Ictal and interictal EEG abnormalities in ADHD children recorded over night by video-polysomnography

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Summary
In this paper we explore the prevalence of ictal and interictal epileptiform discharges (IEDs) and sleep disorders in ADHD children referred to a sleep clinic for all night video-PSG. Forty-two ADHD outpatients (35 males and 7 females) underwent video-PSG and a behavioural/neuropsychological assessment. Spearman correlation coefficients (p < 0.05 criterion level) were used to assess the association between cognitive, behavioural, clinical (co-morbidity), sleep (sleep efficiency) and EEG (seizures, IEDs, localization of IEDs foci) variables. Sleep disorders were found in 86% of ADHD children; among these, 26% had RLS. 53.1% of ADHD children had IEDs (28.2% centro-temporal spikes, 12.5% frontal spikes, 9.3% temporal—occipital spikes and 2.3% generalized S—W). Nocturnal seizures were recorded in three patients: two with atypical interictal rolandic spikes and one with left frontal slow abnormalities. A significant relationship (p < 0.05) emerges between nocturnal seizures and WISC-R IQ score and visual—spatial memory test and between some cognitive variables and interictal rolandic spikes. High levels of inattention, impulsivity/hyperactivity and oppositional behaviours were related (p < 0.01 or 0.05) with Restless Leg Syndrome diagnosis. In conclusion, ADHD is a condition often associated with EEG epileptiform abnormalities. Seizures/IEDs presence seems to play a role on cognitive abilities, conversely sleep disorders have a stronger impact on behavioural rather than cognitive indicators.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a common childhood problem estimated to affect 3–5% of school-aged children. It is characterized by a persistent pattern of inattentiveness (ADHD-I) and/or hyperactive impulsive behaviour (ADHD-H). Diagnosis requires onset before age 7 and impaired function (DSM IV). The core behavioural symptoms of ADHD are inappropriate patterns of inattentiveness, impulsivity and hyperactivity, although other common childhood disorders may be comorbid with ADHD, such as Oppositional Defiant Disorder, learning difficulties, dyspraxia, Tic Disorder. Recent literature draws attention to the role and prevalence of EEG abnormalities in ADHD children (Hughes et al., 2000).

The relationship between ADHD and epilepsy has been explored by many authors who considered the prevalence of ADHD in samples of children with epilepsy (Shubert, 2005). Describing a higher risk of ADHD in children with generalized or frontal epilepsy. The prevalence for interictal epileptiform discharges (IEDs) data range from 4.9% (Richer et al., 2002) to 60% (Abdeldayem and Salim, 2005) in ADHD children without clinical seizures, whereas the background incidence of epileptiform abnormalities in normal school-aged children is estimated around 2–3%. IEDs are predominantly focal, mostly bilateral or right sided and, especially in the predominantly hyperactive type ADHD, distributed over rolandic areas (Holtmann et al., 2003). The effects of subclinical electroencephalographic epileptiform activity during sleep on cognition and behaviour have been studied mostly in children with rolandic epilepsy (Nicolai et al., 2006).

As for seizures occurrence in ADHD some authors (Williams et al., 2001; Ishii et al., 2003) found that no risk of unprovoked seizures was associated with ADHD while others (Hesdorffer et al., 2004) report a OR of 3.7 for de novo seizures in ADHD-inattentive type. Aldenkamp et al. (2004) underlined the impact of both seizures and paroxysmal activity on cognitive development, especially on “state dependent processes” such as attention, information processing and behaviour.

Conversely, well-established data exist about sleep disorders in ADHD children (O’Brien and Gozal, 2004; Frolich et al., 2005). Among all, especially Sleep Related Movement Disorders (SRMD) such as Periodic Limb Movement Disorders (PLMD) and Restless Leg Syndrome (RLS) have been reported with a high prevalence. Their co-occurrence is hypothesized to be related to a common genetic substrate relying on dopaminergic deficit (Wagner et al., 2004).

Few previous reports explored the yielding power of sleep to record IEDs in ADHD children (Larsson and Wilson, 2005). Due to all these previous reports we decided to look at the prevalence of IEDs and seizures in ADHD children referred to a sleep clinic for all night video-PSG, exploring the possibility of co-diagnosing sleep disorders and IEDs in order to study the influence of these variables on behavioural and cognitive performances.

