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ATTENTION AND BEHAVIOR DISORDERS

ADHD AND GENETIC SYNDROMES

Researchers at the University of Rome, Italy, review the genetic and neurobiological links between ADHD symptoms and genetic syndromes, and discuss the possible common pathways underlying these associations. A PubMed search of English medical publications from 1993 to 2010 found 9 articles pertaining to fragile X syndrome (FXS) and ADHD, 7 involving neurofibromatosis (NF1), 5 velo-cardio-facial/DiGeorge syndrome, 4 tuberous sclerosis, 3 Turner syndrome, 2 Williams, and 1 Klinefelter syndrome. Approximately 60% boys with FXS met diagnostic behavioral criteria for ADHD-inattentive type (31%), hyperactive type (7%), or ADHD-combined type (15%). FXS is caused by loss of function of the Fmr1 gene that encodes the FX mental retardation protein (FMRP). Absence of FMRP leads to dysregulation of many genes, and alterations of neurotransmitter pathways and synaptic connections. Structural imaging studies show alterations in size of hippocampus, amygdala, caudate, thalamus, cerebellar vermis, and superior temporal gyrus, areas involved in regulation of memory, learning, sensory processing, and motor behavior. NF1 neuropsychological phenotype is characterized by deficits in visuospatial and visuoperceptual, executive functioning, and sustained attention. ADHD, especially the inattentive type, affects one-third of children with NF1, 40% of children with DiGeorge, 22q11 deletion, syndrome, and 30–60% with tuberous sclerosis complex (TBC). Epilepsy of frontal lobe type, a common complication of TSC cortical tubers, contributes to the interference with brain circuits involved in attention and executive dysfunction of ADHD. The TSC2 gene is highly expressed in frontal and temporal regions. Genome scan studies demonstrate linkage on several chromosomes, including the 16p13 region, where the TSC2 gene is located. The

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genetic dysregulation associated with these various syndromes, and environmental risk factors, cause abnormalities in neuronal migration and synaptic development, leading to defects in neurotransmitter metabolism and cortical organization. The resulting deficits in attention, motor control and executive function are characteristic of ADHD. ADHD is the final behavioral and cognitive phenotype in a cascade resulting from the genetic syndrome and factors in the environment. (Lo-Castro A, D'Agati E, Curatolo P. ADHD and genetic syndromes. **Brain Dev** June 2011;33:456-461). (Response: Adriana Lo-Castro, Department of Neuroscience, Pediatric Neurology Unit, "Tor Vergata" University of Rome-Italy, Viale Oxford, 81, 00133, Rome, Italy. E-mail: a.locastro@libero.it).

COMMENT. New genetic techniques have identified several genes and syndromes associated with the behavioral and cognitive phenotype of ADHD. A genome-wide analysis of large, rare chromosomal deletions and duplications known as copy number variants (CNVs) in 366 children with ADHD and matched controls, aged 5-17 years, showed a significantly increased rate of CNVs in ADHD children, especially in those with intellectual disability. An excess of chromosome 16p13.11 duplications was noted in the ADHD group. (Williams NM, et al. **Lancet** Oct 23, 2010;376:1401-1408). It is interesting that the chromosome 16p13 region is involved in tuberous sclerosis, and epilepsy or epileptiform EEG is commonly associated with both TSC and ADHD. The identification of genetic syndromes associated with symptoms of ADHD may lead to more specific therapies.

EXECUTIVE AND INTELLECTUAL FUNCTIONS IN ADHD

The relationship between executive functions (EF), ADHD subtypes, and comorbid diagnoses, and the potential role of IQ were investigated in the Child Neuropsychiatry Unit, Children's Hospital, Rome, Italy. In a cohort of 23 children (aged 5 to 16 years, 20 males and 3 females) with a diagnosis of ADHD, no differences were found between children with different subtypes of ADHD on measures of EF. Differences on EF measures were observed in children with different comorbidities (internalizing vs externalizing disorders). Compared to the internalizing disorders group (depression, phobia, and anxiety), children with externalizing disorders (oppositional defiant or conduct disorders) obtained significantly lower scores on different measures of EF (i.e. verbal working memory and categorical fluency), but the differences were dependent on IQ level. Children with externalizing disorders exhibited significantly lower IQ scores than those with internalizing disorders. Comorbidity patterns, rather than ADHD subtypes, define the neuropsychological features of the ADHD phenotype. General IQ plays a role in influencing the cognitive processes underlying the disorder. (Di Trani M, Casini MP, Capuzzo F, et al. Executive and intellectual functions in attention-deficit/hyperactivity disorder with and without comorbidity. **Brain Dev** June 2011;33:462-469). (Response: Maria Pia Casini, Child Neuropsychiatry Unit, Children's Hospital Bambino Gesu, Piazza Sant'Onofrio 4, I-00165 Rome, Italy. E-mail: mariap.casini@opgb.net).

COMMENT. In an Editorial, Inagaki M (**Brain Dev** 2011;33:454-455) discusses the problems in executive function (EF) experienced by children with ADHD. The