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Welcome to the second issue of The PCMC Journal for the year!

As we write this, it is the last days of 2021. Just as we reflect on how to live in these pandemic times, so do we think how to best continue coming out with the journal. At present we are still on "hybrid mode," producing both an online and print issue. In the very near future, though, we will shift to a purely online model, as it is definitely more efficient to come up with online issues. The important point, though, is to try to be as searchable as possible, as we eagerly await word on our application for inclusion to WPRIM; we are already accessible on HERDIN Plus. Here's to a more productive and less disruptive 2022!

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CONTENTS

SAFETY AND EFFICACY OF BUCCAL MIDAZOLAM COMPARED TO RECTAL DIAZEPAM FOR THE ACUTE TREATMENT OF SEIZURES IN CHILDREN: A META-ANALYSIS

MARA ISABEL B. CALINGO, MARJORIE GRACE M. APIGO, MEL MICHEL G. VILLALUZ

ABSTRACT

OBJECTIVE: To compare the safety and efficacy of buccal midazolam as opposed to rectal diazepam in the treatment of acute seizures in children less than 18 years old.

METHODOLOGY: This is a meta-analysis of randomized controlled trials comparing the use of buccal midazolam and rectal diazepam as treatment for acute seizures in children less than 18 years old. The total population of each study are as follows: 330 patients (Mpimbaza, 2008), 43 patients (Baysun, 2005), and 17 patients, all less than 18 years old, coming into the emergency department due to seizures.

RESULTS: There is no significant difference in the mean duration of seizure in minutes and seizure cessation in ten minutes between the buccal midazolam and rectal diazepam groups (Mean difference 0.39; 95% Confidence interval [CI] -0.18 to 0.96; p=0.17; Risk ratio [RR] 0.99; 95% CI 0.83 to 1,19, p=0.2). There is no significant difference in the risk of respiratory depression between buccal midazolam and rectal diazepam (RR 0.96; 95% CI 0.22 to 4.13; p=0.61).

CONCLUSIONS: The administration of buccal midazolam and rectal diazepam are similar in terms of efficacy and safety in terms of time to seizure cessation, termination of seizure within ten minutes, and risk of respiratory depression.

KEYWORDS: *buccal midazolam, rectal diazepam, seizures*

I. INTRODUCTION

Seizure is one of the most common pediatric neurologic emergencies, accounting for 1% of emergency department (ED) visits for patients aged 18 and below.[1] As prolonged seizures may pose significant morbidity and mortality, there is a need for immediate management with AEDs. According to the American Epilepsy Society (AES) 2016 Guidelines on the Treatment of Convulsive Status Epilepticus in Children and Adults, first line options are as follows: intramuscular (IM) midazolam, intravenous (IV) lorazepam, and IV diazepam. In the absence of such mentioned, the next options may be IV phenobarbital, rectal diazepam (RD), intranasal midazolam, or buccal midazolam (BM).[12] IV lorazepam has been shown to be more effective than diazepam

or phenytoin in stopping seizures.[7] However, lorazepam is not available locally. IV access may not be easily established in children in active seizure for the administration of benzodiazepines, hence other routes are usually required.

Buccal Midazolam has been approved by the National Institute for Health and Care Excellence (NICE) as one of the first line medications for prolonged convulsive seizures.[20] In the 2012 Pharmacologic Update, it has been recommended that buccal midazolam be administered if unable to secure immediate IV access for lorazepam or diazepam.[20] The use of intranasal and buccal midazolam are effective and safe in various literature (Level B recommendation, AES Guidelines 2016). McIntyre et al (2005), showed that buccal midazolam has controlled seizures in 56% of children compared with rectal diazepam at 27%. However, a local study by Antonio et al (2016), showed no statistical difference among the effectiveness and safety of midazolam and diazepam via the buccal and rectal route.

This meta-analysis aims to assess the safety and efficacy of buccal midazolam as opposed to rectal diazepam in the treatment of acute seizures in children less than 18 years old. The results of this study may aid in making future recommendations and local guidelines in the acute management of seizures in children.

II. METHODOLOGY

This study is a systematic review and meta-analysis; reporting was accomplished in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guidelines[11].

We performed a systematic computerized literature search from various search engines and databases such as PubMed, Cochrane Library, Ovid, EMBASE, and grey literature. The keywords used in literature search were "buccal midazolam" [MeSH], "rectal diazepam" [MeSH], "seizures" [MeSH], and "randomized controlled trial" [MeSH]. Articles were then uploaded to Endnote X9 (Thomas Reuters), wherein duplicates were removed. Remaining articles were screened based on title and abstract, then full text manuscripts.

This review included studies comparing the use of buccal midazolam and rectal diazepam as treatment for acute seizures. Studies were included if they met the following inclusion criteria: (1) Randomized-control trials (RCT), (2) study population of children less than 18 years old, and (3) studies were done in a hospital ED setting. Studies that included chronic epileptic patients receiving antiepileptic drugs were not excluded in this study.

Studies were excluded if they met the following exclusion criteria: (1) non RCTs, (2) studies with patients who received emergency anti-seizure medications or rescue treatment prior to ED consult

We extracted relevant data from the eligible studies, namely year of study and

publication, location, design, methods of randomization, baseline population characteristics, dosage of AEDs, time to seizure cessation, and side effects of AEDs.

The investigator and an independent party assessed articles for risk of bias using the Version 2 of the Cochrane risk-of-bias assessment tool for randomized trials. All eligible studies underwent assessment of risk of bias; results were presented in tabular form. A flowchart of study selection is shown in figure 1:

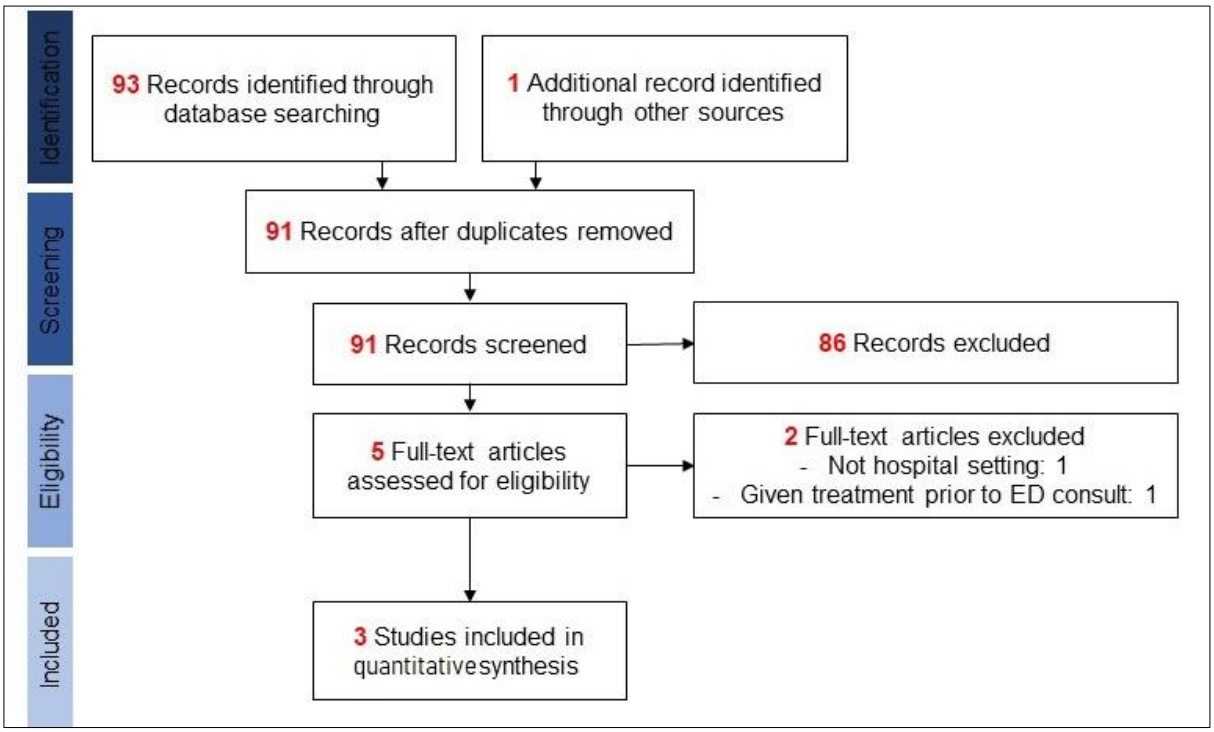


Figure 1. PRISMA Flow Chart of Literature Search

The meta-analysis was performed using the Reviewer Manager Software, version 5.3 (Cochrane Collaboration, UK). The overall effect estimate was calculated as the mean difference (with 95% CI) for continuous outcome (i.e duration of seizure in minutes) and as the risk ratio (with 95% CI) for dichotomous outcomes (i.e termination of seizure within 10 minutes and presence of respiratory depression). Random effects meta-analyses were used to pool the data, using the inverse variance approach for continuous outcome and the Mantel-Haenszel method for dichotomous outcomes. Quantification of the effect of heterogeneity was assessed by means of I^2. The predefined heterogeneity are as follows: low and not important with values <40%; moderate with I^2 values of 40 to 60%; substantial heterogeneity at 50 to 90% and considerable heterogeneity at 75% to 100%, respectively.

III. RESULTS

The initial search through databases and other sources yielded 94 references, including both articles and reviews. Most articles were excluded due to different study designs and other primary outcomes used. Five full text articles were reviewed for eligibility; two were excluded due to a non-hospital setting and treatment prior to ED consult. A total of three studies were then included in the analyses.

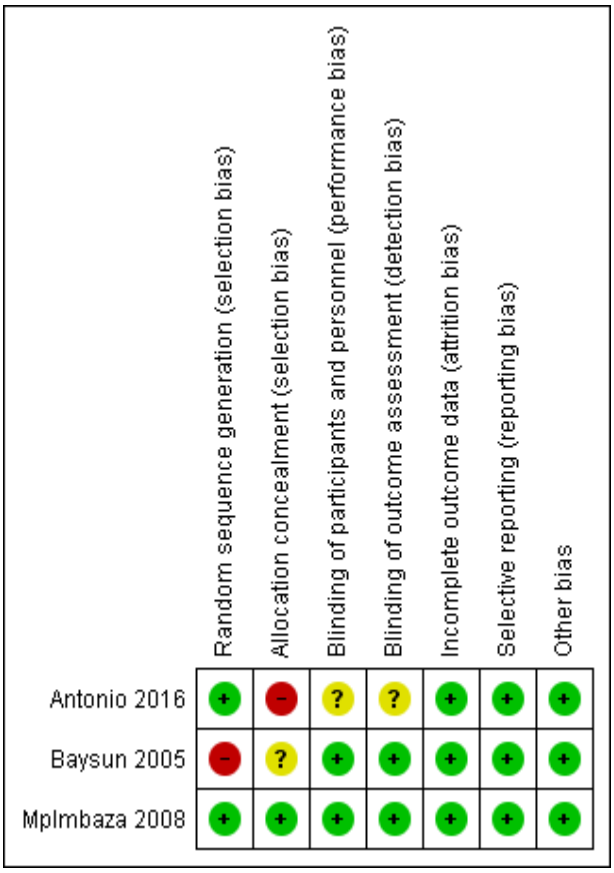
A. Study Characteristics

This review included data from three randomized controlled trials done in Uganda, Turkey, and the Philippines last 2005-2016. The total population of each study are as follows: 330 patients (Mpimbaza, 2008), 43 patients (Baysun, 2005), and 17 patients (Antonio, 2016). Characteristics of the studies included are summarized in the table below:

Table: Summary of Study Characteristics

Author Year Country	Study Design	Population	Outcome measures
Baysun[16] 2005 Turkey	Randomized controlled trial	Patients aged 2 months to 12 years RD: 20 patients BM: 23 patients	Observation of the cessation of convulsive activity within 10 minutes Side effects of both medications
MpImbaza[15] 2008 Uganda	Randomized controlled trial	Patients aged 3 months to 12 years RD: 165 patients BM: 165 patients	Cessation of visible seizure activity within 10 minutes without recurrence in the subsequent hour Side effects of both medications
Antonio[9] 2016 Philippines	Randomized controlled trial	Patients aged 1 month to 15 years RD: 8 BM: 9	Cessation of visible signs of seizure activity within 10 minutes of administration of the randomized drug without respiratory depression and without another seizure within 1 hour Side effects of both medications

The population in the studies were divided into rectal diazepam and buccal midazolam groups. Patients were either given buccal midazolam or rectal diazepam at 0.5mg/kg, maximum of 10mg/kg/dose. Midazolam was squirted into the buccal cavity between the gum and cheek mucosa, while diazepam was mixed with distilled water then given per rectum. Outcome measures included observation of cessation of visible seizure activity within 10 minutes of administration of RD and BM, and side effects like respiratory depression and hypersensitivity. Mpimbaza (2008) noted treatment failure in 71 of 165 patients who received rectal midazolam, against 50 of 165 patients who received buccal midazolam.(15) Baysun (2005) and Antonio (2016) revealed that midazolam was as effective as diazepam, with no statistically significant difference in effectiveness and risk for complications.(9,16) All three articles were screened for risk of bias using the Version 2 of the Cochrane risk-of-bias assessment tool for randomized trials. The risk of bias analysis summary is presented in Figure 2.



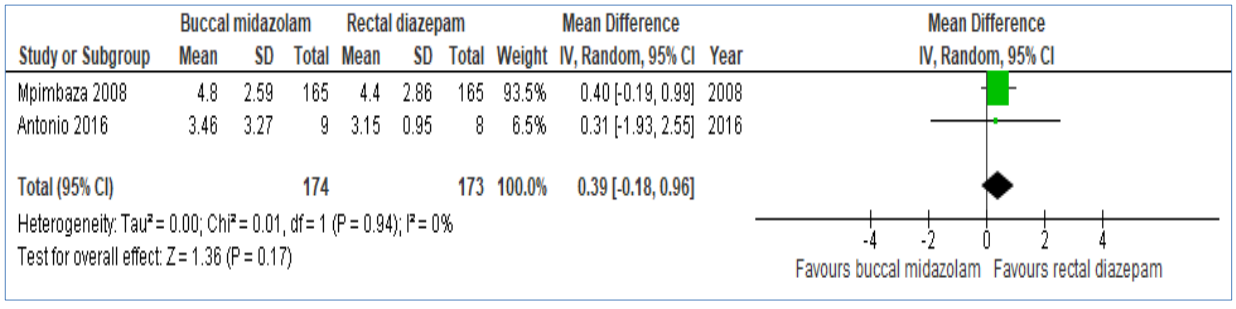
Green = low risk; yellow = unclear risk; red = high risk.

Figure 2. Risk of Bias Analysis Summary.

B. Comparison of Study Treatment Outcomes

Time to Seizure Cessation

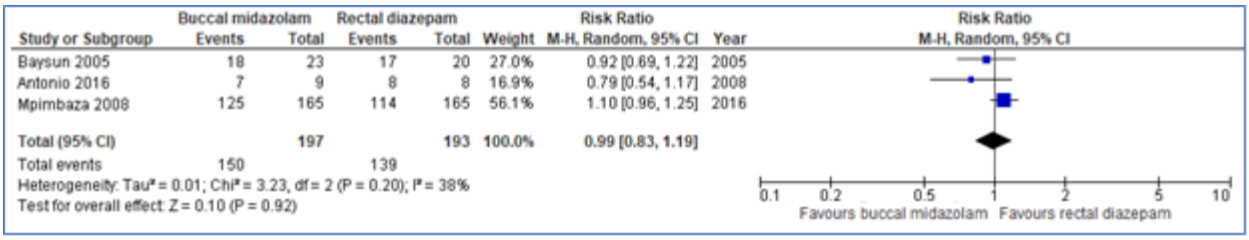
Buccal midazolam and rectal diazepam are comparable in terms of duration of seizures and seizure cessation within 10 minutes.



BM: Buccal midazolam; RD: Rectal diazepam

Figure 3. BM versus RD in duration of seizure in minutes.

Two studies with recorded duration of seizure were compared. In pooled analysis, there is no significant difference in the mean duration of seizure in minutes between the buccal midazolam and rectal diazepam groups (Mean difference 0.39; 95% CI -0.18 to 0.96; p = 0.17) as seen in Figure 3. Statistical heterogeneity is minimal (I^2 = 0%).

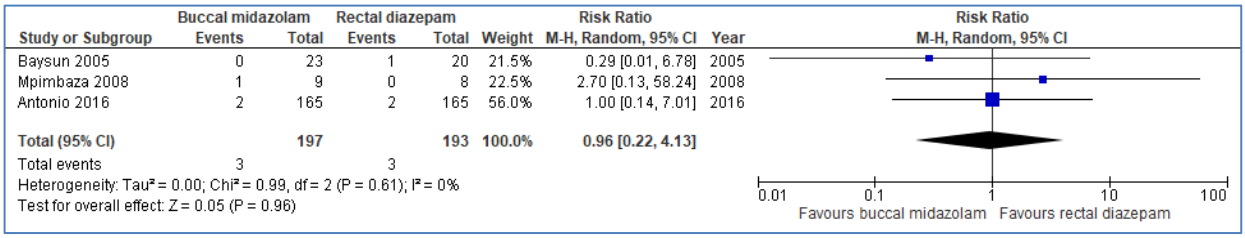


BM: Buccal midazolam; RD: Rectal diazepam

Figure 4. BM versus RD in cessation of seizure within 10 minutes.

Termination of seizure within ten minutes is similar between the buccal midazolam and rectal diazepam groups (Risk ratio 0.99; 95% CI 0.83 to 1.19; p = 0.2) as seen in Figure 4. The level of heterogeneity is also minimal (I^2 = 38%).

Side effects and adverse events



BM: Buccal midazolam; RD: Rectal diazepam

Figure 5. BM versus RD in risk of respiratory complications.

There is no difference in the risk of respiratory depression between buccal midazolam and rectal diazepam (Risk ratio 0.96; 95% CI 0.22 to 4.13; p=0.61) as seen in Figure 5. The level of heterogeneity is minimal (I^2 = 0%). Other side effects reported but not included in the analysis due to limited number of studies (n=1) include non-paroxysmal cough, aphasia, intense pruritus, and death.

