An overview of Attention Deficit Hyperactivity Disorder

By

Maha Sadek

Submitted in partial fulfillment of the requirements
For the degree of Pharm.D

Thesis advisor Lydia Sholy Pharm.D

School of pharmacy
Lebanese American University
June 1999

I grant to the Lebanese American University the right to use this work, irrespective of any copyright, for the University's own purpose without cost to the University or its students, agents and employees.

LEBANESE AMERICAN UNIVERSITY

GRADUATE STUDIES

We hereby approve the thesis of:

Maha Sadek

Candidate for the Pharm. D Degree

Shihadeh N. Nayfeh, Ph.D . [redacted]

Lydia Sholy, Pharm. D [redacted]

Gabriel Maliha, M.D., Ph.D . [redacted] .....

Date: ..July..7...1999

We also certify that the written approval has been obtained for any proprietary material contained therein.

Table of Content

ACKNOLEDGMENT

I would like to thank my advisor Dr Lydia Sholy for her support and help during my Pharmacy Studies.

Thank is also due to Dr Shehadeh Nayfeh and Dr Gabriel Maliha for being on my Thesis committee.

I would like to express my sincere gratitude to Dr John Fayyad who was of great help and advise.

Finally, I would like to thank my friends and my family for their long support.

I-General Introduction

Childhood is recognized in psychiatry as a period of vulnerability and progressive development toward adult personality and character. More recently, the psychiatric disorders of children are coming into focus as serious, treatable conditions and as precursors of adult psychopathology. These psychopathological entities emerge in combinations, interact with each other over time, change in presentation during maturation, and can be obscured or amplified by intervening developmental events. A primary psychiatric disorder in childhood can lead to secondary developmental complications such as conduct disorder or school failure, or more persistently to low self-esteem and disorders of social assertiveness and other change that these entities exert in the lives of children, and of the adults they become (Popper C, Steinguard R, 1994). The recognition and management of psychiatric disorders in the specialized populations of children, adolescents, and people with developmental disabilities are complicated by a number of issues. These include symptom interpretation, diagnostic issues, research limitations, environmental influences such as family dysfunction, and societal attitudes regarding psychiatric illness and medication usage in these groups (Young L, Koda Kimble MA, 1995). The adult outcome of childhood psychopathology depends partly on the ways in which the psychopathology is amplified or contained by

individual, family, cultural, and therapeutic forces. Where were adult psychiatric patients during their childhood? Part of the answer rests in our ability to see disease in children. Now we know that all "adult" psychiatric disorders in DSM-IV can begin during childhood. Any diagnosis can be used as a primary diagnostic label in a child. Behavior disorders are highly prevalent in "normal" schoolchildren and in child psychiatric patients. For this large class of child psychiatric disorders, parents generally appear more distressed than the child and typically bring a reluctant child for help. The child often sees no personal problems or else views the parents as "the problem." These conditions are called externalizing disorders, emphasizing that children and adolescents with these disorders "act out" their conflicts, feelings, and impulses. Disruptive behavior and attention-deficit disorders is a DSM-IV umbrella term that encompasses attention-deficit/hyperactivity disorder, conduct disorder, and oppositional defiant disorder in children. These disorders are often present concurrently in the same child and are identified with different components of behavioral unmanageability (Popper C, Steinguard R, 1994).

II- Historical Review About ADHD

Originally described in antiquity and documented anecdotally throughout the world literature, ADHD was first identified on a large scale in the early 20th century, when children with von Economo's encephalitis developed symptoms of hyperactivity, impulsivity, and inattention. These impulsive children have since been given labels of "minimal brain damage", "minimal brain dysfunction", "hyperkinetic syndrome", and "hyperactivity syndrome". Rosenthal and Allen explain that although they are often used interchangeably, the terms hyperkinesis, minimal brain dysfunction, and learning disability actually focus on somewhat different aspects. They note that the hyperkinetic syndrome (Huey L, 1991), en though more than motor systems alone are involved (Popper C, Steinguard R, 1994) is a psychiatric disorder of the total personality characterized by symptoms and exclusion criteria that would be similar to those currently used to describe ADD (attention deficit disorders) attention problems, increased activity, impulsivity, absence of psychosis or mental retardation and so on. Hyperkinesis is thus a descriptive designation. Minimal brain dysfunction (Huey L, 1991), even though overt neurological damage produces similar dysfunction (Popper C, Steinguard R, 1994),implies a neurologic etiology presuming the presence of brain dysfunction on the basis of history (e.g. birth complications, central nervous system infection or injury;

accompanying perceptual and motor deficits and equivocal signs of neurologic abnormality ("soft" signs) elicited on physical examination, electroencephalography, or neuropsychological testing). Many of those soft signs can also be normally found in younger children and will diminish or disappear with maturity. Learning disability is an educational term when learning efficiency is impaired because of deficits in perceptual, integrative, relational or expressive processes; these deficits are not due to sense organ defects(Huey L, 1991). Brain damage was also used even though there is no direct evidence of brain damage," as well as "Hyperactivity syndrome" even though 50% of all "normal" boys are rated as "hyperactive" by their parents and teachers.

In clinical practice, the disorder is often claimed to be "diagnosed" after a therapeutic response to an empirical trial of psychostimulant medication. However, drug-responsiveness cannot be taken as a biological marker of a single disorder. Because many behavioral conditions respond to psychostimulants, this diagnostic procedure is invalid. (Popper C, Steinguard R, 1994).

The first empirically based official set of diagnostic criteria for what is now referred to as ADHD was delineated in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980.(Goldman L, et all, 1998) Attention-deficit

hyperactivity disorder (ADHD) is the term the Diagnostic and Statistical Manual of Mental Disorders, third edition , revised (DSM-III-R) has designated for what the DSM-III had termed attention-deficit disorder (ADD). Although the DSM-III divided ADD into a childhood form and a residual type (ADD,RT), the DSM-III-R has recognized that the natural history of ADD is analogous to that of infantile autism: both persist into adulthood life. (Garfinkel, 1989)

Early focus on the focus of the centrality of hyperactivity shifted toward giving weight to attentional problems and impulsivity as well which was reflected in the 1987 revision (DSM-III). (Goldman L, et all, 1998)

Currently, Attention deficit hyperactivity disorder (ADHD) is defined by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), as persistent inattentive and/or hyperactive behaviors that are not age appropriate. These behaviors are pervasive, as demonstrated by their presence in at least 2 environments (e.g. school and home), and are sufficiently severe so as to interfere with social or academic functioning. To meet DSM-IV criteria, patients must demonstrate symptoms of ADHD before the age of 7 years, and symptoms must have been ongoing for longer than 6 months. The world health organization's international classification of Disease (ICD-!)) recognizes these behaviors as hyperkinetic disorder. The ICD

construct denotes onset usually before the age of 5, with major areas of impairment being the inability to complete activities requiring concentration or attention, and excessive and indiscriminate motor behaviors. The ICD-10 construct notes that hyperkinetic disorder is commonly associated with delayed motor and language development (Cyr M, Brown C, 1998).

III-Clinical Description

Abiding by the classification of DSM-IV and depending on the number of symptoms present, ADHD is classified as either predominantly inattentive, predominantly hyperactive-impulsive, or both. If at least 6 symptoms of inattentiveness have been present during the previous 6 months, with fewer than 6 symptoms of hyperactivity-impulsivity, then the classification of predominantly inattentive type is made. The converse would qualify for the predominantly hyperactive-impulsive type, whereas the combined type requires at least 6 symptoms in each category. Symptoms of inattentiveness and hyperactivity-impulsivity as defined in the DSM-IV are listed in the following table (Cyr M, Brown C, 1998).

Children or adults with attention-deficit/hyperactivity disorder (ADHD) show the behavioral characteristics of motor hyperactivity (or impulsivity), the cognitive characteristics of inattention (such as short attention span and distractibility), or both. The DSM-IV criteria no longer suggest that ADHD is a child's disorder, a loose mix of annoying behaviors and scattered attention, or a problem that may be seen in just one setting. Although ADHD is now understood to afflict people of all ages, most of the available research has concentrated on children and adolescents. Many documented findings about ADHD in children and adolescents have led to working hypotheses and speculations about ADHD in adults. So far, most

findings on ADHD in adults have been consistent with prior findings in youths with ADHD. (Popper C, Steinguard R, 1994).

Children with ADHD are most often presented for evaluation when they fail to meet developmental expectations at school either underachieving or flunking classes, and after all parenting interventions to correct their disruptive behaviors are of no avail. They often are labeled "lazy", "stupid" or "trouble maker"(Fayyad J, 1998).

