Investigators at Frenchay Hospital, Bristol, UK, retrospectively reviewed case notes and imaging in 9 consecutive children (age range 18 months to 16 years) with cerebral venous sinus thrombosis (CVST) who were treated using endovascular methods after medical therapy with heparin had failed. Six had superior sagittal sinus and transverse sinus involvement, 6 had straight sinus and 5 had vein of Galen and internal cerebral vein involvement. Three had preprocedural parenchymal hemorrhage and 6 showed edema/venous infarction. Predisposing conditions were anemia, diarrhea, and vomiting, nephrotic syndrome, and hypoplastic left heart; none was identified in 5 children. A thrombolytic agent (rtPA) was used in 8 patients. Diagnosis of CVST was made by CT, CT venography, MRI, or MR venography. Seven children were comatose, one had raised intracranial pressure with progressive cranial nerve palsies, 5 had suffered hemiparesis, 3 had suffered seizures, and one had a fluctuating hemiparesis at time of endovascular treatment. Endovascular methods used included local tissue thrombolytic plasminogen activator (in 8 patients), microguidewire and catheter disruption (6 patients), balloon angioplasty (in 2), and thromboaspiration using the Penumbra mechanical thrombectomy device (in 4). Partial recanalization was achieved in all and excellent recanalization in 2 patients. Good functional outcomes were obtained in 8 (89%). One child died with uncontrolled intracranial venous hypertension. Endovascular therapy may have a role in treatment of CVST in children when conventional medical therapy has failed and outcome is poor and deteriorating. (Mortimer AM, Bradley MD, O’Leary S, Renowden SA. Endovascular treatment of children with cerebral venous sinus thrombosis: A case series. Pediatr Neurol 2013 Nov;49(5):305-12). (Response: Dr Mortimer, Dept. of Neuroradiology, Frenchay Hospital, Bristol, UK. E-mail: alex_mortimer@hotmail.com).
COMMENT. Children with CVST and severe neurological deterioration despite anticoagulation may have a favorable response to endovascular treatment. Clinical deterioration after medical treatment is an indication for endovascular therapy. Larger scale studies are required to establish the role of endovascular treatment of deteriorating cases of pediatric CVST. Indicators of a poor prognosis are coma, involvement of the deep venous system, and parenchymal hemorrhage. Anticoagulation may be associated with an increase in size of a hematoma or de novo hemorrhage (Moharir MD, Shroff M, Stephens D, et al. Anticoagulants in pediatric cerebral sinovenous thrombosis: a safety and outcome study. Ann Neurol 2010 May;67(5):590-9).

Stroke therapy for children is discussed in an editorial (Roach ES. Pediatr Neurol 2013 Nov;49(5):301-2). Until age-specific studies are available, pediatric neurologists must accept methods and results of trials in adults. Thrombolysis with tPA in adults must be administered within 4.5 hours of symptom onset for a favorable risk-benefit ratio to be maintained. Administration of tPA after this time increases the risk of hemorrhage. Use of tPA in children is not approved by the FDA, but a trial is now underway (Amlie-Lefond C, et al. Thrombolysis in acute childhood stroke: design and challenges of the thrombolysis in pediatric stroke clinical trial. Neuroepidemiology 2009;32(4):279-86).

ENCEPHALITIS AND ENCEPHALOPATHIES

DIAGNOSTIC ALGORITHM FOR ENCEPHALITIS

Diagnostic algorithm for initial evaluation of encephalitis in children is proposed with a consensus statement from the International Encephalitis Consortium, a committee begun in 2010 to serve as a practical aid to clinicians evaluating patients with suspected encephalitis. Encephalitis is defined as inflammation of the brain parenchyma associated with neurologic dysfunction. Major diagnostic criterion is an altered mental status lasting >24 hours. Minor criteria include fever, seizures, focal neurologic findings, CSF WBC count >5/cubic mm, MRI parenchymal lesion, or EEG abnormality indicative of encephalitis (>3 required for probable or confirmed encephalitis).

Routine studies proposed include CSF, serum, imaging (MRI preferred), EEG, throat sample for Mycoplasma pneumoniae PCR, and throat and stool specimens for enterovirus PCR. Specific signs and symptoms of encephalitis include abnormal behavior, psychotic features, seizures or movement disorder indicating need for NMDAR antibody test in serum and CSF; vesicular rash indicating VZV PCR from CSF; respiratory symptoms indicating Mycoplasma pneumoniae PCR in CSF; and limbic symptoms indicating autoimmune limbic encephalitis testing HHV6/7 PCR (CSF). (Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: Consensus statement of the International Encephalitis Consortium. Clin Infect Dis 2013 Oct;57(8):1114-28). (Response: Ann Venkatesan MD, PhD, Johns Hopkins University School of Medicine, 600 N Wolfe St, Baltimore, MD 21287. E-mail: avenkat2@jhmi.edu).

