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

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SEIZURE DISORDERS

NOVEL TISSUE MARKER OF EPILEPTIC FOCI IN RESECTIONS

The neurosurgeon relies on the expertise of the neurologist, electoencephalographer and neuroradiologist to determine the extent of resection of brain tissue in the treatment of medically refractive childhood seizures. Electroencephalographic telemetry (EEG), intraoperative electrocorticography (ECoG) and MRI are effective in the localization of epileptic structural foci associated with cortical dysplasias and other brain anomalies. Neuropathologists at the Alberta Children's Hospital and University of Calgary have demonstrated a novel immunocytochemical tissue marker of epileptic foci in a study of 45 surgical patients, ages 16 months to 23 years, the majority having histological diagnoses of focal cortical dysplasia or tuberous sclerosis. Balloon cells and giant atypical cells in tuberous sclerosis were intensely reactive. In every surgical resection, the heat shock protein, a-B-crystallin was isolated and upregulated at or near to the epileptic focus identified by preoperative EEG monitoring and intraoperative ECoG. In some cases with extensive resections that involved mesial temporal sclerosis, absence of epileptiform activity on ECoG correlated with negative crystalline reactivity. a-B-crystallin reactivity involved glial cells of white matter underlying epileptogenic cortex, astrocytes and oligodendrocytes, including some cases with no demonstrable histological lesion. Presence or absence of histological structural lesions was independent of a-B-crystallin expression. A gradient of reactivity occurred over a 3cm diameter in some cases, with highest intensity at center of the EEG- and ECoG-identified foci. No correlation was noted with microglial activation, inflammation or gliosis. Hippocampal gliosis and focal neuronal loss in Ammon's horn and dentate gyrus did not predict a more intense immunoreactivity of a-B-crystallin. Autopsy brain tissue of children with no epilepsy or neurological disease and fetal brain tissue as controls were non-reactive. Immunoreactive a-B-crystallin is considered a reliable tissue marker of epileptic

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foci, even in the absence of a structural lesion. (Sarnat HB, Flores-Sarnat L. a-B-crystallin as a tissue marker of epileptic foci in paediatric resections. **Can J Neurol Sci** September 2009;36:566-574). (Respond: Harvey B Sarnat, Alberta Children's Hospital, 2888 Shaganappi Trail NW, Calgary, Alberta, T3B 6A8, Canada. E-mail: Harvey.sarnat@albertahealthservices.ca).

COMMENT. Chemistry of the brain research dates back to 1884, with the publication in London of a book by JLW Thudichum, the father of the specialty. Recognition of *Neurochemistry* as a specific field of research was delayed until 1955, when Elliott. Page, and Quastel, aided by many contributors, edited their classic volume, published by Charles C Thomas, and dedicated to the memory of Thudichum. The "chemistry of human epilepsy" was covered in a chapter by Elliott KAC of the Montreal Neurological Institute, Canada. It is fitting that the present advance in our understanding of the subject reported by the Drs Sarnat also emanates from Canada. Elliott and his co-worker, Tower, were interested in acetylcholine and the epileptic focus. Focal tissue failed to store acetylcholine in the bound, inactive form. They postulated that the abnormal activity of an epileptic focus might be a response of normal neurons to an abnormal local chemical environment. Impairments of local circulatory control around epileptogenic foci, as reported by Penfield and associates, could cause variations in local concentration of oxygen, glucose, carbon dioxide and other products of metabolism, and pH. (Penfield WP, Erickson TC. *Epilepsy and Cerebral Localization,* Springfield, IL, Thomas, 1941). The present report advances our understanding of the epileptic process and demonstrates a novel immunocytochemical test for epileptogenic brain tissue, independent of the histological findings. Intense a-B-crystallin reactivity at the periphery of resected brain tissue might indicate incomplete removal of a focus and an increased risk of seizure recurrence.

