

# DEVELOPMENT, COGNITION & PSYCHIATRY

## FP51

### CHILDREN WITH AUTISM AND EPILEPSY: A DESCRIPTIVE CLINICAL COHORT STUDY FROM SOUTH AFRICA

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**Introduction:** Seventy percent of children with an Autism Spectrum Disorder (ASD) have a co-morbid disorder <sup>2</sup> of which epilepsy is one of the most common<sup>3</sup>. In children with an ASD intellectual disability<sup>1</sup>; female gender<sup>1</sup> and age > 10 years<sup>4</sup> are additional risk factors for epilepsy. In resource poor settings such as South Africa little is known about the prevalence of epilepsy or its particular phenotype in children with ASDs.

**Methods:** A retrospective folder review of children diagnosed with an ASD attending a tertiary neurodevelopmental clinic in South Africa over a five year period (2009-2013). The children were identified using the computerised hospital diagnostic coding system and cross-referenced against clinical databases. Folders of relevant patients were then individually reviewed and relevant data collected. Local ethics committee approval was obtained.

**Results:** Seven hundred and thirty-three children (<13 years) with an ASD were seen over this time period. The prevalence of epilepsy in this cohort will be described.

**Conclusion:** Both autism and epilepsy are chronic disorders with significant impact on the lives of the children and their families. Identifying children with both these disorders may facilitate improved health care delivery and collaboration between specialist teams. This will be the first South African review of the profile of epilepsy in ASDs.

## FP52

### COGNITIVE PROFILE, NEUROPSYCHOLOGICAL DISORDERS AND CONCERNS IN PATIENTS WITH NEUROFIBROMATOSIS TYPE 1

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**Introduction:** Patients with Neurofibromatosis type 1 (NF1) often show learning disabilities and cognitive difficulties, causing concerns in parents.

**Aim:** To describe the cognitive and neuropsychological profile and parent's concerns in patients with NF1.

**Methods and materials:** Descriptive cross sectional study of patients with NF1. Patients underwent a neuropsychological evaluation to determine cognitive profiles.

**Results:** We included 40 patients (60% male) with a mean age of 9.75 years (SD ± 3.8). The average Full scale Intelligence Quotient (IQ) was 88.53 (SD ± 11.18). 40% of patients showed a significant discrepancy between verbal and performance IQ.

Parent's most common concerns were: attentional problems (50%), learning problems (30%) and motor skills (10%) nevertheless 25% did not report any difficulties. Evaluations showed: coordination disorders (50%), Attention Deficit Hyperactivity Disorder (ADHD) 32.5%, Non-Verbal Learning Disorder (NVLD) 27.5%, expressive language disorders (50%), borderline IQ (5%), intellectual disability (2.5%). 60% fulfilled more than one of the previous diagnosis, 80% presented at least one diagnosis.

**Conclusion:** We observed a higher prevalence of ADHD, NVLD, language and fine motor disorders. Results indicated that most patients had more than one neurocognitive disorder. Parents detected fewer difficulties than formal tests did. We emphasize therefore the importance of formal testing in order to start early and appropriate treatment.

## FP53

### CONNERS' CONTINUOUS PERFORMANCE TEST PROFILE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN RELATION TO THEIR INTELLECTUAL PERFORMANCE

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**Introduction:** Attention Deficit Hyperactivity Disorder (ADHD) constitutes a high prevalence disorder. The effect of intelligence in vigilance tasks has been studied, with discordant results. Therefore we are interested in comparing the Conners' Continuous Performance Test II (CPTII) performance according to intellectual performance.

**Aim:** To analyse CPT II profiles in children with ADHD in relation to their intellectual performance (IP).

**Methods and Materials:** Descriptive, analytical, cross sectional study. We included patients with ADHD diagnosis (DSM IV). Patients were divided into two groups according to their Full scale intellectual quotient (FIQ, Weschler scale): Normal intellectual performance (IP) for those with FIQ 80 and above, or low IP for those with FIQ 79 or below. The Conners' Parent Rating Scale - Revised (short version) was also administered.