COMMENT. The definition proposed is chosen to capture both encephalitis and encephalopathy. Encephalopathy is a clinical state of altered mental status, manifesting as
confusion, disorientation, behavioral changes, or other cognitive impairments, with or without inflammation of brain tissue. Encephalitis is characterized by brain inflammation resulting from direct infection of the brain parenchyma (e.g., Bartonella or influenza), a post-infectious process as in ADEM or a noninfectious condition such as NMDAR encephalitis. The definition covers infectious and noninfectious encephalitis and encephalopathy of presumed infectious etiology. Specific etiologies are identified in <50% of cases.

**Proteomes in plasma and CSF of children with cerebral malaria** were found to differ from those with acute bacterial meningitis and nonspecific encephalopathies. Pathogenic states in children with impaired consciousness in malaria endemic areas could be reflected by changes in protein biomarkers in both plasma and CSF. (Gitau EN et al. *J Infect Dis* 2013 Nov 1;208(9):1494-503).

**POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME**

Investigators at Children’s Hospital of Montefiore, Albert Einstein College of Medicine, NY, determined the incidence of posterior reversible encephalopathy syndrome (PRES) in a pediatric critical care unit. Ten patients <21 years of age with PRES (incidence of 1 in 259 admissions, 0.4%) were studied. Nine patients presented with generalized tonic and/or clonic seizures. Continuous EEG showed generalized slowing but no epileptiform activity. Risk factors included hypertension, cytotoxic medication use, and anemia. Comorbidities included systemic lupus erythematosus, inflammatory bowel disease, ulcerative colitis, liver cirrhosis, pulmonary embolism, renal insufficiency, septic shock, and acute chest syndrome. One-year follow-up showed no residual neurological deficits and resolution of white matter signal abnormalities on neuroimaging. (Raj S, Overby P, Erdfarb A, Ushay HM. Posterior reversible encephalopathy syndrome; incidence and associated factors in a pediatric critical care population. *Pediatr Neurol* 2013 Nov;49(5):335-9). (Response: Dr Raj, The Children’s Hospital at Montefiore, Bronx, NY 10467. E-mail: drshashiraj@gmail.com).

**COMMENT.** PRES, also referred to as hypertensive encephalopathy or reversible posterior leukoencephalopathy syndrome, is a clinical syndrome that results from disruption of the blood-brain barrier and vasogenic edema, demonstrated on MRI with hyperintense signals in the posterior cerebral white matter.

**PRES in an infant 35 days old** is reported from the Mayo Clinic. The syndrome is rare in children less than 1 year. The infant had a history of obstructive sleep apnea, laryngomalacia, and choanal atresia. While undergoing bronchoscopy, she developed apneic episodes with stiffening of extremities. EEG revealed occipital lobe onset seizures, and MRI showed hyperintense T2 signal in both posterior temporal and parieto-occipital lobes. A labile blood pressure was normalized and seizures abated with fosphenytoin and levetiracetam. At 3 month of age, resolution of MRI abnormality confirmed the diagnosis of PRES. (Mrelashvili A, Watson RE, Wong-Kisiel LC. *Pediatr Neurol* 2013 Nov;49(5):387-8).
PRES and risk of epilepsy. The incidence of subsequent epilepsy was 2.25 fold higher in patients with hypertensive encephalopathy (HE) than in controls, in a nationwide population-based study in Taiwan. The incidence of epilepsy was higher in men, younger patients with HE, and in those with brain disorders. (Chung TT, et al. Epilepsy Behav 2013 Nov;29(2):374-8).

SEIZURE DISORDERS

SCN1A AND SUSCEPTIBILITY TO MTL EPILEPSY, HIPPOCAMPAL SCLEROSIS AND FEBRILE SEIZURES

Investigators at the Department of Clinical and Experimental Epilepsy, Institute of Neurology, Queen Square, London, and other centers in the UK and Europe conducted a genome-wide association study in 1018 people with mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis and 7552 control subjects, with (n=757) and without (n=803) a history of febrile seizures. Meta-analysis revealed a genome-wide significant association for MTLE with hippocampal sclerosis with febrile seizures at the sodium channel gene cluster on chromosome 2q24.3. No genetic association with febrile seizures was found in a cohort of 172 individuals with febrile seizures who did not develop epilepsy during follow-up to age 13 years. The findings suggest SCN1A involvement and common genetic variation in the epilepsy syndrome of MTLE, hippocampal sclerosis with febrile seizures. (Kasperaviciute, D, Catarino CB, Matarin M, et al. Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A. Brain 2013 Oct;136(Pt 10):3140-50). (Response: Sanjay M Sisodiya PhD, FRCP. Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, 33 Queen Square London, WC1N 3BG, UK. E-mail: s.sisodiya@ucl.ac.uk).

