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GENETIC DISORDERS

The Genetics of Febrile Seizures

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Related Article: Seinfeld SA, Pellock JM, Kjeldsen MJ, Nakken KO, Corey LA. Epilepsy after Febrile Seizures: twins suggest genetic influence. Pediatr Neurol 2015 Oct 15. [Epub ahead of print]
Keywords: Febrile seizures; Epilepsy; Twin studies

Investigators from Virginia Commonwealth University, Norwegian Center for Epilepsy and University of Southern Denmark carried out twin studies to analyse the genetic influence of developing epilepsy after febrile seizures. The subjects analysed were twin pairs that had a history of febrile seizures and data were obtained using twin registries and validated questionnaires. Febrile seizures were documented in 1051 twins (900 pairs). 61% had simple febrile seizures, 12% had complex febrile seizures, 7% had febrile status epilepticus and the remainder were unclassified. 78 twins were found to have developed epilepsy. Amongst these, the highest rates of epilepsy (22.2%) were found in those who had febrile status epilepticus, which was the smallest group. In the simple, complex and unclassified groups, the risk of developing epilepsy was 2.6%, 12% and 14.2% respectively. The authors concluded that twins with complex febrile seizures and febrile status epilepticus are at an increased risk of developing epilepsy. Amongst monozygotic twin pairs, 50 subjects who had a febrile seizure and subsequent epilepsy had a cotwin with febrile seizures. There were 28 dizygotic twins who were concordant. In both groups, the concordance rate was found to be highest in those with simple febrile seizures. The authors therefore infer that having simple febrile seizures increases the familial risk of seizures. [1]

COMMENTARY. The cause of febrile seizures is multifactorial in nature and whereas there is increasing evidence for susceptibility genes, we know no single gene to be responsible. Identification of genetic mutations has been successful in certain groups of children prone to recurrent febrile seizures, particularly those with SCN1A mutations often associated with family members with Dravet syndrome and Generalised Epilepsy with Febrile Seizures Plus (GEFS+) [2,3]. This twin study does not state whether the grouping of the children into different febrile seizure groups (simple, complex, status etc) is defined by their first seizure or not. This is an important omission as many children will have different or at least indistinguishable seizure types during their febrile seizure career. It is seizure-type which defines recurrence and future epilepsy risk.

Some retrospective studies have shown that adults with temporal lobe epilepsy have a history of complex febrile seizures or febrile status epilepticus [4]. However, inferring a direct causal link remains controversial. A different hypothesis suggests that the seizures may have occurred due to a pre-existing hippocampal abnormality, caused by a genetic predisposition or earlier insults [5]. Recent prospective outcome studies of febrile status epilepticus have shown contradictory results, necessitating further research. This study adds to the current literature by demonstrating that there may be a strong genetic component even for simple febrile seizures. The opportunity for further research is offered by the approach of low-cost complete genome sequencing. This should add to our understanding of the interaction between genome and environment and associated epigenetic mechanisms.

Disclosures

The authors have declared that no competing interests exist.

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GENETIC DISORDERS

Incidental Findings: The Importance of Pretest Counseling

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Related Article: Lefebvre M, Sanlaville D, Marle N, Thauvin-Robinet C, Gautier E, El Chehadeh S et al. Genetic counselling difficulties and ethical implications of incidental findings from array-CGH: A 7-year national survey. Clin Genet 2015 Nov 19. [Epub ahead of print].
Keywords: aCGH; ethical issues; incidental findings; pre-test information

Researchers at the University of Bourgogne in Dijon, France surveyed French geneticists who were members of the "Association Français des Généticiens" on incidental findings (IF) found on array-based comparative genomic hybridization (aCGH) technology retrospectively over a seven-year period. Data analyzed on 65 cases had IF for autosomal dominant conditions with a range of penetrance, X-linked conditions, and heterozygous carriers of an autosomal recessive condition. Overall, 79% were classified as pathogenic or likely pathogenic, and as a variant of uncertain significance in 21% of cases. Of the 65 cases, all but four warranted some type of preventive care, change of management, or genetic counseling. These four results were not returned to the patients. One was chosen to not be returned due to the lack of pretest counseling on IF. The respondents reported difficulty in returning IF to patients 29% of the time, especially in the case where a possibility of an IF was not anticipated by the clinician. Only 21 (48%) reported using a consent process and pretest counseling on the possibility of IF. [1]

COMMENTARY. The availability of advanced genetic technology enables analyses for multiple disorders to be done concurrently. This has led to the incidental finding of medical information unrelated to the clinical indication for testing. The struggles surrounding incidental or secondary findings (IF/SF) are not new, however, this paper exemplifies the continued dilemmas surrounding the informed consent process and the lack of clear direction for providers in disclosing IF information to patients.

