ARTICLE

Neurodevelopmental comorbidities and seizure characteristics of children with focal epilepsy below eight years old in Philippine Children's Medical Center: A cross-sectional analytical study

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OBJECTIVES: This study aims to describe the clinical characteristics, treatment received and outcome of patients diagnosed with HLH at the Philippine Children's Medical Center from 2004 to 2017

MATERIALS AND METHODS: This cross-sectional analytical study was conducted from June 10, 2023 to June 1, 2024 at the Philippine Children's Medical Center. Children aged 0 to 7 years and 11 months, recently diagnosed with focal epilepsy, were evaluated using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5-TR) criteria. The level of early child development was determined based on the total Battelle Developmental Inventory-2 developmental quotient score.

RESULTS: The study examined 246 children with focal epilepsy. Significant findings included those children with NDD had a higher median age (4.67 years) compared to those without NDD (3.37 years) ($p < .001$). A higher proportion of non-NDD children were under one year old. Children without NDD had mothers with higher educational attainment ($p = .015$) and came from families with higher incomes ($p = .003$). Neonatal complications such as hypoxic-ischemic encephalopathy (HIE) and sepsis were more common in children with NDD ($p = .005$ and $p = .006$). Phenobarbital use was more frequent in children with NDD ($p = .001$), who also had more abnormal EEG and neuroimaging findings ($p < .001$). Neurodevelopmental evaluations were conducted later for children with NDD ($p < .001$). A significant number (75.20%) of children exhibited neurodevelopmental problems, with global developmental delay being most prevalent. Crude analysis showed associations between age, number of antiseizure medications, and delays in evaluation with increased odds of NDD.

CONCLUSIONS: : The study offers insights into children with focal epilepsy, emphasizing the impact of low socioeconomic status, age, birth complications and multiple anti-seizure medications. These findings are vital for clinicians to modify care plans through a multidisciplinary approach to enhance outcomes and improve quality of life in this high-risk population.

KEYWORDS: *focal epilepsy, neurodevelopmental disorders, global developmental delay, intellectual disability, hypoxic-ischemic encephalopathy, sepsis*

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The authors affirm that this manuscript is original, has been read and approved by all contributing authors, that each author meets the established criteria for authorship, and that the content represents a truthful and accurate account of the work conducted.

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INTRODUCTION

Epilepsy is a brain disorder characterized by a persistent predisposition to generate seizures. It includes various neurobiological, cognitive, psychological and social effects that result from recurring seizures.[1] It is the most frequent chronic neurologic condition in childhood, and it affects 0.5% to 1% of children.[2] Epilepsy is not an isolated disease but has broader implications for the pathophysiology of many other conditions. [3] As with any medical condition, epilepsy is associated with several comorbidities including cognitive and behavioral disorders. In some patients, such comorbidities may have a greater effect than the epilepsy itself, greatly affecting daily lives.[4] The disorders that most often cause cognitive and behavioral impairments are neurodevelopmental disorders (NDD). In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition- Text Revision,[5] NDD as a diagnostic category is defined as a group of conditions with onset during the developmental period, leading to deficits that impair functioning -Global Developmental Delay (GDD), Intellectual disability (ID), Communication Disorders, Autism Spectrum Disorder (ASD), Attention-Deficit/ Hyperactivity Disorder (ADHD), Neurodevelopmental Motor Disorders and Specific Learning Disorders. Many studies, particularly in the field of genetics, have reported that NDD and epilepsy have a common biological background.[6] Thus, NDD and epilepsy often co-occur. The incidence of NDD in patients with epilepsy is higher than that in the general population. Autism is more prevalent in children with epilepsy, affecting approximately 20%, and similarly, epilepsy is more common in children with autism, with reported rates also around approximately 20%. [7] ADHD was also found to be present in 30-40% of children with epilepsy according to a study conducted by the International League Against epilepsy (ILAE). [8] However, despite the well-established evidence of a connection between epilepsy and NDDs, the mechanisms underlying this comorbidity is still not well understood.

Epilepsy is a significant public health issue, particularly in children, due to its medical, social, and economic impacts. It causes a substantial burden not only because of seizures but also due to comorbidities, disabilities, and associated stigma. [9] Understanding the neurodevelopmental comorbidities and development levels in children with epilepsy can help identify factors contributing to this burden. While the prevalence of these comorbidities varies globally, most epidemiological data come from developed countries, despite over 80% of births occurring in low and middle-income countries. This lack of precise data in poorer regions hinders effective public health planning, highlighting the importance of local data. [10]

David G. Newborg developed the Battelle Developmental Inventory, 2nd edition (BDI-2) and defined it as a "thorough, standardized tool used to evaluate crucial developmental abilities in children ages 0 to 7 years and 11 months." It provides a means of assessing the skill level and growth of the child with a disability or delay. Foundational abilities are developed during this period hence it is critical in development.[11] Consequently, any insult that may arise at this stage can have permanent implications on their learning and overall growth in life.[12]

This study aims to determine the prevalence of neurodevelopmental comorbidities and their association with the clinical profile of children with focal epilepsy treated at the Philippine Children's Medical Center from 2023 to 2024. Specifically, it describes the demographic and clinical profiles, including maternal and birth history, seizure characteristics, and treatments; assesses the age of initial neurodevelopmental evaluation and the presence of comorbidities using DSM-5-TR criteria and BDI-2; and examines the associations between various clinical factors and NDDs.

