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TRAUMATIC BRAIN DISORDERS

RISK OF EPILEPSY AFTER TRAUMATIC BRAIN INJURY

The risk of epilepsy after traumatic brain injury was evaluated in a population-based study at Aarhus University Hospital, Denmark. Data from the Danish Civil Registration System identified 1,605,216 births, 1977-2002. During the study period, 78,572 people had at least one traumatic brain injury, and in the same period, 17,470 developed epilepsy, of whom 1017 had a preceding brain injury. Brain injury is classified as "mild" ('concussion,' loss of consciousness <30 min, amnesia <24 hrs, confusion/disorientation, or focal [temporary] neurological deficit); or "severe" (structural brain injury or skull fracture). Relative to no brain injury, the risk of epilepsy was two times higher after mild brain injury, seven times higher after severe brain injury, and two times higher after skull fracture. Risk of epilepsy was highest during the first years after both mild ($p<0.0001$) and severe ($p<0.0001$) brain injury, and the risk remained high for >10 years. Risk of epilepsy after skull fracture did not vary with time since injury ($p=0.16$). All age groups were affected, and risk increased with age for mild ($p<0.0001$) and severe ($p=0.02$) brain injury. Risks were highest in people older than 15 years at time of injury, and in those with long duration of hospital stay for severe brain injury ($p<0.0001$) or skull fracture ($p=0.02$). Duration of hospital stay was not a risk factor following mild brain injury. Risk was slightly higher in females than males. Patients with a family history of epilepsy had a notably higher risk of epilepsy after mild and severe brain injury. (Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. **Lancet** 2009 Feb 20 (Epub ahead of print). (Respond: Dr Jacob Christensen, Department of Neurology, Aarhus University Hospital, Norrebrogade 44, DK-8000 Aarhus C, Denmark. E-mail: jacob@farm.au.dk).

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COMMENT. Traumatic brain injury (TBI) is known to carry an increased risk of epilepsy, but factors that modify the incidence of epilepsy are not well defined. In a previous population-based study in Olmsted County, Minnesota, involving 4541 children and adults, the overall standardized incidence ratio for post-traumatic epilepsy was 3.1. For patients who had sustained a mild injury (loss of consciousness or amnesia for <30 min), the incidence ratio was 1.5, with no increase after 5 years; following moderate injury (loss of consciousness 30 min to 24 hrs or skull fracture) it was 2.9; and after severe injury (loss of consciousness or amnesia >24 hrs, subdural hematoma, or brain contusion) the incidence ratio was 17.0 (Annegers JF et al. **N Engl J Med** 1998;338:20-24). Patients in the Minnesota study with an increased incidence of epilepsy after 5 years had a history of severe brain injury and were age 65 yrs or older. In the Danish study, the risk of epilepsy was high for more than 10 years even after mild brain injury (concussion) in younger patients. Family history of epilepsy and mild brain injury independently contributed to the risk of post-traumatic epilepsy in children and young adults.

Prophylactic phenytoin does not reduce the incidence of early or late seizures following brain injury in children (Teasell R et al. **Brain Inj** 2007;21:201-214). Despite disappointing results of trials of prophylactic antiepileptic medication in head injury patients (Temkin NR. **Epilepsia** 2001;42:515-524), the Danish authors suggest their data warrant further study of newer agents in high risk patients. The evidence suggests that prevention of injury offers greater promise of success than prophylactic medication in reducing the prevalence of post-traumatic epilepsy.

