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

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BRAIN NEOPLASMS

OUTCOME OF INFANTS WITH INTRACRANIAL TUMORS

Investigators at British Columbia Children's Hospital, Vancouver, Canada evaluated by retrospective chart review the long-term outcome and its predictors in all infants with a primary intracranial tumor seen at BCCH in the 23-year period, 1982-2005. Of 35 infants (18 [51.4%] male) diagnosed with tumors, 30 underwent surgical resection, 14 received adjuvant chemotherapy, 5 had delayed radiotherapy; 20 (57%) survived, 12 (34%) had a good outcome and 23 (66%), a poor outcome. Of those with poor outcome, 15 (43%) died before age 5 years, 6 (23%) were alive with partial or severe disability, and 2 died at ages 5.5 and 7 years.

Intracranial pressure was raised at presentation in 21 (60%) patients, with increasing head size in 20 (57%), and vomiting in 16 (45.7%). Seizures occurred in 5 (14.3%), limb weakness in 4 (11.4%), and poor feeding in 4 (11.4%). Less frequent presenting features included nystagmus in 3 (8.6%), torticollis in 2 (5.7%), and apnea in 2 (5.7%). Among survivors, 14 of 20 (70%) had neurologic deficits; these included seizures in 8 (40%), speech difficulties 8 (40%), limb weakness 6 (30%), ataxia 3 (15%), and cranial nerve deficits in 2 (10%). Other complications included endocrine dysfunction in 5 (25%), visual deficits in 9 (45%) and auditory deficits in 3 (15%) children. Other late, treatment related, problems in 10 (50%) patients included alopecia, VP shunt, and 2nd malignancies. Ten of 20 survivors were attending regular school or had a skilled job.

Location of tumor was supratentorial in 25 (71%) (32% astrocytoma) and infratentorial in 10 (29%) (50% atypical teratoid rhabdoid tumor). Older age and an infratentorial tumor location are predictors of a poor outcome. The histological grade of tumor (I-IV) is the only independent predictor of survival ($p=0.002$) and functional outcome ($p<0.001$). (Pillai S, Metrie M, Dunham C, Sargent M, Hukin J, Steinbok P. Intracranial tumors in infants: long-term functional outcome, survival, and its predictors. **Childs Nerv Syst** 2012 April;28(5):547-555). (Respond: Dr Steinbok. E-mail: psteinbok@cw.bc.ca).

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COMMENT. More than half of infants with brain tumors survive more than 5 years after diagnosis, and a third have a good functional outcome. Older infants and those with infratentorial tumors have a poor prognosis. The histological grade of tumor is the most reliable predictor of 5-year survival and functional outcome. For an infant with an infratentorial or high-grade III or IV tumor the chances of survival are small. Extent of resection and adjuvant chemotherapy are not reliable prognostic indicators.

Compared to brain neoplasms in childhood, those originating in infants are more likely to be supratentorial, more aggressive, and patients who survive have a high incidence of neurological, endocrine, and developmental complications. Because of frequency of adverse effects, post-surgery radiation therapy is delayed, and chemotherapy is preferred.

Seizures and Brain Tumors. Symptoms of raised intracranial pressure, with bulging fontanelle and vomiting, are most frequent presenting manifestations of infants with intracranial tumors, but seizures may also occur early, especially with supratentorial tumors. Seizures associated with infratentorial tumor are typically manifested by opisthotonus and respiratory irregularities, including vertigo in older patients. Penfield W and Jasper HH (***Epilepsy and the Functional Anatomy of the Human Brain.*** Boston: Little, Brown, 1954;p284) coined the term *ictus infratentorialis* for seizures thought to originate in the brainstem; they found no clinical evidence of seizures due to involvement of the cerebellum itself.

In the British Columbia study, seizure was an early symptom of infantile intracranial tumor in 14% of the cohort. In a total of 291 children with intracranial tumors treated at the Mayo Clinic, 1950-1960, seizures occurred in 50 (17%). The seizure-associated tumor was supratentorial in 62% and infratentorial in 38%. The EEG was abnormal in 96% of patients with supratentorial tumor and of localizing value in 88% of tumors that involved the cerebral cortex. (Millichap JG et al. **Neurology** 1962;12:329-336).

