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URL: http://www.cdc.gov / ncidod/EID/eid.htm

b. Electronic Medium: CD-ROM Monograph

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reeves JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0 San Diego: CMEA; 1995.

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EDITORIAL

Mental Health Law: Quo Vadis?

Republic Act 11036 or the Mental Health Law establishes a national mental health policy for the purpose of enhancing the delivery of integrated mental health services, and promoting and protecting the rights of persons utilizing psychiatric, neurologic and psychosocial health services.

The IRR states in its objectives firstly to strengthen effective leadership and governance for mental health by formulating, developing and implementing national policies, strategies, programs and regulations on mental health. This would involve different sectors in both in the government and private sectors working hand in hand in the formulation and enhancement of said policies. The Internal Review Board constitutes representatives from the Department of Health (DOH), Commission of Human Rights (CHR), a nominated representative from the Philippine Council for Mental Health and other members from which expertise is needed.

Second is the development and establishment of a comprehensive, integrated, effective and efficient national mental health care system responsive to psychiatric, neurologic, and psychosocial needs of the Filipino people. With the current system of health care delivery in our country, integration of the different agencies is vital to be able to deliver a more efficient system of mental health care. The establishment for psychiatric and neurological services in regional, provincial and tertiary hospitals as well as the duties and responsibilities of mental health facilities are a priority.

Third is the protection of rights and freedoms of persons with psychiatric, neurologic and psychosocial health needs. Patients' rights are imperative especially with heightened awareness from the public of both health providers and patient's responsibilities. Social media and advocacy forums have provided avenues in spreading information about these basic rights and mental health conditions such as suicide prevention and persons with disability.

Next is the strengthening of information systems, evidence and research for mental health as well in basic health services as well as the promotion of mental health in educational institutions, workplace and in communities. However, research regarding neurological and psychiatric conditions is still centered within training institutions and universities. There is a

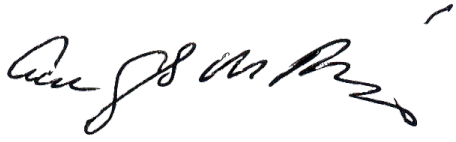
EDITORIAL

need for integrative research in the grassroots involving mental health awareness in communities to educate health workers in the management of basic neurological and psychiatric conditions, and the integration of mental health into the educational system with development of curricula with the Department of Education (DepEd) Commission on Higher Education, Commission on Higher Education (CHED) and Technical Education and Skills Development Authority.

Lastly, the Philippine Council for Mental Health composed of secretaries of DOH, DepEd, DOLE, DILG, Chair of CHR and CHED, and representatives from academe and research, medical and health professional organizations and NGOs were tasked to develop and periodically update the national multi-sectoral strategic plan to accomplish the Mental Health Law's objectives.

With the rights and services accorded, it is not only patients but also family members, caregivers or legal representatives, who are afforded the corresponding privileges. Interestingly, mental health professionals also require a safe working environment and continuing professional education and the choice whether to accept or decline treatment to patients.

The signing of the IRR is a welcome change especially for individuals with mental health conditions and those who take care of them. The continued implementation and collaboration of the various sectors is needed to ensure the success of the law that aims to improve the services and state of its primary stakeholders.



Arnold Angelo M. Pineda, MD, PhD
Editor-in-Chief

ORIGINAL SCIENTIFIC ARTICLES

Clinico-radiologic Profile of a Dorsal Variant of Posterior Cortical Atrophy in a 55- year old Female

Jeryl T. Yu, MD, Jacqueline Dominguez, MD, FPNA, Ma. Socorro Martinez, MD, FPNA, Franz Marie Cruz, MD, DPBO, and Ron Pilotin, MD, FPCR

ABSTRACT

Posterior Cortical Atrophy is a group of neurodegenerative disorders characterized by early, prominent and progressive impairment of visuospatial and visuoperceptual functions in the context of relatively preserved memory and insight in the early phases. Initial visual symptoms are vague, compelling patients to seek ophthalmologic consult. They present with simultagnosia and spatial disorientation, which are often missed by routine ophthalmologic and neurologic exams, causing delay in diagnosis. As the disease progresses, Posterior Cortical Atrophy ultimately leads to a more diffuse pattern of cognitive dysfunction. The underlying pathology is believed to be Alzheimer's Disease and a greater level of amyloid plaques is correlated with earlier clinical symptoms of Posterior Cortical Atrophy. The clinical features of reported cases are heterogenous, leading to a classification of different variants and underlying pathologies. We report the serial clinical, cognitive and imaging data of a variant of Posterior Cortical Atrophy primarily affecting the dorsal stream.

Keywords: Posterior Cortical Atrophy, Alzheimer's Disease, simultagnosia, ApoE polymorphism, amyloid, Dorsal variant, FDG-PET, Neuropsychological testing

INTRODUCTION

Posterior Cortical Atrophy (PCA) is a progressive dementia with a young onset (late 50s and early 60s[1]) presenting with visuospatial and visuoperceptual challenges. Alzheimer's Disease is the most common underlying disease pathology and as the disease progresses, PCA ultimately leads to a more diffuse pattern of cognitive dysfunction. The clinical features of reported cases are heterogenous, leading to a classification of different variants and underlying pathologies.

