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SEIZURE DISORDERS

CHROMOSOMAL MICROARRAY TESTING AND EPILEPSY

Investigators at the Boston Children's Hospital, MA, and other centers evaluated the role of copy number variants (CNVs) detected using chromosomal microarray (CMA) testing in 805 patients seen between 2006 and 2011 and having ICD-9 codes for epilepsy or seizures. They observed 437 CNVs in 323 patients (1-4 per patient), including 185 (42%) deletions and 252 (58%) duplications. Forty (9%) were confirmed de novo, 186 (43%) were inherited, and parental data were unavailable for 211 (48%). CNV size ranged from 18kb to 142Mb (excluding full trisomies), and 34% were >500kb. The epilepsy phenotype was explained by a CNV in at least 40 cases (5%), including 29 patients with epilepsy associated syndromes and 11 with likely disease-associated CNVs involving epilepsy genes or "hotspots" (e.g., 1q21.1, 15q11.2, 16p13.11) that predispose to epilepsy.

Genetic syndromes associated with epilepsy and confirmed by CNV testing included 22q11 duplication (4 cases), Mowat-Wilson (3 cases), Wolf-Hirschhorn (3 cases), Dravet (2), Williams (2), Kleeftstra (2), Angelman (2), Phelan-McDermid (2), and benign familial neonatal convulsions, totalling 3.6%. CMA is recommended in the diagnosis of unexplained epilepsy. (Olson H, Shen Y, Avallone J, et al. Copy number variation plays an important role in clinical epilepsy. *Ann Neurol* 2014 Jun;75(6):943-58).

COMMENTARY. The advantages of the CNV to the patient with an unexplained epilepsy, parents, and clinician include an earlier more definitive diagnosis, an estimate

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of prognosis, and in some cases, more specific treatment. Screening for rare CNVs is a valuable routine diagnostic workup in patients with unclassified epilepsies and complex phenotypes; 88 rare CNVs were discovered in 71 of 222 patients (31.9%) [1]. A chromosomal microarray (CMA) screen of 215 patients with a broad range of neurological phenotypes of unknown etiology found 30 (14%) were abnormal; phenotypes included infantile spasms, other epilepsies, and cortical malformations [2].

CMA is recommended especially in unclassified epilepsy patients with dysmorphic features, developmental delay, autistic spectrum disorder, family history of epilepsy, or parental consanguinity. More directed genetic testing for specific epilepsy genes or genetic neurological syndromes is indicated for patients with a characteristic phenotype [3].

References.

1. Helbig I, et al. *Eur J Hum Genet.* 2014 Jul;22(7):896-901.
2. Howell KB, et al. *J Paediatr Child Health.* 2013 Sep;49(9):716-24.
3. Millichap JG. *Neurological Syndromes : A Clinical Guide to Symptoms and Diagnosis.* New York: Springer; 2013:279.

COMPARISON OF 5- AND 30-MINUTE STATUS EPILEPTICUS

Investigators at Boston Children's Hospital and other centers compared the characteristics of patients with status epilepticus (SE) lasting 5-29 min with those with SE lasting >30 min. Of a total 445 patients with a median age at SE of 5.5 (2.8-10.5) years, 296 (66.5%) had SE lasting 5-29 min, and in 149 (33.5%) SE lasted >30 min. Patients with SE >30 min were younger than those with SE 5-29 min at time of seizure onset (median 1 vs 2.1 years, $p=0.0007$). SE as the first seizure presentation was more frequent in patients with SE >30 min (24.2% vs 12.2%, $p=0.002$). MRI abnormalities tended to be more frequent in patients with SE >30 min (70.5% vs 57.1%, $p=0.061$). Shorter vs longer SE cases showed no differences in seizure frequency, seizure types (febrile vs nonfebrile), developmental delay, and EEG abnormalities at baseline. At a median follow-up of 3.7 years after SE, 21 patients (4.7%) had died (median time of 3.1 years after SE), mostly unrelated to epilepsy. The odds of dying showed an increase of 0.005 per min of SE duration. SE thresholds of either 5 or 30 min identify groups of patient with similar electroclinical characteristics. (Fernandez IS, Vendrame M, Kapur K, et al. Comparison of pediatric patients with status epilepticus lasting 5-29 min versus >30 min. *Epilepsy Behav* 2014 Jun 17;37C:1-6).

