Neurological Soft Signs in ADHD Patients 6 to 18 Years Old at a University Hospital: A Cross-Sectional Study

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PURPOSE

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children which persists into adulthood. Evidence suggests that the condition is etiologically related to delayed brain maturation. Detection of the presence of neurological soft signs can be a means to assess neuromaturation. The objective of this study was to assess the prevalence of neurological soft signs in ADHD patients and to determine any correlation between the presence of neurological soft signs with age, gender, severity, and type of ADHD which could give further insights into this disorder.

METHODS

A Cross-sectional study was conducted at the Child Neurology and Developmental Pediatrics outpatient clinic which included patients 6-18 years old diagnosed with ADHD as well as healthy controls. Patients with other neurodevelopmental conditions (intellectual disability, metabolic disorder, cerebral palsy, abnormal MRI findings), or any condition that may lead to failure to complete the given tasks such as physical handicap were excluded. Neurological soft signs were measured by utilizing the Physical and Neurological Evaluation for Soft Signs (PANESS) scale.

KEY FINDINGS

A total of 48 patients between 6 and 18 years of age (24 ADHD patients and 24 healthy control) were examined. Neurological soft signs were significantly higher in patients with ADHD and were present regardless of gender, type, and severity of ADHD. ADHD patients performed worse on given tasks as evidenced by higher PANESS scores. There was a weak negative correlation between neurological soft signs and age, indicating that soft sign scores decrease with increasing age. There was no statistically significant difference in neurological soft signs scores between those with medication versus without treatment, except for the dysrhythmia which was significantly higher in the drug-naive group.

SIGNIFICANCE

Neurological soft signs are common in patients with ADHD and add scientific evidence to the predictive value of neurological soft signs as indicators of the severity of functional impairment in ADHD. The prevalence of neurological soft signs is much higher in children with ADHD than in controls which may have the potential to improve sensitivity in the diagnosis of ADHD.

Key words: Neurological soft signs, ADHD, PANESS

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is believed to be the most common childhood behavioral disorder in children, affecting around 5.2% of school-age population globally.[1] It is characterized by inattention, hyperactivity/impulsivity, or combined, and symptoms must be present before 12 years of age.[2] According to the ADHD society of the Philippines, an estimate of 3-5% of the population aged 0-14 years old are affected with ADHD.[3] In the past 2 years, 6% of the patients seen at the Developmental Pediatrics outpatient clinic of the University of Santo Tomas Hospital have been diagnosed with ADHD. ADHD is

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not merely a descriptive behavioral disorder but affects areas of the brain subserving important executive functions such as problem solving, planning ahead, understanding others' actions, and impulse control.

Neurological soft signs (NSS) are non-normative performance on a neurological examination of motor and sensory functioning in the absence of a focal lesion. They are grouped into categories comprising of: integrative sensory functioning, motor coordination, and complex motor sequencing, manifesting as poor coordination, speed or accuracy of limb or axial movements, including those required to keep the balance, dysrhythmias, and overflow are often found during the clinical examination of young children.[4] The links between neurological soft signs in children with attention deficit hyperactivity disorder and their executive function, symptoms of inattention, and hyperactivity-impulsivity remain unclear. But since ADHD is etiologically related to delayed maturation, neurological soft signs could be a tool to assess this. Examination for subtle signs, such as speed of movement, dysrhythmia and overflow with timed movements, provide important information that could increase our understanding of the neurobiological bases of ADHD and the clinical implications of neurological soft signs.[4]

Children with ADHD have been found to differ significantly in terms of soft signs. Scientific contributions on NSS in ADHD have been reviewed and that they support the occurrence of an alteration in the neural networks for motor control inhibition, at the base of the patho-physiology of NSS in children with ADHD, as well as a possible central role of dopamine in this neural circuits.[5] The Revised Neurological Examination for Subtle Signs[6] is sensitive to soft developmental changes and to revealing soft motor deficits in central nervous system development. Denckla proposed a clear distinction between "soft signs" that, although soft, are abnormal at any age and those that would be normal if found in a younger child. Though it is common to detect soft signs in typically developing younger children, persistence of soft signs into later childhood and adolescence implies motor dysfunction and could be a marker for atypical neurological development.[7]

In our review of literature, there are no studies on this subject among Filipino children. This study aims to assess the presence of neurological soft signs among ADHD patients in comparison with healthy controls, and to determine the correlation of NSS with severity and type of ADHD.

STUDY GOALS AND OBJECTIVES

The aim of the study was to compare the prevalence of neurological soft signs in ADHD patients and healthy children 6 to 18 years old seen at the Child Neurology clinics and to determine the clinical correlates of neurological soft signs in patients with ADHD.

STUDY DESIGN AND DURATION OF THE STUDY

This was a cross-sectional study utilizing a scale conducted among ADHD patients and healthy children from March to October 2018 with a duration of 8 months.

DEFINITION OF TERMS

ADHD (attention deficit hyperactivity disorder) – a disorder that manifests in childhood with symptoms of hyperactivity, impulsivity, and/or inattention. The symptoms affect cognitive, academic, behavioral, emotional, and social functioning.
Neurological soft signs - non-normative performance on a neurological examination of motor and sensory functioning in the absence of a focal lesion.
Physical and Neurological Examination for Soft Signs- a tool used to assess neurological soft signs by measuring salient components of motor function, including lateral preference, gaits, balance, motor persistence, coordination, overflow, dysrhythmia, and timed movements

METHODS

In this Institutional Review Board-approved study, purposive sampling was done. All patients diagnosed with ADHD seen at the UST Hospital Child Neurology and Developmental Pediatrics outpatient clinic were screened. ADHD criteria based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was reviewed prior to inclusion. Children from the pediatrics OPD with normal development were included in the healthy control group. The prenatal and birth history as well as developmental and past medical history was reviewed. A thorough physical and neurological examination was done. Excluded in the study were

those having other neurodevelopmental conditions such as intellectual disability, metabolic disorders, cerebral palsy and those with abnormal neuroimaging findings. Children with physical handicap as well as those who failed to complete the given tasks were excluded from the study. The principal investigator explained the study and informed consent to the parents and child during the outpatient consultation. Parental consent was then obtained. Verbal assent was obtained for patients who are aged 7 years old and above. For patients 12 to less than 15 years old, simplified assent form and parental consent were obtained. For patients aged 15 to under 18 years, a co-signed informed consent was obtained with parents. Each patient was provided a copy of the signed informed consent and/or verbal assent. The patients included underwent the examination for neurological soft signs using the PANESS scale. The data was then analyzed statistically.

