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J. GORDON MILLICHAP, M.D., F.R.C.P., EDITOR

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NEONATAL DISORDERS

CHORIOAMNIONITIS AND EARLY BRAIN DEVELOPMENT

The association of chorioamnionitis and early postnatal risk factors for white matter injury (WMI) and its effect on early brain development were determined in a study at University of British Columbia, Vancouver, Canada. Thirty-one (34%) of 92 preterm newborns (24-32 weeks gestation), studied at a median age of 31.9 weeks and again at 40.3 weeks gestation, were exposed to histopathological chorioamnionitis, and 26 (28%) had WMI. Chorioamnionitis was not associated with an increased risk of noncystic WMI ($p=0.6$) on MR imaging, and did not affect brain development ($p>0.1$) in early life or at term-equivalent age. Culture positive postnatal infections (*Staphylococcus* species) and hypotension requiring therapy were significant risk factors for WMI ($p=0.03$). WMI was associated with lower metabolic (N-acetylaspartate/choline) ($p=0.009$), and lower microstructural (WM fractional anisotropy) ($p=0.01$) development. Neonatal outcomes were similar in newborns with and without chorioamnionitis, but newborns with WMI were neurologically more impaired than those without. (Chau V, Poskitt KJ, McFadden DE, et al. Effect of chorioamnionitis on brain development and injury in premature newborns. **Ann Neurol** Aug 2009;66:155-164). (Respond: Dr SP Miller, British Columbia Children's Hospital, Department of Pediatrics/Division of Neurology, University of British Columbia, K3-180, 4480 Oak St, Vancouver, BC, V6H 3V4, Canada. E-mail: smiller6@cw.bc.ca).

COMMENT. Postnatal infections, especially staphylococcal, and hypotension are associated with white matter injury (WMI) in the premature infant, and WMI affects early brain metabolism and development. In contrast to some reports, the above study shows that histopathological chorioamnionitis is not associated with increased risk of WMI or

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abnormalities of brain development. Focal or multifocal noncystic WMI is the most prevalent pattern of brain injury in premature newborns (Hamrick SE et al. 2004, cited by authors).

A previous meta-analysis report from UCSF demonstrates that chorioamnionitis is a risk factor for cerebral palsy and/or cystic periventricular leukomalacia in the term and preterm neonate. (Wu YW, Colford JM Jr. **JAMA** 2000;284:1417-1424). Studies evaluating risk of cerebral palsy following maternal fever or infection were not included in the meta-analysis, a factor possibly accounting for the different conclusion vs the Canadian study.

In an editorial, Linda de Vries (Wilhelmina Children's Hospital, Utrecht, the Netherlands) expands on measurement of cytokines in newborns with WMI, and the finding that chorioamnionitis with or without funisitis makes a very low birth weight infant more susceptible to hypotension at time of birth. (**Ann Neurol** 2009;66:127-129).

EARLY EEG FINDINGS AND HI-ENCEPHALOPATHY OUTCOMES

The value of the EEG as a predictor of outcome in term infants with hypoxic-ischemic encephalopathy (HIE) was determined in a study at Cork University Maternity Hospital and St Vincent's University Hospital, Dublin, Ireland. Continuous video-EEG was recorded from <6 hours to 72 hours after delivery. One-hour EEG segments at 6, 12, 24, and 48 hours of age were analyzed visually, and neurologic outcome was assessed at 24 months. Of 44 infants who completed follow-up, 20 (45%) had abnormal neurodevelopmental outcomes. Clinical Sarnat scoring at 24 hours classified 18 infants with grade I HIE, 17 with grade II, and 9, grade III. EEG abnormalities were greatest on the earliest recordings of all cases and improved with time. Best predictive ability occurred at 6 hours of age. Normal/mildly abnormal EEG at 6, 12, or 24 hours had 100% positive predictive values for normal outcome, and negative predictive values of 67% to 76%. At 24 hours, the number of infants assigned to each EEG grade was 6 normal, 11 moderately abnormal, 9 severe, and 3 isoelectric. Background amplitude of <30 mcV, interburst interval of >30 sec, electrographic seizures, and absence of sleep-wake cycling at 48 hours were associated with abnormal outcome. Normal EEG within 6 hours after birth was associated with normal neurodevelopment at 24 months. (Murray DM, Boylan GB, Ryan CA, Connolly S. Early EEG findings in hypoxic-ischemic encephalopathy predict outcomes at 2 years. **Pediatrics** Oct 2009;124:e459-e467). (Respond: Deidre M Murray MD PhD, Department of Pediatrics and Child Health, Clinical Investigation Unit, Cork University Hospital, Wilton, Cork. Ireland. E-mail: d.murray@ucc.ie).

