

PEDIATRIC NEUROLOGY BRIEFS

A MONTHLY JOURNAL REVIEW

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Vol. 27, No. 7

July 2013

VASCULAR DISORDERS

FIBROMUSCULAR DYSPLASIA AND CHILDHOOD STROKE

Investigators at the Alberta Children's Hospital Research Institute, University of Calgary; the Hospital for Sick Children, Toronto, and other centers in Canada screened Canadian pediatric stroke registries and the literature and found 81 cases (15 new, 66 from the literature) of pediatric stroke associated with fibromuscular dysplasia or renal arteriopathy. Twenty-seven patients had pathologically proven fibromuscular dysplasia, with predominant intimal fibroplasia in 89%; none had typical adult medial fibroplasia. Stroke was ischemic in 63% and hemorrhagic in 37%; multifocal in 40%. Onset was early and <12 months in 33%. Angiography showed a focal, stenotic arteriopathy in 78% and "string of beads" in 22%. Renal arteriopathy (63%) with hypertension (92%) was common, with systemic arteriopathy in 72%, and moya-moya in 35%. Therapies were anti-inflammatory in 29% and anti-thrombotic in 27%, and outcomes were poor in 63%, with stroke recurrence in 36%. Patients with clinically suspected fibromuscular dysplasias (n=31) were older, normotensive, and with string-of-beads angiography and good outcome. (Kirton A, Crone M, Benseler S, et al. Fibromuscular dysplasia and childhood stroke. **Brain** 2013 Jun;136(Pt 6):1846-56). (Response: Dr Adam Kirton. E-mail: adam.kirton@albertahealthservices.ca).

COMMENT. Fibromuscular dysplasias (FMDs) are a group of idiopathic, non-inflammatory arteriopathies with medial fibroplasia, typically affecting young adult females, with renal and cerebral vessel involvement, "string-of-beads" angiography, hypertension, and stroke (Slovut DP, et al. **N Engl J Med** 2004;350(18):1862-71). Three main categories of FMD are classified as medial, intimal, and perimedial fibroplasia, based on the site of disease in the arterial wall. Most pathologically proven cases of FMD reported in children do not have medial fibroplasia and the characteristic "string-of-beads" sign on angiography, and intimal fibroplasia predominates. Arterial imaging,

PEDIATRIC NEUROLOGY BRIEFS © 1987-2013, ISSN 1043-3155 (print) 2166-6482 (online), is published monthly and covers selected articles from the world literature. The editor is Pediatric Neurologist at the Ann & Robert H. Lurie Children's Hospital of Chicago; Professor Emeritus, Northwestern University Feinberg School of Medicine. PNB is a continuing education service designed to expedite and facilitate the review of current scientific information for physicians and other health professionals. Apply to PediatricNeurologyBriefs.com for Subscriptions (12 issues, January-December). Digital Edition PDF: \$72 (Residents/Fellows \$36); Print + Digital: \$96 within US/UK, \$128 outside US/UK. Institutions: Digital \$188, Print + Digital \$228. Mail: Pediatric Neurology Briefs Publishers, PO Box 11391, Chicago, IL 60611

craniocervical and systemic, should be considered in pediatric stroke when fibromuscular dysplasia is suspected. In a case-report of a 12-year-old boy with ischemic stroke caused by intracranial fibromuscular dysplasia, preliminary imaging investigations included CT and MR angiography, but a definitive diagnosis was reached following a conventional cerebral angiogram (Shea KJ, et al. **Pediatr Neurol** 2011 Mar;44(3):214-7).

MYOPATHIES

CONGENITAL RYR1-ASSOCIATED MYOPATHIES

Investigators from the Children's Hospital of Philadelphia, NINDS, and other centers in the US and France, report a series of 11 patients with severe neonatal RYR1-associated myopathy confirmed by genetic testing. Clinical features included decreased fetal movements, hypotonia, poor feeding, respiratory impairment, arthrogryposis, ophthalmoplegia, and femur fracture and hip dislocation at birth. RYR1 mutations were dominant in 4 patients and recessive in 7. Muscle ultrasound in 6 patients showed relative sparing of the rectus femoris muscle. All patients with dominant mutations had classic central cores on muscle biopsy; patients with recessive mutations showed histologic heterogeneity. (Bharucha-Goebel DX, Santi M, Medne L, et al. Severe congenital RYR1-associated myopathy. The expanding clinicopathologic and genetic spectrum. **Neurology** 2013 Apr 23;80(17):1584-9). (Resp.: Dr Bonnermann. Carsten.bonnermann@nih.gov).