COMMENT. In addition to MTLEHS + FS, genetically-determined, epilepsy syndromes in which febrile seizures are a prominent feature include Dravet syndrome, and genetic epilepsy with febrile seizures plus. The authors suggest that focusing on clinically recognized syndromes or constellations (Berg AT, et al. Epilepsia 2010 Apr;51(4):676-85) could reduce heterogeneity before genomic analyses and lead to discovery of more narrowly-defined syndromes. Genetic association studies should uncover the cause of some epilepsies and facilitate prevention or a cure.

TNK2 mutations in severe autosomal recessive infantile onset epilepsy with intellectual disability. The proband, a girl, presented at age 19 months with focal seizures resembling MTLE, and characterized by unresponsiveness, hypertonia, automatisms and secondary generalization. Seizures recurred several times a day and were refractory to medication. Birth and early development were normal, and cognitive regression with autistic features occurred soon after seizure onset. MRI was normal. Video-EEG recording and PET scan showed right anteromedial temporal lobe seizure onset, but temporal lobectomy at age 4.5 years failed to control seizures. The resected tissue showed no abnormality. Two younger brothers had a similar history to that of the proband. The cognitive regression with absence of myoclonus, normal MRI, and unremarkable interictal EEG distinguish this phenotype from known infantile onset

**SUBCLINICAL POSTTRAUMATIC SEIZURES DETECTED BY CONTINUOUS VIDEO-EEGMONITORING**

Investigators at Mattel Children’s Hospital, UCLA, and University of Colorado, used continuous video-EEG monitoring (cEEG) to study the incidence and risk factors for subclinical early posttraumatic seizures (EPTS) in 87 consecutive, unselected (mild – severe), acute traumatic brain injury (TBI) patients requiring admission to the PICU. Thirty-seven (42.5%) had seizures: subclinical in 16.1% (only subclinical in 6.9%), status epilepticus (SE) in 18.4%, and subclinical SE in 13.8%. Risk factors for subclinical seizures and SE included younger age, abusive head trauma, and intraaxial bleed. SE and subclinical SE were associated with increased hospital length of stay. cEEG monitoring significantly improves detection of seizures and is the only way to detect subclinical seizures (SE). (Arndt DH, Lerner JT, Matsumoto JH, et al. Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort. Epilepsia 2013 Oct;54(10):1780-8). (Response: Jason T Lerner, 10833 Le Conte, 22-474 MDCC, Los Angeles, CA 90095. E-mail: jlerner@mednet.ucla.edu).

COMMENT. Continuous EEG monitoring is recommended in young children with TBI, particularly in those with abusive head trauma and in those with intraaxial blood on CT. Rapid detection and treatment of EPTS may be of benefit in the immediate management of patients with TBI, but control of subclinical EPTS may not prevent occurrence of late posttraumatic epilepsy nor reflect long-term adverse effects of AEDs on the developing brain.

**PROGNOSIS OF EPILEPSY**

Investigators from the Institute of Neurology, Queen Square, London, UK, report results of longitudinal cohort studies of prognosis in epilepsy in adults and children and focus particularly on the National General Practice Study of Epilepsy (NGPSE) in 1195 patients initiated in 1983. Other longitudinal studies include the Mayo Clinic Record Linkage Study, the Tonbridge Study and the Study from Turku, confined to children and initiated in the 1970s. The findings are summarized as follows: 1) Epilepsy prognosis is frequently good, 65-85% cases entering long-term remission; 2) prognosis is better in newly diagnosed cases than in patients with chronic epilepsy; 3) early response to treatment is usually an indication of a good long-term prognosis; 4) the longer the remission, the less likely a subsequent recurrence; 5) the longer seizures recur, the poorer the long-term outlook; 6) delaying treatment, even for many years, does not worsen long-term prognosis; 7) continuous and burst patterns are more common than intermittent seizure patterns; 8) mortality may occur at any time in the course of epilepsy but is highest in the early years after diagnosis and is largely due to the underlying cause; 9) febrile seizure prognosis is generally good with ~6-7% developing late epilepsy (rate of
epilepsy developing is higher in those with FS occurring before age 1 year or after age 3 years, and with complex FS); and 10) clinical factors associated with a poor prognosis include a neurodeficit, poor response to initial therapy, and some epilepsy syndromes. (Shorvon SD, Goodridge DMG. Longitudinal cohort studies of the prognosis of epilepsy: contribution of the National General Practice Study of Epilepsy and other studies. Brain 2013 Nov;136(Pt 11):3497-510). (Response: Professor Simon Shorvon, E-mail: S.shorvon@ucl.ac.uk).

