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

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DEVELOPMENTAL DISORDERS

DEVELOPMENTAL OUTCOME OF VERY PRETERM INFANTS AT ADOLESCENCE CORRELATED WITH GREY AND WHITE MATTER ABNORMALITIES ON MRI

MRI data of brains of 218 adolescents (ages 14-15 years) born very preterm, < 33 weeks gestation (VPT), and 128 controls born at term were compared, using voxel-based morphometry, and the findings correlated with neurodevelopmental outcome in a study at King's College London Institute of Psychiatry and Centre for Neuroimaging Sciences, Maudsley NHS Trust, London, UK. VPT subjects showed reduced grey matter (GM) in temporal, frontal, occipital cortices and cerebellum and increases in adjacent GM predominantly in temporal and frontal lobes. White matter (WM) was decreased in the brainstem, internal capsule, temporal and frontal regions, and showed excesses in temporal, parietal and frontal regions. The areas showing increased and decreased GM and WM volumes were structurally associated. The greatest WM and GM alterations occurred in VPT individuals with evidence of periventricular hemorrhage and ventricular dilatation on neonatal ultrasound. VPT adolescents had lower scores than controls on measures of language and executive function and their cognitive function was more likely to be impaired (27% vs 14%, respectively; p=0.013). Gestational age was positively correlated with GM and WM volumes. Specific cognitive deficits and neurodevelopmental delay associated with VPT birth may be related at least in part to altered grey and white matter volumes. (Nosarti C, Giouroukou E, Healy E, et al. Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. **Brain** January 2008;131:205-217). (Respond: Dr Chiara Nosarti, Department of Psychiatry, PO Box 63, King's College London Institute of Psychiatry, 16 De Crespigny Park, Denmark Hill, London SE5 8AF, UK).

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COMMENT. Previous studies have shown that infants born very preterm (VPT), <33 weeks gestation and of low birth weight (<2500g), are at risk of hemorrhage and hypoxic-ischemic damage that results in dilated ventricles, loss of white matter, and enlarged subarachnoid space (Volpe JJ. **Pediatrics** 2003;112:176-180); (Inder TE et al. **J Pediatr** 2003;143:171-179). Subarachnoid fluid collections in very low birth weight infants, sometimes called "external hydrocephalus," may be associated with transient macrocrania and neurodevelopmental abnormalities (hypertonia and hyperreflexia) that resolve by 18 months of age. (Al-Saedi SA et al. **J Pediatr** 1996;128:234-236). Half of VPT adolescents show persisting brain abnormalities, with smaller cortical volumes and larger lateral ventricles compared to controls. (Cooke RW et al. **Arch Dis Child Fetal Neonatal Ed** 1999;81 (F):116-121).

Computational morphometry used to process MRI data in the present study identifies focal localized changes in GM and WM concentration. The findings suggest that alterations in grey and white matter volume demonstrated in temporal, frontal, cerebellar and other regions of brain may be responsible for the cognitive impairments found in adolescents born VPT. The cerebral developmental changes following VPT birth result not only in GM and WM loss, but also in cortical and subcortical tissue excesses, often in adjacent and structurally associated areas. Infants who experience the greatest degree of perinatal insult exhibit the most severe GM and WM alterations and have the highest risk of neurodevelopmental compromise. When VPT birth is complicated by severe brain injury, brain plasticity compensates for resulting cell loss, with production of extra cells and synapses that normally become 'pruned' during later development. These compensatory processes are particularly extensive in preterm infants showing the most severe neonatal ultrasound abnormalities.

Selective vulnerability varies with the stage of development of different brain regions. GM volume in frontal lobes increases during preadolescence, the prefrontal areas reaching full maturity in late adolescence. Temporal lobe GM development peaks in mid-adolescence. VPT children may show not only a global delay in brain maturation but also, differences in GM and WM volumes. Identification of these brain volume changes by MRI in early life may be used as a clinical marker of increased risk of cognitive impairment at a later age, and may lead to educational intervention.

