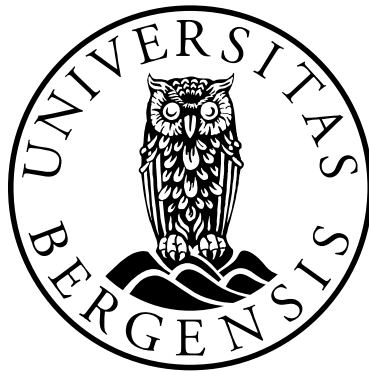


# **Attention deficit/hyperactivity disorder and occurrence of epilepsy, interictal epileptiform discharges and two years follow-up in children**

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I graduated from Belgrade University school of Medicine in 1991 and my first experience with child neurology and child psychiatry, epilepsy, ADHD symptoms and EEG was made in Belgrade, while working at the Clinic for Neurology and Psychiatry for Children and Youth for 10 years. In 1998, I got the opportunity to work at Kork Epilepsy Center in Kork, Germany, where I met children with pharmaco-resistant epilepsy and ADHD for the first time. I met inspiring colleagues and spent valuable time in both institutions, which contributed to awakening and developing interest in the field of epilepsy, ADHD and EEG in me.

Finally, in 2001 I started to work at the Stavanger University Hospital (at that time Rogalad Central Hospital), which made it possible for me to investigate the relationships between ADHD symptoms, EEG findings and epilepsy and to make this study.

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1. Socanski D, Aurlien D, Herigstad A, Thomsen PH, Larsen TK. Epilepsy in a large cohort of children diagnosed with attention deficit/hyperactivity disorders (ADHD). *Seizure*: 2013;22: 651-655.
2. Socanski D, Herigstad A, Thomsen PH, Aarsland D, Larsen TK. Epileptiform abnormalities in children diagnosed with attention deficit/hyperactivity disorder. *Epilepsy & behavior: E&B*. 2010; 19: 483-486.
3. Socanski D, Aurlien D, Herigstad A, Thomsen PH, Larsen TK. Attention deficit/hyperactivity disorder and interictal epileptiform discharges: it is safe to use methylphenidate? *Seizure*: 2015; 25:80-3.

## **ABSTRACT**

The detection and treatment of both attention deficit/hyperactivity disorder (ADHD) and epilepsy in young patients are challenging. In some cases, the occurrence of interictal epileptiform discharges (IEDs) flowers the picture, and some clinicians are reluctant to use methylphenidate (MPH) in such cases. Many studies discussed ADHD in children with epilepsy, but only a few investigated relationships between ADHD, IEDs and epilepsy in children with ADHD. It is unclear whether it is safe to use MPH in children with ADHD and comorbid epilepsy and/or IEDs.

**Aims:** We investigated the occurrence of epilepsy and IEDs on awake EEG at baseline in a large sample of children diagnosed with ADHD. Finally, we studied whether the use of MPH would increase the risk for epilepsy in a 2 year prospective, and whether IEDs at baseline influence the occurrence of epileptic seizures (SZs), the use of MPH and the use of antiepileptic drugs (AEDs).

**Methods:** This is a retrospective chart review of all children aged between 6-14 years diagnosed with ADHD over a 6 year period (2000-2005). First, we examined the prevalence and characteristics of epilepsy in children with ADHD and compared it with a general pediatric population, and initial use of MPH in cases with and without epilepsy. Second, we investigated the occurrence of IED on awake EEG at baseline in all children who performed a routine EEG. The clinical characteristics of ADHD children (ADHD inattentive subtype, comorbidities) in cases with and without IEDs were analyzed. Finally, we compared the patients with IEDs (IEDs group) with matched controls (age and gender) without IEDs (non-IEDs group) in a 2 year follow-up. We wanted to examine the use of MPH (initial use, positive response, maintenance on MPH), the use of AEDs, and whether it was safe to use MPH in cases with IEDs (seizure risk) during the first 2 years of treatment. A control EEG was carried out in the IEDs group.

**Results:** We found that 2.3 % of children (N=607) had epilepsy. This is significantly higher than in the general pediatric population (0.5%). In all children, the diagnosis of epilepsy was made before ADHD diagnosis. We were able to carry out baseline EEG in 517 cases and IEDs were found in 39 (7.5%), or in 27 (5.4%), if patients with previous epilepsy were excluded. When we compare this rate with rates of IEDs reported in healthy children, it is unclear whether any differences exist. The cases with IEDs more often had inattentive type of ADHD

regardless of previous history of epilepsy. Of the children with IEDs, only children with previous difficult to treat epilepsy developed SZs during the 2 year follow-up, but without any change in SZ frequency. The groups with and without IEDs did not have significant differences in the use of MPH. Some cases from the IEDs group temporarily used AEDs because of diagnostic uncertainties.

**Conclusions:**

Epilepsy and IEDs occur more often in children with ADHD compared to the general pediatric population and healthy children. The groups with and without IEDs had similar use of MPH during the two 2 year follow-up. The occurrence of IEDs at baseline was not associated with an increased SZ risk during the 2 year follow-up despite the use of MPH.

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## Abbreviations

ADHD	Attention deficit/hyperactivity disorder
ADHD-C	ADHD predominantly combined type
ADHD-I	ADHD predominantly inattentive type
AED	Antiepileptic drug
ASD	Autism spectrum disorder
BECTS	Benign childhood epilepsy with centrotemporal spikes
CAE	Childhood absence epilepsy
CBZ	Carbamazepine
CPSZ	Complex partial seizure
CSWS	Continuous spike and wave activity during slow-wave sleep
EEG	Electroencephalogram
GTCSZ	Generalized tonic-clonic seizure
IEDs	Interictal epileptiform discharges
IGE	idiopathic generalized epilepsy
ILAE	International League Against Epilepsy
JAE	Juvenile absence epilepsy
JME	Juvenile myoclonic epilepsy
LEV	Levetiracetam
LKS	Landau Kleffner syndrome
LTG	Lamotrigine
MPH	Methylphenidate
MTA	Multimodal Treatment Study of ADHD
NICE	National Institute for Health and Clinical Excellence
PFC	Prefrontal cortex
PGE	Primary generalized epilepsy
SPSZ	Simple partial seizure
SZ	Epileptic seizure
TCI	Transient cognitive impairment
TS	Tourette syndrome
VPA	Valproate

## 1. INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) and epilepsy are common neuropsychiatric disorders. ADHD occurs in 3-7 % of all children (American Psychiatric Association 1994, American Psychiatric Association 2000), whereas the prevalence of epilepsy in the general population is between 0.4 and 1% (Sander 2003). ADHD has an overall pooled estimate of 7.2% (95% confidence interval: 6.7 to 7.8), and there is no statistically significant difference between different editions of the Diagnostic and Statistic Manual of mental Disorders (DSM) (Thomas, Sanders et al. 2015). ADHD occurs approximately three times more often in boys in community samples, and five to nine times more often in clinical samples (American Psychiatric Association 1994). Biederman and colleagues (2002) evaluated the impact of gender on the clinical features of ADHD and suggested that girls with ADHD were at less risk for comorbid disruptive behavior disorder than boys with ADHD. Because disruptive behavior disorder drives referral, this finding might explain the substantial discrepancy in the male/female ratio. Furthermore, this gender discrepancy suggests that girls with ADHD might be under-identified and under-treated (Biederman, Mick et al. 2002). In children and adolescents with epilepsy, there is no gender difference (Freitag, May et al. 2001), but there is broad agreement between studies that females have a marginally lower incidence of epilepsy and unprovoked seizure than males. This difference is usually attributed to male's greater exposure to risk factors for lesional epilepsy and acute symptomatic seizures. On the other hand, idiopathic generalized epilepsies, which may represent some 15-20% of all epilepsies, are more common among females (McHugh and Delanty 2008).

ADHD is a condition that can be devastating for both patients and relatives. There is probably a higher rate for epilepsy in this disorder, thus the treatment with MPH is often discussed. Some clinicians are even reluctant to treat ADHD with MPH even when no SZs, but only IEDs are present. In addition, the diagnosis and treatment of both ADHD and epilepsy in children are challenging in some cases. From a clinical point of view it also seems to be unclear whether it is safe to use MPH in such cases (SZs or IEDs) over time.

## **1.1 ADHD**

### **1.1.1 Definition of ADHD**

According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) definition (2000), ADHD essential features are:

- A. Persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequently displayed and is more severe than is typically observed in individuals at comparable level of development.
- B. Some hyperactive-impulsive or inattentive symptoms must have been present before seven years of age.
- C. Some impairment from the symptoms must be present in at least two settings.
- D. There must be clear evidence of interference with developmentally appropriate social, academic or occupational functioning.
- E. The disturbance does not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorders and is not better accounted for by another mental disorder.

ADHD is divided into three subtypes:

1. ADHD Predominantly Inattentive Type (ADHD-I): This subtype is used if six (or more) symptoms of inattention (but fewer than six symptoms of hyperactivity-impulsivity) have persisted for at least six months.
2. ADHD Predominantly Hyperactive-Impulsive Type: This subtype should be used if six (or more) symptoms of hyperactivity-impulsivity (but fewer than six of inattention) have persisted for at least six months.
3. ADHD Combined Type (ADHD-C): This subtype should be used if six (or more) symptoms of inattention and six (or more) symptoms of hyperactivity-impulsivity have persisted for at least six months.

The International Classification of Diseases 10<sup>th</sup> edition (ICD-10) has been the standard diagnostic tool in Europe since 1994 (World Health Organization 1992). In ICD-10 ADHD is labelled hyperkinetic disorder (HKD)(World Health Organization 1999). HKD suits best a severe subgroup of the DSM-IV combined type ADHD and affects about 1.5% of primary school-age boys (National Institute for Health and Clinical Excellence 2008). HKD

(F90) has following subtypes: F 90.0 Disturbance of activity and attention, F90.1 Hyperkinetic conduct disorder (hyperkinetic disorder associated with conduct disorder), F90.8 Other hyperkinetic disorders, F90.9 Hyperkinetic disorder, unspecified. Inattentive type of ADHD is in ICD-10 usually diagnosed with F98.8 Other specified behavior and emotional disorders with onset usually occurring in childhood and adolescence (including Attention deficit disorder without hyperactivity). Diagnosis of ADHD should be considered in all age groups. Diagnosis should be made when symptoms of hyperactivity, impulsivity and inattention meet the criteria in DSM-IV or ICD-10; are associated with at least moderate psychological, social and/or educational or occupational impairment based on interview and/or observation in multiple settings; are persistent and trait-like (i.e. not episodic) (National Institute for Health and Clinical Excellence 2008, National Institute for Mental Health and Clinical Excellence 2009).

Recently the DSM has been revised. According to DSM-V (American Psychiatric Association 2013), ADHD-C is characterized by 6 or more symptoms of hyperactivity/impulsivity, and 6 or more symptoms of inattention from a list of 9 symptoms in each category. ADHD-I requires 6 or more symptoms of inattention, and less than 6 symptoms of hyperactivity/impulsivity. For youth aged 17 years and above, 5 rather than 6 symptoms in each category are required. ADHD-I is further defined to contain a sluggish cognitive tempo group (patients are passive, slow, and daydreamy). Others cases are closer to ADHD-C, but they have subclinical levels of hyperactivity/impulsivity. The DSM-V highlights that a change of subtype throughout the life span is not uncommon. At least some of the symptoms must be present in more than one setting before the age of 12, and should not be better explained by other conditions. In DSM-V, an autism spectrum disorder (ASD) diagnosis does not exclude a diagnosis of ADHD.

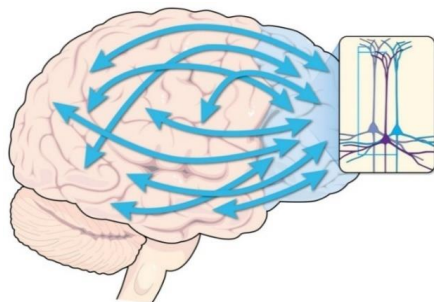
### **1.1.2 Aetiology of ADHD**

The aetiology of ADHD is complex, with multiple genetic and non-genetic factors implicated (Curatolo, Paloscia et al. 2009, Faraone and Mick 2010). Causal factors are primarily genetics but environmental influences such as smoking during pregnancy or preterm birth are contributing factors (Thomsen, Plessen et al. 2014). At a molecular level, alternations in any single neurotransmitter system are unlikely to explain the complexity of

ADHD, rather the disorder has been linked to dysfunctions in several systems, including the dopaminergic, adrenergic, serotonergic and cholinergic pathways (Cortese 2012). Genetic studies showing a heritability of ~60-75% suggest that a plethora of genes, each one with a small but significant effect, interact with environment factors to increase the susceptibility to develop ADHD (Cortese 2012). However, some evidences have converged to suggest that catecholamine neurotransmission is impaired in the brains of patients with ADHD (Arnsten 2006, Brennan and Arnsten 2008, Arnsten 2009, Arnsten and Pliszka 2011). Arnsten and Pliszka (2011) summarized catecholamine influences on prefrontal cortical function and pointed out that prefrontal cortex (PFC) is essential for the “top down” regulation of attention, behavior, and emotion, and that this brain region is underactive in many patients with ADHD. The PFC is known to be especially sensitive to its neurochemical environment; relatively small changes in the levels of norepinephrine and dopamine can produce significant changes in its function. Studies in animals have shown that norepinephrine and dopamine enhance PFC function through actions at postsynaptic  $\alpha$ 2A-adrenoreceptors and dopamine D1-receptors, respectively. Stimulant medication and atomoxetine appear to enhance PFC function through increasing endogenous adrenergic and dopaminergic stimulation of  $\alpha$ 2A-receptors and D1 receptors (Figure 1,2 and 3). Furthermore, stimulants methylphenidate (MPH), dexamphetamine and the non-stimulant atomoxetine increase synaptic catecholamine concentrations in the brain, particularly in the prefrontal cortex, although their precise mechanisms of action differ. The primary molecular targets of MPH are plasma membrane dopamine and noradrenaline transporters (Figure 4) (Markowitz, DeVane et al. 2006, Hodgkins, Shaw et al. 2012).

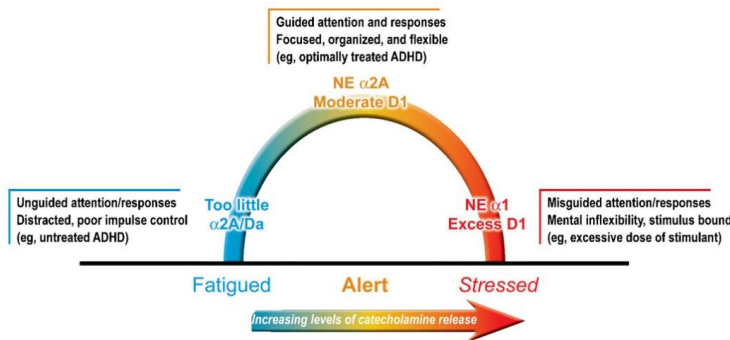
**Figure 1.** (Arnsten and Pliszka, 2011)

The PFC regulates attention, behavior, and emotion through extensive network connections with other brain regions. Networks of neurons within the PFC (insert) excite each other to maintain representations of goals and rules used to guide attention, behavior, and emotion.