COMMENT. Classic central core disease (CCD) due to mutations in the RYR1 gene typically presents with mild to moderate hypotonia, developmental delay, proximal muscle weakness, and occasional hip dislocation. The present series of patients has a more severe neonatal RYR1-associated myopathy caused by both dominant and recessive mutations of the gene and expands the clinical spectrum of central core disease. Sparing of the rectus femoris muscle on ultrasound should prompt evaluation for RYR1-associated myopathy.

Subtypes of congenital myopathies in UK. Of 54 patients with muscle biopsies available, diagnosed over a 5-year period at Great Ormond Street Hospital for Children, London, 29 (54%) had a core myopathy (central core disease, multi-minicore disease), 9 (17%) had nemaline myopathy, 7 (13%) had myotubular/centronuclear myopathy, 2 (4%) had congenital fibre type disproportion, 6 (11%) had isolated type 1 predominance and 1 (2%) a mixed core-rod myopathy. Of 44 with a genetic diagnosis, RYR1 was mutated in 26 (59%). The genetic defect was unidentified in 1/3 of congenital myopathies (Maggi L, Scoto M, Cirak S, et al. **Neuromuscul Disord** 2013 Mar;23(3):195-205).

RYR1 MUTATIONS, EXERTIONAL MYALGIA AND RHABDOMYOLYSIS

Investigators at Guy's & St Thomas' Hospital, London, UK, and other centers sequenced RYR1 in 39 unrelated families with rhabdomyolysis and/or exertional myalgia and identified 9 heterozygous RYR1 mutations in 14 families, 5 of them previously associated with malignant hyperthermia (MH). Index cases presented from 3 to 45 years

with rhabdomyolysis, with or without exertional myalgia (n=12), but no or little associated weakness; CK levels were markedly increased during episodes. Rhabdomyolysis was triggered by exercise and heat, viral infection and drugs. Familial RYR1 mutations were confirmed in relatives. (Dlamini N, Voermans NC, Lillis S, et al. Mutations in RYR1 are a common cause of exertional myalgia and rhabdomyolysis. **Neuromuscul Disord** 2013 Apr 28. pii: S0960-8966(13)00094-1 [Epub ahead of print]). (Response: Dr H Jungbluth, Children's Neurosciences Centre, St Thomas' Hospital, London SE1 7EH, UK. E-mail: Heinz.jungbluth@ghstt.nhs.uk).

COMMENT. Patients presenting with unexplained rhabdomyolysis and/or exertional myalgia and other family members should be tested for RYR1 mutations.

Malignant hyperthermia susceptibility of core myopathies. Due to their genetic linkage to mutations in the ryanodine receptor gene (RYR1), core myopathies (in particular, central core disease) carry a high risk of malignant hyperthermia susceptibility during anesthesia. (Brislin RP, Theroux MC. **Paediatr Anaesth** 2013 Apr 25 [Epub ahead of print]).

GLUCOCORTICOIDS FOR DUCHENNE MUSCULAR DYSTROPHY

Investigators at the Dubowitz Neuromuscular Centre, Great Ormond Street Hospital, and other centers in the UK, conducted a prospective longitudinal study across 17 neuromuscular centers in the UK of 360 boys aged 3-15 years with Duchenne muscular dystrophy who were treated with daily or intermittent (10 days on/10 days off) prednisolone for a mean duration of 4 years. The median loss of ambulation was 12 years in intermittent and 14.5 years in daily treatment; height restriction for intermittent versus daily regimen was 1.57 (p=0.13) and the median age for loss of ambulation did not differ. Boys on an intermittent regimen declined faster than those receiving daily treatment (p<0.001). Moderate to severe side effects were more common in the daily regimen, including Cushingoid features, hyperactive behavior and hypertension. Body mass index mean score was higher and height restriction was more severe in the daily regimen than in the intermittent regimen. (Ricotti V, Ridout DA, Scott E, et al. Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. **J Neurol Neurosurg Psychiatry** 2013 Jun;84(6):698-705). (Respond: Dr Francesco Muntoni, Dubowitz Neuromuscular Centre, UCL Institute of Child Health, 30 Guilford St., London WC1N 1EH, UK; E-Mail: f.muntoni@ucl.ac.uk).

