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SEIZURE DISORDERS

Photosensitivity and *CHD2* Variants

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Related Article: Galizia EC, Myers CT, Leu C, de Kovel CG, Afrikanova T, Cordero-Maldonado ML, et al. *CHD2* variants are a risk factor for photosensitivity in epilepsy. Brain. 2015;138(Pt 5):1198-207.
Keywords: Eyelid Myoclonia with Absences; Photosensitive; Seizure

Investigators from multinational institutions hypothesized that disruption of *CHD2*, which encodes chromodomain helicase DNA-binding protein 2, would be associated with common forms of photosensitive epilepsy or photosensitivity manifesting as a photoparoxysmal response alone. They studied 580 patients with photosensitive epilepsy, defined as the presence of photoparoxysmal response with history of epilepsy or seizures reproducible by flickering lights. They also studied 55 patients with photoparoxysmal responses, but no seizures. *CHD2* sequencing was performed in this cohort and compared to a previously published cohort of 34,427 individuals, for which phenotypic data was not available. Unique *CHD2* variants were identified in 11 (11/1160 alleles; 0.95%) cases compared to 128 (128/68854 alleles; 0.19%) of controls, which suggests an over-representation in this population. Eyelid myoclonia with absences (EMA) had the highest frequency of unique variants (3/36 cases), more than expected for controls as a whole. Only one unique variant was identified in the group of photoparoxysmal responses without seizures. Investigators also studied functional consequences using *CHD2* loss in zebrafish. Morpholino injected larvae were thought to have more discharges and enhanced photoparoxysmal responses. Authors identify *CHD2* as a photosensitive epilepsy gene and an important contributor to both the absence seizures with eyelid myoclonia seizure type and eyelid myoclonia with absences epilepsy syndrome. [1]

COMMENTARY. Photosensitivity is an abnormal cortical response to flickering lights due to a genetically determined trait. When an electrographic correlate is identified it is known as a photoparoxysmal response. Photosensitive epilepsy, on the other hand is when the visual stimuli triggers seizures. [1] Photoparoxysmal responses have been described in certain epilepsy syndromes (Genetic Generalized Epilepsies, Eyelid Myoclonia with and without absence seizures, Dravet Syndrome, Myoclonic Atonic Epilepsy (MAE)), neurodegenerative diseases, and even normal individuals. [2] A more recent study attempted to assess the impact of *CHD2* mutations in a cohort of patients with MAE. [3] A *CHD2* mutation was found in 1/20 (5%) patients with Myoclonic Atonic Epilepsy. Photoparoxysmal responses and photoinduced seizures were described in this patient who was found to have a mutation not described in the cohort above. They concluded that although this gene might not be very significant in MAE, it may be responsible for generalized epilepsy with myoclonic-atonic and possibly atonic-myoclonic seizures, as well as intellectual disability and photosensitivity. As we continue to learn more about *CHD2* mutations, the different epilepsy phenotypes, and photoparoxsymal responses associated with this gene, we will learn more about the pathophysiology and perhaps be able to develop new target treatments for epilepsy.

Disclosures

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

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SEIZURE DISORDERS

Ketone Bodies Mediate Antiseizure Effects

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Related Article: Kim Y, Simeone KA, Simeone TA, Pandya JD, Wilke JC, Ahn Y et al. Ketone bodies mediate antiseizure effects through mitochondrial permeability transition. Ann Neurol 2015 Jul;78(1):77–87.
Keywords: Ketogenic Diet; Ketone Bodies; Epilepsy

Investigators from The Barrow Neurological Institute, Creighton University, University of Kentucky and the University of Calgary Faculty of Medicine investigated the effect of ketone bodies and the ketogenic diet on epileptic Kcna1-null mice. The Kcna1-null mouse is an animal model that represents human temporal lobe epilepsy. The mice were found to have a reduction in spontaneous recurrent seizures after treatment with the ketogenic diet when compared to Kcna1-null mice fed with a standard diet. In addition, seizure reduction in the Kcna1-null mice was also noted when the mice were administered ketones (beta-hydroxybutyrate) via implanted pump and fed an ad lib standard diet. They were found to have normal glucose levels. These results were replicated in vitro, on slice cultures prepared from Kcna1-null mice. Investigators also showed that the antiseizure properties of the ketogenic diet were mitigated when the mitochondrial permeability transition pore was activated. They found that ketone bodies were able to raise the threshold for calcium-induced mitochondrial permeability transition, which decreased activation of the mitochondrial permeability transition pore and thus hypothesized the blockade of this process is part of ketone body antiepileptic mechanism.

