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MOVEMENT DISORDERS

Structural Connectivity in Gilles de la Tourette Syndrome

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Related Article: Worbe Y, Marrakchi-Kacem L, Lecomte S, Valabregue R, Poupon F, Guevara P, et al. Altered structural connectivity of cortico-striato-pallido-thalamic networks in Gilles de la Tourette syndrome. Brain. 2015;138(Pt 2):472-82.
Keywords: Gilles de la Tourette Syndrome; Cortico-Basal Ganglia Networks; Structural Connectivity; Tractography

Investigators from Centre de Reference National Maladie Rare 'Syndrome Gilles de la Tourette' and Sorbonne University report white matter abnormalities in the pathways connecting the cerebral cortex, basal ganglia, and thalamus in a group of 49 adults with Tourette syndrome (TS). High-resolution diffusion tensor imaging and fractional anisotropy probabilistic techniques were utilized to examine the connectivity of white matter tracts in the cortico-striato-pallido-thalamo-cortico (CSPTC) networks. Patients with TS had white matter abnormalities in neuronal pathways connecting the striatum, basal ganglia, and thalamus to the cerebral cortex, including the primary motor cortex, primary somatosensory cortex, and supplementary motor area. The reported enhanced connectivity of the motor cortex was positively associated with increased motor tic severity, regardless of medication, age, or gender. The cortico-striatal pathways showed elevated fractional anisotropy and diminished radial diffusivity, suggesting microstructural abnormalities in the white matter tracts. Authors reported that these abnormal connections were predominantly observed in females when compared to males. [1]

COMMENTARY. The mechanism of TS is complex and not fully understood. Neuro-pathological, electrophysiological, and functional neuroimaging studies have led to increased knowledge in understanding the dysfunctional neuronal processing of CSPTC networks in TS. Recent advances in diffusion tensor imaging (DTI) enhanced our ability to investigate white matter structures and tracts in the basal ganglia. Prior research using DTI showed abnormalities in the white matter tracts of the somatosensory, fronto-striatal and motor pathways in TS [2, 3]. Alterations in the microstructure of white matter tracts have also been described in adults and adolescents with TS, specifically reduced white matter connectivity in the corpus callosum. This reduction in white matter microstructure was associated with reductions in tic severity [4-6]. The current study adds important information to this body of literature. The authors showed enhanced connectivity in the CSPTC white matter pathways of the motor cortex that was positively associated with increased motor tic severity. Additionally, authors reported that these abnormal connections were predominantly in females. These data may suggest that women with TS are less likely to have resolution of their tics in adulthood when compared to men. Interestingly, Lichter et al. reported that women with TS tend to have more disruption in function from their tics when compared to men [7]. It may be that the increased connectivity in the CSPTC pathways in women with Tourette syndrome contributes to their reported increased tic burden. In light of new technology, future DTI studies could further elucidate the pathophysiology and abnormal trajectory of white matter tracts in adults and adolescents with TS and how it relates to tic severity.

Disclosures

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

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SEIZURE DISORDERS

KCNA2-Related Epileptic Encephalopathy

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Related Article: Syrbe S, Hedrich UB, Riesch E, Djemie T, Muller S, Moller RS, et al. De novo loss- or gain-of-function mutations in KCNA2 cause epileptic encephalopathy. Nat Genet. 2015;9(10).
Keywords: KCNA2; Dominant-Negative Effect; Epilepsy

Investigators from the University Leipzig and University of Tübingen report mutations of *KCNA2* as a novel cause of epileptic encephalopathy. They identified four de novo mutations in *KCNA2* in six unrelated patients using next generation sequencing.

Four individuals had *KCNA2* mutations that resulted in dominant-negative loss of protein function. Seizure onset was at 8-17 months. EEG became abnormal with multifocal epileptiform discharges. All had delayed speech development and mild to moderate intellectual disability. All became seizure free between 4-15 years of age. Two additional individuals presented with a more severe epileptic encephalopathy phenotype. They had an earlier age of onset, pharmacoresistant seizures, generalized epileptiform discharges with background slowing on EEG, moderate to severe intellectual disability, and moderate to severe ataxia. *KCNA2* mutations associated with the more severe phenotype resulted in pronounced gain-of-function effects. [1]