The separate assessment of inattention and hyperactivity/ impulsivity becomes clinically necessary, because each may have at least a partially distinct prognosis and response to treatment. When motor activity in all children is expected to be high (e.g., in cafeteria, at recess, and during gym), activity levels are similar in both hyperactive and normal children. However, ADHD children are most different from normal children during structured classroom activities. Even at their quietest, ADHD children show excessive activity. Motor activity remains increased during sleep, suggesting that "attention" is not the central or primary area of deficit. Persons with ADHD tend to be symptomatic in many if not all settings, but the intensity of symptoms varies across settings (Popper C, Steinguard R, 1994). The assessment relies heavily on accurate history taking from multiple sources of information (e.g. child, parent, other caretakers and schoolteachers). A thorough psychiatric history must be taken to examine

criteria for the disorder and to rule out other associated and comorbid conditions (Fayyad J, 1998). Thus, the overall approach to diagnosis may involve a comprehensive interview with the child's caregivers; a mental status examination of the child; a medical evaluation for general health and neurologic status; a cognitive assessment of ability and achievement; use of ADHD-focused parent and teacher rating scales; and school reports and other adjunctive evaluations if necessary (speech, language assessment, ect) depending on clinical findings. An evaluation can be performed by a clinician with the skills and knowledge to carry out those components (Goldman L, et all,1998).

The younger the child, the more pervasive is the motor restlessness. When a child is inattentive, he or she can neither process the classwork nor rapidly produce goal-directed work without refocusing from another person. Another key dimension of the ADHD child's behavior is impulsivity. This triad leads the child with ADHD to act without forethought of the consequences; he or she appears to be unaware of danger and the relationship between cause and effect and shows to "take dares" other children would walk away from. Gross motor activity forms the final part of the clinical triad necessary to make the diagnosis of ADHD. The clinician should inquire about activities in which the child

must employ some type of motor inhibition to complete an age-appropriate task.

At home, the school-age child with ADHD often has trouble listening to adults, often looks away, doesn't make eye contact, and is restless. The child always seems preoccupied, distracted, or "on the way in a hurry" to some other activity, even though this is not the case. School-age children display inattentiveness at home by not completing homework or chores or by not seeming to listen. (Garfinkel, 1989)

The preschooler child with true attention deficit disorder, which persists over time, generally has such additional symptoms as temper tantrums, argumentative behavior, aggressive behavior (hitting others and taking others possessions), and fearless behavior which leads to frequent accidental injury and noisy boisterous behavior. Noncompliance is often a major problem with these youngsters as is sleep disturbance (Cantwell D., 1996).

Classically, the hyperactive school-age child forgets what he or she was sent to do In class, children are asked to sit still, remain quiet, and work; children with ADHD end up squirming their chairs, humming, making noises, and disturbing other children. In contrast to children with the predominantly hyperactive type of ADHD, these predominantly inattentive children show mild anxiety and shyness, more sluggishness and

drowsiness, less impulsivity, less conduct disorder and behavior problems, and more mood and anxiety disorder (Garfinkel, 1989). Symptoms can vary with environmental structure, sensory stimulation, and emotional state, as well as with physiological factors such as general alertness, hunger, and sleep deprivation. Emotional impulsivity, seen in anger and fighting, can be readily triggered in response to minor provocation. Once anger is felt, it can stimulate a further increase in impulsivity (i.e., anger can stimulate itself). Most children experience more environmental and affective "pressure" at school than at home, and the "overflow" into hyperactivity and impulsivity is particularly clear in the classroom. Hyperactivity/impulsivity and inattention are also increased in noisy places or group settings, such as hallways or crowded waiting rooms. Depending on whether the home or the hospital unit is more stimulating or disruptive, an ADHD child can become more symptomatic or can "improve" when hospitalized. The child may appear quite different to observers in different environments. Symptoms are often more apparent to the teacher in noisy or crowded settings than to the physician in a quiet office (Popper C, Steinguard R, 1994).

The clinical presentation of attention deficit disorder in adolescents has not been studied systematically as in younger children. Barkley suggests that not only do the symptoms manifestations change with age, but also that a

lower number of symptoms should be considered as indicative of the diagnosis in the adolescent age range and possibly the adult age range. The core symptoms may manifest now as an internal sense of restlessness rather than gross motor activity. Their inattention and cognitive problems may lead to poorly organized approaches to school and work and poor follow-through on tasks. Failing to complete independent academic work is a hallmark in the adolescent age range, and a continuation of risky types of behaviors (Cantwell D, 1996).

ADHD in adults presents three major diagnostic problems. The first is that the diagnosis requires a history of ADHD in childhood, the second is that in several studies it appeared to occur frequently with other diagnoses (comorbidity), and the third is that some of its clinical features mimic those of other disorders (Shaffer D, 1994)

Adults with attention deficit hyperactivity disorder have a pattern of demographic, psychosocial, psychiatric, and cognitive features that mirrors well-documented findings among children with the disorder (Biederman J, 1993).

Adults have a higher rate of substance abuse, antisocial personality disorder, depression, and anxiety than controls, and the cognitive deficits may persist even in uncomplicated cases. (Young L & Koda-kimble MA,

1995) These findings further support the validity of the diagnosis for adults (Biederman J, et all, 1993).

A variety of different symptoms in adults have been described. The presence of disorganization continues to have an impact in the workplace, often requiring written lists of activities to be used as reminders. Poor concentration may continue to persist into adult life, leading to shifting activities, not finishing projects, and moving from one activity to another. Procrastination is present as is the presence of intermittent explosive outbursts, which may be related to comorbid mood symptomatology or may be a special type of labile mood (Cantwell D, 1996).

The affective and cognitive experiences of a person with ADHD may be compared to perceptions under a light strobe. Sudden attentional shifts and brief flashes of experience lead to a constantly changing view of the world: disconnected appearances impair the person's ability to form complex cognitions, respond emotionally, and learn social norms. The shifting in attention complicates learning about human emotions and complex thinking (Popper C, Steinguard R, 1994).

IV-Epidemiology

The point prevalence of ADHD in the population has been reported to range from 1.7 percent to 17.8 percent this wide variation may be explained by differences in informants, culture, and the degree of impairment needed for diagnosis (Elia J, 1999). The prevalence of childhood ADHD has been reported to be higher in the United States than in other countries. This difference has been hypothesized to result from advanced technologies (such as lead-containing gasoline, paints, and synthetic food additives), but is more likely due to diagnostic practices (Popper C, Steinguard R, 1994). It is difficult to compare international prevalence data of the diverse diagnostic criteria and methods of assessment used as well as cultural differences in the interpretation of behavior. Nevertheless, no striking cultural differences have been reported (Elia J, 1999). ADHD often appears in combination with other psychiatric disorders and is present in 30% to 50% of childhood psychiatric outpatients and 40% to 70% of child psychiatric inpatients (Popper C, Steinguard R, 1994).

The current criteria, with inclusion of hyperactive-impulsive and inattentive subtypes, have resulted, predictably, in higher rates of diagnosis. Sex ratios have also varied (Elia J, 1999). The prevalence of ADHD is estimated to be between 3% to 5% of school-age children. This figure does not take into account preschool, adolescent, and adult population

(Cantwell D, 1996). Children with ADHD make up to 50% of some psychiatric populations. The evolution of criteria from DSM-III to DSM-IV, although based on a progressively larger empirical base, has broadened the case definition, so that more children appear to be affected. As a result, girls have been diagnosed as having ADHD more frequently than they were in the past (Goldman L, 1998). Among children referred to child psychiatrists or psychologists the boy to girl ratio varies from 3:1 to 9:1, whereas in community surveys of school-age children it is closer to 2:1. In contrast, among older adolescents the ratio is 1:1, and among young adults, women predominate (2:1). The different sex ratios in clinical and population-based studies of children suggest the effects of referral bias. (Elia J, 1999)

In a review of the literature investigation gender-based differences in childhood disorders, Eme concluded that existing studies indicate that childhood disorders are generally more prevalent among males, but more severe among females. (Gaub M, Carlson C, 1997)

Girls are generally believed to constitute 10% to 25% of ADHD children, although this may be an underestimate resulting from diagnostic expectations. There are suggestions that women may constitute a higher proportion of the adult ADHD population and may present for treatment more frequently than do men. However, ADHD girls appear to show more

fear, depression and mood swings, and cognitive and language problems (Elia J, 1999) Researchers have demonstrated that the prevalence rate for ADHD among boys declined by nearly 20% per year between the ages of 10 and 20 years while the prevalence among girls remained relatively constant across these same ages (Gaub M, Carlsom C, 1997).

The conceptual model adopted by Wender is that adult ADHD is a continuation of a disorder that has its origins in childhood. A history of inattention and hyperactivity in

Childhood are thus logically necessary features (Shaffer D, 1994).