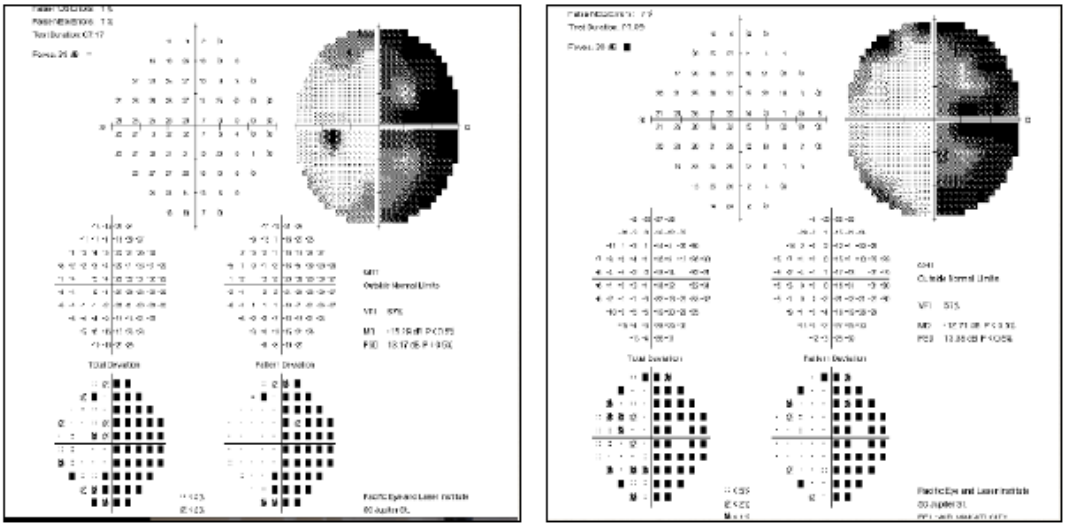
CASE REPORT

A 55-year old right-handed woman, previously healthy, was referred from Ophthalmology service for evaluation of visual changes and progressive symptoms of cognitive decline over the past four years. She had fourteen years of formal education and a degree in Management and previously taught Chinese language. There was no history of head trauma, infection, psychiatric disease, or illicit drug use and no family history of neurodegenerative diseases.

She initially reported difficulty reading and writing. She wrote sentences with missing words and could not write in one line. Most striking was her inability to locate things that were directly in front of her. Ophthalmology consult revealed right homonymous hemianopsia on perimetry (Fig 1). She described the Boston cookie theft picture in a piece-meal fashion. Focusing on multiple objects on a screen presented challenges. However, she was able to name objects when presented individually.

Clock drawing test was unsatisfactory with missing numbers (Fig. 2). Over the next two years, she had difficulty with simple arithmetic. She wore clothes inside out, wore a shoe on one foot and a slipper on the other. She was lost in places previously familiar to her and would follow unfamiliar individuals in a crowd. She confused items, rooms and faces, eventually needing assistance in choosing clothes for dressing, meal preparation, using the telephone, traveling, handling finances and taking medications. Examination showed a patient who was disoriented to time, place and person.

Fig 1. Formal perimetry testing showed right homonymous hemianopsia



Neuropsychological evaluation revealed moderate to severe cognitive impairment in all explored domains (Table 1). All visual tasks were severely impaired, particularly attempts to integrate a complex visual picture into a meaningful whole. Full lateral and vertical gaze were possible when she carefully followed a moving object but jerky saccades were noted when initiating gaze. She had difficulty reaching for a stationary object held in front of her. A strong tendency to fix gaze on a single object was noted. She interpreted Ishihara color vision testing plates as "candies". New learning was limited. She was only able to draw a circle and write her name. Follow-up tests of constructional praxis showed progressive impairment in spatial orientation (Figs 2 & 3). Word-finding difficulty was evident. She had impaired calculation, right-left disorientation, agraphesthesia, astereognosis, and finger agnosia.

Laboratory tests were negative for thyroid disease, metabolic disorders, and inflammatory or auto-immune diseases. Cranial MRI showed hippo-campal volume of 6.83 (0.51% of the intracranial volume), which is within 63 normative percentile.

Predominant parieto-occipital atrophy, more evident in the left hemisphere was also noted (Fig 4). FDG-PET showed marked posterior hypo-metabolism bilaterally (Fig 5). Genetic testing showed ApoE e3/e3 on genotyping by PCR. Multimer Detection System test for AD ratio was normal.

DISCUSSION

Posterior Cortical Atrophy presents with predominantly visual symptoms, with simultangnosia as the most frequent (above 90%)[3] deficit in PCA. Problems with describing the Boston cookie theft picture and inability to read pseudoisochromatic plates are highly conspicuous for simultagnosia[1]. In simultagnosia, there is inability to synthesize the overall meaning of the visual scene despite being able to recognize single elements. A controversial visual finding is a homonymous visual field deficit in the absence of a corresponding structural lesion on brain imaging. This is due to higher order visuospatial deficits that may compromise interpretation of the visual field tests and occurrence may precede a higher order visual disorder[4,5].

Neuropsychological testing of patients with PCA reveals poorer performance IQ compared with

Table 1. Comparison of Psychometric Score results done in 2017 and 2018.

Test	July 7, 2017		October 2, 2018		Remarks
	Score	Classification	Score	Classification	
ADAS-COG	43	Severe Impairment	No Data	No Data	No Data
Montreal Cognitive Assessment Philippines (MoCA-P) (30)	2	Severe Cognitive Impairment	2	Severe Cognitive Impairment	No Change
Verbal fluency (Total # Animals)	3	Moderate Impairment	5	Moderate Impairment	No Change
Boston Naming Test (15)	3	Moderate Impairment	3	Moderate Impairment	No Change
Word List Memory Task (30)	6	Moderate Impairment	No Data	No Data	No Data
Constructional Praxis (11)	2	Moderate Impairment	0	Moderate Impairment	No Change
Word List Recall (10)	1	Moderate Impairment	1	Moderate Impairment	No Change
Word List Recognition	7.5	Moderate Impairment	4	Moderate Impairment	No Change
Recall of Constructional Praxis (14)	0	Moderate Impairment	0	Moderate Impairment	No Change
Logical Memory (10)	0	Mild Impairment	0	Mild Impairment	No Change
Trailmaking Test A (180 seconds)	Unsuccessfully Accomplished	Baseline	Unsuccessfully Accomplished	Baseline	No Change
Trailmaking Test B (300 seconds)	Unsuccessfully Accomplished	Baseline	Unsuccessfully Accomplished	Baseline	No Change
Digit Symbol (#correct)	Unsuccessfully Accomplished	Baseline	Unsuccessfully Accomplished	Baseline	No Change
Geriatric Depression Scale for Dementia	Unsuccessfully Accomplished	Baseline	Unsuccessfully Accomplished	Baseline	No Change

Fig 2. Clock drawing test in 2014 (left), 2017 (middle), and 2018 (right) highlight progressive deficits in constructional ability.

