

# PEDIATRIC NEUROLOGY BRIEFS

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### VASCULAR DISORDERS

#### **Childhood Stroke Risk Associated with Congenital Heart Disease** 18

Laurence Ducharme-Crevier, MD and Mark S. Wainwright MD, PhD  
*Pediatr Neurol Briefs* 2015;29(3):18. <http://dx.doi.org/10.15844/pedneurbriefs-29-3-1>

### SEIZURE DISORDERS

#### **Prognosis with Incidental Rolandic Spikes** 19

Tracy S. Gertler, MD, PhD and Cynthia V. Stack, MD  
*Pediatr Neurol Briefs* 2015;29(3):19. <http://dx.doi.org/10.15844/pedneurbriefs-29-3-2>

#### **Continuous EEG in Critically Ill Children** 20

Jonathan E. Kurz, MD, PhD and Mark S. Wainwright MD, PhD  
*Pediatr Neurol Briefs* 2015;29(3):20. <http://dx.doi.org/10.15844/pedneurbriefs-29-3-3>

#### **Neuropsychological-EEG Activation in Genetic Generalized Epilepsy** 21

J. Gordon Millichap, MD and John J. Millichap, MD  
*Pediatr Neurol Briefs* 2015;29(3):21. <http://dx.doi.org/10.15844/pedneurbriefs-29-3-4>

### PERINATAL DISORDERS

#### **Gait Training and Ankle Dorsiflexors in Cerebral Palsy** 22

J. Gordon Millichap, MD  
*Pediatr Neurol Briefs* 2015;29(3):22. <http://dx.doi.org/10.15844/pedneurbriefs-29-3-5>

### HEADACHE DISORDERS

#### **Acute Treatment Regimens for Migraine in the ED** 23

J. Gordon Millichap, MD  
*Pediatr Neurol Briefs* 2015;29(3):23. <http://dx.doi.org/10.15844/pedneurbriefs-29-3-6>

### SLEEP DISORDERS

#### **Differential Diagnosis of Kleine-Levin Syndrome** 24

J. Gordon Millichap, MD  
*Pediatr Neurol Briefs* 2015;29(3):24. <http://dx.doi.org/10.15844/pedneurbriefs-29-3-7>

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**VASCULAR DISORDERS****Childhood Stroke and Congenital Heart Disease**Laurence Ducharme-Crevier, MD<sup>1,2</sup> and Mark S. Wainwright MD, PhD<sup>1,2\*</sup><sup>1</sup>Ruth D. & Ken M. Davee Pediatric Neurocritical Care Program, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL<sup>2</sup>Departments of Pediatrics and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL

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**Related Article:** Fox CK, Sidney S, Fullerton HJ. Community-based case-control study of childhood stroke risk associated with congenital heart disease. *Stroke*. 2015;46(2):336-40.**Keywords:** Epidemiology; Stroke; Pediatrics; Congenital Heart Disease

Investigators from the University of California performed a case-control study of the association of stroke with congenital heart disease (CHD) within a population of 2.5 million children in Northern California [1]. Cases of ischemic or hemorrhagic stroke were identified from review of medical records using a combination clinical symptoms and neuroimaging as they have previously described [2]. Among the 412 cases of stroke, 15 (4%) had a history of CHD. In contrast, 7 of the 1236 stroke-free controls had a history of CHD (prevalence 0.6%). Both cyanotic and acyanotic CHD were associated with stroke. Children with stroke and CHD presented at a younger age than non-CHD children. Children with CHD and previous cardiac surgery had a 31-fold increased stroke risk compared with healthy children. Importantly, the majority of the non-neonatal cases of stroke with CHD occurred after hospital discharge. Almost half the children with stroke, CDH and previous cardiac procedure presented within 5 years of their most recent cardiac surgery. The risk for stroke persists long after cardiac surgery as one patient presented with stroke 18 years after the last intervention. Both groups were similar in regard to therapy strategy, as 55% of all stroke patients were treated with an antithrombotic agent. A high proportion of patients had a neurological deficit at the time of hospital discharge. [1]

COMMENTARY. The importance of CHD as a risk factor for ischemic and hemorrhagic pediatric stroke is well established [3]. This new study reports a lower proportion of ischemic stroke attributed to CHD, probably in the context of a community-based study rather than referral-based. Of note, both cyanotic and non-cyanotic lesions were associated with stroke in children. A key finding of this study are the data that suggest a long-term increase in this risk for stroke after surgery for CHD. While the study is limited by the small number of cases of stroke and controls with CHD these results identify a long-term risk for stroke in children with CHD. There is a growing population of adult survivors of CHD and recognition of the cognitive issues faced by these patients [4]. The results of this study underscore the importance of anticipatory guidance for parents and caregivers after hospital discharge. The findings highlight an important gap in our

understanding of the approach to neuroprotection in the post-operative period and stroke prophylaxis during long-term recovery for this expanding population.