CT AND MRI GUIDELINES IN RECENT-ONSET EPILEPSY

The International League Against Epilepsy (ILAE) Subcommittee for Pediatric Neuroimaging examined the value of, and indications for, neuroimaging in the evaluation of children with newly diagnosed epilepsy. Retrospective and prospective published series with 30 or more subjects receiving CT and MRI to evaluate new-onset seizures were reviewed. Imaging studies were abnormal in nearly 50% of children with localization-related new-onset seizures, 15-20% of imaging studies provided information on etiology and/or seizure focus, and 2-4% potentially altered immediate management. A significant imaging abnormality was almost always associated with a history of a localization-related seizure, abnormal neurologic examination, or focal EEG. Childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and benign childhood epilepsy with centrotemporal spikes were not associated with a structural imaging abnormality. Imaging is helpful in establishing seizure etiology, predicting prognosis, and in treatment. Imaging is recommended in children with new-onset localization-related epilepsy, when epilepsy classification is in doubt, and when an epilepsy syndrome with remore symptomatic cause is suspected. MRI is preferred to CT because of superior resolution, and lack of radiation. (Gaillard WD, Chiron C, Cross JH et al. for the ILAE. Guidelines for imaging infants and children with recent-onset epilepsy. **Epilepsia** Sept 2009;50:2147-2153). (Respond: WD Gaillard MD, Department of

Neuroscience, Children's National Medical Center, 111 Michigan Ave NW, Washington, DC 20010. E-mail: wgaillar@cnmc.org).

COMMENT. Imaging is most useful for children with localization-related or remote symptomatic generalized epilepsy. MRI abnormalities are more frequent in infants with seizures than in older children because of presentation of cortical malformations. The authors advise that children younger than 2 years require special MRI sequences because immature myelination may obscure the diagnosis of cortical dysplasia. If the MRI is interpreted as normal and seizures persist, repeat imaging at 6-month intervals is advised, when myelination is more mature and dysplasias can be distinguished. Gadolinium contrast is reserved for suspected tumor, vascular malformation, inflammation, and infectious disorders.

LONG-TERM OUTCOME OF JUVENILE MYOCLONIC EPILEPSY

All patients developing juvenile myoclonic epilepsy (JME) by 16 years of age in Nova Scotia between 1977 and 1985 were contacted in 2006-2008 to determine long-term seizure and social outcome, in a study at Dalhousie University, Halifax, Canada. Of 24 patients (17 women) with JME, 23 were contacted at a mean age of 36 +/- 4.8 years. Age at first seizure was 10.4 +/- 4.3 years. At 25-year follow-up, 11 (48%) had discontinued AED treatment: 6 were seizure-free (without AEDs) for 5-23 years, 3 had only myoclonic seizures, and 2 had rare seizures. Of those with continued seizures, 8 (36%) had episodes of convulsive status epilepticus, and 3 had intractable epilepsy. Seventy percent enjoyed satisfactory health, work, friendships, and social life, 87% graduated high school, and 69% were employed. Nine were taking antidepressants. Ten women had been pregnant and 4 men were fathers. Eleven pregnancies (80%) were unplanned, and at least 1 unfavorable social outcome was noted in 76%. (Camfield CS, Camfield PR. Juvenile myoclonic epilepsy 25 years after seizure onset: A population-based study. **Neurology** Sept 29, 2009;73:1041-1045). (Response and reprints: Dr Carol S Camfield, IWK Health Centre, PO Box 9700, 5850 University Ave, Halifax, Nova Scotia, Canada B3K 6R8. E-mail: camfield@dal.ca).

COMMENT. One-third patients with JME at 25-year follow-up have seizures well controlled and AED discontinued, in contrast to the generally poor seizure outcome in previous reports. Three-quarters have experienced at least one major unfavorable social event, but 70% report satisfaction with their social life.

VASCULAR DISORDERS

CEREBRAL VENOUS SINUS THROMBOSIS CASE SERIES

Presenting features, co-morbid conditions, treatment, and outcome of cerebral venous sinus thrombosis (CVST) in a consecutive series of children are reported from Department of Paediatric Neurology, Bristol Royal Hospital for Children, UK. Twenty-one children (10 male) were diagnosed with CVST (using electronic databases and international codes) and treated in a single pediatric neurology center over a period of 8.25 years. Ages ranged from 1.4 to 16.9 years (median 7.1 years); neonates were not included. Presenting symptoms in

