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SEIZURE DISORDERS

Todd Paralysis in Rolandic Epilepsy

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Related Article: Dai AI, Demiryurek S. The Clinical Implications of Todd Paralysis in Children with Benign Rolandic Epilepsy. J Child Neurol. 2015 Jun 9. [Epub ahead of print]
Keywords: Post-Ictal Paresis; Rolandic Epilepsy; Migraine

Investigators from University of Gaziantep, Turkey described the clinical and EEG findings of patients with benign epilepsy of childhood with centrotemporal spikes (BECTS) experiencing postictal Todd paralysis. The study was conducted at the Division of Pediatric Neurology, Gaziantep University. The authors investigated a total of 108 BECTS children, aged 2-16 years, between 2011 and 2014. Detailed information regarding patient's clinical manifestations, seizure duration, and postictal features were collected. A 125-item questionnaire including diagnostic criteria from the International Classification of Headache Disorders, 2nd edition, was administered.

Overall, 12 patients (11% of the total) experienced postictal transient motor deficits, i.e., Todd paralysis. There were 6 boys and 6 girls, with average age of 8.08 years. Statistical analysis failed to find any difference between children with or without postictal paralysis, including seizure semiology or duration and EEG findings.

In the large majority of the patients (11 out of 12) Todd paralysis occurred only once in their life and followed a focal motor seizure involving predominantly the upper extremity and the face. There was significant difference ($p < .0001$) in the incidence of migraine in patients who did not have Todd paralysis (13/96, 13.5%) compared to patients who experienced Todd paralysis (10/12, 83.3%).
All migraine patients were successfully treated with anticonvulsants, usually carbamazepine or levetiracetam. [1]

COMMENTARY. BECTS is one of the most frequent epileptic syndromes in children [2]. Migraine is strongly comorbid in RE. Prevalence of migraine in BECTS probands is 15% versus 7% in nonepilepsy probands, and in siblings of RE probands prevalence was 14% versus 4% in nonepilepsy siblings [3], suggesting shared susceptibility to migraine and rolandic epilepsy that is not directly mediated by epileptic seizures. In addition, epilepsy and migraine frequently show a clinical overlap and children with migraine frequently show EEG abnormalities, including rolandic discharges [4]. Moreover, migraine is commonly associated with other epilepsy syndromes, including other forms of idiopathic childhood epilepsies, e.g., Panayiotopoulos syndrome [2]. Despite the fact that migraine and epilepsy are clearly distinct disorders, it has been suggested that they could share some pathophysiologic mechanisms and clinical manifestations. Furthermore, it is likely that any of triggering factors, irrespective of their nature (genetically determined or not), could potentially lead to a paroxysmal and transient cortical excitability change leading to prolonged neuronal depolarization (seizure) or spreading depression (migraine) [5].

In summary, the present study confirms that there is a comorbidity of migraine and rolandic epilepsy and those children who experience postictal Todd paralysis are more likely to have migraine [1]. The reasons for this finding are unclear. Nevertheless, the awareness of this post-ictal phenomenon and its spontaneous resolution within hours from the onset is crucial in the paediatric setting as early diagnosis may prevent unneeded hospitalization and further investigations, as well as helping to reduce parents' concerns.

Disclosures

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

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SEIZURE DISORDERS

Neuropsychological Effects of Anticonvulsants

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Related Article: Jung E, Yu R, Yoon JR, Eun BL, Kwon SH, Lee YJ et al. Neuropsychological effects of levetiracetam and carbamazepine in children with focal epilepsy. Neurology 2015 Jun;84(23):2312–2319.
Keywords: Levetiracetam; Carbamazepine; Epilepsy; Cognitive Effects; Neuropsychological

Investigators from 7 centers in Korea conducted a prospective, multicenter study with patients randomized into two open-label, parallel groups and treated with either levetiracetam (LVT) or carbamazepine (CBZ) monotherapy for newly diagnosed focal epilepsy. The study's primary goal was evaluation of the neuropsychological effects of levetiracetam in comparison with carbamazepine, as well as, secondarily, the medications' respective efficacy and tolerability. Neither group experienced a worsening of general intellectual abilities. Both medications were effective in controlling seizures. There was a trend toward more frequent adverse events in CBZ patients compared to LVT. Nevertheless, the authors recommended LVT monotherapy for newly diagnosed focal epilepsy due to larger number of patients discontinuing treatment of CBZ due to adverse events, perceived poor efficacy of CBZ, and other miscellaneous reasons. [1]

