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NEUROMUSCULAR DISORDERS

SMALL-FIBER POLYNEUROPATHY AND PAIN SYNDROMES

Investigators at the Massachusetts General Hospital, Boston, MA, tested the hypothesis that acquired small-fiber polyneuropathy (SFPN) contributes to unexplained widespread pain syndromes in children and adolescents. Medical records of 41 consecutive patients were analyzed for objective diagnostic test data for SFPN. These included skin biopsy, nerve biopsy, and autonomic function testing, plus histories, symptoms and signs, and treatments. Healthy matched volunteers acted as normal controls for SFPN tests.

In this polyethnic patient sample, age at illness onset averaged 12.3 +/- 5.7 years; 73% were female, 68% chronically disabled, and 68% had been hospitalized. Objective diagnostic test results were definite for SFPN in 59%, probable in 17%, and possible in 22%. Only 1 had normal SFPN test results. Somatic complaints other than pain were reported in 98% patients and were consistent with SFPN dysautonomia (90% cardiovascular, 82% gastrointestinal, and 34% urological). Chronic fatigue was reported in 83% and chronic headache in 63%. Neurological examinations identified reduced sensation in 68% and vasomotor abnormalities in 55%, including erythromelalgia in 23%. Tests for causality of pain revealed only a history of autoimmune disease elicited in 33% and serologic markers of disordered immunity in 89%. Treatment with corticosteroids and/or IV immunoglobulin benefited 80% of patients (12/15), both objectively and subjectively. (Oaklander AL, Klein MM. Evidence of small-fiber polyneuropathy in unexplained, juvenile-onset, widespread pain syndromes. **Pediatrics** 2013 Apr;131(4):e1091-e1100).

COMMENT. Chronic, diffuse pain syndromes involving small nonmyelinated-C fiber peripheral nerves, especially in the extremities and feet, and the autonomic nervous system are a well-known but little understood disorder of the elderly, often referred to as

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"burning feet syndrome." The cause may be nutritional, vitamin B deficiencies, diabetes, hypothyroidism, spinal stenosis, or genetic (Dyck PJ et al. Burning feet as the only manifestation of dominantly inherited sensory neuropathy. **Mayo Clin Proc** 1983 Jul;58(7):426-9), but often idiopathic (Ropper AH, Samuels MA eds. Diseases of the peripheral nerves. In: **Adams and Victor's Principals of Neurology**. New York, McGraw Hill Medical, 2009, Chap 46;1296-7). SFPN in children is rarely reported. It appears to be an autoimmune disorder, but symptoms of dysesthesia and hyperesthesia are also encountered in children with ADHD and PDD, associated with an abnormal microarray, deletion 17p12 (Personal case report) (Grozeva D, et al. **Schizophr Res** 2012 Mar;135(1-3):1-7).

Diagnostic testing for small fiber neuropathy.

SFPN is characterized by loss of sensation (thermal and pinprick hypoesthesia) and positive sensory symptoms (burning pain, allodynia, hyperalgesia). Clinical neurological examination and routine neurophysiologic tests are often insufficiently sensitive, but skin biopsy and recent availability of normative reference values are of proven value in the diagnosis of damaged small nerve fibers (Lauria G, Lombardi R. Small fiber neuropathy: is skin biopsy the holy grail? **Curr Diab Rep** 2012 Aug;12(4):384-92). In an earlier study of 486 patients with SFPN, skin biopsy had a diagnostic efficiency of 88.4%, clinical examination of 54.6% and quantitative sensory testing of 46.9% (Devigili G, et al. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. **Brain** 2008 Jul;131(Pt 7):1912-25).

