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CONGENITAL DEVELOPMENTAL DISORDERS

CLINICAL MANIFESTATIONS OF SOTOS SYNDROME

The major clinical criteria for the diagnosis of Sotos syndrome were evaluated by geneticists in a retrospective analysis of patients examined at the Children's Hospital, Goudi, Athens, Greece. These criteria were compared with those determined by meta-analysis of reports in the literature. Of a total of 22 patients (10 male and 12 female; aged between 2 months and 12 years) referred between 1996 and 2007 and initially enrolled in the study, 19 had typical Sotos syndrome; 3 with atypical facial characteristics were 'Sotos-like', (Douglas et al, 2003) and were excluded. All patients were re-evaluated regularly, including heart triplex ultrasonography and cranial MRI, and clinical findings were distinguished from those of similar overgrowth syndromes such as Weaver, and Beckwith-Wiedemann (Douglas et al, 2003). Molecular analysis was conducted later to confirm the diagnosis in some cases.

The criteria required for a diagnosis of Sotos syndrome in previous studies (Douglas et al, 2003) included a distinctive facial gestalt, height and head circumference >97th percentile, advanced bone age, and developmental delay. Of 19 patients in the present series, 6 met all required clinical criteria, 10 lacked one criterion, and 3 lacked two criteria. Facial features included prominent forehead, dolichocephaly, down slant palpebral fissures, hypertelorism, pointed chin, and premature teeth eruption. Typical facial gestalt and macrocephaly were present in all patients, overgrowth (>97th percentile) in 16, and advanced bone age in 12. MRI findings were abnormal in 14 patients, and included dilated ventricles (10/19), demyelination (5/19), and corpus callosum thinning (5/19). Genitourinary anomalies included cryptorchidism (4/19), and bladder diverticulae (2/19). Developmental delay was present in 16/19 cases, with severe mental retardation in 9. In the meta-analysis of 6 published series, facial gestalt was a constant finding, overgrowth and advanced bone age were strongly significant (P<0.001 and <0.009, respectively), and urinary malformations

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showed a slight increase in prevalence (P<0.042). The frequency of developmental delay, brain abnormalities, and congenital heart defect was not significant.

Sotos syndrome is a genetic disorder caused by NSD1 mutations or deletions. The diagnosis is based on two major clinical criteria, a typical facial gestalt and macrocephaly. Advanced bone age, height, and learning difficulties are not specific for Sotos syndrome, and occur in other overgrowth syndromes. (Leventopoulos G, Kitsiou-Tzeli S, Kritikos K, et al. A clinical study of Sotos syndrome patients with review of the literature. **Pediatr Neurol** May 2009;40:357-364). (Respond: Dr Leventopoulos, Fokidos 53, Goudi, Athens 11527, Greece. E-mail: levent2669@hotmail.com).

COMMENT. Sotos syndrome, or cerebral gigantism, was originally described as a syndrome of excessively rapid growth with acromegalic features and a non-progressive neurologic disorder (Sotos JF et al. **N Engl J Med** 1964;27:109-116). In early childhood, head circumference and height are >97th percentile, but after puberty, growth is normal. Neurologic defects include hypotonia, gait dyspraxia, developmental delay, mild mental retardation, and seizures, 50% febrile. NSD1 mutations, frequent in European-origin patients, and microdeletions, in Japanese, account for genotype-phenotype differences involving prevalence of overgrowth, and cardiovascular and urogenital malformations. (Nagai T et al. **J Med Genet** 2003;40:285-289). Clinically, the diagnosis of Sotos syndrome should be suspected in children born with typical facial features and macrocephaly, especially if these cardinal manifestations are associated with excessive growth, advanced bone age, mental retardation, congenital heart defect, or genitourinary anomaly.