Screening tool

The revised PANESS scale consists of 21 items that test lateral preferences, gait and station, and coordination (10 of the items are timed). Items include various walking (on the heels, on the toes, and on the sides of the feet), rapid alternating movements, and balancing tasks. It is an observational scale having 21 questions covering gait, stance, laterality, quality of rapid movements, impersistence score, involuntary movement score, repetitive speed of movement score, and sequenced speed of movement score, asymmetrical movement score.[7]

PANESS administration

Requiring only a stopwatch and record form, the PANESS measures salient components of motor function, including lateral preference, gaits, balance, motor persistence, coordination, overflow, dysrhythmia, and timed movements (repetitive and patterned). Lateral preference (hand, foot, eye) is assessed by asking the child to demonstrate a variety of lateralized tasks with the hand, the foot, and the eye.

Assessment of gaits includes asking the child to walk ten paces on heels, toes, and sides of feet, as well as walking ten paces in tandem both forwards and backwards.

Balance is measured by having the child stand on one foot and then hop on one foot; both the right and left foot were tested. Motor persistence and involuntary movements are assessed with three "station" tasks: 1) standing tandem, 2) standing with feet together, arms outstretched with fingers spread and eyes closed, and 3) standing with eyes closed, mouth open and tongue protruding. Motor coordination is examined using a finger-to-nose task in which the child alternates placement of index finger from his/her nose to the examiner's index finger. The task is performed bilaterally. The timed activities assessed in the PANESS include 3 sets of "repetitive" and three sets of "patterned" movements—all performed on the right and left while seated.

Repetitive movements are simple flexion movements that are repeated as quickly as possible, including toe tapping, hand patting, finger-tapping. Patterned movements are alternating patterns of more complex movements performed quickly as possible, including heel-toe tap, hand pronate/supinate, and finger sequence. For all timed movements, the child is instructed to "Do all of these movements as quickly as you can, and as best as you can," the examiner then demonstrates the correct movement and allows the child to briefly practice. Once the child demonstrates a steady pace, the examiner begins timing. The "time to do 20 touches" is recorded for each movement, and includes 20 toe taps, 10 sets of heel-toe taps, 20 hand pats, 10 sets of hand pronate/supinate alternations, 20 finger taps, and 5 sets of finger sequences. Finally, tongue wagging is assessed by asking the child to move his/her tongue laterally back and forth while protruded, touching the corners of the mouth 20 times.

PANESS scoring

Hand preference is determined based on performance of the pantomimed tasks. The child is considered right- (left-) handed if he/she uses right (left) hand to perform 9 or more of the 11 pantomimed tasks. If the child uses his/her non-dominant hand to perform 3 or more of the 11 tasks, he/she is considered "mixed" handed, and left-handed norms are used for scoring. Gaits are scored by counting the number of errors. Overflow movements are considered to represent inefficiency in performing a motor task, and can represent failure of inhibition of prepotent movement.

Overflow is documented during both gaits and timed activities. For gaits, the examiner observes for "foot-to-hand overflow" which involves flexion of hand and wrist while the child is walking on heels, toes and sides of the feet. Awkward posturing of arms, hands or body, is also recorded during stressed gaits. Balance tasks are scored by counting the number of hops for each foot and the time standing on each foot. During tasks of motor persistence, the time the child stands and maintains closed eyes is recorded. In addition, choreiform movements of arms, fingers and tongue are recorded during performance of all station tasks. Errors observed during gait and station tasks are summed and reported as right, left, total "axial" scores. In the finger-to-nose motor coordination task, dysmetria, limb tremor, intention tremor, and past pointing are recorded. For timed movements, overflow is categorized by the proximity of the extraneous movement to the intended movement.

Proximal overflow involves movement of a muscle group in close proximity to the intended movement, and also includes exaggerated movement of the intended body part (e.g., lifting at elbow rather than wrist during hand patting; movement of ring and pinkie finger when tapping index finger to thumb). Orofacial overflow involves movement of mouth, tongue, and facial muscles during hand and/or leg movements. Mirror overflow involves unintended contra-lateral movements of homologous muscles, often observed in distal limbs, which accompany voluntary movements.[8] During timed movements, the time to complete 20 touches, dysrhythmia, and the presence of overflow are recorded. Based on initial findings during the development of the PANESS[6], some tasks were scored (or not scored) as errors based on the age of the child. Some subtle signs are expected in younger children, but not older children (e.g., foot-to-hand overflow when walking on sides of feet is expected in children under 10-years-old, but not those 10 years and older). Thus, an 8-year old showing overflow on that task would not be scored, whereas an 11-year-old with overflow would be scored.

Scores from each section of the PANESS are used to create four summary variables. For these four summary variables, the scores are expressed as either as mean time in seconds or as a sum of right- and left-sided errors. The summary variables include: (1) Total Gaits and Stations, which includes total axial (gait, station and balance tasks) performance errors and total involuntary movements (i.e., tremor, choreiform, abnormal posture); (2) Total Overflow, observed during stressed gaits and timed movements, (3) Total Dysrythmia, observed during timed movements; and, (4) Total Timed Movements, including all thirteen repetitive and patterned movements, and tongue wagging[18].

Sample size:
The target minimum sample size of 48 subjects was achieved, with 24 patients each for the control and the children with ADHD group based on a level of significance of 5% and a power of 80%. The proportions of normal patients expected to have neurological soft signs are 50% (assumed) and 84% in the control and children with ADHD group, respectively.

Sample size formula: [9]

$$N \geq \frac{\left[z_{\alpha}\sqrt{P(1-P)\left(\frac{1}{q_1}+\frac{1}{q_2}\right)} + z_{\beta}\sqrt{\left(\frac{P_1(1-P_1)}{q_1}\right)+\left(\frac{P_2(1-P_2)}{q_2}\right)} \right]^2}{(P_1-P_2)^2}$$

Where:
q1 = proportion of subjects in the control group
q2 = proportion of subjects in the intervention group
Z α/2 = specified size of the critical region (5%) = 1.960
Z β/2 = chosen level of power (80%) = 0.842
P1 = assumed proportion of subjects with observed NSS in the control group = 50%
P2 = assumed proportion of subjects with observed agitation in the intervention group = 84%2
P = q1P1 + q2P2 = (0.5)(0.5) + (0.5)(0.84) = 0.67
N = minimum total number of subjects

Statistical Analysis

Univariate analysis

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion was used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables.