**Disclosures**

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

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**SEIZURE DISORDERS****Prognosis with Incidental Rolandic Spikes**Tracy S. Gertler, MD, PhD<sup>1,2</sup> and Cynthia V. Stack, MD<sup>1,2\*</sup><sup>1</sup>*Division of Neurology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL*<sup>2</sup>*Departments of Pediatrics and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL*\*Correspondence: Dr. Cynthia V. Stack, E-mail: [cstack@luriechildrens.org](mailto:cstack@luriechildrens.org)**Related Article:** McNally MA, Kossoff EH. Incidental rolandic spikes: Long-term outcomes and impact of treatment. *Epilepsy Behav.* 2015. Epub 2015/01/28.**Keywords:** Cognition; EEG; Epilepsy; Levetiracetam; Rolandic

Investigators from Johns Hopkins University reported a cohort of 27 patients with incidentally-noted rolandic spikes (RS) on EEG. The cohort included children aged 3-9, mostly male, with 19% comorbid ADHD and 19% familial epilepsy. Of 27 patients, 7 developed seizures, including 3 with benign rolandic epilepsy (BRE) and 1 with febrile seizures and learning difficulties. The patient with febrile seizures and 6 additional patients were offered levetiracetam. Of 7 patients given levetiracetam, five reportedly 'improved'; the remaining 2 were not affected and lost to follow-up. [1]

COMMENTARY. While BRE is defined by characteristic seizures and an EEG with RS, the significance of RS found incidentally is more enigmatic. To begin, the true incidence of this finding may depend on both phenotype and type of EEG. Though the incidence of asymptomatic RS is reported as 2–3% of children aged 5–12 [2], the incidence varies based on psychiatric comorbidities such as autism and ADHD, and the type (i.e. with sleep-deprivation), and duration of EEG performed.

As a diagnosis of BRE confers an additional risk of language and memory deficits, it is tempting to speculate that a child with a similarly abnormal EEG and comparable learning impairments without seizures would benefit from anticonvulsant therapy. As the authors previously described improved speech following treatment of BRE with levetiracetam [3], the same medication is a rational starting point. Yet, we still lack consensus about whether BRE should be treated at all, if seizures remain infrequent, irrespective of concurrent cognitive impairment [4].

This study hints at a larger question, which is whether RS are truly 'incidental,' or rather a biomarker for mild cerebral dysfunction. Indeed, it is debated whether characteristics of RS rather than seizure burden itself have a clearer prognostic role in terms of cognitive impairment [5]. A recent sibling-controlled study used neuropsychological testing to investigate cognition in patients with abnormal EEGs compared to siblings without RS; stereotypic language and memory impairments common to both groups suggested an inherited susceptibility independent of the EEG [6]. Similarly, in an analogous subset of patients with GRIN2A mutations, a spectrum of seizures and cognitive

difficulties appear to be epiphenomena of the same molecular bias [7].

McNally and Kossoff [1] suggest that RS may underlie cognitive abnormalities, and are thus sufficient when dually present to warrant an empiric trial of levetiracetam. Pending future prospective controlled trials and a better understanding of the gene underlying an inherited susceptibility, an EEG with RS, BRE, and cognitive impairment, the decision to treat remains a clinical judgement.

**Disclosures**

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

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**SEIZURE DISORDERS****Continuous EEG in Critically Ill Children**Jonathan E. Kurz, MD, PhD<sup>1,2</sup> and Mark S. Wainwright, MD, PhD<sup>1,2\*</sup><sup>1</sup>Ruth D. & Ken M. Davee Pediatric Neurocritical Care Program, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL<sup>2</sup>Departments of Pediatrics and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL

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**Related Article:** Herman ST, Abend NS, Bleck TP, Chapman KE, Drislane FW, Emerson RG, et al. Consensus Statement on Continuous EEG in Critically Ill Adults and Children, Part I: Indications. *J Clin Neurophysiol.* 2015. Epub 2015/01/30.**Keywords:** EEG; Critical Care; Pediatrics.