DEVELOPMENTAL COORDINATION DISORDER IN SCHOOL-AGE CHILDREN

The prevalence of developmental coordination disorder (DCD) in children, at 7 years of age, in a large UK birth cohort was determined using DSM-IV criteria, in a study at the University of Bristol, UK; and Utrecht University, Netherlands. Children with neurologic disorders or IQ of <70 were excluded. By using tests that measured manual dexterity, ball skills, balance, handwriting skills and activities of daily living, 119 of 6990 children met criteria for DCD, with a prevalence of 1.7%, 17/1000 at a mean age of 7.5 years. The gender ratio was 1.8:1 male to female. When an additional 222 children with "probable DCD" were included, the risk of DCD was 4.9%. The risk of DCD was greater in children of lower socioeconomic backgrounds, birth weight <2500 g, and born at <37 weeks' gestation. DCD is an important often overlooked cause of disability in school age children. (Lingham R, Hunt L, Golding J, Jongmans M, Emond A. Prevalence of developmental coordination disorder using the DSM-IV at 7 years of age: a UK population-based study. **Pediatrics** April 2009;123:e693-e700). (Respond: Raghu Lingam MBChB, MRCPCH, University of Bristol, Dept Community-Based Medicine, Bristol B566JS, UK. E-mail: raghu.lingam@bristol.ac.uk).

COMMENT. A similar study using different measures of coordination was conducted in apparently normal schoolchildren born extremely preterm (<29 weeks or birth weight <1000 g) at Westmead Hospital, New South Wales, Sydney, Australia. (Goyen T-A, Lui K. **Arch Dis Child** April 2009;94:298-302). At age 8 years, the prevalence of DCD was 42% in

this high-risk population compared with 8% for matched classroom full-term controls. Motor assessment at 3 years of age using Peabody Fine Motor Scales is highly predictive of subsequent DCD at school age. Early identification of DCD allows early intervention to prevent school problems and loss of self-esteem. Differences in the prevalence rates of DCD in various reports could be explained by different methods of measurement. The incidence of ADHD, commonly complicated by DCD, in these cohorts would be of interest.

PRESENTING SYMPTOMS OF CHIARI TYPE I MALFORMATION

Clinical and radiographic predictors of neurologic symptoms were investigated in a population-based retrospective study of 51 children identified with Chiari I malformation at the University of California, and Kaiser Department of Radiology, San Francisco. The patients represented 1% of children who had head or spine MRI during the study period, 1997-1998. The mean age at diagnosis was 11 years. Tonsillar ectopia ranged from 5 to 32 mm; 22% were >10 mm. Cerebellar tonsils were abnormally pointed in 55% of cases, with CSF compression in 57%. Syringomyelia occurred in 6 (12%) of the Chiari I patients. Nineteen (37%) patients were diagnosed incidentally, MRIs performed for atypical symptoms such as seizures and scoliosis.

Of the 51 patients, 32 (63%) had symptoms at diagnosis. Headache was the most common presenting complaint, occurring in 28 (55%) patients, neck pain in 12%, vertigo (8%), sensory changes (6%), and ataxia or incoordination (6%). Other symptoms at time of diagnosis included leg weakness, tinnitus, hearing loss, dysarthria, loss of consciousness and scoliosis with syrinx, each occurring in 1 patient. Patients were followed for a mean of 6.4 years, and headache was the most common complaint, occurring in 61% of the 51 patients during the study period. Headache was moderate or severe and required frequent follow-up. Of 3 who had suboccipital decompression surgery for intractable daily headaches, 2 had complete resolution for up to 7 years of follow-up, and 1 relapsed after 12 months.

Older age at diagnosis was predictive of headache occurrence, while none of the radiological characteristics, including degree of ectopia, were associated with headache or other neurologic symptoms. Half of all children with Chiari I (49%) had significant neurologic symptoms. Borderline tonsillar ectopia (2-4 mm), in 19 patients (0.4% of all head and spine MRIs), although considered a normal variant, was associated with headache in 74%, severe in 16%. Occipital headache occurred in 11%. None of the borderline cases showed pointed tonsils or retrocerebellar CSF compression ($P<0.0001$). (Aitken LA, Lindan CE, Sidney S, et al. Chiari type I malformation in a pediatric population. **Pediatr Neurol** June 2009;40:449-454). (Respond: Dr Wu, UCSF Division of Child Neurology, 350 Parnassus, Suite 609, San Francisco, CA 94117. E-mail: wuy@neuropeds.ucsf.edu).