Materials and Methods

This study utilized a cross-sectional analytical study design to determine the neurodevelopmental disorders in children with focal epilepsy, seen at the Philippine Children's Medical Center. The subjects for this study were patients 0 to 7 years and 11 months old seen at the OPD and in-patient referrals of Philippine Children's Medical Center from 2023 to 2024 who were newly diagnosed with focal epilepsy. Patients who previously underwent neurodevelopmental evaluation were excluded from the study. A non-probability consecutive sampling was utilized for this study. The sample size required for estimating the proportion of neurodevelopmental comorbidities was computed using the following equation by Daniel and Cross (2013). The study by Reilly et al [22] stated that the prevalence of neurodevelopment comorbidities is at 80%. Using these parameters, the minimum number of children required for estimating the proportion of neurodevelopmental comorbidities of children 0 to 7 years and 11 months old diagnosed with epilepsy is at least 246.

The specific goal of the study is to determine the presence of NDD of children 0 to 7 years and 11 months old diagnosed with focal epilepsy using the DSM-5-TR criteria and to measure the current general level of development as measured by the BDI-2 total developmental quotient score. A detailed history and chart review was also done to determine the association of the clinical profile and presence/ absence of neurodevelopmental disorders.

Descriptive statistics were utilized to summarize the general and clinical characteristics of the study participants. Categorical variables were assessed using frequency and proportion, while non-normally distributed continuous variables were evaluated using median and interquartile range. The Shapiro-Wilk test was used to determine the normality of continuous variables.

Odds ratios and their corresponding 95% confidence intervals were calculated using binary logistic regression to investigate the association between clinical profile and neurodevelopmental disorders. Variables with a p-value less than 0.20 were included in the multivariate logistic regression analysis. The null hypothesis was rejected at an α-level of 0.05. Missing data were neither replaced nor estimated. Data analysis was performed using R version 4.2.2.

Ethical Considerations

The Institutional Review Board-Ethics Committee of Philippine Children's Medical Center approved the study approval prior to commencement. This study was done in compliance to Data Privacy Act (2012) and National Ethical Guidelines for Health and Health-Related Research (2017). This study included vulnerable participants such as children and people with disabilities and measures were taken to minimize harm. These measures included explaining the risks and benefits of the study to caregivers, obtaining informed consent, ensuring anonymity and confidentiality, and providing contact details for concerns. Participation was voluntary, and the standard of care was maintained regardless of consent. Research records were securely stored, with physical files locked and electronic data encrypted. Identifiable information was coded and kept separate from research data, with access limited only to the research team. Records were stored for three years after the study, then destroyed. The study results will be shared with the participants and the community, which will facilitate better detection and treatment of neurodevelopmental disorders in children with epilepsy. All investigators have completed Good Clinical Practice training.

RESULTS

The demographic characteristics of 246 children diagnosed with focal epilepsy are presented in Table 1. The cohort was categorized into two groups: those with NDD and those without NDD. The median age of the entire sample was 4.08 years. Children with NDD had a significantly higher median age of 4.67 years compared to 3.37 years for those without NDD ($p < .001$). There was also a significant variation in age distribution between the groups ($p < .001$). Notably, children under one year accounted for 7.72%

of the total cases, with a greater proportion in the non-NDD group (21.31%) compared to the NDD group (3.24%). Gender distribution was consistent across the groups, with 58.54% males and 41.46% females in the overall cohort, and no significant differences between the NDD and non-NDD groups (p = .951). Mothers' education levels varied significantly between the groups (p = .015), with a higher percentage of mothers in the non-NDD group attaining higher educational levels compared to the NDD group. In contrast, fathers' educational levels did not show significant differences between the groups (p = .613). Monthly family income also differed significantly (p = .003), with families of children without NDD having higher income levels compared to those with NDD.

The maternal and birth history data are presented in Table 2. The average maternal age was 27.5 years (IQR: 23-32), with no significant difference between mothers of children with and without NDD (p = .355). The majority of children (84.15%) were born at term, and normal spontaneous delivery was the most common mode of delivery (76.02%). Neonatal complications, including hypoxic-ischemic encephalopathy (HIE) (13.01%) and sepsis (21.54%), were significantly more prevalent in children with NDD (p = .005 and p = .006, respectively).

The clinical profile and seizure characteristics are detailed in Table 3. The age at seizure onset varied, with 19.11% of children experiencing their first seizure before one month of age. This was more common among children with NDD (22.70%) compared to those without NDD (8.20%). The majority of seizures were focal motor in onset (94.31%), with no significant difference in seizure types between children with and without NDD (p = .392). Levetiracetam (54.88%) and Phenobarbital (39.02%) were the most commonly used anti-seizure medications (ASMs). Phenobarbital use was significantly higher in children with NDD (45.41%) than in those without NDD (19.67%) (p = .001). The number of ASMs used varied, with a higher number of medications being significantly associated with the presence of NDD (p = .005). EEG findings were more likely to be abnormal in children with NDD (75.68%) compared to those without NDD (40.98%) (p < .001), indicating more severe epileptic activity in the former group. Neuroimaging results were abnormal in 41.87% of the overall cohort, with a higher prevalence of abnormalities in children with NDD (50.81%) compared to those without NDD (14.75%) (p < .001).