Investigators from the Critical Care Continuous EEG Task Force of the American Clinical Neurophysiology Society reported a consensus statement on indications for the use of critical care continuous electroencephalographic monitoring (ccEEG) in adults and children [1]. The consensus statement is based on observational trials and expert opinion, and defines indications for ccEEG with the goal of early identification and treatment of neurologic pathologies that might not be apparent by clinical exam alone. This statement also provides recommendations for ccEEG duration, as well as review and interpretation frequency. ccEEG is recommended for the identification of non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE) [2]. Specific populations at risk for NCS or NCSE include patients with persistent alteration of mental status after an acute supratentorial brain injury, after generalized convulsive status epilepticus or clinical seizures, or with encephalopathy of unknown etiology. ccEEG is also recommended in at-risk patients that require pharmacologic neuromuscular blockade, in patients with periodic discharges on a routine or emergent EEG, and for titration of continuous intravenous anticonvulsants or pharmacologically-induced coma.

Assessment of the electrographic background with ccEEG may also help predict outcome in a range of acute neurologic conditions, and could allow for early detection and treatment of cerebral ischemia in at-risk patients. ccEEG recording for at least 24 hours is recommended in most cases, although the authors acknowledge that there may be situations where shorter or longer periods of recording are necessary. Review of ccEEG by technologists is suggested as often as feasible, with interpretation by neurophysiologists at least twice daily. [1]

**COMMENTARY.** Observational studies in both pediatric and adult intensive care units have found frequent NCS and NCSE in critically ill patients, with rates of electrographic seizure ranging from 10 to 40% in children [3,4]. While the use of ccEEG is increasing, ccEEG indications, duration and review frequency vary considerably between institutions [5]. In part, this reflects the limitations of the current literature; although studies suggest an association between electrographic seizure

burden and poor outcomes in critically ill children [6], no randomized, controlled trials have examined the impact of ccEEG use on seizure control or patient outcomes. ccEEG can be resource-intensive, and institutions have developed varying strategies for the allocation of these resources in the absence of high-quality data to guide patient management.

This consensus statement provides a valuable starting point for development of ccEEG protocols based on the best currently available evidence. The clinical impact of ccEEG on seizure management and patient outcome remains an important area of ongoing research.

**Disclosures**

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

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**SEIZURE DISORDERS****Neuropsychological-EEG Activation in Genetic Generalized Epilepsy**J. Gordon Millichap, MD<sup>1,2</sup>  and John J. Millichap, MD<sup>1,2\*</sup> <sup>1</sup>Division of Neurology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL<sup>2</sup>Departments of Pediatrics and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL

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**Related Article:** Gelziniene G, Endziniene M, Jurkeviciene G. EEG activation by neuropsychological tasks in idiopathic generalized epilepsy of adolescence. *Brain Dev.* 2015;37(4):409-17.**Keywords:** Adolescence; Cognitive; Epileptiform discharges; Idiopathic generalized epilepsy; Neuropsychological activation

Investigators from Lithuanian University of Health Sciences, Kaunas, evaluated the effects of neuropsychological activation (NPA) tasks on epileptiform discharges (ED) in adolescents with idiopathic generalized epilepsy (IGE) and in comparison with hyperventilation and photic stimulation. Patients with IGE aged 14-17 years had a baseline video-EEG with habitual activation procedures followed by NPA tasks. The protocol of NPA included reading a Lithuanian fable, mentally and aloud, retelling the story, writing 4 sentences, mental and written calculation, and drawing a face. The tasks were classified as action-programming (written, calculation, drawing, reading, and writing), and thinking (mental calculation and mental reading). During at least one NPA task epileptiform EEG discharges were registered in 12 (20.3%) cases. None had a clinical seizure during tasks. Provocative effects of NPA tasks were more prevalent in photosensitive cases, especially action-programming NPA type ( $p=0.04$ ). The provocative effects of NPA were comparable to those of hyperventilation (23.7%) and photic stimulation (30.5%;  $p>0.05$ ). In the group of patients with ED on base-line EEG, no ED were registered during NPA in 14 (70%) out of 20 cases and the effect of NPA was regarded as inhibitory. NPA had no effect on 33 (84.6%) cases out of 39 without ED on base-line EEG. NPA is recommended in selected cases of IGE when routine EEG is not informative or when sleep EEG is not obtained. [1]