COMMENT. Early EEG is a reliable predictor of neurodevelopmental outcome in term infants with HIE. EEG abnormalities evolving in the first 48 hours of life predict a poor outcome, and normal EEG at 6 hours of age is predictive of a normal outcome at 2 years. Early EEG study at 6 to 12 hours and repeat study at 48 hours should predict outcomes successfully in 95% of cases. EEG seizures detected by continuous monitoring correlate with poor outcome.

Neonatal EEG in periventricular leukomalacia (PVL). In a study at Anjo Kosei Hospital and other centers in Japan, EEG findings varied with the severity of PVL (noncystic, localized cystic, and extensive cystic) and the timing of recording. To detect PVL, >2 EEG recordings are recommended, 1 within 48 hours after birth for acute stage abnormalities, and

1 in the second week to detect chronic stage abnormalities. (Kidokoro H et al. **Pediatrics** Oct 2009;124:e468-e475). (E-mail: kidokoro@kosei.anjo.aichi.jp).

Dr Joseph J Volpe, in an editorial, comments that the report by Kidokoro and associates shows that the EEG may be important in diagnosis, timing, and severity of PVL (**Pediatrics** Oct 2009;124:e542-e544), but the infants in this study were a severely affected subset of the premature population. In general, MRI in the neonatal period is the most effcctive method of identifying white-matter injury in premature infants. Ultrasonography is useful in detection of severe injury. The timing of the insult by EEG is useful in the decision to order potentially protective interventions such as antioxidants etc.

EFFECT OF NEONATAL SEIZURES ON COGNITIVE OUTCOME OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY

The independent effect of clinical neonatal seizures and their treatment on longterm neurodevelopmental outcome in 77 term newborns at risk for hypoxic-ischemic encephalopathy (HIE) was determined in a study at University of California San Francisco. Clinical seizures were recorded and graded prospectively assigning points (0-10) for frequency, status, medications, and EEG abnormal background and epileptiform discharges. Eleven children (14.3%) had severe neonatal seizures (composite seizure score >4), 14 (18.2%) had mild/moderate seizures (score 1 to 3), and 52 (67.5%) had no seizures (seizure score 0). Of the 25 infants with seizures, EEG was abnormal in 14 (56%). The severity of HIE measured by MRI was most highly associated with cognitive outcome, measured by WPPSI-R and neuromotor score, at age 4 years. The pattern of the HIE correlated with severity of seizures (P<0.0001); basal nuclei predominant patern was associated with severe seizures, and the watershed pattern with mild/moderate seizures. Children with severe seizures had a lower FSIQ than those with mild/moderate seizures (P<0.0001). (Glass HC, Glidden D, Jeremy RJ, Barkovich AJ, Ferriero DM, Miller SP. Clinical neonatal seizures are independently associated with outcome in infants at risk for hypoxic-ischemic bnrain injury. **J Pediatr** September 2009;155:318-323). (Respond: Hannah C Glass MDCM, University of California San Francisco, Department of Neurology, Box 0663, 521 Parnassus Ave, C-215, San Francisco, CA 94143. E-mail: Hannah.Glass@ucsf.edu).

COMMENT. The authors conclude that clinical neonatal seizures with birth asphyxia are associated with worse neurodevelopmental outcome, independent of the severity of hypoxic-ischemic brain injury. The effect of the seizures themselves could not be differentiated from the cognitive effects of treatment with phenobarbital and phenytoin, however. Also, almost half of patients with clinical seizures had a normal EEG. Seizure severity was graded by frequency, medication use, and EEG, but not by seizure pattern. According to Volpe JJ (**N Engl J Med** 1973;289:413; also, In Gluck L. Editor. *Intrauterine Asphyxia and the Developing Fetal Brain.* Chicago. Year Book Med Pub, 1977), virtually all infants with HIE related seizures have "subtle" seizures. Subtle seizures are manifested by 1) tonic horizontal deviation or jerking of eyes; 2) eye-lid blinking or fluttering; 3) sucking, smacking of lips; 4) 'swimming" or "rowing" movements of limbs; and/or 5) apneic spells. Infants also exhibit multifocal clonic seizures or decerebrate/decorticate tonic seizures in

addition to subtle seizures, but not generalized tonic-clonic seizures, the type expected to result in brain injury.