The median age at initial neurodevelopmental evaluation was higher for children with NDD (4 years) compared to those without NDD (2.92 years) (p < .001). The interval from epilepsy diagnosis to the first neurodevelopmental evaluation was longer in children with NDD (4.34 years)

compared to those without NDD (3.04 years) ($p < .001$). A significant proportion of patients (75.20%) had some type of neurodevelopmental problem, with global developmental delay being the most prevalent (54.05%). The Battelle Developmental Inventory - 2 confirmed that 87.57% of children with NDD had significant developmental delays, compared to none in the non-NDD group ($p < .001$). Patients using three anti-seizure medications (ASMs) had significantly higher odds of NDD in the crude analysis (crude OR = 13.85, 95% CI: 1.82-1777.61, $p = .005$). In crude analyses, both the age at initial neurodevelopmental evaluation (crude OR = 1.33, 95% CI: 1.15-1.55, $p < .001$) and the interval from diagnosis to evaluation (crude OR = 1.79, 95% CI: 1.40-2.40, $p < .001$) were associated with NDD, suggesting that delays in developmental assessment are correlated with an increased likelihood of NDD diagnosis.

The multivariate analysis included 191 patients. The final model's explanatory power was indicated by Cragg-Uhler and McFadden Pseudo-R^2 values of 48.40% and 35.41%, respectively, with a significant overall model fit ($p < .001$). This indicates that the model is effective and offers valuable understanding of the complex nature of NDDs in children with epilepsy. However, it also reveals that other factors, not addressed in this study, could influence the results.

Table 1. *Demographic Profile of Patients (n = 246)*

	Overall (n = 246)	With NDD (n = 185)	Without NDD (n = 61)	p-value
	Frequency (%); Median (IQR)			
Age, years	4.08 (2.29-7.92)	4.67 (3-6.33)	3.37 (1.50-5.92)	<.001§
< 1 year	19 (7.72)	6 (3.24)	13 (21.31)	<.001‡
1 to <2 years	24 (9.76)	16 (8.65)	8 (13.11)	
2 to <3 years	34 (13.82)	24 (12.97)	10 (16.39)	
3 to <4 years	37 (15.04)	28 (15.14)	9 (14.75)	
4 to <5 years	28 (11.38)	24 (12.97)	4 (6.56)	
5 to <6 years	29 (11.79)	27 (14.59)	2 (3.28)	
6 to <7 years	37 (15.04)	27 (14.59)	10 (16.39)	
7 years	38 (15.45)	33 (17.84)	5 (8.20)	
Sex				.951†
Male	144 (58.54)	109 (58.92)	35 (57.38)	
Female	102 (41.46)	76 (41.08)	26 (42.62)	

	Overall (n = 246)	With NDD (n = 185)	Without NDD (n = 61)	p-value
	Frequency (%); Median (IQR)			
Mother's educational attainment				.015‡
Elementary undergraduate	0	0	0	
Elementary graduate	5 (2.03)	3 (1.62)	2 (3.28)	
High school undergraduate	12 (4.88)	6 (3.24)	6 (9.84)	
High school graduate	108 (43.90)	83 (44.86)	25 (40.98)	
Vocational undergraduate	1 (0.41)	1 (0.54)	0	
Vocational graduate	18 (7.32)	17 (9.19)	1 (1.64)	
College undergraduate	47 (19.11)	38 (20.54)	9 (14.75)	
College graduate	53 (21.54)	37 (20)	16 (26.23)	
Post graduate degree	2 (0.81)	0	2 (3.28)	
Father's educational attainment				.613‡
Elementary undergraduate	2 (0.81)	1 (0.54)	1 (1.64)	
Elementary graduate	5 (2.03)	4 (2.16)	1 (1.64)	
High school undergraduate	13 (5.28)	11 (5.95)	2 (3.28)	
High school graduate	118 (47.97)	89 (48.11)	29 (47.54)	
Vocational undergraduate	1 (0.41)	1 (0.54)	0	
Vocational graduate	31 (12.60)	26 (14.05)	5 (8.20)	
College undergraduate	30 (12.20)	21 (11.35)	9 (14.75)	
College graduate	39 (15.85)	28 (15.14)	11 (18.03)	
Post graduate degree	1 (0.41)	0	1 (1.64)	
Not applicable	6 (2.44)	4 (2.16)	2 (3.28)	
Mother's occupation				.073‡
Unemployed	170 (69.11)	132 (71.35)	38 (62.30)	
Management, business, and financial occupations	2 (0.81)	0	2 (3.28)	
Professional and related occupations	10 (4.07)	8 (4.32)	2 (3.28)	
Service occupations	35 (14.23)	26 (14.05)	9 (14.75)	
Sales and related occupations	17 (6.91)	13 (7.03)	4 (6.56)	
Office and administrative support occupations	12 (4.88)	6 (3.24)	6 (9.84)	

