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SYNCOPE

SYMPTOMS, SIGNS, AND EEG CHANGES DURING REFLEX SYNCOPE

Investigators at Leiden University Medical Centre, The Netherlands, studied the symptoms, video data of signs, and EEG changes during tilt-induced vasovagal syncope in 69 subjects, age range 12-84 years (mean 46 years). Reflex syncope occurred during 92 (12.8%) of a total of 720 tilt-table tests, presyncope in 101 (14.1%), and orthostatic hypotension in 84 (11.7%). The average duration of loss of consciousness was 22.4 s (range 4-55 s). EEG slowing preceded the onset of loss of consciousness. Flattening of the EEG indicates more profound circulatory changes and cerebral hypoperfusion than EEG slowing alone. 'Slow-flat-slow'-EEG is associated with a lower minimum blood pressure, longer maximum RR-interval, more frequent asystole, and longer duration of loss of consciousness than the 'slow'-EEG group.

Clinical signs during syncope were of 4 types, based on their relation to the EEG: Type A signs include loss of consciousness, eye opening and general stiffening and occur during the first slow and flat phases in the EEG and end in the second slow phase. Type B signs (myoclonic jerks) occur when the EEG is slow, and are abolished with EEG flattening. Type C signs (making sounds, roving eye movements, and stertorous breathing) occur only in the EEG flat phase, whereas type D signs (dropping the jaw and snoring) occur either in slow or flat phases. The occurrence of specific clinical signs depends on whether the EEG shows flattening. Events occurring before syncope included sweating, pallor and yawning; during syncope, eyes open, dilated pupils, oral automatisms, head and jaw dropping, and arm raising; and after syncope, sweating and pallor. Whether the pattern of signs may be used to infer cause of the syncope remains to

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be determined. Syncope resulting in short, shallow hypoperfusion will elicit signs corresponding to the slow EEG pattern, whereas a cause resulting in a quick circulatory standstill will result in signs typical of slow-flat-slow EEG pattern. Whereas eyes are open in syncope and in seizures, they are commonly closed in psychogenic attacks [1]. (van Dijk JG, Thijs RD, van Zwet E, et al. The semiology of tilt-induced reflex syncope in relation to electroencephalographic changes. **Brain** 2014 Feb;137(Pt 2):576-85).

COMMENTARY. Syncope is defined as a transient loss of consciousness resulting from cerebral hypoperfusion/hypoxia. Vasovagal reflex syncope is the most common form of syncope, sometimes called neurocardiogenic or neurally mediated syncope. The autonomic nervous system is activated, resulting in low blood pressure, decreased cardiac output, vasodilatation and bradycardia. Recognized usually by the pattern of symptoms and signs only, the present study provides a correlation between symptoms, signs, video and EEG data, leading toward a more definite diagnosis. Vasovagal syncope is differentiated from other, rare causes of syncope, including cardiac (ventricular tachycardia, long QT syndrome, Wolff-Parkinson-White syndrome, and atrioventricular block), and non-cardiovascular pseudo-syncopes (reflex anoxic seizures or psychogenic causes) [2].

The differentiation of syncope from seizure (faint from fit) [3] is often difficult. One authority finds in patients presenting with anoxic-epileptic seizures the epileptic component is usually clonic, whereas the nonepileptic convulsive syncope is an arrhythmic tonic extension or spasm [4]. Opisthotonus is common in asystolic syncope in young children but was not seen in the present cohort of older patients [5]. In a study of 141 children referred for evaluation of syncope, 78% had simple neurocardiogenic syncope, 38% had syncopal convulsions, and 2.8% had concurrent epilepsy. The EEG performed in 91 (64%) subjects was diagnostic for epilepsy in 1 (1.4%). MRI, and/or EKG/Holter monitoring/stress testing were primarily normal or nondiagnostic. A detailed medical history was the most useful diagnostic tool [6].