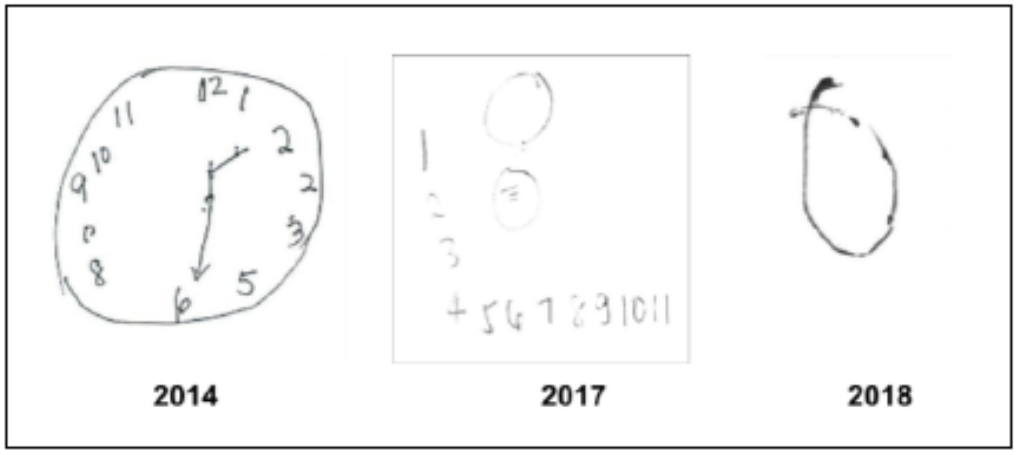


Fig 3. Copying figures (2017 vs 2018) test showed line distortion and lack of elements due to visual deficits.

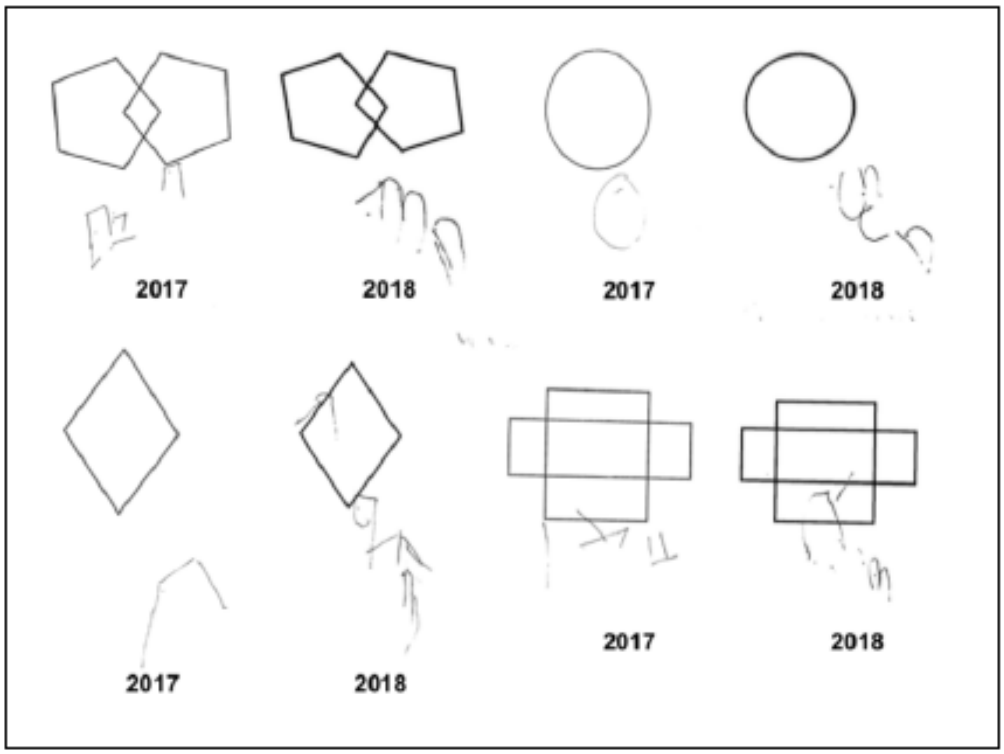


Fig. 4. Comparison of Cranial Magnetic Resonance Imaging (2014 and 2017) T1-weighted sequence, axial (2014, A;2017, B) and sagittal (2014, C; 2017, D) views. Cerebral volume loss is present, predominantly in the parietal and occipital lobes (blue arrow), seen in the widening of the posterior cingulate and parieto-occipital sulci bilaterally (red arrow), more evident in the left hemisphere.