COMMENTARY. Longer SE duration (>30 min) probably reflects a more severe underlying cause for SE, but patients with shorter (5-29 min) SE have comparable electroclinical characteristics to those with longer SE duration. Since seizures are more difficult to treat and carry a poorer outcome the longer they last [1][2], seizures lasting 5 min or longer are treated as aggressively as those > 30 min duration. Seizures (5-29 min) are considered as "impending" SE and those > 30 min as "established" SE.

References.

1. Eriksson K, et al. *Neurology.* 2005 Oct 25;65(8):1316-8.
2. Seinfeld S, et al. *Epilepsia.* 2014 Mar;55(3):388-95.

ORAL PREDNISOLONE VS. IM CORTICOTROPIN AND HYPSSARRHYTHMIA* IN WEST SYNDROME

Investigators at University of Colombo, Sri Lanka, studied the efficacy of oral prednisolone (40-60 mg/day) and intramuscular adrenocorticotrophin hormone (40-60 IU synthetic ACTH every other day) for 14 days in improving hypsarrhythmia in children (age 2 mos-2 yrs) with previously untreated West syndrome. Children with tuberous sclerosis were excluded. Eighty of 92 patients (48 randomized to prednisolone and 44 to ACTH) completed the evaluation. Hypsarrhythmia severity score significantly improved with hormonal therapy ($p < 0.01$); improvement in the prednisolone arm was significantly greater than that in the ACTH arm ($p < 0.01$). The score system adapted from Kramer et al [1], with a maximum of 16, employed a 10-sec segment of the most representative record. Frequent crying, irritability, weight gain, increased appetite, and abdominal distension were more common with prednisolone (but not significantly). Clinical outcome assessment (spasm control) is ongoing. (Wanigasinghe J, Arambepola C, Ranganathan SS, Sumanasena S. The efficacy of moderate-to-high dose oral prednisolone versus low-to-moderate dose intramuscular corticotropin for improvement of hypsarrhythmia in West syndrome: a randomized, single-blind, parallel clinical trial. *Pediatr Neurol* 2014 Jul;51(1):24-30).

COMMENTARY. Comparative studies of the efficacy of prednisolone and ACTH are difficult to evaluate because of the variations and imbalance of dosages employed. The relative optimum dosages are not known. An editorial suggests that the reported EEG improvement following prednisolone may be at least as good as synthetic ACTH but the superiority of prednisolone is still unclear. Study limitations include brevity of the EEG, especially during sleep, and lack of clinical and developmental outcomes [2]. After ACTH, oral corticosteroids remain the second most commonly used treatment for infantile spasms (with the exception of vigabatrin for patients with tuberous sclerosis).

ACTH vs Prednisolone for Spasms Post Vigabatrin Failure. According to the experience at the Hospital for Sick Children, Toronto, Canada, when vigabatrin is ineffective and ACTH unavailable, short-term prednisolone is recommended. While ACTH is more likely to provide short-term relief from spasms, prednisolone is equally effective in the long-term resolution of spasms [3].

Infantile spasms and vitamin B12 deficiency. Investigators in Ankara, Turkey, report two unrelated infants with infantile spasms associated with vitamin B12 deficiency related to maternal nutritional deficiency. After a month of treatment with ACTH, phenobarbital and vitamin B12, both infants' abnormalities resolved. After 3 months, the EEG was normal and ACTH and phenobarbital were discontinued. At 9 months following treatment with vitamin B12, psychomotor developments are improved and the EEG remains normal. For diagnostic clarity, initial treatment with vitamin B12 alone would have been preferred. However, vitamin B12 deficiency should be considered as a cause of infantile spasms in an infant whose mother has severe nutritional deficiency [4][5].

* *Hypsarrhythmia* was originally spelled with one ‘r’ by the Drs Gibbs who coined the term in 1952 [6]. They wished to emphasize that “the term applied to a *specific* type of electroencephalographic abnormality” [7], and feared that their definition would be confused by a literal translation of the two ‘r’ Greek root, “mountainous arrhythmia” [8]. The one ‘r’ spelling was the rule in the 1950s-60s [9]. The two ‘r’ spelling became convention in the literature by the mid 1970s [10], with the Gibbs’ intended meaning faithfully maintained and accepted for both spellings today.