order of prevalence were headache in 15 [71.4%], vomiting (14 [66.6%]), visual disturbance (8 [38.1%]), lethargy/malaise (4 [19.1%]), irritability (3 [14.3%]), limb weakness (2 [9.5%]), unsteady gait (2 [9.5%]), and seizures in 2 [9.5%] patients. Neurological abnormal signs included papilledema in 16 [76.2%], fever (6 [28.6%]), sixth nerve palsy (6 [28,6%]), hemiparesis (5 [23.8%]), decreased level of consciousness (3 [14.3%]), visual field defect (2 [9.5%]), and ataxia in 2 [9.5%]. Patients without papilledema were the youngest, 3.4 years or less. Ear infection (otitis media/mastoiditis) was the most frequent etiological factor, in 13 [61.9%] patients. Other predisposing factors were anemia in 4 and thrombocytosis in 3, nephrotic syndrome in 3, dehydration (3), oral contraceptive (2), group A streptococcal septicemia (2), and pituitary germinoma in 1. Thrombosis was located in superficial sinuses in 21 and deep sinuses in 6. Transverse lateral sinuses were involved in 19 and superior sagittal in 10. CT scans were falsely negative in five of 16 children examined. MRI/MRvenography was diagnostic in all patients. All 21 patients received heparin infusions, and 4 severe cases were treated by local thrombolysis using tissue plasminogen activator, with benefit in 3. All 15 children with infection received antibiotics. Adverse outcome occurred in 45%: 2 died, 8 were treated for chronic intracranial hypertension, 2 had residual hemiparesis, and 1 residual sixth nerve palsy. (Mallick AA, Sharples PM, Calvert SE, et al. Cerebral venous sinus thrmbosis: a case series including thrombolysis. **Arch Dis Child** 2009;94:790-794). (Respond: Dr PE Jardine, Department of Paediatric Neurology, Level 6 UHB Education Centre, Upper Maudlin Street, Bristol BS2 8AE, UK. E-mail: Philip.Jardine@bristol.ac.uk).

COMMENT. Cerebral venous sinus thrombosis (CVST) is rare in children and occurs more frequently in neonates. In one recent study of 70 patients, ages ranging from 6 days to 12 years, 25 (35%) were neonates. (Wasay M et al. **J Child Neurol** 2008;23(1):26-31) Seizures were the most frequent presenting feature, occurring in 59%. This finding contrasts with the present series that excludes neonates and in which seizures occurred in only 9.5%. Seizures were reported in 58% of 160 consecutive children (newborn to 18 years of age) with CVST enrolled in a Canadian Registry in six years from 1992-1998. Occurrence of seizures was followed by a poor outcome. (deVeber G et al. **N Engl J Med** 2001;345(24):1777-8). A report of four neonates with CVST and seizures who developed infantile spasms with hypsarrhythmia at 7-11 months of age demonstrates the poor long-term outcome of neonatal CVST that presents with seizures. (Soman TB et al. **J Child Neurol** 2006;21(2):126-131).

Diagnosis of CVST is frequently overlooked because presenting symptoms are varied and nonspecific. Headache is the most frequent presenting symptom in older children and adults, affecting 95% of patients with isolated lateral sinus involvement. (Damak M et al. **Stroke** 2009;40(2):476-481). Presence of comorbid factors, especially ear infection, should alert the probability of CVST in a child presenting with headache, vomiting and papilledema. Imaging with CT is unreliable, with a high incidence of false negatives, and MRI/MRV is recommended but sometimes difficult to interpret due to anatomical variation. The right transverse sinus is commonly dominant, and the left transverse sinus may be narrowed and atretic. (Renowden S. **Eur Radiol** 2004;14:215-226; Connor SE, Jarosz JM. **Clin Radiol** 2002;57(6):449-461).

Dramatic increase in venous thromboembolism (VTE) is reported in Children's Hospitals in the United States from 2001 to 2007 (Raffini L et al. **Pediatrics** Oct 2009;124:1001-1008). The increase was observed at all ages, including neonates. Of 15,000

cases, 1206 involved the intracranial venous sinuses. Pediatric malignancy was the most common comorbid condition associated with recurrent VTE.