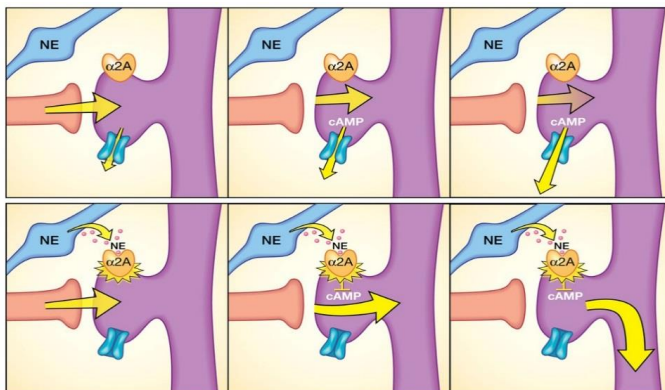
**Figure 2.** (Arnsten and Pliszka, 2011)

The PFC is very sensitive to its neurochemical environment; both insufficient and excessive catecholamine release impair PFC function. The catecholamines norepinephrine (NE) and dopamine (DA) are released in the PFC according to arousal state: very little during fatigue (and boredom?), a moderate amount of phasic release to relevant stimuli during alert, nonstressed waking, and high tonic release under stressful conditions. Moderate levels of NE engage postsynaptic  $\alpha$ 2A-receptors to improve PFC function, while higher levels engage  $\alpha$ 1- and  $\beta$ -receptors, which impair PFC function. Thus, optimal regulation of PFC function depends on postsynaptic  $\alpha$ 2A- and moderate D1-receptor stimulation. Animal studies suggest that therapeutic doses of stimulants improve PFC function by increasing endogenous noradrenergic and dopaminergic stimulation of  $\alpha$ 2A- and D1-receptors, respectively. ADHD.



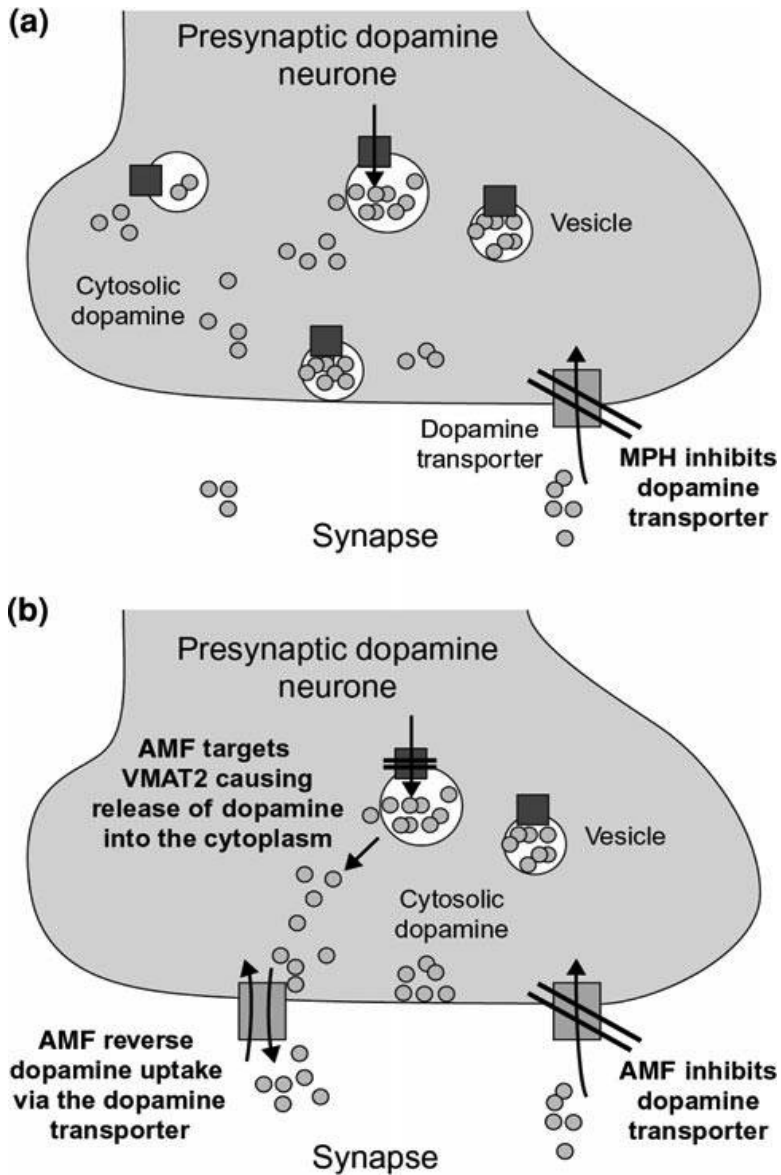
**Figure 3.** (Arnsten and Pliszka, 2011)

Stimulation of post-synaptic,  $\alpha$ 2A-receptors on PFC neurons by norepinephrine (NE) or guanfacine strengthens the functional connections between prefrontal cortex (PFC) neurons. Many  $\alpha$ 2A-receptors are found on the dendritic spines where PFC neurons form network connections. **Top row:** When there is no  $\alpha$ 2A-receptor stimulation, cyclic adenosine monophosphate (cAMP) levels are high, potassium channels open, weakening nearby synaptic inputs. As a result, PFC network firing decreases, and there is weakened capability to regulate attention, behavior, or emotion. **Bottom row:** When  $\alpha$ 2A-receptors are stimulated by NE or by guanfacine, they close nearby potassium channels, increasing the efficacy of network inputs, and facilitating PFC function.



**Figure 4. (Hodgkins, Shaw et al. 2012)**

Overlapping but distinct putative mechanisms of action of a methylphenidate (MPH) and b amphetamine (AMF) at the dopamine synapse. VMAT2 vesicular monoamine transporter 2.



ADHD is one of the most common neurobehavioural disorders in childhood and impacts on many aspects of development, including social, emotional and cognitive functioning, in the home and school environment. It exists across different cultures, has a significant global impact, and should be diagnosed and effectively treated whenever it occurs (Remschmidt 2005).

### **1.1.3 ADHD treatment**

There is general agreement that a comprehensive, multimodal treatment plan should be developed by the clinician, patient and family working closely together. In this plan, psychoeducation, parent/caregiver management training, behavioural and educational intervention, and medications are balanced to create the optimum treatment paradigm for each individual with ADHD (Taylor, Dopfner et al. 2004, Helsedirektoratet 2005, Pliszka 2007, Pliszka 2007, National Institute for Mental Health and Clinical Excellence 2009, Wolraich, Brown et al. 2011, Hodgkins, Shaw et al. 2012, Helsedirektoratet 2014).

#### **1.1.3.1 Pharmacological treatment**

In severe cases (except preschoolers), medication may be the first line of treatment. Methylphenidate (MPH) is the most used drug for ADHD. In clinical practice a trial with stimulants is indicated in children with ADHD who show symptoms that are sufficiently severe to cause impairment at home and at school (Zeiner, Bryhn et al. 1999). NICE clinical guideline (2008) recommended that *“Depending on a range of factors such as presence of coexisting conditions, side effects and patient preference, the child or young person may be offered methylphenidate, atomoxetine or dexamphetamine”*. MPH is available in immediate-release preparations, which should be given in two or three divided doses, or modified-release preparations, which should be given as a single dose in the morning. Common adverse events of MPH treatment are insomnia, loss of appetite, stomach pain and headache, and a regular monitoring of MPH treatment is required (Graham and Coghill 2008, Graham, Banaschewski et al. 2011).



### **1.1.3.2 Non-pharmacological treatment**

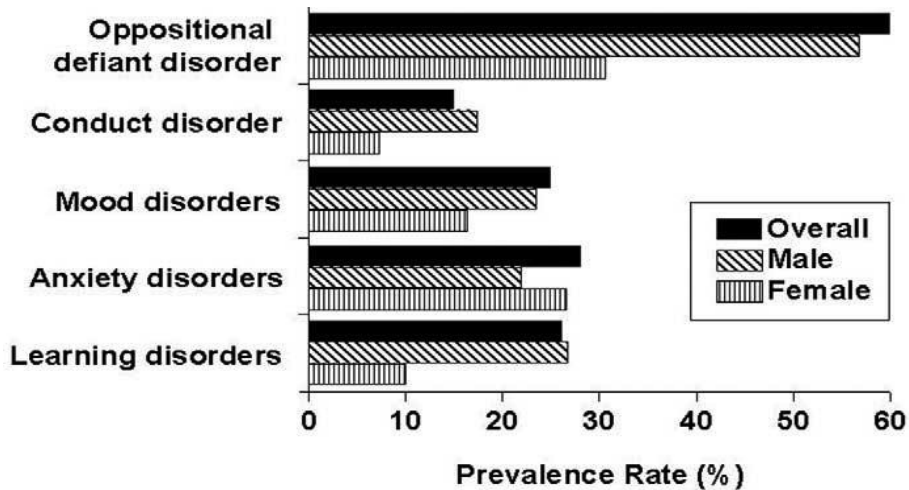
Neurofeedback is a non-invasive, alternative or complementary treatment for ADHD (Arns, Drinkenburg et al. 2012, Duric, Assmus et al. 2012, Arns, Heinrich et al. 2014, Gevensleben, Kleemeyer et al. 2014, Holtmann, Sonuga-Barke et al. 2014). It is a type of biofeedback that uses real-time displays of brain activity – most commonly EEG, to teach self-regulation of brain function. Neurofeedback is commonly provided using video or sound, with positive feedback for desired brain activity (one learns to enhance the EEG desired frequencies) and negative feedback for brain activity that is undesirable (to suppress the undesired frequencies). Quantitative EEG (Q-EEG) has been used in ADHD assessment and developing of models of ADHD. Children with ADHD often have too many (excess) slow theta brain waves and decreased alpha/beta frequencies (Monastra 2008, Ogrim, Kropotov et al. 2012, Arns, Conners et al. 2013). Treatment with a high-protein, low carbohydrate and sugar-free diet, has been tried in children and adolescents with ADHD and positive effects and improved learning were found. Sonuga-Barke et al (2013) undertook meta-analyses of the efficacy of dietary (restricted elimination diets, artificial food color exclusions, and free fatty acid supplementation) and psychological (cognitive training, neurofeedback, and behavioral interventions) ADHD treatments. The authors concluded that nonpharmacological treatments are available for ADHD, although their efficacy remains uncertain (Sonuga-Barke, Brandeis et al. 2013). A recent study (Cortese, Ferrin et al. 2015), performed meta-analyses of randomized controlled trials to examine the effects of cognitive training on ADHD symptoms, neuropsychological deficits, and academic skills in children/adolescents with ADHD. The authors concluded that despite improving working memory performance, cognitive training had limited effects on ADHD symptoms according to assessments based on blinded measures.

### **1.1.5 ADHD and comorbidity**

Comorbidity can be defined as two or more diseases occurring in the same individual. ADHD is often comorbid with other psychiatric disorders/conditions and more unspecific psychosocial problems. The most common comorbidities are oppositional defiant disorder (40-60%), anxiety (25-40%), and mood disorders (20%) (Salmeron 2009). Furthermore, autism spectrum disorder (ASD) and Tourette Syndrome (TS), cerebral palsy are also well

known (Bjorgaas, Hysing et al. 2012, Suren, Bakken et al. 2012). The prevalence rates of common comorbid diagnoses of childhood ADHD and how these diagnoses are affected with respect to gender are illustrated in figure 5 (Biederman, Faraone et al. 1996, Pliszka 1998, Spencer, Biederman et al. 1999, Biederman, Monuteaux et al. 2005).

**Figure 5.** Approximate prevalence of comorbid diagnoses in children with ADHD.



The MTA Study (1999) found that of 579 children with ADHD-C, 40% had ODD, 34% anxiety disorder, 14% conduct disorder, 12 % mania/hypomania and 11% tic disorder, (table 1)

**Table 1. ADHD and comorbidities (The MTA Cooperative Group 1999)**

Comorbidities, No (%)	N = 579 (100%)
Anxiety disorder	194 (33.5)
Conduct disorder	83 (14.3)
Opositional-defiant disorder	231 (39.9)
Affective disorders	22 (3.8)
Tic disorder	63 (10.9)
Mania/hypomania	13 (2.2)
Other (eg. Bulimia, enuresis)	1 (0.2)

Gillbert (2010) pointed out that co-existence of disorders including ADHD, oppositional defiant disorder, tic disorder, developmental coordination disorder, and autism spectrum disorder and sharing of symptoms across disorders (sometimes referred to as comorbidity) is the rule rather than the exception in child psychiatry and developmental

medicine. He suggested an acronym ESSENCE that refers to Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (Gillberg 2010). It is a term he has coined to refer to the reality of children (and their parents) presenting in clinical settings with symptoms of impairment before age 3 (-5) years in the fields of (a) general development, (b) communication and language, (c) social inter-relatedness, (d) motor coordination, (e) attention, (f) activity, (g) behavior, (h) mood, and/or (i) sleep. Major problems in at least one ESSENCE domain before age 5 years often signals major problems in the same or overlapping domains years later. Some preschool children have impairing symptoms belonging to different diagnostic categories, but not necessarily exceeding the diagnostic threshold. ADHD symptoms may be part of a broader clinical picture, and a broad perspective and teamwork are required.

## **1.2 Epileptic seizure and epilepsy**

### **1.2.1 Definition of epileptic seizure and epilepsy**

According to the 2005 proposal from the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (Fisher, van Emde Boas et al. 2005) an epileptic seizure (SZ) is a: *“transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain”*, and epilepsy is a *“disorder of the brain characterized by an predisposition to generate SZ and by the neurobiologic, cognitive, psychological, and social consequences of this condition*. The definition of epilepsy requires the occurrence of at least one SZ, but it is most often practically applied as having two unprovoked seizures >24 h apart. The ILAE Commission on Epidemiology and Prognosis (1993) defined epilepsy as two or more SZs occurring at least 24 hours apart, and unprovoked by any immediate identifiable cause (Commission on Epidemiology and Prognosis International League Against Epilepsy 1993). The epilepsy was defined as *active* if at least one SZ had occurred during the last 5 years, regardless of antiepileptic drug (AED) treatment, and *refractory* if the patient continued to experience seizures during the last year of follow-up, despite a previous adequate trial of more than two appropriately selected AEDs. The last proposal from ILAE suggested a practical clinical definition of epilepsy (Fisher, Acevedo et al. 2014). *“Epilepsy was defined conceptually in 2005 as a disorder of the brain*

*characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having two unprovoked seizures >24 h apart. The ILAE accepted recommendations of a task force altering the practical definition for special circumstances that do not meet the two unprovoked seizures criteria. The task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals who either had an age dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last 10 years and off antiseizure medicines for at least the last 5 years. "Resolved" is not necessarily identical to the conventional view of "remission or "cure." Different practical definitions may be formed and used for various specific purposes. This revised definition of epilepsy brings the term in concordance with common use.*

### **1.2.2 Classification of epileptic seizures, epilepsies and epileptic syndromes**

The most used classifications in clinical praxis and in the scientific publications are proposals for classification of SZs (Commission on Classification and Terminology of the International League Against Epilepsy 1981) (Table 2), and the classification of epilepsies and epileptic syndromes (Commission on Classification and Terminology of the International League Against Epilepsy 1989) (Table 3). SZs are classified as partial, generalized or unclassified according to clinical and EEG (ictal and interictal) manifestations. Partial SZs are those in which, in general, the first clinical and EEG changes indicate initial activation of a system of neurons limited to a part of one cerebral hemisphere. Partial SZs are divided into: A. Simple partial SZs (consciousness not impaired), 1. With motor sign; B. Complex partial SZs (with impairment of consciousness; may sometimes begin with simple symptomatology); C. Partial SZs evolving to generalized SZs (this may be generalized tonic-clonic, tonic or clonic) (above the discharges becomes secondarily and rapidly generalized). Generalized SZs are those in which the first clinical changes indicate initial involvement of both hemispheres. Consciousness may be impaired and this impairment may be the initial manifestation. Motor manifestations are bilateral. The ictal EEG patterns initially are bilateral and presumably

reflect neuronal discharges, which are widespread in both hemispheres. Generalized SZs include absence SZs, atypical absence SZs, myoclonic SZs, clonic SZs, tonic SZs, tonic-clonic SZs and atonic SZs. A simplified classification of SZs is presented in table 4. Syndromic classification (ILAE, 1989) of epilepsies and epileptic syndrome are categorized as 1. Localization related (focal, local, partial) epilepsies and syndromes. 2. Generalized epilepsies and syndromes. 3. Epilepsies and syndromes undetermined as to whether they are focal or generalized. 4. Special syndromes. Depending on aetiology the localization-related and generalized epilepsies and epilepsy syndrome are classified as symptomatic, cryptogenic and idiopathic. In idiopathic epilepsies the aetiology is presumed to be genetic. In symptomatic epilepsies there is an identified cause (e.g. a brain tumor or traumatic brain injury). In cryptogenic cases the cause of epilepsy is unknown, but presumed to be symptomatic.