References.

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3. Jones K, et al. *J Child Neurol*. 2014 Jun 25.
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HEADACHE DISORDERS

LONG-TERM PROGNOSIS OF PEDIATRIC HEADACHES

Investigators from Dalhousie University, Halifax, Canada, conducted a follow-up telephone interview of patients with a history of headaches diagnosed in 1983. Of 60 patients in the study, follow-up was achieved for 28 (47%). Over the 30 years since diagnosis, 8 (29%) patients reported a complete resolution. The type of headache varied between migraine and tension-type over the 30-year time interval, only 3 patients maintaining the same headache type at all four time periods between 1983 and 2013. Prescription medication to control the headache was the primary treatment (a triptan) in only one patient, and nonprescription analgesia, self-relaxation and/or hypnosis, and precipitant avoidance were the most commonly used interventions. (Dooley JM, Augustine HF, Brna PM, Digby AM. The prognosis of pediatric headaches-a 30-year follow-up study. **Pediatr Neurol** 2014 Jul;51(1):85-7).

COMMENTARY. Headaches persist for up to 30 years in 70% of children monitored at four 10-year time periods since diagnosis in 1983. Simple analgesia and avoidance of precipitants are the most effective methods of management of pediatric headaches. The goal of treatment is prevention or control, not cure. These results are similar to those obtained in a previous long-term follow-up study of 73 children with migraine; only 23% were migraine-free at 23 years and more than 50% continued to have migraine headaches at 50 year follow-up [1]. In children, diet is a factor in the etiology of migraine often difficult to control [2].

References.

1. Bille BA. *Cephalalgia*. 1997 Jun;17(4):488-91.
2. Millichap JG, Yee MM. *Pediatr Neurol*. 2003 Jan;28(1):9-15.

HEADACHE AND SLEEP DISORDERS

Investigators from Sapienza University, Italy, studied the prevalence and treatment of sleep disorders in children with migraine. Treatment of insomnia, sleep apnea, sleep bruxism and restless legs syndrome often leads to improvement of migraine. Prodromal symptoms of migraine (yawning, drowsiness, irritability, mood changes, hyperactivity) support a direct role for the dopaminergic system that is also involved in sleep-related movement disorders. Child education and lifestyle modification including sleep hygiene have a significant role in the management of migraine. Comorbid sleep disorders should be screened in children with migraine. (Guidetti V, Dosi C, Bruni O. Sleep and headache in children: specific pattern in migraine, implication for the treatment. **Cephalalgia** 2014 Jun 27. [Epub ahead of print]).

COMMENTARY. The association of migraine and sleep disorders, especially restless legs syndrome, is discussed by another Italian group of investigators [1].

References.

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VASCULAR DISORDERS

PERIVENTRICULAR HEMORRHAGIC INFARCTION (PVHI) OR PERIVENTRICULAR LEUKOMALACIA (PVL)

Investigators from Okazaki City Hospital, and other centers in Japan retrospectively evaluated the clinical features, ultrasonography, and EEG findings in 22 preterm infants with PVHI and 49 with PVL. Gestational age and birth weight were significantly lower in infants with PVHI than those with PVL. EEGs performed serially beginning immediately after birth were normal in the majority of infants with PVHI on days 1-2. EEG abnormalities appeared after ultrasonography abnormalities. The majority of infants with PVL (28 (85%) of 33) showed acute-stage EEG abnormalities on days 1-2. Acute-stage EEG abnormalities were more frequent in infants with PVHI than in those with PVL on days 5-14 ($p<0.05$). The rate of infants with acute-stage EEG abnormalities decreased with age, whereas the rate of infants with chronic-stage EEG abnormalities increased with age. Normal EEG before ultrasonography abnormalities was more common in infants with PVHI than in those with PVL. PVHI causes mostly postnatal injury, whereas PVL is presumed to cause mostly pre- or perinatal injury. (Tsuji T, Okumura A, Kidokoro H, et al. Differences between periventricular hemorrhagic infarction and periventricular leukomalacia. **Brain Dev** 2014 Aug;36(7):555-62).