Accurate figures concerning the prevalence of ADHD in the adult population are not yet available. (Popper C, Steinguard R, 1994). Using data from the follow-up study of Mannuzza et al., the finding suggest that around 10% of people with childhood hyperactivity will have clinically significant ADHD in adulthood, the likely prevalence of adult ADHD can be projected from epidemiological studies of children and adolescents. (Shaffer D, 1994)

Other follow-up studies show that the disorder persists into adulthood in 10% to 60% of childhood-onset cases. Its high prevalence in childhood, combined with the follow-up results, suggests that approximately 2% of adults may suffer from ADHD. If so, this would make ADHD a relatively

common adult disorder that may be underidentified in adult psychiatry clinics (Biederman J et all, 1995)

In one follow up study, 31% of young adults diagnosed as ADHD in childhood still had the full syndrome, and 9% had two of three symptoms of ADHD (attention deficit, impulsivity, hyperactivity) Twenty percent were diagnosed as antisocial disorder, and 12% had substance abuse disorder. Those who still had ADHD were likely to manifest other symptoms. Another study estimated that 66% of adults with a history of ADHD still had residual symptoms at a 15 year follow-up. There is some evidence that children with ADHD who are treated with stimulants have a better outcome as adults. (Young L, Koda-kimble MA, 1995)

The rate of the disorder in children of adults with the disorder was significantly higher than the previously reported rate of ADHD among siblings of children with the disorder. The adult form of this disorder may have stronger familial etiological risk factors than its pediatric form. If these results are confirmed, families selected through adult probands with ADHD might be especially useful for testing genetic hypotheses about the disorder. (Biedrman J, et all, 1995)

V-Etiology

There is no known single etiological factor that accounts for all cases of ADHD (Fayyad J, 1998). There is no evidence that only one attention deficit or that a single brain mechanism is responsible for all manifestations of ADHD (Popper C, Steinguard R, 1994). Like other psychiatric disorders in childhood and adulthood, a variety of biological, psychological and social factors converge into a final common pathway to manifest as a disorder (Fayyad J, 1998). Clinical research has yielded a wide variety of biological findings on ADHD (and ADHD look-alikes) that potentially contribute to the descriptive and etiological understanding of this disorder. There are a variety of presumed neuromedical etiologies of ADHD, including brain damage, neurological disorder, low birth weight, and neurotoxin exposure. Obstetrical problems during pregnancy or delivery (such as bleeding or perinatal hypoxia) can cause neurological trauma (Popper C, Steinguard R, 1994).

Family studies indicate a genetic etiological component. ADHD runs in families, particularly in male relatives of ADHD children (Popper C, Steinguard R, 1994) . Children with ADHD alone have an elevated rate of first-degree relatives with ADHD (Stoudmine A, 1998) . ADHD was diagnosed more than five times more frequently among the relatives of affected children than among the controls.(Lombroso P, 1994)In one study

of children referred to both psychiatric and pediatric clinics, relatives of children with ADHD showed an increased prevalence of ADHD, conduct disorder and antisocial personality disorder, mood disorders, anxiety disorders, and substance abuse, even after the investigators controlled for socioeconomic class and family intactness (Stoudmine A, 1998). In adopted ADHD children, biological parents have more psychopathology than do adopting parents. (Garfinkel, 1989)

Adoption studies support that the running in families is genetic rather than environmental. (Cantwell D, 1996)

There is no evidence of a single gene defect or of a specific mechanism of genetic transmission in ADHD, and the hereditary component will probably be explained as polygenic. (Popper C, Steinguard R, 1994)

ADHD has a substantial genetic component, with a heritability of 0.75 to 0.91 (Levy F, Hay D, 1997). Genetic studies have focused largely on candidate genes involved in dopaminergic transmission, for several reasons. Dopaminergic drugs are clinically efficacious, imaging studies have implicated frontostriatal circuitry (which is rich in dopaminergic innervation) in ADHD, and dopamine-transporter DAT-knockout mice have been developed that are hyperactive and unresponsive to amphetamine A common variant (polymorhism) of the noncoding region of the gene for the dopamine transporter (DAT1), which inactivates

dopamine, was found to be associated with ADHD in two studies. The gene for dopamine receptor D4 (DRD4) encodes one of the receptors that mediate postsynaptic dopamine action; polymorphism in this gene appears to affect receptor function. A variant with seven tandem repeats was associated with ADHD in two studies but not in another (Elia J, 1999) Prenatal factors are probably more important than birth complications such as obstetrical difficulties and perinatal asphyxia in the etiology of these neuropsychiatric disorders; that is, prenatal predisposing factors appear to produce both the birth complications and the ADHD (Popper C, Steinguard R, 1994). Repeated hypoxic-ischemic events and ischemia-induced liberation of glutamate are particularly common in prematurity, a fact which explain the high incidence of ADHD in this patient group (Lou Hc, 1996).

Intrauterine exposure to toxic substances, including alcohol or lead, can produce teratogenic effects on behavior (Popper C, Steinguard R, 1994). It appears that the prenatal exposure to alcohol creates in some children an fetal alcohol effect FEA picture which manifests itself in behavioral problems consistent with ADHD and comorbid conduct disorder, explosive variety, or ADHD with comorbid mood disorder. (O'Malley K, 1994). There is also a strong and significant positive association between smoking mothers during their pregnancy and ADHD in their children that

could not be attributed to socioeconomic status parental ADHD, and parental IQ. Therefore a link between in utero exposure to nicotine and subsequent ADHD in the child should be considered. Maternal smoking has been linked to low birth weight, which has been associated with ADH (Milberger S, 1996; Charbol H, et all, 1997)

Children with ADHD have higher average blood lead levels than their siblings (Popper C, Steinguard R, 1994). Early ideas were that this condition was some type of "brain damage"(Cantwell D, 1996). For ADHD with onset after toddlerhood, neurological trauma, encephalitis, or CNS infection is sometimes demonstrable. Overt neurological disorders, most commonly seizures and cerebral palsy, are diagnosable in 5% of children with ADHD (Popper C, Steinguard R, 1994).

More recent studies of brain morphology involve modern and much more sophisticated measures. Hynd et al. produced magnetic resonance imaging findings, suggesting that children with ADD had normal plana temporal, but abnormal frontal lobes (Cantwell D, 1996)

Findings on the electroencephalogram (EEG) are abnormal in 20% of ADHD children (vs. 15% generally), and computed tomography (CT) scans are typically normal.

ADHD-like symptoms are typically observed in humans with lesions and disorders of the relevant regions of the frontal cortex. These frontal

regions are believed to inhibit subcortically guided automatic (i.e., "impulsive") responses to sensory stimulation from external sources, and to prepare the brain for voluntary movements based on external stimuli. Brain localization is probably crucial to specific ADHD symptoms and might be related to variations in clinical presentation of ADHD. Among children with right hemisphere syndrome (i.e., cortical dysfunctions of the right hemisphere), 93% were found to have ADHD-like symptoms (Popper C, Steinguard R, 1994).

Biochemical models of ADHD have been the driving force behind a number of psychopharmacological investigations (Garfinkel, 1989). Laboratory studies the role of dopamine (in the limbic or caudate regions) and norepinephrine (in the reticular formation) has yielded contradictory findings (Grice D, et all, 1994). In order to bring together observations from the basic sciences, the hyperactive behavior of these children, and the beneficial affects of dopamine agonists (dextoamphetamine and methylphenidate) an etiologic dopamine hypothesis of this disorder has been formulated. (Garfinkel, 1989)

The dopamine hypothesis is supported by findings that 1) the stimulants have strong (though not exclusively) dopaminergic effects, and their therapeutic effects are reduced when dopamine receptors are blocked; 2) experimental rats with neonatal lesions of their dopamine neuronal systems

have motoric hyperactivity and learning deficits, which are reversed by psychostimulants; 3) children with von Economo's encephalitis had an ADHD-like clinical picture (and adults had parkinsonism); and 4) low levels of the dopamine metabolite homovanillic acid appear in the cerebrospinal fluid (CSF) of children with ADHD. However, dopamine receptor blockers also exert therapeutic effects, and not all dopamine agonists are therapeutic (Popper C, Steinguard R, 1994). Hypotheses regarding the etiology of ADHD also invoke malfunction of the noradrenergic system. Dextroamphetamine, monoamine oxidase inhibitors, and desipramine are among the most effective agents in the treatment of ADHD; all these medications reproducibly suppress 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in plasma and urine (MHPG is the major metabolite of CNS norepinephrine in humans). In addition, children with ADHD were observed to have greater vascular pressor responses on standing compared with control subjects (despite equal increases in plasma norepinephrine), suggesting that postsynaptic a-adrenergic receptors may be supersensitive in children with ADHD (Grice D, et all, 1994). The norepinephrine hypothesis is supported by 1) therapeutic efficacy of tricyclic antidepressants and monoamine oxidase (MAO) inhibitors (though both also modify serotonin transmission) as well as clonidine, and 2) reports of low levels of 3-methoxy-4-hydroxyphenylglycol (MHPG).