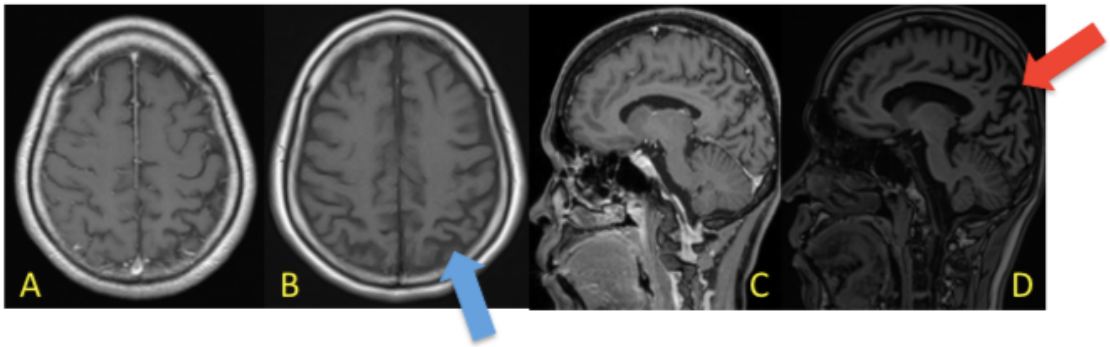
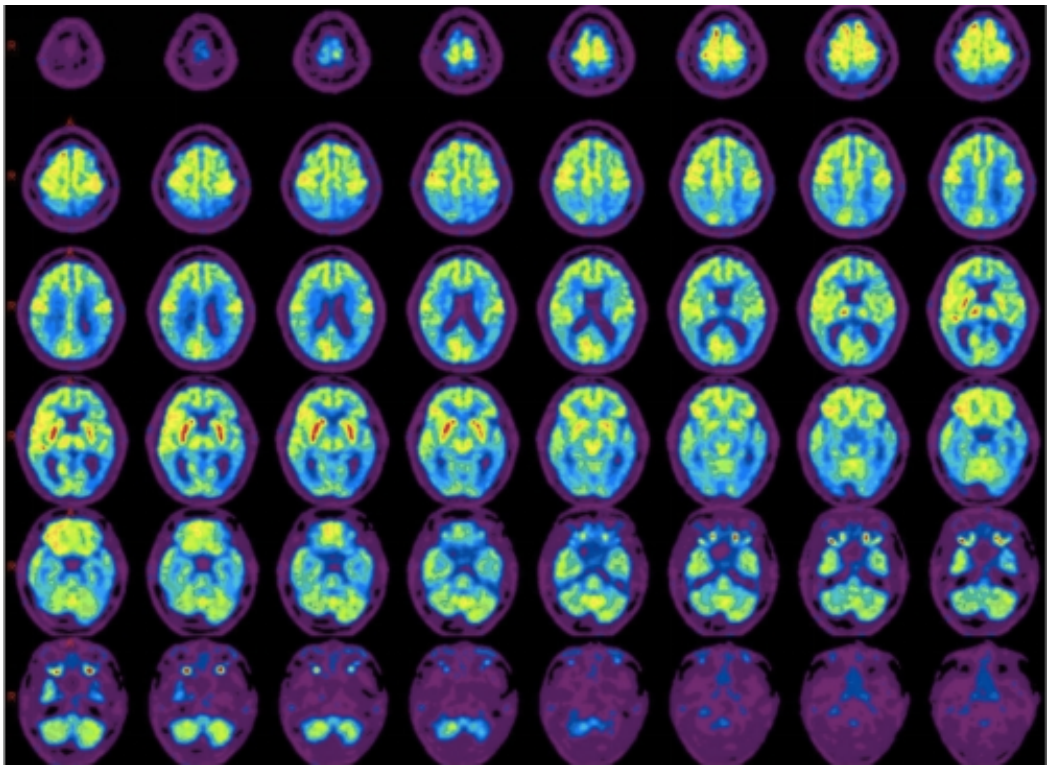


Fig 5. Fluoro-deoxyglucose PET images. Generalized decreased FDG uptake in the biparietal, bitemporal and bioccipital lobes with mild decreased uptake in the bifrontal lobes.



verbal IQ[1]. Perceptual organization and processing speed presented as a bigger challenge compared to verbal comprehension and working memory (Table 2) due to visual disorientation (failure to track), ocular apraxia (failure to generate saccades), reverse-size phenomenon (difficulty reading large texts) and optic ataxia (inability to reach for objects under visual guidance)1. Naming and defining function of objects without cues was manageable but tasks involving visual perception such as picture completion, block design and Rey-Osterrieth complex figure tests were unsuccessfully completed.

Serial imaging studies showed widening of the posterior cingulate and parieto-occipital sulci and marked hypometabolism in the occipitoparietal regions, particularly the bilateral parietal lobes

Table 2. Verbal IQ vs Performance IQ (2018)

SUBTEST	Raw Score	Scaled Score	Qualitative Description
Verbal Comprehension Subtests			
Similarities	4	1	Extremely Low
Vocabulary	15	4	Borderline
Information	2	2	Extremely Low
Perceptual Reasoning Subtests			
Block Design	0	1	Extremely Low
Matrix Reasoning	0	1	Extremely Low
Visual Puzzles	0	1	Extremely Low
Working Memory Subtests			
Digit Span	3	1	Extremely Low
Arithmetic	0	1	Extremely Low
Processing Speed Subtests			
Symbol Search	0	1	Extremely Low
Coding	0	1	Extremely Low

Table 3. Semiquantitative evaluation of the percentages of Fluoro-deoxyglucose uptake when compared to the basal ganglia. Measurements showed generalized decrease update most prominent in the bi-parietal lobes.

	Right	Left
Frontal	75-100	60-100
Parietal	40	40
Temporal	40-75	40
Occipital	40-70	40-70
Caudate nuclei	100	90
Putamen	100	100
Thalamus	100	75
Cerebellum	60	60

(Table 3). This is consistent with the Biparietal/ Dorsal variant of Posterior Cortical Atrophy[3] with features of the Balint's syndrome in contrast to the Occipitotempral/Ventral variant in which impaired visuoperceptive functions are more prominent. Simultanagnosia was associated with hypometabolism in the right occipital lobe, posterior cingulum and visual cortex. Optic ataxia was associated with involvement of the left occipital and visual cortex, while oculomotor apraxia with left parietal lobe and posterior cingulum[6]. These areas of hypometabolism explain deficits consistent with posterior parietal and occipital pathologies. The underlying pathology of PCA is believed to be Alzheimer's Disease with the ApoE e4 poly-morphism[7]. However, genotyping in this patient revealed ApoE e3/e3 alleles. Previous literature studies support the hypothesis that a greater load of amyloid plaques is correlated with earlier clinical symptoms of PCA, especially in the posterior lobes. However, the patient's Multimer Detection System test for AD ratio was normal. This case may provide new insight into the role of ApoE e3 allele and amyloid levels in the etiology of Posterior Cortical Atrophy.

SUMMARY

The dorsal variant of posterior cortical atrophy presents with simultagnosia and compromised visuospatial function, reflected in poorer performance IQ compared to verbal IQ. Cranial MRI and PET scans show bilateral parieto-occipital atrophy and hypometabolism. Although greater amyloid burden is expected for a patient with early clinical symptoms, this case demonstrates otherwise. Due to the presenile onset of disease and variability of clinical features as the initial presentation, recognition of these symptoms is crucial to avoid misdiagnosis.