	Overall (n = 246)	With NDD (n = 185)	Without NDD (n = 61)	p-value
	Frequency (%); Median (IQR)			
Father's occupation				.451‡
Unemployed	16 (6.50)	13 (7.03)	3 (4.92)	
Management, business, and	2 (0.81)	2 (1.08)	0	
Professional and related oc-	11 (4.47)	11 (5.95)	0	
Service occupations	114 (46.34)	81 (43.78)	33 (54.10)	
Sales and related occupa-	21 (8.54)	16 (8.65)	5 (8.20)	
Office and administrative	26 (10.57)	17 (9.19)	9 (14.75)	
Construction and extraction	41 (16.67)	32 (17.30)	9 (14.75)	
Installation, maintenance,	4 (1.63)	3 (1.62)	1 (1.64)	
Production occupations	1 (0.41)	1 (0.54)	0	
Transportation and material moving occupations	10 (4.07)	9 (4.86)	1 (1.64)	
Monthly family income, PHP				.003†
< 5,000	41 (16.67)	34 (18.38)	7 (11.48)	
5,000- 9,999	123 (50)	101 (54.59)	22 (36.07)	
10,000-19,999	59 (23.98)	37 (20)	22 (36.07)	
> 20,000	23 (9.35)	13 (7.03)	10 (16.39)	

Statistical tests used: §–Mann-Whitney U test; †–Chi-square test; ‡–Fisher's exact test.

Table 2. *Maternal and Birth History (n = 246)*

	Overall (n = 246)	With NDD (n = 185)	Without NDD (n = 61)	p-value
	Frequency (%); Median (IQR)			
Maternal age, years	27.50 (23-32)	28 (23-31)	27 (25-33)	.355§
Gravidity	2 (1-3)	2 (1-3)	2 (1-3)	.896§
Parity	1 (0-2)	1 (0-2)	1 (1-2)	.681§
Term births [n=180]	1.50 (1-2)	1 (1-2)	2 (1-2)	.802§
Preterm births [n=180]	0 (0-0)	0 (0-0)	0 (0-0)	.095§
Abortions [n=180]	0 (0-0)	0 (0-0)	0 (0-0)	.770§
Living children [n=180]	1 (1-2)	1 (1-2)	2 (1-2)	.851§
Prenatal check-up				.458‡
Regular	237 (96.34)	177 (95.68)	60 (98.36)	
Irregular	9 (3.66)	8 (4.32)	1 (1.64)	

	Overall (n = 246)	With NDD (n = 185)	Without NDD (n = 61)	p-value
	Frequency (%); Median (IQR)			
Maternal illnesses				
Fever/infection	7 (2.85)	5 (2.70)	2 (3.28)	>.999‡
Rashes	2 (0.81)	2 (1.08)	0	>.999‡
Vaginal bleeding	5 (2.03)	5 (2.70)	0	.337‡
Gestational hypertension	11 (4.47)	10 (5.41)	1 (1.64)	.301‡
Gestational diabetes	5 (2.03)	2 (1.08)	3 (4.92)	.099‡
UTI	51 (20.73)	39 (21.08)	12 (19.67)	.958†
Goiter	2 (0.81)	2 (1.08)	0	>.999‡
Bronchial asthma	1 (0.41)	0	1 (1.64)	.248‡
Chicken pox	1 (0.41)	1 (0.54)	0	>.999‡
Placenta accreta	1 (0.41)	1 (0.54)	0	>.999‡
COVID infection	1 (0.41)	1 (0.54)	0	>.999‡
Amoebiasis	1 (0.41)	1 (0.54)	0	>.999‡
None	169 (68.70)	124 (67.03)	45 (73.77)	.409†
Maternal medications				
Antibiotics	53 (21.54)	41 (22.16)	12 (19.67)	.818†
Antihypertensive	8 (3.25)	7 (3.78)	1 (1.64)	.683‡
Anti diabetic	2 (0.81)	1 (0.54)	1 (1.64)	.435‡
Thyroid medication	2 (0.81)	2 (1.08)	0	>.999‡
Tocolytics	5 (2.03)	5 (2.70)	0	.337‡
Antipyretics/ NSAIDs	2 (0.81)	1 (0.54)	1 (1.64)	.435‡
None	179 (72.76)	131 (70.81)	48 (78.69)	.302†
Gestational age				.380†
Term	207 (84.15)	153 (82.70)	54 (88.52)	
Preterm	39 (15.85)	32 (17.30)	7 (11.48)	
Post term	0	0	0	
Mode of delivery				.254‡
Normal spontaneous delivery	187 (76.02)	144 (77.84)	43 (70.49)	
Cesarean section	57 (23.17)	40 (21.62)	17 (27.87)	
Instrumentation	2 (0.81)	1 (0.54)	1 (1.64)	
Birthweight				.219‡
Normal	195 (79.27)	145 (78.38)	50 (81.97)	
Low birth weight	44 (17.89)	34 (18.38)	10 (16.39)	
Very low birth weight	6 (2.44)	(3.24)	0	
Macrosomic	1 (0.41)	0	1 (1.64)	