ETIOLOGY AND TREATMENT OF DEVELOPMENTAL STAMMERING

The etiology and treatment of developmental stammering in childhood (DS, also called idiopathic stammering or stuttering) are reviewed by a speech pathologist and psychologist at the University of Reading, UK. Prevalence is estimated at 1 to 3% of the population. DS is distinguished from neurogenic stammering (secondary to stroke, tumor, or degenerative disease) and psychogenic stammering. DS usually develops in pre-school age groups, the mean age at onset of 4 years, with 75% cases beginning before age 6. The cause is multifactorial, demands placed on the child exceeding the capacity to manage speech and language variables. The evidence for a genetic component to stammering is strong, twin studies showing concordance in monozygotic twins of 75 – 89%. Some children with DS are linguistically advanced while others are delayed. A mismatch between motor speech and language abilities may cause impairment in fluency, when articulation skills are not

sufficiently developed to keep pace with verbal output. Another theory invokes a faulty auditory processing, that may respond to delayed auditory feedback therapy. Neuroimaging in adults who stammer may show hemispheric asymmetries, and neurochemical studies report both increased and decreased levels of dopamine. Risperidone, a D2 antagonist, may reduce severity of stammering in some adults. Treatment recommendations in children vary from an indirect approach, with changes in the child's environment to reduce demands, to direct intervention, targeting speech output and capacity. Complete recovery, with or without therapy, is common before adolescence. Approximately 74% of children who stammer recover, 89% of young females. Boys are affected most frequently; those with a late onset of DS have the poorest prognosis, especially when complicated by speech and language delay. (Ward D. The aetiology and treatment of developmental stammering in childhood. **Arch Dis Child** January 2008;93:68-71). (Respond: Dr David Ward, School of Psychology and Clinical Language Sciences, University of Reading, Reading RG6 6AL, UK).

COMMENT. Stammering is developmental (idiopathic) or acquired. Particularly in adults, it may be secondary to organic brain disease or of psychogenic origin. In children it is most likely developmental and usually transient, requiring only an adjustment of parental handling or school pressure. If persistent and complicated by seizures or other neurologic manifestations, investigations should include an EEG and MRI. In rare cases, the differential diagnosis may include Landau-Kleffner syndrome; symptoms are associated with an acute onset of loss of speech comprehension and auditory agnosia, seizures and/or a paroxysmal EEG with bitemporal discharges. (Morrell F et al. **Brain** 1995;118:1529-1546).

Structural and functional abnormalities of the motor system in developmental stuttering are reported by researchers at the Departments of Experimental Psychology and Clinical Neurology, University of Oxford; and Department of Psychology, University College London, UK. (Watkins KE, Smith SM, Davis S, Howell P. **Brain** January 2008;131(1):50-59). Using functional and diffusion imaging, motor and language areas were examined in brains of 12 young subjects (aged 14-27 years;avg 18 years; 1 left-hander) who stutter. During speech production, people who stutter show overactivity relative to controls in the anterior insula, cerebellum and midbrain bilaterally and underactivity in the ventral premotor, Rolandic opercular and sensorimotor cortex bilaterally and Heschl's gyrus in the left hemisphere. The overactivity in the midbrain, at the level of the substantia nigra, red and subthalamic nuclei, is consistent with a previous report of excess dopamine in adults who stutter. Areas with underactivity are associated with articulation and speech production, and show loss of white matter. Stuttering is related to disruption in neural systems that support the execution of fluent speech.