COATS SYNDROME IN FACIOSCAPULOHUMERAL DYSTROPHY TYPE 1

Investigators at University of Rochester Medical Center, NY; Hopital Archet-CHU de Nice, France; and Albert Einstein College of Medicine, NY, studied the frequency of Coats syndrome and its association with D4Z4 contraction size in 408 patients identified with facioscapulohumeral dystrophy type 1 (FSHD1). Three patients (0.8%) had a history of Coats disease, and 14 patients had FSHD and Coats syndrome confirmed by ophthalmologic examination. Median age at diagnosis of Coats syndrome was 10 years. The median D4Z4 fragment size was 13 kilobases. Close surveillance for retinal complications is recommended in FSHD1 patients with D4Z4 fragments <15kb. (Statland JM, Sacconi S, Farmakidis C, Donlin-Smith CM, Chung M, Tawil R. Coats syndrome in facioscapulohumeral dystrophy type 1. **Neurology** 2013 Mar 26;80(13):1247-50). (Response: Dr Statland: Jeffrey_Statland@URMC.Rochester.edu).

COMMENT. Coats disease, characterized by exudative retinitis and telangiectases of the retina, with slow progression to retinal detachment, may occur alone as an idiopathic form, unilateral, in males with onset at age 1-20 years, or as a syndrome, associated with FSHD1 and high-frequency hearing loss. FSHD1 is caused by a loss of D4Z4 repeat units on chromosome 4q35. Coats disease in the FSHD-associated syndrome is bilateral, it occurs at any age, and most frequently in female patients with FSHD and large contractions (allele size <15 kb). Contraction size (<15 kb) rather than age or FSHD severity should determine the need for annual retinal examinations for retinal vascular

involvement and possible surgery. An early sign of Coats disease is a yellow-eye in flash photography, a reflection off cholesterol deposits in retinal blood vessels.

Coats disease is named after George Coats (Coats G. Forms of retinal disease with massive exudation. **Royal London Ophthalmic Hospital Reports**. 1908;17(3):440-525). A syndrome characterized by retinal, hearing, muscle and mental disorders was described 60 years later by Robert G. Small (Small RG. Coats' disease and muscular dystrophy. **Transactions of the American Academy of Ophthalmology and Oto-Laryngology, Rochester, MN.** 1968 Mar-Apr;72(2):225-31).

SMA TYPE III MIMICS MUSCULAR DYSTROPHY

Researchers at the National Neuroscience Institute, Riyadh, Saudi Arabia, report a series of 8 patients with type III spinal muscular atrophy who were referred with a diagnosis of muscular dystrophy. Developmental milestones were normal until early juvenile or teens years when they showed a slowly progressive proximal weakness involving limb-girdle muscles. A clumsy gait was associated with frequent falls and difficulty in climbing stairs. Seven patients were products of consanguineous marriage. Hypertrophy of calves in 3 patients contrasted with generalized muscle wasting. Tongue fasciculation occurred in 2 patients, deep tendon reflexes were diminished in 7, and spinal scoliosis developed in 5. Muscle biopsy had nonspecific myopathic features in 3 patients, and nerve conduction studies showed normal, mildly neurogenic or myopathic changes. Serum creatine kinase levels varied from normal to significantly elevated. The diagnosis of SMA III was confirmed by gene testing where deletions of exon 7 were detected in all patients. (Alsaman AS, AlShaikh NM. Type III spinal muscular atrophy mimicking muscular dystrophies. **Pediatr Neurol** 2013 May;48(5):363-6). (Response: Dr Alsaman. E-mail: aalsaman@kfmc.med.sa).

COMMENT. In the diagnosis of SMA type III, the presence of dystrophic features such as calf muscle hypertrophy, limb-girdle muscle weakness, elevated serum CPK, and myopathic or dystrophic muscle biopsy findings will sometimes lead to confusion with muscular dystrophy. Diagnosis is confirmed with a molecular genetic polymerase chain reaction-based test for 5q telomeric SMN1 mutation.