**Results:** 125 patients were included, 72% belonged to the normal IP group. The age in this group was lower (9.4 years vs 10.5; p=0.03), and the FIQ score was 93.25 vs. 68.42 (p<0.001). Patients from the low IP group presented more omissions when compared to normal IP group (63.28 vs 54.87; p< 0.02) and slower response time (66.28 vs. 55.86; p<0.001). Both groups reported above cut-off scores for inattention and hyperactivity indexes in Conners' scale.

**Conclusion:** Profiles in CPT differed according to Intellectual Performance. We observed that CPTII was more useful in detecting attention failures in patients with low IP, despite the fact that both groups had clinical indicators of inattention.

## FP54

### SCHOOLING OF EPILEPTIC CHILDREN. FACTORS ASSOCIATED WITH THE NEED FOR SCHOOL SUPPORT

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**Introduction:** Patients with epilepsy often have academic difficulties, even with normal intellectual performance.

**Aim:** To determine the prevalence of school support (SS) in epileptic patients and to analyze associated factors.

**Material and methods:** Descriptive analytical cross-sectional study. Patients were divided into two groups: Idiopathic Epilepsy (IE) and Non Idiopathic Epilepsy (NIE). SS was defined by the need for grade retention, mainstream schooling with coaching assistance, or special education.

**Results:** We included 175 patients; the median age was 4 years (IQR 2-8). 51% of the population belonged to the IE group. The overall prevalence of SS was 34%. However, the need of SS in NIE was 52% vs. 13.4% in IE (p<0.01). Other variables associated with SS in the univariate analysis were: refractory epilepsy OR 4.09 (95% CI 1.82 to 9.26), polytherapy OR 3.68 (95% CI 1.80 to 7.57) and intellectual disability OR 8.90 (95% CI 3.68 to 20.99); p < 0.01. In the multivariate analysis, the variables that were independently associated were: NIE OR 5.73 (95% CI 2.52-13.01); p< 0.01, and intellectual disability OR 4.55 (IC95% CI 2.02-10.20); p <0.01. ROC analysis of this model showed an area under the curve of 0.79.

**Conclusions:** Epileptic patients have a high prevalence of school support. The variables that were independently associated were the presence of non- idiopathic epilepsy and intellectual disability. This group of patients should be closely monitored for possible struggles in school.

**FP55****FMR1 INTRON 1 METHYLATION ANALYSIS: AN EPIGENETIC BIOMARKER FOR THE NEURODEVELOPMENTAL PHENOTYPE OF CHILDREN WITH FRAGILE X.**

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**Introduction:** Fragile X syndrome (FXS) is the leading cause of inherited intellectual disability and is usually caused by a CGG expansion in the *FMR1* gene and the associated epigenetic silencing. Recent studies have shown that *FMR1* intron 1 methylation is significantly associated with verbal cognitive impairment in adults, but this has not been shown in children. Furthermore, variation in *FMR1* intron 1 methylation between blood, saliva and buccal samples has not been previously described.

**Methods:** A cohort of 40 children carriers of *FMR1* expanded alleles, depending on their age, were administered either The Mullen Scale of Early Learning, the Wechsler Preschool and Primary Scale of Intelligence III edition or The Wechsler Intelligence Scale for Children IV edition. Molecular parameters included CGGs repeats size and *FMR1* intron 1 methylation in venous blood, saliva and buccal swabs samples.

**Results:** Preliminary analysis of 10 participants has shown a significant correlation between *FMR1* intron 1 methylation in blood, saliva and buccal samples and overall cognitive functioning ( $p < 0.001$ ). There was no significant difference in methylation of this region between tissue types.

**Discussion:** *FMR1* intron 1 methylation can be analysed in saliva and/or buccal swabs samples as a non-invasive alternative to venous blood for diagnosis of FXS. The pending analysis of the entire cohort with additional clinical data aims to unravel the potential prognostic applications of these biomarkers for the type and severity of neurodevelopmental impairments in FXS children.

**FP56****THE FIRST EUROPEAN STUDIES OF LISDEXAMFETAMINE DIMESYLATE IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER**

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**Introduction:** Lisdexamphetamine dimesylate (LDX) is a long-acting prodrug stimulant for the treatment of attention-deficit/hyperactivity disorder (ADHD).

**Objective:** Review efficacy and safety data from two double-blind randomized trials (SPD489-325 and SPD489-326) in patients with ADHD (6–17 years).