COMMENT. Ethics committee approval had been obtained at the beginning of the study, which did not require patient consent for collection of anonymized prognostic data. In 2007 a government appointed committee ruled that, with some exceptions, the patient’s consent was required for collection of personal data from the general practitioner. The reduction in available data that followed has resulted in the premature termination of the study. The authors comment that this ill-advised decision by government appointed committees has harmed large-scale epidemiological studies in Britain, and specifically resulted in loss of 30-year follow-up of a large cohort of patients with epilepsy and reasons for a persistently high mortality.

INTRACRANIAL TUMORS

DIAGNOSIS OF INTRACRANIAL GERM CELL TUMORS

Investigators from the Massachusetts General Hospital, Boston, studied the manifestations and time to diagnosis of 70 children with germ cell tumors (GCTs) treated between 1998 and 2012. The median duration of symptoms before diagnostic MRI was 6 months (range, 2 days to 72 months). Diagnosis was delayed (>6 months) in 38 (54%). The delay increased the risk of disseminated disease. Thirty patients (43%) had nongerminomatous tumors (NGGCTs) and 40 (57%) were diagnosed with pure germinomas (PGs). The majority of primary tumors were located in the suprasellar region (28% of NGGCT and 40% of PG) followed by the pineal region (23% of NGGCT and 33% of PG). All isolated pineal region tumors occurred in male patients; suprasellar tumors occurred in females in 61%.

Symptoms of GCT were headache (69%), nausea and vomiting (50%), polyuria and/or polydipsia in 59%, double vision (34%), visual field cuts or impaired visual acuity in 27%, poor growth (17%), and premature puberty in 14%. Pineal tumors presented with symptoms of hydrocephalus, whereas suprasellar tumors caused endocrinopathies. Ophthalmic symptoms occurred in all patients: pineal located tumors caused diplopia and Parinaud syndrome symptoms in 61%, and suprasellar tumors caused visual acuity and/or visual field limitations in 29%. Patients with GCT were evaluated by a broad spectrum of pediatric specialists, and patients with delayed diagnosis were seen by 2 or more physicians and subspecialists: a neurologist in 17%, ophthalmologist 27%, or endocrinologist 34%. An endocrinopathy, especially diabetes insipidus (in 50%), was diagnosed before the diagnosis of brain tumor. Progressive enlargement of the infundibulum led to biopsy, and diagnosis was confirmed by abnormal levels of human chorionic gonadotropin in the CSF and elevated serum alpha-fetoprotein. (Sethi RV, Marino R, Niemierko A, Tarbell NJ, Yock TI, MacDonald SM. Delayed diagnosis in
(Reprints: Shannon M MacDonald MD, Dept. of Radiation Oncology, MGH, 55 Fruit St, Yawkey 112, Boston, MA 02114. E-mail: smacdonald@partners.org).

**COMMENT. Bifocal germ cell tumors: synchronous tumors or metastases?**
Bifocal germ cell tumors in the suprasellar and pineal regions are reported in 23 (12.8%) of 181 patients with intracranial GCTs treated at Seoul National University Children’s Hospital, Korea (Phi JH, Kim SK, Lee J, et al. J Neurosurg Pediatr 2013 Feb;11(2):107-14). Eleven patients (47.8%) presenting with bifocal GCTs exhibited tumor seeding, compatible with bifocal lesions. Patients with bifocal germinomas show significantly shorter survival than those with germinomas from a single site. Bifocal GCTs may result from the metastatic spread of suprasellar or pineal GCTs and are a sign of disseminated disease and poor prognosis.