Shorvon (2011) proposed a classification (database) of the etiologies of epilepsy into four main categories 1. Idiopathic epilepsy— an epilepsy of predominately genetic or presumed genetic origin in which there is no gross neuroanatomic or neuropathologic abnormality. Included here are epilepsies of presumed multigenic or complex inheritance, but for which currently the genetic basis has not been elucidated. 2. Symptomatic epilepsy— an epilepsy of an acquired or genetic cause, associated with gross anatomic or pathologic abnormalities, and/or clinical features, indicative of underlying disease or condition. We thus include in this category developmental and congenital disorders associated with cerebral pathologic changes, whether genetic or acquired (or indeed cryptogenic) in origin. Also included are single gene and other genetic disorders in which epilepsy is only one feature of a broader phenotype with other cerebral or systemic effects. 3. Provoked epilepsy— an epilepsy in which a specific systemic or environmental factor is the predominant cause of the seizures and in which there are no gross causative neuroanatomic or neuropathologic changes. Some “provoked epilepsies” will have a genetic basis and some an acquired basis, but in many no inherent cause can be identified. The reflex epilepsies are included in this category (which are usually genetic) as well as the epilepsies with a marked seizure precipitant. 4. Cryptogenic epilepsy— an epilepsy of presumed symptomatic nature in which the cause has not been identified. The number of such cases is diminishing, but currently this is still an important category, accounting for at least 40% of adult-onset cases of epilepsy (Shorvon 2011).

**Table 2. Classification of epileptic seizure (ILAE, 1981)**

<p><b>Partial seizures (beginning locally)</b></p> <ul style="list-style-type: none"> <li>- <b>Simple partial seizures (without impaired consciousness)</b> <ul style="list-style-type: none"> <li>with motor symptoms</li> <li>with somatosensory or special sensory symptoms</li> <li>with autonomic symptoms</li> <li>with psychological symptoms</li> </ul> </li> <li>- <b>Complex partial seizures (with impaired consciousness)</b> <ul style="list-style-type: none"> <li>simple partial onset followed by impaired consciousness</li> <li>impaired consciousness at onset</li> </ul> </li> </ul> <p><b>Partial seizures evolving into secondary generalized seizures</b></p>
<p><b>Generalized seizures (convulsive or non-convulsive)</b></p> <ul style="list-style-type: none"> <li>- <b>Absence seizures</b> <ul style="list-style-type: none"> <li>typical</li> <li>atypical</li> </ul> </li> <li>- <b>Myoclonic seizures</b></li> <li>- <b>Clonic seizures</b></li> <li>- <b>Tonic seizures</b></li> <li>- <b>Tonic-clonic seizures</b></li> <li>- <b>Atonic seizures</b></li> </ul>
<p><b>Unclassified seizures</b></p>

**Table 3. Simplified classification of epileptic seizures**

<b>Partial seizures</b>	<b>Generalized seizures</b>
<ul style="list-style-type: none"> <li>- Simple – preservation of awareness</li> <li>- Complex – impairment of consciousness</li> <li>- Secondary generalized</li> </ul>	<ul style="list-style-type: none"> <li>- Absence</li> <li>- Myoclonic</li> <li>- Tonic-clonic</li> <li>- Tonic</li> <li>- Atonic</li> </ul>

**Table 4. Classification of epilepsies and epileptic syndromes (ILAE, 1989)**

<p><b>Localization-related (focal, local or partial) epilepsies and syndromes</b></p> <ul style="list-style-type: none"> <li>- <b>Idiopathic epilepsy with age-related onset</b> benign childhood epilepsy with centrotemporal spikes childhood epilepsy with occipital paroxysms</li> <li>- <b>Symptomatic epilepsy</b></li> </ul>
<p><b>Generalized epilepsies and syndromes</b></p> <ul style="list-style-type: none"> <li>- <b>Idiopathic epilepsy with age-related onset (listed in order of age onset)</b> benign neonatal familial convulsions benign neonatal non-familial convulsions benign myoclonic epilepsy in infancy childhood absence epilepsy (formerly known as pyknolepsy) juvenile myoclonic epilepsy (formerly known as impulsive petit mal) epilepsy with generalized tonic-clonic seizures on awaking</li> <li>- <b>Other idiopathic epilepsy</b></li> <li>- <b>Idiopathic or symptomatic epilepsy (listed in order of age onset)</b> West syndrome (infantile spasms) Lennox-Gastaut syndrome( childhood epileptic encephalopathy) epilepsy with myoclonic-astatic seizures epilepsy with myoclonic absence seizures</li> <li>- <b>Symptomatic epilepsy</b></li> <li>- <b>Non-specific syndromes</b> early myoclonic encephalopathy early infantile epileptic encephalopathy</li> <li>- <b>Specific syndrome (epileptic seizures as a complication of a disease, such as phenylketonuria, juvenile Gaucher’s disease oryndrome Lundborg’s progressive myoclonic epilepsy)</b></li> </ul>
<p><b>Epilepsies and syndromes with both generalized and focal seizures</b></p> <ul style="list-style-type: none"> <li>- <b>Neonatal seizures</b></li> <li>- <b>Severe myoclonic epilepsy in infancy</b></li> <li>- <b>Epilepsy with continuous spike waves during slow-wave sleep</b></li> <li>- <b>Acquired epileptic aphasia (Landau-Kleffner syndrome)</b></li> </ul>
<p><b>Epilepsies without unequivocal generalized or focal seizures</b></p> <ul style="list-style-type: none"> <li>- <b>Situation-related seizures</b> febrile convulsions seizures related to other identifiable situations, such as stress, hormonal changes, drugs, alcohol withdrawal or sleep deprivation</li> <li>- <b>Isolated apparently unprovoked epileptic events</b></li> <li>- <b>Epilepsies characterized by specific modus of seizure precipitation</b></li> </ul>
<p><b>Chronic progressive epilepsy partialis continua of childhood</b></p>

### **1.2.3 Epilepsies which often occur in school age**

Of the localization related epilepsies and syndromes, Benign childhood epilepsy with centrotemporal spikes (BECTS) and childhood idiopathic occipital epilepsy occur most frequently. Childhood idiopathic occipital epilepsy is later subdivided into two forms: early form Panayiotopoulos syndrome and late form (Gastaut). Of the generalized epilepsies and syndromes, Childhood absence epilepsy (CAE) and Juvenile myoclonic epilepsy (JME) often occur (Park, Shahid et al. 2015).

#### **1.2.3.1 Benign childhood epilepsy with centrotemporal spikes (BECTS)**

BECTS is the most common epilepsy of the idiopathic localization related epilepsies and syndromes, accounting for about 15% of children with epilepsy (Park, Shahid et al. 2015). The "benign" nature is thought to be due to the absence of focal neurological deficits, sensitivity to AEDs, and spontaneous resolution by age 16 years with many children requiring no treatment. BECTS is characterized by brief, simple, partial, hemifacial motor SZs, frequently having associated somatosensory symptoms that have a tendency to evolve into generalized tonic-clonic SZs. Both SZs types are often related to sleep. Onset occurs between the ages of 3 and 13 years (peak 9–10 years). Genetic predisposition is frequent, and there is a male predominance. The EEG has blunt high voltage centrotemporal spikes (rolandic spikes) often followed by slow waves that are activated by sleep and tend to spread or shift from side to side. Some patients have only short periods of SZ activity and unimpaired mental development, others a long-lasting epilepsy characterized by highly different SZ symptoms, massive epileptiform activity on EEG and persistent mental handicap after remission of epilepsy (Aicardi 2000, Hahn, Pistohl et al. 2001). Some patients sometimes has an atypical form, which offers a broad spectrum and a variable clinical course. In the extreme course it can evolve into Landau Kleffner Syndrome (LKS) or continuous spike and waves during sleep (CSWS). LKS is an acquired epileptic aphasia disorder in which children, usually 3-8 years of age who have developed age-appropriate speech, experience language regression with verbal auditory agnosia, abnormal epileptiform activity, behavioral disturbances, and sometimes overt SZs. CSWS is an age-related epileptic encephalopathy that presents with neurocognitive regression, SZs, and an EEG pattern of electrical status epilepticus during sleep. Patients usually present around 5 years of age with infrequent



nocturnal unilateral motor SZs that progress within 1 to 2 years to a severe epileptic encephalopathy with frequent SZs of different types, marked neurocognitive regression, and an almost continuous spike-wave EEG pattern during slow-wave sleep (Loddenkemper, Fernandez et al. 2011).

#### **1.2.3.2 Panayiotopoulos syndrome**

Panayiotopoulos syndrome (Panayiotopoulos, Michael et al. 2008, Park, Shahid et al. 2015) is a benign focal epilepsy that primarily occurs between ages 3 and 6 years. The clinical hallmark of PS is emesis (70%-80% of seizures). The SZs are mostly nocturnal and consciousness is retained. The duration of emesis is typically over 6 minutes, with around half lasting over 30 minutes. In 90% of patients, emesis is followed by eye deviation or opening (60%-80%), visual hallucinations, and generalized or hemi-convulsions. Two-thirds occur in sleep, during which time the frequency of EEG spikes are also increased. EEG shows predominantly occipital or multifocal spikes. Prognosis is excellent as in BECTS with no evidence that long-term prognosis is worse in untreated patients. The majority of patients have less than 10 SZs in total, and an AED may not be indicated. One-tenth of children with PS have BECTS or develop it later before all SZs remit by ages 15-16 years.

#### **1.2.3.3 Late onset idiopathic occipital epilepsy (Gastaut)**

This is a relatively rare form of pure occipital epilepsy, which accounts for about 2%-7% of benign childhood focal SZs with the mean age of onset between 8 and 11 years (Park, Shahid et al. 2015). SZs are occipital in origin and primarily manifest as elementary or formed (patients can delineate the nature of the object that they "see") visual hallucinations, sudden blindness, or both. The SZs are brief, frequent, and diurnal. These may be followed by hemi-sensory, motor signs or unresponsiveness. Approximately one-third of the patients can have a severe postictal, prolonged headache at times associated with nausea or vomiting with additional migrainous features. In fact, 19% of the patients have a family history of migraine headaches. The headache occurs immediately or within 10 minutes after visual hallucinations. Consciousness is intact during the visual hallucinations or blindness. The majority of the untreated patients experience visual SZs that range in frequency from several per day to a couple per month. However, SZs propagation to convulsions is less frequent.

Interictal EEG is normal; however, unilateral or bilateral, synchronous or asynchronous, spike-wave complexes occur only with the eyes closed. Visual fixation suppresses the discharges, even in complete darkness as long as the patient can visually fixate on an object, such as a dot of red light. The clinical course is considered benign.

#### **1.2.3.4 Childhood absence epilepsy (CAE)**

Childhood absence epilepsy is an age-dependent, idiopathic, generalized epilepsy with a characteristic absence SZs appearance. Absence SZs are usually brief in duration (4-20 seconds), but can occur frequently (10 to 100 times per day) with abrupt onset/offset associated with impaired consciousness. Immediately after the SZs the child resumes pre-absence activity (Park, Shahid et al. 2015). Age of onset is 4-10 years with peak incidence at 5-6 years. Prevalence is 8%-15% of all childhood epilepsies. Impairment of consciousness as characterized by loss of awareness, unresponsiveness, and behavioral arrest is an essential feature of CAE. About two-thirds of these children have associated repeated blinking, lip smacking, picking/rubbing, head retraction, trunk arching, or twitching of the eyelids, eyebrows, or mouth. Some slumping of posture can be seen due to decreased axial muscle tone, but falls due to atonia do not occur. Pallor is common, but urinary incontinence is exceptional. About one-third of the children have at least one GTC SZs. In 83% of the patients, SZs are induced by unnatural hyperventilation and not associated with physiologic hyperventilation. Differential diagnosis includes inattention or daydreaming. Ictal EEG of CAE is easily recognized. It is characterized by high-amplitude, bisynchronous, and symmetric discharges of rhythmic 3 Hz "spike-and-slow" wave complexes that start and end abruptly. Interictally, paroxysmal activity consisting of fragments of generalized spike-wave discharges can be seen in up to 92% of patients. EEG abnormalities may persist into adulthood after resolution of seizures. Prognosis is excellent for remission of SZs (56%-84%) and AED withdrawal (Callenbach, Bouma et al. 2009).

#### **1.2.3.5 Juvenile myoclonic epilepsy (JME)**

JME, also a genetically mediated generalized epilepsy, comprises 5%-10% of all epilepsy syndromes, and peaks in early adolescence between ages 13 and 15 years. Multiple SZ types may be present in a patient. SZs typically occur after awakening in the mornings.

Patients often complain of suddenly dropping objects, morning clumsiness, or jitters, which are, in fact, myoclonic SZs (Park, Shahid et al. 2015). Patients have myoclonic jerks (97%), GTC SZs (79%), absence SZs (33%), or all three types (21%). Sleep deprivation and fatigue are the most common precipitating factors. Photic stimulation during EEG may induce an electrographic SZ in up to one-half of patients "termed photoconvulsive response". SZs are sensitive to valproate, rendering at least 80% of patients SZ free. Valproate may not be a drug of choice for an adolescent girl due to, among other risks, its teratogenic effect on the fetus. JME is thought to be a lifelong condition even with the use of AEDs.

### **1.3 Electroencephalogram (EEG), interictal epileptiform discharges (IED)**

EEG in humans was developed by the German psychiatrist Hans Berger who recorded the first human EEG in 1924 and published his discovery in 1929 (Über das Elektrenenkephalogram des Menschen) (Berger 1929). An EEG recording detects electrical brain activity using small, flat metal discs (electrodes) filled with a conductive gel, attached to a person's scalp. The brain waves are recorded and then amplified so that they can be more easily seen and examined. The International 10-20 system for electrode placement is illustrated in figure 6; Brain electrical activity in figure 7; EEG pattern in figure 8.