COMMENTARY. PVHI and PVL are well-defined white matter injuries in preterm infants that are accompanied by neurological sequelae. Cranial ultrasonography (US) in infants with PVHI shows periventricular intraparenchymal echodensity (IPE) at 1-3 days after birth, whereas cystic changes in deep white matter are seen in infants with cystic PVL at 1-3 weeks.

Ultrasound vs MRI for detecting intracranial hemorrhage in preterm neonates.

Investigators at Johns Hopkins Hospital studied 12 premature neonates with a mean gestational age of 32 weeks, comparing US and MRI for detection of grade I-III germinal matrix hemorrhage (GMH) and PVH. US had high sensitivity (100%) and specificity (93%) in detecting grade III GMH but poor sensitivity (0%) in detection of intraventricular hemorrhage (grade II GMH). US is first line of imaging for brain injury in the evaluation of premature neonates with suspected intracranial hemorrhage, but usefulness of MRI and susceptibility-weighted imaging for predicting long-term neurological outcome remains to be determined [1].

References.

1. Intrapiromkul J, et al. J Neuroradiol. 2013 May;40(2):81-8.

AUTOIMMUNE DISORDERS

RITUXIMAB IN AUTOIMMUNE CNS DISEASE

Investigators at University of Sydney, Australia, and 14 international centers assessed the utility and safety of rituximab in 144 children (median age 8 years, range 0.7-17; 103 female) with autoimmune and inflammatory disorders of the CNS. These included NMDAR encephalitis in 39 patients, opsoclonus myoclonus ataxia syndrome in 32, neuromyelitis optica spectrum disorder in 20, lupus erythematosus in 18, and other neuroinflammatory disorders in 35. A standardized questionnaire and Rankin Scale were used for a retrospective evaluation of treatment outcome. Infusion adverse events occurred in 18/144 (12.5%), including anaphylaxis in 3, and infection in 11 (7.6%), 2 of whom died. Benefit was reported in 125 (87%) patients, greater in patients treated early. The off-label use of rituximab should be restricted to disorders having significant morbidity and mortality. (Dale RC, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. **Neurology** 2014 Jul 8;83(2):142-50).

COMMENTARY. Suggested guidelines for rituximab treatment in children with neuroimmunologic conditions are listed in an editorial [1]. Originally approved by the FDA in 1997 for the treatment of B-cell non-Hodgkin lymphoma and later for rheumatoid arthritis, more recently it has been used in a variety of autoimmune disorders including multiple sclerosis.

References.

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ENCEPHALITIS / ENCEPHALOPATHY

DYSPLASTIC NEURONS IN OVARIAN TERATOMAS IN NMDAR ENCEPHALITIS

Investigators at University of Toronto, Canada, report detection of atypical (dysplastic) neuronal elements in 4 of 5 teratomas resected from cases with NMDAR

encephalitis but not in 39 controls. These atypical neurons resembled gangliogliomas (n=3) or ganglioneuroblastoma (n=1). Abnormal neuroglial elements were closely related to immune infiltrates resected from 4 of 4 cases. Abnormal neurons within teratomas distinguish cases with NMDAR encephalitis from controls and may promote the development of autoimmunity. (Day GS, et al. Abnormal neurons in teratomas in NMDAR encephalitis. **JAMA Neurology** 2014 Jun;71(6):717-24).

COMMENTARY. The authors propose that pathological examination of teratomas removed from patients with NMDAR encephalitis should first focus on areas containing CNS tissue and second on neurons closely approximated by inflammatory infiltrates. The colocalization of dysplastic CNS neurons and inflammatory infiltrates support an autoimmune cause for the clinical encephalitic presentation [1].

Broca's aphasia: a new phenotype of anti NMDAR encephalitis.

Investigators at Le Kremlin-Bicetre and centers in Paris, France, report a novel case of anti NMDAR encephalitis in a 4-year-old girl who presented with partial seizures that evolved to sudden and isolated Broca's aphasia and subsequently resolved. Anti NMDAR antibodies were positive in CSF and serum [2].

References.