COMMENT. Glucocorticoids are recommended in the international standards of care guideline for DMD and benefits are confirmed by Cochrane systematic reviews (Bushby K, et al. **Neuromuscul Disord** 2004 Sep;14(8-9):526-34). The most effective treatment postulated is prednisolone/prednisone or the equivalent deflazacort (Manzur AY, et al. **Cochrane Database Syst Rev** 2008 Jan 23;(1):CD003725). The intermittent and daily regimens are equally effective in gain of function until 6 years of age. After age 7 years, boys on an intermittent regimen decline more rapidly than those on daily therapy. Side effects are a greater problem with daily compared to intermittent therapy.

SEIZURE DISORDERS

DEVELOPMENT AND BEHAVIOR FOLLOWING FIRST FEBRILE SEIZURE

Investigators at New York Presbyterian Hospital determined the effect of a first febrile seizure (FS) on development, using measures of cognition, motor ability, and adaptive behavior. Children (n=159) from a low socioeconomic environment, evaluated within one month of the ED visit for a first FS and one year later, showed no difference in performance compared to that in 142 controls. Within-group differences in cognition occurred in cases and controls, the decline in cases reaching significance. Factors independent of the FS that were associated with group changes in function and delay in developmental milestones over time included poor socioeconomic status, TV watching, fewer books, and lack of breastfeeding. The mean decline over time in cognition was greater in children with complex FS compared to children with simple FS, and children with complex FS were more likely to come from low-income households. Simple FS occurred in 65.8% (N=104), and complex FS in 34.2% (N=54). (Leaffer EB, Hinton VJ, Hesdorffer DC. Longitudinal assessment of skill development in children with first febrile seizure. **Epilepsy Behav** 2013 Jul;28(1):83-7). (Response: Dr Hesdorffer. E-mail: dch5@columbia.edu).

COMMENT. The authors conclude that a first FS does not pose an increased risk of poor developmental outcome over time, but a decline in cognition and behavior following a FS may be associated with an impaired socioeconomic environment or a FS that is complex in type.

NEUROPSYCHOLOGICAL IMPAIRMENT AND ROLANDIC EPILEPSY

Investigators at Universities of Chieti and Salerno, Italy, evaluated the neuropsychological profile of children with rolandic epilepsy (RE) at onset and of their healthy siblings. A significant impairment in language, attention, and short- and long-term memory but no impairment in visual-spatial memory was found in both patients and siblings. Verbal comprehension and working memory scores showed a positive correlation in both groups, supporting the hypothesis of a specific neurocognitive phenotype and shared genetic susceptibility in RE. (Verrotti A, Matricardi S, Di Giacomo DL, Rapino D, Chiarelli F, Coppola G. Neuropsychological impairment in children with Rolandic epilepsy and in their siblings. **Epilepsy Behav** 2013 Jul;28(1):108-12). (Dr S Matricardi. E-mail: sara.matricardi@yahoo.it).

COMMENT. Early recognition of the neuropsychological impairments in patients with RE should be useful in addressing educational needs and IEP resources for patients.

INFECTIOUS DISEASES

DIAGNOSTIC FEATURES OF NEUROBRUCELLOSIS

Investigators at Ankara Numune Training and Research Hospital, a tertiary care community hospital in Turkey, performed a prospective observational study between February 2002 and March 2005 of patients >16 years of age with laboratory confirmed brucellosis. The diagnosis of brucellosis was based on clinical findings and a serum agglutinin titer of >1:160 in serum tube agglutination or a positive blood culture. Lumbar puncture was performed on patients with neurological symptoms or signs, including headache, neck stiffness, confusion, or changes in personality. Neurobrucellosis among laboratory-confirmed brucellosis patients was diagnosed by any one of the following criteria: 1) neurologic symptoms or signs; 2) brucella organism isolated from the CSF and/or anti-Brucella antibodies in CSF; 3) lymphocytosis, increased protein, and decreased glucose in CSF; or 4) MRI or CT abnormalities.