BIOLOGICALLY TARGETED THERAPY OF PEDIATRIC BRAIN TUMORS

Investigators at the Mayo Clinic, Rochester, MN; George Washington University, and Children's National Brain Tumor Institute, Washington, DC review the molecular pathways implicated in pediatric brain tumors, biologic agents that target these pathways, and current clinical trials of these novel therapies. Two major classes of newer biological agents include monoclonal antibodies against growth factor ligands or ligand-binding sites and the small molecule inhibitors that target the intracellular tyrosine kinase domains. The overexpression of the epidermal growth factor receptors found in brainstem gliomas, ependymomas, and medulloblastomas make these receptors a rational therapeutic target. Other targets for biological therapy include the platelet-derived growth factor receptor, angiogenesis inhibitors, and the Sonic Hedgehog pathway that plays a role in embryogenesis and is implicated in the pathogenesis of medulloblastoma. Tumors exhibit immune tolerance, and the induction of immunological responses to tumors using tumor vaccines offers a further promising approach to treatment. (Nageswara Rao AA, Scafidi J, Wells EM, Packer RJ. **Pediatr Neurol** 2012 Apr;46(4):203-211).(Respond: Dr

Packer, Children's National Medical Center, 111 Michigan Ave NW, Washington, DC 20010. E-mail: rpacker@childrensnational.org).

COMMENT. With a clearer understanding of tumorigenesis, molecular growth pathways, and immune mechanisms in pathogenesis of brain tumors, clinical trials of novel biologic agents are showing better CNS penetration and lower toxicity profiles compared with conventional chemotherapy. The effects of newer targeted agents on the developing nervous system must be further investigated since the pediatric brain may be more vulnerable to toxicity. (Wells EM et al. **Pediatr Neurol** 2012 Apr;46(4):212-221).

PATHOPHYSIOLOGY OF IDIOPATHIC INTRACRANIAL HYPERTENSION

Investigators at Emory University, Atlanta, GA review the epidemiology, pathophysiology and management of idiopathic intracranial hypertension (IIH), sometimes called pseudotumor cerebri or benign intracranial hypertension, terms now considered inappropriate. Theories regarding the pathophysiology of IIH involve obesity in young women and adipose tissue as an actively secreting endocrine tissue, vitamin A metabolism, and cerebral venous abnormalities, but the definitive etiology is unknown. No evidence based consensus or formal guideline is developed regarding management. Diagnostic lumbar puncture (CSF opening pressure >25 cm water) is a valuable intervention in treatment, and dietary modification to correct obesity is essential. The efficacy of acetazolamide, CSF shunting and cerebral transverse venous sinus stenting remains to be established.

Male patients are affected less frequently than female but their visual prognosis is worse. Various medications may cause or precipitate IIH, including tetracycline, cyclosporine, lithium, oral contraceptives, and tamoxifen. Obstructive sleep apnea is an obesity and IIH-associated factor. Proposed mechanisms for IIH include increased brain water content, excess CSF production, reduced CSF absorption, and increased cerebral venous pressure. Stenosis (not thrombosis) of a dominant transverse sinus (TSS) is a frequent finding and can impair venous drainage; correction of TSS following lumbar puncture or CSF shunt may be associated with relief of IIH and headache. Venous sinus stenosis leads to venous hypertension, decreased CSF absorption, increased ICP, and venous sinus compression. MRI findings in IIH include TSS, flattening of the posterior pole of eyes, dilation and tortuosity of optic nerve sheaths, and empty sella.

Therapy involves lumbar puncture, weight reduction, and carbonic anhydrase inhibitors, acetazolamide and the weak inhibitor, topiramate. Surgery and optic nerve sheath fenestration or LP or VP shunt is performed in patients with visual loss and papilledema. (Biousse V, Bruce BB, Newman NJ. Update on the pathophysiology and management of idiopathic intracranial hypertension. **J Neurol Neurosurg Psychiatry** 2012 May;83:488-494). (Respond: Dr V Biousse, Neuro-Ophthalmology Unit, Emory Eye Center, 1365-B Clifton Rd NE, Atlanta, GA 30322. E-mail: vbiouss@emory.edu).