The investigators also found evidence of protective effects secondary to the ketogenic diet. Kcn1-null mice showed significant difficulties in spatial learning and memory when compared to wild type mice. Treatment with the ketogenic diet restored these deficits to levels seen in the wild type mice. This was re-demonstrated in vitro, as the Kcn1-null mice demonstrated impairment in CA1 hippocampal long term potentiation, which was restored by the ketogenic diet or administration of beta-hydroxybutyrate alone. [1]

COMMENTARY. The ketogenic diet is an important factor in the treatment of pediatric refractory epilepsy. A meta-analysis of available data suggests that a 50% reduction of seizures can been seen in up to 1/3 of patients on the diet [2]. In this paper the authors report evidence toward a new target in the ketogenic diet, which supports prior literature suggesting the ketogenic diet's effects rely on multiple mechanisms of action. Rho and Sankar suggested multiple mechanisms, including enhancement of the GABA system, direct effects from acetone and acetoacetate, increased energy substrates, decreased oxygen species or enhancing glutathione [3]. Similar to many effective antiseizure medications, the multifaceted pathways in the ketogenic diet lend themselves to a broad spectrum of seizure control, which can be more effective than singular therapies. Testing the ketogenic diet utilizing different mouse models yields new insight into the different mechanisms.

The authors also provide evidence ketone bodies may restore deficits in learning and memory. Cognitive dysfunction is common in pediatric epilepsy [4]. However, causation is not clear and cognitive deficits may arise from factors other than seizures or interictal epileptiform discharges. The authors provide evidence for a treatment that may improve cognition and thereby quality of life, raising another possible target of treatment.

Finally, this paper adds to the building evidence that administration of ketone bodies has a direct positive effect, independent of hypoglycemia. Detailed understanding of the multiple mechanisms of dietary treatment may also allow for modification of other existing dietary therapies.

Disclosures

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

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NEUROMUSCULAR DISORDERS

Orofacial EMG in Congenital Multiple Cranial Neuropathies

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Related Article: Renault F, Flores-Guevara R, Baudon JJ, Vazquez MP. Congenital multiple cranial neuropathies: relevance of orofacial electromyography in infants. Muscle Nerve 2015 Nov;52(5):754–758.
Keywords: Infant; Cranial Neuropathies; EMG

Investigators from Armand-Trousseau hospital and University of Paris studied 90 infants aged birth to 6 months with multiple cranial nerve involvement. Neurophysiologic studies using blink responses (BR's) and electromyography (EMG) of the muscles of the face, tongue and soft palate were performed to investigate for orofacial function.

Neurogenic pattern was noted with involvement of facial nerve in 82/90 patients, abnormal BR's in 40/63, pharyngeal plexus in 56/89 and hypoglossal nerve in 25/90. Poor outcome (presence or absence of neurological disabilities, need for respiratory assistance, gastrostomy and prolonged enteral feeding) and death was higher (P=0.02) where EMG identified >= 4 affected cranial nerves. There was however no significance associated with involvement of lower cranial nerves and poor outcome. [1]

COMMENTARY. Studies of cranial nerves in children using EMG is a time intense process involving a trained electromyographer and equally trained supportive staff. The investigators previously published studies where orofacial EMG's were performed in children [2] for assessing brainstem involvement [3] and dysphagia in infants with facial malformations [4]. They combined the techniques to study all children referred to their center for orofacial dysfunction and observed outcome related to the number of cranial nerves involved.

Orofacial dysfunction is assumed to be of suprabulbar origin and although the cerebral cortex is more vulnerable to ischemia, neuropathological studies have shown brainstem involvement in birth asphyxia [5] and prenatal ischemia [6]. There are reports of hypoglossal involvement in children where periventricular leukomalacia or hemorrhagic infarction was thought to be the cause of dysphagia [7]. In fact, 14 patients of this study were thought to have a cortical vascular insult at birth with orofacial dysfunction but EMG studies showed face, tongue and soft palate neurogenic changes.

The study highlights that EMG's are not only useful for peripheral nerves and the muscles they innervate, but can be employed for cranial nerve assessment. Localizations with respect to brainstem pathology can be inferred by testing multiple cranial nerve innervations in the facial and bulbar muscles. Neurophysiology is also helpful as clinical exam alone detected 3 times less facial nerve involvement compared to EMG, especially when the involvement was bilateral. EMG aided in diagnosis of lingual and pharyngeal abnormalities that were difficult to pick up clinically.