Of 128 patients with LP, 48 (37.5%) were diagnosed with neurobrucellosis, 45 had a CSF agglutination titer of >1.8, and 7 (15%) had Brucella bacteria isolated from CSF. Of 48 patients with neurobrucellosis, 16 (33%) were female, ages ranged from 13-77 years (median age 42 years), and 32 (65%) raised livestock. Consumption of cheese produced from unpasteurized milk was the source of infection in 41 (85%) patients. In addition to fever, myalgia, sweating, and weight loss, neurobrucellosis patients presented with headache, blurred vision, loss of hearing, and confusion. Neurological symptoms also included behavioral changes, agitation, muscle weakness, disorientation, neck rigidity, paresthesias, and rarely, diplopia, facial paralysis, and ataxia. Following treatment with ceftriaxone, rifampicin, and doxycycline for 6 months, one patient died of cardiac failure while the remainder showed no relapse after 3, 6, and 9 months follow-up. Three patients with cranial nerve involvement (facial paralysis in 1, and sensorineural hearing loss in 2) recovered with sequelae. (Güven T, Ugur K, Ergonui O, et al. Neurobrucellosis: Clinical and diagnostic features. *Clin Infect Dis* 2013 May;56(10):1407-12). (Response: Onder Ergonui MD, MPH, Koc University, School of Medicine, Istanbul, Turkey. E-mail: oergonui@ku.edu.tr).

COMMENT. Brucellosis in children is usually a mild self-limited disease compared with the more chronic disease in adults. Physical findings include lymphadenopathy, hepatosplenomegaly, and arthritis. Serious complications include meningitis, endocarditis, and osteomyelitis. Most cases occur in travelers returning from endemic areas such as the Mediterranean or Middle East (AAP. Brucellosis. In: Pickering LK, ed. **Red Book**: 2012 Report of the Committee on Infectious Diseases. 29th ed. Elk Grove Village, IL: AAP; 2012:256-258).

Manifestations of neurobrucellosis include encephalitis, meningoencephalitis, radiculitis, myelitis, and neuropathies. In the present study, the diagnosis is based on neurological symptoms and signs, and laboratory findings. In endemic regions, the diagnosis should be considered in a patient with severe and persistent headache.

More than 20 references to studies of neurobrucellosis in children are listed in a PubMed search for the last decade 2002-12, the majority from Turkey or Saudi Arabia. Children <12 years of age constituted 21% (115/545) of the total brucellosis admissions

to a major Riyadh hospital in the period 1984-1995. Consumption of unpasteurized camel milk was the main source of infection. Arthritis was the dominant symptom in 70% (Shaalan MA et al. **Int J Infect Dis** 2002 Sep;6(3):182-6).

NEURO CUTANEOUS DISORDERS

STURGE-WEBER SYNDROME LINKED TO GNAQ MUTATION

Investigators from Johns Hopkins School of Medicine, the Hugo W Moser Research Institute at Kennedy Krieger, Baltimore; Duke University; and Medical College of Wisconsin, Milwaukee, performed whole-genome sequencing of DNA from paired samples of tissue from 3 persons with the Sturge-Weber syndrome (SWS). GNAQ somatic mosaic mutations were identified in 88% of participants (23 of 26) with the SWS and from 92% of participants (12 of 13) with nonsyndromic port-wine stains, but not in any of samples from 4 participants with an unrelated cerebrovascular malformation or in any of the samples from 6 controls. The prevalence of the mutant allele in affected tissues ranged from 1.0 to 18.1%. SWS and port-wine stains are caused by a somatic activating mutation in GNAQ. (Shirley MD, Tang H, Gallione CJ, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. **N Engl J Med** 2013 May 23;368(21):1971-9). (Reprints: Dr Pevsner, Department of Neurology, Kennedy Krieger Institute, 707 N Broadway, Baltimore, MD 21205. Email: Pevsner@kennedykrieger.org).

