of 41 treated with ESM and 56% of 18 who received VPA. Early remission and drug resistance were similar in each group. Complete remission (seizure free for 5 years and 5 years off medication) occurred in 31 (76%) treated with ESM and 7 (39%) who received VPA (p=0.007). ESM was associated with a higher rate of complete remission than VPA. In 53 children followed >10 years, remission was 76%

in the ESM group versus 44% receiving VPA (p=0.06). Atypical EEG features including polyspike-wave and focal findings, occurring in 17% ESM- and 61% VPA-treated, did not independently predict outcome (p=0.15). However, children with atypical EEG features versus those without were less likely to remit completely (50% vs 71%,p=0.03). Outcome was associated with initial treatment in patients with or without atypical EEG features; a higher proportion of patients achieved complete remission if first treated with ESM versus VPA. Five-year and 10-year remission, regardless of continued treatment, occurred more often in children initially treated with ESM versus VPA. These clinical findings are congruent with laboratory studies in genetic absence rat models and are supportive of potential disease-modifying effects of ESM in CAE. (Berg AT, Levy SR, Testa FM, Blumenfeld H. Long-term seizure remission in childhood absence epilepsy: Might initial treatment matter? **Epilepsia** 2014 Apr;55(4):551-7).

COMMENTARY. A disease-modifying or "curative" effect of ethosuximide in children with CAE is an interesting and novel concept in the drug treatment of epilepsy. For complete remission, the characteristic 3-Hz generalized spike-and-wave discharge should be absent in the wake EEG, with hyperventilation and photic stimulation, in sleep, and after AEDs are discontinued. Long-term follow-up with both clinical and EEG evidence of continued drug-free remission would be of interest.

Pretreatment EEG and CAE outcome. A study of the relationship between EEG characteristics prior to treatment of CAE, measures of attention, and the response to initial AED treatment with ESM, VPA, or LTG found a predictive relationship between the shortest seizure and response to treatment; the longer the pre-treatment seizure, the more treatment-responsive and better the outcome [1].

Adverse effects of Ethosuximide. While ethosuximide is considered the drug of choice for the control of CAE, its adverse effects may sometimes be serious and no less troublesome than those of valproic acid or lamotrigine. Gastric disturbances are the most common side effects. Next most common are CNS symptoms including fatigue, headache, dizziness, hiccups, and euphoria. Non-dose-related side effects include skin rash, erythema multiforme, systemic lupus erythematosus, eosinophilia, leukopenia, and rarely, pancytopenia. Behavioral changes and psychotic episodes are reported [2].

In a retrospective review of records of 128 CAE patients, the seizure-free rate after ESM (84%) is significantly higher than that of VPA (62%) and LTG (53%) at 3 months but at 9 months, there is no significant difference in seizure-free rates. Rates of normalization of EEG at 12 months and of adverse events are similar for ESM, VPA, and LTG [3]. In a larger controlled clinical trial of the AEDs in 446 children with CAE, almost two thirds of 125 subjects with treatment failure due to lack of seizure control were in the LTG cohort. The VPA cohort had a higher rate of adverse events not seen in the ESM cohort. ESM is considered the optimal initial monotherapy for CAE [4].

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VASCULAR DISORDERS

ETIOLOGY OF BRAIN ATTACKS IN CHILDREN

Investigators at the Royal Children's Hospital Melbourne, Australia, studied the presenting features, scope, and prevalence of conditions causing brain attack symptoms in children aged 12 month to 18 years presenting to a tertiary pediatric ED. Brain attack is defined as apparently abrupt-onset focal brain dysfunction. Exclusion criteria include epilepsy, hydrocephalus, head trauma, and isolated headache. Of 287 children (46% male) with 301 presentations over 17 months, 35% arrived by ambulance. Median symptom duration before arrival was 6 hours (range 2-28 hrs.); median time from triage to medical assessment was 22 min (range, 6-55 min). Common symptoms included headache, vomiting, focal weakness, numbness, visual disturbance, seizures, and altered consciousness. Common signs included focal weakness, numbness, ataxia, or speech disturbance. CT imaging in 30% was abnormal in 27%, and MRI in 31% was abnormal in 62%. Diagnoses included migraine (28%), seizures (15%), Bell palsy (10%), stroke (7%), and conversion disorders (6%). Relative proportions of conditions in adults (obtained by meta-analysis) and children differed significantly for stroke, migraine, seizures, and conversion disorders. Brain attack etiologies in children differ from those in adults; stroke is a relatively infrequent diagnosis (7%) in children and accounts for 73% of cases in adults. (Mackay MT, Chua ZK, Lee M, et al. Stroke and nonstroke brain attacks in children. **Neurology** 2014 Apr 22;82(16):1434-40).