**NEUROMUSCULAR DISORDERS**

**SPASMODIC MUSCLE CRAMPS AND WILSON DISEASE**

Investigators at Ann & Robert H. Lurie Children’s Hospital of Chicago report a case of Wilson disease (WD) in a 10-year-old-boy presenting with 3 months of increasingly severe spasmodic muscle cramps and weakness in lower extremities, upper extremities, and cramps in face and chest. Calf palpation was tender, and hyperpigmented flat lesions were present over ankles, knees, and elbows. Eye exam showed Kayser-Fleischer rings and sunflower cataracts. Creatine kinase, aspartate aminotransferase, and alanine aminotransferase were elevated, hemoglobin was low, and urinalysis revealed myoglobinuria. MRI of muscle and muscle biopsy were negative, serum ceruloplasmin was low, 24 h urine copper was elevated, and liver biopsy showed fibrosis and positive staining for copper. Rhabdomyolysis developed after the operation, attributed to the use of succinylcholine. Brain MRI showed symmetric changes in the basal ganglia. Following trientine chelation therapy for WD, symptoms and laboratory abnormalities resolved. (Rosen JM, Kuntz N, Melin-Aldana H, Bass LM. Spasmodic muscle cramps and weakness as presenting symptoms in Wilson disease. Pediatrics 2013 Oct;132(4):e1039-42). (Response: John M Rosen MD, Children’s Mercy Hospitals and Clinics, 2401 Gillham Road, Kansas City, MO 64108. E-mail: jmrosen@cmh.edu).

**COMMENT.** The clinical presentation of WD or hepatolenticular degeneration is variable and a number of different syndromes are recognized in addition to the classical syndrome described by Wilson in 1912. The classical syndrome, in children of 10 to 15 years, presents with bulbar symptoms. Rigidity of skeletal musculature follows, and an extrapyramidal type of hypertonus resembling that of the Parkinsonian syndrome is associated with a constant tremor. Tendon reflexes are usually normal. Any stimulus provokes spasms, and a diagnosis of tetanus may be entertained. Myotonia is also described. (Ford FR. Diseases of the Nervous System. In Infancy, Childhood and Adolescence. 4th ed. Springfield, IL: Charles C Thomas; 1960. p. 756-62.). The Rosen, Kuntz et al case-report describes a WD syndrome with muscle cramps.
**COENZYME Q10 DEFICIENCY AND TYPE 2C MUSCLE FIBERS**

Investigators at Washington University School of Medicine, St Louis, MO, evaluated retrospectively clinical, laboratory, and muscle histochemistry and oxidative enzyme characteristics in 49 children with suspected mitochondrial disorders. Children (n=18) with CoQ10 deficiency in muscle were compared to 31 with normal CoQ10 values. Motor delay/hypotonia and cognitive/language delay were the most frequent clinical features in CoQ10-deficient and control groups. Seizures or epileptiform EEG occurred in 56%. Type 2C muscle fibers were 5.5-fold more frequent in CoQ10-deficient patients compared with mitochondrial and nonmitochondrial controls (P<0.0001). Type 2C fiber frequency of >5% had 89% sensitivity and 84% specificity for CoQ10 deficiency in these patients. No biopsy showed active myopathy. Multiple abnormalities in muscle oxidative enzyme activities were more frequent in CoQ10-deficient patients than controls. (Sommerville RB, Zaidman CM, Pestronk A. Coenzyme Q10 deficiency in children: Frequent type 2C muscle fibers with normal morphology. *Muscle Nerve* 2013 Nov;48(5):722-6). (Response: RB Sommerville; E-mail: sommervileb@neuro.wusti.edu).

**COMMENT.** An increased frequency of type 2C fibers in morphologically normal muscle is a sensitive and specific histological marker of CoQ10 deficiency in a child suspected of having a mitochondrial disorder. Clinical syndromes associated with CoQ10 deficiency are diverse and include myopathy, cerebellar ataxia, nephrotic syndrome, and encephalopathy including Leigh syndrome. Early diagnosis is important since some cases are responsive to treatment with CoQ10 supplementation.

**NEUROPHYSIOLOGICAL TESTING IN NORMAL CHILDREN**

Investigators in Belgrade, Serbia, and Newcastle upon Tyne, UK, reviewed the literature (Ovid Medline, 1948-2012) for citations on repetitive nerve stimulation (RNS) and single fiber electromyography (SFEMG) in children. Five articles contained data on 48 normal children studied with RNS and only 1 article with data on SFEMG in 20 normal children were located. Significant differences in the response to RNS in children compared to adults were identified, emphasizing the need for age appropriate normal values. (Kosac A, Gavillet E, Whittaker RG. Neurophysiological testing in congenital myasthenic syndromes: a systematic review of published normal data. *Muscle Nerve* 2013 Nov;48(5):711-5). (Response: RG Whittaker; e-mail: roger.whittaker@ncl.ac.uk).