IV. DISCUSSION

Seizure activity activates cortical inhibitory mechanisms, principally through γ-aminobutyric acid (GABA)-mediated mechanisms, with termination of ictal activity.[4] Benzodiazepines, the first-line intervention in seizures, are GABA-agonists.[4] Benzodiazepines are effective anticonvulsant agents that rapidly cross the blood-brain barrier and potentiate gamma amino-butyric acid (GABA)

neurotransmission.[1] The potency of each benzodiazepine is dependent on its affinity to the benzodiazepine-GABA–receptor complex.[1] Lorazepam has the highest potency, followed by midazolam and diazepam.[1] Seizures occurring longer than 5 to 10 minutes are at high risk of continuing for at least 30 minutes, thus early treatment is associated with the best outcome.[5]

Diazepam is highly protein-bound (99%).[4] The half-life of the metabolite of diazepam is 20 to 40 hours, but when administered IV is rapidly redistributed into body fat away from the brain, leading to a short therapeutic effect of 15 to 20 minutes.[4] Midazolam is generally very well tolerated, however, the main difficulty with its use is tachyphylaxis, which becomes a problem within 48 hours of initiation.[4]

This meta-analysis showed that there is no significant difference between buccal midazolam and rectal diazepam in terms of seizure duration and seizure cessation within ten minutes. These results support the meta-analysis done by McMullan, et al (2010), which supports the use of midazolam by non-IV routes as favorable alternative to diazepam[14]; and a systematic review done by Sofou (2009) and Doshi (2010), which showed that more children achieved seizure cessation within 10 minutes when treated with buccal midazolam.[17,19]

In terms of risk of respiratory depression between buccal midazolam and rectal diazepam, results of this meta-analysis are consistent with the other meta-analyses, which suggest that midazolam is as safe as diazepam for acute seizures.[14,17]

The primary limitation of this study is the number of studies included. The researcher suggests that for further studies and meta-analyses, literature search be expanded to other routes of administration of midazolam and diazepam, and pre-hospital settings. For better comparison of the said medications, one could also take into consideration the time to administration of medications along with time to seizure cessation.

Conclusion

This meta-analysis suggests that administration of buccal midazolam and rectal diazepam are similar in terms of efficacy and safety, as measured by time to seizure cessation, termination of seizure within ten minutes, and risk of respiratory depression. Results of this meta-analysis, alongside previously published systematic reviews and meta-analyses may serve as a framework for future local studies regarding the use of buccal midazolam in the acute treatment of seizures.

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DETERMINING SATISFACTION WITH INTERPERSONAL RELATIONSHIP WITH NAVIGATOR (SN-I-PH) MEASURE AMONG CAREGIVERS OF FILIPINO CHILDREN WITH CANCER IN A TERTIARY REFERRAL CENTER: A PATIENT NAVIGATION RESEARCH STUDY

TRIXY G. CHU, JULIUS A. LECCIONES

ABSTRACT

BACKGROUND: Patient navigators are trained to provide support and guidance to patients throughout the cancer care continuum. They help "navigate" through the maze of doctors' clinics, outpatient centers, insurance and payment systems, patient-support organizations, and other components of the health care system. Yet there is no existing patient satisfaction tool to assess the patient navigation program in the Philippines for pediatric cancer.

OBJECTIVES: This study aims to evaluate satisfaction with the patient navigation program using a validated Satisfaction with Interpersonal Relationship with Navigator (SN-I-Ph) Measure among Filipino caregivers in a tertiary referral center for childhood cancer.

METHODOLOGY: The tool was first translated for cultural appropriateness, translated, and back translated into Filipino; the content validity and internal consistency were tested. Caregivers of Filipino children with cancer were recruited to answer the survey and the results analyzed.

OUTCOME: Content validity for all 9 items was acceptable with scores of 4.5-5 and internal consistency showed satisfactory results with cronbach alpha of 0.9067. A total of 202 participants were recruited to join the survey. Results showed mean±SD of 42.6±7.8. All the 9 items showed excellent satisfaction.

CONCLUSION: This study showed good satisfaction with the interpersonal relationship of the navigators among caregivers. Participants enrolled in the patient navigation program reported a positive overall experience with the medical care.

RECOMMENDATION: The tool is recommended for use among hospitals with the patient navigation program to assess satisfaction of the caregivers. Further studies can assess caregiver's satisfaction as to logistic aspects as well as how to measure benefits and outcomes with the program.

KEYWORDS: *Patient Navigation, Childhood cancer, Filipino*.

INTRODUCTION

Cancer is a major cause of death. In high-income countries (HICs), most who develop cancer survive, although survival depends strongly on the type of cancer. While in low and middle income countries (LICs and MICs), less than one-third survive, and in some, the proportion is smaller.1 The major contributor to poor outcomes in LIC is that only a few patients come for treatment when their cancer is at an early, curable stage, majority only sought consult when their cancer is already in the late stage.2 One burden in the fight against childhood cancer includes lack of access to effective cancer prevention and treatment.

Effective coordination of care between different clinicians, services and health sectors throughout the patient journey is fundamental to the provision of high-quality standard of care.3 In the 1990s, Dr. Harold P. Freeman, a surgical oncologist at Harlem Hospital, observed that women at his center, largely the African American and the socioeconomically disadvantaged, died from breast cancer at rates much higher than would be expected from national data. Dr. Freeman observed that these women often received their cancer diagnoses late, after their disease has already spread. To reduce these disparities in the cancer outcomes, Freeman designed an innovative approach which he coined “patient navigation” (PN).4 Patient Navigators are trained, culturally sensitive health care workers who provide support and guidance throughout the cancer care continuum. They help people "navigate" through the maze of doctors' offices, clinics, hospitals, outpatient centers, insurance and payment systems, patient-support organizations, and other components of the health care system. Services are designed to support timely delivery of quality standard cancer care to ensure that patients, survivors, and families are satisfied with their encounters with the cancer care system.5 The success of the Harlem program, which showed a deep decline in the percentage of patients diagnosed with late-stage cancers and a corresponding rise in survival, initiated national and international enthusiasm for the patient navigator concept.6

Because patient navigation has the potential to improve cancer outcomes and transform complex and fragmented health care systems to a more patient-centered care, the patient navigation programs have rapidly proliferated.9 In May 2011, the Breast Cancer Medicines Access Program was started in our country through a patient navigation scheme with the goal of promoting early screening and improving survival rates of breast cancer among Filipinos. Data showed that the attrition rate decreased from 62% in 2011 to 18% in 2012.10 Thereafter, in 2013, the patient navigation program for childhood cancer was launched. One of the priority goals of the program is to increase treatment compliance and decrease treatment failure through a decrease in the abandonment rate. The reported abandonment rate of childhood Acute Lymphoblastic Leukemia (ALL) at the Philippine Children’s Medical Center from 44.4% in 2012 remarkably declined to 15.1%, in the span of 1 year with the patient navigation program, and the overall survival for childhood ALL has dramatically

increased to 65.3% from 32.3% (from the Department of Health Rizal Cancer Registry).8,11

In general, studies found patients who are involved in patient navigation programs are satisfied with their care experiences.12 Yet studies that examine patient-navigator relationships are lacking.13 No patient satisfaction tool was yet established to assess the effectiveness of the patient navigation program in the Philippines for pediatric cancer. This study adopted the Interpersonal Relationship with the Navigator (SN-I) Measure. Prior to use in the Filipino setting, this instrument was modified for cultural appropriateness and then translated and validated prior to using it.

The general objective is to evaluate satisfaction with the patient navigators using Satisfaction with Interpersonal Relationship with Navigator (SN-I-Ph) Measure among Filipino caregivers in a Tertiary Referral Center for Childhood Cancer. The specific objectives aim to describe the demographics included age, gender, race/ethnicity, and educational level of the caregivers of Filipino Children with cancer, to validate (English/Filipino) Interpersonal Relationship with the Navigator (SN-I) measure for use with Tagalog-speakers in childhood cancer patient navigation research study, and to determine socio-demographic and clinical factors associated with satisfaction among caregivers of Filipino Children with cancer.

METHODOLOGY

RESEARCH DESIGN: Cross Sectional Analytic with Cross-Language Validation Study

POPULATION: Caregivers of pediatric cancer patients aged 18 years and above diagnosed in a tertiary referral center for childhood cancer

INCLUSION CRITERIA:

- Caregivers enrolled in the patient navigation program aged 18 years old and/or above who can read and write English and Filipino language.

EXCLUSION CRITERIA:

- Inability to read and other cognitive impairment
- Those who will not consent to join the study

PART I Translation process

The translation process consisted of three phases. Phase I was the modification of the questionnaire for cultural appropriateness. Phase II included the translation into Filipino and the testing of its content validity. Phase III was the road test on the evaluation of the internal consistency and the reliability of the Interpersonal Relationship with the Navigator (SN-I) measure.

Subject Selection: The participants were chosen randomly at the Cancer and Hematology Center of the Philippine Children's Medical Center. They were

literate and able to comprehend and communicate well using the English and/or Filipino language.

Data Collection: Modification of the original Satisfaction with Interpersonal Relationship with the Navigator (SN-I) for cultural appropriateness was accomplished by an expert panel consisting of 5 bilingual participants of Pediatric Hematologist/Oncologist, parent, and child life coordinator. Items on the original questionnaire were altered as the expert panel saw fit for cultural adaptation. The modified version was then checked by the moderator to see if the modified content was comprehensive and complete.

Two bilingual experts were recruited for translation and back translation in English/Filipino language. Completed demographic information of the translators including age, gender, race/ethnicity, and educational level were obtained. The use of conversational language was preferred, choosing simpler and more commonly used terms. The translation was examined by members of the same expert panel from Phase I. Semantic accuracy, adequacy and representativeness were rated using a 5-point Likert scale. "1" corresponded to very unsatisfactory, "3" to neutral and "5" to very satisfactory. A space after each item was provided for comments and suggestions for modification. Following the initial review of the expert panel, revisions to the questionnaire were performed accordingly with the supervision of the Filipino translator.

The modified Satisfaction with Interpersonal Relationship with the Navigator (SN-I-Ph) was then back translated into English by another bilingual (Filipino/English) professor, who was unaware of the Satisfaction with Interpersonal Relationship with the Navigator (SN-I). The backward English translation was compared with the original by the authors to assess if the Filipino translation was accurate semantically. The Filipino translation of the items that were not semantically accurate were modified by the Filipino translator and were then back translated again to English. Semantic accuracy was re-assessed by the authors.

A pilot testing of the modified Satisfaction with Interpersonal Relationship with the Navigator (SN-I-Ph) was performed to test clarity and comprehensibility. Content validity was also determined by asking pediatric physicians and oncology nurses to review the translated questionnaire. Using the English version as a reference, each item was rated if the translated question was clear, close to the original version of the question and other similar qualitative questions. The participants were asked to give a comprehensive rating on each of the items using a scale of 1 to 5. A rating of "1" meant that the item was difficult to understand and they had difficulty answering the question while a rating of "5" meant that the item was easy to understand and answer.

Pre-testing of the assessment tool was done on 30 caregivers of children with cancer. Modifications were made according

to the results of the rating performed by the participants during the pilot testing. The respondents who participated in the pre-testing of the questionnaire were not included in the actual study.

Statistical Analysis: Median and mean were used for descriptive statistics both for the rating of the expert panel and for the pilot testing. If the mean score for each item was equal to or more than 3.5 and the median score was equal to or more than 4, the item was considered semantically accurate, culturally relevant and adequate and thus, was not modified. However, if the mean and median scores were below the cut-off, the statement was modified by the Filipino translator. Internal consistency during the pre-testing was computed using cronbach alpha.

PART II. Survey Proper

Eligible participants were invited to participate in the study. Informed consent was obtained by a trained nurse from the Cancer and Hematology Center who had no involvement in the present study and had no involvement in the direct medical care of the patient.

The SN-I-Ph were distributed to the targeted population. Caregivers who received individualized navigation from 2013 onwards were included in the study. The participants were asked to answer the SN-I-Ph, a self-administered questionnaire. It was accomplished at the waiting area of the Cancer and Hematology Center, Out-Patient Division; or the In-Patient Division at bedside; depending on where the caregivers were seen. It took approximately 5 minutes to finish answering the questionnaire (Table 1).

I feel my Navigator…	**Strongly Disagree**	**Disagree**	**Undecided**	**Agree**	**Strongly Agree**	**Don't Know/ Refuse to answer**
is easy to talk to	1	2	3	4	5	98
listens to my problems	1	2	3	4	5	98
is dependable	1	2	3	4	5	98
is easy for me to reach	1	2	3	4	5	98
cares about me personally	1	2	3	4	5	98
is courteous and respectful to me	1	2	3	4	5	98
gives me enough time	1	2	3	4	5	98
figures out the important issues in my health care	1	2	3	4	5	98
makes me feel comfortable	1	2	3	4	5	98

The SN-I employs a Likert scale to evaluate patient perception of their interaction with PN, including communication, empathy, and reliability. Satisfaction with Navigation-Interpersonal scores range from 9 to 45, with higher scores indicating better satisfaction. A cut off score of 4.5 was set to categorize the scale as highly satisfied.

Descriptive statistics was utilized to summarize the clinical characteristics of the subjects. Frequency and proportion was used for nominal variables, median and range for ordinal variables, and mean and SD for interval/ratio variables. Item-level content validity index was used to determine the accepted items. Internal consistency was computed using cronbach alpha. All valid data were included in the analysis. Categorical data was be analyzed using logistic regression. Missing variables was neither replaced nor estimated. STATA 13.1 was used for data analysis.

Bioethical approval from the Institutional Review Board of the Philippine Children's Medical Center was obtained prior to commencement of the study.

RESULTS

PART I Translation process

The modification of the original Satisfaction with Interpersonal Relationship with the Navigator (SN-I) for cultural appropriateness was discussed by the expert panel; each item on the original questionnaire was discussed and reviewed, and the expert panel decided to modify the term "reach" to "contact", as reach could also mean attain or accomplish but the original scale is referring to reach as "easy to contact or get hold of". As for the other items in the questionnaire, the expert panel saw it fit for cultural adaptation and decided that no modification was needed.

Two bilingual experts were recruited for translation and back translation in English/Filipino language. The translations were examined by members of the same expert panel from Phase I. Semantic accuracy, adequacy and representativeness was rated by the group using a 5-point Likert scale with "5" as very satisfactory, revisions to the questionnaire were made until the results became satisfactory to cut off value of >4.5.

In the back-translation process, although item number 3 "maaasahan" was back-translated as "I can rely on", this is considered by the group as similar to "dependable". Item 6 "may paggalang sa akin" is back-translated to "treats me with respect", in the original scale courteous and respectful are actually synonymous terms and the Filipino translation of both words is the same which is "paggalang" hence it was agreed upon by the group to use one term for both to avoid confusion.

Content validity was determined by asking the experts to review the translated questionnaire. The experts were requested to rate the forward translated questionnaire from 1-5, with 1 as Very Dissatisfied and 5 as Very Satisfied. This was done to ensure that the Filipino questionnaire was able to capture the clinical questions related to the patients. For all of the 9 questions, the

experts rating were significantly higher than 3 (Neutral), indicating satisfactory rating for the translated questions.

Reliability

The internal consistency of the forward translated version of Satisfaction with Interpersonal Relationship with the Navigator (SN-I-Ph) was analyzed. The questionnaire was administered to 30 respondents. Items 1 and 2 showed excellent internal consistency with $\alpha \geq 9$, items 3, 4, 5, 6, 7, 8 and 9 showed good internal consistency $0.9 > \alpha \geq 8$. For the 9 questions tested, the answers of the respondents showed excellent internal consistency based on the total computed cronbach alpha of 0.9067.

PART II. Survey Proper

A total of 202 participants were recruited to join the study. Table 4 shows the socio-demographic and clinical profile of the caregivers of the Filipino children with cancer diagnosed in a tertiary referral center for childhood cancer. The mean age of the participants was at 36.8 years ± 8.8 standard deviation. There were more female participants compared to male at a ratio of 5.3:1. Majority of the caregivers were mothers comprising of 80.7%, the fathers were 15.3% and the rest at 4%. As per language preference, majority of the participants are bilingual (Filipino and English) at 56.9% while the pure Filipino speaking are 43.1%. As to the educational attainment, the greater proportion of the population was high school graduates at 43.7%, followed by college graduates at 33.6%, college undergraduate at 7.9%, and the remaining 13.9%. Majority of the participants were unemployed at 76.7%. Monthly income was noted to be less than 5000 pesos in 80.2%. Most of the caregivers have health insurance at 93.1%. Hematologic malignancies comprised 74.3% as the classification of the childhood cancer of the participating caregivers, and the rest were solid tumors at 25.7%. The years of diagnosis was distributed every 2 years as this was the transition period of the nurse navigators. Majority of the participants have their child ongoing treatment at 77.7%, off treatment at 19.8% and the remaining 2.5% were on oral metronomics therapy.