BRAINSTEM MALFORMATIONS

Malformations of the brainstem in 138 patients identified aver a 10 year period are classified according to MRI findings and by embryological cause in a study at University of California at San Francisco, and University of Chicago, IL. The pons was involved in 114, midbrain in 45, and medulla in 14. More than 1 region was affected in 53 patients. Malformations were classified in four groups: 1) disorder of brainstem segmentation or induction; 2) segmental hypoplasia; 3) postsegmentation malformation (associated with migration abnormalities); and 4) abnormal cortical organization. *Segmentation anomalies*

included short pons, short midbrain/long pons with large cerebellum, and thick, short medulla. *Segmental hypoplasia* involving the pons in 59 patients was associated with microcephaly in 34. *Postsegmentation anomalies* included midbrain enlargement, enlarged quadrigeminal plates, midline clefts, 33 with congenital muscular dystrophies and O-glycosylation defects (10 with Walker-Warburg syndrome, 7 with muscle-eye-brain disease, and 2 with Fukuyama CMD), and 19 with Joubert's syndrome and the characteristic molar tooth malformation. *Associated cortical organization abnormalities* included polymicrogyria and cerebellar hypolasia with pontine hypoplasia in 11 patients. Disorders involving the cranial nerves usually had no brainstem abnormalities on imaging other than hypoplasia of the affected nerves. (Barkovich AJ, Millen KJ, Dobyns WB. A developmental classification of malformations of the brainstem. **Ann Neurol** Dec 2007;62:625-639). (Respond: Dr Barkovich, Neuroradiology Room L371, University of California at San Francisco, 505 Parnassus Avenue, San Francisco, CA 94143).

COMMENT. Brainstem malformations appear to be more common than generally recognized. This study and proposed classification should alert neurologists and radiologists to the diagnosis of congenital malformation of the brainstem in infants and children with nonprogressive cranial nerve and long tract signs. We can look forward to an anticipated separate account of cerebellar malformations from the same institutions. Intrauterine ischemic atrophy rather than a primary developmental malformation is suggested in some reports of brainstem lesions presenting with congenital apnea and failure of central respiratory drive (Cortez C, Kinney HC. **J Neuropathol Exp Neurol** 1996;55:841-849; Reviewed by Sarnat HB. Recent advances in congenital malformations. In: **Progress in Pediatric Neurology III**, Chicago, PNB Publ, 1997;365-369).

ACUTE BRAINSTEM SYMPTOMS WITH CHIARI TYPE 1 MALFORMATION

Two children who presented with rapidly worsening neurological symptoms attributable to a previously undiagnosed Chiari malformation Type 1 are reported from Children's Hospital, Birmingham, AL. One patient became hypopneic and dysphagic and developed a right hemiparesis in less than a 48-hour period. Another patient presented with a rapidly worsening right hemiparesis, ataxia, and anisocoria. MRI revealed the Chiari 1 in both patients, and a syrinx was also identified in the second patient. Following surgical posterior fossa decompression, symptoms immediately improved. (Wellons JC III, Tubbs S, Bui CJ, Grabb PA, Oakes WJ. Urgent surgical intervention in pediatric patients with Chiari malformation Type 1. Report of two cases. **J Neurosurg: Pediatrics** 2007;107(1). (Respond: Dr W Jerry Oakes, Division of Neurosurgery, Section of Pediatric Neurosurgery, Children's Hospital, Birmingham, AL).

COMMENT. Acute presentation of Chiari malformation Type 1 (CM-1) is rare, especially in children. Chiari 1 should be included in the differential diagnosis of acute onset of brainstem or long tract signs. In a study of CM-1 at the Children's Hospital, Birmingham, UK, abnormalities of the skull base were identified by MRI measurements, indicative of a mesodermal defect. (Sgouros S et al. **J Neurosurg (3 Suppl Pediatrics)** 2007;107:188-192).