COMMENTARY. *KCNA2* joins a growing list of voltage-gated potassium channel genes associated with epileptic encephalopathy, including *KCNQ2*, *KCNQ3*, *KCNT1* and *KCNB1* [1-4]. *KCNA2* encodes $K_V1.2$, a voltage-gated potassium channel subunit that contributes to repolarization of the neuronal membrane following an action potential. Mutations in *KCNA2* that interfere with normal Kv1.2 function result in impaired electrical signaling and altered membrane excitability. Loss-of-function mutations are predicted to impair membrane repolarization, resulting in neuronal hyperexcitability and a propensity for repetitive firing. Consistent with this, complete absence of $K_V1.2$ in homozygous mice resulted in spontaneous seizures and premature death, and heterozygous deletion resulted in increased seizure susceptibility [5]. Mutations were also identified that exhibited gain-of-function effects [1]. At the level of a single neuron, the observed effects predict $K_V1.2$ channels that are open at resting membrane potentials, resulting in neuronal hypoexcitability. However, based on the more severe phenotype of the patients, the net effect within neuronal networks is hyperexcitability. Additional studies will be required to determine the effect of *KCNA2* mutations at the level of the network.

Thus far, the phenotypes associated with *KCNA2* mutations comprise two distinct groups based on age of onset, seizure semiology, and electroclinical features. These distinctive clinical phenotypes appear to correlate with differential effects of the mutations on protein function [1]. Patients with gain-of-function mutations have a more severe phenotype and do not achieve seizure freedom. In contrast, patients with loss-of-function mutations have later seizure onset, and achieve seizure freedom in childhood. This nascent genotype-phenotype correlation is reminiscent of *KCNQ2*-associated epileptic encephalopathy, where loss-of-function mutations are associated with neonatal onset, while gain-of-function mutations are associated with infantile onset [3,6]. Studies with *KCNA2* mutations from additional patients will be required to confirm the genotype-phenotype relationship. If the relationship holds, it will be useful for predicting disease progression and guiding management.

Disclosures

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

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SEIZURE DISORDERS

[Not Quite] The Ketogenic Diet in a Pill

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Related Article: Sada N, Lee S, Katsu T, Otsuki T, Inoue T. Epilepsy treatment. Targeting LDH enzymes with a stiripentol analog to treat epilepsy. Science. 2015;347(6228):1362-7.
Keywords: Lactate Dehydrogenase; Epilepsy; Stiripentol; Ketogenic Diet

Researchers at Okayama University, Japan showed lactate dehydrogenase (LDH) inhibition suppresses neuronal excitation in vitro, reduces EEG discharges and seizures in rodent models, and may provide a novel mechanism for anticonvulsant medications in human patients. Using basal ganglia brain slices to investigate the mechanism of the ketogenic diet (KD), they found neurons became hyperpolarized not from the ketone bodies per se, but from the reduced glucose concentration that accompany the switch to ketone bodies-based cerebral metabolism. Then through a series of experiments, they pinpointed pyruvate and oxaloacetate as the specific molecules that affect the K-ATP channel and membrane potential: less glucose leads to less pyruvate and oxaloacetate, which opens the K-ATP channels and hyperpolarizes the neurons. In vitro they reproduced this ketone bodies-induced neuronal suppression by inhibiting LDH, the enzyme that reversibly converts lactate to pyruvate. The researchers also inhibited LDH in vivo to reduce seizures and EEG paroxysmal discharges in pilocarpine and kainate rodent models. They then screened 20 current anticonvulsants and found that stiripentol alone had significant LDH inhibitor action. Lastly, they showed that isosafrole, a stiripentol analog and a more potent LDH inhibitor, had anticonvulsant activity and was well tolerated in rodent models. [1]

COMMENTARY. The authors report two important new findings: (1) the neuronal inhibition associated with the KD correlate with reduced pyruvate and oxaloacetate levels, and (2) LDH inhibitors that lower pyruvate and oxaloacetate levels work as anticonvulsants in vitro and in vivo models. Despite this shared mechanism, KD and LDH inhibitors have an important difference: LDH inhibitors do not provide an alternative fuel to make up for the lost pyruvate and oxaloacetate. LDH inhibition, therefore, may be more akin to selective fasting than the ketogenic diet. It's easier to imagine using LDH inhibitors to enhance the action of the ketogenic diet than to replace it. Either way, LDH inhibitors now join 2-deoxy-D-glucose [2] as potential compounds that inhibit seizures by altering cerebral metabolism.