COMMENT. Headache is a frequent presenting symptom of Chiari I malformation in children, but the malformation is often discovered incidentally in children without characteristic symptoms. Although 5 mm of tonsillar ectopia is the accepted cutoff for the diagnosis of Chiari I, patients with lesser degrees of ectopia may also develop typical symptoms and syringomyelia.

MUSCLE DISEASES

UPDATE AND REVIEW OF CONGENITAL MYOPATHIES

Congenital myopathies are reviewed by neuropathology researchers in New Delhi, India, and Mainz, Germany. The term 'congenital myopathy' (CM) was introduced with the discovery of 'central core disease,' a non-progressive myopathy described by Shy and Magee (1956). Molecular genetics, enzyme and immunohistochemical tests and electron microscopy have led to a better understanding of CM and their classification. CM is either structured or unstructured, with or without structural changes. Structured CM include, *central core disease* (autosomal dominant, mildly progressive or static; or autosomal recessive, more severe with onset in the first decade); *multi-minicore disease* (proximal muscle weakness, spinal rigidity, scoliosis, respiratory impairment, and external ophthalmoplegia); *myotubular myopathies* (type 1 fiber atrophy and central nuclei); *X-linked myotubular myopathy* (rapidly fatal in newborn boys, presenting with hypotonia and respiratory insufficiency, and arthrogryposis multiplex); *centronuclear myopathy* (autosomal dominant or recessive, or sporadic, neonatal and childhood forms, mildly progressive, central nuclei, type 1 predominance); *nemaline myopathy* (thread like rod inclusions on Gomori trichrome stains, 6 different forms, congenital to adult); *actin aggregate myopathy* (similar to nemaline myopathy, early onset, rapid course, rarely benign); *desminopathy* (slowly progressive, second to fourth decade distal weakness onset, cardiomyopathy, autosomal dominant or recessive); *a-B-crystallinopathy* (similar to desminopathies, a myofibrillary myopathy); *hyaline body myopathy* (subsarcolemmal hyalinized bodies, rich in myofibrillary ATPase and myosin).
Unstructured CM: *congenital fiber type disproportion* (non-progressive childhood CM with relatively good prognosis, type 1 fiber predominance).

No clinical symptomatology is specific for an individual CM, but some clinical findings are more frequent in certain CMs; eg. ptosis or extraocular muscle weakness in multicore disease, nemaline myopathy, centronuclear myopathy, and congenital fiber type disproportion; scoliosis in desminopathies, and central core disease. (Sharma MC, Jain D, Sarkar C, Goebel HH. Congenital myopathies – a comprehensive update of recent advancements. **Acta Neurol Scand** May 009;119:281-292). (Respond: Dr MC Sharma, Department of Pathology, All India Institute of Medical Sciences, New Delhi-110029, India. E-mail: sharmamehar@yahoo.co.in).

COMMENT. An expertise in enzyme and immunohistochemical methods, electron microscopy, and molecular genetics is required to distinguish the rapidly expanding differential diagnosis of congenital myopathies. Clinical symptomatology is largely nonspecific.

BENIGN RECURRENT SIXTH CRANIAL NERVE PALSIES

A retrospective chart review of a cohort of 253 pediatric patients with sixth nerve palsies uncovered 30 cases of benign sixth nerve palsy, of which 9 were recurrent, in a study at University of Pennsylvania School of Medicine, Philadelphia. Sixth nerve palsy occurred alone in 225 patients, and the etiologies were as follows: 90 (40%) had neoplasms, 25

(11.1%) were ascribed to increased intracranial pressure, 23 (10.2%) to trauma, 14 (6.2%) an infectious etiology, 10 (4.4%) to vascular disease, 9 (4%) inflammatory disorders, 6 (2.7%) were congenital, 2 (0.9%) secondary to surgery unrelated to neoplasm, and 1 (0.4%) to radiation necrosis.