CEREBRAL PALSIES

IPSILATERAL CORTICOSPINAL PROJECTIONS FROM NONINFARCTED CORTEX IN HEMIPLEGIC CEREBRAL PALSY

Transcranial magnetic stimulation (TMS) was used to characterize corticospinal tract development from each hemisphere over the first 2 years in 13 patients with perinatal stroke compared to 46 healthy controls, in a study at University of Newcastle, Newcastle on Tyne, UK; and University of Pisa, Italy. In infants with unilateral cerebral infarction, TMS responses from the affected cortex became progressively more abnormal and were eventually lost in 7. Ipsilateral corticospinal axons projecting from the noninfarcted cortex were hypertrophied, and MRI demonstrated hypertrophy of the corticospinal tract projecting from the noninfarcted hemisphere. Initial TMS findings soon after the stroke did not predict subsequent impairment, but subsequent loss of TMS responses and hypertrophy of ipsilateral corticospinal axons from noninfarcted cortex did predict severe hemiplegia by 2 years of age. In 25 infants with bilateral lesions, development was normal when TMS responses were maintained from both hemispheres. These findings may explain why signs of hemiplegic cerebral palsy following neonatal stroke appear late and progress over the first 2 years of life. Increased ipsilateral projections from the noninfarcted cortex compound the disability by competing with and displacing surviving contralateral projections from the infarcted cortex. (Eyre JA, Smith M, Dabydeen L et al. Is hemiplegic cerebral palsy equivalent to amblyopia of the corticospinal system? **Ann Neurol** Nov 2007;62:493-503). (Respond: Prof Janet A Eyre, Developmental Neuroscience, Sir James Spence Institute of Child Health, Royal Victoria Infirmary, Queens Victoria Road, Newcastle upon Tyne, NE3 1LP, UK).

COMMENT. Neonates with stroke may be asymptomatic except for seizures, and hemiplegia develops slowly over 2 years, sometimes with loss of previously acquired motor skills. The authors of the above report hypothesize that activity-dependent displacement of surviving contralateral corticospinal projections from the infarcted hemisphere by more active ipsilateral projections from the noninfarcted hemisphere is associated with hypertrophy of the corticospinal tract originating in the noninfarcted hemisphere. The authors draw a parallel of their findings in neonatal stroke with that of the visual system where loss of vision in one eye is followed by retraction of the deprived geniculocortical arbors and a compensatory expansion of the terminal geniculocortical arbors of the open eye. They cite Wiesel and Hubel, 1965, who describe in kittens the progressive loss of responsiveness by the visual cortex to an eye deprived of vision, providing a model of plasticity of the cortex in response to activity in sensory afferents. During development similar activity-dependent mechanisms and consequences may apply to the development of corticospinal tracts. The findings contradict the view that cerebral palsy arises from a nonprogressive lesion of the brain, since the extent of the lesion is shown to expand postnatally. Based on these findings, the authors postulate that activity-dependent mechanisms might be harnessed therapeutically to enhance the competitive mechanism by some form of stimulation that will lessen the degree of the lesion.

CORTICOSPINAL DYSGENESIS AND CONGENITAL HEMIPLEGIA

A diffusion tensor imaging technique was compared with conventional MRI to measure and quantify corticospinal dysgenesis in 12 patients with congenital hemiplegia and 12 matched control subjects, in a study at Universite Catholique de Louvain, Brussels, Belgium. A symmetry index computed between the area of the contralateral and ipsilateral corticospinal tracts was similar for the two methods, but the diffusion tensor imaging indexes were significantly smaller. This suggests that the use of the conventional MRI measurement of the cross-sectional area of cerebral peduncles on T1 MRI might lead to an underestimate of cortical dysgenesis. Hand-movement deficits, particularly precision grasping, and stereognosis were examined and correlated with the neuroimaging findings. The symmetry index computed from MRI peduncle measurements correlated solely with deficits in stereognosis, while the diffusion tensor imaging index correlated with stereognosis, digital and manual dexterities, and a measure of manual ability in daily life activities. (Bleyenheuft Y, Grandin CB, Cosnard G, Olivier E, Thonnard J-L. Corticospinal dysgenesis and upper-limb deficits in congenital hemiplegia: a diffusion tensor imaging study. **Pediatrics** Dec 2007;120(6):e1502-e1511). (Respond: Jean-Louis Thonnard PhD, Universite Catholique de Louvain, Unite de Readaptation, Ave Mounier 53, 1200 Bruxelles, Belgium).