Many hypotheses have been proposed for the anticonvulsant mechanism of the ketogenic diet. They include changes in the water and electrolyte balance, changes in cerebral energy reserve, direct anticonvulsant effects of ketone bodies and fatty acids, and indirect action by increasing GABA/glutamate ratio [3-5]. The novel mechanism proposed in this paper integrates three appealing ideas in neuroscience: (1) astrocytes providing energy to neurons via the lactate shuttle, (2) K-ATP channel functioning as a molecular link between cerebral metabolism and electrical activity, and (3) basal ganglia (subthalamic nucleus and substantia nigra pars reticulata) playing a key role in the propagation and termination of seizures [6-8].

Disclosures

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

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SEIZURE DISORDERS

Diurnal and Seasonal Occurrence of Febrile Seizures

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Related Article: Mikkonen K, Uhari M, Pokka T, Rantala H. Diurnal and seasonal occurrence of febrile seizures. Pediatr Neurol. 2015;52(4):424-7.
Keywords: Children; Daylight; Diurnal Variation; Febrile Seizure; Melatonin; Seasonal Variation

Investigators from University of Oulu, Finland, evaluated the diurnal and seasonal occurrence of the first febrile seizures (FS) in 461 children in a population-based study of 1522 children. The first FS occurred most often in the evening, peaking between 6 and 10 PM (31%), and least often at night, in the early morning hours between 2 and 6 AM (8%) (P<0.001). This diurnal pattern was repeated in different seasons according to the variance in daylight duration. FS occurred irregularly throughout the year, most frequently in the winter, concurrently with the febrile episodes, and least frequently in the summer. The diurnal and seasonal variations in the occurrence of FS did not follow the amount of daylight throughout the day or year or variation in the secretion of melatonin. Rather, FS are strongly associated with episodes of fever, infections, and elevated body temperature. The maximum temperature of the fever in patients with FS (mean 39.7 °C, range 37.6-42.0 °C) was similar throughout the year. [1]

COMMENTARY. The seasonal and diurnal variations in the occurrence of febrile seizures (FS) observed in children in Finland [1] are reported also in Japanese [2] and in US children [3]. The frequency of FS is highest in the winter and lowest in summer months in all 3 geographic areas, and approximately 5 times greater in the evening than in early morning [2]. FS propensity is not related to circadian rhythm or amount of daylight but rather to the elevation in temperature. The maximum occurrence of FS at 4.00 pm, and the minimum, at 4 am, is similar to the pattern of human body temperature [2]. The elevation in temperature is usually associated with a viral infection, especially human herpesvirus-6 [4].

Several factors may be involved in the cause of FS, including age dependency (3 months to 5 years; maximum 12-18 months), genetic susceptibility (family history, autosomal dominant with reduced penetrance, or multifactorial), cytokine and immune response to infection, fever and height of body temperature. The maximum height of a fever, not the rate of rise, is the main determinant of risk of FSs, a finding demonstrated in animals [5] and confirmed in clinical studies [6,7]. In a study of 110 children with febrile seizures, the difference between temperature recordings associated with and those without FS was highly significant (P<0.001). Seizures occurred when the degree of fever reached or surpassed the threshold convulsive temperature for each patient [6].

Disclosures

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

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HEADACHE DISORDERS

Blunt Head Trauma and Headache

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Related Article: Dayan PS, Holmes JF, Hoyle J, Jr., Atabaki S, Tunik MG, Lichenstein R, et al. Headache in traumatic brain injuries from blunt head trauma. Pediatrics. 2015;135(3):504-12.
Keywords: Blunt Head Trauma; Headache; Traumatic Brain Injury