EEG is an important examination most used in the diagnosis and management of epilepsies, but, it can also be used to examine a variety of brain functions including sleep (the different stages of sleep) and different neuropsychiatric disorders. Since Gibbs and colleagues discovered spike and wave discharges in epilepsy in 1935, the EEG has been used to diagnose and manage epilepsy (Gibbs, Davis et al. 1935). EEG continues to play a pivotal role. Epileptiform activity, the interictal spike remain the hallmark of epilepsy, demonstrating cortical hyperexcitability and hypersynchrony, and is present in the "normal" interictal state. The definition of epileptiform activity is given in Chatrian's glossary of terms as *"distinctive waves or complexes, distinguished from background activity and resembling those recorded in a proportion of human subjects suffering from epileptic disorders"*(Chatrian (Chairman), Bergamini et al. 1974). These waves or complexes can appear as isolated focal spikes or sharp waves, generalized polyspikes, spike and wave or paroxysmal fast activity, and sometimes as abrupt rhythmic evolution of the background that heralds seizures. Spike:

an EEG transient (20 to 70 ms). Spikes are usually diphasic, i.e. composed of a negative and a positive deflection. Spike wave complex: a spike followed by a wave with the same polarity. Depending on the number of cycles per second, they are referred to as slow spike-waves (2.5 c/s or less) or spike-waves (3c/s or faster). Sharp wave: a wave of great amplitude lasting between 70 and 200 ms, to be distinguished from spikes which are of shorter duration. Sharp-slow complex: a sequence of two or more slow waves, generally of higher amplitude. Polyspike complex: a sequence of two or more spikes. Polyspike wave complex: a sequence of two or more spikes followed immediately by one or more slow waves with the same polarity. IEDs defined as spikes or spike-wave complexes, isolated or occurring serially (in runs) occur without evident clinical signs of epileptic seizure. The IEDs index may be estimated, in wakefulness and in sleep, as the percentage of time in five categories (0%, <1%, 1-10%, ≥10-50% and ≥50%) (Ebus, Arends et al. 2012). The spike index has been applied to quantify “interictal nocturnal focal epileptiform activity”, which is suggested as a general term for the epileptiform activity enhanced by sleep. It was Larsson and colleagues (2009) who suggested the definition of spike index that gives a semiautonomic and relatively robust algorithm for assessment (Larsson, Wilson et al. 2009).

### **1.3.1 IEDs, transient cognitive impairment (TCI) and antiepileptic drugs (AEDs)**

IEDs occur more often in patients with epilepsy than in healthy children. Ten years after Berger published his EEG discovery, Schwab (Schwab 1939, Schwab 1949) observed disruption in responding that coincided with epileptiform discharges on EEG. He proposed that cognitive processing can be temporarily disrupted by IED, the isolated spike and sharp wave electrical discharges that are generated by epileptogenic cells even when people with epilepsy are not having seizures. Aarts and colleagues (1984) labeled this phenomenon “transitory cognitive impairment”(Aarts, Binnie et al. 1984), and it has also been referenced by the similar name, “transient cognitive impairment” (Aldenkamp and Arends 2004). Several authors have provided selective review of the TCI literature (Kasteleijn-Nolst Trenite 1995, Aldenkamp 1997, Aldenkamp and Arends 2004).

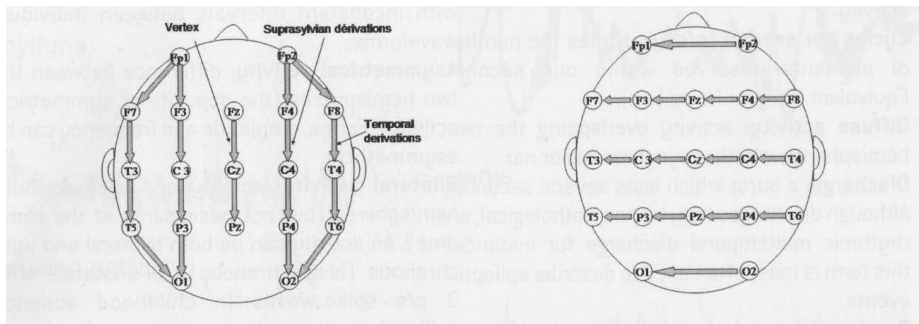
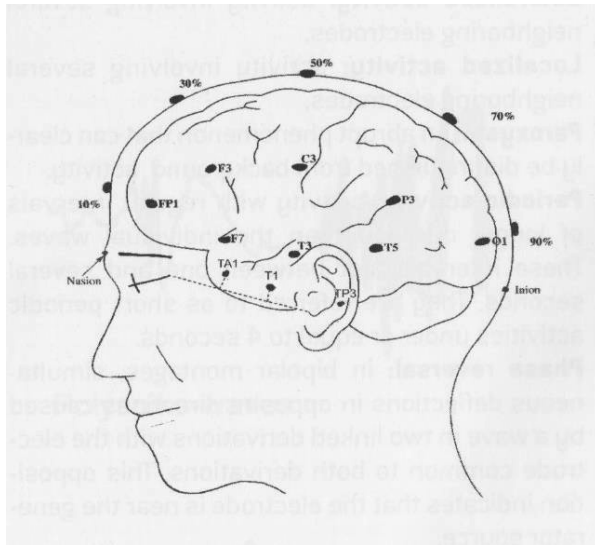
Fastenau (2011) summarized correlation between IED and cognition in people with epilepsy. *“The relationships between IEDs and cognitive functioning can be detected even when the two are measured a day, 2-3 months, or several years apart. The effects are more*

readily detected when IEDs last 3 seconds or longer and during tasks that are sufficiently complex to be taxing to the individual. TCI occurs in the context of both focal and generalized IEDs. When the IEDs are focal, the cognitive deficits tend to correspond with the focus (e.g., linguistic disruption or errors with left hemisphere discharges in right handers. Generalized symptomatic syndrome appears to carry the most risk for the TCI (especially in the form of slower processing); the risk and impact appear to be compounded disproportionately (compared to generalized idiopathic or localized syndromes) by frequent IEDs, AED polytherapy, and concomitant slow wave activity on the EEG. Relationships between IEDs on EEG and neuropsychological deficits in a non-simultaneous paradigm (especially with a latency of months or years) as well as stable cognitive deficits raised several possible explanations: This pattern could reflect the ongoing nature of the transient disruptions, cumulative effects of the IEDs over time, or an underlying pathology giving rise to both IEDs and also the cognitive difficulties.”(Fastenau 2011). AEDs are commonly used for treatment of epilepsy, and in general, IEDs are not considered an indication for AED treatment (Boutros 2009), although it may be considered in some cases (Laporte, Sebire et al. 2002, Pressler, Robinson et al. 2005, Nicolai, Ebus et al. 2012). However, AEDs are recommended in specific cases such as LKF syndrome or continuous spike and wave activity during slow-wave sleep (CSWS) (Mintz, Legoff et al. 2009, Bakke, Larsson et al. 2011, Larsson, Bakke et al. 2012, Van Bogaert, Urbain et al. 2012, Chen, Cai et al. 2015, Uliel-Sibony and Kramer 2015). Surgery has also been applied (Mikati and Shamseddine 2005). Different medications have been used to suppress IED on EEG: valproate (VPA), ethosuccinimide (ESM), lamotrigine (LTG), diazepam, clobazam, corticosteroids and levetiracetam (LEV).

Van Bogaert and coworkers (2012) reported that “*neurophysiological and functional neuroimaging evidence suggests that IED may impact cognition through either transient effects on brain processing mechanisms, or through more long-lasting effects leading to prolonged inhibition of brain areas distant from but connected with the epileptic focus (i.e. remote inhibition effect). Sustained IED may also impair sleep-related learning consolidation processes. Nowadays, the benefits of anti-epileptic treatment aimed at reducing IED are not established except in specific situations like epileptic particularly encephalopathies with CSWS. Well-designed pharmacological studies are still necessary to address this issue.*” (Van Bogaert, Urbain et al. 2012).

**Figure 6. The International 10-20 system for electrode placement**

(Luders and Noachtar 1994)



Fp2/Fpz/Fp1: frontal-polar (right/midline/left)

F4/Fz/F3: frontal (right/midline/left)

C4/Cz/C3: central (right/midline/left)

P4/Pz/P3: parietal (right/midline/left)

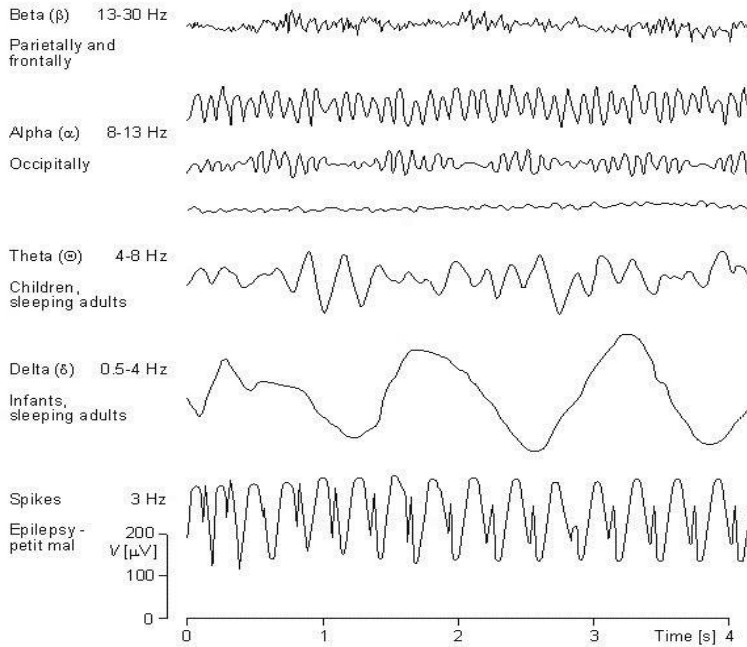
O2/Oz/O1: occipital (right/midline/left)

F8/F7: inferior frontal or anterior temporal (right/left)

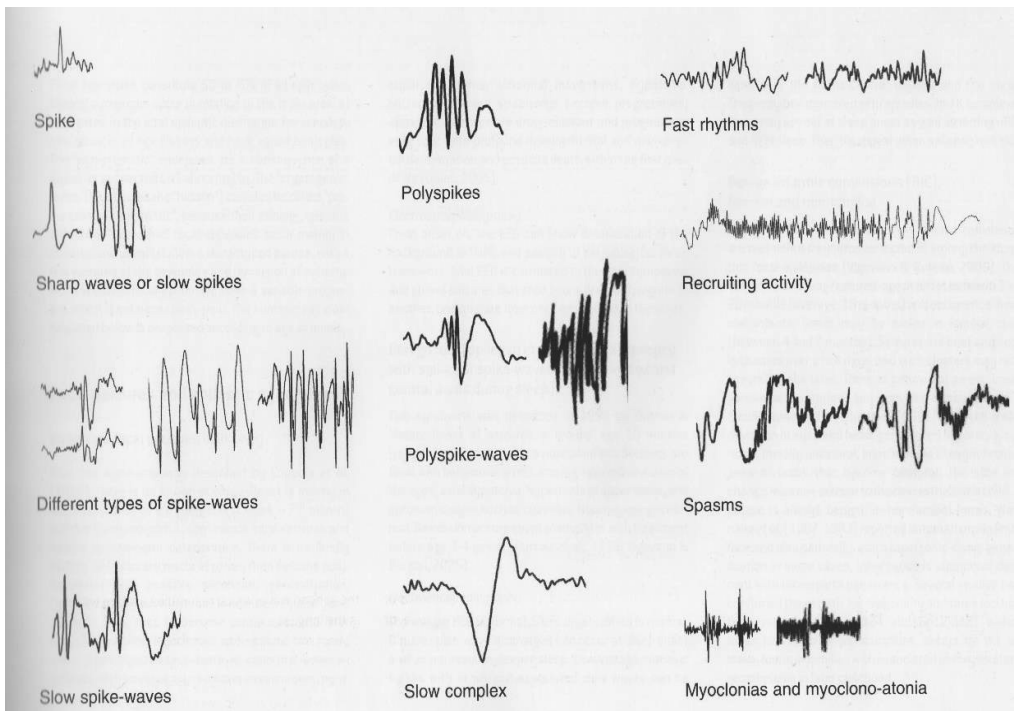
T4/T3: midtemporal (right/left)

T6/T5: posterior temporal (right/left)

**Figure 7. Brain electrical activity (Luders and Noachtar 1994)**



**Figure 8. EEG Patterns (Luders and Noachtar 1994)**



#### 1.4 IEDs and ADHD

IEDs suggestive of epilepsy are also found in normal children. A study from Sweden reported that 2.4 % (18 out of 743 otherwise healthy children) had IEDs during wakefulness and light sleep (Eeg-Olofsson, Petersen et al. 1971). One study (Capdevila, Dayyat et al. 2008) reported prevalence of IEDs (1.45%) (14 out of 970) in otherwise healthy children during sleep who conducted polysomnographic study. The largest study reported a rate of 3.5% (133 of 3724 children) in awake EEG; this study from Italy did not state if photic stimulation was used as an activation procedure (Cavazzuti, Cappella et al. 1980). A recent study from Germany reported the highest prevalence of IEDs in awake EEG, 6.5% (25 of 382 children who took an EEG and had minor head trauma) (Borusiak, Zilbauer et al. 2010).

From a clinical perspective the occurrence of IEDs in children with ADHD is even more controversial since a sample of clinicians is reluctant to use MPH in such cases. Studies of IEDs in patients with ADHD have revealed a higher rate of IEDs compared to normal controls. The prevalence of IEDs in ADHD varies from 4.8 to 15.4%, if awake EEG recording was used (Hemmer, Pasternak et al. 2001, Richer, Shevell et al. 2002, Holtmann, Becker et al. 2003), and between 17 to 53% if sleep EEG was used (Hughes, DeLeo et al. 2000, Silvestri, Gagliano et al. 2007, Millichap, Stack et al. 2011, Altunel, Altunel et al. 2013, Zaimoglu, Turkdogan et al. 2015) (Table 6). Holtman and colleagues (2003) found rolandic spikes in 5.6% of children with ADHD without epilepsy (Holtmann, Becker et al. 2003), which is higher than reported in normal children (Eeg-Olofsson, Petersen et al. 1971). They also found that children with rolandic spikes tended to exhibit more hyperactive-impulsive symptoms (Holtmann, Matei et al. 2006). On the other side, Hesdorffer and colleagues (2004) did not find rolandic spikes among 41 children with ADHD out of 106 children with incident unprovoked SZs and epilepsy (Hesdorffer, Ludvigsson et al. 2004). Hemmer and colleagues (2001) reported the highest prevalence (15.4%) of IED on awake routine EEGs in 234 children with ADHD for whom treatment with stimulant medications was planned (Hemmer, Pasternak et al. 2001).



**Table 5. IEDs in healthy children and in children with ADHD without epilepsy.**

Study	Year	Country	Group	Age	N	% IED awake	% IED sleep
<b>IEDs in healthy children</b>							
Eeg-Olofsson et al.	1971	Sweden	Healthy otherwise	1-15	743	2.4	8.7
Cavazzuti et al.	1980	Italy	Healthy	6-13	3724	3.5	
Okubo et al.	1994	Japan	Healthy	6-12	1057	5	
Capdevila	2008	USA	Healthy otherwise	5-8	970		1.5
Borusiak et al.	2010	Germany	Healthy	6-13	382	6.5	
<b>IEDs in children with ADHD</b>							
Hughes	2000	USA	ADHD	3-18	176		30
Hemmer et al.	2001	USA	ADHD	3-20	234	15.4	
Richer et al.	2002	Canada	ADHD	5-16	347	6.1	
Matoth et al.	2002	Israel	ADHD	5-16	126	4.8	
Castaneda-Cabrero	2003	Spain	ADHD		15	13	27
Holtmann et al.	2003	Germany	ADHD	2-16	483	5.6	
Bernal Lafuente	2004	Spain	ADHD	8	48		16.7
Silvestri et al.	2007	Italy	ADHD	6-12	42		53
Fonseca	2008	Brasil	ADHD	8-11	30	10	
Millichap et al.	2011	USA	ADHD		624		26.1
Kanazawa	2014	Japan	ADHD	6-20	145		22.1
Zaimoglu et al.	2015	Turkey	ADHD	6-13	148		26.4

### 1.5 Epilepsy in children with ADHD

We conducted a search in databases such as PubMed with keywords ADHD, epilepsy, and epileptiform discharges. We identified 30 studies discussing this association. Although ADHD is the most common neurobehavioral disorder in children, only a few publications have studied epilepsy in ADHD population and their relationships from this perspective (Ishii,

Takahashi et al. 2003, Wisniewska, Baranowska et al. 2007, Davis, Katusic et al. 2010). Two of them had small samples of ADHD patients i.e. 68 and 28 (Ishii, Takahashi et al. 2003, Wisniewska, Baranowska et al. 2007). The largest study that we found had 130 children with ADHD (Williams, Schulz et al. 2001), and reported a higher occurrence of epilepsy (2%) than expected in the general population (1%). A recent study compared the incidence and characteristic of epilepsy among population-based, research identified cohorts of children with (N=358) and without ADHD (N=728), based on medical record review to age 20. It found that cases with ADHD were 2.7 times more likely to have epilepsy than controls, had earlier SZ onset, and a trend toward more frequent SZs. The authors concluded that epilepsy in children with ADHD appeared to be more severe than in those without, and that clinicians appeared to be reluctant to diagnose and treat ADHD in children with epilepsy (Davis, Katusic et al. 2010). Methods and diagnostic criteria vary widely in studies investigating associations between epilepsy and ADHD, and considerable gaps remain in our knowledge regarding the extent of SZs and epileptic syndromes in children with ADHD.