**Methods:** In SPD489-325, patients received placebo, dose-optimized LDX or reference treatment (osmotic-release oral system methylphenidate [OROS-MPH]) for  $\leq 7$  weeks. The primary efficacy measure was ADHD Rating Scale IV (ADHD-RS-IV) total score. Statistical comparison of LDX versus OROS-MPH was not pre-specified. In SPD489-326, a  $\geq 26$ -week open-label LDX treatment period preceded a 6-week, placebo-controlled, randomized-withdrawal period (RWP). The primary endpoint was treatment failure ( $\geq 50\%$  increase in ADHD-RS-IV total score and  $\geq 2$ -point increase in Clinical Global Impressions-Severity score from RWP baseline). Efficacy was assessed in the full analysis sets.

**Results:** In SPD489-325 ( $n=317$ ), placebo-adjusted least-squares-mean changes in ADHD-RS-IV total score from baseline to endpoint were: LDX,  $-18.6$  (95% confidence interval [CI]:  $-21.5, -15.7$ ;  $p < 0.001$ ; effect size 1.80) and OROS MPH,  $-13.0$  ( $-15.9, -10.2$ ;  $p < 0.001$ ; 1.26). In SPD489-326 ( $n=262$ , open-label period;  $n=153$ , RWP), 15.8% and 67.5% of patients receiving LDX and placebo, respectively, met treatment failure criteria at RWP endpoint (difference:  $-51.7\%$ ; 95% CI:  $-65.0\%, -38.5\%$ ;  $p < 0.001$ ). Treatment-emergent adverse events occurring in  $\geq 10\%$  of LDX-treated patients were decreased appetite, headache, decreased weight, insomnia, anorexia and nasopharyngitis.

**Conclusions:** Short-term LDX treatment improved symptoms of ADHD in children and adolescents. Continued LDX treatment was associated with maintenance of efficacy compared with placebo. The LDX safety profile was generally consistent with that of stimulant therapy.

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**FP57****PHARMACOKINETICS AND PHARMACODYNAMICS OF THE PRODRUG STIMULANT LISDEXAMFETAMINE DIMESYLATE IN CHILDREN AND ADOLESCENTS WITH ADHD**

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**Introduction:** Data will be presented on the systemic exposure to *d*-amphetamine and the duration of therapeutic action of the *d*-amphetamine prodrug lisdexamphetamine dimesylate (LDX).

**Methods:** In study NRP104.103, plasma *d*-amphetamine was measured after single doses of LDX (30mg, 50mg or 70mg) in patients (6–12 years) with attention-deficit/hyperactivity disorder (ADHD). Study SPD489-325 was a 7-week, randomized, double blind, placebo- and active-controlled trial of LDX (30mg, 50mg or 70mg) in patients (6–17 years) with ADHD. Osmotic-release oral system methylphenidate (OROS-MPH) was the reference treatment. On days 0, 28 and 49, patients were assessed using the Conners' Parent Rating Scale-Revised (CPRS-R) at 10:00, 14:00 and 18:00hrs following dosing at 07:00hrs.

**Results:** Of 18 patients randomized in NRP104.103, 17 completed the study. Plasma *d*-amphetamine concentrations peaked with mean  $T_{max}$  in the range 3.41–3.58h, and declined with mean half-life in the range 8.61–8.90h. Of 336 patients randomized in SPD489-325, 317 comprised the full analysis set and 196 completed the study. Compared with placebo, both LDX and OROS-MPH treatment significantly improved CPRS-R scores at all three assessment times ( $p < 0.001$ ) with effect sizes of 1.424, 1.411 and 1.300 for LDX and 1.036, 0.976 and 0.922 for OROS-MPH, respectively. Post-hoc analyses showed improvements were significantly greater ( $p < 0.02$ ) for LDX than OROS-MPH, with effect sizes of 0.387, 0.435 and 0.377 at each time point.

**Conclusion:** Following an early morning dose of LDX, improvements in CPRS-R scores in children with ADHD are maintained throughout the day, consistent with the plasma *d*-amphetamine concentration-time profile.