**COMMENTARY.** Matsuoka H of Tohoku University, Japan, has written extensively on neuropsychological EEG activation in patients with epilepsy [2]. In 480 patients with various epilepsies, NPA tasks provoked epileptic discharges in 38 (7.9%) patients, and were accompanied by myoclonic seizures in 15 patients, absence seizures in 8 and simple partial seizures in one. Mental activities associated with use of the hands i.e. writing (68.4%), written calculation (55.3%) and spatial construction (63.2%) provoked the most discharges followed by mental calculation (7.9%) and reading (5.3%). Action-programming type activities were most provocative in 32 of 38 (84.2%) patients, followed by thinking type

activities in 4 (10.5%). Seizure-precipitating mental activities were almost always related to IGE and rarely (2 of 38 patients) related to temporal lobe epilepsy. In IGE patients, those with myoclonic seizures were more susceptible than absence or GTCS. Matsuoka considers the neuropsychological approach to epilepsy indispensable for assessment of cognitive function during pre- and postsurgical evaluation and for disclosing the semiology of nonconvulsive status epilepticus [3]. Whereas IGE patients with myoclonic seizures are vulnerable to higher mental activity, cognitive-motor function may have an inhibitory effect on EEG discharges in the majority of epilepsy patients [4].

**Disclosures**

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

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**PERINATAL DISORDERS****Gait Training and Ankle Dorsiflexors in Cerebral Palsy**J. Gordon Millichap, MD<sup>1,2\*</sup> <sup>1</sup>Division of Neurology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL<sup>2</sup>Departments of Pediatrics and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL

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**Related Article:** Willerslev-Olsen M, Petersen TH, Farmer SF, Nielsen JB. Gait training facilitates central drive to ankle dorsiflexors in children with cerebral palsy. *Brain*. 2015;138(Pt 3):589-603.**Keywords:** Cerebral Palsy; Coherence; Development; Gait

Investigators at University of Copenhagen, Denmark, evaluated whether 4 weeks of 30 min daily treadmill training with an incline may facilitate corticospinal transmission and improve control of the ankle joint in 16 children, aged 5-14 years, with cerebral palsy. Gait training was accompanied by significant increases in gait speed, incline on the treadmill, the maximal voluntary dorsiflexion torque, and the weight exerted on the heel. EMG-EMG coherence in beta and gamma frequency bands recorded from the tibialis anterior increased significantly. Daily intensive gait training increases beta and gamma oscillatory drive in ankle dorsiflexor motor neurons and improves toe lift and heel strike in children with cerebral palsy and corticospinal dysfunction, especially at <10 years of age. [1]

COMMENTARY. Cerebral palsy with toe-walking is hemi- or diplegic [1]. Rarely, an asymmetric toe-walking can be dystonic and transient [2] and an explanation for "idiopathic" toe walking. Under 2 years of age, toe walking may not be pathologic; when persistent after the age of 2 years and in the absence of neurological or orthopedic abnormalities, toe-walking is referred to as idiopathic. The type of treatment is based on age and severity of the abnormality. An equinus contracture can develop, sometimes leading to casting, and/or operative treatment. In studies comparing casting and operative treatment of children with idiopathic toe walking, no significant differences between groups were found [3]. Treadmill interventions in children up to 6 years of age with Down syndrome, at risk of motor delay, led to earlier onset of independent walking [4]. Treadmill intervention may have a general effect on motor development in both children with corticospinal tract dysfunction and in those at risk of motor delay.

**Disclosures**

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

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**HEADACHE DISORDERS****Acute Treatment Regimens for Migraine in the ED**J. Gordon Millichap, MD<sup>1,2\*</sup> <sup>1</sup>Division of Neurology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL<sup>2</sup>Departments of Pediatrics and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL

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**Related Article:** Bachur RG, Monuteaux MC, Neuman MI. A comparison of acute treatment regimens for migraine in the emergency department. *Pediatrics*. 2015;135(2):232-8.**Keywords:** Emergency; Headache; Migraine; Therapeutics

Researchers at Children's Hospital, Boston, studied the comparative effectiveness of acute medication regimens for the prevention of ED visits with migraine. Children aged 7 to 18 years with a principal diagnosis of migraine headache were evaluated retrospectively using data from 35 pediatric EDs (2009-2012). The primary outcome was a revisit to the ED within 3 days. Of 32,124 children identified with migraine, 27,317 (85%) were discharged and 5.5% had a return ED visit within 3 days. Only 1 in 18 children with acute migraine required a revisit to the ED within 3 days.