Table 2. Socio-Demographic and Clinical Profile of the Caregivers of Filipino Children with Cancer in a Tertiary Referral Center for Childhood Cancer

Characteristic	Caregivers of Filipino Children with Cancer (N = 202)
	Frequency (%);Mean ± SD
Age (years)	36.8 ± 8.8
Gender	
Male	33 (16.3%)
Female	169 (83.7%)
Relationship to the patient	
Father	31 (15.3%)
Mother	163 (80.7%)
Grandfather	1 (0.5%)
Grandmother	5 (2.5%)
Uncle	1 (0.5%)
Aunt	1 (0.5%)
Language Preference	
Bilingual (English/Filipino)	115 (56.9%)
Filipino only	87 (43.1%)
Educational Attainment	
College Graduate	68 (33.6%)
College Undergraduate	16 (7.9%)
High School Graduate	88 (43.7%)
High School Undergraduate	15 (7.4%)
Elementary Graduate	13 (6.4%)
Elementary Undergraduate	2 (1%)
Employment Status	
Full time employment	40 (19.8%)
Part time employment	7 (3.5%)
Unemployed	155 (76.7%)
Monthly Income	
Less than P 5000	162 (80.2%)
More than P 5000 but < P 9999.99	15 (7.4%)
More than P 10000 but < P29999.99	21 (10.4%)
More than P 30000 but < P49999.99	3 (1.5%)
More than P 50000	1 (0.5%)
Health Insurance (Philhealth)	
With Health Insurance	188 (93.1%)
Without Health Insurance	14 (6.9%)

Characteristic	Caregivers of Filipino Children with Cancer (N = 202)
	Frequency (%);Mean ± SD
Diagnosis	
Hematologic Malignancy	150 (74.3%)
ALL Standard Risk	75 (37.1%)
ALL High Risk	52 (26.4%)
ALL Relapse	8 (4.0%)
AML	8 (4.0%)
JMML	2 (1.0%)
LCH	5 (2.5%)
Solid Tumor	52 (25.7%)
Hodgkin's Lymphoma	5 (2.5%)
Non-Hodgkin's Lymphoma	5 (2.0%)
Ependymoma	1 (0.5%)
Germ Cell Tumor	5 (2.5%)
Hepatoblastoma	2 (1.0%)
Neuroblastoma	6 (3.0%)
PNET	3 (1.5%)
Pineal Parenchymal Tumor	1 (0.5%)
Astrocytoma	1 (0.5%)
Rhabdomyosarcoma	7 (3.5%)
Wilms' Tumor	6 (3.0%)
Retinoblastoma	6 (2.0%)
Osteosarcoma	2 (1.0%)
Lymphoblastic Lymphoma	2 (1.0%)
Year of Diagnosis	
2013-2014	27 (13.4%)
2015-2016	49 (24.2%)
2017-2018	126 (62.4%)
Treatment Status	
On-going treatment	157 (77.7%)
Oral Metronomics	5 (2.5%)
Off Treatment	40 (19.8%)

The SN-I employs a Likert scale to evaluate the patient perception of their interaction with the navigator. The sum of the scores for all 9 questions range from 9 to 45, with higher scores indicating better satisfaction. The general satisfaction score average was 42.12 (range 20-45). The results of the 202 participants showed mean±SD of 42.6±7.8. A cut off score of 4.5 for each item was set to be categorized as

highly satisfied. All the 9 items showed excellent satisfaction.

Socio-demographic and clinical factors associated with satisfaction among caregivers of Filipino children with cancer was analyzed using odds ratio in logistic regression. A cut off score of 4.5 was set to categorize as the participant as very satisfied and less than 4.5 as somehow satisfied. Out of the 202 participants, 187 (92.6%) were categorized as very satisfied and 15 (7.4%) as somehow satisfied. Odds ratio of close to 1 would indicate no relationship to the clinical factors, while that at >1 would show positive relationship and <1 negative relationship. The age of the caregivers as well as gender, educational attainment, language preference, employment status, monthly income, health insurance, diagnosis showed no clinical significance as to the level of satisfaction of the participants. As to the year the patients were diagnosed, those who were diagnosed 2013-2014 showed a trend in the result with odds ratio of more than 1 implying that the subjects were much satisfied with services of the patient navigators employed 2015-2016 and 2017-2018. All the socio-demographic and clinical factors showed no clinical significance (Table 3).

Table 3. Socio-Demographic and Clinical Factors associated with Satisfaction among Caregivers of Filipino Children with Cancer

Factors	Very Satisfied (N = 187)	Somehow Satisfied (N = 15)	Odds Ratio	P-Value
Age (years)	36.8±8.9	35.6±7.3	1.01	0.594
Gender				
Female	157 (84.0%)	12 (80.0%)	Reference	Reference
Male	30 (16.0%)	3 (20.0%)	0.76	0.691
Relationship to the Patient	151 (80.8%)	12 (80.0%)	Reference	Reference
Mother	28 (15.0%)	3 (20.0%)	0.74	0.659
Father	8 (4.2%)	0	-	-
Others				
Educational Attainment				
College Level	79 (42.3%)	5 (33.3%)	0.58	0.351
Secondary Level	93 (49.7%)	10 (66.7%)	Reference	Reference
Primary Level	15 (8.0%)	0	-	-
Language Preference				
Bilingual	110 (58.8%)	5 (33.3%)	Reference	Reference
(English/Filipino)	77 (41.2%)	10 (66.7%)	0.35	0.064
Filipino only				
Employment Status	42 (22.5%)	5 (33.3%)	0.58	0.342
Employed	145 (77.5%)	10 (66.7%)	Reference	Reference

Factors	Very Satisfied (N = 187)	Somehow Satisfied (N = 15)	Odds Ratio	P-Value
Unemployed				
Monthly Income				
Less than P 5000	152 (81.3%)	10 (66.7%)	Reference	Reference
More than P 5000	35 (18.7%)	5 (33.3%)	0.46	0.188
Health Insurance				
With Health Insurance	173 (92.5%)	15 (100.0%)	Reference	Reference
Without Health Insurance	14 (7.5%)	0	-	-
Diagnosis				
Hematologic	138 (73.8%)	12 (80.0%)	Reference	Reference
Malignancy Solid Tumor	49 (26.2%)	3 (20.0%)	0.70	0.599
Year of Diagnosis				
2013-2014	24 (12.8%)	3 (20.0%)	2.94	0.255
2015-2016	47 (25.1%)	2 (13.3%)	1.45	0.593
2017-2018	116 (62.1%)	10 (66.7%)	Reference	Reference

DISCUSSION

Patient navigation is rapidly becoming an integral aspect of the cancer-related care process on a continuum from cancer screening to diagnostic resolution to cancer treatment and survivorship.15 Patient navigators vary in educational and socioeconomic status backgrounds ranging from lay health workers (i.e., trained paraprofessional) to health professionals (e.g., nurse and social worker).16 Irrespective of their educational and training background navigators generally provide support to patients that can be categorized as emotional (e.g., direct emotional such as accompanying patients to visits or indirect emotional such as through referral to a support group or mental health treatment) or instrumental/technical (e.g., assistance with insurance, arranging transportation, assisting with financial aid), and educational (e.g., sharing approved information, explanation of medical terms, and coaching).17 The Philippine childhood cancer patient navigation program employs oncology nurses as patient navigators. The patient navigators undergo a two day training module and workshop prior to commencement of their responsibilities. In our institution, oncology nurse navigators are transitioned every 2 years hence, since 2013, there have been 3 sets of different navigators who were employed in the cancer center.

The patient satisfaction with interpersonal relationship with the navigator measure was developed to assess a key dimension of patient navigation: perceptions of the interpersonal/relational aspects of navigation. This measure represents the first validated scale for patient satisfaction with their navigator. Currently, there are no gold standard measures to assess the patient

navigator relationship. The 9-items scale assesses key aspects of navigator performance including time spent, dependability and accessibility, in addition to more affective-laden aspects such as listening, respect and caring. As navigation becomes increasingly integrated into cancer care, it is critical to have valid measures for its assessment.18

There was a validation study of the patient satisfaction with interpersonal relationship with the navigator (PSN-I) measure to a Spanish version done by Jean-Pierre et. al. The scale was translated and back translated to Spanish and English and administered to Spanish fluent participants. They also conducted a psychometric validation as well as internal consistency and correlations analyses to examine divergence and convergence of the scale. The PSN-I was found suitable measure of satisfaction with a patient navigation for the Spanish group.19

In a study done at the Masachusetts General Hospital, they compared to groups: patients who benefited from the patient navigation program and the group who did not. They found out that patients who received patient navigation had higher satisfaction scores with overall medical care.14

Our study showed well satisfied caregivers with the interpersonal relationship of the navigators in our institution through the use of the Satisfaction with Interpersonal Relationship with Navigator (SN-I-Ph) Measure among Filipino caregivers. The SN-I-Ph is an acceptable tool in parallel with the study done by Jean-Pierre et. al., for assessing important dimensions of the effort of the navigators including time spent with patients, navigator's dependability and accessibility, and important interpersonal characteristics of patient navigators such as abilities to listen, respect and care for patients. The translation to the Filipino language of the questionnaire showed acceptable content validity and good reliability. The SN-I-Ph was administered by a research assistant and not by the patient n avigators to avoid any issue related to social desirability biases. The age of the caregivers as well as gender, educational attainment, language preference, employment status, monthly income, health insurance, diagnosis showed no clinical significance as to the level of satisfaction of the participants. All of the socio-demographic and clinical factors showed no clinical significance.

This study was not able to establish a correlation as to the degree of satisfaction to the clinical factors since majority of the caregivers showed highly satisfied results even with a higher cut off score of 4.7. We attempted to determine if there will be a significant difference as to the different set of navigators employed in the cancer center every 2 years, but the logistic regression analysis failed to show any clinically significance.

Our study has some limitations. First, our study took place in a single institution with an established patient navigation program, which may not be the same as the other institutions. In addition, our data are entirely patient-reported and therefore

subject to recall bias as all patients (old and new) whether diagnosed recently or previously were included in the study.

Health professionals value the patient navigation program and credit the program with; better patient preparedness, providing more support for patients, improved collaboration among health professionals, more efficient clinical involvement with patients, and identification of service gaps. Navigators have become one of the primary sources of assistance for patients, along with family doctors, oncologists, and staff at the cancer centers. The patient navigator does not replace other sources of support, but rather complements and reinforces the support, information and education provided especially by physicians.20 Their role in bridging the gaps towards treatment compliance is vital for cancer survival.

CONCLUSIONS

Addressing barriers to cancer care through the patient navigation program is an essential part of the cancer care continuum and should be employed among hospitals with cancer programs. Caregivers of children with cancer who initially have a negative outlook with the disease process and prognosis reported a more positive overall experience with medical care when they are enrolled in the patient navigation program.

This study showed well satisfied caregivers with the interpersonal relationship of the navigators in our institution through the use of the Satisfaction with Interpersonal Relationship with Navigator (SN-I-Ph) Measure among Filipino caregivers. The translation to the Filipino language of the questionnaire showed acceptable content validity and good reliability. The age of the caregivers as well as gender, educational attainment, language preference, employment status, monthly income, health insurance, diagnosis showed no clinical significance as to the level of satisfaction of the participants. All of the socio-demographic and clinical factors showed no clinical significance. It is our hope that the government will continue to support the patient navigation program in the country to improve treatment compliance and decrease abandonment rate, giving every child fighting for cancer a chance to be cured.

Nurse navigator program is a promising resolution for patient care inadequacies, effective means for reducing barrier in oncology care and increase patient satisfaction and quality of care. This model has been already implemented in most of the developed countries and is now being adopted in the Philippines. Some cancer centers in the Philippines are yet familiar with the patient navigation concept and have not incorporated this program in their institutions. It is recommended that this program should be encourage for use nationwide and extended to other chronic diseases in childhood such as neurologic, nephrologic, rheumatologic and other diseases.

The SN-I-Ph assesses only one dimension of navigation program, the patient-navigator interpersonal relationship. We do not know yet whether this aspect of

patient navigation is associated with other patient navigation outcomes such as timely receipt of care, patient adherence, or improvements in health status. Further studies for assessment of caregiver's satisfaction as to the logistic aspects as well as how to measure benefits and improved outcomes with the program is suggested.

The Filipino version of the satisfaction with interpersonal relationship with navigator (SN-I-Ph) measure among caregivers is recommended for application with other institutions that have the patient navigation program for childhood cancer to establish satisfaction with their own navigation program across the cancer care continuum.

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DIRECT COST OF HOSPITALIZATION OF PEDIATRIC FOCAL EPILEPSY PATIENTS IN A TERTIARY MEDICAL CENTER

JERIC D. DIMAANO, MADELYN P. PASCUAL

ABSTRACT

OBJECTIVES: To determine the cost of hospitalization, percentage distribution of expenses, and average expenditures covered by PhilHealth, hospital share and patient's share in financing the hospitalization of pediatric focal epilepsy patients in a tertiary government hospital.

METHODOLOGY: This is descriptive retrospective research of patients diagnosed and managed as focal epilepsy from July to December 2018. Mean, standard deviation and percentage distribution of expenses were determined.

RESULTS: The mean cost of hospitalization is 21,545.96 Php and the laboratory cost contributes the most to the total cost with a mean of 6,046.08 Php. The mean cost shouldered by PhilHealth is 3,734.26 Php which is 17.33% of the total cost of hospitalization.

CONCLUSION: The laboratory cost makes up most of the hospital cost. Philhealth covers a small percentage of the hospitalization cost of pediatric focal epilepsy patients with most of the total cost shortly followed by the patient's share.

KEYWORDS: *Hospitalization cost analysis, Pediatric focal epilepsy, PhilHealth coverage.*

INTRODUCTION

The International League Against Epilepsy describes epilepsy as one of the most frequent neurological diseases, characterized by abnormal electrical activity resulting to seizures or unusual behaviour, sensations and sometimes loss of awareness.[1]. According to a multicenter cross-sectional study by Ahmed Hussein Subki, et al. on the impact of pediatric epilepsy on children and families, an estimated 70% of people with epilepsy could be seizure free if properly diagnosed and treated, yet about three quarters of individuals with epilepsy in low-income countries do not receive the treatment they need increasing their risk of dying prematurely [3]. Reasons for this premature mortality in middle- and low-income countries are more commonly related to lack of access to health facilities when seizures are long-lasting or occur approximate without recovery in between, and preventable causes like drowning, head injuries and burns[4].

Epilepsy patients are more likely to have more physical problems (such as fractures and bruising from injuries related to seizures), as well as higher rates of psychological conditions, including anxiety and depression. Likewise, epilepsy increases the risk of premature death up to three times higher than in the general population, with the highest rates of premature mortality

found in low- and middle-income countries and in rural areas[2]. About 0.5% of the global burden of disease is due to epilepsy, a time-based measure that combines years of life lost due to premature mortality and time lived in less than full health. Various studies have shown the significant economic implications caused by epilepsy in terms of health-care needs, premature death and lost work productivity. [6,7,8] In the Philippines, apart from the economic burden already posed by epilepsy itself, there are also issues with poor health-seeking behavior, inadequate hospital facilities and personnel in the countryside, expensive medications, and the persistent dismissal of epilepsy as a public health concern by the authorities. These may explain the treatment gap of epilepsy which has remained unaddressed in the country for decades.[9] Another concern is poor PhilHealth coverage and there is no existing Z-package for epilepsy, there is currently just a case rate disease in Philhealth covering a total of Php 7,800 of the hospital cost [10].

This study was done to provide data that is valuable to policy makers to come up with policies and regulations. This aims to assess the direct cost of hospitalization of children with epilepsy and determining the financial benefit from PhilHealth in terms of coverage of hospitalization cost due to epilepsy. It can help determine the extent to which this health agency can provide financial protection for its members and can be used to revise existing policies to improve health services provision to patients with epilepsy.

OBJECTIVES OF THE STUDY

General Objective: To determine the direct cost of hospitalization of pediatric focal epilepsy patients in a tertiary hospital from July to December 2018.

Specific Objectives:

1. To determine the average total direct cost of hospitalization due to focal epilepsy.

2. To determine the percentage distribution of expenses incurred and its average costs during hospitalization.

3. To determine the proportion of direct hospital expenses and the average expenditures covered by PhilHealth, hospital share and patient's share in relation to the financing of the hospitalization.

METHODOLOGY

This is descriptive retrospective research of patients diagnosed and managed as focal epilepsy from July to December 2018. This study included pediatric patients ages 1 month - 18 years old diagnosed and managed as focal epilepsy based on the final diagnosis with ICD codes G40.0, G40.1, G40.2 and G40.3 (Localization-related focal idiopathic epilepsy and epileptic syndrome with seizures of localized onset, localization-related focal symptomatic epilepsy and epileptic syndrome with simple partial seizures, localization-related focal symptomatic epilepsy and epileptic syndrome with complex partial seizures, and generalized idiopathic epilepsy and epileptic syndromes respectively) who were members of Philhealth during their admission at the

Philippine Children's Medical Center from July to December 2018. The following were excluded in the study: non-members or dependent of Philhealth, admitted under private service, presence of co-morbidity diseases at time of admission and insufficient data during the time of review. All admitted pediatric focal epilepsy patients from July to December 2018 which amounted to 30 patients were used for the study.

The Medical Records Section Officer generated a list of patients diagnosed with Focal Epilepsy or with the ICD codes G40.0, G40.1, G40.2 and G40.3 admitted from July to December 2018. With the use of the inclusion and exclusion criteria, the Medical records Section Officer generated the final list of eligible patients for the study. The final list of study participants was placed in a sealed envelope by the Medical records Section Officer and was given to the Billing Section for retrieval and reprinting of hospital bills. A research assistant was appointed to remove any identifying information from the printed hospital bill (patient's name, parent's and/or guardian's name, address, name of attending physician, admission number) by cutting and covering with permanent ink. A numerical coding system for identification was provided to the anonymize hospital bill. These coded hospital bills were then given to the investigator for data collection. The following information were collected using a structured form: age, length of hospitalization, social services classification, No Balance Billing policy coverage, actual hospital bill, PhilHealth coverage, hospital share, patient's share, and the distribution of hospital expenses (laboratory, intravenous fluids, medications, medical supplies, floor procedures, room boarding). All cost data were presented in peso (PhP) where the estimated rate of conversion as of 2019 was $1=50.89. The data collected was tabulated in Microsoft Excel program. Quantitative variables were summarized as mean, standard deviation and percentage distribution of expenses were determined.

RESULTS

The Medical Records Section generated a list with 30 pediatric focal epilepsy patients with the use of the study's inclusion criteria. Of the patients included, the mean age was 7.5 years and the mean length of hospitalization is 6.3 days (Table 1).

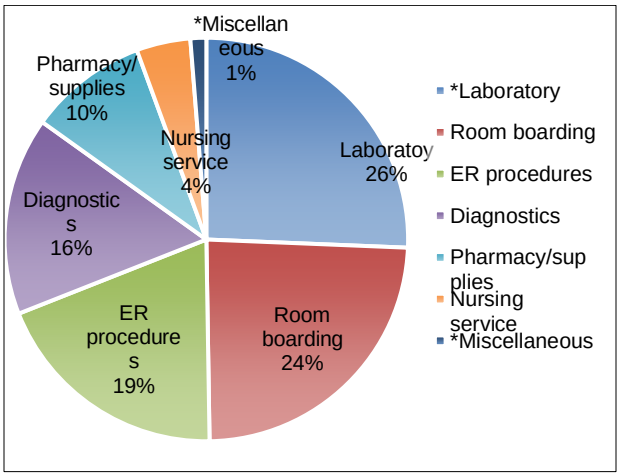
Table 1. Focal Epilepsy patient characteristics

Variables	Mean, SD	Median	Range
Age, years	7.50 (5.47)	7.00	1.00 – 17.00
Length of hospitalisation, days	6.30 (7.06)	3.50	1.00 – 30.00

The mean cost of hospitalization is 21,545.96 Php and the laboratory cost contributes the most to the total hospital bill with a mean of 6,046.08 Php (Table 2).