Benign sixth nerve palsy and recurrent cases had the following characteristics: a) isolated unilateral abduction palsy; b) without ptosis, papilledema or other neurologic signs; c) normal brain MRI; d) spontaneous improvement; e) without infection, inflammatory or other disease identified. The mean age at evaluation of the 30 (13.3%) benign cases was 3 years. MRIs performed in 28 (93%), and lumbar punctures in 6 were normal, Acetylcholine receptor antibody testing was negative in 11 (37%), and lyme antibody titres, and anti-Gq1b antibody testing were normal. Only one child had some residual abduction deficit at 3-year follow-up. Four patients, including 3 with recurrences, had residual esotropia but full ductions, and all were referred for strabismus surgery. (Mahoney NR, Liu GT. Benign recurrent sixth (abducens) nerve palsies in children. **Arch Dis Child** May 2009;94:394-396). (Respond: Dr Nicholas R Mahoney, Scheie Eye Institute, 51 North 39th Street, Philadelphia, PA 19104. E-mail: nicholas.mahoney@uphs.upenn.edu).

COMMENT. Proposed etiologies for benign sixth nerve palsies include ophthalmoplegic migraine, myasthenia gravis, and inflammation secondary to viral infections or vaccination (Lee MS, 1999). Age and gender are important, the age being younger in the recurrent cases, and girls are affected more frequently than boys. Cases related to vaccination are also prone to recurrence. (Yousuf et al, 2007). The cases in the above study were idiopathic.

METABOLIC DISORDERS

VOLTAGE SENSORS IN HYPOKALEMIC PERIODIC PARALYSIS

Researchers at the National Hospital, Queen Square, London, UK, conducted automated DNA sequencing of the S4 regions of *CACNA1S* and *SCN4A* in 83 patients with hypokalemic periodic paralysis (HypoPP). CACNA1S mutations were identified in 64 cases, and SCN4A or other CACNA1S mutations in 10, including 4 with new mutations. All mutations neutralized arginine residues in S4 segments. The patients with new mutations had the typical HypoPP phenotype: onset of attacks of muscle paralysis in first or second decade, at night or early morning, and low serum potassium. The findings were consistent with the gating pore cation leak hypothesis of HypoPP, and arginine mutations in S4 segments are involved in 90% cases. (Matthews E, Labrum R, Sweeny MG, et al. Voltage sensor charge loss accounts for most cases of hypokalemic periodic paralysis. **Neurology** May 5, 2009;72:1544-1547). (Response and reprints: Prof MG Hanna, Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK. E-mail: m.hanna@ion.ucl.ac.uk).

COMMENT. In an editorial, Cannon SC proposes that the remaining 10% of HypoPP families with no identified mutation will also prove to be channelopathies, from a new class of molecular defect or different channel. (**Neurology** 2009;72:1540-1541).

ATTENTION DEFICIT AND BEHAVIORAL DISORDERS

ALTERED ANANDAMIDE DEGRADATION IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

Anandamide (AEA) metabolism was investigated in 15 drug-free boys with ADHD (aged 6.5-13 years) and 15 age- and gender-matched healthy controls, in a study at Universita Tor Vergata, Rome, Italy. AEA, an endocannabinoid, reduces the activity of the dopamine transporter. The activity of fatty acid amide hydrolyse (FAAH), which is responsible for AEA degradation, was significantly decreased in lymphocytes from peripheral blood of subjects with ADHD. This finding suggests that AEA catabolism is dysregulated in ADHD, whereas the synthesis of AEA was unaltered. Stimulation of dopamine (DA) D2 class receptors inhibits FAAH activity and increases the level of AEA in the brain. A complex interaction between DA and the AEA endocannabinoid system (ECS) is found experimentally, and ECS is implicated in other DA-related disorders such as Parkinsonism. Dysfunction of the dopamine system is proposed to explain the clinical manifestations of ADHD. (Centonze D, Bari M, Di Michele B, et al. Altered anandamide degradation in attention-deficit/hyperactivity disorder. **Neurology** April 28, 2009;72:1526-1527).(Respond and reprints: Dr Diego Centonze, Clinica Neurologica, Universita Tor Vergata, Via Montpellier 1, 00133 Rome, Italy. E-mail: centonze@uniroma2.it).