(The finding complicates this latter point that psychostimulant treatment lowers MHPG even further.) Although not well replicated, these neurochemical findings in humans are mainly consistent with the contribution of norepinephrine and dopamine in modifying attention and behavior. Combining both models in a study of rats with selective neonatal depletions of catecholaminergic systems, it appears that dopamine depletion causes attentional problems and that norepinephrine depletion causes hyperactivity (Popper C, Steinguard R, 1994). In one study of amino acids that are precursors of neurotransmitters, adults with ADHD showed a substantial therapeutic response to pharmacologic doses of tyrosine, the precursor of dopamine but also the precursor of norepinephrine (Garfinkel, 1989).

Studies of serotonin have been generally inconsistent but often show elevations of blood serotonin in ADHD children. These findings may be contaminated by the low serotonin levels that would be expected in the highly aggressive children, but the serotonin levels appear to be normally distributed and so do not support a subtyping of ADHD children. (Hales Robert, 1994) Most recently, the clinical profile of ADHD has been predictively linked in a subset of patients to the presence of a mutation in the human thyroid receptor-b gene. The latter is a syndrome in which elevations in triiodothyronine (T3) and thyroxine (T4) are accompanied by

inappropriately high levels of thyrotropin-releasing hormone. To varying degrees, peripheral and central tissues are believed to be resistant to the metabolic impact of thyroid hormone because of structural abnormalities of the cellular thyroid receptor deriving from specific mutations in exons 9 and 10 of the hTRb gene. Such mutations were found in 13 of the 18 families studied. In addition, the likelihood of having ADHD was found to be 10 times higher in children with generalized resistance to thyroid hormone and 15 times higher in affected adults (Grice D, 1994). In a recent study by Hauser and coworkers, subjects with generalized resistance to thyroid hormone were studied for the presence or absence of ADHD. In this study sample, ADHD is strongly associated with a specific mutation-giving rise to generalized resistance to thyroid hormone (Lombroso P, et all. 1994). In another study evidence has been supplied for the lack of an association between ADHD and thyroid function. The decrease shown in this study in most of the thyroid function tests is compatible with pattern described for normal development. Therefore there is no need for the routine thyroid function in ADHD children (Tozen P, et all, 1997)

Studies have been performed using techniques including single photon emission tomography (SPECT) and positron emission tomography (PET). SPECT studies revealed cerebral hypoperfusion of the frontal lobes

(especially white matter) and the caudate nuclei and hyperperfusion in primary sensory regions of the occipital and temporal cortex sensory. (Cantwell D, 1996)

Psychostimulant medication increased blood flow in the basal ganglia (consistent with activation of dopamine neurons) and decreased flow in primary sensory and motor cortex. Similarly, a positron-emission tomography (PET) scan study of adults with ADHD demonstrated an overall reduction in cerebral glucose metabolism of 8%, with significant reductions in 30 of the 60 brain regions examined, with the largest decreases in the premotor cortex and superior prefrontal cortex (Grice D, et all, 1994).

These findings are consistent with the hypothesis of hypofrontality in children and adults with ADHD, but also support the notion that abnormalities in other brain regions may be relevant to the pathophysiology of ADHD. In sleep studies, ADHD children show decreased REM latency (similar to that seen in adults with major depressive disorder), increased motoric activity during sleep (i.e., restlessness), and increased sleep latency (i.e., time required to fall asleep), but no other consistent EEG architectural changes (Popper C, Steinguard R, 1994). The splenial area of the corpus callosum is smaller in children with ADHD than in a sample of normally developing children.

These smaller areas may relate to commonly seen sustained attention deficits which in turn negatively impact on the development of more advanced levels of attention such as self-regulation (Semrud-Clikeman M, 1994).

There is no evidence that ADHD can arise from social or enviromental factors. However, in a child at risk for ADHD, social adversity, psychological trauma, family discord, dysfunctional parenting and child rearing can exacerbate the already existing disorder (Fayyad J, 1998).

VI-Comorbid Conditions And Differential Diagnosis.

Attention-deficit/hyperactivity disorder is commonly seen in association with other psychiatric disorders, particularly conduct disorder. Concomitant disorders can appear fully coincidentally (i.e., independently), but usually operate as exacerbating (i.e., interactive), mechanistically related (i.e., having common or shared cause), or etiological (i.e., causal) factors (Jensen P, et all 1997).

Between 10% and 20% of children with ADHD in both community and clinical samples have mood disorders, 20% have conduct disorders and up to 40% may have oppositional defiant disorder. Only about 7% of those with ADHD have tics or tourette syndrome, but 60% of those with Tourette syndrome have ADHD (Goldman, L et all. 1998).

For example, ADHD is often seen comorbidity with mood and anxiety disorders (typically with each disorder exacerbating the course of the other disorder), but ADHD-like symptoms can also be due to the mood and anxiety disorders. (Popper C, Steinguard R, 1994). About a quarter of children with ADHD will meet criteria for an anxiety disorder, compared with 5% to 15% of the general population. The prevalence of an affective disorder in ADHD patients is discrepant and it shows rates of 9% to 38% for depressive disorders. Epidemiologic studies have not found high rates

of bipolar disorder with ADHD children (Pliszka S 1998). There is also a high prevalence of ADHD in all learning, motor skills, and communication disorders (Popper C, Steinguard R, 1994). About 20% to 30 % of ADHD children will be learning disabled in the area of reading, spelling, or arithmetic (Pliszka S, 1998).

ADHD occurs so commonly in association with psychotic disorders (including schizophrenia) and pervasive developmental disorders (including autistic disorder) that these disorders are considered relative exclusion criteria for ADHD.

ADHD often presents comorbidly with mental retardation, but it is then considered a separate diagnosis (Popper C, Steinguard R, 1994). Other problems associated with ADHD are frequent disturbances, enuresis, difficulties with motor coordination, speech delays in very young children, poor academic performance and general health problems (e.g. upper respiratory and ear infections and asthma (Fayyad J, 1998).

Overall, perhaps as many as 65% of children with ADHD will have 1 or more comorbid conditions although their presence will not be recognized without appropriate questioning and evaluation (Goldman L, et all, 1998).

Children with the predominantly inattentive type of ADHD only occasionally have conduct disorder, suggesting that the aggressivity often seen with conduct disorder is linked to the hyperactivity/impulsivity and

not to the inattention. Children with the combination of ADHD and conduct disorder show high levels of family psychopathology; whereas children with the predominantly inattentive type of ADHD are linked to neurological disorders, lower IQ, and other cognitive deficits. The most frequent outcome of childhood ADHD is clinical normalcy, but features of impulsivity persist into adolescence in 70% of ADHD children and into adulthood in 30% to 50%.

On average , symptoms diminish by about 50% every 5 years between the ages of 10 and 25. Hyperactivity itself declines more quickly than impulsivity or inattentiveness.

Patients with ADHD have an increased risk of developing substance use disorder the ratio increase from adolescents to adults regardless of whether there is comorbidity (Goldman L, et all.1998).

VII-Treatment

Multimodal treatment of ADHD is currently the standard of care for ADHD children with major behavioral problems, aggressivity, ego developmental difficulties, concomitant biopsychiatric or neurological disorders, or learning disorders. Satterfield et al.'s study of multimodal treatment is generally encouraging: a combination of medication, special education, and psychotherapy resulted in improved education, attentional functioning, reduced antisocial activity, and better psychosocial adjustment (Popper C, Steinguard R, 1994).

The role of psychosocial interventions in treating ADHD remains equivocal. Education and support for parents, family members and teachers about the illness, treatment and expected treatment outcomes are crucial and can be provided through programmed group training sessions (Cyr M, Brown C, 1998)

Training parents to use contingent rewards, response-cost management, and time-outs, and to cooperate with school in a school-home daily report card and point token response cost system is highly effective and is employed for treatment of defiance and aggressivity. Behavioral treatment can help impulse control, although generalization beyond the treatment setting may be limited.

Behavioral methods can be as effective as psychostimulants for modifying classroom behavior, but do not generalize well to other situations and are more costly (Cantwell D, 1996). School-Focused interventions are aimed at enhancing academic performance, improving classroom behavior and improving peer relations (Cyr M, Brown C, 1998). The most appropriate classroom environment is probably a structured classroom with the child placed in the front of the room, close to the teacher where he or she is less easily distracted and more able to focus (Cantwell D, 1996).

Cognitive-behavior therapy is used for the teaching of problem-solving strategies, self-monitoring, verbal mediation (using internal speech) for self-praise and self-instruction, and seeing rather than glossing over errors (Popper C, Steinguard R, 1994).

The child -focused interventions include the use of individual psychotherapy to treat any depression, low self-esteem, anxiety, or other types of associated symptomatology (Cantwell D, 1996).