Bivariate analysis

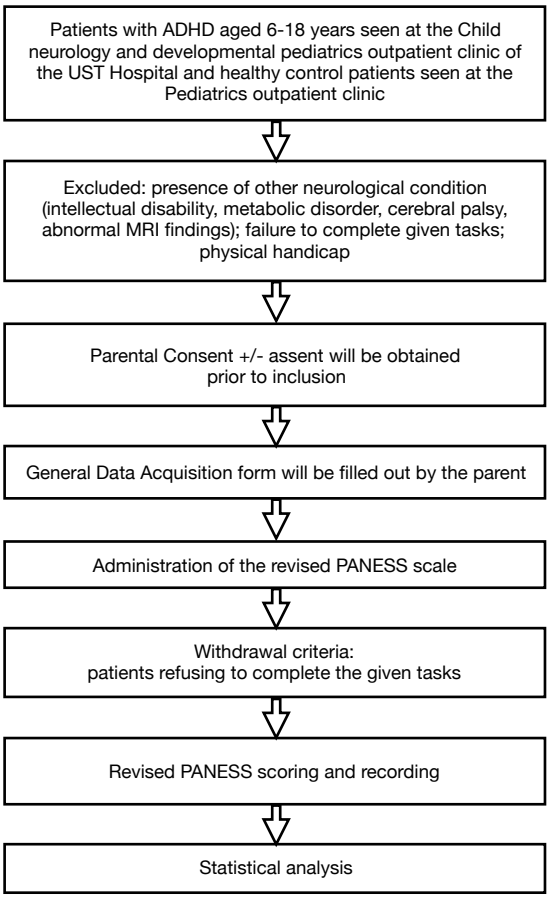
Independent Sample T-test, Mann-Whitney U/ Wilcoxon Sign rank test, and Fisher's Exact/Chi-square test was used to determine the difference of

mean, median and frequency between groups, respectively.

Multivariate analysis
One-way ANOVA and Kruskal-Wallis test was used to determine the difference of mean and median of NSS scores.

All valid data shall be included. Missing data shall neither be replaced nor estimated. Null hypothesis was rejected at 5% alpha level of significance. Data analysis was done via STATA 15.

Figure 1. NSS Study Flowchart from Recruitment to Data Analysis



ETHICAL CONSIDERATIONS

The study was conducted upon approval by the Institutional Review Board and was preceded by a written documentation of informed consent and/or assent. Participation in the study was purely voluntary and without financial compensation. The interviews were recorded only in writing, and not recorded via video nor audio. The responses and patient information were kept strictly confidential by the primary investigator. A unique alphanumeric code was issued to each patient. The data will be stored in the primary investigator's personal database, which is password-protected and the anticipated duration of storage will be at least five years.

CONFLICT OF INTEREST

All Investigators of this study declare no conflict of interest.

RESULTS

A total of 48 patients were included in the study for analysis. We evaluated neurological soft signs in a total of 48 children, 24 of whom were diagnosed to have ADHD. The average age in the ADHD group was 8 years old, and 79% were male. In the healthy control group, the average age was 9 years old, and 54% were male (see Table 1). Comparing the ADHD and healthy controls, we had similar characteristics in terms of age, sex and dexterity. There was no significant difference in terms of perinatal and birth events between the ADHD and healthy control group. In the ADHD group, 70% reported to have a family history of ADHD, 75% currently on medication, and 20% are on occupational therapy (see Table 1).

ADHD was furthered classified as to type and severity in accordance with the DSM-5 diagnostic criteria. In the 24 children with ADHD, the most common type was mixed type with 45.83%, and of mild severity comprising of 62.5% (see Table 1.1). We considered a neurological soft sign to be positive if the child scored above zero for that specific item. Across all categories, the children with ADHD had a higher proportion of positive signs, except for "dysrhythmia and miscellaneous/ involuntary" movements (Table 2).

We also compared actual motor functions scores between the two groups. Similar to Table 2, the scores were consistently higher across motor function categories in the ADHD group (Table 3). The median PANESS score in the ADHD group was 35, which was significantly higher than that of the control group at 8.5 points ($p<0.001$).

Table 1. Demographic profile of 48 pediatric patients examined for neurological soft signs

	Total (n=48)	Control (n=24)	ADHD (n=24)	p-value
	Mean ± SD; Frequency (%); Median (Range)			
Age	9 (6 - 19)	9 (6 - 19)	8 (6 - 19)	0.211*
Sex				0.066†
Male	32 (66.67)	13 (54.17)	19 (79.17)	
Female	16 (33.33)	11 (45.83)	5 (20.83)	
Dexterity				0.318‡
Left	12 (25)	8 (33.33)	4 (16.67)	
Right	36 (75)	16 (66.67)	20 (83.33)	
Pertinent prenatal history				1.000‡
Term	46 (95.83)	23 (95.83)	23 (95.83)	
Pre-term	2 (4.17)	1 (4.17)	1 (4.17)	
Birth history				0.330†
CS	13 (27.08)	5 (20.83)	8 (33.33)	
NSD	35 (72.92)	19 (79.17)	16 (66.67)	
Family history				
Intellectual disability	10 (20.83)	8 (33.33)	2 (8.33)	0.072‡
ADHD	17 (35.42)	0	17 (70.83)	**<0.001‡**
Under medication	18 (37.5)	0	18 (75)	**<0.001‡**
Occupational therapy	5 (10.42)	0	5 (20.83)	0.05‡

*Statistical tests used: * - Wilcoxon rank sum test; † - Chi-square test; ‡ - Fisher's exact test*

Table 1.1 Distribution of type and severity of ADHD in 24 children

	Frequency (%)
Type	
Inattentive	5 (20.83)
Impulsive	8 (33.33)
Mixed	11 (45.83)
Severity	
Mild	15 (62.50)
Moderate	9 (37.50)
Severe	0