The ACMG has addressed informed consent for IF/SF [2]. However, these processes remain inconsistent for IF/SF encountered via aCGH and large NGS panels which test for groups of disorders and are not limited to analysis of only phenotypically indicated diseases. A recent review of large NGS epilepsy panels highlighted the importance of knowing the content of these panels so that accurate pretest information can be provided to improve the informed consent process [3]. While it is unrealistic to provide counseling on every IF possible, it is realistic to provide anticipatory guidance as to the range of impact of these IF.

The reporting of difficulty in the disclosure of IF by the providers, especially when not anticipated, validates previous recommendations that all practitioners anticipate and plan for IF in pretest discussions with patients [4]. An approach where IF are expected would normalize the scenario for patients and providers so that a shared-decision-making process can be utilized to promote the delivery and receiving of results. The need to delineate what is required to provide accurate information to guide these discussions has been recognized [5]. Such resources will prove crucial for adequate informed consent and understanding for both clinicians and patients. With this endpoint in mind, further recommendations, guidelines, education, and resources for pretest counseling and consent requirements surrounding IF/SF need to be formalized to ensure consistent practice.

Disclosures

The authors have declared that no competing interests exist.

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SEIZURE DISORDERS

Incidence of Dravet Syndrome in a US Population

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Related Article: Wu YW, Sullivan J, McDaniel SS, Meisler MH, Walsh EM, Li SX et al. Incidence of Dravet Syndrome in a US Population. Pediatrics 2015 Nov;136(5):e1310–e1315.
Keywords: Epilepsy; Genetics; Pediatrics

Investigators from the University of California, San Francisco and Kaiser Permanente report the incidence of Dravet Syndrome in a population based cohort. The cohort was identified by reviewing records of patients treated in Kaiser Permanente Northern California (KPNC) system from January 1, 2007 to June 30, 2010. KPNC has a catchment area with over 3.5 million members and consists of approximately half of the insured population in Northern California.

The study was a retrospective chart review of all infants born within the KPNC system during the specified timeframe. Records were reviewed and a clinical diagnosis of Dravet Syndrome was made if the patient met 4 of the 5 following criteria: 1. Normal or near normal cognition prior to onset, 2. Two or more febrile or afebrile seizures in the first year of life, 3. Myoclonic, hemiclonic or generalized tonic-clonic seizures, 4. Two or more seizures lasting longer than 10 minutes, 5. Failure to respond to a first-line antiepileptic medication with continued seizures after two years of age. All patients who met the clinical diagnosis criteria for Dravet Syndrome had SCN1A gene sequencing performed.

There were 125,547 births in the study population, of which 730 infants had two or more seizure visits prior to the age of one year. Eight infants met 4 of the 5 clinical criteria for Dravet Syndrome, equivalent to an incidence of 1 per 15,700 births). Six of the eight patients were found to have de novo mutations that were predicted to be pathogenic, equivalent to an incidence of 1 per 20,900. [1]

COMMENTARY. Dravet Syndrome is a rare pediatric epilepsy syndrome encompassing a range of cognitive delays and refractory epilepsy. The authors provide estimates of its incidence based on well-defined clinical features ascertained in the first year of life and on genetic testing. Although the incidence of Dravet Syndrome was somewhat higher than others have found, the percentage of Dravet patients with a SCN1A mutation (75%) is similar to previous reports. Early diagnosis of Dravet Syndrome is important, as it may guide providers in selecting drugs demonstrated to be most effective and in steering away from drugs known to exacerbate seizures in Dravet Syndrome. Patients with suspected Dravet Syndrome and other pediatric refractory epilepsy could benefit greatly from earlier diagnosis, potentially provided by early genetic testing.