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HEADACHE DISORDERS

POST-LUMBAR PUNCTURE HEADACHE AND NEEDLE GAUGE

Investigators from the Oncology Unit, Royal Children's Hospital, Melbourne, Australia, compared the frequency of headache and procedure time following lumbar puncture (LP) in a randomized crossover trial using a 25-gauge compared to a 22-gauge needle. LP headache occurs within 7 days after the procedure, becomes worse within 1.5 min of standing up and improves within 30 min of lying down. As part of their treatment

for leukemia, 93 children, aged 4-15 years, were allocated a random sequence of 4 LPs, two with a 22-guage needle and two with a 25-gauge needle, all performed under general anesthesia (sevoflurane). A single needle insertion was used in 320 (94%) procedures; multiple attempts were required in 21 (9 with 22-gauge needle and 12 with 25-gauge (p=0.5).

Analysis of 341 LPs showed an incidence of 7.2% post-LP headache that followed the use of a 22-gauge needle was not significantly different from an incidence of 4.6% when using a 25-gauge needle (p=0.3). Also, the incidence of any headache following LP was not related to needle size (18% with 22-gauge needle and 15% with 25-gauge needle; p=0.4). Having one LP headache did not predispose to recurrence; only one child had two LP headaches. LP procedure time (time for collection of 22 drops [1 ml] CSF) was doubled when using the 25-gauge needle. Incidence of post-LP headache was not lower in younger children and was unrelated to age; it was higher in girls than in boys (11% vs 3%, respectively, p=0.014). The overall functional impact of post-LP headache in a child with leukemia was assessed as moderate or severe in 55% of families. (Crock C, Orsini F, Lee KJ, Phillips RJ. Headache after lumbar puncture: randomized crossover trial of 22-gauge versus 25-gauge needles. **Arch Dis Child** 2014 Mar;99(3):203-7).

COMMENTARY. Incidence of post-LP headache in children treated for leukemia is higher following use of a 22-gauge compared to a 25-gauge needle, but the difference is not significant. The authors conclude that either gauge may be appropriate for LP in a child. In contrast, adults have a significantly lower incidence of LP headache when using smaller diameter needles and needles with a blunt, pencil-type point rather than the traditional cutting point [1][2].

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ROLE OF PACAP IN MIGRAINE HEADACHES

Investigators at Danish Headache Centre, University of Copenhagen, Glostrup, Denmark, studied the incidence of migraine during and after intravenous infusion of pituitary adenylate cyclase-activating polypeptide-38 (PACAP38) and vasoactive intestinal polypeptide (VIP) in 22 female migraine patients without aura (mean age 24 years [range 19-36]). Sixteen patients (73%) reported migraine-like attacks after PACAP38 and 4 after VIP (18%) infusion (P=0.002). Three of 4 patients who reported migraine-like attacks after VIP also reported attacks after PACAP38. Both peptides induced dilatation of extracranial (P<0.05) but not intracranial arteries (P>0.05). PACAP38-induced vasodilatation lasted >2 h whereas VIP-induced dilatation was normalized after 2 h. Plasma PACAP38 levels were elevated at 1 h after starting infusion only in patients who reported migraine attacks. PACAP38 has a high affinity for the PAC1 receptor. Activation of the PAC1 receptor may explain the mechanism of migraine and offer a target for development of anti-migraine drugs. (Amin FM, Hougard A, et al. Investigation of the pathophysiological mechanisms of migraine attacks induced by pituitary adenylate cyclase-activating polypeptide-38. **Brain** 2014 Mar;137:779-94).

COMMENTARY. A commentary from the Department of Neurology, University of Szeged, Hungary, discusses the trigemino-vascular theory of migraine and the pain-transmission link between the vascular and neuronal regions [1]. PACAP and other neuropeptides have essential roles in activation of the trigemino-vascular system. PACAP38 is present in the trigeminal ganglion and caudal trigeminal nucleus. The effects of PACAP38 are mediated through G-protein-linked receptors, including PAC1. The clinical study by Amin et al [2] is consistent with previous laboratory animal studies comparing the effects of nitroglycerol and PACAP on the trigemino-vascular system [3].