VASCULAR DISORDERS

INTRACEREBRAL HEMORRHAGE, ACUTE SYMPTOMATIC SEIZURES, AND EPILEPSY

Investigators at Yale University School of Medicine, New Haven, CT; Children's Hospital of Philadelphia; Vanderbilt University, Nashville, TN; and Johns Hopkins University, studied the incidence and risk factors for seizures and epilepsy in 73 children with spontaneous intracerebral hemorrhage (ICH) including 20 perinatal subjects (>37 weeks gestation to 28 days) and 53 aged >28 days to <18 years at presentation. Acute symptomatic seizures occurred in 35 subjects (48%); they were a presenting symptom of ICH in 12 perinatal (60%) and 19 childhood (36%) subjects, and they occurred after

presentation in 7. Electroencephalographic-only seizures occurred in 9 of 32 subjects (28%) with continuous EEG monitoring. One-year and 2-year remote symptomatic seizure-free survival rates were 82% and 67%, respectively. One-year and two-year epilepsy-free survival rates were 96% and 87%, respectively. Elevated intracranial pressure requiring acute intervention was a risk factor for seizures after presentation (P=0.01), for remote symptomatic seizures (P=0.03), and epilepsy (P=0.04). Single remote symptomatic seizures occur in many, and epilepsy is estimated to develop in 13% patients at 2 years after ICH presentation. (Beslow LA, Abend NS, Gindville MC, et al. Pediatric intracerebral hemorrhage. Acute symptomatic seizures and epilepsy. **JAMA Neurol** 2013 Apr 1;70(4):448-54). (Respond: Beslow LA, Section of Child Neurology, Yale University, New Haven CT. E-mail: lauren.beslow@yale.edu).

COMMENT. Acute symptomatic seizures were defined as those occurring up to 7 days after the incident ICH, and remote symptomatic seizures as occurring beyond 7 days from ICH presentation. An editorial points out that acute symptomatic seizures with ICH occur more frequently in children (60%) than in adult reports (7%-31%) (Heyer GL, Roach ES. **JAMA Neurology** 2013 Apr 1;70(4):437).

Hemisphere specific motor control mechanisms in post-stroke rehabilitation. Left hemisphere damage is associated with greater errors in movement direction of the contralateral limb while errors in movement extent are greatest after right hemisphere damage. The differential deficits induced by right or left hemisphere lesions must be considered during post-stroke rehabilitation. (Mani S et al. **Brain** 2013 Apr;136(Pt 4):1288-303).

RISK FACTORS FOR ARACHNOID CYST HEMORRHAGE

Neurosurgeons at Primary Children's Medical Center, University of Utah, Salt Lake City, evaluated factors that are associated with rupture of arachnoid cysts (intracystic hemorrhage, subdural hematoma, or adjacent subdural hygroma) in children with previously asymptomatic arachnoid cysts. Two unruptured nonhemorrhagic controls were matched to each case. A total of 309 patients with treated and untreated arachnoid cysts were identified between 2005 and 2010, an institutional prevalence of 1.9%. After exclusion of surgical cases, 232 remained in the study. Risk factors evaluated included arachnoid cyst size, recent head trauma, and altitude at residence. Fourteen cases (6%) presented with either rupture or hemorrhage. Larger cyst size and diameter was significantly associated with cyst rupture/hemorrhage ($p<0.001$). Recent history of trauma was also associated with outcome ($p<0.01$). Altitude was not a risk factor. Children with rupture/hemorrhage were more likely to present with headache or signs or symptoms of raised intracranial pressure, including midline shift. None suffered neurological sequelae. (Cress M, Kestle JRW, Holubkov R, Riva-Chambrin J. Risk factors for pediatric arachnoid cyst rupture/hemorrhage: A case-control study. **Neurosurgery** 2013 May;72(5):716-22). (Response: Jay Riva-Chambrin MD. E-mail: Jay.Riva-Cambrin@hsc.utah.edu).

COMMENT. Cyst size and recent head trauma are risk factors for cyst rupture.