This study also underscores a poor outcome based on the number of cranial nerve involvement and not the cranial nerve type based on location in the brainstem. It is surprising that lower cranial nerves thought to induce a higher risk of airway compromise and aspiration, were not associated with poor outcome.

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LEARNING AND COGNITIVE DISORDERS

Focal MRI and Learning Disability with Reduced Automaticity

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Related Article: Urion DK, Huff HV, Carullo MP. MRI in assessing children with learning disability, focal findings, and reduced automaticity. Neurology 2015 Aug;85(7):604–609.
Keywords: Automaticity; Brain MRI; Learning Disability

Investigators from the Boston Children's Hospital, Harvard Medical School, MA, performed a retrospective analysis of 1,587 children referred for a learning disability, and 127 had a focal deficit demonstrated on either a neurologic or neuropsychological evaluation. Children with abnormalities in learning and a focal deficit were compared in terms of deficits in automaticity or difficulty in changing from controlled to automatic processing. Automaticity was measured by a Rapid Automatized Naming, Rapid Alternating Stimulus Naming, or the timed motor performance battery from the Physical and Neurological Examination for Soft Signs. Data were compared in children with and without disorders of automaticity regarding type of brain structure abnormality. Of 87 with a brain MRI, 40 (46%) were abnormal; abnormalities involved cerebellum (5), white matter (25), corpus callosum (9), and gray matter (11). These with focal abnormalities were compared with a sample of 150 patients with learning disabilities and no focal abnormalities, including the MRI. In the focal MRI group, reduced verbal automaticity was associated with cerebellar abnormalities, whereas reduced automaticity on motor or motor and verbal tasks was associated with white matter abnormalities. Reduced automaticity of retrieval and slow timed motor performance are highly associated with MRI findings. [1]

COMMENTARY. Previous studies of neurological and MRI profiles of children with cognitive disorders concerned children with developmental language impairment (DLI)[2], and children with memory and learning outcomes 5 years after traumatic brain injury [3]. Investigators from the San Diego School of Medicine, La Jolla, CA, reported 12 (34%) of 35 children aged 5 to 14 years with DLI had abnormalities on the MRI, while only one of 27 control children had abnormal scans [2]. Abnormal MRI findings included ventricular enlargement in 5, central volume loss in 3, and white matter abnormalities in 4. Children with DLI were significantly delayed in motor milestones, especially walking, in addition to speech. Neurological examination abnormalities included synkinesis, fine motor impairments, and hyperreflexia. Children with DLI may need more comprehensive intervention than language therapy alone.

Investigators from the University of Melbourne, Australia, examined the effects of injury severity on long-term memory in 55 children who sustained traumatic brain injury 5 years earlier and compared with 17 healthy controls. Injury severity affected complex memory, with no significant effects on working memory. Diffuse axonal injury predicted outcome on complex memory tasks, but focal cortical damage was not predictive of working or complex memory [3]. The detection of focal brain abnormalities on MRI in children with learning disorders is dependent on the use of higher-resolution scans; the percentage of patients who exhibited brain lesions on MRI when using a 3.0T machine was 60% compared to 32% on a 1.5T machine [1].

Disclosures

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

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MOVEMENT DISORDERS

ADCY5 Mutations and Benign Hereditary Chorea

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Related Article: Mencacci NE, Erro R, Wiethoff S, Hersheson J, Ryten M, Balint B et al. *ADCY5* mutations are another cause of benign hereditary chorea. Neurology 2015 Jul;85(1):80–88.
Keywords: Hereditary Chorea; Genes; Mutation Analysis

Investigators from the Institute of Neurology, London, UK, and centers in Italy, Germany, and Greece, studied 18 unrelated cases of benign hereditary chorea BHC (7 familial, 11 sporadic) who were negative for *NKX2-1* mutations. The diagnosis of BHC was based on a childhood-onset movement disorder, predominantly characterized by chorea alone, with no facial myokymia. *ADCY5* and *NKX2-1* expression during brain development and in the adult human brain was assessed using microarray analysis of postmortem brain tissue. A familial case with a mild clinical presentation inherited the mutation from the affected father, whereas in a sporadic case the mutation was de novo. The nonparoxysmal generalized chorea, and dystonia in severe cases, showed significant progression of symptoms in *ADCY5* mutation carriers, in contrast to BHC secondary to *NKX2-1* mutations that showed an opposite trend, with improvement after childhood. Prominent dystonic posturing in the most severely affected *ADCY5* mutation cases of BHC is worsened by action, excitement or stress and is not a feature of the *NKX2-1* mutation cases. *ADCY5* genetic analysis should be performed in cases of benign choreiform movement disorder, even in the absence of facial myokymia. [1]