Subtle seizures described as "breast-stroke swimming movements" were previously reported in studies of seizure patterns in newborn animals (Millichap JG. **Proc Soc Exp Biol and Med** 1957;96:125-129). Transient opisthotonus, tremors, and clonic movements were also characteristic of newborn seizure patterns, but in rats aged 1 to 15 days subjected to graded electroshock, a generalized tonic clonic seizure could not be elicited. Failure to induce convulsions in the newborn rat was associated with a low level of carbonic anhydrase in the brain. The maximal seizure pattern was correlated with increasing age and the higher maturational levels of carbonic anhydrase in the brain of older animals. Observation of the newborn seizure pattern in addition to seizure frequency and EEG discharges might permit closer correlation with severity of HIE and outcome. If neonatal seizures do contribute to HIE brain injury, inhibition of the development of brain carbonic anhydrase would be expected to lessen the severity of neonatal seizures and result in improved neurodevelopmental outcome. Detailed EEG monitoring is essential for confirmation of diagnosis of neonatal seizures, especially subtle seizures.

DEVELOPMENTAL CORRELATES OF MICROCEPHALY

Developmental and motor function at age 2 years of 958 children born before the 28th week of gestation were assessed at Boston and Harvard Universities and other centers, comparing those with microcephaly at birth or 2 years with children with normal head circumference. A total of 11% of infants in the sample had microcephaly at 2 years. Microcephaly at 2 years, but not at birth, was predictive of severe motor and cognitive impairments at 2 years. Of children with congenital microcephaly, 71% had normal head circumference at 2 years and similar neurodevelopmental outcomes to those with normal head circumference at birth and 2 years. Among children with microcephaly at 2 years, more than half had a Mental Developmental Index <70, and almost a third had cerebral palsy, rates 3 times greater than among children without microcephaly. Neonatal cranial ultrasound showing white matter damage increased risk of poor neurodevelopmental outcome. (Kuban KCK, Allred EN, O'Shea TM, et al. Developmental correlates of head circumference at birth and two years in a cohort of extremely low gestational age newborns. **J Pediatr** Sept 2009;155:344-349). (Response: Karl Kuban MD, SMEpi, One Boston Medical Center Place, Dowling 3 South, Boston, MA 02118. E-mail: karl.kuban@bmc.org).

COMMENT. Extremely low gestational age newborns (in the ELGANs epidemiological study) are at risk of neurodevelopmental dysfunction and autism (Kuban K. **J Pediatr** 2009;154:535-540). Microcephaly at 2 years, but not at birth, is associated with cognitive and motor impairment at age 2. Almost three-fourths of ELGANs with congenital microcephaly outgrow the problem by age 2 years. Congenital microcephaly is only a risk factor for CP or cognitive impairment if the microcephaly persists.

CAUSES OF NEONATAL HYPOGLYCEMIC BRAIN INJURY

Perinatal factors associated with hypoglycemic brain injury were studied by review of medical records in 60 hypoglycemic neonates at Tottori University, Yonago, Japan. Patients

were classified in 2 groups: Group I, 12 patients, abnormal, with mental retardation, developmental delay, cerebral palsy or epilepsy; and Group II, 48 patients, normal at follow-up. Proportion of infants small for gestational age (<10th percentile) was high in both groups (75% vs 58%) but was not associated with brain injury. Very low blood glucose levels (<15 mg/dl) occurred in 50% of Group I vs 14.6% of Group II (p=0.015). Duration of hypoglycemia was longer in Group I (median, 14 h) than in Group II (median, 1.75 h) (p<0.001). Associated factors more frequent in Group I than in Group II included toxemia (33.3% vs 8.3%, p=0.043), fetal distress (58.3% vs 14.5%, p=0.004), Apgar score <5 at 1 min (33.5% and 6.4%, p=0.025), neonatal seizures (53.8% vs 4.3%, p<0.001), and pathological jaundice (41.7% vs 6.4%, p=0.006). Eight of 9 patients in Group I had abnormal MRI at follow-up, showing cortical atrophy and white matter lesions, with occipital and parietal predominance. Apgar scores were partially correlated with the extent of brain lesions. Brain injury in neonates with prolonged hypoglycemia may be exacerbated by associated factors such as hypoxia, seizures, and jaundice. (Montassir H, Maegaki Y, Ogura K, et al. Associated factors in neonatal hypoglycemic brain injury. **Brain Dev** October 2009;31:649-656). (Respond: Dr Hesham Montassir, Tottori University, Yonago, Japan. E-mail: hishammontassir@gmail.com).