Table 2. Comparison of prevalence of neurological soft signs in ADHD and healthy children as to gaits/stations and timed movements tasks

	Total (n=48)	Control (n=24)	ADHD (n=24)	p-value
	Frequency (%)			
Gaits and Stations				
Axial	24 (50)	3 (12.5)	21 (87.5)	**<0.001‡**
Right	17 (35.42)	2 (8.33)	15 (62.5)	**<0.001‡**
Left	19 (39.58)	2 (8.33)	17 (70.83)	**<0.001‡**
Overflow	19 (39.58)	1 (4.17)	18 (75)	**<0.001‡**
Right	19 (39.58)	1 (4.17)	18 (75)	**<0.001‡**
Left	19 (39.58)	1 (4.17)	18 (75)	**<0.001‡**
Miscellaneous/Involuntary	39 (81.25)	16 (66.67)	23 (95.83)	**0.023‡**
Right	33 (68.75)	11 (45.83)	22 (91.67)	**0.001‡**
Left	33 (68.75)	11 (45.83)	22 (91.67)	**0.001‡**
Timed movements				
Overflow	32 (66.67)	11 (45.83)	21 (87.5)	**0.005‡**
Right	27 (56.25)	6 (25)	21 (87.5)	**<0.001‡**
Left	27 (56.25)	6 (25)	21 (87.5)	**<0.001‡**
Dysrhythmia	41 (85.42)	18 (75)	23 (95.30)	0.097‡
Right	33 (68.75)	13 (54.17)	20 (83.33)	0.06‡
Left	36 (75)	16 (66.67)	20 (83.33)	0.318‡
Miscellaneous/Involuntary	4 (8.33)	0	4 (16.67)	0.109‡
Right	4 (8.33)	0	4 (16.67)	0.109‡
Left	3 (6.25)	0	3 (12.5)	0.234‡
SFA	41 (85.42)	17 (70.83)	24 (100)	**0.009‡**
Right	36 (75)	13 (54.17)	23 (95.83)	**0.002‡**
Left	36 (75)	13 (54.17)	23 (95.83)	**0.002‡**

*Statistical tests used: * - Wilcoxon rank sum test; † - Chi-square test; ‡ - Fisher's exact test*

Table 3. Comparison of motor function in children with ADHD vs normal developing children

	Total (n=48)	Control (n=24)	ADHD (n=24)	p-value
	Mean ± SD; Median (Range)			
Gaits and Stations	3.5 (0 - 29)	2 (0 - 8)	14.5 (0 - 29)	**<0.001***
Axial	0.5 (0 - 16)	0 (0 - 4)	3.5 (0 - 16)	**<0.001***
Right	0 (0 - 8)	0 (0 - 2)	1 (0 - 8)	**<0.001***
Left	0 (0 - 8)	0 (0 - 2)	1 (0 - 8)	**<0.001***
Overflow	0 (0 - 6)	0 (0 - 2)	4 (0 - 6)	**<0.001***
Right	0 (0 - 3)	0 (0 - 1)	2 (0 - 3)	**<0.001***
Left	0 (0 - 3)	0 (0 - 1)	2 (0 - 3)	**<0.001***
Miscellaneous/Involuntary	3.67 ± 2.88	1.54 ± 1.44	5.79 ± 2.32	**<0.001§**
Right	1.48 ± 1.34	0.5 ± 0.59	2.46 ± 1.14	**<0.001§**
Left	1.48 ± 1.34	0.5 ± 0.59	2.46 ±1.14	**<0.001§**
Timed movements	13 (1 - 45)	7 (1 - 19)	21 (8 - 45)	**<0.001***
Overflow	2.5 (0 - 16)	0 (0 - 8)	5.5 (0 - 16)	**<0.001***
Right	1 (0 - 8)	0 (0 - 4)	3 (0 - 8)	**<0.001***
Left	1 (0 - 7)	0 (0 - 4)	3 (0 - 7)	**<0.001***
Dysrhythmia	3 (0 - 11)	2 (0 - 6)	3.5 (0 - 11)	**0.009***
Right	1 (0 - 5)	1 (0 - 3)	2 (0 - 5)	**0.014***
Left	1.44 ± 1.13	1 ± 0.83	1.88 ± 1.23	**0.006§**
Miscellaneous/Involuntary	0.17 ± 0.56	0	0.33 ± 0.76	**0.037§**
Right	0 (0 - 2)	0 (0-0)	0 (0 - 2)	**0.043***
Left	0 (0 - 1)	0 (0-0)	0 (0 - 1)	0.077*
SFA	6.5 (0 - 26)	3.5 (0 - 18)	11.5 (2 - 26)	**<0.001***
Right	3.5 (0 - 12)	1 (0 - 8)	6 (0 - 12)	**<0.001***
Left	2 (0 - 12)	1 (0 - 8)	4.5 (0 - 12)	**<0.001***
Total Right Overflow	1.5 (0 - 10)	0 (0 - 4)	5.5 (0 - 10)	**<0.001***
Total Left Overflow	1.5 (0 - 10)	0 (0 - 4)	5.5 (0 - 10)	**<0.001***
Total Overall Overflow	3.5 (0 - 20)	0 (0 - 8)	11.5 (0 - 20)	**<0.001***
PANESS Total	20 (1 - 67)	8.5 (1 - 20)	35 (18 - 67)	**<0.001***

*Statistical tests used: * - Wilcoxon rank sum test; § - Independent sample T-test*