SEIZURE DISORDERS

CORTICAL EXCITABILITY MEASURES IN PATIENTS AND UNAFFECTED SIBLINGS

Researchers at St Vincent's Hospital, Victoria, Australia, measured cortical excitability using transcranial magnetic stimulation in 157 patients with epilepsy (95 generalized and 62 focal) and their asymptomatic siblings and results were compared to those of 12 controls and 20 of their siblings. No differences were observed in cortical excitability between healthy controls and their siblings. Compared to controls, cortical excitability was higher in siblings of patients with generalized or focal seizures. Motor threshold was lower in patients with juvenile myoclonic epilepsy compared with their siblings. The disturbance in cortical excitability appears to involve intracortical inhibitory circuits even in siblings of patients with a structural abnormality and acquired epilepsy. (Badawy RAB, Vogrin SJ, Lai A, Cook MJ. Capturing the epileptic trait: cortical excitability measures in patients and their unaffected siblings. **Brain** 2013 Apr;136(Pt 4):1177-91). (Response: Dr Radwa Badawy. E-mail: badawyr@unimelb.edu.au).

COMMENT. The authors conclude that certain genetic factors that predispose to epilepsy and a complex genetic/environmental interaction determine the clinical phenotype.

Gene mutations in progressive myoclonus epilepsies.

A mutation in the potassium channel associated gene CNTN2 was the cause of a cortical myoclonic tremor and epilepsy in a consanguineous Egyptian family (Stogmann E, et al. **Brain** 2013 Apr;136(Pt 4):1155-60)

A mutation in the GOSR2 gene was identified in 12 patients with "North Sea" progressive myoclonus epilepsy. Early onset ataxia at 2 years of age was followed by myoclonic seizures at average age 6.5 years, followed by multiple seizure types. All patients developed scoliosis by adolescence, an important diagnostic clue, some had pes cavus or syndactyly, and all had elevated serum creatine kinase (mean 734 IU) and normal muscle biopsies. EEG showed generalized S/W with posterior predominance and photosensitivity. With progressive decline, patients became wheelchair bound by mean age 13 years. The cases all came from countries bounding the North Sea. The relentless course distinguished "North Sea" progressive myoclonus epilepsy (PME) from other PMEs (Lomax LB, et al. **Brain** 2013 Apr;136(Pt 4):1146-54). Other PMEs include Unverricht-Lundborg disease (gene CSTB mutation), Lafora's disease (EPM2A), Northern with mental retardation (CLN8), and teenage-onset PME (CLNB) (Andrade DM, et al. **Pediatr Neurol** 2012 Sep;47(3):205-8).

TREATMENT OF SYMPTOMATIC INFANTILE SPASMS

Investigators at Tokyo Women's Medical University studied the clinical, radiological, and EEG characteristics of 69 patients with infantile spasms (IS) followed for 3-74 months (mean 18 months) after initial cessation of epileptic spasms (ES).

Subjects were classified as focal (fIS)(n=23) and diffuse (dIS)(n=46). ES responded to the initial ACTH trial in 100% fIS vs 80% of dIS (p=0.02). Subsequent seizure relapse occurred in 74% fIS cf 38% of the dIS group (p=0.0006). A second ACTH course of therapy in fIS group resulted in a short- or long-term remission. Approximately one-third of fIS patients maintained remission despite focal epileptic EEG abnormalities. Focal resection and corpus callostomy achieved only a short-term remission. Grouping patients as fIS and dIS provides practical information regarding long-term outcome and treatment strategies. (Fujii A, Oguni H, Hirano Y, Shioda M, Osawa M. A long-term, clinical study on symptomatic infantile spasms with focal features. **Brain Dev** 2013 May;35(5):379-85). (Response: Dr Hirokazu Oguni. E-mail: hoguni@ped.twmu.ac.jp).