COMMENT. Neonatal seizures with hypoglycemia are correlated with duration of hypoglycemia and neurological outcome. Seizures may begin at onset of hypoglycemia but usually appear after 12 h of continuous hypoglycemia. (Pildes RS et al. A prospective controlled study of neonatal hypoglycemia. **Pediatrics** 1974;54:5-14).

Of 27 infants and children with seizures associated with hypoglycemia reported from the Mayo Clinic, only 2 had an onset of seizures in the neonatal period, and in 20 the etiology of hypoglycemia was unknown. Neurologic disease preceded the onset of symptoms in 50% of the 20 patients with cryptogenic hypoglycemia. Evidence for a primary neurological cause for seizures included birth injury, kernicterus, hydrocephalus, and cerebral dysgenesis. Level of blood sugar at time of seizure in patients with primary neurologic disorder was significantly lower than in patients with normal neurologic findings. Occurrence of seizures was not closely correlated with the level of blood sugar. A primary cerebral lesion should be considered as an etiologic factor in some neonatal and childhood hypoglycemic seizures. (Etheridge JE Jr, Millichap JG. Hypoglycemia and seizures in childhood. Etiologic significance of primary cerebral lesions. **Neurology** 1964;14:397-404).

SEIZURE DISORDERS

BRAIN SODIUM CHANNEL AND FEBRILE SEIZURE MECHANISM

Researchers at the University of Melbourne, Australia, measured the effect of temperature on brain sodium channel, $Na_v1.2$, properties, using a computer model of the dentate gyrus granule cell. In animal models thermogenic seizures are hippocampal in origin (Dube C et al. 2000). The voltage dependance of activation became 7.6mV more negative when the temperature was increased from 37C to 41C. The direct effect of heat caused an increase in gating rates of sodium ion channels and a more negative activation with increased neuronal excitability. This dramatic increase in excitability due to increased temperature may be an important factor in the mechanism of a febrile seizure. (Thomas EA, Hawkins RJ,

Richards KL, Xu R, Gazina EV, Petrou S. Heat opens axon initial segment sodium channels. A febrile seizure mechanism? **Ann Neurol** Aug 2009;66:219-226). (Respond: Dr Petrou, Howard Florey Institute, University of Melbourne, Parkville, Victoria 3010 Australia. E-mail: spetrou@unimelb.edu.au).

COMMENT. The mechanism of febrile seizures is dependent on several factors, but especially height of body temperature and an individual's febrile convulsive threshold. In addition to genetic susceptibility and cytokines, the neurotropic properties of certain viruses, age and level of immaturity, and water and electrolyte balance are contributing factors. (Millichap JG. **Brain Dev** 2009; Dube CM et al. **Brain Dev** 2009;31:366-371**).** The above study provides further explanations for the febrile seizure mecanism at a molecular level, and specifically the effect of body temperature on brain sodium channels.