Ream and Mikati at Duke University medical center reported on their pilot program for genetic testing in new epilepsy patients. Twenty-five pediatric patients with refractory epilepsy completed genetic testing, of which 15 had a positive result. Patients with generalized epilepsy or epileptic encephalopathy were more likely to have a pathogenic variant. Of the different methods, karyotype testing had the lowest yield (1 out of 7 patients tested, 14.3%), while epilepsy gene panel testing had the highest yield (6 of 13 patients tested, 46.2%). Of the six patients tested with whole exome Sequencing, 100% had pathogenic variants, although only one of the six patients had a specific diagnosis as a result of the testing [2]. Mercimek-Mahmutoglu et al. at The Hospital for Sick Children found 28% of patients in a cohort of patients referred for epileptic encephalopathy had an identifiable genetic cause [3].

As genetic testing becomes more refined and available the opportunity for earlier diagnosis and treatment will become greater. Multicenter collaboration will be essential for developing optimal approaches for the diagnosis, treatment and management of Dravet Syndrome and other rare epilepsies.

Disclosures

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SEIZURE DISORDERS

Prediction of Infantile Spasms Recurrence after ACTH Therapy

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Related Article: Hayashi Y, Yoshinaga H, Akiyama T, Endoh F, Ohtsuka Y, Kobayashi K. Predictive factors for relapse of epileptic spasms after adrenocorticotropic hormone therapy in West syndrome. Brain Dev 2016 Jan;38(1):32–39.
Keywords: EEG; Infantile Spasms; ACTH; West syndrome

Investigators from Okayama University Hospital, Japan, studied the predictive value of serial EEG findings (every 2 to 4 weeks) in relapse of epileptic spasms after synthetic ACTH therapy in patients with West syndrome (WS). EEGs were performed for more than 40 min, both awake and asleep. Thirty-nine WS patients (18 cryptogenic, and 31 symptomatic) received ACTH therapy for the first time and were followed for more than 3 years. The total duration of ACTH therapy ranged from 11 to 37 days (mean, 23.5 days). Sixteen (41%) showed seizure relapse and 23 patients (59.0%) had no seizure relapse. Immediately on completion of ACTH therapy, seizure outcome was associated with etiology (p=0.003). No seizure recurrence occurred in the cryptogenic group whereas 51.6% of the symptomatic group had recurrence of seizures. At one month after ACTH, only the presence of epileptic discharges (p=0.001) had a significant association with seizure outcome, regardless of etiology. All relapsed patients were in the symptomatic group. The time to relapse after completion of ACTH therapy ranged from 5 days to 25 months (mean: 6.6 months). The group with no epileptic discharges on EEG showed a significantly higher seizure-free rate than those with epileptic discharges at 1 month after ACTH (p=0.0091). Serial EEG findings after ACTH therapy for WS are significantly related and may be used to predict relapse of epileptic spasms. [1]

COMMENTARY. In both cryptogenic and symptomatic patients in this study, the group with no epileptic discharges on EEG at 2 weeks and at one month after the end of ACTH therapy showed a significantly better seizure control. The presence of epileptic discharges, especially multifocal spikes before 2 months' post treatment, can be used to predict imminent relapse [1]. In the present study [1], the age at onset, and presumably of treatment, of spasms ranged from 2 to 15 months (mean: 6.7 months); the response in relation to age was not specifically determined, but the overall early age might predict a generally favorable response.

In addition to the EEG and etiology, factors important in the prediction of prognosis of WS not addressed in this study are the age at diagnosis and treatment, and the level of development at diagnosis. In a study of 21 patients treated with ACTH, the outcome was related significantly to the age at diagnosis and treatment: 80% of infants less than 1-year-old were benefited whereas only 22% of those over 1 year showed reduction in seizures and EEG improvement after ACTH therapy [2]. Patients of normal or borderline intelligence tended to respond to ACTH more frequently than did those with lowered mental development quotients <70 [2]. Predicting relapse of WS with EEG following treatment is important for clinical decision making and shares the same significance as screening for a pre-hypsarhythmia EEG pattern in at risk infants prior to the onset of infantile spasms [3].

Disclosures

The author(s) have declared that no competing interests exist.