Although no studies support the effectiveness of psychotherapy alone in treating ADHD, it can be a critical part of multimodal treatment for certain individuals.

Approximately 75% of ADHD children respond therapeutically to psychostimulants (Popper C, Steinguard R, 1994). Six controlled studies of stimulants in adult ADHD reported response rates varying from 25% to

78% with an average of 54%, comparable results to pediatric populations (Hornig M, 1998).

The most commonly prescribed and studied psychostimulants include methylphenidate, dextroamphetmine, and magnesium pemoline. (Findling R, Dogin J, 1998). Recently, the medication Aderall, which had been previously available as Obetrol, has been remarketed and advertised as a treatment for ADHD. Aderall consists of equal parts of four amphetamines: amphetamine sulfate, amphetamine aspartate, dextroamphetamine sulfate, and dextroamphetamine sacharate (Swanson J, et all, 1998). Methylphenidate is much more widely prescribed than other stimulants, because it has been studied more often (Elia J, et all, 1998).

It is common practice to treat with a short-acting psychostimulant. It is recommended that treatment with methylphenidate be initiated at 5mg bid. School-age patients respond to a dose 0.3-0.8 mg/kg higher dose may have adverse effects on concentration and learning. D-amphetamine dose is (5-40 mg) , Aderall is usually initiated as a 5 mg dose given once or bid, Pemoline starting dose is 37.5 ; there are sustained-release preparations of methylphenidate and dextroamphetamine which are effective for up to 8 hours (Findling R, 1998). If one psychostimulant fails, there is a 25% chance that the other will be helpful. A "rebound" period can then ensue, during which behavioral symptoms may become more severe than at

baseline and tics may emerge (Popper C, Steinguard R, 1994). Adverse effects of stimulants are similar in frequency, severity, and duration. Decreased appetite is reported in approximately 80% and about 10%to 15% of weight loss; insomnia is reported in 3 to 85% with sleep delays of about an hour; abdominal pain, irritability, headaches, dry mouth, dizziness, and depression are less frequent. Cardiovascular effects limited to variable increases in heart rate and blood pressure are most evident at rest and diminish with exertion; transient tics motor or vocal my occur (Elia J, et all, 1998). Pemoline carries a 1% to 3% risk of hepatotoxic metabolite formation (Popper C, Steinguard R, 1994). There are cases of pemoline induced liver failure resulting in liver transplantation, therefore baseline liver function tests should be obtained and closely monitored (Adcock kG, 1998). Psychostimulant effects in ADHD include a clinical improvement in impulsivity, hyperactivity, inattention, and emotional lability (Popper C, Steinguard R, 1994).

Methylphenidate does not affect the ultimate stature of school age patients treated with this drug. It has been reported that ADHD itself may lead to a temporary reduction in growth velocity that may be manifest through mid-adolescence and is not related to psychostimulant therapy (Spencer T, 1998).

Tricyclic antidepressants are the most extensively studied antidepressants. The most studied are imipramine and desipramine (Findling R, 1998). Unfortunately sudden death has been reported with these two drugs. Although less extensively studied amitriptyline and nortriptyline have also been described as being helpful in ameliorating symptoms of ADHD. Bupropion has been effective in several early trials (Elia J, et all, 1998) Fluoxetine as well as venlafaxine have also shown benefit in children with ADHD (Findling R, 1998). Monoamine oxidase inhibitor antidepressants are also clinically effective but are not typically used for treating ADHD because of the dietary restrictions and potential risks (Cyr M, Brown C, 1998).

Clonidine an $\alpha 2$ agonist appears to be a very useful and underused treatment for ADHD but more extensive documentation is needed. Both antidepressants and clonidine may be more helpful for behavioral (impulsivity and hyperactivity) than attentional symptoms. Guanfacine an $\alpha 2A$ agonist has a longer half life and is less hypotensive and sedating than clonidine. Both drugs are given in patients with ADHD and tourette syndrome (Cohn L, et all, 1997). Carbamazepine is commonly used in England, but formal demonstration of its efficacy is unavailable (Popper C, Steinguard R, 1994).

Major tranquilizers in low-dose range (e.g., chlorpromazine 10-50 mg four times a day) can also be considered, but their effects are nonspecific and their side effects make them unsuitable for long-term treatment (Findling R, 1998).

Lithium is generally not effective and is reported to worsen the symptoms of typical ADHD; however, it can be helpful if the "ADHD" is bipolar disorder presenting with impulsivity, inattention, and hyperactivity (Cantwell D, 1996). Propranolol has beneficial effects at very high dose (528 mg/day) despite the high doses it was very well tolerated (Spencer T, 1996).

Drug treatment may continue for several years, with periodic dose adjustments needed for changes in body weight, varying environmental or developmental stress, or metabolic (and drug-induced autometabolic) changes of drug biotransformation rate (Popper C, Steinguard R, 1994).

Observational measures, computerised tests of attention and measures of academic productivity and accuracy may also be useful in assessing drug effect. (Losier B, 1996). Assessment includes clinical interviews and standardised rating scales from parents and teachers. Testing of intelligence and academic achievement usually may be required in some cases where other learning disorders are suspected. (Barkley R, 1990)

The ratings of classroom peers show a closer correlation to teachers than to parents' ratings, suggesting that ADHD is largely determined by situation.

Self-ratings have been developed for adolescents, but not yet for children. Children may be aware of their ADHD and of "getting into trouble," but are less effective than parents as observers of their own behavior.

Certain laboratory tests, mostly variations on the continuous performance test (CPT), have been used clinically to measure attentiveness and responsiveness to changing sensory cues. Although these tests (computerized or otherwise) have been used to monitor treatment or to adjust medication dosages (Losier B, 1996).

This study was conducted to examine patients characteristics and treatment (pharmacotherapy, psychotherapy, behavioral therapy and parent training, educational programming) of ADHD. The study had two major aims: evaluate the outcome of pharmacotherapy in patients who have baseline as well as follow up measures, and to see if comorbid enuresis respond to the addition of stimulant.

VIII-Methods

Subjects

The study group consisted of 295 patients seen at the outpatient clinic at IDRAC (Institute of Developmental Research and Applied Care) or MIND (Medical Institute of Neuropsychological Disorders) with Attention Deficit and Hyperactivity symptoms. Those patients were evaluated at the clinic from October 97 till March 99. Criteria for inclusion in this study required that all subjects were clinically diagnosed as ADHD patients according to DSM-IV criteria. Excluded from the sample were patients who presented with symptoms of attention deficit, hyperactivity and impulsivity but did not fulfil the criteria for the disorder. The eligible subjects (n=271) ranged in age from 2 years to 24 years with a mean of 9.39 years and a standard deviation of 3.83. The ratio male to female was 3:1; boys (75.3%) and girls (24.7%). Those patients were referred by their pediatrician, or by their school, or by a psychologist, or their parents detected the problem and decided to refer them.

In this study, the subjects are stratified into different subgroups. 40 patients had concomittant enuresis, the age of this group ranged from 3 to 13 years the mean age was 7.45 year and the standard deviation was 2.5. Ritalin was given to 34 of these patients despite their enuresis. 81 patients underwent the CPT (Continuous Performance Test) age ranged between 3

and 22, the mean was 10.6 and the standard deviation was 3.6. 19 of these had a CPT at baseline and one on the pharmacological treatment. Another subgroup consists of 69 patient, age ranged between 4 and 18 with a mean of 8.9 and a standard deviation of 2.8. This group had either a baseline Du Paul ADHD scale done either by their teachers or by their parents; 16 of them had in addition to the baseline scale a scale done on pharmacologic treatment.

Design

The study was retrospective and descriptive. Its aim was to evaluate patient characteristics and treatment. A special questionnaire was designed to gather the needed data. The questionnaire targeted different questions: patient demographics, developmental history, comorbid condition, family history of ADHD and other psychiatric illness, pharmacologic treatment and its side effects, psychotherapy, behavioral therapy and parent training, outcome of the treatment based on special measures such as CPT (Continuous Performance Test), Du Paul ADHD scale and CGI (clinical global impression).

Procedure

The data gathered was based on the interviews the parents and children had with the treating psychiatrist. During the first interview parents were asked questions in order to assess the disorder their child was suffering

from and to track any additional comorbid condition. In the follow-up visits, the patient and his family were asked to describe the period between the visits to assess the clinical response and any side effect to the medications used. To better assess some of the patients, a CPT and a Du Paul ADHD scale was asked to be done. In order to confirm any mental retardation, borderline IQ, learning disorder or language and communication disorder, the patients were referred to specialists for evaluation.