HEADACHE DISORDERS

DIETARY TREATMENT FOR MIGRAINE UNDER SIX YEARS

Clinical factors and response to treatment were compared in children < 6 years and older children treated for migraine by nonpharmacologic measures in a pediatric headache clinic at Schneider Children's Medical Center, Petah Tiqwa, Israel. Treatment involved only good sleep hygiene, additive-free diet, and limited sun exposure. Foods eliminated included smoked lunch-meats, smoked cheese, yellow cheese (high tyramine), chocolate, pizza, and foods containing monosodium glutamate. Of 92 children identified retrospectively in records, 50 boys and 42 girls met study criteria. Ages ranged fromn 3.8 to 17.2 years (mean 9.4 +/- 3.9 years). Thirty-two (15 boys and 17 girls) were aged 6 years or younger at onset of follow-up, and 60 were older. The younger group had a significantly lower frequency of migraine attacks with aura (13 vs 23 patients, P=0.02) and a lower number of migraine attacks per month (6.8 vs 14.08, P= 0.008); disease duration before start of treatment was also shorter (11.34 vs 24.62 months, P= 0.0057). Response to treatment was graded 1 (none), 2 (partial-50% decrease), and 3 (complete- 75% decrease in attacks). Mean ages of patients with grade 1, 2, and 3 responses were 10.588, 9.11, and 8.11 years, respectively (P=0.02). The younger group of patients had a significantly higher percentage with grade 2 or 3 responses as opposed to grade 1 response (73.3% vs 27.7%, P<0.0075). Also, percentages of patients with grade 3 compared to those with grade 1 responses were significantly different in the 2 groups (81.2% vs 38.3%, P<0.001), and on comparison of results for each of the 3 grades (P=0.0003). Nonpharmacological therapy for migraine may be effective in younger children because of shorter disease duration and fewer attacks than in older children. (Eidlitz-Markus T, Haimi-Cohen Y, Steier D, Zeharia A. Effectiveness of nonpharmacologic treatment for migraine in young children. **Headache** Oct 2009;xx:xx). (Respond: Dr T Eidlitz-Markus, Ambulatory Day Care Center, Schneider Children's Medical Center of Israel, Petah Tiqwa 49202, Israel).

COMMENT. The nonpharmacological, "conservative" therapy as described above is predominantly dietary, eliminating additives and foods commonly recognized as migraine triggers, especially cheese and chocolate (Egger J et al. **Lancet** 1983;2:865-869; Egger J et al. **J Pediatr** 1989;114:51-58; Millichap JG, Yee MM. **Pediatr Neurol** 2003;28:9-15). Elimination diets, such as the Feingold additive-free diet, advocated in the treatment of the hyperactive child, was found in controlled studies to be mildly effective only in some small groups of younger children. The diet was ineffective in older children (NIH Consensus Panel 1982). Elimination and oligoallergenic diets continue to be used in some European and Australian centers for the treatment of childhood neurobehavioral disorders. Interest in dietary therapy for childhood hyperactivity has waned in the United States, and few neurologists use elimination diets for migraine in practice.

Age seems to be a factor in the effectiveness of dietary therapy for migraine. According to the above, children under 6 years are expected to derive most benefit. However, before eliminating certain foods, specific headache triggers should first be identified by

completion of headache diaries. Simultaneous elimination of all known triggers is not generally recommended for nutritional reasons. A well-balanced diet is important, and skipping of meals or fasting should be avoided.

CRANIAL AUTONOMIC SYMPTOMS IN MIGRAINE

Cranial autonomic symptoms (CAS) in patients with migraine and cluster headaches (CH) were characterized and compared in a prospective study of consecutive patients attending a headache clinic at Taipei Veterans General Hospital, Taiwan. CAS items surveyed were conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, eyelid edema, and forehead/facial sweating. Of a total of 884 patients, 786 (625 women/161 men, mean age 40.1 (12.9) years) had migraine and 98 patients (11 women/87 men, mean age 36.2 (10.5) years) had CH. Migraine diagnoses were episodic without aura in 48%, with aura in 5%, chronic in 39%, and probable migraine in 8%. In the CH group, 99% had episodic CH and 1% had chronic CH, a typical low incidence of chronic cases among Asians.