In a Norwegian nationwide patient register study, for children aged 0 to 11 years, which contained diagnoses assigned by Norwegian specialist health services (hospitals and outpatients clinics), it was found that children with ADHD had comorbid diagnoses such as autism spectrum disorder (6.4%) and epilepsy (5.3%) (Suren, Bakken et al. 2012). The prevalence of autism spectrum disorders and ADHD varied between the counties, from 0.3% to 1.5% for autism spectrum disorders and from 1.1% to 3.5% for ADHD. The variations across counties in the prevalence of autism spectrum disorders and ADHD are most likely due to variations in diagnostic practices (Suren, Bakken et al. 2013).

ADHD and epilepsy may occur as comorbid conditions, and a number of studies in different study populations have indicated relationships between epilepsy and ADHD/ADHD symptoms (Oostrom, Schouten et al. 2002, Davies, Heyman et al. 2003, Dunn, Austin et al. 2003, Oostrom, Schouten et al. 2003, Dunn and Kronenberger 2005, Alexopoulos, Kotagal et al. 2006, Cornaggia, Beghi et al. 2006, Sherman, Slick et al. 2007, Davis, Katusic et al. 2010, Piccinelli, Beghi et al. 2010, Austin, Perkins et al. 2011, Ottman, Lipton et al. 2011, Reilly 2011, Suren, Bakken et al. 2012, Cohen, Senecky et al. 2013, Suren, Bakken et al. 2013)

**Table 6. Epilepsy in children with ADHD**

Study	Country	Study population	Age y	N	Epilepsy	%
Williams et al, 2001	USA	ADHD	4-16	130	3	2.3
Ishii et al, 2003	Japan	ADHD	4-19	68	5	7.3
Wisniewska et al, 2007	Poland	ADHD	7-13	28	2	7.1
Davis et al, 2010	USA	cohort with ADHD cohort without	<20	358 728	8 6	2.3 0.9
Suren et al, 2012	Norway	ADHD (Norwegian Patient Register),	0-11	6345	335	5.3

### 1.5 ADHD in patients with epilepsy

The possibility that children with epilepsy have a higher risk of having ADHD symptoms compared with the general pediatric population was reported by many publications (Dunn, Austin et al. 2003, Gillberg, Gillberg et al. 2004, Tan and Appleton 2005, Dunn, Austin et al. 2009, Kaufmann, Goldberg-Stern et al. 2009, Boyes 2010, Parisi, Moavero et al. 2010, Kang, Yum et al. 2015). Many studies vary in the diagnostic criteria used for ADHD or problems with attention (or for disorders of attention) in children with epilepsy. Patients with epilepsy could have attention problems but their symptoms are not present in this grade to allow ADHD diagnosis as a categorical disorder based on criteria from the DSM-IV and defined by symptoms and duration of illness and heterogenic aetiology. In comparison, attention is a neuropsychological construct that defines the processes involved in perception, selection, and maintaining or detaching from stimuli (Dunn and Kronenberger 2005). Sustained attention, selective attention, and divided attention were most often assessed in studies of children with epilepsy (Sanchez-Carpintero and Neville 2003). Sustained attention, usually defined by scores on a continuous performance task, was most consistently impaired in children with epilepsy.

The majority of studies have considered ADHD in patients who have been diagnosed with epilepsy (Dunn, Austin et al. 2003, Thome-Souza, Kuczynski et al. 2004, Dunn and

Kronenberger 2005, Cornaggia, Beghi et al. 2006, Hermann, Jones et al. 2007, Jones, Watson et al. 2007, Caplan, Siddarth et al. 2008, Austin, Perkins et al. 2011, Braakman, Vaessen et al. 2011), rather than the other way around. A similar finding of ADHD was reported in children (5-16 years of age) with complex partial seizures (25%) compared to a group with primary generalized epilepsy (26%) (Caplan, Arbelle et al. 1998). Dunn and colleagues (2003) reported in a study of 175 children with epilepsy without significant developmental delays, who had at least a 6-month history of epilepsy, that children with epilepsy had a higher risk for symptoms of ADHD than the general population. ADHD in children with epilepsy differed from other samples of children with ADHD by having a larger proportion of children with ADHD-I and by an equal incidence in males and females (Dunn, Austin et al. 2003). One study from Norway also reported that in a group of 362 children, 6-14 years, almost all with epilepsy and admitted to a tertiary epilepsy center, 20.4% had a certain diagnosis of ADHD, and 9.1% were suspected of having ADHD but not tested (Wannag, Eriksson et al. 2010). Clinical studies have suggested that the prevalence of ADHD in epilepsy patients may be as high as 30-40 %, with ADHD-I more common than ADHD-C (Dunn and Kronenberger 2005).

**Table 7. ADHD in epilepsy patients**

Study	Country	Study population	Age y	N	ADHD	%
Dunn et al. 2001	USA	Epilepsy at least 6 months	9-14	175	ADHD sympt.	38
Davies et al, 2003	UK	Epidemiological 10,316 cases with epi	5-15	25 complicated 42 uncomplcat.	ADHD	12 0
Hesdorffer et al. 2004	Iceland	a population-based case-control study of all newly diagnosed unprovoked SZs	3- 16	109 with SZs 218 controls	ADHD	41 18
Cohen et al. 2013	Israel	community-based primary care practice	6-13	Epilepsy patients	ADHD	27.7
Kim et al. 2014	Korea	BECTS cases		74, BECTS	ADHD	64.9
Kang et al. 2015	Korea	Newly and recently epilepsy patients	6-16	149 cases	ADHD	49.2

However, some studies claim that attention difficulties are not characteristic of schoolchildren with newly diagnosed idiopathic or cryptogenic epilepsy (Ostrom, Schouten et al. 2002), that behavioral problems are not persistent in the majority of these children (Ostrom, Schouten et al. 2003), and report a similar rate of ADHD in children with uncomplicated epilepsy as in the same-age general population (Davies, Heyman et al. 2003).

### **1.7 Follow-up studies**

The MTA study, a large multisite, randomized study of treatment for ADHD-C in 579 children without seizure disorders compared treatment with medication to behavior therapy or combination of both (The MTA Cooperative Group 1999). The study found that medication management, or behavior therapy, or their combination had the significant advantage over behavior therapy, and usual community care after 14 and 24 months follow-up. In contrast, the treatment groups did not differ significantly on any measure at 36 months (Jensen, Arnold et al. 2007). One explanation of this outcome is that some children with ADHD do have improvement in their symptoms that is likely based on brain maturation. ADHD is characterized by a delay in cortical maturation, most prominent in prefrontal regions. This is probably related to cognitive processes including attention and motor planning (Shaw, Eckstrand et al. 2007). Although ADHD is in some patients a relatively mild disorder and many children may outgrow ADHD, it is known that up to 60% of children with ADHD continue to have significant symptoms as adults (Biederman and Faraone 2004, Harpin 2005). Hinshaw and Arnold (2015) highlight the key paradox that whereas ADHD clearly responds to medication and behavioral treatment in the short term, evidence for long-term effectiveness remains elusive. They emphasize a call for greater understanding of relevant developmental processes in the attempt to promote optimal, generalized, and lasting treatments for this important and impairing neurodevelopmental disorder (Hinshaw and Arnold 2015)

Barkley and colleagues (2002) suggested that previous follow-up studies that relied on self-reports might have substantially underestimated persistence of ADHD into adulthood. The apparent prognosis of ADHD depends on what definition of persistence one

uses (Biederman, Mick et al. 2000, Barkley, Fischer et al. 2002). Faraone and coworkers (2006) analyzed data from published follow-up studies, and examined the persistence of ADHD into adulthood. As expected, studies have shown a lower rate of ADHD symptoms. When they define those meeting only the full criteria for ADHD as having 'persistent ADHD', the rate of persistence is low, approximately 15% at age 25 years. But when more unspecific definitions of persistence are used, such as cases consistent with the DSM-IV' definition of ADHD in partial remission, the rate of persistence is much higher, approximately 65%. Their results show that estimates of ADHD's persistence rely heavily on how one defines persistence. Yet, regardless of definition, their analyses show that evidence for ADHD lessens with age. More work is needed to determine if this reflects true remission of ADHD symptoms or is due to developmental insensitivity of diagnostic criteria for the disorder (Faraone, Biederman et al. 2006).

#### **1.7.1 Follow-up of ADHD with comorbid epilepsy/IEDs and the use of MPH**

Short-term effects of MPH have been documented with at least 70% response to treatment with an effect size of 0.8 to 1 on rating scales looking at core symptoms (Harpin 2008). Long-term effects of MPH are not well documented despite their long history as treatment for ADHD. The medication is known to be effective over at least 2 years, but long-term studies evaluating pharmacological effects regarding function and impairment are still needed.

Several studies have reported that MPH is safe to use in both children with ADHD with well controlled epilepsy (Feldman, Crumrine et al. 1989, Gross-Tsur, Manor et al. 1997, Kaufmann, Goldberg-Stern et al. 2009), and difficult to treat epilepsy (Koneski, Casella et al. 2011, Brunklaus, Dorris et al. 2013, Fosi, Lax-Pericall et al. 2013, Santos, Palmiini et al. 2013), and that 61-73% of children with epilepsy had benefit from MPH. One study reported that the use of a combination of behavioral management and MPH 0.3-1mg/kg/day for 3 months improved ADHD symptoms in 61% of 18 patients with learning disability and refractory epilepsy (Fosi, Lax-Pericall et al. 2013). A recent study (2015) reported that MPH improves the quality of life of children and adolescents with ADHD and difficult-to-treat epilepsies. The study was an open-label, noncontrolled trial with intention-to-treat analysis following 30 patients for 6 months. Subjects received MPH following 3 months of baseline, during which

AEDs were adjusted. Their epilepsy, ADHD, and quality-of-life variables were assessed. Only one patient withdrew because of SZ worsening. The authors concluded that these preliminary data suggest that MPH treatment is safe and effective in patients with ADHD and difficult-to-treat epilepsies, positively impacting on quality-of-life scores (Radziuk, Kieling et al. 2015). Graham and colleagues (2011) reported that preliminary evidence for MPH supports efficacy on ADHD symptoms and a low SZ risk in patients with infrequent SZs, and that studies in children with more active epilepsy seem justified (Graham, Banaschewski et al. 2011).

The SZ risk in children with ADHD with IEDs, and without SZs has been discussed in some publications. Hemmer and coworkers (2001) investigated the seizure risk in non-epileptic patients with ADHD who used stimulants, were diagnosed between 1993 and 1998, and were followed either by office visit or by telephone in 1999. They found that 3 out of 30 patients with IED had a SZs during follow-up. The patients had long latencies to SZ occurrence, (10 months, 14 months and 3 years). They concluded that epileptiform EEG in patients with ADHD was suggested to predict considerable risk for the eventual occurrence of SZs (Hemmer, Pasternak et al. 2001). In contrast, another study, Richer and coworkers (2002) examined 347 children with ADHD with one routine EEG and found IEDs in 6.1%. The study group was formed from all patients referred to a single, community-based pediatric neurologist between January 1999 and December 1999 inclusive. They found no clear association between IEDs and the development of SZs (Richer, Shevell et al. 2002). In their study, 3 of the 21 children with IED developed a seizure disorder. The diagnosis of a seizure disorder was already suspected in 2 of the 3 children before the EEG recording at the time of the initial clinical evaluation. The remainder (18/21) had no recorded SZs despite observed epileptiform abnormalities. One study examined the use of MPH for ADHD in patients with epilepsy or EEG abnormalities. Patients with ADHD and active SZs (n=57) and patients with ADHD and EEG abnormalities (n=62), 6-16 years of age, were included in the study. A subgroup of 15 nonepileptic patients had epileptiform EEG at baseline and none of them had a seizure during the study period of one year (Gucuyener, Erdemoglu et al. 2003).

## 2. AIMS OF THE STUDY

During the 6-year period between January 1 2000 and December 31 2005, we carried out a study on all children with first referral for ADHD to our clinic at Stavanger University Hospital, Department for Child and Adolescent Psychiatry. In the assessment, one awake EEG was carried out when possible.

The study was initiated to examine relationships between ADHD, epilepsy and the occurrence of IEDs on EEG. In addition, we studied the clinical course of children with ADHD with and without IED, during a 2 year follow-up in order to estimate whether it is safe (SZ risk) to use MPH, and the use of AEDs. Our objectives were:

1) Estimate the occurrence of epilepsy in a large representative ADHD population. Investigate the clinical characteristics of epilepsy in children with ADHD and compare them with the occurrence of epilepsy and clinical characteristics of epilepsy in the general pediatric population. The clinical characteristics of children with ADHD, with and without epilepsy, and the initial use of MPH were analyzed.

2) Estimate the occurrence of IEDs on awake EEG in all children who performed a routine EEG at baseline, and compare it to the occurrence of IEDs in healthy children. We also compared clinical correlates of patients with and without IEDs.

3) Evaluate the 2-years clinical course of children with and without IEDs and examine whether it is safe to use MPH in children with IEDs (with and without previous epilepsy).

We formulated the following hypotheses:

1. Children with ADHD more often have comorbid epilepsy than children in the general pediatric population.

2. Children with ADHD more often have IEDs on routine, awake EEG, than healthy children.

3. It is safe to give MPH during the first two years of treatment despite the occurrence of IEDs at baseline.



### **3. MATERIAL AND METHODS**

#### **3.1. Participants**

The medical records of all children aged 6-14 years who received a diagnosis of ADHD were reviewed. All children with suspected ADHD were referred to awake EEG recording, as part of the assessment. Rogaland is the southern County of western Norway, and the northern and southern region of Rogaland is divided by a fjord (Boknafjorden). Children living in South and midth Rogaland were included in the study. The communities that constitute the area of South Rogaland are: Egersund, Lund, Sokndal, Sandes, Stavanger, Bjerkreim, Hå, Klepp, Time, Gjesdal, Sola, Randaberg, Strand, Hjelmeland, Finnøy, Kvitsøy and Forsand. The population of the South Rogaland region included approximately 44,880 children aged from 6 to 15 years, according to the Official Bureau of Statistics (Statistics Norway 2015). Our department is the only child and adolescent psychiatry department in the area, there are no private clinics and we thus assume that all patients in the area with suspected ADHD were referred to the department.