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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

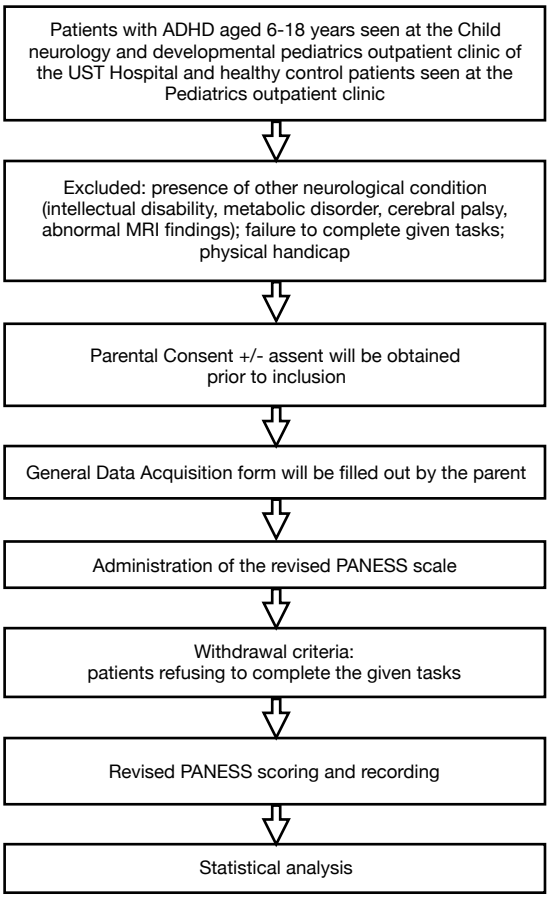
Independent Sample T-test, Mann-Whitney U/ Wilcoxon Sign rank test, and Fisher's Exact/Chi-square test was used to determine the difference of

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.

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Refractory and Super Refractory Status Epilepticus in the Philippines: A 10-Year Retrospective Study

Liz Edenberg P. Quiles, MD and Marc Laurence C. Fernandez, MD, FPNA

PURPOSE

Super refractory status epilepticus (SRSE) is an uncommon, but important clinical problem with high morbidity and mortality. Studies concerning SRSE has been limited and there are no existing Philippine data. The study aims to determine the status of Refractory (RSE) and SRSE within a 10-year period in a Tertiary Hospital.

METHODS

This is a retrospective study of adult patients with prolonged seizures admitted at The Medical City, Philippines from January 2009- July 2018. Multinomial Logistic Regression was used to assess probability of good or poor outcome. Significant Correlation is defined by P value of <0.05.

RESULTS

The Incidence of RSE is as high as 38% (n=64) and 35% (n=58) for SRSE. Mortality rate is 39.1% in RSE and 62.1% in SRSE. Poor functional outcome is observed in RSE and SRSE wherein the majority was Alive Dependent. Significant factor increasing likelihood of being Alive Dependent is the absence of Arrest.

CONCLUSION

Factors associated with likelihood of being alive and independent includes Status Epilepticus and younger age therefore aggressive seizure control to prevent progression to SRSE will give higher likelihood of good functional outcome and elderly patients warrant closer and more adept seizure control for better functional outcome.

Keywords: status epilepticus, refractory status epilepticus, super refractory status epilepticus, Philippines, Seizures

INTRODUCTION

BACKGROUND AND RATIONALE

Seizures are classified as status epilepticus (SE) if it fails to cease or if patients fail to regain consciousness by 5 minutes. Beyond said time point, mechanisms responsible for termination fail or mechanisms that initiate abnormally prolonged seizures predominate. This has been associated with detrimental and long-term consequences: neuronal injury and death. Achieving seizure freedom in such individuals include correction and proper treatment of the underlying pathology. Some even requiring 2 or more antiepileptic drugs (AEDs) or an anesthetic drug to achieve seizure freedom, hence classified refractory (RSE). Persistence beyond 24 hours or recurrence of seizures upon withdrawal or down titration of an anesthetic have been reported in literature hence the introduction of the new classification: Super Refractory Status Epilepticus. (SRSE) [1,2].

In the London-Innsbruck Colloquium last 2011, a new classification of status epilepticus has been introduced: Super-refractory status epilepticus. In certain time points, a seizure is well established to be detrimental, better yet mechanisms to inhibit overall activity are said to fail hence the need for adept seizure control[1,2].

Since its introduction in 2011, studies involving super refractory status epilepticus has been limited.

This research was conducted at The Medical City, Ortigas Avenue, Pasig City.
This paper has been presented at the PNA Annual research contest last November 2018.

Hence the need to take a closer look as to what are the demographics and clinical profile of patients with status epilepticus, determine the factors that affect outcome and control of seizures that might be handful in predicting seizure patients that have high probability of developing refractory or worse, super refractory status epilepticus.
Seizures are classified as Status Epilepticus at time point 1 of five minutes. This is a condition the results either from failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures[3].

Time point 2, beyond 30 minutes is the time where a continuous seizure activity is said to produce long term detrimental neurological consequences such as: Neuronal death, neuronal injury and alteration of neuronal networks. These said time points are all based on animal studies and no data supplying estimates on human are available[3].

Super Refractory Status Epilepticus is defined as status epilepticus that continues or recurs 24h or more after the onset of anesthetic therapy, including those cases where status epilepticus recurs on reduction or withdrawal of anesthesia. It is an uncommon, but very important clinical problem that is associated with high morbidity and mortality[1].

There are many existing data regarding predictive factors of refractory status epilepticus, in the Philippines, there is one. In the study of Fernandez et al, as of 2011, incidence of refractory status epilepticus is at 16% with first onset seizures and abnormal cranial imaging identified as significantly associated with RSE. The highest disease to cause RSE has been found out to be acute viral meningoencephalitis. Studies concerning super refractory status epilepticus have been limited. A study in India reported 13% incidence of SRSE, with 43% mortality rate [4]. In Scandinavia, 4% incidence with 37.9% mortality for SRSE [5]. In Finland, incidence of SRSE was reported to be 22% and mortality rate at 36% [6].