Methods

Patients

Forty-two consecutive ADHD outpatients (35 males and 7 females; mean age 8.9 years, S.D 2.8) were included in this study. They were referred by Pediatric Neurology and Psychiatry to our Sleep Clinic from October 2004 to May 2006, within a sleep disorders screening project in ADHD children. All children were referred independently from any reported symptoms regarding possible nocturnal seizures or any sleep disorder. Each referred subject had previously met DSMIV criteria for ADHD of any subtype (APA, 1994): 32 children presented the hyperactive or combined type (76.1) and 10 the inattentive type (23.8). Oppositional-defiant disorder (ODD) was present in 27/42 children (64.2%). Both children and parents were assessed by means of a semi-structured psychiatric interview (Kiddie–Sads). All children underwent neurological examination in order to exclude neurological disease. Subjects with known seizures or intellectual disability were preventively excluded from the study. Neuroimaging by magnetic resonance imaging (MRI), was negative in all patients. Co-morbidity between ADHD and other developmental disorders (reading disability, language, Tic, sleep and eating disorders, dyspraxia) was screened in all subjects. All patients were recruited at the moment of their first diagnosis, and none received any medications until they all underwent overnight polysomnographic evaluation. Written informed consent was obtained from the parents of all participants.

Measures

Neuropsychological and behavioural measures

All children underwent neuropsychological assessment including cognitive, memory, visual-perception and attention ability. Also behaviour rating scales were collected from parents and teachers for all patients.

Intellectual ability

Each child was tested on the complete form of the Revised Wechsler Intelligence Scale for Children (WISC-R). All sub-scales scores were used to estimate the cognitive profile of the subjects. All verbal subtests (information, similarities, vocabulary, arithmetic, comprehension, digit span) and performance subtests (picture completion, block design, object assembly, coding, mazes) were evaluated.

Memory

Three TOMAL (Test of Memory and Learning, Reynolds and Bigler, 1995) subtests were administered: word selective reminding (WSR TOMAL), paired recall (PR TOMAL), memory-for-location (MFL TOMAL). These subtests evaluate verbal and visual—spatial short term memory.

Visual perception

The Visual-Motor Integration Test (VMI, Beery and Buktenica, 2000) measures visual-motor integration ability by means a copying task of geometric figures.
Attention
Small bells test (Biancardi and Stoppa, 1997) measures selective-visual attention ability. It is a figure cancellation task consisting of groups of objects’ pictures randomly interspersed with a designated target object (small bell). The child is instructed to cross out all target objects. The test considers two scores: the first one is the total number of objects detected during the trial (accuracy); the second one is the number of bells detected in the first 30 s (speed).

Behaviour rating scales
ADHD-RS (Du Paul et al., 1998) were completed as the first stage of the initial assessment by a trained clinician with experience in ADHD. On the basis of the informant’s descriptions of the child’s behaviours, the interviewer rates the frequency and severity of the child’s behaviours on 4-point scales (0–3). At the second stage, parents and teachers were asked to rate child behaviour, using the Conners’ Teachers Rating Scale (CTRS), Conners’ Parents Rating Scales (CPRS) (Conners, 1989) and SNAP IV Rating Scales (short form) (Swanson, 1992).

As for the SNAP-IV the interview provides measures on three separate subscales: (1) Inattention (time spent on a single activity), (2) Activity Level (rating of restlessness, fidgetiness, and activity level, in structured situations such as meals and car trips) and (3) defiance/antisocial behaviour (items concerning temper tantrums, lying, stealing, defiance, disobedience, trucancy, and destructiveness).

Sleep and neurophysiological assessment

Sleep questionnaire
All children filled out a validated pediatric sleep questionnaire and went through a structured sleep interview with their parents before all night video-PSG.

Nocturnal video-polysomnography (video-PSG)
Sleep EEG recording included 18 leads (21 electrodes, 10–20 system), EOG, submental, bilateral anterior tibialis and masseter EMGs, oronasal flow, thoracic and abdominal pneumograms, ECG and oxymetry. In order to assess sleep quality with a simple global evaluation, we did take into consideration sleep efficiency (total sleep time/total time in bed %), of all variables referring to sleep structure and continuity.