At the index visit, the most common medications included nonopioid analgesics (66%), dopamine antagonists (50%), diphenhydramine (33%), and ondansetron (21%). Triptans and opiate medications were used infrequently (3% each). Children receiving metoclopramide had a 31% increased odds for an ED revisit within 3 days compared with prochlorperazine. Diphenhydramine with dopamine antagonists was associated with 27% increased odds of an ED revisit compared with dopamine antagonists alone. Prochlorperazine is superior to metoclopramide in preventing a revisit, and diphenhydramine is associated with increased rates of return visit. [1]

**COMMENTARY.** A review of symptomatic treatment of migraine in children in the Netherlands found a total of 10 trials with a total of 1575 patients. Acetaminophen, ibuprofen, and nasal-spray sumatriptan were all effective compared to placebo [2]. In a study that included 14 trials (only 1 in the ED), ibuprofen and acetaminophen were more effective than placebo, whereas the efficacy of intranasal sumatriptan was unclear [3]. In a current Canadian Headache Society systematic review of treatment of migraine pain in adults in emergency settings, prochlorperazine is strongly recommended whereas the use of several compounds, including acetaminophen and sodium valproate, is not recommended [4].

Inadequate acute treatment of migraine episodes is associated with an increased risk of new-onset chronic migraine over the course of 1 year [5]. Among 5,681 patients with episodic migraine in 2006, 3.1% progressed to chronic migraine in 2007. In the group with maximum

treatment efficacy of acute migraine, only 1.9% developed chronic migraine, whereas among those with very poor treatment efficacy, 6.8% developed chronic migraine. Further studies of the treatment of acute migraine are indicated.

**Disclosures**

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

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**SLEEP DISORDERS****Differential Diagnosis of Kleine-Levin Syndrome**J. Gordon Millichap, MD<sup>1,2\*</sup> <sup>1</sup>Division of Neurology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL<sup>2</sup>Departments of Pediatrics and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL

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**Related Article:** Lavault S, Golmard JL, Groos E, Brion A, Dauvilliers Y, Lecendreux M, et al. Kleine-Levin syndrome in 120 patients: Differential diagnosis and long episodes. *Ann Neurol*. 2015;77(3):529-40.**Keywords:** Kleine-Levin syndrome; Hypersomnia; Differential diagnosis

Investigators at Pitie-Salpetriere and Robert Debre Hospitals, and other centers in France, evaluated consecutive patients referred for suspected Kleine-Levin (KLS) syndrome, detailed differential diagnoses, and examined characteristics of patients with prolonged (>30 days) episodes. Of 166 referred patients, 120 had typical primary KLS syndrome (secondary to brain diseases, n=4, atypical syndrome, n=7, mostly psychiatric, n=29, incomplete data, n=6). Patients were more male (64%) than female (p=0.002), most were Caucasian whereas Jewish origin was exceptional (5%), they were more often of premature birth, had more frequent birth and developmental abnormalities (45%) than controls, most (80%) were teenagers at onset (10% were <12 years), and a family history of epilepsy was more frequent than in controls. Initial episodes were prolonged (32 vs 11 days) in 34 and short in 85. Patients with prolonged episodes were older at first interview than those with short episodes, and the disease course was longer (9 vs 6 years). During episodes, patients with prolonged episodes had shorter sleep time, higher levels of anxiety and agitation, and more feelings of disembodiment and amnesia. Between episodes, they were more tired, needed more naps, fell asleep more rapidly, and had higher anxiety/depression scores. The most frequent symptoms were sleep disorders, cognitive impairment, altered perception, eating disorders (more or less than normal), and apathy. Mental disorders are frequent differential diagnoses. An infection (URI, gastroenteritis, mononucleosis, H1N1 influenza) was present in 42% of patients at KLS onset. Other triggering factors included vaccination, sleep deprivation, stress, mental effort, alcohol, traveling, menses, marijuana, and head trauma. [1]

COMMENTARY. The eponym "Kleine-Levin syndrome" as defined above [1] was coined by Critchley and Hoffman [2] in 1942. The diagnostic characteristics are episodic hypersomnia, altered mental state, cognitive impairment, hallucinations, delusions, hyperphagia, and hypersexual behavior during episodes. Data from a multinational series of 108 patients [3] highlight hypersomnia, cognitive disturbance, and derealization as core symptoms, compared to less frequent symptoms of disinhibited behavior, including megaphagia in 60% and

hypersexuality in 30%. Suspected causes include hypothalamic dysfunction or autoimmune disorder, and precipitants are infection, alcohol or head trauma. No known genetic marker is described. The diagnosis is by exclusion, ruling out narcolepsy, temporal lobe epilepsy, Kluver-Bucy syndrome, metabolic disorders, bipolar and other mental disorders, and MS. The emphasis of cases with a prolonged course and residual abnormalities including apathy contradicts the concept of a generally benign disorder and warrants further diagnostic testing and early treatment trials [1]. A PubMed search uncovers several reports of KLS following viral encephalitis [4] and occasional cases that responded to antiepileptic medications (carbamazepine, valproate, and lamotrigine).

**Disclosures**

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

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