Up to the present, there are no existing Philippine data about the incidence, predictive factors or mortality rate of super refractory status epilepticus in the Philippines.

OBJECTIVES

General Objectives

To know the status of prolonged seizures within a 10- year period in a tertiary hospital in the Philippines.

Specific Objectives

1. To determine the incidence of refractory status epilepticus and super refractory status epilepticus within a 10-year period in a tertiary hospital in the Philippines.
2. To determine the demographic characteristics of patients that developed refractory and super refractory status epilepticus.
3. To determine the mortality rate of refractory and super refractory status epilepticus.
4. To determine the predictive factors of a patient developing refractory and super refractory status epilepticus as to functional outcome

METHODS

STUDY DESIGN

This is a retrospective study of all adult patients admitted at a tertiary hospital from January 2009-July 2018. Inclusion criteria included all Adult patients (aged 18 years old and above) diagnosed to have prolonged seizures referred or admitted under the Adult Neurology Service. The seizures are classified as status epilepticus, refractory status epilepticus and Super refractory status epilepticus.

SETTING

The study was conducted in an 800-bed capacity tertiary hospital. The hospital is accredited by the Joint Commission of International Accreditation (JCI) that ensures high quality health-care service to the patients. The Intensive Care Unit of this hospital is manned by certified Critical Care Specialists/Neurocritical Care intensivists. The study has been approved by the Institutional Review Board of The Medical City in Pasig City, Philippines.

PARTICIPANTS

The following definitions for classification have been used: Status Epilepticus (SE) defined as seizures lasting for 5 minutes or longer, or no regain of consciousness for approximately 5 minutes from seizure onset. Refractory Status Epilepticus (RSE) defined as generalized convulsive seizure unresponsive to treatment with 2 AEDS or requiring anesthetic agent. Super Refractory Status Epilepticus (SRSE) defined as

seizures that continues for 24 hours or more after the onset of anesthesia or those that recurs on the reduction or withdrawal of anesthesia.

VARIABLES

The following variables have been obtained: Gender, Co-morbidities, Code time, Electroencephalogram results, Neuroimaging results, Length of hospital stay, Length of ICU stay, Number of Antiepileptic drugs (AEDs) used, Duration of Seizures and Survival. Age is subdivided into those between 18-34 years of age, 35 to 64 years of age and 65 year and older. The Etiology has been classified according to ILAE classification of Epilepsy as Unknown, Genetic, Structural, Metabolic, Infectious and Immune[7]. Functional outcome was determined using Modified Rankin scale shown in Table 1.

Table 1. Modified Rankin Scale Score

	Definition
0	No symptoms
1	No significant disability despite symptoms able to do usual duties and activities
2	Slight disability; unable to perform all previous activities but able to look after self without assistance
3	Moderate disability; requires some help but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requires constant nursing care and attention
6	Death

DATA SOURCES

All pertinent data in the study have been obtained through manual chart review such as demographic characteristics, co-morbidities, duration of hospitalization and ICU stay, EEG and neuroimaging findings. The seizures have been classified as Status Epilepticus (SE) defined as seizures lasting for 5 minutes or longer, or no regain of consciousness for approximately 5 minutes from seizure onset. Refractory status Epilepticus (RSE) defined as generalized convulsive seizure unresponsive to treatment with 2 AEDS or requiring anesthetic agent. Super Refractory Status Epilepticus (SRSE) defined as seizures that continues for 24 hours or more after the onset of anesthesia or those that recurs on the reduction or withdrawal of anesthesia.

BIAS

This study can have potential recall bias on manual chart review of patients.

STUDY SIZE

The study design is a retrospective analysis and no sample size was needed.

STATISTICAL METHODS

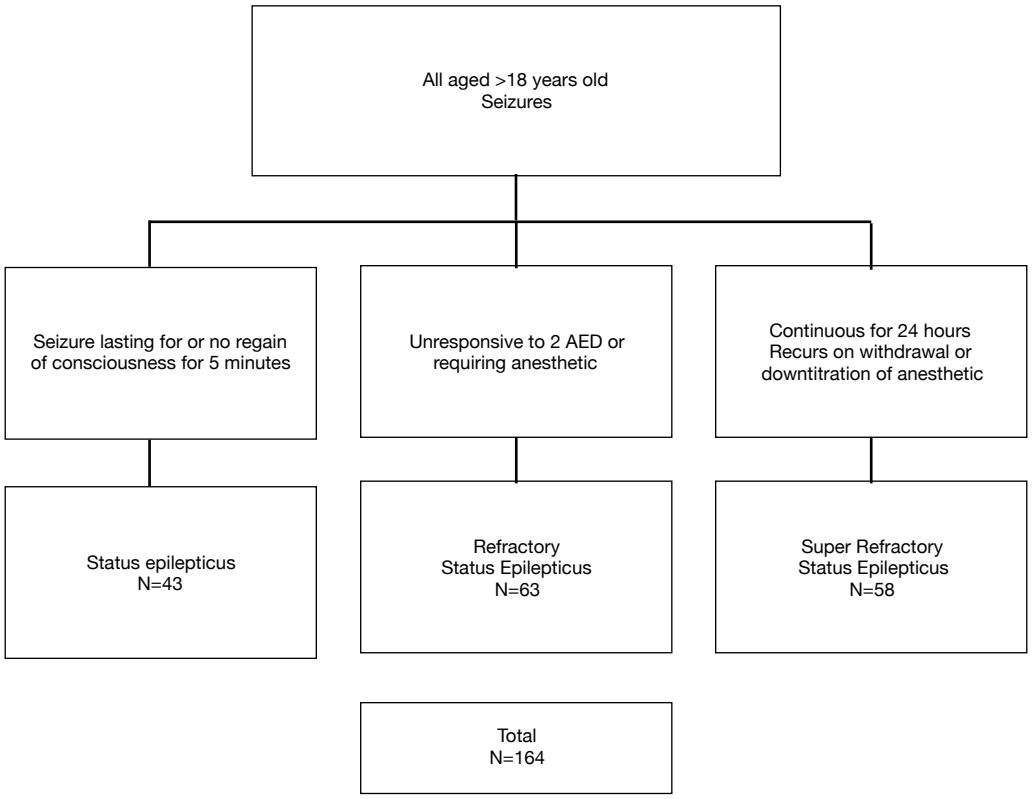
Frequency, Mean and standard deviation was used in the Descriptive analysis. Multinomial Logistic Regression was used to assess probability of good or poor outcome. Significant Correlation is defined by P value of <0.05. Data were analyzed using STATA 14.1.