ANTIPYRETICS AND FEBRILE SEIZURE RECURRENCE

The efficacy of antipyretic agents in prevention of febrile seizures was examined in a randomized, placebo-controlled, double-blind trial at various hospitals in Finland. A total of 231 children who experienced their first febrile seizure, Jan 1, 1997-Dec 31, 2003, were observed for 2 years. Febrile episodes were treated first with rectal diclofenac or placebo. After 8 hours, treatment was continued with oral ibuprofen, acetaminophen, or placebo. Of 851 febrile episodes, 89 (10%) were associated with a febrile seizure. Febrile seizures occurred in 54 (23.4%) of the 231 children. Recurrence rates were not significantly different in the antipyretic and placebo groups: 23.4% (46 of 197) in those treated with antipyretic, and 23.5% (8 of 34) in those receiving placebo (P=0.99). Fever was significantly higher during episodes with seizure vs those without seizure (39.7C vs 38.9C, P<0.001), independent of the medication. Antipyretic agents were ineffective in the prevention of febrile seizure recurrence. All the antipyretics failed to lower the body temperature in children with fever that was associated with febrile seizure recurrence, but they lowered the temperature in episodes not leading to a febrile seizure. Children with recurrences had received extra antipyretic agents more frequently than those without recurrences. (Strengell T, Uhari M, Tarkka R, et al. Antipyretic agents for preventing recurrences of febrile seizures. **Arch Pediatr Adolesc Med** Sept 2009;163:799-804). (Respond: Heikki Rantala MD, PhD, Department of Pediatrics, University of Oulu, PO Box 5000, Oulu 90014, Finland. E-mail: heikki.rantala@oulu.fi).

COMMENT. The ineffectiveness of commonly prescribed antipyretics in the prevention of recurrence of febrile seizures, as demonstrated in this controlled study, is in agreement with the majority of previous randomized trials. Antipyretics may be useful only in improving the general wellbeing of the febrile child. In patients with a prior complex febrile seizure, to prevent recurrence, many pediatric neurologists recommend a combination of antipyretic with diazepam, administered orally at first sign of fever.

While antipyretics failed to prevent or control temperature elevation that resulted in seizure recurrence, they were effective in lowering temperature in episodes unassociated with seizure. The principal aim in therapy is the prevention of an elevation of temperature above the threshold level at which a seizure has previously occurred. Commonly employed antipyretics, while facilitating heat dissipation by increased peripheral blood flow and

sweating, have no effect on heat production and temperature elevation. They begin to act when the fever has reached its highest point (Goodman and Gilman, 1955). In laboratory studies of antipyretic agents, aspirin and acetaminophen failed, whereas barbiturates were effective in retarding temperature elevation induced by radiotherm diathermy in animals. High doses of salicylates that cause hyperventilation and respiratory alkalosis lowered the threshold convulsive temperature and exacerbated the hyperthermia-induced seizure. (Millichap JG et al. **Neurology** 1960;10:575). The prevention of febrile seizures by anticonvulsant medications may be as much antipyretic as anticonvulsant effect. Future research in the development of more effective antipyretics should target heat production more than heat dissipation. The authors from Finland comment on the inhibition of different prostaglandins by antipyretics and the potential for different effects on seizure recurrence.

FEBRILE SEIZURES AND COGNITIVE OUTCOME

The association between febrile seizures and cognitive function in young adulthood was examined in a population-based study of Danish conscripts at Aarhus University Hospital, Denmark. Men with a history of epilepsy were excluded. Analysis of health-care databases found that 2.8% of 18,276 eligible conscripts had a record of hospitalization for febrile seizures. Prevalence of IQ scores in the bottom quartile (<37) was 25.3% and 27.6% for men with and without febrile seizures, respectively. Low IQ scores were slightly more prevalent in men born premature (30%), small for gestational age (32%), mother <20 years (36%), or parity >3 (33%). Adjusted prevalence ratios for having a group IQ score in the bottom quartile was 1.09 for men with febrile seizures and 1.08 for those without.. The prevalence ratios according to age at febrile seizure onset were 1.38 for 3 months to <1 yr; 0.98 for 1 to 2 years; and 1.14 for 3 to 5 years. Except for men whose febrile seizures occurred before age 1 year, there was little evidence of low cognitive function associated with a history of febrile seizures. (Noergaard M, Ehrenstein V, Mahon BE, Nielsen GL, Rothman KJ, Sorensen HT. Febrile seizures and cognitive function in young adult life: a prevalence study in Danish conscripts. **J Pediatr** Sept 2009;155:404-409). (Respond: Mette Noergaard MD PhD, Dept Clinical Epidemiology, Aarthus University Hospital, Sdr Skovve 15, DK-9000 Aalborg, Denmark. E-mail: m.noergaard@rn.dk).