COMMENT. These findings identify a single mechanism for the SWS and nonsyndromic port-wine stains and they document a molecular basis for these malformations, causally related to a mutation in a specific gene, GNAQ. The authors hypothesize that the port-wine stains may represent a late origin of the somatic GNAQ mutation in vascular endothelial cells, whereas the SWS mutation may occur earlier in embryonic development. A child born with a port-wine stain in the distribution of the ophthalmic branch of the trigeminal nerve has a 26% chance of having SWS (Ch'ng S, Tan ST. **J Plast Reconstr Aesthet Surg** 2008 Aug;61(8):889-93; cited by Shirley MD et al. 2013).

INTRACRANIAL HYPERTENSION

CLINICAL SPECTRUM OF PSEUDOTUMOR CEREBRI

Investigators at Erciyes University, Kayseri, Turkey, studied the etiological and clinical features, treatment, and prognosis of pseudotumor cerebri (PTC) in 42 consecutive patients (average age at symptom onset 10 years; range 12 months to 17 years). Girls outnumbered boys, 27 (64%) to 15 (36%). Obesity was associated in 11 (26.2%) patients. Headache in 32 (76%) was the most common presenting symptom. Headache was acute in 13 (31%), chronic daily in 12 (28.8%), acute recurrent in 4 (9.5%), and chronic relapsing in 3 (7.1%). Diplopia occurred in 18 (42.9%), visual loss in 14 (33.3%), vomiting in 15 (35.7%). Papilledema was present in all patients, and VIth cranial nerve paralysis in 8 (19.1%), one bilateral. Mean CSF opening pressure was 350 +/- 96 mm water. One had venous sinus thrombosis on MR venography.

Etiology was unidentified in 30 patients (71%) and termed primary PTC-HH. Secondary causes were detected in 12 (28.6%), defined as secondary PTC, and these included familial Mediterranean fever in 2, preceding trauma (2), and one of each of the following: mycophenolate mofetil-induced PTC, hypervitaminosis A, corticosteroid withdrawal with nephrotic syndrome, oral contraceptives, Guillain-Barre syndrome, urinary tract infection, varicella-zoster virus infection and dural venous sinus thrombosis with otitis media. Treatment included LP, acetazolamide (effective in 14 (37.8%)), and topiramate (effective in 13 of 17 patients (82.4%)). Mean duration of medical treatment was 9 months (range 1-48 months). Ventricular peritoneal shunt was beneficial in 3 patients with impaired visual fields, and visual acuity was normal in all patients at follow-up. (Per H, Canpolat M, Gumus H, et al. Clinical spectrum of the pseudotumor cerebri in children: Etiological, clinical features, treatment and prognosis. **Brain Dev** 2013 Jun;35(6):561-8). (Respond: Huseyin Per, Erciyes University, Division of Pediatric Neurology, Talas, Kayseri 38039, Turkey. E-mail: hper@erciyes.edu.tr).

COMMENT. Criteria for the diagnosis of idiopathic intracranial hypertension (HH) or pseudotumor cerebri (PTC) are as follows: 1) symptoms and signs of increased intracranial pressure or papilledema, 2) elevated CSF pressure at LP, 3) normal CSF composition, and 4) normal brain imaging (Per H et al. **Brain Dev** 2013 Jun;35:561-8). Treatable associated disorders should be excluded or treated. Topiramate appeared more effective than acetazolamide in this study and may be used as the drug of choice. Prompt diagnosis and management are important to prevent loss of visual field and acuity.

SLEEP DISORDERS

THALAMIC GLUTAMATE/GLUTAMINE IN RESTLESS LEGS SYNDROME

Investigators at Johns Hopkins University, Baltimore, MD, studied glutaminergic activity and arousal in 28 adults with restless legs syndrome (RLS) and 20 matched controls, using proton magnetic resonance spectroscopy. The thalamic glutamate/glutamine/creatine ratio was higher in patients with RLS than controls ($p=0.016$) and correlated significantly with the wake time during the sleep period ($p=0.007$) and all other RLS-related polysomnographic sleep variables ($p<0.05$) except for periodic leg movements during sleep (PLMS/hour). Glutamate metabolism is strongly related to arousal sleep disturbance but not to PLMS motor features of RLS. This finding contrasts with the reverse for dopamine that shows a limited relation to arousal sleep disturbance but strong relation to PLMS. (Allen RP, Barker PB, Horska A, Earley C J. Thalamic glutamate/glutamine in restless legs syndrome. **Neurology** 2013 May 28;80(22):2028-34). (Response: Dr RP Allen, E-mail: richardjhu@mac.com).