RELATION OF AGE AT INSULT TO OUTCOME OF BRAIN INJURY

Cognitive and behavioral outcomes for children who sustain early brain insult (EBI) were evaluated in relation to age at insult in a study at Royal Children's Hospital, Victoria, Australia. Grouped according to age at time of focal brain insult, 36 sustained congenital (first-second trimester) injuries, 33 perinatal (third trimester to 1 month post-natal), 23 were in infancy (2 months to 2 years after birth), 19 preschool (3 to 6 years), 31 mid-childhood (7-9 years), and 19 late childhood (after age 10 years). Children were tested for intelligence, academic ability, executive function, and behavior. Children with EBI were at increased risk for impairment in all domains of cognition and behavior, with mean scores falling 1SD below expectations. Low scores in arithmetic were especially common, occurring in 63% of EBI children. EBI before 2 years resulted in global cognitive deficits, whereas injury sustained after 2 years of age was followed by near normal cognitive development. In contrast, behavior was worse in older children with EBI from 7 to 9 years compared to those sustaining injury from 3 to 6 years. The age at the time of brain insult is important in predicting risk of cognitive and behavioral outcomes in children with EBI, but patterns of vulnerability differ with respect to age at insult. (Anderson V, Spencer-Smith M, Leventer R, et al. Childhood brain insult: can age at insult help us predict outcome? **Brain** Jan 2009;132:45-56). (Respond: Vicki Anderson, Department of Psychology, Royal Children's Hospital, Flemington Road, Parkville, Victoria, 3052, Australia. E-mail: vicki.anderson@rch.org.au).

COMMENT. Children who sustain an early brain insult are at increased risk of developing impairments of cognition and behavior. Injury in the pre- or perinatal period or in

early childhood results in cognitive deficits whereas injury in later childhood is more likely to result in behavioral problems. The findings indicate an increased vulnerability of the young brain and a lack of evidence to support theories of brain plasticity. Children with a history of brain injury before, at birth or before 2 years of age are at risk of persistent impairments of learning that require early interventional therapy.

HEADACHE DISORDERS

MIGRAINE AND SUICIDAL IDEATION IN ADOLESCENTS

The relationship between migraine and suicidal ideation (self-reported thoughts of suicide-related behaviors) in a sample of young adolescents was determined in a study at Taipei Veterans General Hospital, Taipei, Taiwan. Students in three middle schools completed a validated headache questionnaire, the Adolescent Depression Inventory (ADI), and the Pediatric Migraine Disability Assessment questionnaire. The questionnaires assessed the headache profile during the past 3 months and symptoms of depression in the past month. "I think about killing myself" was the indicator of self-reported suicidal ideation. Suicidal ideation in the past month was reported in 8.5% of 3,963 adolescents (2040 male and 1923 female; mean age 14.0 +/- 0.9 years) who completed the study. According to the International Classification of Headache Disorders, 928 subjects (23.4%) were diagnosed with migraine; 138 (3.5%) had migraine with aura, 346 (8.7%) migraine without aura, and 444 (11.2%) with probable migraine. The frequency of suicidal ideation was 6.2% in nonmigraine subjects compared to 16.1% in subjects with migraine ($p<0.001$), and 23.9% in subjects with migraine with aura ($p<0.001$). Subjects with suicidal ideation had a higher frequency of headache and headache-related disability. After controlling for depression and sociodemographic factors, the association of migraine and suicidal ideation occurred only for migraine with aura ($p=0.025$) and high frequency headache (>7 days/month; $p=0.013$), but not for migraine without aura, probable migraine or for migraine disability score. (Wang S-J, Fuh J-L, Juang K-D, Lu S-R. Migraine and suicidal ideation in adolescents aged 13 to 15 years. **Neurology** March 31, 2009;72(13):1146-1152). (Respond and reprints: Dr Shuu-Jiun Wang, The Neurological Institute, Taipei Veterans General Hospital, Taipei, 112, Taiwan. E-mail: sjwang@vghtpe.gov.tw).

COMMENT. One in four young adolescents with migraine with aura and one in four with frequent headaches (>7 days/month) report suicidal ideation. The frequency of suicidal ideation is one in 2.5 for subjects with both risk factors. The association of migraine with aura and suicidal ideation is independent of depression and pain. Alterations of the serotonergic system have been demonstrated in subjects with both migraine with aura and suicide. (Post RM et al. **Neurology** 1994;44 (suppl 7):537-547). The current authors have previously shown that adolescents with chronic daily headaches (>15 days/month) are at increased risk of suicide. (Wang SJ et al. **Neurology** 2007;68:1468-1473). The influence of prophylactic medications such as antiepileptics and antidepressants was not evaluated in this study, but chronic prophylactic migraine therapy was used infrequently in this age group. The study demonstrates the importance of evaluation for risk factors of suicidal thoughts in young adolescents with migraine with aura.