RESULTS

The patients are identified using manual chart review of patient's records. A total of 165 patient had prolonged seizures where 43 had status epilepticus, 64 had refractory status epilepticus and 58 had super refractory status epilepticus (Figure 1). All have been included in the analysis.

Table 2 shows the comparison of frequencies and distribution of variables between SE, RSE and SRSE patients. Majority of the patients having SE and SRSE are between 35-64 years old, while those patients who had RSE are aged 65 years old and above. In terms of gender, majority of patients with RSE and SRSE are females. Structural Etiology had been the leading cause of SE at 62.8%, while metabolic etiology has been the number one cause for RSE and SRSE at 51.6% and 72.4% respectively. The number of antiepileptic drugs for SE are least 2, while at least 3 for RSE and SRSE with at least 2 co-morbidities for SE, RSE and SRSE. The most frequent comorbidity for SE, RSE and SRSE was Hypertension at 55.8%, 73.4% and 62.1%

Figure 1. Diagram of classification of seizures of the patients



respectively. Functional Outcome has been favorable in patients who had SE, wherein majority of the patients are Alive Independent. Poor functional outcome has been observed in RSE and SRSE wherein the majority was Alive Dependent. All have high mortality rates, with SRSE being most fatal with 62.1% mortality, 39.1 % for RSE and 16.3% for SE. The length of hospitalization has been noted to be longer as seizure type worsens with the longest for patients with SRSE. A total of 8/43 patients with SE, 12/64 of patients with RSE and 6/58 patients with SRSE had no neuroimaging, among those who had neuroimaging, majority on all types underwent Cranial CT scan. In patients with SE 20/43 had no available EEG recordings, 20/64 and 11/58 for RSE and SRSE had no available EEG recording respectively. Among those with available data, 18/23 had abnormal EEG readings, 42/44 and 47/58 for RSE and SRSE had abnormal EEG recordings.

Table 3 shows the Functional outcomes of prolonged seizure patients with arrest. Majority of patients who have had an arrest resulted in subsequent demise while some had been Alive but dependent. Majority of those however who have had no arrest are alive but dependent. No alive and independent patient had prior arrests.

RESULTS AND DISCUSSION

Refractory status epilepticus is a neurological emergency that warrants early and aggressive treatment with already high mortality rates. Super refractory status epilepticus in itself a status epilepticus that is very difficult to manage that is prolonged and persistent is associated with even higher rates of mortality. Since its introduction, studies related to its prognostic and predictive factors have been scarce and no Philippine data is available up to present.

Table 2. Clinical Profile of patients with Status Epilepticus (SE), Refractory Status Epilepticus (RSE) and Super Refractory Status Epilepticus (SRSE)

	SE n(%) n=43	**RSE** n(%) n=64	**SRSE** n(%) n=58
Age Interval			
18-34 yrs old	12 (27.9)	6 (9.4)	8 (13.8)
35-64 yrs old	17 (39.5)	27 (42.2)	31 (53.4)
65 yrs old and above	14 (32.6)	31 (48.4)	19 (32.8)
Gender			
Male	21 (48.8)	29 (46.0)	20 (34.5)
Female	22 (51.2)	35 (55.5)	28 (48.3)
Etiology			
Unknown	4 (9.3)	2 (3.1)	0 (0.0)
Infectious	4 (9.3)	6 (9.4)	5 (8.6)
Metabolic	7 (16.3)	33 (51.6)	42 (72.4)
Immune	1 (2.3)	0 (0.0)	3 (5.2)
Structural	27 (62.8)	23 (35.9)	8 (13.8)
Number of Anti-epileptic drug (mean±SD)	2.47±0.74	2.81±0.91	3.41±1.08
Number of Co-morbidities (mean±SD)	1.88±1.16	2.11±1.16	1.98±1.05
Co-morbidities			
Hypertension	24 (55.8)	47 (73.4)	36 (62.1)
Diabetes Mellitus	16 (37.2)	24 (37.5)	24 (41.4)
Lung Problem	7 (16.3)	8 (12.5)	12 (20.7)
Heart Problem	4 (9.3)	19 (29.7)	19 (32.8)
Cancer	4 (9.3)	5 (7.8)	8 (13.8)
Kidney Disease	8 (18.6)	8 (12.5)	12 (20.7)
Liver Disease	0 (0.0)	1 (1.6)	2 (3.4)
Neurologic Problem	18 (41.9)	23 (35.9)	3 (5.2)
MRS score			
Alive Independent (0-2)	17 (39.5)	6 (9.4)	2 (3.4)
Alive Dependent (3-5)	19 (44.2)	33 (51.6)	20 (34.5)
Died (6)	7 (16.3)	25 (39.1)	36 (62.1)
Arrest			
Yes	1 (2.3)	30 (46.9)	38 (65.5)
No	42 (97.7)	34 (53.1)	20 (34.5)
Duration of Hospitalization (mean±SD)	9.19±7.00	17.22±15.08	23.38±24.69
Neuro Imaging			
No data	8 (18.6)	12 (19.1)	6 (10.3)
CT	29 (67.4)	45 (71.4)	44 (75.9)
MRI	6 (14.0)	7 (11.1)	8 (13.8)
EEG findings			
No data	20 (46.5)	20 (31.8)	11 (19.0)
Normal	5 (11.6)	2 (3.2)	0 (0.0)
Abnormal	18 (41.9)	42 (66.7)	47 (81.0)

In this study the incidence of Refractory status epilepticus amongst those who had prolonged seizures is as high as 38% (n=64), higher than the data reported in the Philippines at 16%[8]. Two studies from Switzerland on the other hand had closer incidence to our study at 33.3% and 37% respectively[5,9]. This is perhaps due to majority of the cases have been admitted at the Neurologic Intensive Care unit and had better monitoring and documentation than previous Philippine data. SRSE on the other hand had an incidence of 35% which is higher than previously reported data in India at 13-16.9%, and Scandinavia at 22%[4, 10,5]. Differences in the reported prevalence may be due to the differences of hospital setting between studies of ICU or in Hospital setting and differences in the definition used to classify SE as SRSE. Previous study reported 4% prevalence of SRSE may be due to the definition used for SRSE. This variation in the operational definitions makes compa-rison somewhat difficult[5].