COMMENTARY. In clinical practice, it is well known that children with epilepsy are at risk for cognitive, behavioral, and emotional problems. Berg et al. demonstrated that 26.4% of children have evidence of subnormal cognitive function when first diagnosed with epilepsy, with independent risk factors including: age at onset <5 years, symptomatic etiology, epileptic encephalopathy, and current AED treatment [2]. Significantly more children with seizures (11.3%) than siblings (4.6%) have behavior problems over time; however, differences diminish as seizures come under better control [3]. One third of children with epilepsy were found to have mood disorders by Caplan et al., making them 5 times more likely to do so than healthy peers [4]. The independent effect of any single AED on cognition, behavior, or emotion, however, is challenging to study for numerous reasons. Most importantly, prolonged administration of AEDs cannot be tested on normal subjects; AEDs can theoretically produce different cognitive effects in different epilepsy syndromes and in children at different ages; recent seizures as well as drug dosages and levels modulate cognitive performance [5]. Selecting an appropriately precise series of targets for cognitive testing on can be cumbersome. While IQ provides an interesting global measure, it obfuscates the study of specific cognitive processes, such as processing speed or attention [5]. Lastly, it is difficult to construct a study sufficiently powered to show unambiguous negative or positive effects of an AED. The current study falls just below its own threshold of 42 subjects per group to provide 80% power with a 5%, 2-tailed level of significance. The cognitive side effects of many AEDs have been tested previously, with phenobarbital and topiramate well known to have adverse effects. In a prior study of adult epilepsy patients, CBZ and LVT were compared using 11 neuropsychological tests evaluating attention and memory. Across all variables tested, the effects of CBZ were worse than LVT. Both performed worse than non-drug patients: in 76% of variables for CBZ and 12% of variables for LVT [6]. These results are comparable to the current study in a pediatric population [1]. Overall, a multiplicity of interrelated factors contributes to cognitive, behavioral, and emotional problems in children with epilepsy, but seizure control and proper medication choice can mitigate these risks.

Disclosures

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

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CNS MALFORMATIONS

PI3K/AKT Pathway and Brain Malformations

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Related Article: Jansen LA, Mirzaa GM, Ishak GE, O'Roak BJ, Hiatt JB, Roden WH et al. PI3K/AKT pathway mutations cause a spectrum of brain malformations from megalencephaly to focal cortical dysplasia. Brain 2015 Jun;138(Pt 6):1613–1628.
Keywords: PI3K/AKT mutations; Cortical dysplasia; Megalencephaly

Investigators from Seattle Children's Research Institute, University of Washington, and collaborating institutions sought to evaluate 10 genes in the PI3K/AKT pathway as it relates epileptogenic brain malformations in patients with megalencephaly, hemimegalencephaly, and focal cortical dysplasia [1]. Malformations of cortical development (MCD) are common causes of intractable pediatric epilepsy and are usually diagnosed clinically, aided by imaging; however final classification is done by routine histopathology using the ILAE consensus classification [2].

They collected epileptic tissue specimens from 33 children with intractable epilepsy due to hemimegalencephaly (HMEG) and focal cortical dysplasia (FCD). Only peripheral blood was available from 1 child with bilateral HMEG. Of the 34 children, one had bilateral HMEG, and the rest had unilateral lesions (16 males, 18 females). 6 lesions were classified as HMEG; 27 as FCD (5 type I, 13 type IIa, 6 type IIb, and 3 type IIId). Of the 34 children, pathogenic mutations were found in 5 (including the bilateral HMEG patient): (1) PIK3CA mutation in the bilateral HMEG, (2) PIK3CA mutation in HMEG with linear epidermal nevus, (3) PIK3CA mutation in a localized FCD IIa, (4) AKT3 mutation in HMEG with cutaneous vascular malformations and unilateral ocular enlargement, and (5) germline PTEN mutation with HMEG. PI3K/AKT pathway activation as examined by western blot analysis showed an increase in phosphorylated AKT activity in the majority of HMEG and FCD tissue specimens. The downstream immunohistochemical marker for mTOR (phospho-S6) was positive in dysmorphic neurons. [1]

COMMENTARY. It makes intuitive sense that disruption of the mTOR (mammalian target of rapamycin) pathway may result in a continuum of changes ranging from cortical dysplasia to megalencephaly, however how many epileptogenic foci are truly caused by mutations? The mTOR pathway is influenced by numerous cell signals (insulin, growth factors, stress) and the principle pathway exerting influence is PI3K/AKT. As AKT phosphorylates mTOR directly, dysregulation of the mTOR pathway can result in abnormal cortical brain development as seen in patients with Tuberous Sclerosis. In addition, from the previous work of Riviere [3] we know that PI3K-AKT signaling plays an important role in vascular, limb and brain development; moreover, megalencephaly-associated mutations result in higher PI3K activity and PI3K-mTOR signaling. This was confirmed here.