COMMENT. The endocannabinoid system plays an important role in brain development (Fride E. **J Neuroendocrinol** 2008;20(suppl 1:75-81), and anandamide (arachidonylethanolamide [AEA]) impairs memory and attention by reducing the activity of the dopamine transporter system. An anandamide transporter inhibitor, 4-OH phenyl-arachidonamide (AM404), is found to reduce the hyperactive behavior elicited by a dopamine D2 receptor agonist in rat brain (Beltramo M et al. **Jrnl Neuroscience** 2000;20:3401-3407). Molecular genetic studies support the involvement of the dopamine receptor and dopamine transporter genes in the etiology of ADHD. Environmental factors such as prenatal exposure to nicotine, premature birth, head injury, and viral infections also play a role. (Millichap JG. **Pediatrics** 2008;121:e358-e365). Relation of dopamine deficits to fetal and perinatal stresses may explain the mechanism of environmental etiologies. (Swanson JM et al. **Neuropsychol Rev** 2007;17:39-59). Preterm birth and cerebral ischemia may contribute to deficient dopaminergic neurotransmission and symptoms of ADHD. Evidence of environmental mediators in ADHD are demonstrated in twin studies, affected twins having greater exposure to risk factors compared with unaffected co-twins. (Lehn H et al. **J Am Acad Child Adolesc Psychiatry** 2007;46:83-91). Gene-environment interaction is an important mechanism in the etiology of ADHD, some genes (DAT1) affecting the individual sensitivity to environmental factors. (Thapar A et al. **Brit J Psychiatry** 2007;190:1-3).

SLEEP DURATION AND BEHAVIORAL SYMPTOMS OF ADHD

To evaluate the association of short sleep duration with behavioral symptoms of ADHD, a cross-sectional study of children born in 1998 in Helsinki, Finland, was conducted

by researchers at the Universities of Helsinki and Oulu, Finland. Sleep quality was measured using actigraphs, and the Sleep Disturbance Scale for Children and the ADHD Rating Scale IV were administered to parents. Of 280 children (134 boys, 146 girls) with a mean age of 8.1 years (range 7.4-8.8), those with a short average sleep duration (<7.7 hours) had higher hyperactivity/impulsivity and ADHD total scores, but similar inattention scores compared with children sleeping 7.7 to 9.4 hours or >9.4 hours. Short sleep duration remained significantly associated with hyperactivity/impulsivity when controlling for basic confounding variables and also for sleeping difficulties and somatic illnesses, but it was not related to inattention or the ADHD total score. Short sleep duration was not correlated with sleeping difficulties, but sleep-breathing disorder was significantly associated with hyperactivity/impulsivity, inattention, and ADHD total score. Parent-reported short sleep duration was not related to hyperactivity/impulsivity, inattention, and the ADHD total score. (Paavonen EJ, Raikkonen K, Lahti J, et al. Short sleep duration and behavioral symptoms of attention-deficit/hyperactivity disorder in healthy 7- to 8-year-old children. **Pediatrics** May 2009;123:e857-e864). (Respond: Dr Paavonen. E-mail: juulia.paavonen@helsinki.fi).

COMMENT. Short sleep duration measured objectively with the actigraph and parent-reported sleeping difficulties are independently associated with increased risk of behavioral symptoms of ADHD. One third of children in the US are estimated to have inadequate sleep (Smaldone A et al. **Pediatrics** 2007;119(suppl 1):S29-S37). Questions regarding sleeping habits are important in the evaluation of children with ADHD, especially in relation to the symptoms hyperactivity/impulsivity and their association with short sleep duration or sleeping difficulties, such as sleep-breathing disorder and snoring. Short sleep duration is not correlated with the symptoms of inattention. A causal relation between sleep duration and behavioral symptoms is not established, but maintaining regular sleeping schedules may help to ameliorate the hyperactivity and impulsivity of ADHD. Sleep duration and sleeping difficulty studies are often inaccurate, relying heavily on parental reports, which are susceptible to bias. In a child with hyperactive behavior, excessive snoring should prompt referral to ENT, and sleeping difficulties may indicate the need for a polysomnograph. However, polysomnographic sleep scores are not related to academic functioning, IQ and neuropsychological test cores are powerful predictors of achievement. (Mayes SD et al. 2008). Inattentive symptoms are sometimes related to daytime sleepiness. (Willoughby MT et al. 2008).