COMMENT. The authors conclude that a second course of ACTH should be considered to treat a relapse of fIS before resorting to surgical therapy. An extremely low-dose ACTH step-up protocol is used to treat West syndrome (WS) in this institution (Oguni H, et al. **Brain Dev** 2006 Jan;28(1):8-13). In an earlier report of 31 infants with WS (cryptogenic WS in 9, symptomatic WS in 22) using ACTH-Z in a dose of 0.005 mg (0.2 IU/kg/day) once daily for at least 2 weeks, up to a maximum of 3 weeks, tapered to zero over the subsequent 1 or 2 weeks, successful control of both spasms and hypsarrhythmia was obtained in 17 patients (55%). In the absence of a response, the dosage was increased to 0.025 mg (1.0 IU/kg/day) for 2 weeks (second treatment course in 8 patients), providing complete suppression of WS in an additional 2 patients. At 1 year or more follow-up, 13 patients (48%) remained seizure-free. Side effects were mild and occurred in 13 patients. This ACTH extremely low-dose step-up method achieved 61% short-term and 48% long-term remission, without significant side effects. The efficacy of low-dose versus high-dose ACTH regimens continues to be debated (Ito M, et al. **Pediatr Neurol** 1990 Jul-Aug;6(4):240-4; Snead OC, et al. **Neurology** 1989 Aug;39(8):1027-31; Snead OC. **Pediatr Neurol** 1990 May-Jun;6(3):147-50).

EVIDENCE-BASED GUIDELINE FOR TREATMENT OF NEUROCYSTICERCOSIS

The Guideline Development Subcommittee of the AAN conducted a literature search and review of 10 Class I or Class II trials of treatment for parenchymal neurocysticercosis. Albendazole therapy, with or without corticosteroids, is probably effective in decreasing both long-term seizure frequency and the number of cysts demonstrable radiologically in adults and children with neurocysticercosis, and is well-tolerated. Insufficient information is available to assess efficacy of praziquantel. Albendazole plus either dexamethasone or prednisolone should be considered, both to decrease the number of active lesions on brain imaging studies (Level B) and to reduce long-term seizure frequency (Level B). The evidence is insufficient to support or refute the use of steroid treatment alone in patients with intraparenchymal neurocysticercosis (Level U). (Baird RA, Wiebe S, Zunt JR, Halperin JJ, Gronseth G, Roos KL. Evidence-based guideline: Treatment of parenchymal neurocysticercosis. **Neurology** 2013 Apr 9;80(15):1424-1429). (Respond: AAN. E-mail: guidelines@aan.com).

COMMENT. Cysticercal cysts evolve through 4 stages: vesicular with living larva, colloidal stage with degenerate larva, granulonodular stage with thickened cyst membrane, and calcification stage. Only cysts in the vesicular and colloidal stages contain the larvae and are amenable to anticysticercal treatment. Cysticercosis, infection with the larval form of Taenia solium, is the most common preventable cause of epilepsy in the developing world (Coyle CM, et al. **PLoS Negl Trop Dis** 2012;6(5):e1500).

ENCEPHALITIS

ANTI-N-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS

Investigators at Universities of Barcelona, Pennsylvania, Oviedo, and Valencia, and the Spanish NMDAR Encephalitis Work Group report the clinical features of 20 pediatric patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis seen in a single center in Spain in the last 4 years. Median patient age was 13 years (range, 8 months-18 years); 70% were female. Initial symptoms were neurologic (dyskinesias or seizures) in 12 (60%) and psychiatric in 40%. By one month after disease onset, all had involuntary movements and changes in behavior and speech. All patients received steroids, IV immunoglobulin or plasma exchange, and 7 rituximab or cyclophosphamide. At a median follow-up of 17.5 months, 85% had substantially recovered, 10% had moderate or severe deficits, and 1 had died. Three patients had previous episodes compatible with anti-NMDAR encephalitis, and 2 had additional relapses. Ovarian teratoma was identified in 2 patients (10%), 1 at disease onset and the other one-year later. A novel characteristic EEG pattern ("extreme delta brush") occurred in one 18-year-old patient. A 2-year-old patient developed anti-NMDAR as post herpes simplex encephalitis choreoathetosis; her recovery was complicated by a bilateral facial weakness and anarthria (Foix-Chavany-Marie syndrome). (Armangue T, Titulaer MJ, Malaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis - Clinical analysis and novel findings in a series of 20 patients. **J Pediatr** 2013 Apr;162(4):850-856.e2). (Reprint requests: Josep Dalmau MD, PhD, E-mail: Josep.dalmau@uphs.upenn.edu).