Table 3.1 Correlation of neurological soft sign scores with the severity of ADHD

	Total (n=24)	Mild (n=15)	Moderate (n=9)	p-value
	Mean ± SD; Median (Range)			
Gaits and Stations	14.04 ± 7.17	13.47 ± 8.13	15 ± 5.5	0.623§
Axial	3.5 (0 - 16)	3 (0 - 16)	4 (0 - 9)	0.764*
Right	1 (0 - 8)	1 (0 - 8)	2 (0 - 4)	0.174*
Left	1 (0 - 8)	1 (0 - 8)	1 (0 - 4)	0.561*
Overflow	3.67 ± 2.55	3.2 ± 2.48	4.44 ± 2.6	0.256§
Right	1.83 ± 1.27	1.6 ± 1.24	2.22 ± 1.3	0.256§
Left	1.83 ± 1.27	1.6 ± 1.24	2.22 ± 1.3	0.256§
Miscellaneous/Involuntary	5.79 ± 2.32	5.47 ± 2.59	6.33 ± 1.8	0.388§
Right	2.46 ± 1.14	2.27 ± 1.22	2.78 ± 0.97	0.298§
Left	2.46 ± 1.14	2.27 ± 1.22	2.78 ± 0.97	0.298§
Timed movements	23.79 ± 10	22.27 ± 9.61	26.33 ± 10.68	0.346§
Overflow	7.33 ± 5	6.2 ± 4.83	9.22 ± 4.97	0.156§
Right	3.54 ± 2.43	2.87 ± 2.2	4.67 ± 2.5	0.079§
Left	3 (0 - 7)	2 (0 - 7)	5 (1 - 7)	0.276*
Dysrhythmia	3.79 ± 2.3	3.27 ± 2.71	4.67 ± 1	0.153§
Right	1.63 ± 1.17	1.4 ± 1.35	2 ± 0.71	0.233§
Left	1.88 ± 1.23	1.53 ± 1.36	2.44 ± 0.73	0.078§
Miscellaneous/Involuntary	0.33 ± 0.76	0.27 ± 0.7	0.44 ± 0.88	0.591§
Right	0 (0 - 2)	0 (0 - 2)	0 (0 - 1)	0.646*
Left	0 (0 - 1)	0 (0 - 1)	0 (0 - 1)	0.275*
SFA	12.33 ± 6.91	12.53 ± 7.39	12 ± 6.44	0.859§
Right	5.79 ± 3.22	5.93 ± 3.33	5.56 ± 3.21	0.787§
Left	5.29 ± 3.41	5.53 ± 3.56	4.89 ± 3.3	0.664§
Total Right Overflow	5.38 ± 3.09	4.47 ± 3.16	6.89 ± 2.42	0.061§
Total Left Overflow	5.21 ± 3.23	4.6 ± 3.42	6.22 ± 2.77	0.242§
Total Overall Overflow	11 ± 6.44	9.4 ± 6.73	13.67 ± 5.22	0.118§
PANESS Total	37.83 ± 13.78	35.73 ± 15.06	41.33 ± 11.28	0.347§

*Statistical tests used: * - Wilcoxon rank sum test; § - Independent sample T-test*

Table 3.2 Correlation of neurological soft sign scores with the different types of ADHD

	Inattentive (n=5)	Impulsive-Hyperactive (n=8)	Mixed type (n=11)	p-value
	Mean ± SD; Median (Range)			
Gaits and Stations	9.6 ± 10.11	17.63 ± 6.82	13.45 ± 4.91	0.135ǁ
Axial	1 (0 - 16)	5.5 ± (2 - 16)	4 (0 - 8)	0.183¶
Right	0 (0 - 8)	1 (0 - 8)	2 (0 - 3)	0.277¶
Left	1 (0 - 8)	2 (0 - 5)	1 (0 - 3)	0.333¶
Overflow	2.4 ± 2.61	4.75 ± 2.12	3.45 ± 2.7	0.262ǁ
Right	1.2 ± 1.3	2.38 ± 1.06	1.73 ± 1.35	0.262ǁ
Left	1.2 ± 1.3	2.38 ± 1.06	1.73 ± 1.35	0.262ǁ
Miscellaneous/Involuntary	3.2 ± 2.86	6.5 ± 1.41	6.45 ± 1.86	**0.012ǁ**
Right	1.2 ± 1.3	2.75 ± 0.71	2.82 ± 0.98	**0.014ǁ**
Left	1.2 ± 1.3	2.75 ± 0.71	2.82 ± 0.98	**0.014ǁ**
Timed movements	24.2 ± 8.23	20 ± 10.16	26.36 ± 10.57	0.407ǁ
Overflow	4.2 ± 3.19	7.88 ± 4.7	8.36 ± 5.63	0.295ǁ
Right	2 ± 1.41	3.63 ± 2.26	4.18 ± 2.75	0.258ǁ
Left	2 (0 - 4)	4.5 (0 - 7)	5 (0 - 7)	0.350¶
Dysrhythmia	2.8 ± 2.68	3.5 ± 3.21	4.45 ± 1.04	0.391ǁ
Right	1.2 ± 1.3	1.38 ± 1.6	2 ± 0.63	0.358ǁ
Left	1.2 ± 1.3	1.88 ± 1.46	2.18 ± 0.98	0.348ǁ
Miscellaneous/Involuntary	0 ± 0	0.5 ± 0.93	0.36 ± 0.81	0.528ǁ
Right	0 (0 - 0)	0 (0 - 2)	0 (0 - 1)	0.487¶
Left	0 (0 - 0)	0 (0 - 1)	0 (0 - 1)	0.608¶
SFA	17.2 ± 5.4	8.13 ± 5.54	13.18 ± 7.05	0.053ǁ
Right	7.8 ± 2.49	4.13 ± 2.95	6.09 ± 3.3	0.121ǁ
Left	7.8 ± 3.03	3.25 ± 2.43	5.64 ± 3.5	0.05ǁ
Total Right Overflow	3.2 ± 2.59	6 ± 2.93	5.91 ± 3.21	0.215ǁ
Total Left Overflow	3 ± 2.55	6.25 ± 3.2	5.45 ± 3.3	0.204ǁ
Total Overall Overflow	6.6 ± 5.55	12.63 ± 6.09	11.82 ± 6.68	0.228ǁ
PANESS Total	33.8 ± 17.75	37.63 ± 14.71	39.82 ± 12.12	0.737ǁ

Statistical tests used: ǁ - One way ANOVA; ¶ - Kruskal Wallis test

Table 3.3 Correlation of neurological soft sign scores as to ADHD pharmacotherapy