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NEUROMUSCULAR DISORDERS

PHARYNGEAL-CERVICAL-BRACHIAL VARIANT OF GUILLAIN-BARRE SYNDROME

Investigators from National University Hospital, Singapore, review the clinical features of 13 cases of pharyngeal-cervical-brachial (PCB) variant of Guillain-Barre syndrome (GBS) and outline new diagnostic criteria. In a series of 100 patients with PCB reported previously from Japan [1] the age of onset ranged from 5-83 years (median age 43), antecedent upper respiratory tract infections and diarrhea occurred in 71% and 30%, respectively (similar to GBS), and 31% had serological evidence of Campylobacter jejuni infection. Cytomegalovirus, Epstein-Barr virus, Mycoplasma pneumoniae and Hemophilus influenzae were associated infrequently (6-1%). PCB is defined as 'pure' in patients presenting with rapidly progressive oropharyngeal and cervicobrachial weakness associated with areflexia/hyporeflexia but without ophthalmoplegia or leg weakness [2]. In contrast, some recent series describe sensory disturbance in the upper limbs, and normal or exaggerated reflexes. GBS forms a continuum of overlapping syndromes, those cases with ophthalmoplegia and ataxia overlapping with Fisher syndrome. One half of patients with PCB carry IgG anti-GT1a antibodies that cross-react with GQ1b, whereas most patients with Miller Fisher syndrome carry IgG and GQ1b antibodies that always cross-react with GT1a. Significant overlap between the clinical and serological profiles of these syndromes suggests a PCB/Fisher syndrome continuous spectrum. The neurophysiological findings in PCB are axonal rather than demyelinating. Myasthenia gravis, botulism and other myopathic disorders are differentiated from PCB by the absence of sensory deficits or areflexia. (Wakerly BR, Yuki N. Pharyngeal-cervical-brachial variant of Guillain-Barre syndrome. **J Neurol Neurosurg Psychiatry** 2014 Mar;85(3):339-44).

COMMENTARY. The diagnostic criteria for PCB variant of GBS include: 1) symmetric oropharyngeal weakness, arm weakness and areflexia/hyporeflexia; 2) absence of leg weakness, ataxia and disturbed consciousness; and 3) 12hr-28day interval

between onset and weakness. Supportive findings include: antecedent infection, CSF albumino-cytological dissociation, neurophysiological evidence of neuropathy, and presence of IgG anti-GT1a or anti-GQ1b antibodies. Brain MRI may be indicated to exclude brainstem ischemia, inflammation or brain tumor.

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RECURRENT MILLER FISHER SYNDROME

Investigators from University of Siena, Italy, describe 2 children with recurrent Miller Fisher syndrome. Episodes occurred at age 11.5 and 13 years in Patient 1 and at age 8 and 13 years in Patient 2. Both patients responded to treatment with steroids. Patient 1 presented with diplopia, unsteady gait and clumsiness. Neurologic examination showed ataxia, hyporeflexia, and ophthalmoplegia. Treatment with iv immunoglobulin was effective initially, but failed to prevent progressive weakness during the second attack that subsequently responded to steroid therapy. Patient 2 presented with paresthesia of hands and diplopia, ataxia, paresis of 6^{th} and 7^{th} cranial nerves, muscle weakness, and hyporeflexia. Recovery from both the initial and second attack followed steroid therapy. (Grosso S, Verrotti A, Tei M, Cornacchione S, Giannini F, Balestri P. Recurrent Miller Fisher syndrome in children. **Pediatr Neurol** 2014 Mar;50(3):269-71).

COMMENTARY. Recurrent Miller Fisher syndrome [1] is rare in childhood, and the second attack may be more aggressive and resistant to therapy. Steroids may be indicated if iv immunoglobulin is ineffective [2].