COMMENT. Factors independently cited by the authors as predictive of a worse prognosis in IIH include male gender, African American race, obesity, anemia, obstructive sleep apnea, and fulminant onset of IIH.

INFECTIOUS DISORDERS

ACUTE CEREBELLITIS WITH PARVOVIRUS INFECTION

An immunocompetent 5-year-old girl with acute cerebellitis associated with parvovirus B19 (PVB19) infection is reported from Nishi-Kobe Medical Center and Tokyo Medical University, Japan. She was hospitalized with seizures of the upper extremity and impaired consciousness after 3 days with fever. CSF showed 229 cells/mcL, predominantly polymorphs, 144 mg/dL protein, and 56 mg/dL glucose (blood glucose 74 mg/dL). EEG showed high-voltage delta in bilateral occipital regions, with diagnosis of encephalopathy. Brain diffusion-weighted MRI showed hyperintensity in the bilateral dentate nuclei, suggesting a diagnosis of acute cerebellitis. On the 10th day a repeat MRI showed hyperintensity in the cerebellar hemispheres. Following treatment with ceftriaxone, dexamethasone, methylprednisolone and acyclovir, she could sit alone on the 16th day and could walk with a wide stance on the 26th day. Mutism persisted until the 20th day, and 3 months later, slurred speech and intention tremor persisted. Follow-up MRI 6 months later showed cerebellar atrophy. A maculopapular rash appeared on the 10th day involving face and extremities, suggesting erythema infectiosum and confirmed by elevated serum PVB19 IgM and IgG antibodies, using enzyme immunosorbent assay. PCR analyses detected PVB19 DNA in the CSF and plasma, and also HHV6. HHV6-IgG antibody was positive and HHV6-IgM antibody was negative, consistent with a history of exanthema subitum. PCR for herpes simplex virus 1 and 2, HHV6, 7, and 8, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, JC and BK virus was negative. Collectively, cerebellitis and concurrent encephalitis were likely caused by CNS PVB19 infection with reactivation of latent HHV6. (Uchida Y, Matsubara K, Morio T, et al. Acute cerebellitis and concurrent encephalitis associated with parvovirus B19 infection. **Pediatr Infect Dis** 2012 April;31(4):427). (Respond: Yoshiko Uchida MD, Department of Pediatrics, Nishi-Kobe Medical Center, Kobe, Japan).

COMMENT. Parvovirus B19 infection (erythema infectiosum, Fifth disease) has a distinctive rash preceded by mild systemic symptoms including fever. The rash is intensely red with a "slapped cheek" appearance and circumoral pallor. (AAP **Red Book.** 27th ed. Elk Grove Village, IL; AAP 2006;484-487). Viral infections in addition to parvovirus B19 sometimes complicated by cerebellitis, and listed by the authors, include rotavirus, adenovirus type 3, HHV-6, and influenza virus. Of 31 childhood PVB19 CNS infections previously reported, 2 developed ataxia, but cerebellar involvement was not confirmed by MRI (Douvoyiannis M et al. **Clin Infect Dis** 2009;48:1713-1723).

Cerebellitis with preeruptive varicella. A 5-year-old boy admitted to the Mayo Clinic with cerebellar ataxia and symptoms of raised intracranial pressure was investigated for a presumed diagnosis of cerebral tumor and subsequently developed a generalized maculopapulovesicular rash of varicella. Ten days later, at time of discharge, the ataxia, papilledema and neck stiffness had improved but diplopia and strabismus persisted for 3 weeks. The ataxia and raised CSF pressure antedated the exanthema of varicella by 11 days. In 15 previous reports of preeruptive neurologic complications of varicella, cerebellar ataxia was mentioned in one. (Goldston AS, Millichap JG, Miller RH. **Amer J Dis Child** 1963 Aug;106:197-200).