Patients who had CPT (n=81) were assessed for a false negative test, and a comparison of a baseline and a on treatment tests was done using the Wilcoxon Signed Rank test. Teachers who fulfilled the Du Paul scale for ADHD were assessed for confirmation of the clinical diagnosis; afterwards a comparison between baseline and on treatment scale using the Wilcoxon Signed Ranks test was done.

Enuresis was evaluated after intake of Ritalin as improving, staying the same, or worsening.

CGI (clinical global impression) is another measure for response of patients; it is assessed on monthly basis.

Measures

Many measures were used in this study:

CPT:(Continuous Performance Test)

This task developed by Rosvold (1956) is widely considered to be a useful measure of attention (Aman M,et al, 1991). In our computer version letters were presented randomly every 3 to 5 seconds. The letters were presented for 0.3 seconds intervals and the test took 10 minutes to complete. The child's task was to press a lever whenever the x appeared and otherwise to refrain from responding. Three measures were derived total number of atypicals, number of mildly atypicals and number of markedly atypicals.

Du Paul ADHD scale:

George Du Paul developed this scale for evaluating the occurrence of ADHD; 14 items were taken from the DSM-III-R and placed in rating scale format. Sum the total number of points for all 14 items. If the scores exceed 1.5 standard deviation above the mean for age and sex, it is a clinically significant score.

CGI: clinical global impression

It is a scale from 1 till 5, 1 stands for no symptoms, 2 for mild symptoms, 3 for moderate symptoms, 4 for severe symptoms, and 5 for severe

symptoms. The observer who gathered retrospectively the data assigns the scores.

Du Paul ADHD RATING SCALE

Circle the number in the one column which best describes the child.

	Not at all	Just a little	Pretty much	Very much
1. Often fidgets or squirms in seat.	0	1	2	3
2. Has difficulty remaining seated.	0	1	2	3
3. Is easily distracted .	0	1	2	3
4. Has difficulty awaiting turn in groups.	0	1	2	3
5. Often blurts out answers to questions.	0	1	2	3
6. Has difficulty following instructions.	0	1	2	3
7. Has difficulty sustaining attention to tasks.	0	1	2	3
8. Often shifts from one uncompleted activity to another.	0	1	2	3
9. Has difficulty playing quietly.	0	1	2	3
10. Often talks excessively.	0	1	2	3
11. Often interrupts or intrudes on others .	0	1	2	3
12. Often does not seem to listen.	0	1	2	3
13. Often loses things necessary for tasks.	0	1	2	3
14. Often engages in physically dangerous activities without considering consequences.	0	1	2	3

IX-Results

The sample consisted of 271 patients diagnosed with ADHD. Age ranged from 2 to 24 years; the mean was 9.39 with a standard deviation of 3.83. Male to female ratio was 3:1. (See table 1).

Table 1

Age	
minimum	2
maximum	24
mean	9.39
standard deviation	3.83
Sex	
male	204
female	67
Ratio	3:1

18.5% of the patients had ADHD predominantly inattentive, 4.4% had the predominantly hyperactive/impulsive type and 77.1% had the combined type. (see table2).

Table. 2

	n=271	%
ADHD predominantly inattentive	50	(18.5%)
ADHDpredominantly hyperactive/impulsive	12	(4.4%)
ADHD combined type	209	(77.1%)

42.1% of the patients were self referred at the outpatients clinics The rest 16.6%, 15.9%,

25.5% were referred by their school, pediatrician, and psychologist respectively. (see table 3).

Table. 3

	n=271	%
Parents	114	(42.1%)
School	45	(16.6%)
pediatrician	43	(15.9%)
Others	69	(25.5%)

The study focused on several aspects of patient characteristics and treatment. In their developmental history see table, patients were assessed for alcohol intake and smoking during pregnancy; hypoxia at birth, maternal stress, prematurity, IUGR, and poor maternal health. Poor maternal health was considered positive for a history of infection, toxemia, anemia and others. (see table 4).

ADHD patients are known to have a family history of ADHD and other psychiatric illness. The prevalence of ADHD in fathers was 30.3%, ADHD in mothers 11.8%, ADHD in siblings 14.4%, with 12.9% having only one sibling with a positive ADHD and ADHD in a second degree relatives 25.1%. (see table 5).

Table. 4

	n=271	%
Alcohol intake during pregnancy		
Yes	4	(1.5%)
No	267	(98.5%)
Alcohol amount		
number		
missing	4	(1.5%)
Smoking during pregnancy		
Yes	38	(14%)
No	233	(86%)
Number of cigarettes smoked per		
day	1	(0.4%)
4	1	(0.4%)
5	1	(0.4%)
10	2	(0.7%)
15	1	(0.4%)
20	1	(0.4%)
60	31	(11.4%)
missing value		
Hypoxia at birth		
Yes	38	(14%)
No	233	(86%)
Maternal Stress		
Yes	47	(17.3%)
No	224	(82.7%)
Prematurity		
Yes	15	(5.5%)
No	256	(94.5%)
Poor maternal health		
Yes	14	(5.2%)
No	257	(94.8%)
IUGR		
Yes	1	(0.4%)
No	270	(99.6%)

***The amount was not specified**

The family history of other psychiatric illness was highest in terms of anxiety 7.75% and depression 12.1% (see table 6).

Table. 5

	n=271	%
ADHD in Father		
Yes	82	(30.3%)
No	189	(69.7%)
ADHD in Mother		
Yes	32	(11.8%)
No	239	(88.2%)
ADHD in Siblings		
Yes	39	(14.4%)
No	232	(85.6%)
Number of Siblings		
1	35	(12.9%)
2	4	(1.5%)
ADHD in second degree relative	68	(25.1%)
Yes	203	(74.9%)
NO		

Table. 6

	n=271	%
No positive family history	97	(72.7%)
Anxiety	21	(7.75%)
Depression	33	(12.1%)
Obsessive compulsive disorder	6	(2.2%)
Cyclothimia	1	(0.4%)
Social phobia	3	(1.1%)
Bipolar	5	(1.8%)
Alcoholic	2	(0.4%)
Panic attack	2	(0.4%)
Schyzophrenia	2	(0.4%)

In addition to ADHD, patients had other comorbid conditions. With regard to mood disorders 12.5 % of the patients had depression, 3.7% had bipolar disorder, 2.2% had dysthymia, and 0.7% had cyclothymia. Under the anxiety disorders 5.5% had separation anxiety disorder, 4.8% had generalised anxiety disorder, 3% had obsessive-compulsive disorder, 2.6%

had social phobia, 0.7% had panic disorder, and 0.7% had PTSD. In addition to the previous categories of disorders, the patients were also screened for language and communication disorder 12.5%, learning disorder 6.3%, enuresis 14.8%, encorporesis 3%, mental retardation 11.1%, borderline IQ 11.8%.(see table7).

Table. 7

psychiatric condition	n=271	%	male	female
Conduct disorder	3	(1.1%)	2	1
Depression	34	(12.5%)	24	10
Separation anxiety	15	(5.5%)	11	4
Bipolar disorder	8	(3%)	7	1
General anxiety	13	(4.8%)	9	4
Obsessive compulsive disorder	8	(3%)	7	1
Mental retardation	30	(11.1%)	19	11
Borderline IQ	32	(11.8%)	20	12
Fragile X	0	(0%)	0	50
Pervasive developmental disorder	9	(3.3%)	7	2
Tic disorder	21	(7.7%)	18	3
Language and communication	34	(12.5%)	29	5
disorder	17	(6.3%)	10	7
Learning disorder	40	(14.8%)	38	2
Enuresis	8	(3%)	8	0
Encorporesis	21	(7.7%)	17	4
Stereotypes	4	(1.5%)	3	1
Adjustment disorder	7	(2.6%)	4	3
Social phobia	6	(2.2%)	5	1
Dysthymia	5	(1.8%)	4	1
Psychotic features	4	(1.5%)	1	3
Coordination disorder	1	(0.4%)	1	0
Drug abuse	2	(0.7%)	0	2
Panic disorder	1	(0.4%)	1	0
Schyzophrenia	2	(0.7%)	2	0
Hypomania	2	(0.7%)	2	0
PTSD	2	(0.7%)	2	0
Cyclothymia				

Male:Female=3:1

Different treatment plans were implemented for ADHD patient depending on child and family's individual needs. In addition to pharmacotherapy, when indicated, psychotherapy was utilised by 22.5% of the patients, behavioral therapy and parent training was utilised by 32.5% of the cases and around 9% of the patients were referred in a special education program; most of these patients had mental retardation or borderline IQ. (See table 8).

Table. 8

	n=271	%
Behavioral therapy and parent training	88	(32.5%)
Psychotherapy	61	(22.5%)
Educational programming	24	(8.9%)

It is well known that the drugs of choice in ADHD are psychostimulants. Methylphenidate is much more widely prescribed than Dextroamphetamine because it has been studied more often. It was also suggested, without evidence that it was more effective and had fewer adverse effects than Dextoamphetamine (Elia J, 1999). Because it is the only available stimulant in Lebanon, 203 patients were prescribed Ritalin after being diagnosed with ADHD. Some were not prescribed Ritalin for reasons that are listed in (see table9).