	With medication (n=18)	Without medication (n=6)	p-value
	Mean ± SD; Median (Range)		
Gaits and Stations	13 ± 7.43	17.17 ± 5.74	0.225§
Axial	3 (0 – 16)	4.5 (1 – 16)	0.401*
Right	1 (0 – 8)	1.5 (0 – 8)	0.863*
Left	1 (0 – 5)	1.5 (0 – 8)	0.393*
Overflow	3.22 ± 2.67	5 ± 1.67	0.142§
Right	1.61 ± 1.33	2.5 ± 0.84	0.142§
Left	1.61 ± 1.33	2.5 ± 0.84	0.142§
Miscellaneous/Involuntary	5.67 ± 2.45	6.17 ± 2.04	0.658§
Right	2.39 ± 1.2	2.67 ± 1.03	0.617§
Left	2.39 ± 1.2	2.67 ± 1.03	0.617§
Timed movements	24.28 ± 9.6	22.33 ±11.94	0.689§
Overflow	7.78 ± 5.11	6 ± 4.86	0.463§
Right	3.78 ± 2.56	2.83 ± 2.04	0.422§
Left	4.5 (0 – 7)	1.5 (0 – 7)	0.361*
Dysrhythmia	3.22 ± 1.73	5.5 ± 3.08	**0.033§**
Right	1.39 ± 0.98	2.33 ± 1.51	0.088§
Left	1.56 ± 1.1	2.83 ± 1.17	**0.024§**
Miscellaneous/Involuntary	0 (0 – 2)	0 (0 – 2)	1.000*
Right	0 (0 – 2)	0 (0 - 1)	0.959*
Left	0 (0 – 1)	0 (0 - 1)	0.727*
SFA	12.94 ± 6.34	10.5 ± 8.8	0.465§
Right	5.94 ± 3.15	5.33 ± 3.67	0.696§
Left	5.56 ± 2.94	4.5 ± 4.81	0.523§
Total Right Overflow	5.39 ± 3.27	5.33 ± 2.73	0.971§
Total Left Overflow	5.28 ±3.34	5 ± 3.16	0.890§
Total Overall Overflow	11 ± 6.71	11 ± 6.13	1.000§
PANESS Total	37.28 ± 13.8	39.5 ± 14.88	0.741§

Statistical tests used: - Wilcoxon rank sum test; § - Independent sample T-test*

Table 3.4 Correlation of neurological soft sign scores as to occupational therapy

	With occupational therapy (n=5)	Without occupational therapy (n=19)	p-value
	Mean ± SD; Median (Range)		
Gaits and Stations	11.8 ± 4.92	14.63 ± 7.65	0.444§
Axial	3 (0 – 8)	4 (0 – 16)	0.519*
Right	2 (0 – 3)	1 (0 – 8)	0.854*
Left	1 (0 – 3)	1 (0 – 8)	0.560*
Overflow	2.8 ± 2.28	3.89 ± 2.62	0.405§
Right	1.4 ± 1.14	1.95 ± 1.31	0.405§
Left	1.4 ± 1.14	1.95 ± 1.31	0.405§
Miscellaneous/Involuntary	6.2 ± 2.28	5.68 ± 2.38	0.668§
Right	2.6 ± 1.14	2.42 ± 1.17	0.763§
Left	2.6 ± 1.14	2.42 ± 1.17	0.763§
Timed movements	24.8 ± 10.89	23.53 ± 10.05	0.806§
Overflow	8.8 ± 6.57	6.95 ± 4.65	0.473§
Right	4.4 ± 3.05	3.32 ± 2.29	0.387§
Left	6 (0 – 7)	2 (0 – 7)	0.563*
Dysrhythmia	4.4 ± 1.14	3.63 ± 2.52	0.519§
Right	1.8 ± 0.84	1.58 ± 1.26	0.716§
Left	2.6 ± 0.55	1.68 ± 1.29	0.141§
Miscellaneous/Involuntary	0 (0 – 2)	0 (0 – 2)	0.826*
Right	0 (0 – 1)	0 (0 – 2)	0.869*
Left	0 (0 – 1)	0 (0 - 1)	0.577*
SFA	11.2 ± 5.26	12.63 ± 7.37	0.690§
Right	5.6 ± 2.51	5.84 ± 3.44	0.885§
Left	4.8 ± 2.17	5.42 ± 3.7	0.725§
Total Right Overflow	5.8 ± 3.83	5.26 ± 2.98	0.738§
Total Left Overflow	5.4 ± 4.1	5.16 ± 3.1	0.885§
Total Overall Overflow	11.6 ± 8.17	10.84 ± 6.17	0.821§
PANESS Total	36.6 ± 13.41	38.16 ± 14.22	0.828§

Statistical tests used: - Wilcoxon rank sum test; § - Independent sample T-test*

Table 4. Correlation of neurological soft sign scores as to both healthy and ADHD group as to age

	Overall	ADHD	Control
	Correlation Coefficient		
Gaits and Stations	**-0.325****	-0.178	-0.397
Axial	-0.221	-0.04	-0.156
Right	-0.125	0.108	-0.255
Left	-0.176	-0.054	-0.133
Overflow	**-0.371****	**-0.467****	-0.307
Right	**-0.371****	**-0.467****	-0.307
Left	**-0.371****	**-0.467****	-0.307
Miscellaneous/Involuntary	**-0.285****	-0.128	-0.311
Right	**-0.306****	-0.158	-0.374
Left	**-0.306****	-0.158	-0.374
Timed movements	0.081	0.345	-0.244
Overflow	-0.284	-0.144	-0.384
Right	**-0.292****	-0.109	**-0.48****
Left	-0.234	-0.103	-0.284
Dysrhythmia	-0.269	-0.042	**-0.478****
Right	-0.106	0.169	-0.356
Left	**-0.429****	-0.352	**-0.506****
Miscellaneous/Involuntary	0.003	0.041	-
Right	0.008	0.058	-
Left	-0.066	-0.083	-
SFA	0.154	**0.607****	0.123
Right	0.143	**0.562****	0.17
Left	0.219	**0.627****	0.18
Total Right Overflow	**-0.336****	-0.241	**-0.497****
Total Left Overflow	**-0.293****	-0.264	-0.3
Total Overall Overflow	**-0.317****	-0.24	**-0.404**
PANESS Total	-0.202	0.099	-0.337

Correlation interpretation: [0-0.2] Very weak; (0.2-0.4] Weak; (0.4-0.6] Moderate; (0.6-0.8] Strong; (0.8-1) Very strong; 1: Perfect; (-) indirect, (+) direct
*** - significant (p-value <0.05)*

Table 5. NSS scores between males and females (n = 48)