COMMENT. Diffusion tensor imaging symmetry index may prove useful in predicting motor and sensory deficits in children with congenital cerebral dysgenesis.

SEIZURE DISORDERS

SURGERY FOR INTRACTABLE TEMPORAL LOBE EPILEPSY IN YOUNG CHILDREN

The results of temporal resection for medically intractable epilepsy in 20 children less than age 5 years with at least 2 years follow-up are reported from Miami Children's Hospital, Florida. The mean age at surgery was 26 months, and the mean age at seizure onset was 12 months. Seizures were typical psychomotor in 4 patients, with staring and oral or gestural automatisms; and psychomotor plus in 7, with aura and frightened appearance, staring, decreased responsiveness followed by movements that were contraversive, lateralized tonic or clonic, and asymmetric tonic posturing. Motor symptoms were prominent in 3, with tonic asymmetric posturing followed by circling and vegetative signs. Clusters of epileptic spasms occurred in 6, mainly clonic. Interictal EEGs showed lateralizing abnormalities in 15 that were concordant, and ictal EEGs were lateralizing and concordant in 18 and nonlateralizing in 2. Brain MRI revealed localizing pathology in 16, and ictal SPECT was concordant in 4/8 cases. Invasive EEG recording was performed in 6 children to delineate the epileptogenic zone and map language cortex. Electrocorticography was performed in the remaining 14 cases. At mean follow-up of 5.5 years following surgery, 65% were seizure-free and 15% had >90% seizure reduction. The etiologic pathology was a tumor in 8 cases, benign developmental in 4 and malignant astrocytoma in 4. Focal cortical dysplasia was found in 6 cases, one with neurofibromatosis. Hippocampal sclerosis was identified in 4. Other pathologies included encephalitis, prior hypoxic-ischemic event, tuberous sclerosis, and

white matter gliosis, 1 of each. Patients with the most favorable outcome had psychomotor type seizures, tumor, and complete resection without complications. Stroke occurred in 2 and infection and hydrocephalus in 1. (Maton B, Jayakar P, Resnick T, Morrison G, Ragheb J, Duchowny M. Surgery for medically intractable temporal lobe epilepsy during early life. **Epilepsia** Dec 2007;49(1):80-87). (Reprints: Michael Duchowny MD, Miami Children's Hospital, Department of Neurology, 3200 SW 60th Court, Suite 302, Miami, FL 33155).

COMMENT. Cortical resection limited to one temporal lobe for refractory temporal lobe epilepsy is rare in children less than 5 years. This report indicates that surgery in this age group can be associated with favorable outcome, similar to that in older children.

Surgery for epilepsy in children ages 1 – 15 years. A report from Milan, Italy, found that 60% of 113 patients younger than 16 years (mean age at surgery of 8.8 years) were seizure free following excision of the epileptogenic zone for refractory focal seizures (Cossu M et al. **Epilepsia** Dec 2007;49(1):65-72). Variables associated with a significantly lower risk of seizure recurrence were unifocal lesion on MRI, older age at seizure onset, temporal unilobar resection and complete lesionectomy, and glial-neuronal tumor pathology. Results of surgery were strongly dependent on presurgical identification and resection of the epileptogenic zone.

Propeller MRI sequencing for detailed imaging of hippocampal sclerosis. This method is superior to routine MRI sequencies for identifying subtle hippocampal sclerosis (HS), and negates the effects of movement during scans (Eriksson SH et al. **Epilepsia** Dec 2007;49(1):33-39). Signs of HS on MRI are increased hippocampal signal on T2-weighted images and loss of hippocampal volume on T1-weighted images. Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction (PROPELLER) sequence compensates for head motion during the MRI scan.