Chronic pain conditions of various types (migraine, back problems, arthritis, and fibromyalgia) are associated with suicidal ideation and suicidal attempts, and migraine has the strongest link (Ratcliffe GE et al. **Clin J Pain** 2008;24:204-210). In this Canadian study, data were derived from a large nationally representative sample, whereas the Taiwan study was limited to schoolchildren between 13 and 15 years, and questionnaires were validated for this population. The subjects were not referred specifically for headache or migraine and the findings were not explained by a recruitment bias. (Amouroux R et al. **Encephale** 2008;34:504-510. Epub 2007 Dec 26).

REPETITIVE DAILY BLINDNESS WITH HEMIPLEGIC MIGRAINE AND *SCN1A* MUTATIONS

Two novel *SCN1A* mutations are identified in two unrelated families with familial hemiplegic migraine and a unique phenotype of elicited repetitive daily blindness, in a report from Hopital Lariboisiere, and other centers in Paris, France, and Geneva, Switzerland. The proband of family 1 is an 18-year-old woman with recurrent attacks of hemiplegic migraine since age 6, and repeated, daily (up to 10 times per day), stereotyped bilateral transient blindness of maximum 10 sec duration. During the attack, pupils are dilated with absent direct and indirect pupillary reflexes. Visual symptoms are spontaneous or triggered by rubbing the eyes. Blindness occurs without associated headache or other neurologic symptoms, and independently of attacks of hemiplegic migraine that occur irregularly from a maximum of 2 per week to one every 2 years. The neurologic, visual acuity, electroretinogram, and fundus examinations are normal outside the attacks. Brain MRI shows a hypersignal T2-WI lesion in the territory of the right inferior cerebellar artery and a few ischemic sequelae in the left posterior inferior cerebellar artery territory. Parenchymal cerebellar lesions were also present on CT at 6 years of age. The proband's mother, sister, and maternal grandfather had hemiplegic migraine without episodic blindness. Family 2 with the association of episodic blindness and hemiplegic migraine in 4 out of 5 affected members was reported previously. The transient daily blindness is suggestive of a retinal spreading depression, triggered by rubbing the eyes. (Vahedi K, Depienne C, Le Fort D et al. Elicited repetitive daily blindness. A new phenotype associated with hemiplegic migraine and *SCN1A* mutations. **Neurology** March 31, 2009;72:1178-1183). (Respond and reprints: Dr Katayoun Vahedi, APHP-Lariboisiere Hospital, Department of Neurology, 2 rue Ambroise Pare, 75010 Paris, France. E-mail: katayoun.vahedi@lrb.aphp.fr).

COMMENT. Familial hemiplegic migraine, a genetically heterogeneous disorder, is linked to three genes, including *SCN1A*. The unique eye phenotype of elicited repetitive daily blindness cosegregating with familial hemiplegic migraine is previously reported in a single Swiss family. The present report identifies *SCN1A* mutations in both the Swiss and French families with this unique phenotype, and excludes mutation in *CACNA1A* and *ATP1A2*, genes most frequently involved in familial hemiplegic migraine. *SCN1A* is also involved in febrile seizures, GEFS+ and Dravet syndrome.