In isolation, the individual findings are interesting, however when combined, the data suggests a shared pathogenesis for malformations of cortical development. At least for now, those institutions who receive such pathology specimens should utilize a biobank/biorepository. As the authors point out, more cases of HMEG will likely have alterations in the PI3K/AKT/mTOR pathway as compared to FCD. Most of the cases we see in clinical practice at our institution are FCD IIa. Only 1 case of FCD IIa in the current series was remarkable for a mutation in PIK3CA. Therefore, it is possible that other genes/growth factors are influencing the pathways that are outside the immediate realm of the PI3K/AKT/mTOR. Of note, no mutations were seen in the FCD I and FCD IIb cohort of specimens.

While our immediate practice will not be altered by the investigations of Jansen and colleagues, targeted testing of the PI3K/AKT pathway may disclose the etiology of epileptic lesions in patients with cortical dysplasia associated with other cutaneous lesions.

Disclosures

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

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DEMYELINATING DISORDERS

Relation of Posterior Cerebellar Volume to Cognition in MS

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Keywords: Cerebellum; Cognition; Multiple Sclerosis; Pediatric; Volumetric MRI

Investigators from the Montreal Neurological Institute, York University, Universities of Toronto and McGill, Canada, and University of Pennsylvania, studied the relationship between cerebellar pathology and cognitive function in adolescent and pediatric-onset multiple sclerosis (MS). Twenty-eight pediatric-onset relapsing remitting MS patients (21 girls, mean age 16.2 years; mean disease duration 4.3 years) were compared to 33 age- and sex-matched healthy controls. Participants underwent structural MRI and neuropsychological evaluation to assess intelligence, attention, processing speed, language visuo-motor integration, and fine motor dexterity. Associations between cognitive outcomes and cerebellar volume, independent of cerebral volume were examined.

Cognitive and motor performance of the MS group was reduced relative to controls ($p<0.003$). Cerebellar volumes did not differ between groups, but cerebellar posterior lobe volume and infratentorial lesion volume were correlated with extra variance on measures of information processing ($p=0.02$) and vocabulary ($p=0.04$) in patients, but not in controls. The investigators conclude that smaller cerebellar posterior lobe volume, a known region for cognitive processing and increased lesion burden in the posterior fossa, adversely impact cognitive function, an important functional consequence of MS onset during childhood. [1]

COMMENTARY. The cerebellum is involved in cognitive and affective processes in addition to motor function. Cerebellar motor and cognitive dysfunction occur in parallel early in the onset of MS. This association is well documented in adult MS but is less recognized in children with MS, highlighting differences between pediatric and adult cases. Language is particularly vulnerable in pediatric MS, unlike in adults in whom it is usually preserved. Deficits in executive functions considered MS-specific in adults, have been inconsistently reported in children. Data on the correlations of cognitive impairments with clinical and neuroimaging are scarce in children, and the results are often incongruent. Involvement of the corpus callosum and reduced thalamic volume differentiate patients with cognitive impairment from those without. [2]. Cerebellar posterior lobe volume and infratentorial lesion volume account for extra variance on measures of information processing and vocabulary in patients but not in controls. In a further study of the relation between cerebellar MS atrophy and cognitive dysfunction, patients with cerebellar dysfunction performed worse in cognitive tests than controls [3].

Disclosures

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

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NEURODEVELOPMENTAL DISORDERS

Head Circumference and Neurocognitive Outcomes

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Related Article: Wright CM, Emond A. Head growth and neurocognitive outcomes. Pediatrics 2015 Jun;135(6):e1393–e1398.
Keywords: Head Circumference; Wechsler Intelligence Scale for Children; Neurocognitive Disorders

Investigators from Universities of Glasgow and Bristol, UK, determined the value of head circumference (HC) as a screening measure, the incidence of head centile shifting, and the relationship between extremes of head size and later neurodevelopmental problems. Data were obtained from the Avon Longitudinal Study of Parents and Children (ALSPAC), an ongoing prospective population-based study investigating the health and development of children in southwest England. There were 10,851 children with >2 HC measurements. HC was measured routinely at 2, 9, and 18 or 24 months and by researchers at ages 4, 8, 12, and 18 months. At each age, 2% to 3% of children had scores that were <-2 or >2 SDs below or above the mean. More than 15% children showed centile shifts, but less than one-third of these were sustained at subsequent measurements. Only 0.5% showed a sustained shift beyond the normal range. The WISC was used to measure IQ in research clinics at age 8 years for all. Neurocognitive disorders (NCDs) were identified from chart revue. Children with consistently small heads were up to 7 times more likely to have an NCD, but 85% of children with small heads had no NCD, and 93% of children with NCDs had head SD scores within the normal range.