#### **3.2. Assessment**

The diagnosis of ADHD was made according to the Norwegian guidelines for ADHD (Helsedirektoratet, 2005). A structured clinical interview was used to elicit general and clinical information, including seizures and drug treatment, and a clinical neurological and child psychiatry examination was conducted following a structured guide. In addition, standardized psychiatric instruments including Child Behavior Checklist (Achenbach 1991), Conners Parent/Teacher rating scale (Goyette, Conners et al. 1978), and the ADHD rating scale IV (DuPaul, Power et al. 1998) were administered for all children/parents. Based on the clinical interviews and the diagnostic procedures, ADHD and subtypes were diagnosed according to DSM-IV-TR (American Psychiatric Association 2000). Comorbidities accompanying ADHD were registered and classified according to ICD-10. The majority of patients were given the Wechsler Intelligence Scale for Children (WISC) for intelligence assessment (Wechsler 2003). ADHD diagnosis was made by a team of clinicians including a child psychiatrist and a psychologist. If different opinions occurred, the final diagnosis was determined after a consensus meeting.

As part of the routine assessment, a digitized 20 minutes routine EEG with 21 electrodes (10-20 system) was conducted including hyperventilation and photic stimulation during wakefulness without sleep deprivation. The EEGs were classified as either epileptiform or nonepileptiform by three board-licensed clinical neurophysiologists. This group was supervised by the clinical neurophysiologist Anita Herigstad, who also carried out a majority of the classifications, and Dobrinko Socanski, who is a child psychiatrist and child neurologist with special training in electroencephalography. The patients with IEDs were subdivided into those with focal or nonfocal IEDs, and within the focal IEDs group, those with “rolandic” spikes were tabulated separately. Based on the clinical interview, children were classified as having experienced SZs or not.

Epilepsy was defined as two or more SZs occurring at least 24 hours apart, and unprovoked by any immediate identifiable cause (Commission on Epidemiology and Prognosis International League Against Epilepsy 1993). The epilepsy was defined as active if at least one SZ had occurred during the last 5 years, regardless of AED treatment, and refractory if the patient continued to experience SZs during the last year of follow-up, despite a previous adequate trial of more than two appropriately selected AEDs. SZs and syndromes were classified according to the international classification system of the ILAE (Commission on Classification and Terminology of the International League Against Epilepsy 1981, Commission on Classification and Terminology of the International League Against Epilepsy 1989), and identified by review of the medical records, including the clinical description of SZs, the results of a neurological examination, and EEG and neuroimaging findings. All the medical documentation for each patient that was diagnosed with epilepsy was reviewed by child neurologist/child psychiatrist Dobrinko Socanski and by neurologist Dag Aurlien. Epilepsy syndromes were classified according to the available information at the time of ADHD diagnosis. Demographic data and seizure history were recorded. These included age of onset, duration of epilepsy, and medication status regarding AED treatment and degree of seizure control during the last year (SZ free, 1-12 SZs per year, and >12 SZs per year). AED treatment was classified as untreated, monotherapy or polytherapy.

In addition, we examined disorders of psychological development (specific developmental disorders of speech and language, scholastic skills, motor function, other disorders of psychological development, and unspecified disorder of psychological

development) according to the ICD-10), IQ level (IQ>85, IQ<85), the sequence of occurrence of seizures in relationship to the diagnosis of ADHD, length of time between seizure diagnosis and ADHD diagnosis, ADHD subtype, pharmacological treatment for ADHD and initial response to this treatment (defined as a positive response which showed significant reduction in the patients level of ADHD symptoms scores).

In **paper I** we explored the relationships between ADHD and epilepsy in a large population of children ages 6-14 years, in order to achieve a better understanding of these common comorbid neuropsychiatric disorders. We compared age, sex, disorders of psychological development, cognitive level, pharmacological treatment for ADHD, initial response to treatment and ADHD subtype of children in our cohort, with and without epilepsy. In addition, we compared our data with data from a study on the prevalence, classification and severity of epilepsy in children in western Norway (Breivik and Reiher 2008).

**Paper II** describes the occurrence of IEDs in children aged 6-14 years diagnosed with ADHD. The occurrence of IEDs was compared with the occurrence of IEDs in the general pediatric population. Demographic and clinical correlates (characteristics) of cases with IED (IED group) and without IEDs (non-IEDs group) were compared and discussed.

**Paper III** describes a 2 years follow-up of all cases with IEDs (IED group) and compared them with randomly selected cases matched for age and gender without IEDs (non-IEDs group). At baseline, one and two years we measured the SZ occurrence and frequency, the use of AEDs, and the use of MPH. MPH was administered according to the Norwegian Guidelines (Helsedirektoratet 2005), in dosage 0.5-1.2 mg per kilo either three times daily (short-acting MPH) or once per day (slow- acting MPH). During titration with MPH the use of AEDs was stable. The response to MPH was evaluated after several weeks of treatment (4-6 weeks). The response was considered positive if a significant reduction in ADHD symptoms scores was found assessed with the ADHD IV rating scale (DuPaul, Power et al. 1998), in addition to observation by parents and teachers. During follow-up we registered whether MPH was given or not. In the IEDs group at least one follow-up EEG was carried out, and an additional

sleep EEG was performed in 15 cases. Long-term video-EEG monitoring was done in 5 cases due to diagnostic difficulties (suspect SZs).

### **3.3 Statistical analysis**

Continuous variables were compared with the Student t-test for normally distributed data. When skewed, we used the non-parametric test (Mann-Whitney U test). Proportions were compared using the Chi-squared test or Fisher's exact test. Methods for matched samples (paired-samples t-tests, McNemar's tests) were also applied. However, the application of methods for matched samples did not alter the conclusions. A p-value of  $<0.05$  was considered statistically significant.

### **3.4 Approval**

The study was approved by the Norwegian Data Inspectorate and by the Regional Committee on Medical Research Ethics in region West (nr. 010.07). The study was performed in accordance with ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all parents.

#### 4. RESULTS (SUMMARY OF PAPERS I-III)

##### Paper I

Socanski D, Aurlien D, Herigstad A, Thomsen PH, Larsen TK. **Epilepsy in a large cohort of children diagnosed with attention deficit/hyperactivity disorders (ADHD)**. *Seizure*: 2013;22: 651-655.

**Objective:** This retrospective study examined the prevalence and characteristics of epilepsy in a large, unselected cohort of children with ADHD who were diagnosed during a 6 years period, between 2000 and 2006.

**Methods:** We compared age, gender, disorders of psychological development, cognitive level, pharmacological treatment for ADHD, initial response to treatment and ADHD subtype in cases with and without epilepsy. The characteristics of epilepsies were described and our data were compared with data from a study of epilepsy in a large general pediatric population in west Norway (Breivik and Reiher 2008).

**Results:** A total of 607 children (82.4% males) aged 6–14 years with ADHD were identified. Of these 14 (2.3%) had a history of epilepsy and 13 of these had active epilepsy. This is a significantly higher occurrence than previously reported in a Norwegian general pediatric population in which 0.5% of children between 6 and 12 years had epilepsy.

The epilepsy diagnosis preceded the ADHD diagnosis by 1.8 years on average. The patients with and without epilepsy did not differ regarding age, gender, disorders of psychological development, IQ level < 85 or ADHD subtype.

Eleven (78.6%) of the children with epilepsy had been seizure-free for at least one year before ADHD assessment, and our patients were more likely to be seizure free compared to the patients with epilepsy in the general pediatric population (30.8%). Two of the children had 1–12 seizures per year, and one had >12 seizures per year. Two of the children, both seizure-free, were not treated with an AED. Ten children were on AED monotherapy and two on polytherapy. One child with symptomatic epilepsy (hypothalamic tumor) was treated with a combination of lamotrigine and topiramate, and a second case (cryptogenic etiology) with topiramate and ethosuximide. No one was treated with phenobarbital or phenytoin. Of the 14 patients with a history of epilepsy, 11 (78.6%) had focal seizures, seven

also had secondary generalized tonic-clonic seizures and three patients had only primary generalized seizures. Localization related epilepsies were more common (10 cases) than generalized epilepsies (3 cases). BECTS was found in two cases and CAE in two cases. MPH was the pharmacological treatment for ADHD in all 14 children with a history of seizures and initial response to methylphenidate was achieved in 12 (85.7%).

**Conclusions:** Epilepsy was found in a significantly higher rate (2.3%) than would be expected in the general pediatric population (0.5%). The majority of patients had ADHD-combined subtype and mild (an easily treated) epilepsy. All cases with epilepsy and ADHD were treated with MPH, with initial response achieved in 86%.

## **Paper II**

Socanski D, Herigstad A, Thomsen PH, Aarsland D, Larsen TK. **Epileptiform abnormalities in children diagnosed with attention deficit/hyperactivity disorder.** *Epilepsy Behav* 2010; **19**:483-486.

**Objective:** This study describes the occurrence of epileptiform abnormalities (EAs) on awake EEG, and correlates of EAs in children with ADHD.

**Methods:** A total of 607 patients were diagnosed between 2000 and 2005. Routine awake EEGs were obtained in 517 cases, which constituted the study group. Demographic and clinical characteristics of cases with EAs (EAs group) and without EAs (non-EAs group) were compared and analyzed.

**Results:** The patients without EEGs did not differ from the participants with respect to age, gender, or ADHD subtype. The EAs group more often had girls and ADHD-I than the non-EAs group. EAs were found in 39 (7.5%). If patients with previous epilepsy were excluded, we found EAs in 27 (5.4%). When we compare this rate with rates of EAs reported in healthy children, it is unclear whether any differences exist. In 2 cases, EAs were demonstrated only with activation procedures (one patient demonstrated EAs on hyperventilation, and another, on photic stimulation). Among the 39 children with EAs, 21 (53.9%) had generalized EAs, 16 (41%) had focal EAs, and 2 (5.1%) had mixed EAs. Rolandic spikes were observed in 9 cases (1.7% of the total group). Fourteen cases had a previous epilepsy, and the epilepsy was more common in those with EAs (30.8%) than in those without (0.4%).

**Conclusions:** The group with ADHD and EAs were more often female, and more often had ADHD-I, independent of a history of epilepsy.

### **Paper III**

Socanski D, Aurlien D, Herigstad A, Thomsen PH, Larsen TK. **Attention deficit/hyperactivity disorder and interictal epileptiform discharges: It is safe to use methylphenidate?** *Seizure*: 2015;25:80-3.

**Objective:** This study investigated whether it is safe to use methylphenidate (MPH) in children with ADHD with interictal epileptiform discharges (IEDs) during the 2 years follow-up.

**Methods:** The 39 cases with IEDs (IEDs-group) and the control group without IEDs (non-IEDs group) consisted of 39 age and gender matched cases were compared. The occurrence of epileptic seizure (SZ), the use of MPH and the use of antiepileptic drugs (AEDs) at baseline and at the one and two year follow-ups were analyzed in a retrospective study.

**Results:** Due to matching procedures, there were no differences between the groups regarding age and gender. Proportion of disorders of psychological development or IQ level >85 also showed no differences. The majority (92%) had short duration of IEDs, and the IEDs index was <1%. The predominantly inattentive subtype of ADHD was found significantly more often in the IEDs group (41%), when compared to the non-IEDs group (15.4%). At baseline, 12 patients in the IEDs group had active epilepsy (SZs in last 5 years), 3 of them had SZs during the last year (2 had 1-12 SZs and 1 had more than 12 SZs per year). Localization-related epilepsies (75%) were more common than generalized epilepsy (25%). All patients with epilepsy received AEDs; 10 monotherapy and 2 polytherapy. No patients in the non-IEDs group had epilepsy. At one and two year follow-ups, 3 patients who also had SZs at baseline and difficult to treat epilepsy, had SZs, without changes in SZ frequency. At baseline, 36/39 (92.3 %) of patients with IEDs were treated with MPH. The 3 patients that were not given MPH had no previous epilepsy. Initial positive response to MPH was achieved in 30/36 (83.3%) of children with IEDs; 10/12 (83.3%) of the children with epilepsy and 20/24 (83.3%) of the cases without epilepsy. In the non-IEDs group of the 37 initially treated cases, 33/37 (89.2%) had positive effect of MPH treatment. At one and two year follow-ups only 3

patients, all from the IEDs group, had experienced SZs. These three patients had pharmaco-resistant epilepsy at baseline and had no change in SZ frequency. We found no significant differences regarding the use of MPH. Within the IEDs group we did not find statistically significant differences between the cases with and without epilepsy regarding the use of MPH at one and two year follow-ups. At the one year follow-up, 22 patients in the IEDs group were treated with AEDs, 12 of them had epilepsy (monotherapy 10, polytherapy 2). At two years, 12 children from the IEDs group used AEDs, 10 of them had epilepsy (8 monotherapy, 2 polytherapy). We carried out control EEGs in the IEDs group (one case missing). We found IEDs in 12 (31.2%) of the cases (focal in 10 and generalized in 2). In the IEDs-cases with epilepsy, 4 cases had only focal IEDs.

**Conclusions:** The use of MPH was safe during two years of follow-up. IEDs predicted SZs occurrence in children with previous epilepsy, but did not represent an increased SZ risk. We found no statistically significant differences between the groups with respect to MPH use at baseline, at one year and at two years. Ten patients from the IEDs group, who did not have a confirmed epilepsy diagnosis, temporarily used AEDs during the first year of follow-up. A caution is warranted in order not to overestimate the significance of temporarily occurrence of IEDs.

**Table 8. Age at admission, sex distribution, ADHD subtype, and occurrence of IEDs (N=517)**

	EEG/no IEDs n=478	EEG/IEDs all n=39	ADHD/IED without SZs, N=27	ADHD/IED with SZs, N=12	P value
Age, mean±SD	9.3±2.4	9.7±2.7	10.3±2.7	8.5±2.3	
Gender, female	81 (16.9%)	11 (28.1%)	8 (29.6%)	3 (25%)	0.001
ADHD-I	50 (10.5%)	16 (41%)	12 (44.4%)	4 (33.3%)	0.0001
Previous SZs	2/479 (0.4%)	12/39 (30.8%)	0	12	0.0001
EEG					
Focal IEDs		16 (41%)	12	4	
Rolandic		9	7	2	
Generalized IEDs		21 (53.9%)	14	7	
Mixed IEDs		2 (5.1%)	1	1	

All significant differences are between the group without IEDs and the group with IEDs.



**Table 9. Clinical characteristics of epilepsy among 14 children with ADHD**

Epilepsy syndrome	Gender	Age at ADHD (mean: 8.2 y.)	Age at first SZ (mean: 6.4 y.)	SZ types	EEG interictal	AED at ADHD dg	ADHD C or I	Effect of MPH+/_
<b>Localization related</b>								
Idiopathic								
BECTS	M	7	7	P+sGTCSZs	FEA	-	C	+
BECTS	M	7	7	P+sGTCSZs	FEA	CBZ	C	+
CEO	M	8	6	P+sGTCSZs	FEA	VPA	C	?
Symptomatic	M	7	5	P	FEA	LTG+TPM	C	+
Cryptogenic	M	6	6	P+sGTCSZs	NEA	VPA	C	+
	F	5	2	P+sGTCSZs	NEA	LEV	C	+
	F	9	3	P+sGTCSZs	GEA	CBZ	C	+
	M	8	4	P	FEA	OXC	C	+
	M	8	7	P	GEA	TPM+ESM	I	-
	F	12	11	P+sGTCSZs	GEA	OXC	I	+
<b>Generalized</b>								
Idiopathic								
EGMA	M	13	9	GTCSZs	GEA	-	C	+
CAE	F	11	11	Absences	GEA	VPA	C	+
CAE	M	7	7	Absences	GEA	LTG	I	+
<b>Undetermined</b>								
Epilepsies with GTCSZs and P LKS	M	7	5	P	FEA	SUL	I	-

ADHD-C, attention deficit/hyperactivity disorder predominantly combined subtype; ADHD-I, attention deficit/hyperactivity disorder predominantly inattentive subtype; BECTS, benign childhood epilepsy with centrotemporal spikes; CAE, childhood absence epilepsy; CBZ, carbamazepine; CEO, childhood epilepsy with occipital paroxysms; EGMA, epilepsy with grand mal on awakening; ESM, ethosuximide; SZs, epileptic seizures; FEA, focal epileptiform activity; GEA, generalized epileptiform activity; GTCSZs, generalized tonic clonic seizures; LEV, levetiracetam; LTG, lamotrigine; LKS, Landau-Kleffner syndrome; MPH, methylphenidate; NEA, no epileptiform activity; OXC, oxcarbazepine; P, partial seizures; sGTCSZs, secondary generalized tonic clonic seizures; SUL, sulthiame; TPM, topiramate; VPA, valproate

## **DISCUSSION**

### **5.1 Representativeness and reliability**

A total of 607 children with ADHD were included. The study group was recruited from all patients who were referred to the Child and Adolescent Psychiatry Department, Stavanger University Hospital, over a 6 years period (2000-2005). To our knowledge, there were no other facilities in our region that diagnosed or treated patients with ADHD, thus we assume that all cases were referred to our hospital.