COMMENTARY. Migraine is the most common stroke mimic in children, accounting for more than one-quarter of cases, whereas in adults it accounts for less than 3% of cases.

Transient ischemic attacks requiring hospitalization in children. Using a Kids' Inpatient Database, TIA was the primary diagnosis for 531 children, and secondary diagnoses and risk factors for TIA included sickle cell disease (20%), congenital heart disease (11%), migraine (12%), moyamoya disease (10%), and stroke (4%). Mean length of hospital stay decreased from 3.0 days in 2003 to 2.3 days in 2009. During the same period, pediatric admissions for ischemic stroke (n=2590) were ~5-fold more common than for TIA; 4.8 children with stroke were admitted for every child with TIA [1].

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MELAS, STROKE-LIKE EPISODES AND KETOGENIC DIET

Investigators at University of Toronto and McMaster University, Canada, report a 22-year-old woman with multiple episodes of status epilepticus and migratory cortical stroke-like lesions. Ketogenic diet and magnesium resulted in seizure freedom and decrease in frequency of stroke-like episodes following improvement of mitochondrial dysfunction. Initial mitochondrial genetic testing was negative. Diagnosis was established by muscle biopsy for mitochondrial genome sequencing, demonstrating a mitochondrial DNA disease-causing mutation. (Steriade C, Andrade DM, Faghfoury H, Tarnopolsky

MA, Tai P. Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) may respond to adjunctive ketogenic diet. **Pediatr Neurol** 2014 May;50(5): 498-502).

COMMENTARY. A ketogenic diet should be considered for treatment of intractable seizures and stroke-like episodes related to mitochondrial respiratory chain complex (MRC) defects. In a Korean study of 14 patients with MRC defects and various seizure types (5 with infantile spasms, 4 with Lennox-Gastaut syndrome, 1 with Landau-Kleffner syndrome), 50 – 90% seizure control was obtained with the ketogenic diet [1]. A subsequent study in Korea involving 24 cases of MRC defect with seizures, the ketogenic diet controlled seizures in 75% patients [2].

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HEADACHE DISORDERS

HEADACHE AND MIGRAINE WITH SICKLE CELL DISEASE

Investigators from University of Texas Southwestern Medical Center, Dallas, TX, and other centers in the US and London, UK, studied risk factors for headache and migraine in 872 children, age 5 to 15 years (mean age, 9.1 years), with sickle cell disease (hemoglobinSS or hemoglobinSb-thalassemia) and no history of overt stroke or seizures. Recurrent headaches were reported in 317 (36.4%) and migraines in 132 (15.1%). Both were associated with lower hemoglobin and higher rate of hospitalization for pain events requiring hospitalization for treatment with opioids in the previous 3 years. Only six of 317 (1.9%) children reporting recurrent headaches were receiving medication for headache prophylaxis. The prevalence of silent cerebral infarct, diagnosed by MRI and neurological examination, was similar in patients with recurrent headaches and in those without headaches (32.8% and 29%, respectively; P=0.241). Older age, lower Hgb concentration, and higher pain event rate were associated with recurrent headaches and migraines. (Dowling MM, Noetzel MJ, Rodeghier MJ, et al. Headache and migraine in children with sickle cell disease are associated with lower hemoglobin and higher pain event rates but not silent cerebral infarction. **J Pediatr** 2014 May;164(5):1175-1180.e1).

COMMENTARY. Isolated recurrent headaches or migraine in neurologically normal children with sickle cell disease (SCD) might not necessitate additional evaluation with imaging studies, but new severe headaches presenting acutely warrant further investigation, especially when associated with acute CNS events. In a study of children with SCD who presented acutely with headache, headache was the chief complaint in 3.8% of acute care visits, and acute CNS events occurred in 16.9%. Factors associated with acute CNS events included older age, history of stroke, TIA, or seizure, focal neurological findings, and elevated platelets [1].

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‘VISUAL SNOW’ - DISTINCT FROM MIGRAINE AURA

Investigators from University of California, San Francisco; King’s College London, UK; and University of Utah, Salt Lake City, studied patients with ‘visual snow’ to characterize the phenotype and compare it to migraine aura. Of 22 patients referred with this diagnosis, 15 had additional visual symptoms, and 20 had comorbid migraine, 5 with aura. Visual symptoms included palinopsia (trailing and afterimages), entoptic phenomena (floaters, spontaneous photopsia), photophobia, and nyctalopia (impaired night vision). Duration of visual snow symptoms varied from “as long as they could remember” in 25%, to a mean age of onset of 21 +/- 9 years in the remainder. Symptoms were constant in some and progressive in others. Worsening of visual snow symptoms in 36% cases was associated with headache, migraine, migraine with aura, anxiety and depression. First degree relatives were affected in 8 patients. (Schankin CJ, Maniyar FH, Digre KB, Goadsby PJ. ‘Visual snow’ – a disorder distinct from persistent migraine aura. **Brain** 2014 May;137(Pt 5):1419-28).