COMMENT. Since the initial description of NMDAR encephalitis (Dalmau J, et al. **Ann Neurol** 2007 Jan;61(1):25-36), and in children (Florance NR, et al. **Ann Neurol** 2009 Jul;66(1):11-8), this encephalitis has been reported frequently as single case histories, small series, and in one large series of 500 patients (Titulaer MJ, et al. **Neurology** 2012 Apr;78(Meeting Abstracts 1): PL01.001). The present series in children adds to our experience with this intriguing disorder and increases our awareness of the presenting symptoms and diagnosis. The rare link between NMDAR encephalitis and post herpes simplex encephalitis choreoathetosis, and the etiologic significance of ovarian teratoma require further study. The "delta brush" EEG pattern in one patient, previously described in 30% of an adult cohort, may be unique to NMDAR encephalitis and correlates with disease severity (Schmitt SE, et al. **Neurology** 2012 Sep 11;79(11):1094-1100).

HEADACHE DISORDERS

CHILDHOOD MIGRAINE AND INFANTILE COLIC

Investigators at the Robert Debre Hospital, Paris, and other centers in France and Italy report a case-control study of 208 consecutive children aged 6 to 18 years presenting to the ED and diagnosed with migraine and controls with minor trauma. Children with migraine (with or without aura) were more likely to have experienced infantile colic than those without migraine ($p<0.001$). In a second study of 120 children diagnosed with tension-type headache, this association was not found ($p=0.10$). (Romanello S, Spiri D, Marcuzzi E, et al. Association between childhood migraine and history of infantile colic. **JAMA** 2013 Apr 17;309(15):1607-12). (Response: Dr Luigi Titomanlio. E-mail: Luigi.titomanlio@rdb.aphp.fr).

COMMENT. An editorial (Epstein LG, Zee PC. Infantile colic and migraine. **JAMA** 2013 Apr 17;309(15):1636-7) notes that migraine disorders may represent a continuum from colic in infancy to cyclic vomiting syndrome in young children to childhood and adult migraine. Infantile colic is an early form of migraine and is subject to the same genetic factors and environmental triggers. Both are affected by the sleep-wake cycle. Other periodic disorders discussed as migraine variants include benign paroxysmal vertigo and benign paroxysmal torticollis. (Response: Dr Leon G Epstein, Ann & Robert H Lurie Children's Hospital of Chicago. E-mail. L-Epstein@northwestern.edu).

HEADACHE AND VASCULAR EVENTS WITH BRAIN TUMORS

Investigators at the Children's Hospital of Philadelphia, PA, performed a retrospective study of 265 children with brain tumors who received cranial irradiation and developed severe recurrent headache. Review of medical records found that stroke or TIA occurred in 7/37 (19%) with severe headache compared to 6/228 (3%) without these events, when followed for a median of 6.0 years ($p=0.003$). Median time for a first neurovascular event was 4.9 years (range 1.7-5.5 years). (Kranick SM, Campen CJ, Kasner SE, et al. Headache as a risk factor for neurovascular events in pediatric brain tumor patients. **Neurology** 2013 Apr 16;80(16):1452-6). (Response: Dr Kranick. E-mail: sarah.kranick@nih.gov).

COMMENT. Severe recurrent headache is a risk factor for subsequent cerebral ischemia in pediatric brain tumor survivors treated with radiation. The investigators distinguish between these neurovascular events and the syndrome of stroke-like migraine after radiation therapy (SMART). SMART is characterized by neurologic deficits that resolve completely after weeks or months, without EEG evidence of seizures, and transient MRI changes of posterior cortical gyral enhancement following cranial irradiation (Pruitt A, et al. **Neurology** 2006 Aug 22;67(4):676-8; Partap S, et al. **Neurology** 2006 Apr 11;66(7):1105-7). Longer life expectancy of children with brain tumors increases the prevalence of complications and the importance of close neurologic surveillance.