CHARLES BONNET SYNDROME AND HERPES ENCEPHALITIS

Pediatric neurologists at Ondokuz Mayis University, Samsun, Turkey report a 4-year-old boy who presented with fever, headache, drowsiness, and seizures. Neurologic exam revealed drowsiness and meningeal signs. Four days following a 3-week course of acyclovir therapy for herpes encephalitis, he developed visual impairment and visual hallucinations lasting 1 week. Loss of vision became total, with normal appearing fundi. Visual hallucinations included unfamiliar children hiding under his bed, and he spoke to someone unknown. The hallucinations occurred 2-3 times daily and were 2-5 minutes in duration, without behavioral changes or cognitive impairment. MRI showed bilateral optic nerve hyperintensity on T2-weighted contrast-enhanced images, consistent with retrobulbar optic neuritis; hyperintensities also involved the dentate nuclei, cerebellum, basal ganglia, and brainstem. EEG showed diffuse slowing and left temporoparietal spike waves. CSF PCR was positive for herpes simplex virus-1 DNA. Following a 3-week course of corticosteroid therapy, the optic neuritis resolved and vision returned to normal after 1 month. During 1 year follow up while taking oxcarbazepine, he had no seizures nor hallucinations. (Aydin OF, Ince H, Tasdemir HA, Ozyurek H. Charles Bonnet Syndrome after herpes simplex encephalitis. **Pediatr Neurol** 2012 April;46:250-252). (Respond: Dr Aydin, Department of Pediatric Neurology, Faculty of Medicine, Ondokuz Mazyis University, Kurupelit Kampusu, 55139 Samsun, Turkey. E-mail: ofaydin@yahoo.com).

COMMENT. Charles Bonnet syndrome (CBS) is characterized by complex visual hallucinations in association with visual impairment and normal cognitive and behavioral status. The syndrome is described usually in adults with macular degeneration and sometimes with multiple sclerosis. In a 9-year-old partially sighted boy with paroxysmal visual zoopsias the CB syndrome is described as phantom vision (Mewasingh LD et al. **Pediatr Neurol** 2002 Feb;26(2):143-145). Only 3 previous pediatric cases in the literature were cited, two with cone-rod dystrophy. In these children, 6 and 8 years old, formed visual hallucinations noted shortly after loss of vision included geometric shapes, people, and buildings, stationary and in motion. (Schwartz TL, Vahgei L. Charles Bonnet syndrome in children. **J AAPOS** 1998 Oct;2(5):310-313).

CBS should be differentiated from migraine and epilepsy. One report of a case of CBS disappearing with successive monotherapies of carbamazepine and valproic acid but worsening with levetiracetam is suggestive of an epilepsy origin for CBS (Segers K. **Acta Neurol Belg** 2009 Mar;109(1):42-43).

Epilepsy and complex visual hallucinations. Except for one case, a 12-year-old boy with birth trauma and seizures who described seeing colored triangles followed by seeing a "robber coming after him with a gun," Penfield reported no elaborate visual hallucinations elicited by stimulation of the occipital lobes, only gross light, shadows and colors. (Penfield W, Jasper HH. 1954).

Lennox WG reports a girl, aged 9 years, who had generalized tonic-clonic seizures, preceded by visual hallucinations in which small objects or persons, "like a comic book," appeared in one field of vision, and followed by headache or vomiting. The EEG showed triphasic spikes or slow spike-and-wave discharges in the right posterior temporal or occipital area. The father had migraine from childhood and a maternal aunt

had complex partial seizures. This case points to both a migraine and seizure origin for the visual hallucinations. (Lennox WG. ***Epilepsy and Related Disorders.*** Boston: Little, Brown, 1960; Vol 1, p 270). EEG is recommended if CBS develops in a patient with worsening of neurological signs (Ossola M et al. Epileptic mechanisms in Charles Bonnet syndrome. **Epilepsy Behav** 2010 May;18(1-2):119-122).

SEIZURE DISORDERS

ICTAL EPILEPTIC HEADACHE WITH IDIOPATHIC EPILEPSY

Neurologists at the University of Rome, Italy report a 37-year-old woman with drug-resistant generalized epilepsy and headache who had a sudden headache during a 24-h EEG that displayed epileptic activity. Generalized S/W discharges and polyspike and wave discharges persisted for 60 min until the headache disappeared. The case represents a rare example of ictal epileptic headache in generalized idiopathic epilepsy. (Fanella M, Fattouch J, Casciato S, et al. Ictal epileptic headache as "subtle" symptom in generalized idiopathic epilepsy. **Epilepsia** 2012 March;53(4):e67-e70). (Respond: Dr Carlo Di Bonaventura, Department of Neuroscience, Neurology Unit, "Sapienza" University of Rome, Viale dell'Universita 30, 00185 Rome, Italy. E-mail: c_dibonaventura@yahoo.it).