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COMPLEMENTARY/INTEGRATIVE THERAPIES

Complementary/Alternative versus Prescription Medications

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Keywords: Complementary and Alternative Medicine; Headache; Chronic Fatigue; Epilepsy

Investigators from the Mayo Clinic, Rochester MN, determined the use of complementary and alternative medicine (CAM) in an outpatient pediatric neurology clinic, and assessed family attitudes toward the efficacy of CAM versus prescription medications. Questionnaires distributed to 500 consecutive patients alluded to the child's diagnosis, use of CAM, efficacy of CAM and the prescription medication. Of 484 surveys returned, 327 were usable. Only 17.4% admitted initially to the use of CAM to treat neurological problems. At follow-up, 41.6% of patients understood that they used CAM. Disorders treated with a significant increased prevalence of CAM included headache (50.8% with headache used CAM vs 35.7% without headache, p=0.008), chronic fatigue (63.2% vs 38.8%, p=0.005), and sleep disorders (77.1% vs 37.3%, p<0001). Epilepsy was among disorders least likely to be treated with CAM (107/327, 32.7%), Melatonin was the most widely used CAM, followed by probiotics. Gluten-free diet was among the top 10 popular modalities. Only 38.5% of CAM using patients recognize that they are taking CAM, a finding that demonstrates the need to inquire in depth about use of CAM. Patients less satisfied with their prescription medications are more likely to use CAM, reflecting the less tractable nature of their disorders. Few families (4.9%) managed to treat solely with CAM. [1]

COMMENTARY. The Mayo Clinic, renown for its allopathic medicine, must be congratulated on a detailed study of the prevalence of use and perceived efficacy of complementary and alternative medicine (CAM). The list of 56 commonly used CAM modalities showing their frequency of use is particularly of interest and emphasizes the popularity of melatonin, probiotics, music therapy, and omega 3 among parents of patients in this particular clinic. While different communities may demonstrate different patterns of use of CAM, the educational level did not affect the use of CAM in this community. Most pediatric CAM use is not discussed with patients, despite the interest frequently shown by parents [2]. The authors note that patients are less likely to report the use of CAM unless asked about specific modalities. Making the Mayo Clinic list of commonly used CAM modalities available to patients should facilitate the physician-parent discussion and lead to a better understanding of the indications and need for evaluation of this form of therapy. For headache, the most frequently treated disorder using CAM, long-term prophylactic drug therapy is appropriate only after exclusion of headache precipitating trigger factors, including dietary factors [3].

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MOVEMENT DISORDERS

Risk of Tics with Psychostimulants for ADHD

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Related Article: Cohen SC, Mulqueen JM, Ferracioli-Oda E, Stuckelman ZD, Coughlin CG, Leckman JF et al. Meta-Analysis: risk of tics associated with psychostimulant use in randomized, placebo-controlled trials. J Am Acad Child Adolesc Psychiatry 2015 Sep;54(9):728–736.
Keywords: Psychostimulant Medications; Methylphenidate; Amphetamine; Tics; ADHD; Meta-Analysis

Investigators at Yale University, New Haven, CT, conducted a meta-analysis to examine the risk of new onset or worsening of tics caused by psychostimulants used in the treatment of children with ADHD. A PubMed search identified 22 double-blind, randomized, placebo-controlled studies involving 2,385 children with ADHD. New onset tics or worsening of tic symptoms were reported in 5.7% of the psychostimulant group and in 6.5% of the placebo group. The risk associated with psychostimulant treatment was similar to that observed with placebo (p=.962). The risk was not affected by type of psychostimulant, short or long-acting, dose, duration of treatment, nor by participant age. Crossover studies were associated with a significantly greater risk of tics with psychostimulant use compared to parallel group trials. Meta-analysis of controlled trials does not support an association between new onset or worsening of tics and psychostimulant use. The authors conclude that tics occurring during treatment of ADHD are more likely to be coincidental rather than caused by psychostimulants. The meta-analysis findings provide strong support for rechallenging children who develop tics that are temporally related to the initiation of psychostimulants. [1]

COMMENTARY. Neurologists began to recognize tics as an organic disorder in the 1970s, shortly after the introduction of methylphenidate for the treatment of ADHD [2]. US FDA labeling warned against the use of stimulants in children with a personal or family history of tics. Since1983, psychostimulants are required to list tics or a family history of tics as a contraindication to their use for treatment of ADHD. Since then, many controlled trials have demonstrated no effect of psychostimulants on tics, and psychostimulants are as effective in treating ADHD and comorbid tics as in children with ADHD alone [3]. Symptoms of ADHD typically cause greater impairment in academic performance, social relationships, and neuropsychological performance, especially executive functioning, when ADHD is present in children with tics, an argument in favor of the use of psychostimulants.