HC centile shifts within the normal range are common and appear to reflect measurement error. Extreme head size is neither specific nor sensitive for detecting NCDs. Routine measurement of HC is unhelpful as a screening test or predictor of later developmental problems. [1]

COMMENTARY. Measurement of head circumference (HC) in children is prone to error for many reasons, including inexperience of the operator, lack of patient cooperation, and variability in hair growth and volume. The importance of the HC measurement as part of the neurologic examination warrants the personal attention of the neurologist. Technical errors excluded, a change from a normal baseline measurement at birth and 3-5 days to a microcephalic reading (<2nd percentile) or macrocephaly (>98th percentile) at 1 – 6 months would indicate a change necessitating neuroimaging: CT scan or MRI.

Microcephaly presents as primary or acquired [2]. Causes of primary microcephaly include autosomal dominant and autosomal recessive genetic disorders: trisomy 13, 18, and 21; Cornelia de Lange syndrome, Smith-Lemli-Opitz syndrome, and Rett syndrome, and hypothyroidism. Acquired microcephaly is characterized by a normal HC at birth, followed by microcephalic measurements in subsequent months or years, usually due to lack of brain development or growth. Causes of acquired microcephaly include sequelae from stroke, meningitis, encephalitis, toxoplasmosis, rubella, cytomegalovirus, and herpes; in utero teratogen exposure, and hypoxic-ischemic encephalopathy.

Macrocephaly, diagnosed by routine HC measurements during the first 10 months of life, is explained chiefly by hydrocephalus or cysts. A nationwide study of medical records of all Norwegian children <5 years of age hospitalized for intracranial expansion during a 4-year period found hydrocephalus was the primary diagnosis, affecting 173 (58%) of 298 patients; 57 (19%) had intracranial tumors and 68 (23%) had cysts and other primary diagnoses. Increased HC is important mainly in detecting hydrocephalus and cysts, especially in the first 10 months of life [3]. According to Wright et al [1], routine measurement of HC throughout infancy and early childhood is indicated only when an early measurement is outside +2 SDs. The recommendation of HC measurements routinely from birth to 24 months of age should be reconsidered.

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PERIPHERAL NEUROPATHIES

Risk of Neuropathy with Celiac Disease

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Related Article: Thawani SP, Brannagan TH 3rd, Lebwohl B, Green PH, Ludvigsson JF. Risk of Neuropathy Among 28 232 Patients With Biopsy-Verified Celiac Disease. JAMA Neurol 2015 Jul;72(7):806–811.
Keywords: Neuropathy; Celiac Disease; Electroencephalogram

Investigators from Columbia University College of Physicians and Surgeons, New York, Karolinska Institutet, Stockholm, and Orebro University, Sweden, examined the risk of developing neuropathy in a nationwide population-based sample of 28,232 patients with biopsy-verified celiac disease (CD). Data were obtained from small-intestinal biopsies performed at Sweden's 28 pathology departments between June 1969 and February 2008. Risk of neuropathy in CD patients was compared with that of 139,473 age and sex-matched controls. Most study participants were females (61.7%), and 11,763 (41.7%) patients with CD were diagnosed in childhood. Median age of diagnosis was 29 years (range 0-95 years). Patients were followed for a median of 10 years. During follow-up, 198 patients with CD and later diagnosis of neuropathy (0.7%) were identified vs 359 controls (0.3%) with later diagnosis of neuropathy. CD was associated with a 2.5-fold increased risk of later neuropathy (P<.001). Also, risk was increased for chronic inflammatory demyelinating neuropathy (P=.001), autonomic neuropathy (P=.009), and mononeuritis multiplex (P=.006), but not for acute inflammatory demyelinating polyneuropathy (P=.68). Adjusting for educational level, diabetes, autoimmune thyroid disease, and vitamin deficiencies had only a marginal effect on risk estimate. Age and gender did not influence the risk of neuropathy in patients with CD, but risk was highest in the first year after diagnosis of CD. The increased risk for neuropathy was observed both before and after diagnosis of CD. CD screening is recommended in patients with neuropathy. [1]

COMMENTARY. Celiac disease, a common genetically-based food intolerance, may appear at any age and may be manifested by extra-intestinal as well as gastrointestinal symptoms. Diagnosis requires a high degree of suspicion, a screening test of serum autoantibody anti-tissue transglutaminase, confirmation by intestinal biopsy, and response to treatment with a strict gluten-free diet [2]. Neurological disorders that affect 10% of CD patients include ataxia, neuropathy, vestibular dysfunction, migraine and seizures. The epilepsy prevalence is 1% to 5%, and a gluten-free diet sometimes controls seizures with CD that are refractory to AEDs.