EEG Variables
We considered: presence or absence of seizures; presence or absence of epileptiform generalized or focal EEG discharges occurring without apparent clinical events (IEDs); localization of IEDs foci (centro-temporal, frontal, temporal—occipital).

Statistical analysis
Spearman correlation coefficients ($p < 0.05$ criterion level) were used to examine the association between cognitive and behavioural variables and clinical (co-morbidity) and EEG variables.

Results
Demographic and clinical characteristics of the children participating in the survey are presented in Table 1.

Most children/parents (86%) reported sleep disorders during the administration of the structured sleep interview, of which 26% would fit the diagnosis of RLS by the IRLS-SG Criteria for a pediatric population (Allen et al., 2003). The video-PSG confirmed these reports: sleep related movement disorders in 73.8% of children, disorders of arousal in 47.6% and sleep related breathing disorders in 21.4% of children.

None of the subjects affected by ADHD showed intellectual deficit (mean IQ in 94.7, $\pm$ 15.2). 6% had co-morbid Tic disorder; 12.8% language disorders, 33.3% specific learning disorders, 12.8% dyspraxia, 7.6% eating disorder. No seizure history was reported during the interview but 18.7% had an abnormal routine EEG. On video-PSG, 53.1% children had IEDs (28.2% centro-temporal spikes (Fig. 1), 12.5% frontal spikes (Fig. 2), 9.3% temporal—occipital spikes and 2.3% generalized S—W).

Nocturnal seizures were recorded in three patients: two with atypical interictal rolandic spikes and one with left frontal slow abnormalities. Children had two, eight (of which six paroxysmal arousals) and one nocturnal ictal

Table 1 Demographic and clinical characteristics of 42 children with ADHD

| Mean (age) | 8.9 years, $\pm$ 2.8 |
| Sex (M/F) | 35 males/7 females |
| Intelligence quotient | 94.7, $\pm$ 15.2 |
| ADHD subtype (%) | | |
| Hyperactive and combined | 76.1 |
| Inattentive | 23.8 |
| ODD | 64.2 |
| Co-morbidity (%) | | |
| Dyslexia | 33.3 |
| Language disorder | 12.8 |
| Tic disorder | 6 |
| Eating disorder | 7.6 |
| Sleep disorders | 86 |
| Dyspraxia | 12.8 |
| EEG variables (%) | | |
| Abnormal routine EEG | 18.7 |
| Nocturnal seizures | 7.1 |
| IEDs (video-PSG) | 53.1 |
| Frontal | 12.5 |
| Centro-temporal | 28.2 |
| Temporal—occipital | 9.3 |
| Generalized S—W | 2.3 |
| Sleep disorders by structured sleep interview (%) | | |
| Total disorders | 86 |
| Restless Leg Syndrome (RLS) | 26 |
| Sleep disorders by video-PSG (%) | | |
| Sleep related movement disorders | 73.8 |
| Disorders of arousal | 47.6 |
| Sleep related breathing disorders | 21.4 |
EEG abnormalities and ADHD

Figure 1  Sleep stage 2. Atypical interictal rolandic spikes and spike and wave complexes in a child who subsequently showed hypermotor seizures during sleep.

episodes respectively. Seizures semeiology was typical of frontal or insular hypermotor seizures; their origin being right frontal, right central or not clearly identifiable, respectively. No children presented with spikes during their seizures.

Neuropsychological and behavioural variables correlation (Spearman coefficient)

No statistical correlation was found between behavioural indicators and seizures/IEDs presence, while a significant
relationship emerges between some cognitive abilities and epileptic variables. Conversely, a sleep disorder such as RLS, seem to have a stronger impact on behavioural rather than cognitive indicators. In fact there was a significant correlation between RLS diagnosis and inattention, impulsivity/hyperactivity, oppositional behaviours scoring, as emerged by CPRS (p < 0.01), CTRS (p < 0.05), SNAP-I (p < 0.01), SNAP-H (p < 0.05) and SNAP-O (p < 0.05).