INHERITED PROTHROMBOTIC RISK FACTORS IN MIGRAINE, STROKE, OR TRANSIENT ISCHEMIC ATTACK

The prevalence and association of inherited prothrombotic risk factors in children with established diagnoses of stroke, transient ischemic attack, or migraine were studied at Zagreb University School of Medicine, Croatia. Genotypic analyses were performed for factor V G1691A, factor II G2010A, MTHFR C677T, and 4 common platelet glycoprotein polymorphisms. Only factor V was significantly associated with increased risk for arterial ischemic stroke (AIS) in childhood and perinatal arterial ischemic stroke (PAS). Heterozygosity for factor V G1691A was associated with a 7-fold increased risk for AIS, PAS, and transient ischemic attack (TIA). Carriers of human platelet alloantigens had an increased risk of TIA. Human platelet alloantigen-2b allele was associated with a 2.23-fold increased risk for migraine, whereas factors V and II were not implicated. A trend toward an increased risk for migraine in children homozygous for MTHFR C677T, especially migraine with aura, was not statistically significant. (Herak DC, Antolic MR, Krleza JL, et al. Inherited prothrombotic risk factors in children with stroke, transient ischemic attack, or migraine. **Pediatrics** April 2009;123:e653-e660). (Respond: Renata Zadro PhD, Clinical Hospital Center, Kispaticeva 12, Zagreb 10000, Croatia. E-mail: rzadro@mef.hr).

COMMENT. Factor V G1691A is important in susceptibility to arterial ischemic stroke in childhood and the perinatal period, and transient ischemic attacks. Platelet glycoprotein polymorphisms may increase the risk of TIA and migraine.

INFECTIOUS DISORDERS

COMPARISON OF SENSITIVITY OF SERUM AND CSF SAMPLES IN IMMUNODIAGNOSIS OF NEUROCYSTICERCOSIS

Paired serum and CSF samples were obtained from 91 patients with neurocysticercosis (NCC) for detection of *Taenia solium* (TS) antibodies and antigens, in a study at centers in Lima, Peru, Belgium, and the USA. TS antibodies were detected using an enzyme-linked immunotransfer blot (EITB) assay, and antigens, using a monoclonal antibody-based enzyme-linked immunosorbent assay (ELISA). NCC was intraparenchymal in 48 and extraparenchymal in 43 patients. For the intraparenchymal NCC group, the EITB antibody assay yielded more true positive results on serum samples, whereas the ELISA antigen assay yielded slightly more positive results for CSF samples (differences not significant). Patients with calcified NCC were antibody positive and antigen negative. For extraparencymal disease, all samples were antibody positive, and all but 2 were antigen positive, mostly with high antigen levels. (Rodriguez S, Dorny P, Tsang VCW, et al, for the Cysticercosis Working Group in Peru. Detection of *Taenia solium* antigens and anti-*T. solium* antibodies in paired serum and cerebrospinal fluid samples from patients with intraparenchymal or extraparenchymal neurocysticercosis. **J Infect Dis** May 2009;199:1345-1352) (Respond or reprints: Dr Hector H Garcia, Dept of Microbiology, Universidad Peruana Cayetano Heredia, Av H Delgado 430, SMP, Lima 31, Peru. E-mail: hgarcia@jhsph.edu).

COMMENT. The authors conclude that the EITB antibody-detecting assay is equally sensitive on serum and CSF samples. The ELISA assay for antigen detection is more sensitive when performed on CSF samples than serum, but less sensitive than the EITB assay. ELISA, using either serum or CSF samples, is better than EITB in the differentiation of active and inactive NCC. High antigen levels detected by ELISA suggest the presence of subarachnoid NCC, associated with a worse prognosis.

Since neuroimaging is often nonspecific for NCC, immunodiagnosis is usually necessary for confirmation. CSF samples offer no advantage over serum for detection of antibodies by EITB assay. In intraparenchymal cases, although the use of CSF samples for antigen detection by ELISA assay may yield a 13% increase in case identification, the increase over serum samples is not significant. With extraparenchymal disease, most patients are strongly seropositive by EITB assay on either serum or CSF.

The findings in the above study suggest that serum antibody detection by an EITB assay, using purified antigen, is the assay of choice for diagnosis of NCC.