	Overall (n = 246)	With NDD (n = 185)	Without NDD (n = 61)	p-value
	Frequency (%); Median (IQR)			
Birthweight according to gestational age				.208‡
AGA	202 (82.11)	149 (80.54)	53 (86.89)	
SGA	42 (17.07)	35 (18.92)	7 (11.48)	
LGA	2 (0.81)	1 (0.54)	1 (1.64)	
Birth complications				
HIE	32 (13.01)	31 (16.76)	1 (1.64)	.005†
Sepsis	53 (21.54)	48 (25.95)	5 (8.20)	.006†
Meningitis	10 (4.07)	10 (5.41)	0	.071‡
Jaundice	14 (5.69)	12 (6.49)	2 (3.28)	.527‡
Respiratory distress	10 (4.07)	10 (5.41)	0	.071‡
Pneumonia	16 (6.50)	15 (8.11)	1 (1.64)	.129‡
IVH	2 (0.81)	1 (0.54)	1 (1.64)	.435‡
Cystic hygroma	1 (0.41)	1 (0.54)	0	>.999‡
MCA	2 (0.81)	2 (1.08)	0	>.999‡
Bilirubin encephalopathy	1 (0.41)	0	1 (1.64)	.248‡
MAS	1 (0.41)	1 (0.54)	0	>.999‡
Others	3 (1.22)	3 (1.62)	0	>.999‡
None	145 (58.94)	94 (50.81)	51 (83.61)	<.001†
Family history				
Epilepsy	85 (34.55)	60 (32.43)	25 (40.98)	.277‡
Neurodevelopmental disorders	39 (15.85)	28 (15.14)	11 (18.03)	.738‡

Statistical tests used: §–Mann-Whitney U test; †–Chi-square test; ‡–Fisher's exact test.

Table 3. *Clinical Profile of Patients (n = 246)*

	Overall (n = 246)	With NDD (n = 185)	Without NDD (n = 61)	p-value
	Frequency (%); Mean ± SD; Median (IQR)			
Age of seizure onset				.069†
< 1 month old	47 (19.11)	42 (22.70)	5 (8.20)	
1-12 months	111 (45.12)	81 (43.78)	30 (49.18)	
1-3 years	59 (23.98)	40 (21.62)	19 (31.15)	
4-7 years and 11 months	29 (11.79)	22 (11.89)	7 (11.48)	

	Overall (n = 246)	With NDD (n = 185)	Without NDD (n = 61)	p-value
	Frequency (%); Mean ± SD; Median (IQR)			
Seizure type				
Focal				.392‡
Motor	232 (94.31)	174 (94.05)	58 (95.08)	
Nonmotor	7 (2.85)	4 (2.16)	3 (4.92)	
Focal to bilateral tonic clonic	3 (1.22)	3 (1.62)	0	
Generalized				-
Motor	1 (0.41)	1 (0.54)	0	
Nonmotor	0	0	0	
Multiple (2 or more seizure types)				-
Focal	0	0	0	
Generalized	0	0	0	
Focal + generalized	2 (0.81)	2 (1.08)	0	
Unknown	1 (0.41)	1 (0.54)	0	-
Epilepsy syndrome				.655‡
West syndrome	1 (0.41)	1 (0.54)	0	
Otahara syndrome	1 (0.41)	1 (0.54)	0	
BECTS	1 (0.41)	1 (0.54)	0	
LGS	3 (1.22)	3 (1.62)	0	
IES- DEE	1 (0.41)	1 (0.54)	0	
Infantile epileptic spasm syndrome	1 (0.41)	0	1 (1.64)	
Genetic epilepsy	1 (0.41)	1 (0.54)	0	
None	237 (96.34)	177 (95.68)	60 (98.36)	
Duration from seizure onset to start of anti-seizure medication, days	7 (2-60)	7 (2-60)	7 (3-31)	.610§
Type of ASM				
Carbamazepine	5 (2.03)	5 (2.70)	0	.337‡
Levetiracetam	135 (54.88)	103 (55.68)	32 (52.46)	.772†
Oxcarbazepine	29 (11.79)	18 (9.73)	11 (18.03)	.130†
Phenobarbital	96 (39.02)	84 (45.41)	12 (19.67)	.001†
Valproic acid	42 (17.07)	31 (16.76)	11 (18.03)	.973†
Clonazepam	5 (2.03)	5 (2.70)	0	.337‡
Topiramate	20 (8.13)	18 (9.73)	2 (3.28)	.174‡
Perampanel	4 (1.63)	4 (2.16)	0	.575‡
Phenytoin	2 (0.81)	1 (0.54)	1 (1.64)	.435‡
Others	4 (1.63)	4 (2.16)	0	.575‡