COMMENTARY. Benign hereditary chorea (BHC) is a dominantly inherited, childhood-onset hyperkinetic movement disorder characterized by non-progressive chorea and variable degrees of thyroid and respiratory involvement. Loss-of-function mutations in *NKX2-1*, a gene vital to the normal development and function of the brain, lungs, and thyroid, have been identified, leading to the description of a "brain-lung-thyroid syndrome" in some cases [2]. The present report identifies mutations in *ADCY5* as another cause of familial and sporadic BHC [1].

An extended phenotype includes obsessive-compulsive disorder and skeletal abnormalities, pes cavus and kyphosis. In a study and report from the University of Cardiff and other centers in the UK, of 10 probands with BHC and *NKX2-1* mutations, 8 presented with muscle hypotonia and 4 with hypothyroidism; only 3 of the 10 cases had the full triad of "brain-lung-thyroid syndrome [2]. An update from these UK centers highlights additional non-motor characteristics of BHC, such as cognitive impairment and psychiatric symptoms. Evidence for BHC as a developmental disorder involving impaired neural migration is discussed [3].

Investigators at Hopital Trousseau, Paris, France, report the outcome and long-term follow-up in 28 *NKX2-1* mutated BHC patients from 13 families. Chorea presenting in early infancy was associated with hypotonia, delayed walking in 25 of 28, dystonia, myoclonus and tics often associated, and ADHD occurred in 7. Among 14 patients followed until adulthood, 9 had persistent mild chorea, 2 had near total resolution of chorea but persistent myoclonus; 3 recovered completely. Learning difficulties occurred in 20/28, and 3 were mentally retarded. Various combinations of BHC, thyroid (67%) and lung (46%) features were noted. A rapid and sustained lessening of chorea was obtained in 5/8 patients treated with tetrabenazine [4].

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PAROXYSMAL DISORDERS

Alternating Hemiplegia and Cardiac Dysrhythmia

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Related Article: Jaffer F, Avbersek A, Vavassori R, Fons C, Campistol J, Stagnaro M et al. Faulty cardiac repolarization reserve in alternating hemiplegia of childhood broadens the phenotype. Brain 2015 Oct;138(Pt 10):2859–2874.
Keywords: Alternating Hemiplegia of Childhood; ATP1A3; SUDEP; Electrocardiogram

Investigators at the National Hospital for Neurology and Neurosurgery, Queen Square, London, and multiple centers in the UK, Europe, US, Melbourne, Australia, and Canada, analyzed ECG recordings of 52 patients with alternating hemiplegia from 9 countries; all had whole-exome, whole-genome, or direct Sanger sequencing of ATP1A3; 47 had a confirmed missense mutation in ATP1A3. De novo mutation in ATP1A3 is the underlying cause of most cases. Autonomic dysfunction, cardiac symptoms, medication, and family history of cardiac disease or sudden death were recorded. Thirty-two patients were under 16 years of age; 26 were female. Three-quarters had a diagnosis of epilepsy; EEGs were not reported. Half the cohort (26/52) had resting 12-lead electrocardiogram (ECG) abnormalities; 25/26 had repolarization (T wave) abnormalities. These abnormalities were significantly more common in people with alternating hemiplegia than in an age-matched control group of 52 people with epilepsy. The average corrected QT interval was significantly shorter in people with alternating hemiplegia than in the disease control group. J wave or J-point changes were seen in 6 patients with alternating hemiplegia. Over half the affected cohort (28/52) had intraventricular conduction delay, or incomplete right bundle branch block, a much higher proportion than in the normal population or disease control cohort (P=0.0164). Abnormalities in alternating hemiplegia were more common in those >16 years old, compared with those <16 (P=0.0095). ECG changes occurred independently of seizures or plegic episodes. ECG abnormalities are common in alternating hemiplegia, with characteristics reflecting inherited cardiac channelopathies and impaired repolarization reserve. Cardiac dysfunction may account for unexplained premature mortality of patients with alternating hemiplegia. [1]