ANTI-N-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS WITH CATATONIA TREATED BY PLASMAPHERESIS

The case of a 12-year-old girl with anti-methyl-D-aspartate receptor (NMDAR) encephalitis is reported by researchers from Augsburg and Bonn, Germany, and Oxford, UK. She was admitted with an episode of paresthesia and hypotonia of the left leg, and rare episodes of head turning with clonic movements of the left and all extremities. The symptoms were preceded by a 2-day episode of diarrhea 3 weeks before. The EEG, brain MRI, and CSF were normal, and she was discharged with a suspected diagnosis of psychogenic seizures. She was readmitted 2 days later with agitation, hyperventilation and intermittent ocular deviation, followed by intermittent catatonic postures with fever, hyperidrosis, chewing movements and tongue protrusion. She required tube feeding and intermittent oxygen. EEG now showed continuous slowing. The MRI was unremarkable. IgM antibodies against *Campylobacter jejuni* were elevated. Prednisolone was ineffective. At 6 weeks after admission, CSF showed IgG antibody reactivity with hippocampal neurophil, and subsequently, serum antibodies to NMDAR were demonstrated. Plasmapheresis was followed within 2 weeks by speaking words, walking and almost full recovery in 4 weeks. CSF antibody reactivity was no longer detected, and ultrasound and CT were negative for teratoma in the pelvis and mediastinum. (Schimmel M, Bien CG, Vincent A, Schenk W, Penzien J. Successful treatment of anti-N-methyl-D-aspartate receptor encephalitis presenting with catatonia. **Arch Dis Child** April 2009;94:314-316). (Respond: Dr Johannes Penzien, Department of Paediatrics, Klinikum Augsburg, Stenglinstrasse 2, 86156 Augsburg, Germany. E-mail: johann.penzien@klinikum.augsburg.de).

COMMENT. This 12-year-old girl appears to be the youngest patient reported with anti-NMDAR encephalitis. Her presentation with neuropsychiatric symptoms progressing to seizures, catatonia, autonomic dysfunction, hypoventilation, orofacial dyskinesia and dysphagia is typical. Teratoma, absent in this child, may occur in 65% of patients, and sometimes develops 7 years following encephalitis (Dalmau J et al. **Lancet Neurol** 2008;7:327-340)(Iizuka T et al. **Neurology** 2008;70:504-511). An apparent response to plasmapheresis and the association with *Campylobacter* infection are of interest.

NMDAR ANTIBODIES AND NEW-ONSET EPILEPSY

The frequency and significance of antibodies to NMDAR were determined in 19 adolescents and young women, aged 15 to 45 years, with unexplained new-onset epilepsies, seen between Jan 2005 and June 2007 at the University of Bonn, Germany; Univ of Pennsylvania, Philadelphia; and John Radcliffe Hospital, Oxford, UK. Five (25%) patients had anti-NMDAR antibodies, and all 5 had a history of psychiatric symptoms, pleocytosis, seizures, and relapsing-remitting course. All recovered, either spontaneously or following corticosteroid or intravenous immunoglobulin treatment. Only 1 patient had a neoplasm (multiple neuroendocrine tumors including the ovaries). In a control series of 61 patients with other cryptogenic epilepsies and 11 surgically treated patients with epilepsy, one, a 22-year-old man, was NMDAR antibody positive and he had recovered from a severe encephalopathy. (Niehusmann P, Dalmau J, Rudlowski C, et al. Diagnostic value of N-methyl-D-aspartate receptor antibodies in women with new-onset epilepsy. **Arch Neurol** April 2009;66:458-464). (Respond: Christian G Bien MD, Department of Epileptology, University of Bonn, Sigmund-Freud-Str 25, 53105 Bonn, Germany.
E-mail:christian.bien@ukb.uni-bonn.de).

COMMENT. A significant proportion of unexplained new-onset epilepsies in adolescents and young women may be caused by anti-NMDAR encephalitis. Seizures are a common symptom in patients with anti-NMDAR encephalitis, reported in 76 of 100 cases (Dalmau J et al. 2008).