1. Day GS, et al. *JAMA Neurol.* 2014 Jun;71(6):717-24.
2. Deiva K, et al. *Eur J Paediatr Neurol.* 2014 Jun 11. [Epub ahead of print]

ROTAVIRUS-ASSOCIATED ENCEPHALOPATHY AND SUD

Investigators at Fujita University School of Medicine, Toyoake, Aichi, Japan, performed a nation-wide survey to determine the incidence and clinical features of rotavirus-associated encephalitis/encephalopathy (RV-AE) and sudden unexpected death (SUD) in Japan. Of questionnaires sent to hospitals, 963 (70.5%) were returned, reporting 58 cases of RV-AE diagnosed by immunochromatography between 2009 and 2011 and 7 cases of SUD in the same period. Neurological sequelae occurred in 15/58 (25.9%) and fatal outcomes in 7/58 (12.1%); 36/58 (62.1%) had no sequelae. In patients with RV-AE, CSF pleocytosis was observed in 9/40 (22.5%) patients and protein levels were elevated in only 4/40 (10%). Serum sodium was normal in 40%, elevated in 17.8%, and low in 42.2%. CT showed brain edema in 9/34 (26.5%), and MRI was abnormal in 64.7% patients. Elevated lactic dehydrogenase (>500 IU/L) or acidemia (pH<7.15) was an indication of a poor prognosis. Annual incidence of RV-AE was 44 and SUD 4.9 cases. (Kawamura Y, et al. Nationwide survey of rotavirus-associated encephalopathy and sudden unexpected death in Japan. **Brain Dev** 2014 Aug;36(7):601-7).

COMMENTARY. In Japan, the annual number of cases of RV-AE was estimated at 41.1 and of SUD 5.0. In the US, a fatality rate of 1 death per 1616 rotavirus hospitalizations (0.06%) is cited in a 2007 report [1]. Since rotavirus vaccines became available in the US in 2006, ED visits and hospitalizations for RV related complications have decreased by 50,000 cases in children younger than 5 years [2].

References.

1. Fischer TK, et al. J Infect Dis. 2007 Apr 15;195(8):1117-25.
2. American Academy of Pediatrics. Rotavirus infections. In: Pickering LK, ed. Red Book: 2012 Report of the Committee on Infectious Diseases. 29th ed. Elk Grove Village, IL: AAP; 2012:626-29.

TRAUMATIC DISORDERS

CONCUSSION SEVERITY AND SYMPTOM RESOLUTION

Investigators at University of Colorado conducted a prospective longitudinal cohort study of children 8 to 18 years old presenting to the ED <6 hours after concussion. Of 234 subjects enrolled, 179 (76%) completed follow-up, and 38 (21%) experienced delayed symptom resolution (DSR). DSR was defined as 3 or more symptoms 1 month after injury that were absent in the week before injury. Initial symptom severity was not significantly associated with DSR 1 month after concussion but was associated with post-concussion syndrome (PCS). A total of 22 (12%) subjects had PCS. Patients were considered to have PCS if they reported 3 or more symptoms on the Concussion Symptom Inventory that aligned with PCS ICD-10 criteria. These 8 include headache, dizziness, fatigue, irritability, impaired concentration for mental tasks, impaired memory, insomnia, and reduced tolerance to stress, excitement, or alcohol. Three of 6 of the most characteristic symptoms of DSR were also most characteristic of early symptom resolution. Cognitive symptoms were more characteristic of subjects reporting DSR and warrant particular attention in future study. Follow-up is recommended for all patients after ED evaluation of concussion to monitor for DSR. (Grubenhoff JA, Deakyne SJ, Brou L, Bajaj L, Comstock D, Kirkwood MW. Acute concussion symptom severity and delayed symptom resolution. **Pediatrics** 2014 Jul;134(1):54-62).

COMMENTARY. This study shows an inability to predict the resolution or persistence of post-concussive symptoms at the time of injury and ED visit. Follow-up and serial symptom assessment are essential for optimal concussion management in children.

Health-related quality of life following concussion.

Comparison of pre-injury health-related quality-of-life (HRQoL) of children who have sustained mild traumatic brain injury (mTBI), children with mild non-brain injuries, and uninjured children showed that HRQoL of children with mTBI was not significantly different between pre- and post-injury at 1, 3, 6 and 12 months post-injury. Therefore, children who sustain mTBI and have significantly lower HRQoL within the first year post-injury merit further evaluation [1].

References.

1. Pieper P, Garvan C. Brain Inj. 2014;28(1):105-13.