	Total (n=48)	Male (n=32)	Female (n=16)	p-value
	Mean ± SD; Median (Range)			
Overflow	0 (0 – 6)	0 (0 – 6)	0 (0 – 6)	0.251*
Right	0 (0 – 3)	0 (0 – 3)	0 (0 – 3)	0.251*
Left	0 (0 – 3)	0 (0 – 3)	0 (0 – 3)	0.251*
Timed movements	2.5 (0 – 16)	4 (0 – 14)	1 (0 – 16)	0.199*
Overflow				
Right	1 (0 – 8)	2 (0 – 6)	0.5 (0 – 8)	0.302*
Left	1 (0 – 7)	1.5 (0 – 7)	0 (0 – 7)	0.127*
Total Right Overflow	1.5 (0 – 10)	2 (0 – 9)	0.5 (0 – 10)	0.275*
Total Left Overflow	1.5 (0 – 10)	2.5 (0 – 10)	0 (0 – 9)	0.106*
Total Overall Overflow	3.5 (0 – 20)	5 (0 – 20)	1 (0 – 20)	0.175*
Gaits and Station	3.5 (0 – 29)	6 (0 – 29)	2 (0 – 25)	0.087*
Axial	0.5 (0 – 16)	1 (0 – 16)	0 (0 – 16)	0.682*
Right	0 (0 - 8)	0 (0 - 8)	0 (0 - 8)	0.798*
Left	0 (0 - 8)	0 (0 -5)	0 (0 - 8)	0.891*
Miscellaneous/Involuntary	3.67 ± 2.88	4.25 ± 2.77	2.5 ± 2.8	0.046§
Right	1.48 ± 1.34	1.69 ± 1.31	1.06 ± 1.34	0.128§
Left	1.48 ± 1.34	1.69 ± 1.31	1.06 ± 1.34	0.128§
Dysrhythmia	3 (0 – 11)	3 (0 – 11)	2 (0 – 7)	0.394*
Right	1 (0 – 5)	1 (0 – 5)	1 (0 – 3)	0.214*
Left	1.44 ± 1.13	1.5 ± 1.19	1.31 ± 1.01	0.593§

*Statistical tests used: * - Wilcoxon rank sum test; § - Independent sample T-test*

Among ADHD patients, moderate severity ADHD group have higher scores however, there was no statistically significant difference in scores of neurological soft signs between mild and moderate ADHD (see Table 3.1).

We have no statistically significant difference in scores of neurological soft signs between inattentive, impulsive, and mixed types, except for "miscellaneous/involuntary," where the inattentive type had significantly lower scores compared to impulsive and mixed types (see Table 3.2).

There was no statistically significant difference in neurological soft signs scores between those with versus without medication, except for the dysrhythmia which was significantly higher in the drug-naïve group (see Table 3.3).

There was no statistically significant difference in neurological soft signs scores between those with versus without occupational therapy. (see Table 3.4).

Overall, there is a weak negative correlation between neurological soft signs and age. This indicates that soft sign scores decrease with increasing age. In the ADHD group, weak to moderate negative correlation was statistically significant in the overflow movements and slow for age scores. In the control group, we also noted a weak and negative correlation between age and NSS for overflow and dysrhythmia scores (see Table 4).

We had insufficient evidence to demonstrate a difference in overflow scores, gaits, .and station, axial, miscellaneous, and dysrhythmia scores between males and females (see Table 5).

DISCUSSION

Attention deficit hyperactivity disorder (ADHD) is a disorder that manifests in childhood and may persist into adulthood with symptoms of hyperactivity, impulsivity, and/or inattention.[10] Besides the "core" symptoms, the motor ability of ADHD children is often significantly poorer than it should be based on their age and level of intellectual functioning.[4] Several papers have already documented the presence of these soft signs, nonetheless this study delved further on correlating PANESS scores with type and severity of ADHD. Attention was also given in investigating whether these scores could be a means to monitor response to treatment. Neurological soft signs are used as a screening tool for psychopathology, and diagnosis of ADHD.[11] In the past, several standardized neurological test instruments in research and clinical practice have been used to identify and quantify neurological soft signs. One of the first was the Physical and Neurological Examination for Soft Signs (PANESS).[12] In clinical practice the revised neurological examination for subtle signs is sensitive to soft developmental changes and to revealing soft motor deficits in central nervous system development.[6]

The following points were identified in our results: 1) across all categories, ADHD patients had significantly higher proportion of positive soft signs except for miscellaneous/involuntary movements. 2) The PANESS scores in ADHD patients were significantly higher as compared to normal developing children. 3) There was no significant difference in terms of neurological soft signs among the inattentive, impulsive and mixed ADHD types except for the miscellaneous/involuntary" where the inattentive type had significantly lower scores. 4) There was no significant difference in scores of neurological soft signs in terms of gender, severity and treatment of ADHD (except for the dysrhythmia which was significantly higher in the drug-naïve group). 5) Neurological soft signs scores decrease with increasing age.

To better understand the role of motor disorders in the gamut of manifestations of ADHD, we assess the specific areas of the nervous system involved in the production of movement. The frontal lobe embodies one-third of the cerebral cortex and its main roles are for superior executive function, emotional regulation and movement control.[13]

Planning of complex behaviors is subserved by the prefrontal cortex which then produces the complex sequences of movement suitable for the task, and the primary motor cortex is responsible for executing skilled movements. All these areas are connected to diverse subcortical structures forming subcortical circuits.[13]

In addition to the prefrontal cortex, there is also involvement of the basal ganglia and the cerebellum as evidenced by magnetic resonance studies.[14, 15] It has been proposed in neuro-psychologic testing that patients with ADHD have impaired executive functions and/or difficulties with response inhibition.[17,18] These excessive movements seem to reflect the immaturity of the neural networks involved in inhibitory control.[16]

Neurological soft signs in ADHD

As hypothesized, our present study significantly revealed the presence of neurological soft signs in the ADHD group as compared to the healthy control. Patients with ADHD showed multiple motor abnormalities as compared to the control group in terms of overflow movements, imbalance and greater motor slowness as exhibited by higher slow for age (SFA) scores. All ADHD patients significantly performed worse on the PANESS scale as demonstrated by higher PANESS scores. These findings are consistent with results of previous studies that emphasized the motor dysfunction in ADHD patients.