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PARANEOPLASTIC DISORDERS

PARANEOPLASTIC DISORDERS AND OVARIAN TUMORS

Researchers in Chang Gung University, Kaohsiung, and National Cheng Kung University, Tainan, Taiwan, assessed the prevalence and spectrum of paraneoplastic neurological disorders (PND) in children with benign ovarian tumor and the long-term outcome. The charts of 133 female patients below 18 years of age diagnosed with a pathologically proven benign ovarian tumor, Jan 1993 – Dec 2010, were reviewed, mostly mature teratoma. Six patients (4.5%) had neuropsychiatric manifestations, the majority (5) with onset after age 10 years. Depression or low mood, headache, mutism, hypoventilation, seizures, hallucination, vomiting and hypersalivation were the most common symptoms. NMDAR encephalitis in 2 patients and acute disseminated encephalomyelitis in 1 partially resolved after tumor removal and immunotherapy. One patient not receiving immunotherapy had neurological sequelae and long ICU stay. (Hsu

M-H, Huang C-C, Hung P-L, et al. Paraneoplastic neurological disorders in children with benign ovarian tumors. **Brain Dev** 2014 Mar;36(3):248-53).

COMMENTARY. Paraneoplastic disorders (PND) present with multiple manifestations resembling subacute encephalitis, peripheral neuropathy, cerebellar ataxia, opsoclonus myoclonus with neuroblastoma, and other symptoms. Patients with anti-NMDAR encephalitis may present with psychosis, memory deficits, seizures, speech problems, involuntary movements, and breathing disorders. Approximately 50% cases have ovarian tumors, mostly teratoma. In the present study, 5 of 6 (83%) patients with PND and ovarian teratoma had complete remission of symptoms after tumor removal. The authors recommend immunotherapy in all patients following tumor removal, despite apparent recovery after surgery [1].

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DEMYELINATING DISORDERS

POTASSIUM CHANNEL KIR4.1-SPECIFIC ANTIBODIES AND ACQUIRED DEMYELINATING DISEASE

Researchers at Technische Universitat, Munich, and other centers in Germany, studied the prevalence of KIR4.1-IgG by ELISA in 47 children with acquired demyelinating disease (ADD), in 22 with other neurologic diseases, 22 with autoimmune disease, and in 18 healthy controls. Serum antibodies to KIR4.1 were identified in 57% of children with ADD but none with other neurologic disease, autoimmune disease or healthy controls. KIR4.1-IgG titers were predominantly found in children with MS or clinically isolated syndrome and in 1 in 3 with demyelinating encephalitis, similar to the prevalence in adults with ADD. KIR4.1-IgG titers were significantly higher in children with ADD compared with control groups ($p<0.0001$); they were not age-dependent and did not correlate with myelin oligodendrocyte glycoprotein (MOG) antibody responses. MOG-IgG occurs before age 10 y in ADD whereas KIR4.1 antibodies are found in older children and adult patients with MS. (Kraus V, Srivastava R, Kelluri SR, et al. Potassium channel KIR4.1-specific antibodies in children with acquired demyelinating CNS disease. **Neurology** 2014 Feb 11;82(6):470-3).

COMMENTARY. KIR4.1, a potassium channel expressed on oligodendrocytes and astrocytes, contributes to the maintenance of the electrochemical gradient by removing potassium from the extracellular space. Mutations of the KIR4.1 gene cause EAST syndrome characterized by epilepsy, ataxia, sensorineural deafness, and tubulopathy [1]. The prevalence of KIR4.1-IgG in children with MS is similar to adults.

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MOTOR DISORDERS

GENOTYPE-PHENOTYPE CORRELATIONS IN ALTERNATING HEMIPLEGIA

Researchers at the National Center of Neurology and Psychiatry, Kodaira, and multiple centers in Japan, analyze the clinical features and ATP1A3 mutations in 35 Japanese children diagnosed with alternating hemiplegia of childhood (AHC). Gene analysis revealed de novo heterozygous missense mutations of ATP1A3 in 33 patients (7 female and 26 male), Glu815Lys (E815K) in 12 cases (36%), Asp801Asn (D801N) in 10 (30%), and other missense mutations in 11 cases. The Glu815Lys genotype is associated with the most severe AHC phenotype. The clinical features associated with these mutations revealed significant differences in the history of neonatal onset, gross motor level, status epilepticus, and respiratory paralysis in the Glu815Lys group compared with the other groups. The E815K mutation group developed abnormal ocular movements or seizures (status) in the first week after birth, and all patients showed very slow development. In contrast, the D801N mutation group had a later and milder onset and course and none showed severe motor deterioration. Other mutation groups also had a milder clinical course. Flunarizine was administered in 31 patients and was discontinued in 13. Seven of the 13 who discontinued flunarizine had either an abrupt or stepwise severe motor deterioration; none of those who continued flunarizine showed severe motor deterioration. (Sasaki M, Ishii A, Saito Y, et al. Genotype-phenotype correlations in alternating hemiplegia of childhood. **Neurology** 2014 Feb 11;82(6):482-90).