Table 2. Breakdown of Cost of Hospitalization

Item	Range of Cost in Php	Cost in Php (mean, SD)
Total hospital bill	865- 86,671.86	**21,545.96** (21,522.05)
Laboratory	32,516	**6,046.08** (7,219.12)
Room boarding	700- 21,000	**4,510.00** (4,898.37)
Diagnostics	0- 12,239	**4,078.50** (5,918.22)
Pharmacy/supplies	5.5- 14,272	**2,744.29** (4,255.98)
Emergency procedures	0-5,656.38	**2,482.18** (1,381.44)
Nursing service	0-6,779.5	**1,305.93** (2,143.06)
Miscellaneous	0-7,030	**379.00** (1,379.11)



*Laboratory: Drug assays and blood chemistries
*Miscellaneous: Ambulance fee for specimen to be sent out to other institutions

Figure 1. Mean percent contribution of expenses to total hospital bill

There is no significant difference between the mean cost of hospitalizations of patients aged 7 years and below (Php 21,477.12), and patients more than 7years of age (21,635.97) (p=0.984). The total cost of hospitalization is significantly higher among those hospitalized for >15 days (Php 32,583.30) compared to those hospitalized for ≤15 days (Php 10,508.61) (p=0.003). (Table 3).

Table 3. Comparison of total cost of hospitalization by patient characteristics

Variables	Cost in Php (mean, SD)	P value
Age (median)		
≤7 years (*n*=17)	**21,477.12** (22,348.44)	0.984
>7 years (*n*=13)	**21,635.97** (21,294.22)	
Length of hospitalisation (median)	**10,508.61** (8,851.59)	**0.003**
≤15 days (*n*=15)	**32,583.30** (24,901.46)	
>15 days (*n*=15)		

For the sources of funds, PhilHealth share shoulders less of the total hospital bill in contrast with the patient's share and the hospital share with percent contributions computed at 23.99% 26.32% and 35% respectively. (Table 4)

Table 4. Distribution of fund sources

Item	Cost in Php (mean, SD)
Total hospital bill	**21,545.96** (21,522.05)
Hospital share	**8,282.89** (9,568.61)
Patient share	**7,069.79** (10,442.35)
PhilHealth share	**3,734.26** (4,019.30)
Guaranteed funds	**2,459.04** (4,099.37)

DISCUSSION

The cost of hospitalization in this study is mostly comprised of laboratory cost (28%), room boarding (21%), diagnostics cost (19%), pharmaceutical cost (13%), and ER procedures (11.5%), with a mean total hospital cost of 21,545.96 Php (423.38$).Of this, the mean cost of hospitalization shouldered by PhilHealth is 3, 734.26 Php ($73%) (case rate: 7,800 Php)

Majority of the costs of epilepsy are attributed to hospital admissions and drugs; with drug costs dominating in more well controlled epilepsy, while in difficult to control epilepsy both costs of hospital admissions and drugs are significant. This is more observed in newly diagnosed patients[11]. The difference in the level of control of epilepsy could explain the varied degree for the need for further tests and use of additional medications, hence the wide standard deviation of hospital costs.

According to findings of the studies from other countries, the cost of hospitalization ranges from approximately 52,000 Php ($1,022) to 2.4M Php ($47,862) [12,13]. In contrast with this analysis, Pato-Pato showed that the most significant source of hospital cost is on medicines [14].

A study by Wagner in South Africa found the combined average annual outpatient, clinic, and hospital out-of-pocket cost to be 2, 900 Php ($58.41) [15]. On the other hand, this study showed that the average patient's out of pocket share costs 7,069 Php ($139). The result of this study demonstrated inadequate coverage of the medical insurance of these patients and that majority of the total hospital costs burden were shouldered by the hospital (38.4%) and from the patient's out of pocket share (32.8%). Aside from the budget from the government, some sources of funds that the hospital used to shoulder percentage of the costs include donations from sponsors and revenues from pay patients.

This study's results may be used in formulating new policies for better health insurance coverage and lowering the out-of-pocket cost of hospitalized pediatric epilepsy patients here in the Philippines. This study only pertains to the patients with focal epilepsy admitted in a tertiary government hospital.

CONCLUSION

The cost of hospitalization of pediatric focal epilepsy patients can cause a significant economic burden to the family because of its high out-of-pocket cost. Furthermore, this study supported that the actual hospital cost being shouldered by PhilHealth is inadequate and significantly lower than what is shouldered by a government hospital and from the out-of-

pocket patient's share, hence there is a need for improvement in the policies of the medical insurance coverage for these patients.

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EFFICACY AND SAFETY OF LEVETIRACETAM VERSUS PHENOBARBITAL FOR NEONATAL SEIZURES: A SYSTEMATIC REVIEW AND META-ANALYSIS

ERIBERTO R. RAYCO, PAUL MATTHEW PASCO

ABSTRACT

INTRODUCTION: Seizures are the most common neurologic emergency in the neonatal period. Phenobarbital and levetiracetam are the most commonly used anti-epileptic agents. However, there is conflicting evidence regarding their efficacy and safety. This review aims to synthesize data from randomized trials evaluating levetiracetam versus phenobarbital as a first-line antiepileptic drug for seizures in the newborn.

METHODS: A systematic review and meta-analysis following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines was performed. The review considered randomized clinical trials (RCTs) providing information about the efficacy and safety of levetiracetam vs phenobarbital as first line treatment of neonatal seizures. Medline by PubMed, CENTRAL by Cochrane, Embase, Google Scholar, and grey literature for RCTs were searched.

RESULTS: Four randomized controlled trials met the criteria for inclusion. A total of 312 neonates (levetiracetam n=167, phenobarbital n=145) comprised the pooled sample. Seizure freedom did not significantly favour one particular drug. This was also seen throughout subgroup analysis comprising clinical determination of seizure onset and cessation and neonates with hypoxic-ischemic encephalopathy. Significant heterogeniety was seen throughout the analyses. Hypotension was seen more in patients given phenobarbital. No significant association of either drug was seen for respiratory abnormalities and requirement for ventilation. Mortality was not significantly associated with either drug.

CONCLUSION: This meta-analysis combined and synthesized data from four randomized controlled trials comparing levetiracetam and phenobarbital in efficacy and safety for neonatal seizures. The statistical analysis did not lend evidence to support the use of one drug over the over. More studies that employ stringent techniques to minimize bias are needed for a more robust conclusion.

1. INTRODUCTION

Seizures are the most common neurologic emergency in the neonatal period.(1,2) The incidence of seizures in the first 28 days of life is estimated to be 1 to 5 per 1,000 neonates. This occurs most commonly in the first week of life, which is the most vulnerable period.(3,4) Neonatal seizures are manifestations of significant neurological disease processes that may ultimately lead to death. Seizures are also associated with an increased risk for epilepsy and other severe adverse developmental sequelae such as intellectual disability, global developmental delay, and cerebral palsy.(5-7) The significant risk for mortality and morbidity necessitates immediate intervention.

Phenobarbital has long been the gold standard treatment for neonatal seizures. Since 2011, the WHO has recommended the use of phenobarbital as first-line treatment.(8) However, the guidelines set forth are based on limited evidence from a single randomized controlled trial comparing phenobarbital and phenytoin that showed effectiveness in less than half of patients included.(9) Observational studies have similarly shown seizure control with phenobarbital in less than 50% of cases.(10-13) Furthermore, phenobarbital has been shown to have long-term deleterious neurocognitive effects and possible direct neuronal toxicity.(14,15)

The search for a safer and more efficacious treatment has led to the widespread off-label use of other anti-epileptic medications. In a 2008 survey, 47% of neurologists recommended the use of levetiracetam, despite the lack of robust evidence to support its use in neonates.(16) Levetiracetam is a second-generation anti-epileptic medication which has been approved for use only in children older than one month of age.(17) Moreover, two randomized controlled trials in 2016 claimed the relative superiority of phenobarbital over levetiracetam in the newborn period.(18,19) Nonetheless, levetiracetam remains to be commonly used in neonates due to its favorable safety profile, as illustrated in studies where it was shown to have better cognitive and motor outcomes compared to phenobarbital.(20-22)

A systematic review involving only observational studies was then conducted in 2018 to consolidate the available data. The study revealed that levetiracetam was non-inferior to phenobarbital as a primary treatment. (23) This was supported by showing seizure cessation in 77% of patients given levetiracetam versus 46% for phenobarbital. This conclusion, however, was based on studies with small sample sizes with significant heterogeneity in the concomitant anti-epileptic drugs used.

Since then, several randomized controlled studies on the efficacy and safety of levetiracetam in neonatal seizures have emerged (24-26), which have drawn differing conclusions. The objective of this review is to synthesize data from randomized trials evaluating the efficacy and safety of levetiracetam versus phenobarbital as a first-line anti-epileptic drug for seizures in the newborn.

2. METHODS and MATERIALS

A systematic review and meta-analysis following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines was performed. The review considered randomized clinical trials (RCTs) (both open-label and blinded) providing information about the efficacy and safety of levetiracetam for the treatment and prevention of neonatal seizures. Studies were considered if these included either or both term and preterm neonates (aged 0 to 28 days old) whose seizures were established either clinically or electrographically. There were no restrictions on the type of seizure. Studies must have used intravenous levetiracetam as first-line monotherapy for the treatment of neonatal seizures, regardless of dose, frequency, and duration. We considered

studies comparing levetiracetam with phenobarbital only.

We included studies with the following primary outcome measures: at least 50% reduction in seizure frequency; or seizure freedom, defined as the absence of seizures on observation, conventional EEG recordings, or both (27, 28) from baseline to the last evaluation. Included studies were also those that investigated adverse events as secondary outcomes which include, but not limited to the following: decrease in sensorium, irritability, rash, jaundice; infection; or mortality among neonates with seizures.

Studies with the following features were excluded from the analysis: use of anti-epileptic drugs (with the exception of short-acting benzodiazepines) prior to enrollment into the study; elevated serum creatinine level as defined by the study; patients in whom death was imminent; and seizures due to correctable electrolyte abnormalities.

We searched Medline by PubMed, CENTRAL by Cochrane, Embase, Google Scholar, and grey literature for RCTs using the search terms "levetiracetam", "Keppra", "phenobarbital", "neonate", "newborn", "seizure", and "epilepsy". ClinicalTrials.gov and PROSPERO were similarly searched for ongoing or recently completed trials and systematic reviews. Reference lists of studies included were also examined for additional relevant articles. There was no language or date restrictions in the search and selection of studies for inclusion; however, only the studies that can be translated sufficiently by Google Translate will be included.

Two reviewers (ERR and PPR) independently screened the titles and abstracts of retrieved articles against the inclusion criteria. The full text reports were obtained for articles that were judged to be relevant. Disagreement was resolved through consensus. Reasons for exclusion of trials were recorded.

Data from the selected studies were extracted by the reviewers using standardized forms that included the following fields: title; study setting; study duration; total number of study participants; number of participants in subgroups, when applicable; type of seizure; dosage, frequency, and duration of levetiracetam; and relevant efficacy and safety outcomes. Endpoints obtained included cessation of seizures and occurrence of severe adverse effects. We used data from intention-to-treat analyses whenever possible. Attempts were made to contact the authors of the selected studies in order to seek clarification and additional data that was deemed necessary.

Assessment of the risks of bias for each study was independently done by two reviewers (ERR and PPR) using the Cochrane Collaboration tool for assessing the risk of bias. Studies were rated as having "high risk" or "low risk" of bias based on extracted data. For those that were judged as having "unclear risk", an attempt to contact the authors of these studies was done. Disagreements between the two assessors were resolved by discussion.

A meta-analysis was conducted on the studies that were determined to be appropriate for synthesis. Outcomes were analyzed and calculated using the software

Review Manager (RevMan) version 5.4.1 with a random-effects model. The Mantel-Haenszel method was used to combine dichotomous outcomes. Relative risks (RR) were determined with a 95% confidence interval (CI). Heterogeneity was assessed using the Chi-squared ($\chi 2$) test (with a p-value of <0.10) and I2 statistics (with a values of 0 to 49% considered low heterogeneity; 50 to 74%, moderate heterogeneity; and 75% and above, high heterogeneity).

We attempted to explain the source(s) of heterogeneity with subgroup and sensitivity analyses. Subgroup analyses were based on seizure evaluation (clinical seizure or electrographic seizure), differing doses of levetiracetam, and the presence of hypoxic-ischemic encephalopathy among participants. Sensitivity analysis was performed by omitting studies that were assessed to have high risk of bias.

3. RESULTS

Four randomized controlled trials were included in this systematic review (Figure 1).

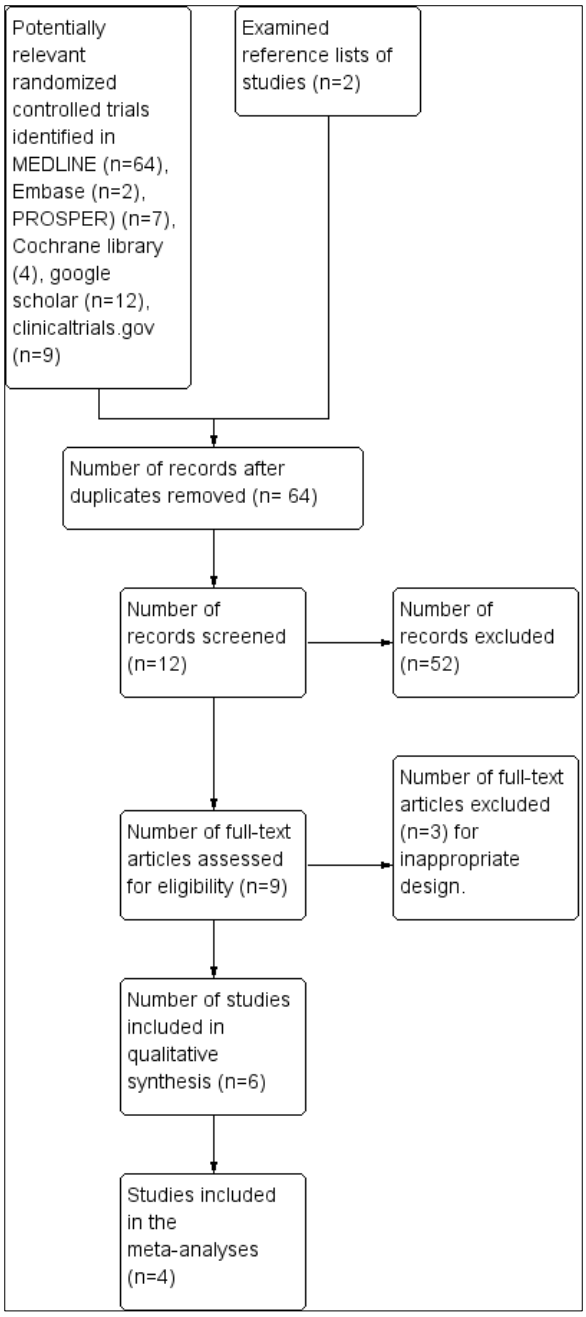

Figure 1. Study flow diagram.

Of the four randomized controlled studies (24-25, 30-31) included in this systematic review, one was double blinded (24), two were open-labeled (25, 30), and one was unclear if blinding was undertaken (31). Three studies included both term and preterm neonates (24-25, 30), while one included only term patients (31). Three of the studies employed cross over to the other study arm after failure of

the primary drug to control the seizures (24-25, 30), while one study instituted institutional protocols (31). All studies employed loading techniques of levetiracetam, albeit at different doses. Two of the studies comprised exclusively of patients with hypoxic-ischemic encephalopathy (30-31), while one included these patients in the population (24). One study employed a continuous EEG monitor for determining seizure onset and cessation (24), while the three other studies used clinical criteria (25, 30-31). (Table 1)

Table 1. Characteristics of of randomized controlled trials included in this meta-analysis.

Study, Country	Design, Duration	Population	Seizure Types	IV LEV Dose	IV PB Dose	Primary Outcome	Secondary Outcome/s
Perveen et al. 2016 India	RCT, open-labeled July 2014 to December 2015	N= 60 (30 LEV, 30 PB) Term and preterm neonates, admitted within 48 hours of birth, with HIE 41 M; 19 F After correction of hypoglycemia and hypocalcaemia	Subtle, Tonic, Clonic, Myoclonic (not quantified)	Load: 60mg/kg Maintenance: 15mg/kg/day q 12 hr for 5 days	Load: 20mg/kg Maintenance: 5mg/kg/day q 12 hr for 5 days	Seizures were considered to be controlled if the baby was seizures free 24 hrs after last seizures.	Adverse events, electrical seizures after control of clinical seizure, time taken to control seizures, and neurological examination until 6 months.
Pervez et al. 2018 Bangladesh	RCT blinding not reported 01 January 2014 to 30 June 2015	N= 69 (34 LEV; 35 PB) Term neonates within 48 hours of birth with HIE 41 M; 28 F After correction of hypoglycemia and hypocalcaemia	Clonic: 56% in Lev, 49% in Pb Subtle: 32% in Lev and 37% in Pb Tonic: 11: in Lev and 14% in Pb None with myoclonic seizures	Load: 50 mg/kg Maintenance: 10 mg/kg/dose 8 hourly	Load: 20-40 mg/kg Maintenance: 2.5 mg/kg/dose 12 hourly	Controlled if convulsion stopped completely and not recurred within 48 hours	Adverse events
Gowda et al. 2019 India	RCT Open-labeled November 2014 to April 2016	N=100 (50 LEV; 50 PB) Term and preterm neonates within 28 days of age. 44 patients with HIE 56 M; 44 F After correction of hypoglycemia and hypocalcemia	Not catergorized	Load: 20 mg/kg Maintenance: 20 mg/kg/day in two divided doses If seizures persists, another loading dose of LEV (20 mg/kg) is given If seizures still persisted,the patient was switched over to PB.	Load: 20 mg/kg Maintenance: 5 mg/kg/day in two divided doses If seizures persists, another loading dose of PB (10mg/kg) is given If seizures still persisted, the patient was switched over to LEV.	Cessation of seizures following the first or second dose of the drug (PB or LEV), and those remaining seizure-free for next 24 hours.	Adverse events occurring within two hours of drug administratio n

Sharpe et al. 2020 NZ, USA	RCT Double blinded, multicenter, phase IIb effificacy, dose-escalation, and safety study 60:40 allocation ratio 21 March 2013 to 31 October 2017	83 mITT, 81 PP 106 analyzed for safety data (53 LEV; 30 PB) Term and preterm (36-44 wks) neonates 57 patients with HIE 55 M; 51 F Excluded patients with correctable metabolic abnormalities (such as hypoglycemia or hypocalcemia)	Not categorized	Load: 40 mg/kg If electrographic seizures persisted or recurred 15 minutes after the first infusion, an additional 20 mg/kg is given Maintenance: 10 mg/kg/dose 8 hourly If seizures still persisted,the patient was switched over to PB.	Load: 20 mg/kg If electrographic seizures persisted or recurred 15 minutes after the first infusion, an additional 20 mg/kg is given Maintenance:1.5 mg/kg/dose 8 hourly If seizures still persisted, the patient was switched over to LEV.	Electrographic seizure freedom for 24 hours Utilizing cEEG monitoring	Adverse events 1- and 48-hour seizure termination rates Subanalysis of patients with HIE treated with hypothermia Post hoc analysis of efficacy as assessed by a neurologist at the bedside Post hoc imputation of analyses for missing primary outcome data

Assessment of included studies was conducted according to Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) (31). The assessments of included studies were classified as at low risk of bias, unclear risk of bias, and high risk of bias (Table 2).