COMMENT. Decreased cognitive function in young adults with a history of febrile seizures before age 1 yr is previously unreported. In another Danish study, children with a febrile seizure early (< 1 yr) or late (> 3 yr) had a higher rate of epilepsy compared to children with onset between 1 and 3 years (Vestergaard M et al. **Am J Epidemiol** 2007;165:911-918). Abnormal MRIs in 11.4% of children with first simple febrile seizures, reported in a NY-Presbyterian Hospital study, was also an unexpected finding, given the presumed benign nature of the febrile seizure. (Hesdorffer DC et al. **Epilepsia** 2008;49:765-771; **Ped Neur Briefs** June 2008;22:47-48). MRI is not usually recommended in children with simple febrile seizures, in accordance with AAP guidelines.

BULGING FONTANELLE AND NEED FOR LUMBAR PUNCTURE

Etiologies of bulging fontanelle and fever and clinical evidence for lumbar puncture were determined from medical records of 153 infants treated at Assaf Harofeh Medical

Center, Israel. Age range was 3-11 months (mean 5.6 mos). CSF pleocytosis occurred in 42 (27.3%), including 1 case of bacterial meningitis (0.6%). Other diagnoses were aseptic meningitis (26.7%), URI infection (18.3%), viral disease NOS (15.6%), roseola infantum (8.5%), and acute otitis media (6.5%). Appearance on admission was good to excellent in 113 (73.6%) infants, none of whom had bacterial meningitis. All infants who appeared well on admission had normal clinical, laboratory and imaging studies and non-bacterial disease. Observation and withholding of lumbar puncture are considered appropriate in febrile infants with bulging fontanelle who appear clinically well. (Shacham S, Kozer E, Bahat H, Mordish Y, Goldman M. Bulging fontanelle in febrile infants: is lumbar puncture mandatory? **Arch Dis Child** 2009;94:690-692). (Respond: Dr S Shacham. E-mail: shirashacham@gmail.com).

COMMENT. Bulging fontanelle and fever alone are not always sufficient indication for lumbar puncture. LP is mandatory if these signs are complicated by febrile seizure, toxemia, rash, nuchal rigidity or other signs of meningitis.

SEVERE, INFANTILE-ONSET SEIZURE PATTERN IN STURGE-WEBER SYNDROME

Researchers at the Hunter Nelson Sturge-Weber Center, Kennedy Krieger Institute, Baltimore, reviewed the records of 100 consecutive children and adults with confirmed Sturge-Weber syndrome (SWS) to determine the nature and prognosis of associated seizures. In 77 patients seen over a 5-year period, median age of seizure onset was 6 months, with 43 (56%) presenting <1 year of age. The port-wine birthmark was unilateral (left face) in 28 (36%), bilateral in 19 (25%), and right in 18 (23%). All patients had at least one complex partial seizure, 11 (14%) also had generalized seizures, including infantile spasms, atonic, and absence, as previously reported (Fukuyama et al, 1979). Thirty-five (45%) patients had clusters of seizures (multiple, recurring over a 24-h period or prolonged >30 min). Young age at seizure onset (<6 months) was associated with increased hemiparesis.

In 30 (39%) patients, a characteristic seizure pattern consisted of sporadic clustering of severe, infantile-onset seizures followed by prolonged seizure-free periods. The cluster pattern was not associated with a worse prognosis. Also, disability was not increased in patients with bihemispheric involvement. (Kossof EH, Ferenc L, Comi AM. An infantile-onset, severe, yet sporadic seizure pattern is common in Sturge-Weber syndrome. **Epilepsia** Sept 2009;50:2154-2157). (Respond: Eric H Kossoff MD, Suite 2158-200 North Wolfe Street, The Johns Hopkins Hospital, Baltimore, MD 21287, (E-mail: ekossoff@jhmi.edu).

COMMENT. The authors comment that this frequently occurring cluster pattern of seizures may cause confusion regarding optimal anticonvulsant therapy and timing of resective surgery. Since the seizure pattern is not accompanied by worsening of cognitive or motor function, chronic anticonvulsant therapy with potential cognitive side effects may be replaced by more frequent use of rescue benzodiazepine treatment at time of clusters, and surgery may be deferred.

GABA effects on excitability of SWS cortex. In contrast to previous data showing excitatory and proconvulsive actions of GABA in epilepsies, GABA had inhibitory and anticonvulsive effects on in vitro SWS pediatric cortex. (Tyzio R, Khlilov I, Represa A, et al. **Ann Neurol** Aug 2009;66:209-218). E-mail: khazipov@inmed.univ-mrs.fr.