	Overall (n = 246)	With NDD (n = 185)	Without NDD (n = 61)	p-value
	Frequency (%); Mean ± SD; Median (IQR)			
Number of antiseizure medications (most recent)				.005‡
1	180 (73.17)	127 (68.65)	53 (86.89)	
2	43 (17.48)	35 (18.92)	8 (13.11)	
3	16 (6.50)	16 (8.65)	0	
4	7 (2.85)	7 (3.78)	0	
Seizure frequency				.116‡
≥ 1/day	150 (60.98)	106 (57.30)	44 (72.13)	
1-6/week	14 (5.69)	11 (5.95)	3 (4.92)	
1-3/month	29 (11.79)	21 (11.35)	8 (13.11)	
1-11/year	49 (19.92)	43 (23.24)	6 (9.84)	
Unknown	4 (1.62)	4 (2.16)	0	
Seizure frequency (most recent)				.500‡
≥ 1/day	38 (15.45)	30 (16.22)	8 (13.11)	
1-6/week	7 (2.85)	6 (3.24)	1 (1.64)	
1-3/month	19 (7.72)	17 (9.19)	2 (3.28)	
1-11/year	170 (69.11)	123 (66.49)	47 (77.05)	
Unknown	12 (4.88)	9 (4.86)	3 (4.92)	
Comorbidities				
NF type 1	2 (0.81)	1 (0.54)	1 (1.64)	.435‡
Hemophilia A	1 (0.41)	1 (0.54)	0	>.999‡
Cerebral palsy				<.001‡
Spastic quadriparesis	57 (23.17)	57 (30.81)	0	
Diplegia	1 (0.41)	1 (0.54)	0	
Mixed type	3 (1.22)	3 (1.62)	0	
Spastic hemiplegia	5 (2.03)	5 (2.70)	0	
Hydrocephalus	4 (1.63)	4 (2.16)	0	.575‡
Tuberous sclerosis	4 (1.63)	3 (1.62)	1 (1.64)	>.999‡
Congenital heart disease	2 (0.81)	1 (0.54)	1 (1.64)	.435‡
Hirschsprung disease	1 (0.41)	0	1 (1.64)	.248‡
Genetic disorder	5 (2.03)	5 (2.70)	0	.337‡
Stroke	1 (0.41)	1 (0.54)	0	>.999‡
Torch syndrome	1 (0.41)	1 (0.54)	0	>.999‡
Dandy walker	1 (0.41)	1 (0.54)	0	>.999‡
MCA	1 (0.41)	1 (0.54)	0	>.999‡
Bacterial meningitis - post	1 (0.41)	1 (0.54)	0	>.999‡
Down syndrome	1 (0.41)	1 (0.54)	0	>.999‡
Galactosemia	1 (0.41)	1 (0.54)	0	>.999‡
Microcephalic	2 (0.81)	2 (1.08)	0	>.999‡
Others	2 (0.81)	2 (1.08)	0	>.999‡
None	153 (62.20)	95 (51.35)	58 (95.08)	<.001†

	Overall (n = 246)	With NDD (n = 185)	Without NDD (n = 61)	p-value
	Frequency (%); Mean ± SD; Median (IQR)			
Video EEG/ EEG findings (initial)				<.001‡ a
Normal	63 (25.61)	36 (19.46)	27 (44.26)	
Abnormal	165 (67.07)	140 (75.68)	25 (40.98)	<.001‡ b
Non-specific	22 (13.33)	17 (9.19)	5 (8.20)	
Focal	94 (56.97)	77 (41.62)	17 (27.87)	
Generalized	6 (3.64)	5 (2.70)	1 (1.64)	
Multifocal	25 (15.15)	24 (12.97)	1 (1.64)	
Focal + generalized	18 (10.91)	17 (9.19)	1 (1.64)	
Not done	18 (7.32)	9 (4.86)	9 (14.75)	
Neuroimaging (initial)				<.001‡
Normal	68 (27.64)	37 (20)	31 (50.82)	
Abnormal	103 (41.87)	94 (50.81)	9 (14.75)	
Not done	75 (30.49)	54 (29.19)	21 (34.43)	
Age of initial neurodevelopmental evaluation, years	4 (2.10-6)	4 (2.50-6)	2.92 (1.50-4.08)	<.001§
Interval from age of diagnosis to age if initial evaluation, years [n=191]	2.55 ± 1.91	4.34 ± 1.97	3.04 ± 2.10	<.001*
Presence of neurodevelopmental disorder (Yes)	185 (75.20)	-	-	-
Global developmental delay	100 (54.05)	-	-	-
Intellectual disability				
Mild	5 (2.70)	-	-	-
Moderate	23 (12.43)	-	-	-
Severe	22 (11.89)	-	-	-
Profound	3 (1.62)	-	-	-
Autism spectrum disorder	11 (5.95)	-	-	-
Attention-deficit/	8 (4.32)	-	-	-
Specific learning disorder (Tic disorders)	1 (0.54)	-	-	-
Communication disorder	16 (8.65)	-	-	-
Battelle developmental inventory - 2 total DQ score				<.001‡
High average	1 (0.41)	1 (0.54)	0	
Average	22 (8.94)	0	22 (36.07)	
Low average	47 (19.11)	13 (7.03)	34 (55.74)	
Mild developmental delay	14 (5.69)	9 (4.86)	5 (8.20)	
Significant developmental	162 (65.85)	162 (87.57)	0	

Statistical tests used: *–Independent T-test; §–Mann-Whitney U test; †–Chi-square test; ‡–Fisher's exact test.

a – p-value representing the comparison of initial video EEG/EEG findings.

b – p-value for analyses involving patients with abnormal findings.