Investigators from New York Presbyterian Morgan Stanley Children's Hospital examined whether having an isolated headache following minor blunt head trauma was suggestive of traumatic brain injury (TBI) among a large cohort of children 2-18 years of age [1]. This was a secondary analysis of data from a prospective observational multi-center cohort study from PECARN (Pediatric Emergency Care Applied Research Network). One group had an "extensive isolated" headache defined by GCS > 15 without loss of consciousness, altered mental status, signs of a basilar fracture, palpable skull fracture, vomiting, seizure, amnesia, scalp hematoma, or neurologic deficits. PECARN isolated headache was a second group [2]. Of 12, 567 children with headaches, 2,462 (19.6%) met the "extensive isolated" definition. CT scans were obtained on 52% of patients with headaches in general and in 18.5% of patients with isolated headache-extensive type. Clinically important TBI (ciTBI) occurred in none of the patients with isolated headaches and in 1.6% patients with non-isolated headaches at presentation. Three of 456 (0.7%) children with isolated headaches – extensive type had TBIs on head CT compared to 4.5% children with non-isolated headaches. After authors adjusted for mechanism of injury, children with isolated headaches–extensive type had significantly lower odds of TBI on CT compared to children with non-isolated headaches at presentation. One patient with PECARN isolated headache needed neurosurgery; however the child also had a temporal/parietal scalp hematoma on exam in addition to a severe headache. Severity, location, or timing of the headache was not found to correlate with ciTBI or TBI. Authors suggest that isolated headache following minor blunt head trauma is not suggestive of TBI in most children when no other symptoms are present. [1]

COMMENTARY. Head trauma in children results in 600,000 emergency room visits per year. The decision to obtain a CT must be balanced against its associated risks. Radiation from CT scans can cause malignancy in children and the risk has an inverse relationship with age. The PECARN prediction rules identified children at very low risk of ciTBI after blunt head trauma for whom CT scans might be avoided. Several studies report that less than 10% of CT scans show TBIs in children with minor head trauma [2,3]. Additionally, in children with GCS scores >14, neurosurgical intervention is rarely needed [4]. Headache is a common complaint following head trauma [2-4]. Pandor et al. performed a meta-analysis on the presence of headache in children and adults. They found that the presence of a headache following minor head trauma, regardless of other symptoms was not associated with an increased overall risk of intracranial hemorrhage on CT; however, when headache was severe or persistent and accompanied other signs of TBI, it did modestly increase the risk of neurosurgery [5]. Headache alone in the PECARN study with no other symptoms had a 0.5% of TBI. The current study added to this knowledge by showing that no children had ciTBI following mild blunt head trauma. Further, TBIs on CT scans are very uncommon when isolated headache is the only symptom. The authors strongly suggest that CTs are not indicated in most children with isolated headache following minor blunt head trauma.

Disclosures

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

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NEUROMUSCULAR DISORDERS

Congenital Insensitivity to Pain (HSNA type IV)

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Related Article: Norcliffe-Kaufmann L, Katz SD, Axelrod F, Kaufmann H. Norepinephrine deficiency with normal blood pressure control in congenital insensitivity to pain with anhidrosis. Ann Neurol. 2015;77(5):743-52.
Keywords: Congenital; Pain; Norepinephrine; Anhidrosis

Investigators from New York University, NY, studied 14 patients with congenital insensitivity to pain with anhidrosis (CIPA), compared to 10 patients with chronically deficient sympathetic activity (pure autonomic failure), and 15 normal age-matched controls. In all patients with CIPA, plasma norepinephrine levels were very low or undetectable and failed to increase in the upright posture despite normal blood pressure. Plasma epinephrine levels were normal and increased when patient was upright. Plasma renin activity also increased appropriately with upright posture. Patients with pure autonomic failure also had very low levels of plasma norepinephrine both supine and when upright, but in contrast to patients with CIPA failed to maintain blood pressure upright.

In CIPA, postganglionic sympathetic neurons are severely depleted, but adrenal medulla chromaffin cells are spared. It is postulated that in the congenital absence of norepinephrine, adrenal epinephrine "takes over" sympathetic neurovascular signaling to increase peripheral vascular resistance and maintain blood pressure. CIPA is inherited as autosomal recessive with mutations in the gene TRKA forming part of the receptor for nerve growth factor (NGF). In skin biopsies of patients with CIPA sweat glands are preserved but lack sympathetic cholinergic innervation, explaining the anhidrosis. [1]

COMMENTARY. Congenital insensitivity to pain with anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy (HSAN) type IV, presents in infancy with oral self-mutilation and burns, sometimes mistaken for child abuse [2]. Other features include multiple bone fractures and musculoskeletal complications, scars, osteomyelitis, joint deformities, ocular complications, and hyperpyrexia. Mental retardation and behavior problems are common. Although considered rare, in Japan this disorder has warranted the formation of a Research Group on CIPA and HSAN types IV and V, with publication of Guidelines of Total Management and Care for CIP [3]. Both types IV and V are characterized by CIP whereas type IV is also complicated by anhidrosis and intellectual disability.