Figure 2. Risk of bias summary.

The four randomized controlled trials (24-25, 30-31) that met the criteria for inclusion in this review comprised a total of 312 neonates (levetiracetam n=167, phenobarbital n=145). The combined data shows that seizure freedom did not significantly favour one particular drug, although control of convulsion leaned towards phenobarbital (RR = 0.71, CI = 0.30-1.71; p = 0.45; I2 = 94%; Fig. 3). This was seen throughout subgroup analysis comprising clinical determination of seizure onset and cessation (RR = 0.75, CI = 0.33-1.69; p = 0.49; I2 = 94%; Fig. 4) and separating for patients with hypoxic-ischemic encephalopathy (RR = 0.58, CI = 0.17-2.02; p = 0.39; I2 = 92%; Fig. 5). Significant heterogeniety was seen throughout the analyses.

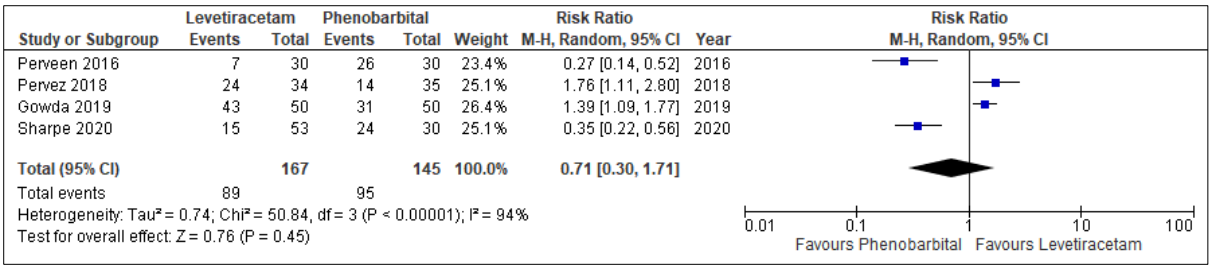

Figure 3. Forest plot of seizure freedom (Levetiracetam versus Phenobarbital)

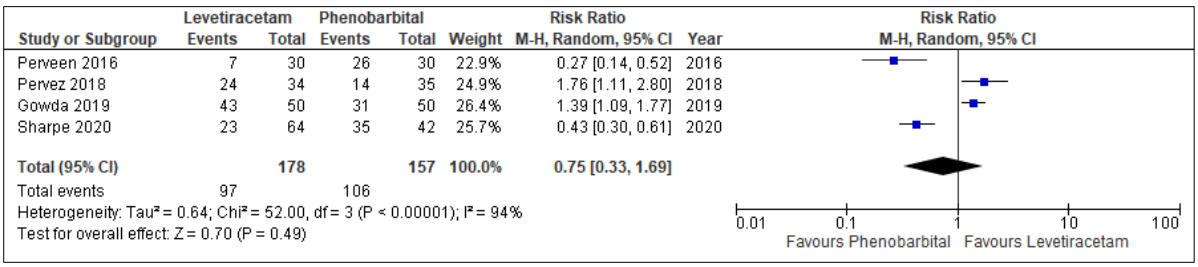

Figure 4. Forest plot using clinical criteria in determining seizure freedom (Levetiracetam versus Phenobarbital)

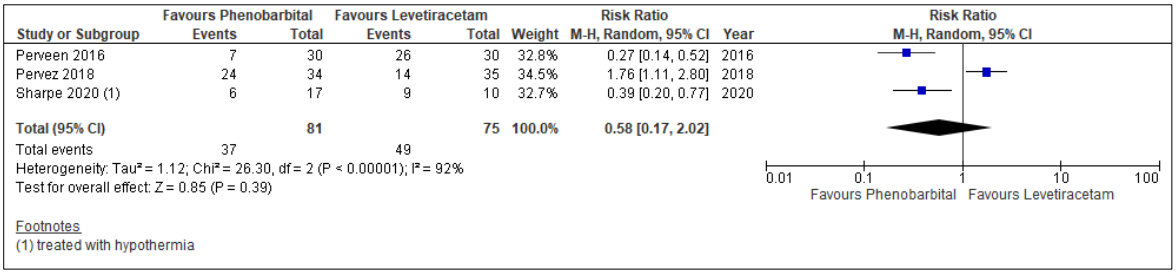

Figure 5. Forest plot of seizure freedom among patients with hypoxic-ischemic encephalopathy (Levetiracetam versus Phenobarbital)

Adverse effects were reported in all of the studies, however one did not indicate the specific events noted (31). Thus, data from the remaining three studies (24-25, 30) were included here. Hypotension and requirement for ventilation were noted in two (24-25), and respiratory abnormalities were see in in three (24-25, 30) of the trials. Data included in this analysis were adverse events seen prior to the patients being administered a second drug to control persistent seizures. Specific adverse effects that were common to the three studies were included in the forest plots. Hypotension was seen more in patients given phenobarbital (RR = 0.12, CI = 0.02-0.88; p = 0.81; I2 = 0%; Fig. 6). No significant association of either drug was seen for respiratory abnormalities (RR = 0.35, CI = 0.07-1.81; p = 0.30; I2 = 16%; Fig. 7) and requirement for ventilation (RR = 0.60, CI = 0.23-1.55; p = 0.45; I2 = 0%; Fig. 8), although a tendency with phenobarbital was seen.

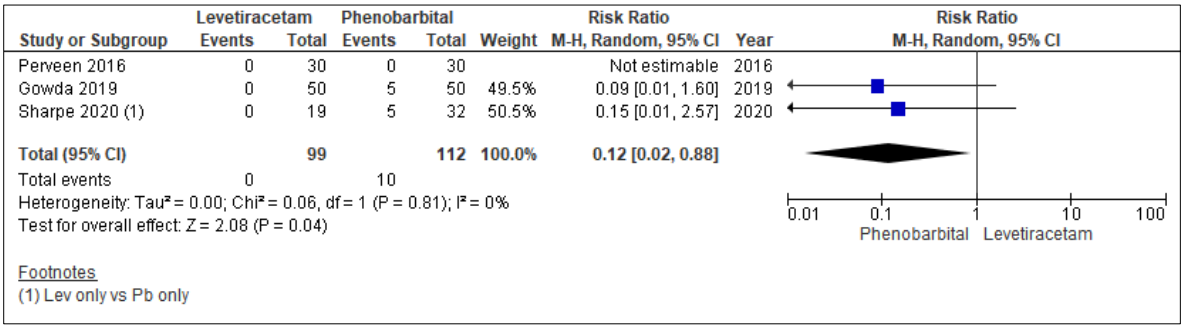

Figure 6. Forest plot of patients having hypotension (Levetiracetam versus Phenobarbital)

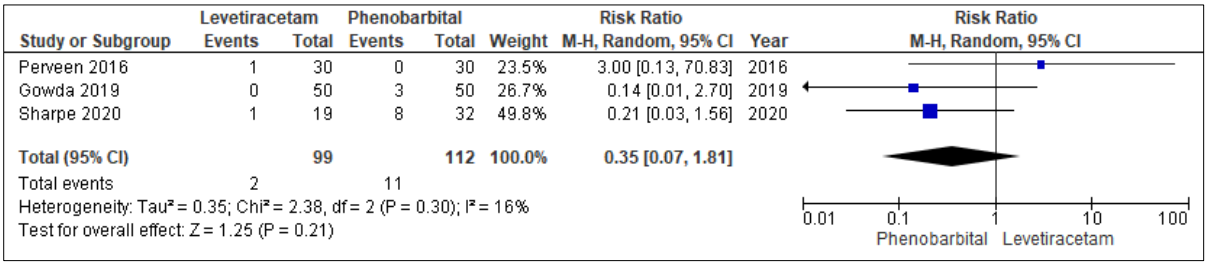

Figure 7. Forest plot of patients having respiratory abnormality (Levetiracetam versus Phenobarbital)

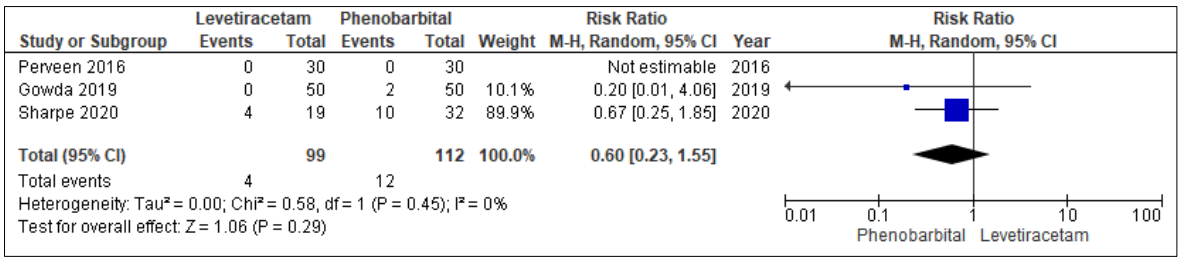

Figure 8. Forest plot of patients needing ventilatory support (Levetiracetam versus Phenobarbital)

Three of the trials (24-25, 30) reported deaths during the study period. Mortality was not significantly associated with either drug (RR = 1.90, CI = 0.55-6.51; p = 0.92; I2 = 0%; Fig. 9).

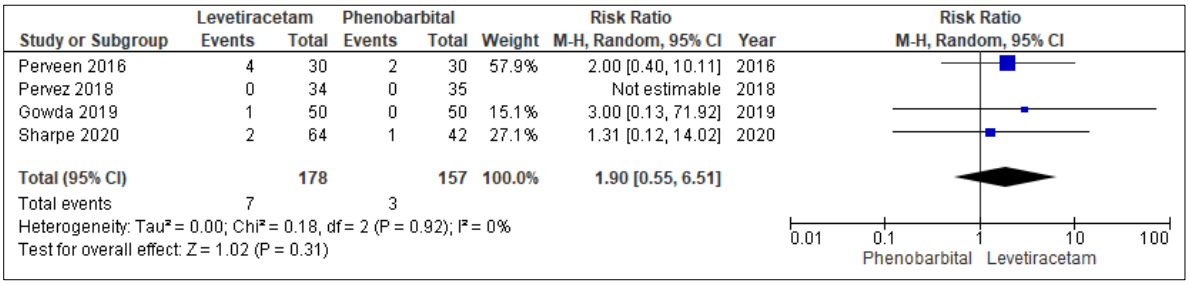

Figure 9. Forest plot of moralities (Levetiracetam versus Phenobarbital)

4. DISCUSSION

Levetiracetam and phenobarbital are two of the most commonly used medications for neonatal seizures. However, our meta-analysis for efficacy did not show significant statistical difference to support the use of one drug over the other for seizure control. This is not surprising since the four randomized controlled studies included in this analysis had differing conclusions. Two studies found increased efficacy of phenobarbital (24, 30) and the other two trials showed data in favour of levetiracetam (25, 31). Although it should be noted that significant heterogeneity was seen in the meta-analysis even after subgroup analysis separating data from seizures determined clinically and data from patients with hypoxic-ischemic encephalopathy. Moreover, of the four trials included, only one was clearly double-blinded (24).

In contrast to analysis of efficacy, analysis of safety did find homogeneity among the studies. Here, we opted to analyze specific adverse events that were common to the studies such that a statistical analysis can be made. Thus, hypotension, respiratory abnormality, and the need for ventilation were selected, Of these, hypotension was seen to be significantly associated with phenobarbital.

Analysis of mortality also showed homogeneity. The data shows a trend of increased mortality with levetiracetam, although no significant statistical difference was seen for either drug.

5. CONCLUSION

This meta-analysis combined and synthesized data from four randomized controlled trials comparing levetiracetam and phenobarbital in efficacy and safety for neonatal seizures. The statistical analysis did not lend evidence to support the use of one drug over the other. More studies that employ stringent techniques to minimize bias are needed in order for a more robust conclusion.

Acknowledgement

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AICARDI SYNDROME: A CASE REPORT

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ABSTRACT

Aicardi Syndrome is an extremely rare genetic disorder characterized by infantile seizures/spasms, agenesis of the corpus callosum, chorioretinal lacunae, and learning disabilities. It is likely caused by a de novo mutation in a gene in the X chromosome. However, the gene that causes this syndrome is still not known. It is diagnosed based on clinical findings. Aicardi syndrome may present as a clinical spectrum, from mild to severe disease. In general, the younger the age at which epilepsy and learning disabilities are diagnosed, the more severe the epilepsy and learning difficulties become later in life. Hence, long-term surveillance and management are warranted. This paper presents a 6-month-old Filipino female who exhibited the classic triad of Aicardi Syndrome: profound seizure episodes; callosal agenesis and interhemispheric cysts; and chorioretinal lacunae. Several anti-epileptic drugs such as Phenobarbital, Clonazepam and Topiramate were given for the seizures. Ophthalmogic examination and retinal camera fluorescein angiogram were advised to be performed regularly as well as consistent neurodevelopmental follow-up.

INTRODUCTION

Dr. Jean Dennis Aicardi, a French Neurologist, studied 8 children with infantile spasms, complete or partial agenesis of the corpus callosum, and a variety of ocular anomalies in 1965 [7]. This constellation of clinical findings, along with learning disabilities, were then termed as a distinct clinical entity known as Aicardi Syndrome. While no gene for Aicardi syndrome has been found, several studies support the theory that Aicardi syndrome is caused by de novo pathogenic variants in an X-chromosome gene that is inactive [11]. There are between 300 and 500 cases of Aicardi syndrome worldwide, according to estimates. Between 2000 and 2005, 5 cases of Aicardi syndrome were recorded in India, ranging in age from 1 to 13 years old, and were diagnosed using the classic triad described above. All the patients had severe psychomotor retardation, necessitating the use of multiple antiepileptic drugs (AEDs) to control their epileptic seizures. Just two of the five cases recorded had 100 percent remission, and both used Vigabatrin as an AED [4]. In Philippine Pediatric Society Registry, 145 out of 4 million cases have been reported with Aicardi Syndrome and only 2 cases have been reported in Philippine Children's Medical Center in a span of 10 years.

Between the ages of four months and four years, involuntary muscle spasms are a common clinical feature of Aicardi syndrome. Intellectual deficiency and developmental delay are present in varying degrees in people with Aicardi syndrome. Many girls have optic nerve developmental defects, and others have microphthalmia (small eyes). In some, skeletal issues such as missing or irregular ribs, as well as

anomalies in the spinal column's vertebrae (including hemivertebrae and butterfly vertebrae), have also been identified. Hence, infants presenting with seizure should undergo neurodiagnostic examination such as cranial ultrasound, cranial CT scan or MRI, and/or EEG to determine the cause of seizure.

Aicardi syndrome is diagnosed clinically based on neurodevelopmental assessment, neuroimaging, and ophthalmologic findings. The inclusion of the classic triad, or two of the classic triad plus at least two other major or supporting features, is one of the updated diagnostic criteria. The prognosis for people with Aicardi syndrome varies depending on how severe their symptoms are. While there is an increased risk of death during childhood and adolescence, survivors reaching adulthood have been recorded. Hence, long-term management by a pediatric neurologist with expertise in the management of infantile spasms is recommended [1].

CASE REPORT

This is the case of a 6-month-old, Filipino female who came in with a chief complaint of seizure, characterized as left versive gaze, tonic extension of right upper extremity and tonic flexion of right lower extremity for four minutes.

She was born to a 33-year-old Gravida 5 Parity 4 (4014) nonsmoker, non-alcoholic beverage drinker mother who was cognizant of pregnancy at the first month age of gestation. Her mother had regular prenatal check-ups at a local hospital. Ultrasonography done at 5 months age of gestation revealed fetal ventriculomegaly. The first congenital anomaly scan done at 6 months age of gestation revealed borderline ventriculomegaly, an intracranial cyst to consider arachnoid cyst measuring 3.5 x 3.3 x 2.3cm with an estimated volume of 13.8mL. A second congenital anomaly scan done at 9 months age of gestation revealed an intracranial cyst measuring 2.4 x 2.8cm, midline supratentorial region in location. Hence, the mother was advised to consult a tertiary hospital for further prenatal management. She had no maternal illness, exposure to viral exanthems or radiation and took multivitamins, ferrous sulfate, folic acid, and calcium regularly.

The patient was born full-term at a local tertiary hospital assisted by an obstetrician via normal spontaneous delivery. There was no premature rupture of membrane, prolonged labor, difficult delivery, cord coil or meconium-stained amniotic fluid. Birth weight was 2.88 kilograms. Apgar scores were 8 and 9. The patient had urine output and bowel movement within 24 hours after birth. Routine newborn care was done. She was given Hepatitis B and BCG vaccines. She was eventually discharged after 72 hours, with good activity and suck. Newborn screening and hearing screening were normal.