SEIZURE DISORDERS

LONG-TERM OUTCOME IN CHILDHOOD-ONSET EPILEPSY

The value of early seizure frequency and etiology in the prediction of long-term seizure and mortality outcome in a population-based cohort of 102 children was determined in a study at University of Turku, Finland, and Epilepsy Research Group, Berlin, Germany. Follow-up was a median of 40 years after the first seizure before the age of 16 years. One-year remission (1YR) had occurred in 95 (93%) of the group, and 7 (7%) never experienced a 1YR, their epilepsy considered drug-resistant. Patients with weekly seizures in the first year of treatment had a 8-fold risk of developing drug resistant epilepsy (P=0.0125), and a 2-fold risk of never entering a terminal 1YR (P=0.001). Weekly seizures prior to treatment carried a slight risk of never entering terminal 1YR (P=0.035). Mortality during follow-up was 13%, and long-term mortality was 9-fold higher for patients with symptomatic epilepsy (P=0.0071). Weekly seizures prior to or during the first year of treatment did not increase mortality. Virtually all (51/52, 98%) children with low seizure frequency and non-symptomatic etiology entered 1YR during 40 years follow-up, and almost all (49/52, 94%) entered 1-year terminal remission. A combination of frequent pretreatment seizures and symptomatic etiology is predictive of intractable epilepsy. (Sillanpaa M, Schmidt D. Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset

epilepsy. **Brain** April 2009;132:989-998). (Respond: Prof Dr Dieter Schmidt, Epilepsy Research Group, Goethestr 5, D-14163 Berlin, Germany. E-mail: dbschmidt@t-online.de).

COMMENT. The long-term outcome of epilepsy in children may be predicted after one year of treatment. Patients with frequent seizures in the first year of treatment, especially those with symptomatic epilepsy, are at increased risk of intractable epilepsy, and should be considered for aggressive therapy.

INFLUENCE OF *SCN1A* GENE MUTATION ON AGE OF ONSET OF FEBRILE SEIZURES IN GEFS+

Twelve multigenerational families with the generalized epilepsy and febrile seizure plus (GEFS+) syndrome and a known clinically relevant epilepsy gene mutation were examined for age of onset of febrile seizures (FS or FS+), in a study at the University of Melbourne, Australia, and centers in the Netherlands and Israel. A total of 105 patients were identified with *SCN1A, SCN1B, or GABRG2* gene mutations. Sixty-two patients presented with a FS; 43 were excluded because the FS was atypical or age of onset was imprecise. The median age of onset of FS was 12 months in subjects with *SCN1A* and *GABRG2* mutations, and 24 months in those with *SCN1B* mutation. The median age of onset in children with an *SCN1A* mutation was significantly lower than for children with an *SCN1B* mutation ($p=0.001$). Age of onset of FS was not significantly different in children with *SCN1A* and *GABRG2* mutations. In 10 families reported in the literature that had mutations available, the findings were similar to the above; median age of onset of FS in patients with *SCN1A* mutations was 11 months compared to 30 months in those with *SCN1B* mutations ($p=0.033$). In patients with GABRG2 mutations, age of onset was 18 months. With all families combined, the median age of onset in those with *SCN1A* and *B* mutations was 12 months and 24 months, respectively ($p<0.001$); in those with *GABRG2* mutations it was 13 months and similar to *SCN1A* group. (Sijben AEJ, Sithinamsuwan P, Radhakrishnan A, et al. Does a *SCN1A* gene mutation confer earlier age of onset of febrile seizures in GEFS+? **Epilepsia** April 2009;50:953-956). (Respond: Prof Ingrid E Scheffer, Director of Paediatrics, Austin Health, Neurosciences, Heidelberg, Victoria 3081, Australia.
E-mail:scheffer@unimelb.edu.au).

COMMENT. The age of onset of febrile seizures is partly dependent on the underlying gene mutation involved. In two independent cohorts of subjects with FS or FS+ and *SCN1A* mutations, the median age of onset was 11-12 months compared with a population median of 18 months. The proceedings of an international symposium on febrile seizures and related conditions, edited by Fukuyama Y et al, are published in **Brain Dev** May 2009;31(5):331-404). Nakayama J reviews the search for FS susceptibility genes in **Brain Dev** 2009;31(5):359-365).

The phenotypic similarities of GEFS+ and autosomal dominant FS (ADFS) are reported in a multigenerational family with febrile and afebrile seizures (Hindocha N et al. **Epilepsia** April 2009;50:937-942). The two mutations identified in families with ADFS are in genes implicated in GEFS+ (*SCN1A* and *GABRG2*). The authors conclude that it is inappropriate to separate GEFS+ and ADFS, given the clinical and genotypic overlap.