Table 4. *Association of Clinical Profile with Neurodevelopmental Disorders*

	Crude Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Age, years	1.28 (1.12-1.48)	<.001	1.10 (0.72-1.70)	.653
Sex				
Male	Reference	-	-	-
Female	0.94 (0.52-1.70)	.832	-	-
Gestational age				
Term	Reference	-	-	-
Preterm	1.61 (0.71-4.17)	.284	-	-
Mode of delivery				
Normal spontaneous delivery	Reference	-	-	-
Cesarean section	0.70 (0.37-1.38)	.296	-	-
Instrumentation	0.30 (0.01-7.66)	.396	-	-
Birthweight				
Normal	Reference	-	-	-
Low birth weight	1.14 (0.55-2.54)	.733	-	-
Very low birth weight	4.51 (0.52-592.33)	.208	-	-
Macrosomic	0.12 (0.001-2.20)	.148	-	-
Birthweight according to gestational age				
AGA	Reference	-	Reference	-
SGA	1.78 (0.78-4.58)	.195	0.57 (0.17-2.02)	.376
LGA	0.36 (0.01-9.10)	.468	0.30 (0.01-49.22)	.532
Birth complications				
HIE	12.08 (2.50-217.35)	.015	3.44 (0.28-498.73)	.379
Sepsis	3.92 (1.62-11.75)	.006	1.53 (0.23-9.58)	.650
Meningitis	7.36 (0.92-951.57)	.062	1.81 (0.11-277.37)	.712
Jaundice	2.05 (0.54-13.40)	.358	-	-
Respiratory distress	7.36 (0.92-951.57)	.062	2.72 (0.22-351.72)	.480
Pneumonia	5.29 (1.04-96.75)	.110	0.66 (0.09-7.68)	.706
IVH	0.33 (0.01-8.33)	.431	-	-
Cystic hygroma	1 (0.05-146.70)	>.999	-	-
MCA	1 (0.05-146.70)	>.999	-	-
Bilirubin encephalopathy	0.11 (0.001-2.07)	.136	0.10 (0.0004-4.39)	.239
MAS	1 (0.05-146.70)	>.999	-	-
Others	2.36 (0.22-318.87)	.532	-	-
None	0.20 (0.09-0.41)	<.001	0.31 (0.05-1.42)	.138
Family history				
Epilepsy	0.69 (0.38-1.26)	.224	-	-
Neurodevelopmental disorders	0.81 (0.38-1.81)	.591	-	-

	Crude Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Age of seizure onset				
< 1 month old	Reference	-	Reference	-
1-12 months	0.32 (0.10-0.83)	.029	0.35 (0.04-1.90)	.238
1-3 years	0.25 (0.08-0.69)	.012	0.36 (0.04-2.18)	.276
4-7 years and 11 months	0.37 (0.10-1.30)	.126	0.27 (0.02-2.65)	.263
Seizure type				
Focal				
Motor	0.33 (0.002-3.18)	.396	-	-
Nonmotor	0.14 (0.001-2.17)	.176	0.16 (0.02-1.33)	.092
Focal to bilateral tonic clonic	0.78 (0.004-162.42)	.906	5.05 (0.002-1684.43)	.663
Generalized				
Motor	1 (0.05-146.70)	>.999	-	-
Multiple (2 or more seizure types)				
Focal + generalized	1.68 (0.13-232.37)	.726	-	-
Unknown	1 (0.05-146.70)	>.999	-	-
Epilepsy syndrome				
West syndrome	1.02 (0.05-150.03)	.989	-	-
Otahara syndrome	1.02 (0.05-150.03)	.989	-	-
BECTS	1.02 (0.05-150.03)	.989	-	-
LGS	2.39 (0.23-322.56)	.526	-	-
IES- DEE	1.02 (0.05-150.03)	.989	-	-
Infantile epileptic spasm syndrome	0.11 (0.001-2.16)	.144	-	-
Genetic epilepsy	1.02 (0.05-150.03)	.989	-	-
None	Reference	-	-	-
Number of antiseizure medications (most recent)				
1	Reference	-	Reference	-
2	1.75 (0.81-4.19)	.161	2.19 (0.72-7.77)	.173
3	13.85 (1.82-1777.61)	.005	6.47 (0.49-973.52)	.179
4	6.29 (0.74-822.25)	.104	0.55 (0.02-4223.55)	.810
Age of initial neurodevelopmental evaluation, years	1.33 (1.15-1.55)	<.001	1.21 (0.78-1.85)	.373
Interval from age of diagnosis to age if initial evaluation, years [n=191]	1.79 (1.40-2.40)	<.001	1.29 (0.87-1.94)	.207

Note: Multivariate analysis (n=191)

Cragg-Uhler Pseudo-R^2 = 48.40%; McFadden Pseudo-R^2 = 35.41%; p-value <.001

Discussion

The socioeconomic data findings in this study emphasize the crucial factors affecting the management and outcomes of epilepsy in children. Lower educational attainment and family income may limit access to healthcare resources, impact treatment adherence, and place a greater burden on families caring for these children. These findings were consistent with results of the systematic review conducted by Huber and Weber in 2022 about the relationship between socioeconomic factors and prevalence, adherence and outcome in childhood epilepsy. According to the study, children belonging to a lower socioeconomic group are at risk of having worse outcomes regarding adherence and hence remission, poorer quality of life and academic achievement.[13]

Analysis of the maternal and birth history of the cohort showed that neonatal complications like hypoxic-ischemic encephalopathy (HIE) and sepsis were significantly more prevalent in children with NDD. HIE results from fetal oxygen deprivation around the time of delivery, leading to brain injury. Similarly, sepsis in neonates often arises from infections during labor or delivery. Poor maternal health and care, including inadequate prenatal care, and other unmanaged maternal illnesses, can exacerbate these risks. Both HIE and sepsis can lead to severe neurological damage, increasing the risk of developing epilepsy in children. These results are consistent with existing literature, which suggests that the neonatal brain is especially vulnerable to hypoxia and infection, potentially leading to long-term developmental issues.[14,15] This is also clearly indicates of how improved maternal and neonatal healthcare practices can improve neonatal outcomes. Hence, they need to be taken into consideration when managing epilepsy and NDD.