COMMENT. An increased glutaminergic activity in RLS demonstrated in this study represents a new RLS abnormality involving thalamocortical activation in a major nondopaminergic neurologic system. The authors (Allen RP, et al) conclude that the combination of glutaminergic (sleep disturbance) and dopaminergic (sensory symptoms, PLMS) abnormalities are involved in the full RLS symptomatology. The elevated

glutamate levels are considered a reflection of “hyperarousal” of RLS, which leads to sleep disturbance at night.

In an editorial (**Neurology** 2013 May 28;80(22):2006-7), Winkelman JW asks the question, is RLS a sleep disorder, a movement disorder, or a chronic pain disorder? He concludes that individual patients should be subtyped into biologically based phenotypes, with or without sleep disturbance, PLMS, or painful RLS. Although the current Hopkins study was confined to older subjects, RLS is also a pediatric problem and is closely associated with brain iron insufficiency and dopaminergic dysfunction. (Connor JR et al. **Brain** 2011 Apr;134(Pt 4):959-68). (Dosman C. et al. **Paediatr Child Health** 2012 Apr;17(4):193-7).

Oral iron and RLS. Oral iron treatment is initiated for RLS if serum ferritin is below 50 ng/mL. In a study of 22 children referred because of sleep disturbances, median age at onset of RLS symptoms was 7.5 months (range, 0-40 months). In addition to kicking or hitting the legs, the most striking symptoms were awakening after 1-3 hours of sleep followed by screaming and crying. Oral iron supplementation had a positive ferritin-concentration-dependent clinical effect. A relation between high PLMS index and low ferritin levels was demonstrated. An increased awareness of RLS in early childhood is recommended (Tilma J, et al. **Acta Paediatr** 2013 May;102(5):e221-6).

NARCOLEPSY AND H1N1 INFLUENZA VACCINATION

The incidence of narcolepsy between January 2000 and December 2010 in children in western Sweden and its relation to the Pandemrix H1N1 influenza vaccination were assessed by collection of data from hospital and clinic medical records and by parent telephone interviews. Of 37 children identified with narcolepsy, 9 had onset of symptoms before the H1N1 vaccination and 28 had onset of symptoms within 12 weeks postvaccination. Median age at onset was 10 years. All patients in the postvaccination group were positive for human leukocyte antigen (HLA)-DQB1*0602. The incidence of narcolepsy was 25 times higher after the vaccination compared with the time period before. Pandemrix H1N1 vaccination is a precipitating factor for narcolepsy. Postvaccination narcolepsy has a lower age at onset and more sudden onset than generally seen. (Szakacs A, Darin N, Hallbook T. Increased childhood incidence of narcolepsy in western Sweden after H1N1 influenza vaccination. **Neurology** 2013 Apr 2;80(14):1315-21). (Response: Dr A Szakacs, County Hospital, Halmstad, Sweden).

COMMENT. An abrupt increase in the incidence of childhood narcolepsy also followed an adjuvanted AH1N1 vaccine in Finland. The incidence of narcolepsy was 9.0 in the vaccinated as compared to 0.7/100,000 person years in unvaccinated individuals, the rate ratio being 12.7 (Nohynek H, et al. **PLoS One** 2012;7(3):e33536). A similar increased risk of narcolepsy followed vaccination with adjuvanted pandemic A/H1N1 2009 vaccine in England (Miller E, et al. **BMJ** 2013 Feb 26;346:f794). In contrast, no increase in narcolepsy diagnoses followed the H1N1 pandemic and vaccination campaign in Denmark, in South Korea (Choe YJ, et al, **Vaccine** 2012 Dec 14;30(52):7439-42), or in China (Han F, et al, **Ann Neurol** 2011 Sep;70(3):410-7). An autoimmune process is considered the most likely mechanism for the narcolepsy following influenza vaccination (Kornum BR, et al. **Curr Opin Neurobiol** 2011 Dec;21(6):897-903).