The patient in the interim was apparently well, with good cry, suck, and activity, until one month prior to admission when she had an episode of seizure described as left versive gaze, associated with tonic extension of right upper extremity and tonic flexion of right lower extremity

lasting for 15 seconds. There was no fever, gastrointestinal losses, post-ictal drowsiness, or drooling. There was no medication given and no consult was sought.

Three weeks prior to admission, she had seizure recurrence of the same semiology and duration. The seizure occurred twice, six hours apart, with no associated fever, losses, or postictal drowsiness. She was then brought to a tertiary hospital in active seizure, characterized as blank stares with circumoral cyanosis. She was hooked to oxygen at 10 lpm. Capillary blood glucose was 103 mg/dL. She was given diazepam at an unknown dose and Phenytoin was given at a loading dose of 20 mg/kg/dose and was subsequently maintained at 10 mg/kg/day. During her hospital stay, she still had seizure recurrences of the same semiology, occurring 10 times each day, lasting for 5 to 15 seconds per episode. Hence, levetiracetam at a dose of 100mg/kg/day and phenobarbital at 5mg/kg/day were also started. She had good activity and suck in between seizure episodes. She was advised for cranial MRI but was not done due to unavailability. She was then discharged after ten days, with seizure of the same semiology, occurring 3 to 4 times a day, lasting for 5 to 15 seconds. Take home medications were levetiracetam at 100 mg/kg/day and phenobarbital 5 mg/kg/day.

A few hours prior to admission, she had an episode of seizure characterized as left versive gaze, tonic extension of right upper extremity and tonic flexion of right lower extremity for four minutes associated with postictal drowsiness, increased sleeping time and decreased activity. At this time, she was described to be lying in bed throughout the day, in contrast to her usual playful disposition. Due to the associated poor activity and increased sleeping time, a consult was made in our institution.

The patient received only one dose of BCG, Hepatitis B, and Oral Polio. All vaccines were administered at a local health center with no noted adverse reactions post-vaccination. Immunization was not updated due to the illness of the patient. The patient was exclusively breastfed since birth. She has no known allergy to food or medication. The patient exhibited head control and social smile at 1 month old, cooed at 3 months old, rolled over at 4 to 5 months, turned to noise and voice at 4 months old, and transferred objects at 5 months old. At 6 months of age, the patient still cannot sit with support.

COURSE IN THE WARD

On the day of admission, the patient was seen awake, playful with good suck, not in cardiorespiratory distress with stable vital signs. Systemic exam was essentially normal. Neurologic examination revealed 3 mm pupils equally brisk reactive to light, intact extraocular muscles with visual tracking, with dazzle on both eyes and with visual threat, no facial asymmetry, tongue and uvula midline, and with spontaneous and equal movement of all extremities. She had reflexes of +2 on all extremities, positive for Babinski and negative for clonus. Laboratory and imaging results such as phenobarbital assay, ALT, AST, and chest radiograph were all normal. She was given diazepam for frank seizure.

Cranial CT scan done during admission showed a cystic focus intimately related to the 3rd ventricle and right parasagittal area measuring 3.0 x 2.14 x 2.85 cm. Considerations were colloid versus arachnoid cyst. There was also a dilated 3rd ventricle with consequent compressive effect to the adjacent lateral ventricles. A cranial MRI was subsequently done, which showed multiple variably sized CSF-intensity thin-walled cysts seen in the interhemispheric region with the following measurements: 2.26 x 1.91 x 1.76 cm (interhemispheric region); 2.8 x 2.67 x 3.01 (interhemispheric region) 1.64 x 8.78 x 2.13 cm area of the 3rd ventricle, and 1.34 x 1.07 x 1.28cm posterior horn of the right lateral ventricle. Callosal agenesis and interhemispheric cysts were also noted. An electroencephalogram (EEG) was performed, which revealed two clinical events consisted with focal seizures coming independently from the right and left hemispheres. There were generalized as well as multifocal epileptiform discharges coming predominantly from the left mid to posterior temporal and left centrotemporal regions as well as independent discharges coming from the right centrotemporal and right mid to posterior temporal head regions. Background activity is slow for age.

Medications given during her stay in the hospital were phenobarbital 3.5 mg/kg/day and leviteracetam 28 mg/kg/dose. Despite the combination of two anti-epileptic drugs, she still had seizure recurrences occurring 1 to 10 times a day. Hence, phenobarbital was increased to 9.3 mg/kg/day. Moreover, there was poor head control, lateral rectus palsy on the right, no dazzle and visual threat on the right, and no tracking of objects. She was then referred to Ophthalmology service who considered Congenital Ptosis, right, and Toxoplasmosis, Right with Alternating Exotropia. Other ophthalmologic findings include chorioretinal lacunae measuring ½ disc diameter seen below the optic disc and 2-disc diameters seen superior to the optic disc. Due to the consideration of toxoplasmosis, she underwent work-up which was positive for Cytomegalovirus 24 hours post-inoculation, but the mother was negative. The patient was then referred to Pediatric Infectious Disease service for the initiation of Ganciclovir. During her stay in the hospital, the patient developed healthcare-associated pneumonia and was eventually infected with SARS-COV2. In the latter part of her hospital stay, the patient was transferred to COVID ward and treated with Vitamin D3 and Zinc sulfate as a COVID confirmed case.

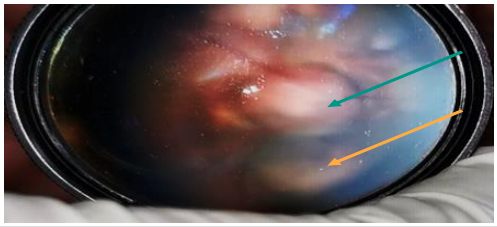
She was discharged last November 4, 2020, with an assessment of Multiple Intracranial Cysts probably secondary to Congenital CMV infection; Focal epilepsy, structural; Ocular toxoplasmosis - bilateral; Congenital ptosis of the right eye; Covid-19 Confirmed (10/7, 10/16, 10/23), ECLIA Non-infectious (10/28). Take home medications were as follows: Phenobarbital (5.2 mg/kg/day), Clonazepam (0.05 mg/kg/day), Topiramate (3.1mg/kg/day), Cotrimoxazole (8 mg/kg/day) and Valganciclovir (33.3 mg/kg/day). Since discharge, the patient would have 1 episode of spasm prior to sleeping increasing to 3 episodes per day with semiology of right versive gaze with clonic spasm. The patient was seen at the Ophthalmology OPD and

was advised to continue Cotrimoxazole. The patient was lost to follow-up with Neurology service.

DISCUSSION

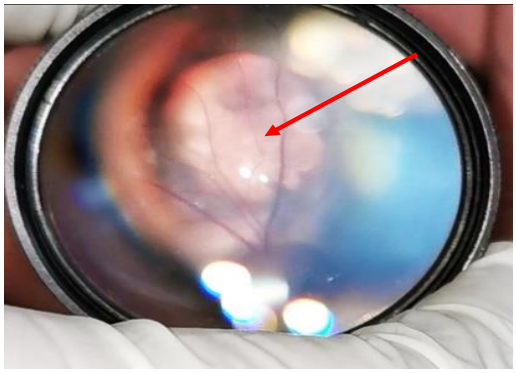
In Aicardi Syndrome, more than 95% present with infantile spasms in the first months of life. Various other seizure types develop over time. The patient presented with mixed focal and generalized seizure as shown in EEG which clinically manifested as infantile spasm. The patient was maintained on multiple anti-epileptic drugs (AEDs) which are Phenobarbital, Clonazepam and Topiramate but still presents with seizure recurrence.

Ophthalmologic exam findings on the patient revealed excavated optic disc with radially oriented retinal vessels, chorioretinal lacunae measuring ½ disc diameter seen below the optic disc, chorioretinal lacunae measuring about 2-disc diameters seen superior to the optic disc, chorioretinal scar seen inferotemporal to the fovea, and multiple cream-colored lesions seen temporal and nasal to the optic disc (Figs 1-2).



Green arrow
Excavated disc (t/c coloboma with radially oriented vessels
Yellow arrow
Chorioretinal lacunae measuring ½ disc diameter seen below the optic disc

Figure 1. Patient's optic disc



Red arrow
chorioretinal lacunae measuring about 2 disc diameters seen superior to the optic disc

Figure 2. Patient's optic disc

Chorioretinal lacunae are considered pathognomonic for Aicardi syndrome. Fundoscopic exam shows thinning of the choroid and sclera with degeneration of the rods and cones appearing as hypopigmented or depigmented regions that are whitish or pink in color. The lacunae are described as having features typical of optic nerve colobomas, but at the edges there are unique convolutions of tubular-like structures lined by pigmented and nonpigmented epithelial cells in close association with the capillaries and photoreceptor folds. The difference between chorioretinal lacunae and coloboma is that the former has defined margins, poorly differentiated or absent choriocapillaris, and a thin but intact Bruch's membrane with attenuated and hypoplastic retinal pigment epithelium [13].

Aicardi syndrome can be diagnosed using neuroimaging. The patient's cranial MRI revealed callosal agenesis and interhemispheric cyst (Fig. 3). Total agenesis (absence), partial agenesis (hypogenesis), thinning (hypoplasia), and thickening (hypoplasia) are all developmental defects or disorders of the

corpus callosum (hyperplasia). The corpus callosum in partial agenesis has a shorter anterior-posterior length due to missing segments such as the splenium and/or the rostrum. Malformations of the corpus callosum are often associated with other cerebral or extra-cerebral anomalies [12]. Agenesis of the corpus callosum (ACC) affects a variety of developmental processes, from midline telencephalic patterning to neuronal specification and commissural axon control. The prevalence has been estimated to be between 1:4000 and 1:5000 live births; however, rates of 2 to 3% have been identified among patients with neurodevelopmental disabilities. The disruption could be caused by genetic, infectious (TORCH infections, Zika virus), vascular, or toxic factors (fetal alcohol syndrome). The most common cause is genetic. In 30 to 45 percent of cases, a "syndromic" diagnosis is made, and in 20 to 35 percent of cases, a monogenic cause is found. People with agenesis of the corpus callosum have a wide presentation of behavioral and cognitive abnormalities – from mild cognitive delays to severe intellectual impairment.

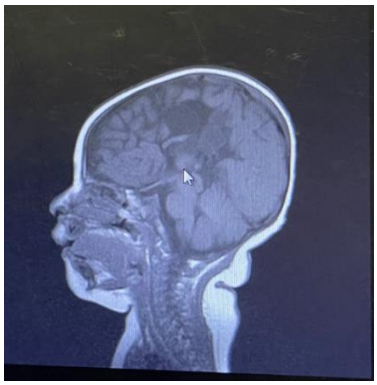


Figure 3. MRI of patient showing Colossal Agenesis

Due to the ophthalmologic findings seen in the patient, one of the differentials was Toxoplasmosis infection. However, the patient's mother tested negative for TORCH infection, and there was also no chorioretinitis or intracranial calcification on subsequent workups.

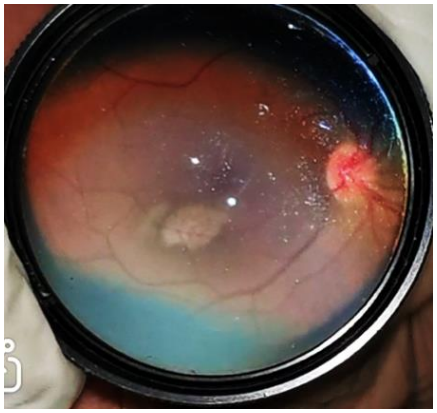


Figure 4. Chorioretinal scar seen inferotemporal to the fovea

As the patient presented with seizures, developmental delay and abnormal ocular findings, congenital cytomegalovirus infection was also considered as another differential diagnosis. On work-up, our patient tested positive for CMV hence, Valganciclovir was started. However, typical ophthalmologic findings of CMV such as retinitis and usual location of lesion did not present in the patient. Thus, Aicardi syndrome is still a strong consideration.

Aicardi syndrome is a neurodevelopmental disorder affecting newborn females. The disease is sporadic, it does not appear to be passed down from parent to child. The mutation that causes Aicardi syndrome has not been identified, but it is thought to be caused by a dominant mutation in an X-linked gene that may be lethal in certain males that appears for the

first time in a family. However, recent evidence suggests that mutations in the TEAD1 gene (chromosome 11) may explain some or all the cases [13]. Hence, genetic counselling is recommended when patient presents with classic features of Aicardi Syndrome.

Medications may be used to suppress the seizure. There is no first line AED identified specific for spasms of Aicardi Syndrome. In a study of Banerjee, 5 children identified with Aicardi Syndrome are treated with multiple AEDs and only 2 children had 100% remission when Vigabatrin was included.

In March 2021, the patient was noted to be playful, with good suck, but still with episodes of seizure and spasm of same semiology occurring for 3 to 4 episodes each day lasting for 15 seconds. However, during these past few months, seizure semiology varied from right versive gaze to blank stares but still with clonic spasm occurring 1 to 2 episodes per day. The patient currently follows up with a neurologist every three months. Valganciclovir and Cotrimoxazole were completed last May 2021. The patient was also seen at PCMC Ophthalmology Department and was advised retinal camera fluorescein angiogram. However, due to financial constraints, her parents were still unable to process the papers for the said procedure. Maintenance medications were revised to as follows: Phenobarbital at 27 mg/kg/day and Topiramate at 2.5 mg/kg/day.

Future plans are to establish regular ophthalmologic examination along with doing a retinal camera fluorescein angiogram. The patient is also yet to be seen by a Neurodevelopmental Pediatrician for evaluation and management.

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OVARIAN NEW GROWTH IN PROGERIA

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ABSTRACT

The Hutchinson-Gilford progeria syndrome (HGPS) is a rare genetic disease that involves single-base gene mutation in the LMNA gene which results in the production of a dysfunctional and mutant lamin A protein called progerin. Progerin is found in increased concentration in normal older individuals hence patients present with phenotypic signs of aging. [1] Based on current studies, there is no established predisposition and association between abdominal masses, specifically ovarian masses in female, adolescent, progeria patients.

This is an adolescent female patient with progeria presenting with an ovarian mass. Further studies to establish the correlation between Hutchinson-Gilford progeria syndrome (HGPS) and abdominal masses specifically masses in the reproductive system have yet to be done. The exact mechanism by which progeria patients become predisposed to developing abdominal masses, specifically ovarian masses is still a grey area in research. Through this case report, routine abdominal ultrasound screening or routine abdominal CT scan can be done to screen for presence of masses in HGPS patients.

INTRODUCTION

The Hutchinson-Gilford Progeria Syndrome (HGPS) or progeria, is a sporadic autosomal dominant disease characterized by symptoms of premature aging. It is a rare genetic disease with an estimated incidence of 1 in 4 million live births and with a prevalence of 1 in 20 million living individuals. There is no known and reported gender, ethnic, or regional bias. [1] It affects both sexes and all races and is known to be present in approximately 40 different countries. According to Progeria Research Foundation, there are 20 recorded cases in North America, 16 cases in Central and Southern America, 16 cases in Central and Southern America, 24 cases in Europe and the Mediterranean regions, 4 cases in Africa, and 18 cases in Asia. [4] In the Philippines, the Philippine Pediatrics Society has no recorded case of Progeria since 2006.

HGPS is caused by a single-base gene mutation in the LMNA gene which results in the production of a dysfunctional and mutant lamin A protein called progerin. The lamin proteins are involved in crucial functions such as creating and maintaining the integrity of the nuclear scaffold, DNA replication, RNA transcription, organization of the nucleus, nuclear pore assembly, chromatin function, cell cycling, senescence, and apoptosis. Progerin is found in increased concentration in normal older individuals compared to younger individuals thus suggesting a role in normal aging. [1] The disease is characterized by its multi-systemic

affectation of the skin, bones, eyes, ears, kidneys, heart, brain, and reproductive development requiring a multidisciplinary approach in its diagnosis and management. Diagnosis has been standardized through a confirmatory genetic test of the LMNA mutation. [4]

While many systems are affected and involved in HGPS, normally functioning systems include the liver, kidneys, thyroid, immune system, gastrointestinal system, and neurological system. No intellectual delays were observed in progeria patients. [1] Aging phenotypes absent in HGPS include predisposition to forming masses, cancer, cataract, increased abdominal fat, and neurodegeneration. No studies and case reports available on online research databases has also presented a case of Progeria with an associated ovarian mass. Research has also shown that progeria patients are resistant to cancer due to the actions of BRD4 gene which inhibits tumorigenic potential of transformed cells. Furthermore, the mitochondrial dysfunction in HGPS leads to decreased ability to be dysplastic or anaplastic thereby making HGSP patients less likely to develop masses and have cancer. [2]

In addition to this, ovarian tumors in the pediatric age group are also not common. Ovarian tumor in the pediatric population has an estimated incidence of 2.6 cases per 100,000 girls per year. Furthermore, ovarian malignancy in children and adolescents is reported only in 10% to 20% of all ovarian masses or neoplasms and comprises approximately 1% to 2% of all childhood malignancies. [3] In a study conducted by Bhattacharyya et al., where they divided the cases into four age groups 1-5, 5-10, 11-15, and 16-20 years old, most of the ovarian tumors are seen in the age group of 16 to 20 years old (80%). [3] This is a report of a case of Progeria in a 14-year-old female with an ovarian mass. This paper will discuss the diagnostic approach and management of this rare phenotypic presentation of Progeria.

CASE REPORT

This is a case of a 14-year-old female who came in with a chief complaint of an ovarian mass. She is a known case of Hutchinson Gilford Progeria Syndrome who initially presented with prominent scalp veins at 6 months as noticed by the mother and was then diagnosed to have an LMNA gene mutation through a gene mutation test. Patient is currently being maintained on Lonafarnib (6mg/kg/day), a protein farnesyltransferase inhibitor (FTI) that inhibits progerin farnesylation, as part of a clinical trial. Patient has been enrolled in a clinical trial since 3 years of age and previously took pravastatin and zoledronate. Surveillance is done every other year since then and would include physical examination, bone scans, CT scans, and 2D echocardiography with Doppler. Last consultation was in 2019 and no consultation was done in 2021 due to the pandemic.