Notwithstanding the clear evidence from meta-analysis that psychostimulants are innocent as a cause of tics in children with ADHD, the experience of the treating neurologist will often favor contrary conclusions and the avoidance of stimulants in a child who develops tics de novo or has significant worsening of tics when starting stimulants. In an editorial, recommendations for the management of this dilemma are outlined: 1) avoid use of stimulants when other causes of inattention (eg anxiety) are present; 2) explain the rates of tics as an adverse event (20% in children with pre-existing tics and 6% in those who have ADHD without tics); 3) tic occurrence waxes and wanes and may even complicate the introduction of a medication such as clonidine, sometimes used to treat tics [4].

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INFECTIOUS/AUTOIMMUNE DISORDERS

Acute Flaccid Myelitis Outbreak

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Related Article: Nelson GR, Bonkowsky JL, Doll E, Green M, Hedlund GL, Moore KR et al. Recognition and management of acute flaccid myelitis in children. Pediatr Neurol 2015 Oct 20. [Epub ahead of print].
Keywords: Flaccid Myelitis; Spinal Gray Matter; Motor Cranial Neuropathy; Enteroviruses

Investigators from the University School of Medicine, Salt Lake City, Utah, report an outbreak of acute flaccid myelitis (AFM) occurring in 2014-2015 in several States and reported to the CDC. The disease was localized to the gray matter of the spinal cord. Eleven children, ages 13 months to 14 years (median, 9 years) presented in the intermountain West with extremity weakness (n=10) or cranial neuropathy (n=1), varying in severity and without apparent etiology. Maximum paralysis occurred within 4 days of onset. Seven children had a prodrome consisting of headache, nausea, vomiting, or cough one to 7 days before onset of weakness; 5 had intermittent, low-grade fever. None described sensory loss. Only one required intubation for respiratory failure. MRI showed T2 hyperintensities involving the anterior horn gray matter of the spinal cord; four children also had T2 hyperintensities involving the brainstem or cerebellar nuclei. CSF pleocytosis in 7 children ranged from 7 to 170 leukocytes/uL. PCR enteroviral and herpesvirus tests were negative. Respiratory film array was positive for influenza AH3 in one child and parainfluenza 2 in another; rhinovirus was detected in a nasopharyngeal swab in one child, thought to be coincidental. Treatments included IV immunoglobulin, corticosteroids, and plasma exchange, all having no beneficial effect, and 9 of 10 (90%) having residual motor deficits at follow-up. As of July 2015, 120 cases of AFM have been reported to the CDC, and no cause has been identified. [1]

COMMENTARY. AFM is a unique type of flaccid paralysis in children, distinct from Guillain-Barre syndrome (GBS) and transverse myelitis (TM). GBS is an ascending paralysis, associated with sensory symptoms, characteristic CSF findings, and favorable prognosis. TM has a prominent sensory loss whereas AFM has focal, poliomyelitis-like spinal cord paralysis with minimal or no sensory symptoms [1]. AFM should be considered in the differential diagnosis of children who present with GBS or TM-like symptoms, and especially in those with persistent weakness.

Testing for enteroviruses is extensive because of their known association with AFM. Of 11 patients presenting with AFM and/or cranial nerve dysfunction during an enterovirus D68 outbreak in Colorado, 9 had brain stem lesions, most commonly involving the pontine tegmentum, and 10 had longitudinally extensive lesions in the central gray matter of the spinal cord. MR imaging showed enhanced ventral cauda equina nerve roots in 4 patients, and ventral cervical nerve roots enhanced in 3. Neuroimaging findings were similar to those described in outbreaks of viral myelitis caused by enterovirus 71 and poliomyelitis [2,3].

Disclosures

The author has declared that no competing interests exist.

References

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