A significant number of patients (75.20%) in this study had NDD. While there have not been recent studies on the worldwide prevalence of NDD in epilepsy, a study by Besag F.M. in 2006 found that around 20-30% of affected children experience behavioral disturbances and cognitive impairments.[16] Furthermore, other studies indicate that 70-76% of children with epilepsy have some form of disability or impairment that hinders their daily functioning.[17] These findings align with previous research, highlighting the high prevalence of NDD among children with epilepsy. Among the these NDDs, global developmental delay was the most common, affecting 54.05% of the cohort. Several studies also have proposed an association between Global developmental delay (GDD) and epilepsy. The impact of epilepsy on GDD can be explained by the effect of seizures on developing brain structures and functions and on repeated brain volume reduction. [18] However, in general, they often go undiagnosed.

Therefore, children with epilepsy should undergo regular screening for neurodevelopmental disorders to facilitate early intervention and to maximize the patients' chances for academic, professional, and social success. [19] Aside from GDD, research by the International League Against Epilepsy has established that epilepsy is more prevalent among children with autism and ADHD compared to the general population. [7,21] Nineteen children in this cohort were diagnosed with ASD or ADHD. Due to the small sample size, this subgroup could not be further analyzed. Future research should focus on this group to explore potential associations.

Focusing on treatment, the early initiation of anti-seizure medications and the predominant use of Levetiracetam and Phenobarbital in our cohorts follows Philippine standard practices for managing pediatric epilepsy. The notable decrease in seizure frequency indicates effective management in a substantial number of patients in the group. Comorbidities in epilepsy like NDD are often related to the underlying etiology, age of onset of epilepsy, frequency and location of seizures, and, potentially, epileptiform abnormalities, as well as anti-seizure medications (ASM). They are mostly observed in early-onset, pharmaco- resistant epilepsy with frequent seizures and severe seizure type.[18] In this study, children diagnosed with NDD were prescribed with more anti-seizure medications. They also exhibited a significantly higher rate of EEG abnormalities compared to children without NDD. Not only do these children need more anti-seizure medications, but they are also more likely to experience frequent seizures. The higher rate of abnormalities in neuroimaging demonstrates the challenges of managing epilepsy in these children. Therefore, special and tailored approaches are necessary to meet their unique needs and effectively address their difficulties.

The high prevalence of neurodevelop-mental disorders among children with focal epilepsy points to the need for comprehensive neurodevelopmental assessment and intervention. The presence of conditions such as global developmental delay, intellectual disability, autism spectrum disorder, and ADHD requires a multidisciplinary approach to care.[20]

Limitations and strengths

The study's sample from a single tertiary care center may not represent the broader population of children with epilepsy, potentially limiting generalizability due to selection bias, as more severe cases are referred to specialized centers, possibly overestimating the prevalence of NDD. Exclusion of milder cases managed in primary care could skew results towards more severe outcomes. To mitigate this, a comprehensive sample of children with focal epilepsy at the

Philippine Children's Medical Center was included, using clear inclusion criteria and efforts to balance severity. However, inherent referral bias remains. Information bias from retrospective data collection and parental recall inaccuracies was mitigated using standardized neurodevelopmental evaluation tools like the BDI - 2 and DSM-5-TR criteria. The cross-sectional design limits causal inferences, and a small sample size reduces statistical power, particularly in subgroups. Despite adjustments for confounders, residual variables may still affect findings, highlighting the need for further longitudinal research. Statistical adjustments controlled for potential confounders, with multivariable analyses isolating the effect of each variable on NDD presence.

Implications and Future Directions

The high prevalence of neurodevelopmental disorder among children with focal epilepsy highlights the need for a comprehensive management that addresses both seizure control and developmental support. Timely detection and diagnosis of NDD in children with epilepsy and giving of appropriate treatment, can significantly improve the prognosis and improve the quality of life. It will also provide the patients a multidisciplinary management, addressing not just the epilepsy but also its common co-morbidities. This study also emphasizes the need to take socioeconomic and perinatal factors into account when providing comprehensive care. Moreover, gaining insight into the mechanisms and rationales behind the effects of various antiseizure drugs on a child's neurodevelopment can potentially enhance the development of more efficient and targeted therapeutic interventions.

Adjusting the treatment of epilepsy to prevent any developmental complications while maximizing anti-seizure effectiveness in children remains one of the key goals for improving the outcomes of children with epilepsy.

Conclusion

The study offers a comprehensive overview of the clinical and neurodevelopmental profile of children with focal epilepsy in a tertiary hospital in the Philippines. It identifies important areas like socioeconomic, maternal, birth-related, and clinical factors that influence the outcomes of these children. Identifying risk factors such as birth complications and the use of multiple anti-seizure medications provides critical insights for clinicians. These findings can inform risk stratification and individualized care plans, aiming to minimize neurodevelopmental impairments and improve quality of life. While age and medication use emerged as significant factors, a multidisciplinary and a targeted approach considering both biological and socio-economic factors is essential for

improving neurodevelopmental outcomes in this vulnerable population.

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