Pitzianti et. al. evaluated the attentional and motor functioning of 27 ADHD patients. Results showed that the ADHD patients had impairments in motor function.[31] In a cross-sectional study by Patankar in 2012, neurological soft signs were found in 84% of the 52 Indian children diagnosed with ADHD.[9] Previous studies in congruence with our findings include those done by Uslu[19] , Meyer and Sagvolden[20] and Pitcher in 2003.[21] The higher prevalence of neurological soft signs in ADHD can be explained by a reduction in size of the inferior frontal gyrus, middle and superior temporal gyrus, and anterior cingulate gyrus.[22] Prefrontal striatal circuits underpin executive function and dys-function and has long been considered an important neuropsychological correlate of ADHD.[15] The current findings in our study are speculated to be a manifestation of the "prefrontal-striatal" model of ADHD.

Clinical correlates of neurological soft signs in ADHD

In our study, there is a weak negative correlation between neurological soft signs and age, indicating that soft sign scores decrease with increasing age. This was consistent with the results obtained by Azza[23] and Dickstein[5] , who found that older patients performed better on the neurological soft signs scale. This can be explicated by the hormonal events of puberty exerting profound effects on brain maturation and behavior.[24] More importantly, decrease in soft signs with age is due to the integration of higher order processes such as attention, with lower level neuromotor inhibitory mechanism.[25] This is contrary to the study done by Hadders-Algra wherein neurological soft signs were shown to be low in the preschool age and that there was a steady increase in the frequency of soft signs.[26]

Gender differences in neurological soft signs were insignificant in our study fitting with that of the study done by Gustafsson which showed higher scores in the male population but was not statistically significant.[27] Interestingly, in the study by Larson and colleagues, there was a gender difference for timed patterned movements, but not for timed repetitive movements, suggestive of the fact that the neural pathways and motor systems underlying patterned movement may mature differently in females than in males.[32] Neurological soft signs were not significantly correlated with the type of ADHD except for the inattentive type which had significantly lower scores in terms of involuntary movements. Very few studies have focused on correlations between types of ADHD and soft signs. This finding is similar with one study, wherein children with inattentive type ADHD had significantly poorer fine motor skills, while children with combined type ADHD were found to experience significantly greater difficulties with gross motor skills.[28] A study done by Patankar revealed that the inattentive type had significant overflow movements which is indicative of delayed motor inhibition.[9]

There was no statistically significant difference in scores of neurological soft signs between mild and moderate ADHD in our study in contrast to Patankar et. al.[9] wherein significant scores were higher in more severe ADHD. When compared to normal children, ADHD children significantly differ with respect to soft signs, the more severe the ADHD, the greater are the soft signs. There is certain correlation of NSS with neuro-developmental disorders such as ADHD.[29] There were no severe ADHD subjects enrolled in our study, but looking at the results, the moderate

group showed higher scores though not statistically significant and could be due to low sample size.

There was no statistically significant difference in neurological soft signs scores between those with versus without methylphenidate medication, except for the dysrhythmia which was significantly higher in the untreated group. Likewise, there was no significant difference in NSS sscores between those undergoing occupational therapy and those who are not. This is somehow consistent with the results of the study by Rubia et. al. who demonstrated the effectiveness of methylphenidate on deficits in motor timing in ADHD children and extended its use from the domain of attentional and inhibitory functions to the domain of executive motor timing.[30] This is different to the study done by Azza and colleagues wherein neurological soft signs were not correlated with medical interventions.[23] All errors in particular items of NSS examination are related with planning and controlling action. The motor planning is related to the pre-supplementary motor area and links between the prefrontal cortex, basal ganglia as well as the cerebellum.[27,28] The effect of methylphenidate in lessening NSS is supposed on the dopamine reuptake in basal ganglia, cerebellum and cerebral cortex interconnection.[4] Therefore, it could be considered that methylphenidate acts in similar regions and may improve NSS.

CONCLUSION

Multiple abnormalities of the motor system have been identified in children with ADHD as compared to healthy controls including persistence of overflow movements, impaired timing of motor responses and deficits in fine motor abilities. Majority of the NSS in ADHD were those of slowness of performance during repetitive tasks and miscellaneous/involuntary movements during untimed tasks. The presence of excessive overflow movements in children with ADHD appears to reflect immaturity of the neural networks involved in inhibitory control. These neurological soft signs which are present in all patients with ADHD were noted to decrease with age.

The prevalence of NSS is much higher in children with ADHD than in control and may be of value in the evaluation of this disorder, to improve sensitivity in the diagnosis. An evaluation in the motor function seems to be appropriate because children with ADHD and motor dysfunction in combination have a higher frequency of other problems such as obsessive-compulsive disease, depression and conduct disorder.[6,18] Neurological soft signs were not correlated with gender, type and severity of ADHD. Majority of the NSS had no significant correlation in terms of treatment except for the dysrhythmia which was significantly lower in patients receiving methylphenidate treatment. We suggest that evaluation of NSS may be useful to monitor effectiveness of pharmacological treatment among individual patients where they will serve as their own control.

STRENGTHS, LIMITATIONS AND RECOMMENDATIONS

The inclusion of healthy control made this study more valid. The inclusion of only ADHD without other co-morbidities such as learning disability and psychiatric disorders has lessened the effects of possible confounding variables.

The value of the present results is limited due to a number of reasons. Firstly, there was a wide age range (6-18 years) limiting the number of children at each age level. With greater numbers of children at each age level, more discrete age-related changes might be identified, and better comparisons to performance could be made for all variables at each age level. Although our target sample size was met, only those with mild and moderate ADHD were included in the study. A larger sample size would still be recommended to increase likelihood of measuring soft signs in severe ADHD patients.

In addition, our sample was recruited from a single tertiary hospital, and therefore is not a nationally representative sample. Lastly, the normative data for PANESS was not of Filipino children hence a possible avenue for future research on this aspect.

In an attempt to elucidate the role of NSS in ADHD patients, it is also worth exploring in future studies the effectiveness of pharmacological treatment by evaluating motor functioning of ADHD patients at baseline and after treatment.

Additional studies on several aspects mentioned above will not only enhance our understanding of the biological bases of ADHD but will also add

scientific evidence to the predictive value of neurological soft signs as indicators of the severity of functional impairment in ADHD as well as outcome predictors.

ACKNOWLEDGEMENT

The authors wish to thank Dr. Martha B. Denckla of Kennedy Krieger Institute for sending us the necessary documents for administering the PANESS scale.

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