Girls with ADHD generally have a greater frequency of the inattentive subtype than boys, but overall, boys outnumber girls with a 4:1 ratio for the ADHD-HI and 2:1 for ADHD-AD. (Wolraich ML et al. 1996). The preponderance of girls in the above study is unusual, but apparently, gender was not a modifying factor.

STRUCTURAL CEREBRAL CHANGES AND CONDUCT DISORDER

Voxel-based morphometry was used to analyze structural MRI scans from 23 boys with callous-unemotional conduct problems (mean age 11 yrs 8 months) and 25 healthy controls, in a study at the Institute of Psychiatry, King's College, London, UK, and other centers in London and Germany. Both grey matter volume and concentration were examined, controlling for cognitive ability and ADHD. Boys with unemotional conduct problems showed increased grey matter concentration in the medial orbito-frontal and anterior

cingulate cortices, and increased grey matter volume and concentration in the temporal lobes bilaterally and the cerebellum. The findings were consistent with a delay in cortical maturation in cortical areas involved in decision making, morality and empathy in boys with callous-unemotional conduct problems. (De Brito SA, Mechelli A, Wilke M, et al. Size matters: increased grey matter in boys with conduct problems and callous-unemotional traits. **Brain** April 2009;132:843-852). (Respond: Dr Stephane A De Brito, Institute of Psychiatry, PO Box 23, King's College, London, UK. E-mail: stephane.debrito@iop.kcl.ac.uk).

COMMENT. Contrary to previous reports of decreased concentration and volume of cortical areas in psychopathic adolescents and adults with conduct disorders, this study found increases in grey matter concentration in orbito-frontal cortex and anterior cingulate cortex in 11-year-old patients. Blair RJR, of the National Institute of Mental Health, Bethesda, MD, in an editorial, remarks on the advances in the science of a neural substrate for lack of emotion, and in driving callous behavior in boys with conduct problems. The progress is not only in tolerance for the field of neurobiology of anti-social behavior but also its sophistication. (**Brain** 2009;132:831-832). Children with callous-unemotional traits have an increased risk for anti-social behavior. A better understanding of the cause should lessen the stigma and facilitate appropriate treatment. Children with ADHD complicated by unemotional conduct disorders should receive psychiatric care to lessen the risk of anti-social behavior.

MOVEMENT DISORDERS

CLONIDINE AND LEVETIRACETAM FOR TICS COMPARED

The efficacy of clonidine and levetiracetam for treating tics in Tourette syndrome was compared in a 15-week randomized, double-blind, flexible dose, crossover study at Johns Hopkins Hospital, Baltimore, MD. In 10 subjects, ages 8-27 years, the mean Total Tic Score improved significantly with clonidine compared with levetiracetam, whereas the Yale Tic Severity Scale did not change. With levetiracetam, none of the measures showed a change. The initial dose of clonidine was 0.05 mg, twice daily, and levetiracetam 10 mg/kg/day, divided twice daily. The mean maximum dose for clonidine was 0.20 mg/day, and for levetiractam, 1,150 mg/day. The mean Tic Score and Tic Severity Scale scores at baseline were similar in treatment groups. Sedation occurred with clonidine in 5 patients and irritability as a side effect of levetiracetam in 4. Clonidine reduced the frequency of tics but levetiracetam had no effect. (Hedderick EF, Morris CM, Singer HS. Double-blind, crossover study of clonidine and levetiracetam in Tourette syndrome. **Pediatr Neurol** 2009;40:420-425). (Respond: Dr Hedderick, Johns Hopkins Hospital, Suite 2158, 200 N Wolfe Street, Baltimore, MD 21231. E-mail: ehedder1@jhmi.edu).

COMMENT. Although this study found a statistically significant improvement in Total Tic Score with clonidine, the authors considered the benefit of limited clinical significance. Previous reports demonstrate a range of results with clonidine, from 0 to 75% reduction in tics (authors reference). As the authors comment, additional direct comparison studies, including placebo, in a larger series would be more meaningful.