Majority of the Etiology of those Patients having RSE and SRSE have metabolic causes at 51.6% and 72.4% respectively, same trend has been previously reported with metabolic being the leading cause of SRSE and RSE[4]. In a report by Jayalakshmi however reported higher incidence of metabolic etiology among elderly. There is no specific gender predilection in multiple studies [5,6,8]. Hypertension has been the most common comorbidity associated with SE, RSE and SRSE at 62.1% similar to the study done in 2017 with hypertension present in SRSE patients at 35.7% [4]. The duration of hospitalization and length of ICU stay was noted to be progressively longer as the Status Epilepticus evolves to RSE and SRSE.

Table number 4 shows the Multinomial Logistic regression of cofounders that affects functional outcome among patients with prolonged seizures. Number of Antiepileptic drugs are noted to have an effect of the likelihood of being alive and dependent. For every 1 additional AED, the odds of being alive and dependent than dead decreases by 2.6%. Seizures that are prolonged and difficult to control, the likelihood of being dead is higher. The odds of being Alive Dependent is 2 times among patients with SE and RSE compared to patient with SRSE. There is slight increase in likelihood of being alive dependent than dead amongst Females compared to Males but was not significant. Patient's without co-morbidities have 3 times more likely to be Alive Dependent.
In terms of being Alive Independent, patients with SE have 24 times more likelihood of being Alive Independent than dead compared to those with SRSE and up to 7 times among RSE patients compared to SRSE. Age is a significant factor associated with higher likelihood of good functional outcome of being Alive Dependent of up to 22 times among SE and 14 times compared to RSE. Females have more likelihood of having poor functional outcome of up to 4 times but was not significant. Patients without comorbidity have 3 times more likelihood to be independent than

Table 3. Functional Outcome Cross-tabulation

	Functional Outcome			
	Died	**Alive Dependent**	**Alive Independent**	**Total**
Arrested				
No	21	50	25	96
Yes	48	21	0	69
Total	69	71	25	165

Table 4: Results of the Multinomial Logistic Regression Functional Outcomes

Functional Outcome[a]	Odds Ratio (OR)	95% Confidence Interval	
		Lower Bound	Upper Bound
Alive Dependent			
Number of AED	0.97	0.63	1.50
SE:SRSE	2.40	0.66	8.67
RSE:SRSE	2.40	0.98	5.87
18-34yo:65yo & above	1.13	0.27	4.74
35-64yo:65yo & above	1.57	0.70	3.55
Female:Male	1.20	0.56	2.57
Co-morbidity Absent:Co-morbidity Present	3.87	0.56	26.89
Arrest Absent:Arrest Present	4.95	2.09	11.73
Alive Independent			
Number of AED	1.17	0.59	2.33
SE:SRSE	24.09	2.32	249.94
RSE:SRSE	7.11	0.84	60.17
18-34yo:65yo & above	22.10	2.53	192.92
35-64yo:65yo & above	13.35	2.21	80.79
Female:Male	3.72	0.95	14.50
Co-morbidity Absent:Co-morbidity Present	3.15	0.26	38.23
Arrest Absent:Arrest Present			

[a]*The reference category is:Died*

dead compared to those with co-morbidities. Previous study reported new handicap in up to 44.2 % of patients who have had RSE and 48.5% in patients with SRSE [5]. Recent studies concerning RSE and SRSE have excluded post arrest patients, however in this study the presence of arrest was noted to have an effect on functional outcome. Patients without arrest have a likelihood of up to 5 times of being Alive Dependent than dead compared to those who had an arrest and no patient who had an arrest had good functional outcome. The neuron in itself being highly dependent on oxygen, several irreversible effects of its insufficiency highly impact functionality and even mortality after.

Increased rate of mortality has been associated in both RSE and SRSE, with reports going up to ranges of 24-38% for RSE and 35-43% in SRSE. In this study mortality rate is as high as 39.1% in RSE and 62.1% in SRSE. The more difficult the seizure control, the higher rates of mortality similar to those previously reported. Factors with significant effect on being live dependent than dying is the presence of arrest. Predictive factors for being Alive and independent than dead are SE, and younger age. This could be brought about by the proposed deleterious effects of prolonged seizures regardless of etiology especially amongst elderly which is known to be more vulnerable to neurologic insult. This warrants more aggressive seizure control in preventing progression to SRSE especially those aged 65 years old and higher to ensure better rates of survival and functionality amongst patients with prolonged seizures.

LIMITATIONS

Limitations of a retrospective study include potential recall bias of the participants in certain seizure characteristics. There is no follow up after discharges of the patients, where patients with poor functional outcome at discharge could potentially have some improvement over time.

CONCLUSION

RSE and SRSE have high rates of mortality and high rates of poor functional outcome. Predictive factors associated with being alive and dependent is the presence of arrest. Those patients who have had an arrest regardless of seizure duration have higher likelihood of being dependent. Factors associated with likelihood of being alive and independent includes Status Epilepticus which is more benign type of prolonged seizure and younger age therefore more aggressive control of seizures in preventing progression to SRSE will give higher likelihood of good functional outcome and elderly patients would need closer and more adept seizure control for better functional outcome.

RECOMMENDATIONS

Studies regarding Super Refractory Status epilepticus has been scarce since its introduction, therefore there is great need for prospective studies that will include post discharge follow up of the functional outcome of patients. The investigators also recommend studying on the incidence, clinical profile and predictive factors of developing seizures in post-arrest patients.

DISCLOSURE

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