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**FP58****ANALYSIS OF MOTOR PERFORMANCE IN INFANTS WITH CONGENITAL HYPOTHYROIDISM WHO BEGAN TREATMENT IN THE FIRST MONTH OF LIFE**

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**Abstract:** Congenital hypothyroidism (CH) is an endocrine disease caused by thyroid hormone deficiency, which leads to neurological disorders if not treated adequately.

**Purpose:** The aim of the present study was to analyse the motor performance of infants with CH who began treatment in the first month of life in comparison to healthy controls.

**Methodology:** The evaluations involved 52 infants [25 with CH (mean age:  $7 \pm 3$  months) and 27 without CH (mean age:  $9 \pm 2$  months)] in follow up at a neonatal reference centre. The Bayley-III scale was used to evaluate fine and gross motor performance, which was categorized as competent or non-competent (risk or emerging risk). Age as the onset of treatment and the normalization of thyroid hormones were also analysed. Statistical analysis involved the chi-squared test ( $p < 0.05$ ).

**Results:** Among the infants with CH, treatment was begun by 17 days of life in 25%, by 23 days in 50% and by 27 days in 75%. At the time of evaluation, all infants had normal thyroid hormone levels. A greater frequency of infants with CH were classified as having non-competent performance [non-competent gross motor performance: 32% of infants with CH vs. 11% of controls ( $p = 0.065$ ); non-competent fine motor performance: 36% of infants with CH vs. 7.5% of controls ( $p = 0.012$ )].

**Conclusion:** Infants with CH who initiated treatment in the first month of life exhibited gross motor performance comparable to infants without CH regarding gross motor skills, but a poorer performance regarding fine motor skills.

#### FP59

### THE IMPORTANCE OF IDENTIFYING NEUROPSYCHOMOTOR DELAYS IN THE DEVELOPMENT OF YOUNG CHILDREN

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**Introduction:** Pre-Schools are the locus of observation of child, enabling prevention and intervention of those considered at risk. This study identified neuropsychomotor development delays in 3 to 42 month old children. It discussed of educators' knowledge about phases of development.

**Methods:** The study was a prospective trial conducted in nine Pre-School. Caretakers completed a questionnaire socioeconomic and the development of the children. Educators answered on child development and signs of delay noted. The children were evaluated and reevaluated by the Scales Bayley III - Screening Test, in the cognitive, language and motor areas. The sample consisted of 343 children both sexes, with similar socioeconomic conditions receiving the same standard of care. Educators received training and parents attended lectures.

**Results:** 343 children assessed, performance was lower than expected mainly in expressive communication, followed by receptive communication, fine motor, gross motor and cognitive. After six months, 313 (91.2%) were reassessed and 18.2% of them had moved from competent to alert and/or at risk; the others maintained or improved rankings. There were no significant differences according to gender. In multivariate analysis, there was a prevalence of biological risk factors; social and environmental risk factors were not significantly relevant. The educators showed no knowledge about the stages development nor condition to identify signs of delays.

**Discussion:** The findings emphasize the importance of surveillance actions for prevention and care in early childhood. They should be continuous, involving guidance to professionals and parents. We suggest a tool to follow children development in the CEIs.

#### FP60

### UNEXPECTED SUBCLINICAL SPIKES: CLINICAL AND NEUROPSYCHOLOGICAL CORRELATIONS

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**Introduction:** "Subclinical Spikes" (SCS) are electrographic spikes without known or observable clinical seizure manifestations, and may be associated with neuropsychological, behavioural and academic impairments. [Mintz et al. 2009]

**Methods:** Retrospective review and analysis of patients without known epilepsy with unexpected SCS found on digital dense array electroencephalography (dEEG).

**Results:** 27 subjects (20 male, 7 female) ranging in age from three to 13 years (mean 7.5 years) with diagnoses of ADHD, learning disorders and/or behavioural issues who had unexpected SCS on dEEG were identified. Baseline spike burden was determined from a 41-minute

routine awake/drowsy dEEG recording, ranging from 0.07 spikes/minute (spm) to 18.53 spm. Nine patients had frontal spikes, 16 central-temporal and two occipital. 12 subjects had magnetic resonance imaging (MRI), all unremarkable except two: venous angioma and temporal arachnoid cyst. 19 subjects (70%) had baseline neuropsychological (NP) assessments, all with significant abnormalities, including cognitive deficits in working memory, attention and processing speed. 10 subjects (37%) were treated with antiepileptic drugs (AED), all associated with significant spike suppression. Five (50%) had a repeat NP assessment after a one-year interval, all with significant NP improvements.