The diagnosis of ADHD was assessed with a multidisciplinary team, which consisted of a child psychiatrist, a psychologist, and other clinicians with experience in ADHD. Inter-rater reliability was not tested, but if diverging conclusions occurred, the diagnosis was made after a discussion in the team and after a consensus meeting. Different ADHD subtypes were assessed using the DSM IV criteria and ADHD IV reporting scale from parent and teachers (DuPaul, Power et al. 1998).

Although all children with ADHD (n=607) were referred to EEG examination, 517 cases underwent EEG recording. The children without EEGs did not differ from the cases in which EEG was performed with respect to age, gender and ADHD subtype respectively. The gender distribution in our sample of 607 children is similar to those reported by others (Barkley 2006).

### **5.2 Epilepsy in ADHD**

We found that 14 children (2.3%) out of 607 with ADHD had history of epilepsy and 13 of these had active epilepsy (SZs during the last five years). This rate of occurrence of active epilepsy was higher than would be expected from epidemiological studies in pediatric populations (0.4–1%) (Sander 2003). Two studies from Norway have reported a similar prevalence of active epilepsy in the general pediatric population; 0.4% in the age group 0–14 years (Breivik and Reiher 2008), and 0.5% (198 of 38,593) between 6 and 12 years (Waalder,

Blom et al. 2000). Disorders of psychological development were also common in our patients (60.5%), but this proportion was not significantly higher among those with epilepsy than those without epilepsy. In addition, we analyzed the influence of IQ level. It is expected that children with IQ < 85 are more likely to have epilepsy (Besag 2002). However, our patients with ADHD, with and without epilepsy, did not differ regarding IQ < 85, thus supporting an association between epilepsy and ADHD, independent of lower IQ level.

Although ADHD is a common neurobehavioral disorder, there are few studies which reported incidence of epilepsy in ADHD. The largest study that we identified included 130 patients with ADHD (Williams, Schulz et al. 2001), and it reported a higher occurrence of epilepsy (2%) than expected in the general population (1%). However, in that study only 3 patients had previous histories of epilepsy. All three children had developmental delays and one was diagnosed with autism one year after inclusion. The authors suggested that these comorbid conditions might place them at a much higher risk of epilepsy. Two other studies had small samples of ADHD patients i.e. 68 and 28 (Ishii, Takahashi et al. 2003, Wisniewska, Baranowska et al. 2007). Epilepsy diagnosis is often considered an exclusion criterion in ADHD-studies and this might explain the apparent lack of studies.

One study (Davis, Katusic et al. 2010), compared the incidence and characteristics of epilepsy among children with (n=358) and without (n=728) ADHD. In this study, the ADHD diagnosis was carried out on retrospective review of school reports and medical records until the age of 20. Consequently, it may appear uncertain whether all the included patients actually suffered from ADHD. They found a 2.7-fold greater incidence of epilepsy among children with ADHD than in the control group (8/358, 2.2% vs 6/728, 0.8%). They reported that in children with ADHD, epilepsy appeared to have earlier onset, was of greater severity and was less likely to respond to AED treatment. In contrast, we found that the majority of our cases with epilepsy had mild (an easily treated) conditions, and that they had already achieved SZ freedom at ADHD assessment. Among our children with epilepsy, 14.3% had symptomatic etiology, 35.7% idiopathic and 24.7% cryptogenic, and freedom from SZs was achieved in 78.6%. Our findings differ from epidemiological studies in pediatric populations (Waalder, Blom et al. 2000, Larsson and Eeg-Olofsson 2006, Breivik and Reiher 2008). A study from western Norway (Waalder, Blom et al. 2000) reported that symptomatic etiology was diagnosed in 46.7%, idiopathic in 28.8% and cryptogenic in 24.7%, and SZ freedom was

achieved in 30.8% of the children. Epileptic syndromes/SZ types in our patients were more often localization related/partial than generalized, similar to the findings in the Norwegian prevalence study (Waalder, Blom et al. 2000). Of epileptic syndromes commonly occurring in school age children, two patients had BECTS, and two had CAE. We also found one patient who satisfied the criteria for LKS, a relatively rare syndrome even though we had a small sample with epilepsy.

We found that ADHD-I is more common in our children with epilepsy (28.6%) than in cases without (12%), but still less common than in pure epilepsy-studies which found ADHD-I present in more than 50% of the cases (Dunn, Austin et al. 2003). Different results may be explained by selection of patients. Our results represent the child psychiatry population (ADHD children with epilepsy) which usually has ADHD-C more often than ADHD-I. Our total study population showed typical predominance of ADHD-C. However, if we look at the ADHD children with IEDs, they more often manifested ADHD-I, and had a larger proportion with SZs than the ADHD children without IEDs. We found that ADHD-I was more common in children with IEDs, independent of a history of epilepsy. To our knowledge, such a relationship has not previously been reported in children without comorbid epilepsy, although it has been observed in patients with epilepsy (Dunn, Austin et al. 2003, Hesdorffer, Ludvigsson et al. 2004, Hermann, Jones et al. 2007, Sherman, Slick et al. 2007). Patients with epilepsy and ADHD may have many factors that influence occurrence of ADHD-I, such as subtle epileptic seizures, antiepileptic treatment, and underlying neurodevelopmental vulnerability. There is also evidence that TCI during frequent subclinical epileptiform discharges can affect attention and cognitive function even in the absence of clinical SZs (Aarts, Binnie et al. 1984, Kasteleijn-Nolst Trenite 1995, Aldenkamp 1997, Laporte, Sebire et al. 2002, Binnie 2003, Aldenkamp and Arends 2004).

### **5.3 ADHD and occurrence of IEDs**

We found that 7.5% of the unselected sample of 517 children with ADHD had IEDs on a routine EEG. When we excluded patients with previous epilepsy, the rate of IEDs was 5.4%. Previous studies on children with ADHD reported that the prevalence of IEDs on awake EEGs varied from 4.8 to 15.4%. Our findings are similar to those reporting 6.1%

(Richer, Shevell et al. 2002) and 4.8% (Matoth, Taustein et al. 2002). Richer and colleagues (2002) examined 347 ADHD children with one routine EEG and found IEDs in 21 (6.1%) cases. Among their cases with IEDs, two children had IEDs activated by photic stimulation. However, if the two cases are taken out, photic activation was not done in the historic control group of healthy children (Cavazzuti, Cappella et al. 1980), then the rate of IEDs is reduced from 6.1 to 4.9%, which is not a statistically significant difference from the rate of IEDs (3.5%) in the control group. The highest rate of IEDs (15.4%) in children with ADHD was reported by Hemmer and colleagues (2001). In this study a broader age group, 3–20 years (N=234) was included, and patients were selected for treatment with stimulants (Hemmer, Pasternak et al. 2001).

In other studies, the proportions of IEDs on EEG in all otherwise healthy children varied from 2.7 to 5.0% (Eeg-Olofsson, Petersen et al. 1971, Cavazzuti, Cappella et al. 1980, Okubo, Matsuura et al. 1994). One study from Sweden (1971) reported that 2.7% out of 743 healthy children had IEDs at rest; however, they included only children younger than 6 years and had strict selection criteria for normality including all otherwise healthy children. The largest study was carried out in Italy (Cavazzuti, Cappella et al. 1980). EEGs were recorded in 3726 children, from 6 to 13 years of age, who were neurologically normal and had no history of SZs. The records were taken during wakefulness, at rest, and during hyperventilation, and in 131 cases (3.5%) IEDs were found. However, it was not stated whether photic stimulation was used as an activation procedure. A study from Japan reported that 5% of 1057 children (Okubo, Matsuura et al. 1994), aged 6-12 years, had IEDs. The highest IEDs occurrence of 6.5% was reported in a study from Germany where 382 children aged 6-13 years whom were assessed with digitalized EEG for minor head trauma (Borusiak, Zilbauer et al. 2010).

Although IEDs usually occur more commonly during sleep, the lowest rate of IEDs (1.45%; 14 of 970) on sleep EEG was reported by Capdevila and coworkers (Capdevila, Dayyat et al. 2008). The study population included all otherwise healthy children between the ages of 5 and 8 years. They were recruited as control subjects from the community as part of several ongoing research projects, and were evaluated by overnight polysomnography. None of these 14 children with IEDs had a history of febrile seizures, ADHD, or any other neurological disorders, and none were receiving any medication. None of the first-degree relatives of these 14 children had a history of SZ disorders.

### 5.3.1 Rolandic spikes

Rolandic spikes (centrotemporal spikes) are hallmark for BECTS or rolandic epilepsy, the most common form of epilepsy in childhood. It accounts for approximately one fourth of epilepsy in school-aged children (Bouma, Bovenkerk et al. 1997). Several studies have reported an association between ADHD and BECTS (Holtmann, Becker et al. 2003, Volkl-Kernstock, Bauch-Prater et al. 2009, Bennett-Back, Keren et al. 2011, Tovia, Goldberg-Stern et al. 2011, Kim, Yum et al. 2014). One study has reported that children with BECTS (during the active phase) exhibited significantly more psycho-pathological features in the parents reported subscales of the CBCL ("Aggressive Behavior", "Attention Problems" and "Anxious/Depressed") than in healthy controls (Volkl-Kernstock, Bauch-Prater et al. 2009). Another study has found that children with ADHD without epilepsy had increased frequency of rolandic spikes (5.6%, 27 out of 483 children, 2–16 years of age) (Holtmann, Becker et al. 2003). This is significantly higher than the reported rate of focal discharges of 2.4% in normal children (Cavazzuti, Cappella et al. 1980). The authors suggested that IEDs in children with ADHD may contribute to the occurrence of ADHD symptoms, and that children with rolandic spikes tended to more often have ADHD-C subtype than ADHD-I.

We found no increased frequency of rolandic spikes. Our finding that 9 (1.7 %) cases with rolandic spikes is similar to the finding in normal population. Two of our nine patients with rolandic spikes had had SZs before being diagnosed with ADHD, suggesting an association between rolandic spikes and SZs, and that both of them may have occurred before ADHD. The prognosis of BECTS is generally considered to be favorable and about 20-30 % of children with rolandic spikes had SZs. On the other side, rolandic spikes on awake EEGs could also be seen in children with the atypical form of BECTS and in children with LKS and CSWS. We did not observe frequent IEDs (more than 10% of the record in the awake EEG), but we cannot exclude that some of our patients may have had IEDs activated by sleep. Many publications reported clear increased frequency of IEDs in ADHD cases on sleep EEG (Hughes, DeLeo et al. 2000, Silvestri, Gagliano et al. 2007, Wannag, Eriksson et al. 2010, Millichap, Stack et al. 2011, Kanazawa 2014). Silvestri and colleagues (2007) found the largest rate (53.1 %). They explored the prevalence of ictal and IEDs and sleep disorders in 42 ADHD children referred to a sleep clinic for all night video-polysomnography. One of the possibilities which may explain this rate is that the study population was more selected,

similar to suspect epilepsy patients and different from ADHD patients who usually attend child psychiatry departments. In our study, sleep EEG (in 15 children) and EEG videomonitoring (in 9 children) were carried out only in cases which needed differential diagnostic consideration (suspect SZs and/or increased amount of IEDs). One of our 39 patients with IEDs had an increased amount of IEDs that satisfied diagnosis of comorbid LKS.

#### **5.4 Is it safe to use MPH? EEG examinations, IEDs and the use of AEDs.**

##### **5.4.1 Treatment of ADHD when IEDs/SZs is comorbid**

Davies and colleagues (2010) reported that among children with ADHD symptoms, those with epilepsy were less likely to receive a clinical diagnosis and treatment of ADHD than those without epilepsy, possibly reflecting a reluctance to diagnose and treat ADHD symptoms in children with epilepsy. However, in our study all patients with epilepsy received MPH. Epilepsy comorbidity was apparently not considered as a reason for not treating ADHD. Our patients with epilepsy tended to have a younger age at ADHD assessment (8.2 years) compared to the patients without epilepsy (9.4 years). One can hypothesize that children with epilepsy may have more ADHD symptoms which may contribute to early detection. An easy (mild) epilepsy was found in the majority of our patients and treatment with AED was successful. AEDs (PB, benzodiazepines and LEV) might have cognitive and behavioral side effects that resemble ADHD symptoms (Socanski, Jovic et al. 1997, Bourgeois 2004, Ijff and Aldenkamp 2013, Halma, de Louw et al. 2014). Among our patients, LEV was monotherapy in one patient, but none of our patients were treated with PB or a benzodiazepine.

##### **5.4.2 MPH use and risk for new SZs**

The use of MPH for children with ADHD with comorbid epilepsy or EEG abnormalities has been questioned. The Physicians' Desk Reference entry for Ritalin states: *“There is some clinical evidence that MPH may lower the convulsive threshold in patients with prior history of seizures, with prior EEG abnormalities in absence of SZs and no prior EEG evidence of*

SZs.”(FAD 2013, PDR Staff 2014) The Norwegian pharmaceutical product compendium (2015) also states: “SZs: use with caution in patients with epilepsy. The threshold for SZs may be lowered in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and rarely in patients without a history of convulsions and no EEG abnormalities. If SZ frequency increases or new-onset seizures occur, methylphenidate should be discontinued.” (Translated by the author)(Legemiddelindustrien 2015).

The SZ risk in ADHD children with IED without SZs has been discussed in some publications. Hemmer and coworkers (2001) investigated the SZ risk in non-epileptic patients with ADHD who used stimulants. The patients were diagnosed between 1993 and 1998, and in 1999 were followed up with either an office visit or telephone contact. They found that 3 out of 30 patients with IED had a SZs during follow-up. The patients had long latencies to SZ occurrence, (10 months, 14 months and 3 years). They suggested that epileptiform EEG in patients with ADHD predict considerable risk for the eventual occurrence of SZs (Hemmer, Pasternak et al. 2001). In contrast to their study, in our 27 children with IEDs without previous history of epilepsy, none developed SZs during follow-up. In addition, the SZ frequency in cases with active epilepsy did not change from baseline. Our finding is concordant with a study by Gucuyener and colleagues (2003), which investigated the use of MPH for ADHD in patients with epilepsy or EEG abnormalities. Patients with ADHD and active SZs (n=57) and patients with ADHD and EEG abnormalities (n=62), 6-16 years of age, were included in the study. A subgroup of 15 nonepileptic patients had epileptiform EEG at baseline and none of them had a SZ during the study period of one year (Gucuyener, Erdemoglu et al. 2003). Several studies have reported that MPH is safe to use in children with ADHD with both well controlled epilepsy (Feldman, Crumrine et al. 1989, Gross-Tsur, Manor et al. 1997, Kaufmann, Goldberg-Stern et al. 2009), and difficult to treat epilepsy (Koneski, Casella et al. 2011, Brunklaus, Dorris et al. 2013, Fosi, Lax-Pericall et al. 2013, Santos, Palmiini et al. 2013), and that 61-73% of children with epilepsy had benefit from MPH. One study reported that the use of a combination of behavioral management and MPH (0.3-1mg/kg/day) for 3 months improved ADHD symptoms in 61% of 18 patients with learning disability and refractory epilepsy (Fosi, Lax-Pericall et al. 2013). Our finding was similar regarding the use of MPH in cases with epilepsy. In addition, we found no differences



in maintenance on MPH at one and two year follow-ups between the IEDs and the non-IEDs groups.