GENETIC VARIATION IN CALCIUM CHANNEL GENE IN IDIOPATHIC GENERALIZED EPILEPSIES

Researchers at Women's And Children's Hospital, North Adelaide, and other centers in Australia and Canada screened 240 individuals from 167 families with idiopathic generalized epilepsy and generalized epilepsy with febrile seizures plus (GEFS+) and 95 controls for variants in the *CACNA1H* gene. They identified 19 novel variants causing amino acid changes associated with the following epilepsy syndromes: childhood absence epilepsy, juvenile absence, juvenile myoclonic, idiopathic generalized with tonic-clonic seizures, and temporal lobe epilepsy. The variants also occurred in unaffected individuals. In some families, the variant segregated with epilepsy, but not in others. It is concluded that variants in *CACNA1H* gene that alter channel properties occur in patients with various generalized epilepsy syndromes, contributing to epilepsy susceptibility but not sufficient to cause epilepsy themselves. (Heron SE, Khosravani H, Varela D, et al. Extended spectrum of idiopathic generalized epilepsies associated with CACNA1H functional variants. **Ann Neurol** Dec 2007;62:560-568). (Respond: Sara E Heron, Department of Genetic Medicine, Women's and Children's Hospital, 72 King William Road, North Adelaide SA 5006, Australia).

COMMENT. Variants in the *CACNA1H* gene are associated with a range of generalized epilepsy syndromes, but additional genes or environmental factors also may influence epilepsy susceptibility in some individuals. These genetic variants can contribute to a risk of epilepsy but are not themselves the cause. (Lowenstein D, Messing R. Editorial. **Ann Neurol** Dec 2007;62:549-551).

ATTENTION DEFICIT DISORDERS

CONTROLLED STUDY OF GUANFACINE XR IN ADHD

A multicenter, double-blind, placebo-controlled, fixed-dosage escalation study of an extended release formulation of guanfacine is reported from the Massachusetts General Hospital, Boston, and other centers in the US and UK. A total of 345 patients aged 6-17 years were randomly assigned to 1 of 3 guanfacine dosage groups (2, 3, or 4 mg/each AM) or placebo for 8 weeks. All groups of children taking guanfacine showed significant improvement in hyperactivity/impulsivity and inattentiveness subscales of the ADHD Rating Scale IV, Clinical Global Impression, Parent's Global Assessment, and Conners' Parent and Teacher Rating Scales-Revised. Adverse events included headache, somnolence, fatigue, abdominal pain, and sedation. Treatment was discontinued because of somnolence in 4.2%, sedation in 3.5%, and headache in 1.5%. Somnolence occurred in 15.8-27.6% patients with doses of 0.04-0.12 mg/kg. Blood pressure and pulse rate decreased as dosages were increased, by a maximum of -10.1 mm Hg (week 4) and -8 bpm (week 4). Mean changes in ECG (PR and QRS intervals) were unremarkable, mean changes in QTcF intervals were 3.7-9.1 msec (dose related), and no patient had a QT interval =/> 480 msec. Seven discontinued treatment because of ECG abnormalities, 4 because of QTc interval prolongation, one in each treatment group. Mean changes in height and weight were unremarkable, and group and individual cortisol and human growth hormone levels showed no excessive suppression or elevation. Guanfacine XR was considered safe and effective compared with placebo. (Biederman J, Melmed RD, Patel A, et al. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. **Pediatrics** January 2008;121:e73-e84). (Respond: Joseph Biederman MD, Pediatric Psychopharmacology, Yawkey Center, Suite 6A, Massachusetts General Hospital, Boston, MA 02114).

COMMENT. Guanfacine is considered a more selective a2-adrenoceptor agonist than clonidine, binding preferentially to receptors in the prefrontal cortex. It has a longer plasma half-life and is less sedating and less hypotensive. The extended release formulation of guanfacine appears to be superior to the immediate release, and is effective in a once daily dosage. In practice, guanfacine XR may be superior to stimulant medications in the younger child with hyperactive behavior and ODD, but the sedative side effect can be troublesome in children of school age. Pretreatment cardiac evaluation with ECG and regular cardiac monitoring are advisable. The potential increase in risk of cardiac complications should limit or discourage the use of a combination of stimulant medication and clonidine or guanfacine.