As for the cognitive abilities, we describe a negative relation (p < 0.05) between the presence of nocturnal seizures and WISC-R IQ total and verbal score, similarities WISC-R subtest score and TOMAL-MFL score (see Table 2). It means that our ADHD children with nocturnal seizures performed worse in some WISC-R verbal cognitive tasks, and in particular in analogical reasoning, and in a short term spatial memory task. A significant relationship emerged also between some cognitive variables and interictal rolandic spikes, the latter being negatively related with TIQ, PIQ and Vocabulary subtest score of WISC-R scale (see Table 2). Language disorder and Dyspraxia co-morbidity was positively related to the presence of frontal interictal spikes (p < 0.05), while Tic co-morbid disorder with the presence of a temporal—occipital focus (see Table 2).

Sleep efficiency (SE%) showed a positive correlation with two WISC-R subtest scores: arithmetics (p < 0.05) and coding (p < 0.01). It was also significantly related to a short term verbal memory task (TOMAL Word Selective Remanding score). Dyspraxia and SE were inversely related: a lower SE% being associated with a higher presence of dyspraxia.

### Discussion

ADHD and epilepsy co-occurrence have been studied by several authors in samples of ADHD as well as in epileptic children. For instance data collected through the use of a structured telephone interview found a prevalence rate of 37% for ADHD-I and 29% for ADHD-H in children with newly diagnosed unprovoked seizures compared to healthy controls (Hesdorffer et al., 2004). Conversely no or slightly (2% versus 1% in the pediatric population) increased risk of seizures associated with ADHD was reported by Williams et al. (2001) and Ishii et al. (2003). In our newly diagnosed ADHD children seizure prevalence accounted for 7.1%. This apparently discrepant prevalence may depend on a data collection bias since in our sample, seizures presence was never reported by parents and was a fortuitous finding on nocturnal video-EEG. Conversely the few data reported by literature refer to telephone interviews. Given the known prevalence of sleep disorders in the ADHD population, it is possible that some of the reported hypermotor behaviours during the night could be diagnosed as nocturnal seizures when properly recorded by an extended EEG montage. For this reason our data could reflect a more objective prevalence of paroxysmal events than previous reports. Many data exist about IEDs prevalence in ADHD children. The positive predictive value of IEDs presence for developing subsequent seizures in ADHD children was 14% in a recent literature review (Richer et al., 2002). The authors run to the conclusion that the routine use of EEG in the evaluation of ADHD is currently unwarranted. However it is well known that even subclinical epileptic discharges alone could cause transient cognitive impairment (TCI). Binnie demonstrated that TCI actually occurs during approximately 1/3 of discharges in 2/3 of patients (Binnie, 1993). Some epileptic syndromes such as Electrical Status Epilepticus During Sleep (ESES) and Landau–Kleffner Syndrome (LK) provide good example of a cause-effect correlation between severe epileptiform EEG discharges and specific cognitive deterioration (Metz-Lutz and Filippini, 2006; Scholtes et al., 2005).
In our ADHD children, seizure presence seems to affect total and verbal WISC-R IQ score with specific falls in anal- 

gorical reasoning and a short term spatial memory task. As for a specific subtests deficient performance, Metz-Lutz and Filippini (2006) found a decrease in two verbal subtests: digit and vocabulary, as well as two from the performance score: block design and coding, in rolandic epilepsy, suggest- ing that these deficits resulted from a long standing effect of reported SW during sleep. Conversely the involvement of 

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As for the presence of IEDs without clinical seizures, in 

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In our sample, the involvement of orbito frontal or mesial frontal regions, as suggested by the hypermotor aspects of our recorded nocturnal seizures, are more linked to disrupted sleep and daytime sleepiness and related with behavioural rather than cognitive disturbance. Lateralization of focus in the absence of a structural lesion does not seem to specifically affect cognitive impairment. It is interesting to notice that at least in two of our children with clearcut interictal bilateral rolandic and occipital foci, seizures appeared to originate, EEG wise, from the right frontal and central leads.

As for the presence of IEDs without clinical seizures, in our population we found an overall presence (53%), by all night EEG recording, mainly distributed over rolandic areas (28.2%), against Holtmann et al., 2003 (5.6%) in daytime routine EEGs, well beyond the usual range in school aged children, thus underlining the exquisite yielding power of all night EEG recording.