Table.9

	n=60	%
Unsatisfactory amelioration of symptoms with stimulant	4	6.6%
Inability to tolerate the untoward effects such as appetite suppression or sleep disturbance	3	5%
Development of tolerance to therapeutic effect of stimulants	2	3.3%
Presence of family history of tics or Tourette's disorder	5	8.3%
Presence of schizophrenia borderline personality disorder or pervasive developmental disorder	4	6.6%
Presence of a significant mood disorder component	15	25%
Presence of symptoms of significant anxiety	7	11.6%
Patient is younger then 6	13	21.6%
Patient has enuresis	3	5%
patient has uncontrolled seizure	4	6.6%

As for the side effects of Ritalin see table 10.

Table. 10

	n=170	%
Decreased appetite/Anorexia	48	28.2%
Nausea	2	1.1%
Seizures	3	1.7%
Abdominal pain	4	2.3%
Transient crying	5	3%
Depressed mood	17	10%
Irritability	30	17.6%
Tics	4	2.3%
Agitation	3	1.7%
Worsening of Psychosis	0	0%
Headache	18	10.5%
Rebound	11	6.4%

The most frequent are decreased appetite 20.7%, and irritability 11.1%.
Side effects of other drugs.

Table .11

	Catapresse n=11	Melleril n=2	Dexedrine n=4	Desipramine n=1	Prozac n=1	Tofranil n=29
Depressed mood	1		1			
Drowsiness	1					
Sedation	1					1
Dry moth		1				
EPSE		1				
Insomnia			1	1		
Seizure					1	
Constipation						1
Headache						1

ugs were minimal. (See table 11).

40 patient had comorbid enuresis, 34 patient were given Ritalin despite their enuresis 13 (38.2%) of them had an improvement in their enuresis. CPT was given for 81 patient, 67 of them (82.7%) had the CPT at baseline. CPT was reported to be false negative in 9 (13.4%) of the 67. 19 patients had CPT done at baseline and after treatment, 9 of them (47.4%) showed a negative CPT after treatment. Wilcoxon Signed Ranks test showed a significant ($0.011<0.05$) decrease in CPT after treatment in comparison to that on baseline. The number of markedly and mildly atypicals also decreased accordingly.

Du Paul ADHD scale was another assessment tool to assess the patients at baseline as well as after treatment. A total of 153 teacher evaluated 56 patient at baseline 74 (48.3%) of them rated the child as having ADHD in

comparison to a population of same sex and age. 16 patients had the questionnaire done at baseline and on treatment (see table 12).

Table. 12

	Not at all	Mild symptoms	Moderate symptoms	Severe symptoms	Very severe symptoms
Baseline			16.2%	65.1%	18.6%
Month 3	13.1%	38%	31%	14.7%	3.1%
Month 6	58.9%	12.4%	7.7%	13.1%	7.7%

The score decreased in 15 and worsened in 1. To analyze the significance of these changes, the Wilcoxon Signed Ranks test was done, revealing a significance of p=0.003. 10 (37%) out of 27 of the parents who evaluated their children at baseline had a false negative scale in comparison to a population of same age and sex.. Every patient seen at IDRAC or MIND was attributed a CGI (clinical global impression) see table 13 for changes from baseline to month 3 and month 6.

The dose of Ritalin was tapered according to the response of every patient. The average dose per day to which children responded increased as expected with the age of the child as follows:

Age group	Average daily dose at 3 months	
2-5 years	15.7 mgs	
6-9 years	18.8 mgs	One way ANOVA p=0.009
10-12 years	23.7 mgs	
Greater than 13 years	26.7 mgs	

X-Discussion

The assessment of patient characteristics yielded different results. Some of the results were consistent with literature some were not. The ratio male to female 3:1 represent a fair ratio that indicate that referrals were not male bias as reported in literature where the ratio balances between 3:1 and 9:1. (Elia J, 1999). Our patients were referred from different sources directly to a psychiatrist, whereas most ADHD patient in the United States are cared by pediatricians and family practitioners, while child psychiatrists, neurologists, and behavioral pediatrician tend to see refractory patients and those with significant comorbidity (Goodman L, et al, 1998).

Comorbidity in this sample was not as high as reported in literature, where as many as 65% of children with ADHD will have 1 or more comorbid condition. Some studies show that between 10% and 20% of children with ADHD in both community and clinical samples have mood disorders, other studies show that depressive disorders range from 9% to 38% in ADHD children. The prevalence of any mood disorder was 17.3% in this sample. Depressive symptoms generally have an onset after the ADHD symptoms and the coexistence of ADHD and MDD does not appear to prolong the depressive episodes or number of depressive episodes. Conduct disorder was prevalent as much as 1% in comparison

to 20% in other studies ADHD. Our sample matched other studies samples with respect to tic disorder, which was 7%. About 20% to 30% of ADHD children will be learning disabled in the area of spelling, reading, or arithmetic this sample showed 6.3% learning disorder among its subjects. (Pliszka, S, 1998). About a quarter of children with ADHD will meet criteria for anxiety disorder (Pliszka,S, 1998), the prevalence of anxiety disorder (SAD separation anxiety disorder and GAD generalized anxiety disorder) in this sample was 8.5% . Only one patient has drug abuse concomitantly with ADHD this patient is an adult, the risk of developing substance use disorders in those with ADHD is increased in adolescent and the risk ratio increases further in adulthood. (Goodman L, 1999).

The family history of any psychiatric illness yielded an increased prevalence of depression (12.1%). Biederman et al examined the prevalence of both ADHD and MDD in relatives of ADHD children with or without MDD. If the child had only ADHD, the rates of ADHD and MDD in first-degree relatives were both elevated over the rates of a control group, a similar pattern was found in the ADHD/MDD group. The fact that relatives of nondepressed ADHD probands also had an increased risk of MDD suggested some common familial links with ADHD and MDD (Pliszka S, 1998). With respect to ADHD in the family there an

increased prevalence of the disorder especially in fathers 30.3%. Adoption studies support the running in families of ADHD is genetic rather than environmental (Cantwell D, 1996). With respect to the development history, many theories were postulated on the effect of smoking, alcohol, hypoxia, prematurity, poor maternal health, maternal stress and others. (Popper C, 1994). In this study the frequency and prevalence of these factors was not high except for smoking 14% this could be due to the fact that parents were asked to recall information dating from years, and as if in this question parents are held responsible of unhealthy behavior that affected the development of their children.

Stimulants are drug of choice. The response rate for any single stimulant drug in ADHD is approximately 70% and up to 90% without major adverse events if drug titration is done carefully. In this study 201 patient were given Ritalin at baseline. Nevertheless some patients were not prescribed a stimulant due to a reason listed in table 9. The decision to prescribe Ritalin or not was taken on individual basis. For example, if a patient presented with anxiety or tic disorder for some Ritalin was prescribed for some but not for others. Despite the fact that Ritalin increases irritability and anxiety, 30% of the ADHD overanxious disorder children did respond well to stimulants and continued treatment with methylphenidate, thus the study did not show that stimulants are absolutely

contraindicated in ADHD/anxiety. For those who were not prescribed Ritalin because of the anxiety component, tricyclic antidepressants and fluoxetine can be safely combined to treat this comorbid group. Lithium and stimulant can be safely combined in the ADHD/manic child without side effects. (Goodman L, et al, 1998). Methylphenidate can be considered as therapeutic for children with ADHD and tic disorder and the lowest effective stimulant dose should be used (Castellanos X.F,, et al, 1997) . The reason for not prescribing Ritalin for preschoolers goes back to the fact that studies indicate that young children respond less well to stimulant therapy, suggesting that preschoolers are more treatment refractory (Spencer T, et al, 1996). Since most side effects of stimulants appear to be dose related, determining the lowest effective dose, which allows maximal therapeutic benefit while minimizing adverse effects, is the goal of safe and effective pharmacotherapy (Findling R, Dogin F, 1998)

Rebound effects of increased excitability, activity, talkativeness, irritability, and insomnia, may be seen as the last dose of the day wears off, it was reported to be in 10.5% the cases (AACAP, 1997).

Since three quarters of treatment review articles assert that multimodal therapy is superior to medication or psychosocial interventions separately, many patients were indicated psychotherapy as well as behavioral therapy and some of them, those mental retardation or borderline IQ, were placed

in a special education program. There is in fact little empirical evidence to support such a conclusion (Goldman L, et al, 1998). Non medication approaches include parent education, parent management training (this technique decreases disruptive behavior, increases parent self confidences and decreases family stress) classroom environmental manipulations, contingency management and daily report cards by teacher, individual psychotherapy for depression, anxiety, and low self esteem (Cantwell D, 1996).