CAS occurred in 56% patients with migraine, and the incidence was similar in all migraine subtypes. Forehead/facial sweating in 28% of migraine patients was the commonest CAS, followed by lacrimation in 24%. Migraine patients with CAS compared to those without had higher frequencies of severe migraine, nausea, photophobia and phonophobia, and vomiting. Patients with CH had a higher frequency of CAS than migraine patients. To differentiate migraine with CAS from CH, the characteristic most predictive of migraine was bilateral CAS with either 1) mild to moderate intensity or 2) CAS occurring without headache. Lacrimation was the CAS with highest positive predictive value, specificity, and second highest sensitivity. (Lai T-H, Fuh J-L, Wang S-J. Cranial autonomic symptoms in migraine: characteristics and comparison with cluster headache. **J Neurol Neurosurg Psychiatry** Oct 2009;80(10):1116-1119). (Respond: Dr S-J Wang, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan 11217. E-mail: sjwang@vghtpe.gov.tw).

COMMENT. More than 50% of adults with migraine have cranial autonomic symptoms (CAS). Patients with CAS have more severe migraine often associated with photophobia, nausea and vomiting. Compared to those with cluster headaches, CAS with migraine are usually bilateral rather than unilateral and less severe.

Prof PJ Goadsby, San Francisco, in an editorial commentary, discusses the anatomy and physiology of CAS (**J Neurol Neurosurg Psychiatry** Oct 2009;80:1057-1058). The trigeminal-autonomic reflex is the basis for the symptoms. The effect is largely lateralized but innervation is also crossed. The pathway can be activated from the brain via connections from hypothalamus to superior salivatory nucleus. Comparing trigeminal autonomic cephalgias (TACS) and migraine, TACs are shorter in duration, sometimes seconds as in SUNCT/SUNA, minutes in paroxysmal hemicrania, and a few hours in cluster headache. In the clinical distinction of cluster headache and migraine, findings pointing to migraine include bilateral pain, attacks longer than 3 hours (>1-2 hours in children), bilateral CAS, bilateral photophobia and phonophobia. Whereas patients with migraine are generally quiet, cluster headache patients are restless. Hemicrania continua response to indomethacin is another differentiating factor. CAS only at the time of headache should help in the distinction from sinus infection. In adults, migraine is more common in women, cluster headache in men.

Cluster headache is uncommon in childhood. Onset is usually in the second and third decade. A retrospective review of cases attending a pediatric neurology clinic in Bristol, UK, between 2000 and 2005 identified 11 patients (7 male, 4 female) with median age of onset of 8.5 years (range 2-14). Median age at diagnosis was 11.5 years (range 7-17). Eight had episodic and 3 had chronic cluster headache. Most had cranial autonomic activation and agitated movement. (Majumdar A, Ahmed MA, Benton S. **Eur J Paediatr Neurol** 2008; Dec 22. (Epub ahead of print).

Maytal J et al modifications of the IHS criteria for pediatric migraine found that decreasing the length of attacks below 2 to 48 hours would increase the sensitivity of diagnosis, but adding associated autonomic symptoms of facial redness or pallor, while improving sensitivity, also decreased the specificity. The addition of CAS while helpful was not recommended. (**Neurology** 1997;48:602-607). Perhaps more attention to autonomic symptoms and behavior in diagnosis of children with migraine would be warranted.

TOPIRAMATE-INDUCED COUGH IN MIGRAINE PROPHYLAXIS

Three adults who developed intractable cough during topiramate prophylaxis of migraine are reported from the University of Padua and other centers in Italy. Cough developed early during the titration phase at dose levels of 75-100 mg/day, and resolved rapidly after withdrawal. Secondary causes of cough, including GERD, were excluded. The cough was episodic, dry, and very annoying, especially at night. Despite effective prevention of headache with topiramate, treatment was discontinued. Literature review revealed no previous case reports of cough as a side effect of topiramate treatment for migraine. (Maggioni F, Mampreso E, Mainardi F, Lisotto C, Malvindi ML, Zanchin G. Topiramate-induced intractable cough during migraine prophylaxis. **Headache** Oct 2009; on line). (Respond: Dr F Maggioni, Dept Neurosciences, University of Padua, Via Giustiniani 5, Padova, 35128, Italy).

COMMENT. Topiramate is a first-line treatment for migraine prophylaxis in adults. Adverse events in 20-25% of patients may require discontinuation of treatment but are rarely severe. They include weight loss, dizziness, somnolence, paresthesias, impaired concentration and memory, and language difficulties. Cough has not been reported and the mechanism is unexplained. No patient received ACE inhibitors for hypertension, a known cause of dry cough in adults. Pubmed search for cough with topiramate treatment of childhood epilepsy or migraine found no reports.