Several literature reports have just underlined the role of Rolandic focus in cognitive dysfunction in subjects with Rolandic spikes (Piccirilli et al., 1994). Problems in attention or language processing in children with rolandic epilepsy are considered a result of a mild epileptic encephalopa- thy due to frequent discharges in sleep (Sánchez-Carpintero and Neville, 2003; Pinton et al., 2006) or to a poor day- 
time alertness related to sleep fragmentation (Kohrman and Carney, 2000). More recent works reported subtle neurocog- nitive deficits in the domain of phonological awareness, visual—spatial memory and drawing with lower academic abilities (Northcott et al., 2005; Pinton et al., 2006) related to rolandic focus. In our sample both TIQ and PIQ scores were inversely related to the presence of centro-temporal IEDs, suggesting a negative impact on cognition for rolandic foci in ADHD children. Moreover, our remarks support the hypothesis that rolandic discharges may play a significant role in the expression of the cognitive disabilities also in ADHD children. A relevant, even if generic finding relies in the association between frontal IEDs and language disorders and dyspraxia when co-morbid with ADHD. Such evidence puts the emphasis upon the frontal involvement in ADHD and could suggest a common origin for both motor and linguistic anomalies. The idea that the frontal cortex is involved in ADHD receives support from structural (Casey et al., 1997; Castellanos et al., 1996; Filipek et al., 1996) and functional (Casey et al., 1997; Castellanos, 1997; Rubia et al., 1999) neuroimaging research. Denckla (2003) suggests that the presence of subtle motor signs at motor examination in ADHD children could provide a confirmation for the biological basis of the observed symptoms and for the involvement of more than one brain system/circuit.

We hypothesize that the co-occurrence of frontal IEDs with two of the most frequent ADHD co-morbid disorders (lan- 

guage and dyspraxia) might constitute a further element in favor of plural circuits involvement and represent a salient diagnostic finding for the definition of ADHD co-morbid prophile.

In the literature there are several indications of a similar neurobiological basis for ADHD, Tic Disorder and Tourette’s Syndrome that are all characterized by an impairment of executive functioning and often co-occur. Children with Tourette’s syndrome plus ADHD have more additional co- 

morbid disorders overall and lower psychosocial function than children with ADHD alone (Spencer et al., 1998). Neu- 

roimaging studies show the involvement of orbito-frontal, midtemporal, and parieto-occipital regions and suggest that a broadly distributed cortical systems may be impaired in the TS (Moriarty et al., 1995; Peterson et al., 2001; Vloet et al., 2006). Impairment of executive functions (EF), in particular inhibitory deficits, may be directly linked to brain abnor- 

malities (Roessner et al., 2006). IEDs presence in the ADHD plus Tic disorder phenotype might have a further disturbing impact on cerebral circuits involved in executive and motor control.

As for sleep variables and co-morbid sleep disorders, we found RLS scores to be significantly related to all behavioural 

ratings while sleep efficiency, reflecting continuity against major disruption, positively and significantly affected verbal and non verbal intellectual abilities and verbal memory, in agreement with findings typical of adult chronic insomnia.

The correlations between the neuropsychologi- 

cal/behavioural and epileptic variables in our sample of ADHD children, suggest that sleep disorders have a stronger impact on behavioural rather than cognitive indicators, as already described by others papers (Chervin et al., 2002; Silvestri et al., 2005). Conversely seizures/IEDs presence seem to play a stronger role on cognitive abilities rather than behavioural patterns in our sample of ADHD children.

We recognize several limitations to our study mainly due to a relatively small sample size from a single site which might not be representative of the entire ADHD population. In particular the fortuitous finding of nocturnal seizures in only three patients makes it difficult to draw any defini- 

tive statement about the additive effect of seizures over cognition.

In conclusion, we suggest that more attention should be 

given to the yielding power of EEG in ADHD. Our findings 

show that ADHD is a condition often associated with EEG 
epileptiform abnormalities, that could contribute to some of the cognitive aspects typical of ADHD. However, further studies are needed to better explain the nature of this asso- 

ciation.

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