Investigators in Gaziantep, Turkey, have determined the frequency of epileptiform discharges in the EEGs of 307 children with CD and 197 age- and sex-matched controls. Of 25 patients with epileptiform discharges (spike/sharp wave discharges) 24 (7.8%) were in the CD group and 1 (0.5%) was in the control group. (P=0.001). Among the 24 with CD, 21 (9.7%) were in the newly diagnosed –untreated CD group and 3 (3.3%) were in a gluten-free diet group (P=0.03). Patients diagnosed with CD and having symptoms suggestive of seizures should be evaluated with an EEG; those with epileptiform discharges should follow strict adherence to a gluten-free diet that may decrease the risk of seizures [3].

Disclosures

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CNS NEOPLASMS

Posterior Reversible Encephalopathy Syndrome in ALL

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Related Article: Tang JH, Tian JM, Sheng M, Hu SY, Li Y, Zhang LY et al. Study of posterior reversible encephalopathy syndrome in children with acute lymphoblastic leukemia after induction chemotherapy. J Child Neurol 2015 Jun 9. [Epub ahead of print]
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Investigators from Soochow University, Suzhou, China, studied the possible pathogenetic mechanisms and treatment of posterior reversible encephalopathy syndrome (PRES) observed in 11 cases of pediatric acute lymphoblastic leukemia (ALL) after induction chemotherapy. The clinical symptoms of PRES disappeared after appropriate treatment in most cases, even though induction chemotherapy continued. During the 1-year follow-up, no recurrence of PRES was observed. PRES should be recognized as an important complication of ALL that is reversible when diagnosed and treated early. Of the 11 children, 7 were boys and 4 girls. They were reviewed at an average age of 8.5 years (range, 5-14 years old). During the ALL inductive treatment (VDLD), 4 patients (36%) had an increase in blood pressure. Intrathecal chemotherapy included methotrexate, cytosine arabinoside, and dexamethasone. During the chemotherapy period (days 7 to 30) patients developed acute brain dysfunction, manifested by headache (10/11), epileptic seizure (7/11), visual impairment (6/11), disturbed consciousness (5/11), and ambulatory instability (2/11). Seizures were generalized convulsive, lasting 1 to 4 minutes. The EEG was abnormal in 9/11 cases, showing diffuse slow waves, usually in the occipital, temporal, and parietal lobe. The EEG repeated 4 weeks later was normal in all except one case. MRI within 2 days of onset revealed multiple lesions, mainly in the occipital, parietal, and frontal lobes. Chemotherapy was discontinued and treatment with mannitol, captopril, and valproic acid started. All patient lesions in the MRI shrunk after 2 weeks, and clinical symptoms of PRES disappeared completely within 2 to 4 weeks. Improvement in MRI lesions occurred later than clinical improvement. During 1-year follow-up, all patients continued treatment with ALL chemotherapy, and no PRES symptoms were observed. [1]

COMMENTARY. Drugs used in VDLD (vincristine, daunorubicin, L-asparaginase, dexamethasone) chemotherapy and intrathecal therapy are likely risk factors for development of PRES in children treated for ALL., the onset in the present series occurring 7 to 30 days after VDLD therapy [1]. A previous report by Kim et al [2] analyzed predisposing factors of 19 pediatric ALL patients who developed PRES; they had all received induction chemotherapy. Many factors have been considered as causative of PRES. Hypertension and toxic effects of various drugs used in therapy are most plausible. Since most chemotherapy is polytherapy, the involvement of a single drug is difficult to determine. Methotrexate neurotoxicity was implicated in a 15-year-old female child with ALL who presented with status epilepticus after receiving intrathecal methotrexate [3]. MRI showed reversible cortical and subcortical high intensity lesions consistent with the diagnosis of PRES. Early diagnosis and treatment of PRES in ALL patients is essential for a favorable prognosis. The most common presenting features of this syndrome are sudden arterial hypertension, pre-eclampsia, uremia, and immunosuppressive drug treatment [4]. Seizures are also of common occurrence.

Disclosures

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

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