The neurotrophin nerve growth factor (NGF) is essential for the development of sensory neurons and pain perception. A homozygous missense mutation in the NGF gene has been identified in HSAN IV and V patients. Genetic studies of these disorders should unravel the mechanism of CIP [4]. In a reference cited by Adams and Victor, the autopsy of a patient who died at age 12 years showed absence of small neurons in dorsal root ganglia, absence of Lissauer tracts and descending spinal tracts of trigeminal nerves, and preserved skin sweat glands but lacking innervation [5].

Disclosures

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

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INFECTIOUS/AUTOIMMUNE DISORDERS

Clinical Features of Infectious and Autoantibody Encephalitis

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Related Article: Pillai SC, Hacohen Y, Tantsis E, Prelog K, Merheb V, Kesson A, et al. Infectious and Autoantibody-Associated Encephalitis: Clinical Features and Long-term Outcome. Pediatrics. 2015;135(4):e974-84.
Keywords: MRI; Autoantibody; Encephalitis; Infection; Outcome

Investigators from University of Sydney, Australia; John Radcliffe Hospital, Oxford, UK; Imperial College, London, UK; and other centers, studied infectious, immune-mediated/autoantibody associated and unknown forms of encephalitis, including frequencies, clinical and radiological phenotypes, and long-term outcome. In a retrospective single-center cohort of 164 Australian children, an infectious encephalitis occurred in 30%, infection-associated encephalopathy in 8%, immune-mediated/autoantibody-associated encephalitis in 34%, and unknown encephalitis in 28%. An etiology was proposed in 118 (72%) patients, of whom 64 (39%) were confirmed, 29 (18%) probable, and 25 (15%) possible. In order of decreasing frequency, subgroups included acute disseminated encephalomyelitis (21%), enterovirus (12%), *Mycoplasma pneumoniae* (7%), N-methyl-D-aspartate receptor antibody (6%), herpes simplex virus (5%), and voltage-gated potassium channel complex antibody (4%). Movement disorders, psychiatric symptoms, agitation, speech dysfunction, CSF oligoclonal bands, MRI limbic encephalitis, and clinical relapse were more common in patients with autoantibodies. Age at presentation was a mean of 5.5 years (range 5 weeks-15.1 years), and 94 (57%) were male. The majority (35%) presented during the Australian winter season. Clinical features were fever (77%), seizures (54%), headache (43%), weakness (37%), agitation (34%), CSF pleocytosis (71%). EEG slowing occurred in 85%, and epileptiform discharges in 21%. Outcome was abnormal in 49% patients, after a median follow-up of 5.8 years. Herpes simplex virus and unknown forms had the worst outcomes. An abnormal outcome was more common in patients with status epilepticus, MR diffusion restriction, and ICU admission. Recognition and treatment of the relatively common immune-mediated/autoantibody-associated cases of encephalitis should be a clinical priority. [1]

COMMENTARY. In this study, using the Granerod classification [2], encephalitis was defined as an acute encephalopathy with >-2 of the following: fever >38 °C, seizures or focal neurologic signs, CSF pleocytosis (>5wbc/uL) or elevated CSF neopterin (>30nmol/L), and EEG slowing or abnormal MRI. Confirmed diagnosis had the organism or autoantibody detected in CSF or brain. A probable diagnosis had serological evidence of acute infection or autoantibody, and a possible diagnosis was based on detection of the organism from stool or nasopharynx. The term infection-associated encephalopathy rather than encephalitis was used for encephalitis related to influenza virus or rotavirus. Encephalopathy is defined as an altered or reduced level of consciousness and change in personality or behavior or confusion lasting >24 hours [3].
In the UK, the Aetiology of Encephalitis Study Group [4] made a diagnosis by first-line laboratory testing in 111 (55%) of 203 patients. HSV was detected in 19%, varicella-zoster virus in 5%, and *Mycobacterium tuberculosis* was identified in 5%. Sixteen (8%) samples showed either N-methyl-d-aspartate receptor or voltage-gated potassium channel complex antibodies. An etiological diagnosis was not determined in one-third of cases, a similar frequency to that found in Australia.

Disclosures

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

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