**Conclusion/Discussion:** Unexpected SCS can be found in patients presenting with cognitive and neurobehavioral disorders not related to epilepsy, and may be associated with impairments of neurological and NP functioning. AEDs can result in improvements in clinical and NP surrogate markers in some patients, associated with concomitant spike suppression, suggesting the concept of "Epilepsy Spectrum Disorders". Further longitudinal studies are needed to define these associations.

#### FP61

### MODULATION OF THE TMS-EVOKED N100 DURING A GO/NO GO TASK IN CHILDREN WITH ADHD

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**Introduction:** The electroencephalographic response following transcranial magnetic stimulation after 100 ms (TMS-evoked N100) is of special interest for the investigation of cortical inhibitory deficits in Attention Deficit Hyperactivity Disorder (ADHD). In healthy subjects, the TMS-evoked N100 decreases during motor response preparation and movement execution and increases during response inhibition. The aim of this study is to investigate the modulation of TMS-evoked N100 at stages of response preparation, activation, execution and inhibition in ADHD patients during a go/nogo task.

**Methods:** 18 children with ADHD and 19 typically developing children, aged 10 to 14 years, all right handed were assessed. TMS was delivered over the left motor cortex, the TMS-N100 was measured at electrode P3. The TMS-evoked N100 was determined at rest and at different time points (50 ms before S2; 150, 300 and 500 ms after S2) in a cued go/nogo task (S1-S2 paradigm).

**Results:** Though the TMS-evoked N100 was not found to be significantly reduced at rest in the ADHD group, a smaller increase in go trials and a smaller decrease after inhibiting a response compared to typically developing children were observed. In go trials, a lower TMS-evoked N100 was associated with a smaller variability of reaction times.

**Conclusion:** A reduced modulation of the TMS-evoked N100 amplitude at response execution and inhibition during a go/nogo task, extends the picture of inhibition deficits at the cortical level in ADHD underlining the relevance of the TMS-evoked N100.

#### FP62

### CORRELATION WITH URINARY NONYLPHENOL LEVELS AND CLINICAL SYMPTOMS IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER

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**Objectives:** Animal studies had revealed that young mice exposed to *p*-nonylphenol (NP), a kind of alkylphenols, might develop motor hyperactivity at adolescence, probably by inhibiting the growth of dopaminergic neurons. This study aimed at clarifying the association between *p*-nonylphenol (NP) exposure and the clinical symptoms of attention-deficit hyperactivity disorder (ADHD) in children.

**Methods:** From July, 2012 to June, 2013, all children newly diagnosed as ADHD in Taipei City Hospital, Zhong-Xiao branch and Yang-Ming branch, were invited to join this study. The diagnosis of ADHD was based on the criteria of DSM-IV-TR. The severity of clinical symptoms of ADHD was quantified by SNAP-IV rating scales, including parent-rating and teacher-rating versions. Blood lead level and urinary NP concentration were analysed for each participant.

**Results:** In total, 35 children with ADHD and 33 normal children as control subjects were enrolled in this study. The average blood lead levels in both groups were similar ( $1.4 \pm 0.6$  v.s.  $1.3 \pm 0.6 \mu\text{g/dL}$ ,  $p=0.49$ ). However, children with ADHD had significantly higher urinary NP concentration than normal controls ( $5.0 \pm 2.3$  v.s.  $3.7 \pm 2.2$  ppb,  $p=0.02$ ). Although there

was no significant correlation found between urinary NP concentration and total SNAP-IV rating scales, a trend association still could be observed between urinary NP levels and hyperactivity/impulsivity scores in teacher-rating SNAP-IV scales (Spearman  $r=0.29$ ,  $p=0.09$ ,  $n=21$ )

**Conclusions:** Significantly elevated urinary NP levels were found in children with ADHD and probably associated with more severe hyperactivity/impulsivity symptoms. These results implied that exposure to NP may be associated with ADHD, especially hyperactivity/impulsivity symptoms.