A finding that this study remarked was the response of enuresis to the addition of Ritalin. It is reported that Ritalin was used to treat giggle incontinence; in this study all patients responded positively with complete cessation of enuresis to varying doses of methylphenidate (Sher P, Reinberg Y, 1996). This topic will be further investigated in the future.

Another objective of this study was to determine whether the CPT, Du Paul ADHD scale and CGI predicted the changes in patients in terms of clinical response; clinical response in this context means statistically or clinically significant reduction in hyperactivity or increase in attention as rated by parents, teachers and / or research raters. But before discussing so it is worth noting that the comparison of the premeditation score and on medication score relied on first small groups of patients in comparison to

the whole sample and second on teacher and research rater perception of change.

Teachers and parents tend to under estimate the prevalence of ADHD in subjects attained by the disorder.

Overall in the CPT group and Du Paul ADHD scale group there was a significant change between baseline and on medication score ($p= 0.011<0.05$, and $p=0.003<0.05$ respectively). Generally, CPT measures have been found to be extremely drug-sensitive in research conducted with children who were ADHD but not developmentally delayed(Handen B.L., et al,1992). CGI also decreased between baseline and after treatment .

Duration of medication intake ranged from 1 to 18 months at the end of the study. The average dose per day to which children responded increased as expected with the age of child with a significance of 0.009 based on the oneway ANOVA

XI-Conclusion

This study described patient characteristics in one center IDRAC or MIND and compared them to the prevalence reported in other studies. The evaluation of the treatment in terms of side effects and clinical response was another objective the study accomplished. An idea of how well children are evaluated and how serious they are rated in comparison to others was elucidated. This should lead to a conclusion that much must be done to enlighten responsible people like teachers and parents that symptoms of inattention and hyperactivity could constitute a disorder that can be treated.

Literature cited

- AACAP, Summary of The Practice Parameters for the Assessment and Treatment of Children, Adolescents and Adults with ADHD, Journal of American Academy of Child and Adolescent Psychiatry, 1997, 36(9):1311-1317)
- Adcock KG, Pemoline Therapy Resulting in Liver Transplantation, *Annals of Pharmacotherapy*, 1998; 32(4): 422-425
- Aman M., et all, Methylphenidate and Thioridazine in the Treatment of intellectually subaverage children: Effects on Cognitive Motor Performance, *Journal of American Child and Adolescent Psychiatry*, 1991, 30(5):816-824) .
- Barkley R, Attention Deficit Hyperactivity Disorder: A Handbook For Diagnosis and Treatment,1990, New York: The Guilford press
- Biederman J, et all, High Risk for Attention Deficit Hyperactivity Disorder Among Children of Parents With Childhood Onset of the Disorder: A Pilot Study, *American Journal of Psychiatry*, 1995; 152:431-435
- Biederman J, et all, Patterns of Psychiatry Comorbidity, Cognition and Psychosocial Functioning in Adults with Attention Deficit Hyperactivity Disorder, *American Journal of Psychiatry*, 1993; 150:1792-1798.
- Cantwell D, Attention Deficit Disorder A review of 10 years, *Journal of American Academy of Child and Adolescent Psychiatry*, 1996; 35(8):978-987.
- Castellanos X.F,, et al, Controlled Stimulant treatment of ADHD and comorbid Tourette's Syndrome: Effects of Stimulant and dose, *Journal of American Academy of Child and Adolescent Psychiatry*, 1997, 36(5):589-596 .
- Charbol H, et all, ADHD and Maternal Smoking during Pregnancy, *American Journal of Psychiatry*, 1997; 154(7):1177.
- Cohn L, et all, Guanfacine use in Children with Attention Deficit Hyperactivity Disorder, *The Annals of Pharmacotherapy*, 1997 ;31:918-919.
- Cyr M, Brown C, Current Drug Therapy Recommandations for Treatment of Atttention Deficit Hyperactivity Disorder, *Drugs*, 1998;56(2):215-223.
- Elia J, et all, Treatment of Attention Deficit Hyperactivity Disorder Wood A, ed., *New England Journal of Medicine*, 1999; 340(10):780-788.
- Fayyad J, Attention Deficit Hyperactivity Disorder, *The Medical Periodical*, 1998: 1(9):21-24.
- Findling R, Dogin J, Psychopharmacoloy of ADHD: Children and Adolescents, *Journal of Clinical Psychiatry*, 1998; 59(7):42-49.
- Garfinkel, et al, Psychiatric Disorders in Children , WBC Saunders:1989.
- Gaub M, Carlson C, Gender Differences in ADHD a Meta Analysis and Critical Review, 1997; *Journal of American Academy of Child and Adolescent Psychiatry*,1997; 36(8):1036-1045.
- Goldman L et all, Diagnosis and Treatment of Attention deficit hyperactivity Disorder in Children and Adolescent, *JAMA*, 1998;279:1100-1107.
- Grice D,et all , Childhood Psychiatric Disorders, *Psychosomatics;*13(12).
- Handen B.L., et al, Effects of Methylphenidate in Children with Mental Retardation and ADHD, *Journal of American Academy of Child and Adolescent Psychiatry*, 1992, 31(3):455-461
- Horning M, Addressing Comorbidity in Adults with Attention-deficit / Hyperactivity disorder, *Journal of Clinical Psychiatry*, 1998;59(7):69-75.
- Huey L, Psychiatry Arnold et all ed, 1991, Lippincott company,USA.

- Jensen P, Comorbidity in ADHD Implications for research, Practice, and DSM-V, *Journal of American Academy of Child and Adolescents Psychiatry*, 1997; 36(8):1065-1079
- Levy F, Hay D, Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large scale twin study, *Journal of American Academy of Child and Adolescent Psychiatry*, 1997;36:737-744
- Lombroso P ,et all, Genetic Mechanisms in Childhood Psychiatric Disorders, *Journal of American Academy of Child and Adolescent Psychiatry*,1994; 33(7):921-938.
- Losier B, et all, Error Patterns on the Continuous Performance Test in Non-medicated and Medicated Samples of Children with or without ADHD a Meta-Analytical Review, *Journal of child Psychology and psychiatry*, 1996, 37 (8): 971-987.
- Lou Hc, Etiology and Pathogenesis of Attention-deficit Hyperactivity disorder ADHD : Significance of Prematurity and Perinatal Hypoxic-Haemodynamic Encephalopathy, *Acta Pediatric*,1996;85:1266-1271.
- Milberg S,et all, IS Maternal Smoking During Pregnancy a Risk Factor for Attention Deficit Hyperactivity Disorder in Children, *American Journal of Psychiatry*, 1996: 153(9):1138-1142.
- O'Malley K, Fetal Alcohol Effect and ADHD, *Journal of American Academy of Child and Adolescent Psychiatry*,1994; 33(7):1059-1060.
- Pliszka S, Comorbidity of Attention-Deficit/Hyperactivity Disorder with Psychiatric Disorder :an Overview, *Journal of Clinical Psychiatry*, 1998;59(7):50-58.
- Popper C, Steingard R, Textbook of Psychiatry. Robert Hales.1994 American Psychiatry Press: USA.
- Sermud-Clikeman M, et all, Attention Deficit Hyperactivity Disorder: MAGNETIC Resonance Imaging Morphometric Analysis of the Corpus Collosum, *Journal of American Academy of Child and Adolescent Psychiatry*,1994;33(6):875-881.
- Shaffer D, Attention Deficit Hyperactivity Disorder in Adults, *American Journal Psychiatry*, 1994; (may).
- Sher P, Reinberg Y, Successful Treatment of Giggle incontinence with Methylphenidate, The Journal of Urology, 1996, 156:656-658.
- Spencer T, et all, Growth Deficits in Children with Attention Deficit Hyperactivity Disorder, *Pediatrics*, 1998; 102:501-506.
-Spencer T, et al, Pharmacotherapy of Attention Deficit Hyperactivity Disorder across The Life Cycle, Journal of American Academy of Child and Adolescent Psychiatry, 1996, 35(4):409-432
- Stoudemine A ed., Clinical Psychiatry for Medical Students 3rd edition, 1998, Lippincott Raven Philadelphia: New York, pp:533-543.
- Swanson J, et all, Analog Classroom Assessment of Aderall in Children with ADHD, *Journal of American Academy of Child Adolescents Psychiatry*, 1998; 37(5):519-526
- Toren P, et all, Thyroid Function in Attention Deficit and Hyperactivity Disorder, *Journal of Psychiatric Residents*,1997; 31:359-363
- Young L, Koda-kimble MA, Applied Therapeutics: The Clinical Use of Drugs, 1995, Applied Therapeutics Inc: USA