COMMENT. In the authors' opinion, "ictal epileptic headache" warrants listing in the international classification of both epilepsy and headache. This case report is a rare example of the entity.

RISK OF EPILEPSY AFTER FEBRILE SEIZURES

Investigators at the Institute of Neurology, London, and at other centers in the UK and the Netherlands conducted a prospective follow-up of 181 infants from the onset of febrile seizures for a median of 21.6 years, to estimate the long-term risk of developing epilepsy. Of these, 175 (97%) were seizure-free in the preceding 5 years, and 171 (94%) were seizure-free and off antiepileptic drugs. Six percent developed epilepsy. In total, 17 (7.7%) had afebrile seizures, of whom 14 (6.4%) had 2 or more afebrile seizures (epilepsy). The mean time to the second afebrile seizure was 5.7 years. At 20 years after the index febrile seizure, 6.7% had developed epilepsy. The risk of developing epilepsy in the cohort over the whole follow-up period was 10 times that of the general population. The standardized incidence ratio was significantly elevated in the 0- to 14-year age groups but not in the 15- to 19-year age group. The risk of developing epilepsy in people who had febrile seizures appears to decrease with time. A history of 4 or more febrile seizures is a risk factor for development of epilepsy. (Neligan A, Bell GS, Giavasi C, et al. Long-term risk of developing epilepsy after febrile seizures. A prospective cohort study. **Neurology** 2012 April 10;78:1166-1170), (Response and reprints: Prof Sander. E-mail: I.sander@ucl.ac.uk).

COMMENT. In this study, no differentiation was made between simple and complex febrile seizures. The association between febrile seizures and later epilepsy is

linked to 3 possibilities: 1) febrile seizures are the first manifestation of epilepsy; 2) they are an age-specific marker of inherent susceptibility to seizures, and 3) prolonged febrile seizures (complex FS) may damage the brain with consequent increased risk of seizures. (Vestergaard M et al. **Am J Epidemiol** 2007;165:911-918). In the Collaborative Perinatal Project, 1% of children with simple febrile seizures had developed epilepsy by age 7 years. In children with complex febrile seizures, the risk was 9.2%, and in the total cohort, the risk was 2%. In children with no febrile seizures, the risk is 0.5%. The risk of epilepsy at 7 years of age in children with simple febrile seizures is two times higher, and in those with complex febrile seizures it is 18 times higher than in children with no febrile seizures. (Nelson KB, Ellenberg JH. **Pediatrics** 1978;61:720-727).

Febrile seizure inheritance and SUD in toddlers. SUD in 6 toddlers reported from Children's Hospital, Boston was associated with an autosomal dominant inheritance of febrile seizures, and with hippocampal abnormalities in one of 3 autopsied cases. The autosomal dominant pattern of inheritance for febrile seizures in affected families was identical to that observed in genetic epilepsy with febrile seizures plus and familial febrile seizures. Febrile seizure may be a marker of a process that leads to SUD, and seizure may or may not be directly involved. Genetic markers are needed to identify febrile seizure patients at risk of SUD. (Holm IA et al. **Pediatr Neurol** 2012 April;46:235-239).