#### **5.4.3 The occurrence of symptoms, EEG examinations, IEDs and the use of AEDs**

The timing of the occurrence of comorbid diagnosis may often be unclear or not reported in many studies (Hesdorffer, Ludvigsson et al. 2004). It may be difficult to delineate ADHD symptoms from subtle seizures, especially in cases with ADHD-I which predominate in epilepsy patients (Dunn, Austin et al. 2003, Hesdorffer, Ludvigsson et al. 2004, Bennett-Back, Keren et al. 2011), as well as in patients with IEDs as we presented in our study. Hesdorffer and colleagues (2004) investigated this in a population-based case-controlled study of newly diagnosed unprovoked seizures among Icelandic children younger than 16 years (109 cases and 218 controls). A structured telephone interview was administered to parents of cases and controls to make ADHD diagnosis according to DSM-IV. The parents were asked whether their child had ever exhibited certain characteristic behaviors before the date of the child's incident unprovoked seizure or epilepsy. They were also asked about the age at which these behaviors began, the age at which the behaviors ended, the effect of the behaviors on home, school, and friends, whether medical care had been sought because of the behaviors; and whether medication was given to treat the behavioral disorder. They found that ADHD occurs more often than expected before unprovoked seizures, suggesting a common antecedent for both conditions. The association was restricted to ADHD-I (Hesdorffer, Ludvigsson et al. 2004). Findings prior to the onset of epilepsy (neuropsychological finding, cognitive function, ADHD symptoms) are often missing or not informative enough. If ADHD symptoms are present among children with short duration of epilepsy, the question arises whether the symptoms are present at the epilepsy onset or develop following the onset and treatment of SZs. One study suggested that psychiatric, cognitive, and academic problems may even antedate the diagnosis of epilepsy and recognition of the first SZ (Hermann, Jones et al. 2007). Another study claimed that attention difficulties are not characteristic of schoolchildren with newly diagnosed idiopathic or cryptogenic epilepsy (Ostrom, Schouten et al. 2002). Similarly, the authors reported that behavioral problems are not persistent in the majority of these children (Ostrom, Schouten et al. 2003). The rate of ADHD in children with uncomplicated epilepsy was also documented as similar to that in the same-age general

population (Davies, Heyman et al. 2003). Therefore, a baseline examination of children at onset of epilepsy or close to the onset of their epilepsy, and following them prospectively may contribute to resolving this question.

Another enigmatic association is that frequent IEDs (in more than 10% of the record) in the awake EEG can impair cognitive performance in children (Ebus, Arends et al. 2012). In some cases as previously reported ADHD symptoms may also be related to frequent epileptiform discharges activated by sleep (Hughes, DeLeo et al. 2000, Silvestri, Gagliano et al. 2007, Wannag, Eriksson et al. 2010, Bakke, Larsson et al. 2011). An association between IEDs during sleep and cognitive impairment has been noted in many studies (Deonna, Davidoff et al. 1997, Scholtes, Hendriks et al. 2005, Holmes and Lenck-Santini 2006, Nicolai, Aldenkamp et al. 2006, Pinton, Ducot et al. 2006). In these patients, a careful assessment including neuropsychological examination is needed before an eventual trial with AEDs. The latest ILAE report regarding neuropsychological assessment (Wilson, Baxendale et al. 2015) recommends the routine screening of cognition, mood, and behavior in new-onset epilepsy, and describes the range of situation when more detailed formal neuropsychological assessment is indicated.

In our study, we found that epilepsy diagnosis was made before ADHD diagnosis in all cases. Our finding supports that after the diagnosis of epilepsy, ADHD symptoms or ADHD may occur with a greater frequency than expected. ADHD symptoms may precede, occur simultaneously with, or occur subsequent to a diagnosis of epilepsy. From a clinical perspective, it is important to be able to differentiate between the onsets of epilepsy and ADHD, and to be able to determine whether a patient with both conditions should receive AED treatment or pharmacological treatment for ADHD, or both, and on what time scale. In our study we identified three patients who were assessed for epilepsy and for ADHD simultaneously. From the information available at assessment, it was not obvious whether they actually suffered from ADHD or whether their symptoms originated from unrecognized SZs (staring, complex partial seizures, absences). After careful assessment, and following diagnosis of epilepsy, these children were also diagnosed with ADHD. The differential diagnosis of epilepsy vs. ADHD might be difficult, but it is important to recognize that they are not mutually exclusive. This finding that in 3 cases ADHD symptoms and SZs occurred

almost at the same time support the suggestion that a common antecedent for both conditions could exist.

EEG examination is usually not required according to DSM-IV, and the significance of epileptiform EEG activity in children with ADHD without SZs is uncertain (Sand, Breivik et al. 2013), and recommendations regarding the relative importance of EEG in ADHD are ambiguous (Becker and Holtmann 2006). A German study suggested that not performing a routine EEG could result in the oversight of subclinical epileptic discharges in a considerable number of children with ADHD, and that assessment of children with ADHD until puberty should include EEGs, regardless of the lack of a prior history of overt SZs or other obvious neurological condition (Becker, Sinzig et al. 2004). The presence of an IEDs helps to confirm a clinical diagnosis of epilepsy, aids in defining the epilepsy syndrome, provides information that assists in planning drug management, and helps to assess candidacy for epilepsy surgery (Pillai and Sperling 2006). On the other side, IEDs also occur in children who do not have SZs. Centrotemporal spikes (rolandic spikes) are age dependent and tend to disappear during the teenage years. Generalized spike-and-wave discharges at 3–4 Hz usually are associated with idiopathic generalized epilepsy, but may also occur in asymptomatic relatives of patients with epilepsy. IEDs also occur in healthy children (Eeg-Olofsson, Petersen et al. 1971, Cavazzuti, Cappella et al. 1980, Okubo, Matsuura et al. 1994, Fisch 2003, Pillai and Sperling 2006, Capdevila, Dayyat et al. 2008). In addition, overreading of EEGs contributes to misdiagnosis (Benbadis 2007), and a caution should be used particularly with those suspected of having ADHD-I because this group is more likely to have IEDs on routine EEG as we found in our study. Diagnosis of ADHD and/or epilepsy may be misinterpreted. The findings of IEDs are usually associated with SZs and in such cases the question often arises whether an AED is indicated as first choice of treatment.

Our results showed that 5.4 % of ADHD children without a previous history of epilepsy had IEDs on a routine EEG. This is similar to findings in healthy general pediatric populations (IEDs varying from 2.7% to 6.5%), depending on which criteria were used to define the healthy population in the different studies (Eeg-Olofsson, Petersen et al. 1971, Cavazzuti, Cappella et al. 1980, Okubo, Matsuura et al. 1994, Borusiak, Zilbauer et al. 2010). On the other side, in many cases for diagnostic clarification, it might be important to do not only a routine awake EEG, but also a sleep EEG, and/or videomonitoring. This differential

diagnostic consideration should be done promptly in children with suspect SZs, language difficulties and attention problems.

One study suggested that suppressing IED with LTG can improve behavior in children with epilepsy and behavioral problems, particularly partial epilepsy (Pressler, Robinson et al. 2005). Several publications have suggested that LEV may have a positive effect on the EEG, behavior, and the cognition of patients with CSWS (Hoppen, Sandrieser et al. 2003, Aeby, Poznanski et al. 2005, von Stulpnagel, Kluger et al. 2010, Bakke, Larsson et al. 2011), and that it improves neuropsychological functioning in children and adolescents who have evidence of subclinical spike production associated with attention and learning difficulties (Mintz, Legoff et al. 2009). In contrast, one study (Carballo, Cersosimo et al. 2010) presented LEV-induced SZs associated with CSWS in children with refractory epilepsies. And another study reported that LEV may have been associated with behavioral problems (Halma, de Louw et al. 2014). The authors systematically reviewed the use of LEV and reported that children using LEV have a risk of developing several behavioral side-effects such as aggression, hostility and nervousness, when compared to children who do not use LEV (Halma, de Louw et al. 2014). In a recent study (Uliel-Sibony and Kramer 2015), 17 children with BECTSs, high spike-wave index  $\geq 30\%$ , and ADHD were evaluated and followed up for at least two years. Patients with neurocognitive deterioration detected by formal testing were excluded. The patients' mean spike-wave index was 60% and that dense electrical activity lasted 1.5 years on average. Six children were formally diagnosed with learning disabilities in addition to ADHD. All of them were treated with an average of three AEDs, mainly for the purpose of normalizing the EEG, but none of them were treated with steroids or high-dose diazepam. The mean duration of follow-up was 5-5 years. A cognitive or behavioral deterioration was not detected in any of them. The authors reported that since many of the children with BECTSs display electrical status epilepticus during sleep, and many present with different comorbidities, mainly ADHD and behavioral disturbances, clinicians are often confronted with the dilemma of how aggressive they should be with their efforts of normalizing the EEG. They suggested that when treating a child with BECTS, high spike index and school difficulties, the most critical parameter that determines the necessity of using second-line antiepileptic agents such as steroids or high-dose diazepam, is a formal psychological evaluation that proves cognitive (I.Q.) decline. Otherwise, these agents may be avoided.

There is no agreement regarding cases indicate the need for medical treatment, nor how long it is needed. In another recent review (Vannest, Tenney et al. 2015), the authors concluded that treatment with AEDs is an option in BECTS, but existing studies have not clearly shown a clear relationship between elimination of centrotemporal spikes and improved cognitive and behavioral outcomes.

In our study an additional sleep EEG was carried out in 15 cases and long-term video-EEG monitoring in 5 cases, in order to clarify differential diagnosis and treatment choices. One of our cases had CSWS on EEG recording and LKD diagnosis, and autism was also diagnosed during the clinical course. This case was treated with LEV, but significant reduction of ADHD symptoms was not found. First, he received stimulants, later he was given atomoxetine in combination with LEV. In a Norwegian study (Zeiner, Gjevik et al. 2011), they reported a significant reduction in ADHD symptoms in 7 out of 14 boys with high functioning autism spectrum disorder and comorbid ADHD who were treated with atomoxetine.

In addition, one should be aware of the possibility of temporary overtreatment with AEDs in cases with IEDs without confirmed epilepsy diagnosis. In some cases with IEDs without evidence of SZs, diagnostic and treatment consideration may include temporary use of AEDs. In our sample, during the first year of follow up, 10 children were temporarily treated with AEDs because this was a study on real-life patients, and the clinicians chose to treat the cases in which the diagnoses was uncertain. In some cases a reduction of attention problems was registered, but a significant reduction of ADHD symptoms was not observed and it was necessary to add MPH. AEDs were discontinued during the second year of follow-up, and the withdrawal from AEDs was not associated with the development of SZs in these cases. At the 2 years follow-up, SZs were registered in only 3 patients with previous difficult to treat epilepsy, but without increased SZ risk in comparison with the baseline.

During follow-up we carried out control EEGs in the IEDs group (one case missing). We found IED in 12 (31.6%) of the cases. In the IEDs-cases with epilepsy, 4 cases had only focal IEDs. EEG normalization during the follow-up and disappearance of IEDs in healthy children were also reported by Cavazzuti and coworkers (1980). Follow-up over an 8-9 year period demonstrated the spontaneous disappearance of EEG abnormalities, usually within school age or, at latest, during adolescence. Only 7 (out of 131) cases developed GTK SZs,

which responded well to AEDs. They concluded that epileptiform EEG patterns are often found in children during school age and have no clinical relationship to epilepsy in the great majority of cases. Half of their patients with EEG abnormalities had behavior problems and/or slight psychomotor ability disturbances (Cavazzuti, Cappella et al. 1980).

ADHD in children is reported to be a risk factor for incident unprovoked seizures and epilepsy (Hesdorffer, Ludvigsson et al. 2004), and is suggested to predispose for epilepsy development, as do autism spectrum disorder and cerebral palsy (Boutros 2009, Shelley and Trimble 2009, So 2010, So 2010). We did not find that the existence of ADHD made our patients (without comorbid difficult to treat epilepsy) sensitive for new SZs. We cannot exclude the possibility that some of them can develop SZs later in life. According to DSM-V and in clinical praxis, the diagnosis of autism spectrum disorder is no longer an exclusion criterion for ADHD. The occurrence of IEDs in such cases (coexistence of ADHD and autism) is expected to and be more increased, and diagnostic assessment needs to be interpreted with caution.

In conclusion, our results suggest that it is safe to use MPH for ADHD in children with and without IEDs (no increased SZ risk), and that the official recommendation to not use MPH in children with epilepsy and/or IEDs should be changed. The initial use, positive response and maintenance on MPH were similar in both groups during the two years of follow-up.

## **5.5 Strengths, limitations and future research**

### **5.5.1 Strengths of the study**

We have a relatively large, highly representative and unselected cohort, as all children suspected of having ADHD were referred to the center and the patients were consecutively assessed. There existed no other treatment facilities in the region. We were able to carry out EEGs in most of the cases.

### **5.5.2 Limitations of the study**

The low number of cases with IEDs (n=39) is a limitation in our study as well as the lack of a prospective and randomized controlled trial during the 2 years follow-up. We also did not carry out a reliability test of diagnosis or measure the exact dosage of MPH. We were not able to carry out a follow-up assessment of all cases due to the lack of resources.

### **5.5.3 Future research**

The group with IEDs and the control group without IEDs were followed up for two years. It could be interesting to assess these two groups at 5 and 10 years after ADHD diagnosis. Although our study did not find any association between IEDs at baseline and risk for new SZs in children without a previous history of epilepsy, this clinically important finding was based on relatively few cases (n=27). Therefore our results should be confirmed in a larger study. The influence of comorbid Tourette's syndrome is under investigation. ADHD symptoms and autistic features could be seen in the same child, and now, according to DSM-V, it is possible to have both diagnoses as comorbid conditions. IEDs occur more frequently in children with autism (up to 30%). It still needs to be clarified whether or not IEDs have influence on the occurrence of ADHD symptoms, cognitive or behavioral disturbances, or autistic symptoms.

## **6. CONCLUSIONS**

Epilepsy was found in 2.3 % (14 of our 607 cases), which is significantly higher than would be expected in the general pediatric population. The epilepsy diagnosis preceded the ADHD diagnosis in all patients, although in 3 cases ADHD symptoms and suspect SZs occurred almost at the same time. The majority of patients had mild epilepsy and ADHD-C.

The frequency of IEDs on routine EEGs in 517 children with ADHD was 7.5%, but when patients with a previous history of epilepsy were excluded, this frequency was 5.4%. The group with ADHD and IEDs were more often females and had a larger proportion of ADHD-I independent of a history of epilepsy, than did the group without IEDs.

IEDs predict the SZ occurrence in children with previously difficult to treat epilepsy, but they do not necessarily suggest an increased SZ risk. Our findings warranted caution regarding the assessment and use of AEDs in ADHD children with IEDs.

The initial response to MPH and maintenance on MPH at the one and two year follow-ups were similar in the cases with and without IED. Our findings may be helpful to clinicians concerning MPH use in ADHD. They demonstrated that despite the occurrence of IED and epilepsy, the use of MPH for children with ADHD was safe during two years of follow-up.



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