COMMENTARY. Alternating hemiplegia of childhood (AHC) is characterized by recurrent flaccid or dystonic hemiplegia of several minutes or days duration, abnormal ocular movements, involuntary movements, hypotonia, and seizures beginning before 18 months of age. Generally clinical features are sporadic and neuroimaging is normal. De novo mutations of the sodium-potassium-ATPase subunit gene (ATP1A3) are the cause. The time of onset and severity of symptoms of AHC are variable. Patients with early onset tend to have a severe deteriorating course, particularly those with E815K mutation, and sometimes as a sequel to fever and status epilepticus. Flunarizine treatment is recommended in the US and Canada [1], but approval in Japan has been withdrawn [2].

Benign, familial nocturnal alternating hemiplegia is distinguished from AHC by the absence of seizures and motor deterioration. It too responds to flunarizine [3] and is considered a migraine variant [4].

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ATTENTION DEFICIT DISORDERS

PUFA SUPPLEMENT IN ADHD: META ANALYSIS

Researchers at Hammersmith Hospital, London, and Academy of Nutritional Medicine, Cambridge, UK, conducted an updated meta-analysis of randomized controlled trials (RCTs) in ADHD, using data on PUFA content obtained from independent fatty acid methyl ester analyses of each study PUFA regimen. Standardized mean differences (SMD) in inattention, hyperactive-impulsive and combined symptoms were assessed as rated by parents, teachers or all raters. The pooled estimate from 18 studies showed that combined ADHD symptoms rated by all raters decreased with PUFA supplementation ($P<0.001$). When analyzed by rater, only parent-rated symptoms decreased significantly. Multivariable meta-regression showed that longer study duration, y-linolenic acid (GLA), and the interaction between GLA and eicosapentaenoic acid (EPA) were associated with significant decreases in inattention. PUFA regimen content was unrelated to changes in hyperactive-impulsive symptoms, but the potential psychoactivity of certain fatty acids in placebo preparations could not be excluded. The meta-analysis provides modest evidence of PUFA effectiveness in ADHD, especially a reduction of inattention symptoms by GLA and EPA. (Puri BK, Martins JG. Which polyunsaturated fatty acids are active in children with attention-deficit hyperactivity disorder receiving PUFA supplementation? A fatty acid validated meta-regression analysis of randomized controlled trials. **Prostaglandins Leukot Essent Fatty Acids** 2014 Feb 3. [Epub ahead of print]).

COMMENTARY. In patients who fail to respond or with parents opposed to medication, dietary methods in treatment of ADHD such as omega-3,-6 supplements may warrant a trial. Polyunsaturated fatty acid (PUFA) preparations contain variable quantities and combinations of omega-3, -6 and -9 fatty acids [1], and the optimal dosage is not well defined. Unlike medication for ADHD, the effect of treatment with fatty acid supplements is judged by weeks or months rather than hours or days. The demonstration that EPA/GLA interaction and not the docosahexaenoic acid (DHA) component of omega-3 account for the decreased inattentiveness provides a more discrete measure of the potential effectiveness of PUFA in ADD. EPA but not DHA is also responsible for the efficacy of omega-3 long chain PUFA supplementation in depression [2].

Interest in the role of diet in the treatment of ADHD extends from centers in London and Cambridge to the University of Southampton in the UK. Evaluation of reviews and meta-analyses of 11 randomized controlled trials found evidence of a small effect of free fatty acid supplements in ADHD, and an uncertain benefit of artificial color elimination [3]. Similar conclusions are expressed by parents of patients in our neurology clinic for ADHD in children and adolescents at Ann & Robert H. Lurie Children's Hospital of Chicago.

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