COMMENTARY. ‘Visual snow’ is described as continuous tiny dots in the entire visual field similar to the noise or static of an analogue TV and lasting longer than 3 months. Frequently comorbid with migraine but considered a unique disorder distinct from migraine with aura, complicated by palinopsia, floaters, photophobia, and nyctalopia, and not explained by intake of psychotropic drugs.

AUTISM SPECTRUM DISORDER

NEOCORTICAL DISORGANIZATION AND AUTISM

Investigators from University of California, San Diego, and other centers in the US, assayed markers for neurons and glia and genes implicated in the risk of autism, in prefrontal, temporal, and occipital neocortex. Postmortem tissue samples were obtained from children with autism and unaffected children between the ages of 2 and 15 years. Prefrontal and temporal cortical tissue from 10 of 11 children with autism and from 1 of 11 unaffected children showed focal patches of abnormal laminar cytoarchitecture and cortical disorganization of neurons, but not glia. No cortical layer was spared, layers 4 and 5 being most affected. A probable dysregulation of layer formation and neuronal differentiation is proposed at prenatal developmental stages of children with autism. (Stoner R, Chow ML, Boyle MP, et al. Patches of disorganization in the neocortex of children with autism. **N Engl J Med** 2014 Mar 27;370(13):1209-19).

COMMENTARY. The authors suggest that the mechanism of this laminar disorganization might result from migration defects or de novo changes in early prenatal development. Both genetic and environmental factors contribute to autism liability. In a Swedish population study [1], the risk of autism spectrum disorder (ASD) in family members of persons with ASD was significantly higher than the risk in the general population, and the risk of ASD recurrence among family members decreased with decreasing genetic relatedness, from a 10-fold increased risk of recurrence in full siblings to a 2-fold increased risk of recurrence in cousins. Genetic factors explained half of the

liability for autism [2]. Another population-based Swedish study based only on twins estimated a heritability of 80% [3].

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PARENTAL OBESITY AND AUTISM SPECTRUM DISORDER

Investigators from Oslo, Norway and other centers studied the associations among maternal prepregnancy BMI, paternal BMI, and the risk of autism spectrum disorder (ASD) in children. A study sample of 92909 children aged 4 to 13.1 (mean 7.4) years was derived from a population-based, prospective Norwegian Mother and Child Cohort Study. Among 419 children diagnosed with ASD at end of follow-up (2012), 162 were diagnosed with autistic disorder, 103 with Asperger disorder, and 154 with PDD. Maternal obesity (BMI >30) was only weakly associated with ASD risk, whereas paternal obesity was associated with an increased risk of autistic disorder (AD) and Asperger disorder. The risk of AD was 0.27% in children of obese fathers and 0.14% in children of fathers with normal weight (BMI <25). The risk of Asperger disorder was 0.38% in children (aged >7 years) of obese fathers and 0.18% in children of normal-weight fathers. The adjusted OR for AD was 1.73 and for Asperger disorder, 2.01. Parental obesity was not associated with PDD. (Suren P, Gunnes N, Roth C, et al. Parental obesity and risk of autism spectrum disorder. **Pediatrics** 2014 May 1;133(5):e1128-e1138).

COMMENTARY. Adverse effects of obesity in relation to childhood ASD concern both child and father. In a sample of 376 Oregon children with ASD, 18.1% of children met criteria for overweight and 17.0% met criteria for obesity [1].

Gluten-free casein-free ketogenic diet for autism and seizures. Pediatric neurologists at the Massachusetts General Hospital, Boston, MA, report a girl with autism and pubertal onset of seizures refractory to AEDs who benefited from treatment with a gluten-free casein-free ketogenic diet, with medium-chain triglycerides. Secondary benefits of the MCT diet included resolution of morbid obesity and improved cognition and behavior. The Childhood Autism Rating Scale score decreased from 49 (severe) to 17 (nonautistic); the child was essentially seizure free after 14 months on the diet; and a lengthy 3 Hz spike-wave EEG pattern improved, showing only occasional short discharges without clinical accompaniments [2]. Despite the limitations of a single case, this report seemed worthy of comment.

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