NEUROBEHAVIORAL DISORDERS

ISOLATED EPILEPTIFORM EEG DISCHARGES AND AUTISM

The relationship between EEG abnormalities and neuropsychiatric disorders, and their possible clinical significance are reviewed by an investigator at Wayne State University, Detroit, MI, with special attention to the EEG and autism. Approximately one third of children with autistic spectrum disorder (ASD) develop epilepsy. Of 46 consecutive children with autism (34 boys, and 12 girls, mean age 7.8 +/- 2.7 years), 35% had epilepsy (Canitano

R et al. **J Child Neurol** 2005;20:27-31). Hughes and Melyn reported 46% with clinical seizures (**Clin EEG Neurosci** 2005;36:15-20), and Tuchman and Rapin, 11% with epilepsy (**Pediatrics** 1997;99:560-566). Contrary to the current view, interictal EEG discharges in the non-epileptic ASD patient are more likely to signal abnormal brain activity than to represent an incidental finding. Deonna and Roulet (**Epilepsia** 2006;47(suppl 2):79-82) suggest a possible role for epilepsy in the causation of autism. Tuchman and Rapin found a correlation between clinical deterioration of autism and the frequency of epileptiform discharges in the EEG of non-epileptic autistic children during sleep. One half of the epileptiform discharges were centrotemporal in location. Further evidence of the importance of spike localization in the EEG of non-epileptic autistic children is reported by Rossi et al (**Brain Dev** 1995;17:169-174) who found that 45% of cases of epileptiform activity was typical of benign childhood partial epilepsy with centrotemporal spikes. Treatment of isolated spikes in children with autism using anticonvulsant drugs, especially valproate, is controversial, despite some reported favorable results (Hollander E et al. **J Clin Psychiatry** 2001;62:530-534). A recommendation against EEG screening of autistic children is considered unwarranted, given the high frequency of epilepsy and isolated EEG abnormalities in this population. That spike foci may create other brain foci has been shown in patients with repeated EEGs, a finding that underlines the nonbenign nature of the isolated epileptiform discharge. The significance of the EEG abnormalities in children with autistic spectrum disorders and other neurobehavioral disorders (eg ADHD) requires further study. (Boutros N. Epileptiform discharges in psychiatric patients: a controversy in need of resurrection. **Clin EEG Neurosci** 0ct 2009;40(4):239-244). (Reprint requests: Nash Boutros MD, Wayne State University, Department of Psychiatry and Behavioral Neurosciences, 2751 East Jefferson, Detroit, MI 48207. E-mail: nboutros@med.wayne.edu).

COMMENT. This review draws attention to the need for greater interest among clinicians in the EEG and childhood neurobehavioral disorders. Controlled trials of anticonvulsant drugs in the treatment of ASD and ADHD may be justified, based on the frequency of epileptiform discharges in non-epileptic children with these disorders. Early diagnosis may be important, as indicated by the progression of EEG abnormalities associated with clinical deterioration of ASD, and development of intellectual disability.

EEG and MRI findings and their relation to intellectual disability in PDD are reported in a retrospective study of 81 patients treated at Ankara University, Turkey. (Unal O et al. **World J Pediatr** Aug 2009;5(3):196-200). One fourth of patients with PDD had EEG and/or MRI abnormalities. Twenty seven percent had abnormal EEGs; 12% had abnormal MRIs, mostly mild cortical atrophy and periventricular leukomalacia. Patients with severe intellectual disability (ID) had a higher rate of EEG abnormalities (50%) than PDD patients without ID (8%), P=0.03. The severity of ID was not associated with abnormal MRI. One third of EEG abnormalities were localized to the temporal lobe.

Causes and pathogenetic pathways of autism are discussed by Benvenuto A et al, Pediatric Neurology Unit, Tor Vergata University, Rome, Italy (**World J Pediatr** 2009;5:169-176). Genetic syndromes, mutations, and metabolic diseases account for less than 20% of autistic patients. Chromosomal abnormalities and potential candidate genes are implicated in the disruption of neural connections, brain growth and synaptic/dendritic morphology in autism.