READING EPILEPSY RESPONSE TO ANTICONVULSANTS

Investigators at the Department of Neurology, Vanderbilt University Medical Center, Nashville, TN report 3 patients with reading epilepsy, a boy aged 14 years, a 26-year-old male, and a 27-year-old woman, 2 having an excellent response to levetiracetam. The boy had tremors in the jaw and tongue when reading silently, and these progressed into loss of consciousness and generalized jerking if reading was continued. These episodes did not occur when reading aloud, skimming material, or doing mathematics. Video-EEG showed bifrontal synchronous sharp waves or spike-and-wave complexes, occasionally becoming generalized with left predominance. MRI was normal. He was treated effectively with divalproex sodium. Tremors did not recur when divalproex was inadvertently discontinued at 3 years after seizure onset, and at 6-year follow-up he was still seizure-free and on no medication. The 2 adults had twitching of the right lips or "mouth jumping" while reading. One had a video-EEG-monitored, generalized tonic-clonic seizure with left fronto-cental predominance, resistant to lamotrigine and controlled with levetiracetam; the other had a complex partial seizure with left mesial temporal sclerosis. Following left amygdalohippocampectomy, the reading epilepsy was partially controlled with carbamazepine and fully controlled with levetiracetam. Levetiracetam is proposed as first-line treatment for primary and secondary reading epilepsy. Spontaneous medication-free remission of primary reading epilepsy may occur within 3 years of seizure onset. (Haykal MA, El-Feki A, Sonmezturk HH, Abou-Khalil BW. New observations in primary and secondary reading epilepsy: excellent response to levetiracetam and early spontaneous remission. **Epilepsy Behav** 2012 April;23:466-470). (Respond: Dr BW Abou-Khalil. E-mail: bassel.abou-khalil@vanderbilt.edu).

COMMENT. Reading epilepsy, a form of reflex epilepsy, first described by Bickford R at the Mayo Clinic in 1956, occurs in 2 forms, primary or idiopathic and secondary and attributed to a structural brain lesion. Levetiracetam may prove superior to valproate and clonazepam in treatment, and spontaneous remission of primary reading epilepsy may occur in idiopathic cases. Generalized tonic-clonic seizures may be avoided by stopping reading at onset of mouth jerking, but anticonvulsant medications are usually required. The left predominance of the EEG seizure discharge in cases of reading epilepsy is in keeping with reports of reduced white matter integrity in the left arcuate fasciculus of dyslexics. (Vandermosten M et al. **Brain** 2012;135:935-948; see **Ped Neur Briefs** 2012 April;26(4):32).

Neurocognitive endophenotype with rolandic epilepsy. Children with rolandic epilepsy (RE) have reading, language, and attention disorders. In 13 probands with RE and 11 epilepsy-free siblings who completed a neurocognitive evaluation, 9% of siblings and 31% of probands were reading impaired, 36% of siblings and 54% of probands were language impaired, and 70% of siblings and 67% of probands had attention impairments. Probands and siblings showed a similar profile of deficits in language and attention. Early psychological evaluation and academic intervention may benefit children with RE. (Smith AB, et al. **Epilepsia** 2012 March;53(4):705-711).

INFLAMMATORY DISORDERS

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Investigators at the Hopital Bicetre and other hospitals in Paris, France studied the CNS symptoms at onset of primary hemophagocytic lymphohistiocytosis (HLH), and differentiated these from other CNS inflammatory diseases. At disease onset, 46 patients included in the study had a median age of 2.5 months (range 0-190 months), and 34 (74%) were under 12 months. Familial HLH was the most frequent genetic defect. Neurologic symptoms were present at onset in 29 children (63%) and were associated with fever, hepato-splenomegaly or lymphadenopathy in 26. The 3 main neurologic symptoms were seizures, impaired consciousness, and meningismus. Microcephaly was diagnosed at birth in 6 boys and developed shortly after birth in 1. CSF was abnormal in 50%. MRI was abnormal in 7 (15%). Unlike patients with ADEM, MRI showed symmetric periventricular lesions, without thalamic and brainstem involvement and with infrequent hyposignal intensity on T1. At end of follow-up (3.6 +/- 3.6 years), 18 (39%) patients had died; 17 of 28 (61%) surviving patients were normal neurologically, 5 (18%) had a severe neurologic outcome, and 6 (21%) had mild cognitive deficits. Risk of abnormal neurologic outcome was related to neurologic symptoms, MRI abnormalities, or abnormal CSF at onset, and was not influenced by age or type of genetic defect. (Deiva K, Mahlaoui N, Beaudonnet F, et al. CNS involvement at the onset of primary hemophagocytic lymphohistiocytosis. **Neurology** 2012 April 10;78:1150-1156).
(Response and reprints: kumaran.deiva@bet.aphp.fr).

COMMENT. Neurologic symptoms are frequent at onset of primary HLH and 50% patients have abnormal CSF. Early diagnosis is essential for a favorable outcome.