Six months prior to admission, patient was noted to have abdominal distension. The abdomen was increased by approximately 1/3 of the normal girth. This was not associated with a palpable mass, diarrhea,

vomiting, constipation, early satiety, bloatedness, or changes in frequency of bowel movement or in the caliber of the stools. No consultation was done, and no medications were taken. The mother claimed that the patient had occasional episodes of abdominal distention growing up. In the interim, there was persistence of the abdominal distension but there was no progression in size. No other associated symptoms were noted.

Two months prior to admission, the patient accidentally slipped and fell on her buttocks which resulted to a right hip dislocation. Patient then underwent closed reduction of the hip with traction. One month prior to admission, during a follow up consultation, a lateral hip CT scan revealed an incidental finding of ovarian mass which prompted further work up. At this time, patient still has abdominal distention that did not progress in terms of size, was associated with occasional bilateral lower quadrant sharp pain of the abdomen with pain severity of 4/10 for which patient has been taking paracetamol. There are no palpable masses, no changes in bowel movement and no urinary symptoms of increased frequency, urgency, and dysuria. A whole abdominal CT scan revealed a large unilocular cystic abdominopelvic mass lesion. Primary consideration was a bilateral ovarian serous cystadenoma.

Two weeks prior to admission, the patient still had persistent symptoms hence, she consulted a Pediatric gynecologist. CA-125, a marker of ovarian epithelial carcinomas was requested and revealed elevated results. Initial assessment was epithelial cell tumor carcinoma hence patient was advised surgery. Patient was then admitted after two weeks.

There are no other members of the family diagnosed with Progeria. There is, however, a family history of diabetes on the maternal side (maternal grandparents), and history of thyroid cancer on paternal side (paternal grandfather). There was no reported family history of ovarian masses and tumors, no hypertension, asthma, and other malignancies noted in the family. In terms of sexual and reproductive history, patient still has no thelarche and menarche.

COURSE IN THE WARDS

The patient was seen awake, conscious, and coherent with stable vital signs: blood pressure of 90/60, heart rate of 98, afebrile at 36.7 degrees Celsius, and O2 saturation at 99%. She is severely underweight and stunted with a weight of 13.5kg, Height of 101 cm ($z < -3$), and BMI of 13.1 ($z < -3$). Patient has dry skin and prominent scalp veins. She has alopecia, minimal subcutaneous fat, abnormal dentition, micrognathia, shrunken chin, and absence of eyebrows and eye lashes, there were no rashes or other skin lesions observed. She had anicteric sclerae with pink palpebral conjunctiva. Examination of the chest revealed symmetric chest expansion with no retractions and with clear breath sounds. She had an adynamic precordium with a normal heart rate, regular rhythm, and no murmurs. The point of maximal impulse was heard best at the fifth left intercostal space in the midclavicular line. There were no lifts, thrills, or heaves. The abdomen was globular

and distended with an abdominal circumference of 61cm, however, on palpation, it was nontender and no mass was palpated. On percussion, it was tympanitic on the upper quadrant with areas of dullness on the lower quadrants on percussion, with normoactive bowel sounds. She had grossly female genitalia with no pubic hair and had prepubertal breast buds (Tanner stage 1). The patient had limited range of motion of bilateral upper and lower extremities due to bilateral shoulder and hip dislocations. She had full and equal pulses, warm extremities, and capillary refill time less than 2 seconds with noted nail dystrophy. Neurological examination of the patient was unremarkable. Initial assessment on admission was ovarian new growth probably serous cystadenoma rule out epithelial cell carcinoma and patient is scheduled for and elective bilateral salpingo-oophorectomy with biopsy of suspicious lesions.

Patient underwent the planned procedure and tolerated the procedure well. Intraoperative findings showed a bilateral ovarian cystic mass with a smooth capsule and a normal looking uterus and fallopian tube. On cut section, the left ovary exuded serous fluid while the right ovary exuded seromucinous fluids. She was extubated immediately after the operation. There was also no bleeding on post-operative site. Patient was deemed stable and fit for discharge after 4th post-operative hospital day. The final pathologic diagnosis of the surgical specimens is bilateral ovarian serous cystadenoma with no significant pathologic changes (Figs. 1-4).

DISCUSSION

Ovarian mass in the pediatric population, specifically in patients who have not yet reached puberty, is uncommon with an estimated incidence of 2.6 cases per 100,000 girls per year. [3] In research conducted by Bhattacharyya et al. that studied 151 cases of ovarian tumors in the pediatric age group, the incidence of malignant ovarian tumors is 22.6%, while 78.4% of the ovarian tumors studied are benign. [3] Among the benign tumors, mature teratoma and serous cystadenoma are seen in all age groups. [3] They also divided the cases of ovarian masses in pediatric patients by age group (1-5, 5-10, 11-15, and 16-20 years old) and most of the ovarian tumors belonged to the age group 16 to 20 years old (80%). [3] In this case, we are presented with a middle adolescent 14-year-old female progeria patient with symptoms of an enlarging abdominal mass, which was incidentally detected on abdominal CT scan to be ovarian in origin.

Risk factors that predispose female patients to form ovarian masses include hormonal fluctuations, irregular menstruation, endometriosis, severe pelvic infections, family history of ovarian mass or cancer, and belonging to the reproductive age group with menarche, all of which are not present in this patient. The predisposition to form masses and cancer is one of the aging phenotypes absent in HGPS. They do not typically develop masses and cancer because they contain a tumor protection mechanism mediated by BRD4 (Bromodomain-containing protein 4). BRD4 inhibits abnormal growth of cells thus

inhibiting the oncogenic transformation of cells through its altered genome-wide binding patterns. [2] However, we are presented with a case of progeria with an ovarian mass.

In terms of sexual development, the patient has not yet reached her thelarche and menarche at 14 years of age and on physical examination the patient's stage of development can be classified as Tanner Stage 1 (prepubertal). Female progeria patients often have delayed sexual maturation and only develop until Tanner Stage II with signs of early breast development and sparse pubic hair. Only half of females with progeria achieve spontaneous menarche by age 14. [6] This pubertal delay is associated with the decrease in leptin levels in progeria patients due to the loss of subcutaneous fat that is important in leptin production. [6] Ovarian masses are also found to be less common in patients who have not yet reached menarche [2].

In this patient, CT scan of the whole abdomen (plain and with contrast) was done which revealed large unilocular cystic abdominopelvic mass lesions with thin capsules and with no ascites. Imaging features more suggestive of benign ovarian tumors include a mass with an entirely cystic component, thin wall (less than 3mm), lack of internal structure, and the absence of ascites. Malignant features in imaging studies include findings of thick and irregular walls, papillary projections, thick septa, and evidence of necrosis. [7] These were not seen in the imaging of the patient's abdomen hence the primary consideration based on the radiologic findings is a benign bilateral ovarian cystadenoma.

Another important laboratory test to further evaluate abdominal masses are tumor markers. In our patient, the tumor marker CA-125 was tested because she presented with an ovarian mass based on initial CT scan and CA-125 is known to be expressed by approximately 80% of ovarian epithelial carcinomas but less frequently by mucinous carcinomas. The marker is also increased in endometrial and tubal carcinoma, and in other malignancies such as those originating in the lung, breast, and pancreas. Our patient had elevated CA-125 results (96.88 U/mL) and this makes ovarian epithelial carcinoma a consideration as well.

The management of ovarian masses depends on the following factors: symptoms, size of the mass, age of the patient, medical history, and menopausal state of the patient. In most cases, unilateral salpingo-oophorectomy or ovarian cystectomy is an adequate treatment for ovarian masses. [8] In this patient, bilateral salpingo-oophorectomy was performed due to the presence of bilateral ovarian tumor. Important surgical considerations for our patient because she is a known case of progeria include difficult intubation because of the facial disproportion, narrowed nasal bridge, and retrognathia. Furthermore, progeria patients have a greater propensity for developing stroke under anesthesia due to the underlying stiffness of the blood vessels that make it challenging to maintain adequate blood pressure during general anesthesia.

The definitive diagnosis of ovarian masses is based on the histopathological examination of the surgical specimens: bilateral ovary and fallopian tubes. The final pathologic diagnoses of the surgical specimens are bilateral serous cystadenoma with no significant pathologic changes. Ovarian cysts are the most common adnexal mass in the pediatric population. [5] Ovarian tumors in the age group of 11-15 years old are mostly benign occurring in 60% of patients. The most common benign ovarian tumor in patients aged 11-15 years old is benign cystic teratoma occurring in 38% of the patients, this is followed by mucinous cystadenoma occurring in 30% of the patients, and lastly serous cystadenoma occurring in 23% of the patients. [3] Despite having an elevated level of tumor marker CA-125 which is a feature of a malignant lesion, patient still had a benign ovarian mass due to the enhanced activity of the BRD4 gene in Progeria which inhibits neoplastic transformation of cells.

Most serous cystadenomas are polyclonal, but monoclonal cystadenomas occur. These ovarian cystadenomas develop as a hyperplastic expansion from epithelial inclusions. [9] Serous cystadenomas are not associated with mutations in either KRAS or BRAF in contrast to serous borderline tumors and low-grade serous carcinoma. Macroscopic findings of serous cystadenoma ranges in size from 1 to more than 30 cm in greatest dimension. They have a smooth outer surface and contain one or more thin-walled cysts filled with clear, watery fluid. Serous cystadenomas are usually unilocular but may be multilocular. [9] In our patient, both ovaries have a smooth capsule with sizes ranging from 9 to 11 cm. On cut section, the left ovarian cyst exuded serous fluid while right ovary exuded seromucinous fluid. In addition to this, the histopathology of serous cystadenomas is composed of cysts and papillae lined by non-stratified or stratified cuboidal to columnar cells resembling fallopian tube epithelium, usually with no or minimal atypia. [9] In our patient, microscopic analysis of both ovaries revealed fragments of cysts lined by a single layer of flat to small cuboidal cells adherent to ovarian stroma with cysts line by an inner layer of granulosa cells and an outer layer of theca cells. No atypical and malignant cells were noted on both specimens (Figs. 1-4). In terms of immunohistochemistry, the immunohistochemical profile of serous cystadenoma is like that of normal ovarian surface epithelium and tubal epithelium. In addition to the positivity with most used epithelial markers, p63 is also positive in most cases. [9] Unfortunately, for this case, no immunohistochemical analysis was done.

As a progeria patient, certain organ systems involved in the disease must be properly screened and managed to limit complications of the disease. Other expected disabilities associated with the syndrome include multiple repeated hip and shoulder dislocations that may affect mobility, hearing loss, hyperopia, corneal ulceration, decreased visual acuity, stroke, and heart disease and subsequent failure. All these expected morbidities associated with progeria would require a multidisciplinary team approach in managing the patient as an outpatient.

The mean life expectancy of a patient with progeria is 13.4 years. [4] Approximately 80% of progeria deaths are caused by heart failure that can be precipitated by respiratory infection and by surgical intervention. Since progeria is a primary vasculopathy with increased vascular stiffening and with a propensity to form atherosclerotic plaques, common end-stage events include hypertension, angina, cardiomegaly, and congestive heart failure. [1] It is important to monitor the patient post-operatively because heart failure can develop following surgical intervention. Respiratory infection can precipitate heart failure hence it is important to avoid prolonged hospitalization of the patient to avoid hospital acquired pneumonia. At this time of the COVID pandemic where the viral disease is still rampant and is highly contagious, it is important to educate the patient, as well as other household members, to always practice social distancing, wear proper protective equipment, and practice adequate personal hygiene. Through these preventive measures, the patient can be protected from getting the disease and consequently avoid having severe respiratory infections.

Anticipatory guidelines include strict fall precaution and avoidance of strenuous activities that may put the patient at risk of head trauma and skeletal injuries that may lead to recurring hip and shoulder dislocations. Anticipatory guidelines for adolescent patients, such as our patient, include self-breast examination, healthy lifestyle through physical activity that is appropriate for the patient, proper diet, avoidance of alcohol, smoking, and drug use, counseling on sexual behavior and risk of acquiring STIs, injury and accident prevention strategies such as use of sports protective gears, use of seatbelts, no driving under the influence of alcohol, and no handgun use. [10] It is also important to complete the immunization of the patient by administering the following vaccines that must be given to adolescent patients: influenza vaccine annually, HPV vaccine (3 doses following the 0, 1-2, and 6-month schedule), and PCV vaccine (1 dose of PCV 13 and 1 dose of PCV 23).

Having a child diagnosed with progeria has a major impact on the family hence genetic counseling must be done to the family as well. HGPS is a sporadic autosomal dominant disease which means that it follows an autosomal dominant inheritance wherein the condition can be passed down from a diagnosed progeria parent to her offspring. One copy of the mutated gene from one parent can cause the genetic condition. For healthy parents who already have a child with progeria, the chance of having another affected child is much higher at about 2-3%. This is due to genetic mosaicism where a parent's gene has the genetic mutation for progeria in a small proportion of their cells, but they do not manifest the disease phenotypically. [11] In this case, the family of the patient underwent genetic counseling and the prognosis of the disease as well as the probability of having another child with progeria was adequately explained to them as well.

The patient recovered well from the operation with no complications. She is now being optimized again to undergo surgical

repair of her bilateral shoulder dislocation so she can regain full functionality and mobility.

SUMMARY

The Hutchinson-Gilford progeria syndrome (HGPS) is a rare genetic condition that requires a multidisciplinary approach in management. This case presents an adolescent female patient with progeria presenting with an ovarian mass. Further studies to establish the correlation between Hutchinson-Gilford progeria syndrome (HGPS) and abdominal masses, specifically masses in the reproductive system have yet to be done. Routine abdominal ultrasound screening or routine abdominal CT scan can be done to detect presence of masses in HGPS patients. Female adolescent patients diagnosed with progeria should also be routinely seen and examined by a pediatric gynecologist for further evaluation of possible reproductive pathologies and delayed sexual development.

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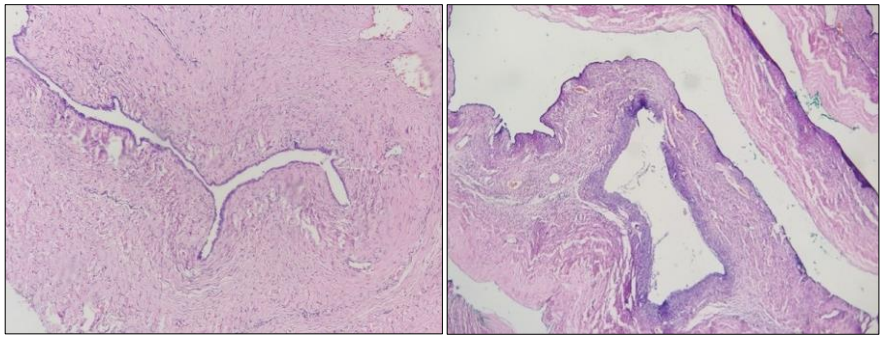

Figure 1. Left Ovary, LPO

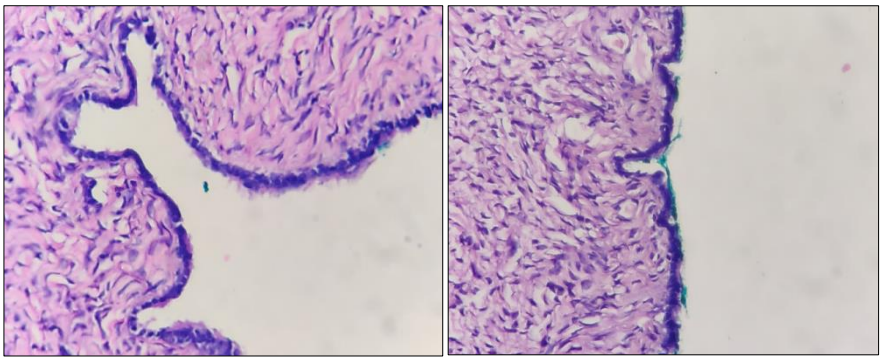

Figure 2. Left ovary, HPO

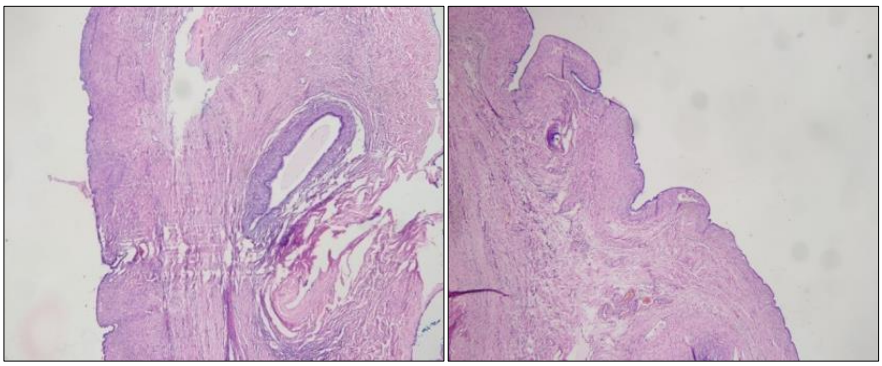

Figure 3. Right ovary, LPO

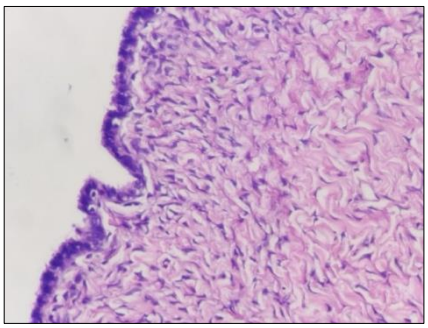

Figure 4. Right ovary, HPO

SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA

ALEXANDER B. SUPLICO JR, MARIA BEATRIZ P. GEPTE

ABSTRACT

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare form of cytotoxic T-cell lymphoma of the skin localized primarily in the subcutaneous adipose tissue. Clinically, the skin lesions mimic lipomas, but histologically resemble panniculitis, which is an inflammation of the subcutaneous fats. Most cases have an excellent prognosis and follow an indolent clinical course with a 5-year overall survival rate of 80%. So far, only a few cases have been reported in the pediatric age group. The diagnosis of SPTCL is based on the combination of clinical presentation, histopathologic examination of the skin lesion, immunohistochemical staining, and molecular analysis. Notably, data on treatment of pediatric SPTCL are even fewer in number, and very few patients undergoing effective treatment have been documented.