COMMENTARY. This study provides a more complete understanding of alternating hemiplegia and its relation to cardiac dysfunction. QT intervals are significantly shorter in alternating hemiplegia patients compared to controls with epilepsy. QT prolongation is reported in individuals with epilepsy, suggesting that the association of alternating hemiplegia with cardiac dysfunction and the change in QT interval are the opposite of that occurring in persons with epilepsy. That alternating hemiplegia is a form of epilepsy is suggested by the frequency of occurrence of seizures and a diagnosis of epilepsy in 40 cases (75%). Electroencephalographic (EEG) confirmation of cases in the present study is not provided. Migraine is also frequently associated and is considered as a cause; flunarizine and topiramate may prevent recurrence whereas anticonvulsants are of no benefit.

To determine the evolution of epileptic seizures in alternating hemiplegia of childhood, Saito Y and associates reviewed clinical findings of 9 patients [2]. Paroxysmal abnormal ocular movements, head turning, and tonic, clonic, or myoclonic limb movements were initial symptoms (birth-8 months) in each patient. Ictal EEG of these episodes and of accompanying hemiplegic periods later in infancy showed generalized slowing. Presumptive epileptic seizures appeared at 2-16 years in 7 patients; ictal EEGs revealed focal slow or fast activities during facial or limb twitching, and sharp waves or polyspike-wave activities during clonic/myoclonic seizures. Status epilepticus in alternating hemiplegia is linked to severe outcome with psychomotor deterioration. The variations in phenotypes may imply multiple causative genes for alternating hemiplegia [2]. A KCNQ1 mutation is recently reported in a family suffering both epilepsy and prolonged QT interval [3].

Disclosures

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NEUROCUTANEOUS SYNDROMES

MRI Screening for Optic Gliomas in Neurofibromatosis Type 1

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Related Article: Prada CE, Hufnagel RB, Hummel TR, Lovell AM, Hopkin RJ, Saal HM et al. The use of magnetic resonance imaging screening for optic pathway gliomas in children with neurofibromatosis type 1. J Pediatr 2015 Oct;167(4):851–856.e1.
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Investigators from Cincinnati Children's Hospital, OH, analysed retrospectively the utility of screening brain/orbital MRIs in 826 children with NF1 (ages 1-9 years; 402 female, 424 male) seen over a 20-year period between 1990 and 2010. Baseline MRIs of brain and orbits with and without contrast were obtained at 15 months of age or at the time NF1 diagnosis was made. Children identified with OPG were followed with repeat MRI every 3-6 months until OPG was stable. Other patients had annual eye exams and were seen by NF team. Optic pathway gliomas (OPGs) were identified in 18%, with a median age at detection of 3 years. Of 149 with OPGs, 96 (64.4%) were prechiasmatic, 42 (28.2%) chiasmatic, and 11 (7.4%) postchiasmatic; 22 (15%) had radiological or clinical progression requiring therapy. Chiasmatic and postchiasmatic tumors required therapy more frequently than prechiasmatic OPGs (P<0001). Patients with visual deficits at diagnosis (12/22) were more likely to have visual decline despite therapy when compared with patients treated based on radiologic progression (P<.012). Hypopituitarism (6/22) and precocious puberty (5/22) were common comorbidities of patients with chiasmatic and postchiasmatic OPGs and were not a feature of prechiasmatic tumors. Time to therapy after MRI diagnosis ranged from 0.2 and 5 years. Early identification of OPG by screening MRI before the development of vision loss may lead to improved visual outcomes. Children with negative brain and orbital MRI screening at age 15 months or later did not develop symptomatic OPGs. [1]

COMMENTARY. Based on the results of this study the authors advocate the routine MRI screening of brain and orbits of children with NF1 [1]. This opinion is in agreement with a 2004 study and report of benefits of MRI screening of 84 children with NF1 [2], and is contrary to an authority who, in 2004, recommended screening only with ophthalmological examinations in young asymptomatic children [3]. In 1997, the OPG Task Force concluded that early detection of tumors would not reduce the rate of loss of vision, and there was no evidence to support MRI screening with MRI [4]. Perhaps, the current data will lead to a further meeting of a Task Force and a change in guidelines for the management of OPGs, with inclusion of brain/orbit MRIs in children with neurofibromatosis type l.

Disclosures

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

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