This is a case report of a 15-year-old female adolescent diagnosed with Subcutaneous panniculitis-like T-cell lymphoma who presented with multiple, non-tender, erythematous to violaceous deep dermal and subcutaneous nodules on the lower extremities associated with myalgia, intermittent moderate-grade fever, and weight loss over the past 7 months. She was initially managed as a case of "growing pain" and acute rheumatic fever, until histopathologic findings of the nodules showed inflammation of the subcutaneous fats, and immunohistochemistry revealed findings consistent with SPTCL. She is currently being treated with multi-agent combination chemotherapy which resulted in improvement of symptoms.

INTRODUCTION

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) was first described by Gonzalez et al in 1991 and has been recognized as a rare type of peripheral T-cell lymphoma characterized by infiltration of the subcutaneous tissues by neoplastic cytotoxic T-cells with variable extensions into the dermis. Clinically, the skin lesions mimic lipomas, but histologically it resembles panniculitis, an inflammation of the subcutaneous fats. [1,2]

SPTCL accounts for less than 1% of all non-Hodgkin's lymphoma and most patients are adults, with the disease being extremely rare in children. Patients typically present with solitary or multiple subcutaneous nodules and plaques involving primarily the lower extremities and trunk, but in children and adolescents it may affect the head and neck. [3,7,11] In the pediatric population, constitutional symptoms are the presenting features in approximately 50% of the cases, including fever, chills, weight loss, myalgia, pancytopenia, and hepatosplenomegaly. [3,6,13]

Histologic features of SPTCL include rimming of adipocytes by atypical lymphocytes, fat necrosis, karyorrhectic debris, and large macrophages with

cytophagocytosis with distinct sparing of the interlobular septa, epidermis, and dermis.[1,3] By immunohistochemistry, the atypical lymphoid cells are positive for CD2, CD3, CD7, CD8, beta F1, and cytotoxic T-cell markers including T-cell intracellular antigen (TIA-1), granzyme B (GzB), and perforin; while negative for CD4, CD56 and CD30. Epstein-Barr Virus (EBV) is generally absent in most cases of sporadic SPTL but can rarely be detected in some variants especially in Asian population where EBV infection is common. The overall 5-year median survival is approximately 80%, although the prognosis is poor if associated with a hemophagocytic syndrome.[5]

CASE REPORT

A 15-year-old female first presented seven months prior to consultation with a sudden myalgia on the back, thighs, and the calves of both legs with no associated trauma or precipitating events. She self-medicated with Diclofenac once daily with temporary relief of symptoms. She remained relatively well until six months prior to consultation, when she had recurrence of myalgia. The patient consulted with a private pediatrician through telemedicine, who initially assessed her to have "growing pains." The mother was apprised that the nature of the pain is self-limiting and is common in children of her age who have increased physical activities. There were no laboratory examinations done or medications prescribed. At the same time, the patient had intermittent fever with a maximum body temperature of 38.8 °C, occurring during the night. Due to the associated febrile episode, the patient's mother sought another consultation with the same pediatrician through telemedicine and was advised admission. A complete blood count showed anemia and additional laboratory examinations revealed elevated Antistreptolysin O (ASO) titer and lactate dehydrogenase (LDH) levels. Two-dimensional echocardiography was done, which showed mild tricuspid and pulmonary regurgitation with thickened anterior mitral valve leaflets. She was then treated as a case of Acute Rheumatic Fever versus Viral Myocarditis. She was given an intramuscular dose of Benzathine Penicillin G at 1.2 million units per dose. The patient was then discharged afebrile after 7 days. Following discharge, the patient received a single intramuscular dose of Benzathine Penicillin G every 21 days. In the interim, despite treatment with antibiotics, the patient continued to experience intermittent moderate-grade fever with a maximum body temperature at 39 °C.

Five months prior to consultation, the patient's mother started to note the appearance of non-tender, twenty-five-centavo-coin-sized, erythematous to violaceous nodules on the popliteal area of both legs (**Figure 1 A-D**). She was brought for consultation to the same physician and there were noted multiple, firm, non-tender, non-moveable, erythematous to violaceous deep dermal and subcutaneous nodules approximately 5 cm in diameter on the popliteal area of both legs and thighs. Due to this finding, she was readmitted for work-up. A complete blood count taken showed anemia and leukopenia with neutrophil predominance, and an elevated Erythrocyte

Sedimentation Rate (ESR). Intramuscular dose of Benzathine Penicillin G was continued, and the patient was started on oral prednisone (2 mg/kg/day) for the impression of carditis secondary to rheumatic fever. She was discharged afebrile after 5 days.

In the interim, the patient continued the monthly dose of intramuscular Benzathine Penicillin G and oral Prednisone with gradual tapering. There was no recurrence of fever; however, the previously described subcutaneous nodules persisted. At the same time, the patient's mother also noted that she had gradual weight loss described as loosening of the patient's clothes despite no change in appetite and activities of daily living.

One month prior to consultation, the patient had a recurrence of fever with a maximum body temperature at 40 °C occurring at night. The subcutaneous nodules became slightly larger than previously described, from a twenty-five-centavo coin to the size of a five-peso coin and became more extensive in distribution covering approximately 40% of the body surface area of the bilateral thighs and legs, now involving the upper limbs (**Figure 1 A-E**). She was then advised to seek consultation with a Pediatric Hematologist-Oncologist for workup of an underlying malignancy due to the persistence of febrile episodes and subcutaneous nodules despite treatment with antibiotic and corticosteroid.

On the day of consultation, the patient was seen by a Pediatric Hematologist-Oncologist in a tertiary hospital and was advised admission for further workup and management, but the parents did not consent due to fear of being exposed to the coronavirus. Instead, she was managed on an outpatient basis. On physical examination, there were noted multiple, non-tender, erythematous to violaceous colored subcutaneous nodules on the bilateral thighs, legs, and upper extremities ranging in size from 5 to 10 cm in diameter (**Figure 1 A-E**). The patient had neither lymphadenopathies nor hepatosplenomegaly. Workups done revealed normocytic and normochromic anemia, leukopenia, elevated levels of ferritin, LDH, and uric acid. Other workups which include serum glutamic pyruvic transaminase (SGPT), antinuclear antibody (ANA) titer, prothrombin time (PT), partial thromboplastin time (PTT), and creatinine were within normal range. Oral prednisone was tapered off and the patient was referred to a dermatologist for excision biopsy of the left thigh mass. Histopathologic examination stained with hematoxylin and eosin showed a lobular, panniculitic infiltration pattern of the lymphocytes. The infiltrate is composed of atypical lymphocytes with irregular, hyperchromatic nuclei, some of which form a ring around adipocytes. The atypical lymphocytes spared the epidermis, dermis and fibrous septae, and showed neither angioinvasive nor angiodestructive features (**Figure 2-4**). Immunohistochemistry involved the use of antibodies against T-, B-, and Natural Killer-cell differentiation antigens including cluster of differentiation (CD) 3, CD4, CD5, CD8, CD20, and CD56. On the other hand, in situ hybridization for the detection of Epstein– Barr virus (EBV)-

encoded RNAs (EBERs) was performed. It revealed that atypical lymphocytes expressed CD3, CD8, and CD5 (**Figure 5-7**); with the absence of CD4, Epstein-Bar Virus-encoded small RNA (EBER), CD56, and CD20 (**Figure 8-9**). T-cell receptor gene rearrangement was not performed due to financial constraints. Based on these clinical and histopathologic findings, a diagnosis of Subcutaneous panniculitis-like T-cell Lymphoma was made. Due to the high serum ferritin level, workup for hemophagocytic lymphohistiocytosis (HLH) was considered; however, the patient's parents did not give consent for additional laboratory tests and staging work-up with bone marrow aspiration and cerebrospinal fluid analysis with cytospin. Instead, the patient was started on dexamethasone (10mg/m^2) as first-line treatment before combination chemotherapy in light of the often-indolent course and favorable prognosis of SPTL (**Figure 10**).

To assess the extent of the disease, Positron Emission Tomography (PET) 2-[fluorine-18] fluoro-2-deoxy-D-glucose (FDG) scan was performed. The scan showed hypermetabolic, diffuse subcutaneous thickening, haziness, and stranding densities in the left upper arm, right epigastric; bilateral posterolateral lumbar regions, pelvic, gluteal, and lower extremities in keeping with known malignancy. Hypermetabolic bilateral inguinal, popliteal, and left paraspinal intramuscular lymph nodes were consistent with active lymphomatous disease. In addition, hypermetabolic foci seen in the tibia were suspicious for metastasis (**Figure 11, 12**).

The patient's parents eventually gave consent for chemotherapy. CSF analysis with cytospin was done prior to chemotherapy which was negative for central nervous system involvement. Options on chemotherapy were reviewed in view of prolonged pre-exposure to steroids and progression of lesions despite prior treatment. The patient's young age, unknown presence of HLH, and protracted course of the disease prompted initiation of treatment with multi-agent combination chemotherapy as per Berlin-Frankfurt-Münster (BFM) 90 protocol, which is typically used for aggressive pediatric non-Hodgkin lymphomas. She underwent chemotherapy protocol as follows: prednisone (60 mg/m^2), dexamethasone (6 mg/m^2), doxorubicin (30 mg/m^2), vincristine (1.5 mg/m^2), cytarabine (75 mg/m^2), 6-mercaptopurine (60 mg/m^2), cyclophosphamide (1000 mg/m^2), high dose methotrexate (5 g/m^2), and L-asparaginase (6000 mg/m^2). The patient had improvement in her systemic symptoms with no recurrence of fever and myalgia, and with the skin lesions subsiding near the completion of the induction phase (**Figure 13**). On subsequent follow-up, the patient had no infectious or treatment-related complications during chemotherapy.

DISCUSSION

Panniculitis refers to the inflammation of subcutaneous fats. In most cases, it can be a sign of an underlying systemic disease. Specificity in diagnosis is difficult since different forms of panniculitides may have similar clinical appearance, thus a histopathologic study with correlation with

clinical features (e.g. including location of the lesions, the presence of systemic symptoms, laboratory findings), immunohistochemical staining, and molecular analysis are done for a definitive diagnosis. [13,14,15]

Panniculitis in the pediatric age group is rarely seen. Apart from Erythema Nodosum as being the most common type of panniculitis in children, other types of panniculitis, such as subcutaneous fat necrosis, is rare. In the absence of a specific diagnostic algorithm, panniculitis in children needs multiple diagnostic workups to ascertain a definite cause, considering that some of them may bear an uncertain prognosis or may be fatal if left untreated. [13,14,15]

Panniculitis can be either primary or idiopathic, or secondary. Secondary etiologies can be classified into the following broad categories: infections (streptococcal, mycobacterial, fungal, parasitic, and viral), inflammatory or connective tissue disease (erythema nodosum, erythema induratum, lipodermatosclerosis, lupus panniculitis, cutaneous polyarteritis nodosa, dermatomyositis-associated panniculitis), malignancy (subcutaneous panniculitis-like T-cell lymphoma), pancreatic disease (pancreatic panniculitis associated with pancreatitis or pancreatic carcinoma), immunodeficiency states (alpha-1 antitrypsin deficiency panniculitis), trauma (cold panniculitis, traumatic panniculitis, factitial panniculitis), and depositions (calciphylaxis, gout). The common clinical features of panniculitis, regardless of etiology, are erythematous, tender, subcutaneous nodules. [13,14,15]

Panniculitis can be classified into lobular or septal panniculitis based on whether the inflammation is seen in the fat lobules or septae, respectively. It can be further classified based on whether the inflammation is found with or without vasculitis and by the predominant cells found. Notably however, the pediatric-specific panniculitides all fall into the lobular pattern histologically. [13,14,15] Panniculitis is rarely caused by malignancy, but this possibility must be considered if the clinical picture does not fit the diagnosis. Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) and Cytophagic Histiocytic Panniculitis (CHP) are the most common malignancy-related panniculitides. [13,14,15]

Subcutaneous panniculitis-like T-cell lymphoma accounts for less than 1% of all non-Hodgkin's lymphoma and most patients are adults, with the disease being extremely rare in children. Median patient age at diagnosis was 39 years with a slight female preponderance with male to female ratio of 0.5. [2,3,4] The overall 5-year median survival is approximately 80%, although the prognosis is poor if associated with a hemophagocytic syndrome, characterized by uncontrolled phagocytosis of blood components, cytopenias, coagulopathy, hepatosplenomegaly, and even death.[5] Being rare in pediatric population, so far, only few cases have been reported in literature with age range of 26-month-old to 17 years of age.

In the Philippines, a case of SPTCL was first reported in our institution by Dr. Michelle Rodriguez in 2005. In the Philippine Pediatric Society registry, there were no SPTCL cases recorded from 2006 to 2021. While under the Panniculitis-unspecified, there were 10 cases recorded.

Although the exact mechanism of the pathogenesis of SPTCL is still mostly unknown, Musick postulated that expression of C-C chemokine receptor type 5 (CCR5) on the neoplastic T-cells and its ligands CCL3, CCL4, and CCL5 located on the adipocyte membrane facilitated the migration of the neoplastic T-cells to the adipocyte membrane. [9] On the other hand, Levy identified a germline mutation causing loss of function of T-cell immunoglobulin mucin 3 (TIM-3) in 60% to 85% of SPTCL patients. TIM-3 acts as a negative immune checkpoint that regulates the effector function of T lymphocytes and myeloid cells. In these patients, TIM-3 deficiency was shown to promote T-lymphocyte and macrophage activation and the production of pro-inflammatory cytokines, challenging the malignant nature of skin T-lymphocyte infiltration. [10]

The diagnosis of SPTCL is based on the combination of clinical presentation, histopathologic examination of the skin lesion, immunohistochemical staining, and molecular analysis. Patients typically present with solitary or multiple subcutaneous nodules and plaques involving primarily the lower extremities and trunk, but in children and adolescents it may affect the head and neck. [2,3,7] Other tissues and organ involvement are rare.[5] In the pediatric population, constitutional symptoms were the presenting features in approximately 50% of the cases, including fever, chills, weight loss, myalgia, pancytopenia, and hepatosplenomegaly. [2,3,10] In our case, prior to diagnosis of SPTCL, the patient had a 7-month history of intermittent moderate-grade fever, myalgia, weight loss, and multiple subcutaneous nodules on both the lower and upper extremities. The patient was initially managed as a case of Acute Rheumatic Fever and despite treatment with antibiotics and corticosteroids, she continued to experience intermittent, moderate-grade fever, and persistence of multiple subcutaneous nodules on both the lower and upper extremities. At the time of consultation with a Pediatric Hematologist-Oncologist, there were multiple, non-tender, erythematous to violaceous nodules ranging in size from 5 to 10 cm affecting the bilateral thighs and legs, and the upper limbs (**Figure 1 A-E**). The patient had neither peripheral lymphadenopathy nor hepatosplenomegaly.

Histologic features include rimming of adipocytes by atypical lymphocytes, fat necrosis, karyorrhectic debris, and large macrophages with cytophagocytosis with distinct sparing of the interlobular septa, epidermis, and dermis. [1,2] In our case, the histopathologic examination of the skin biopsy specimen from the left thigh mass showed a lobular panniculitic infiltration pattern of the lymphocytes. The infiltrate is composed of atypical lymphocytes with irregular, hyperchromatic nuclei, some of which form a ring around adipocytes showing a histologic feature compatible with SPTL. In addition, the atypical

lymphocytes spared the epidermis, dermis and fibrous septae, and showed neither angioinvasive nor angiodestructive features (**Figure 2-4**).

Immunophenotypically, the neoplastic cells in SPTCL are cytotoxic T cells that are positive for CD3 and CD8 and negative for CD4 and CD56. Our case revealed that the atypical lymphocytes expressed $CD3^+$, $CD8^+$, and CD5+, with absence of CD4, Epstein-Barr Virus-encoded small RNA (EBER), CD56, and CD20 (**Figure 5-9),** consistent with SPTCL**.** Epstein-Barr virus was not detected; hence the virus did not appear to play a role in the pathogenesis of this lymphoma.[11] T-cell receptor (TCR) gene rearrangement was not performed because of financial constraints.

Imaging can have an advantage over physical examination for detecting clinically unsuspected SPTCL lesions, both on initial staging and during follow up examination. The SPTCL lesions can be easily assessed using various imaging modality, such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). [3] The Positron Emission Tomography (PET) 2-[fluorine-18] fluoro-2-deoxy-D-glucose (FDG) imaging features of SPTCL include multiple foci of FDG-avid subcutaneous adipose tissue lesions involving the extremities and trunk without visceral disease.[12] Our case revealed multiple foci of increased FDG-avid subcutaneous adipose tissue lesions on the left upper arm, the right epigastric area, bilateral posterolateral lumbar region, pelvic, gluteal, and lower extremities, with involvement of bilateral inguinal, popliteal, and left paraspinal intramuscular lymph nodes (**Figure 11-12**). Several previous studies have demonstrated that FDG PET/CT can be a useful tool for the initial accurate total body staging, restaging following therapy, detecting occult extracutaneous involvement, driving the biopsy towards the most active site, the stratification of prognosis and early therapy assessment. [12]

There is no single-best treatment regimen for SPTCL. The treatment reported in limited cases includes systemic corticosteroids, multidrug chemotherapy regimens such as CHOP (cyclophosphamide, adriamycin, vincristine, prednisone), cyclosporine, and combination therapy, but the overall response rate has been reported to be variable, ranging from 53% to 100% with a duration ranging from 2 to 72 months. Patients with α/β phenotype SPTCL lacking HLH respond well to immunosuppressive agents such as prednisone and cyclosporine, and low-dose chemotherapy involving a single agent, such as cyclophosphamide or methotrexate. The presence of constitutional symptoms, cytopenia, involvement of multiple sites, and coexisting hemophagocytic syndrome tend to be associated with a poor clinical outcome and require combination chemotherapy. Of all the immunosuppressive agents, corticosteroids are the most effective. Notable responses are found in patients with limited skin lesions and absent systemic symptoms. Nevertheless, responses usually are short-lived, with frequent disease recurrences after corticosteroid tapering. However, because of

the expected slow onset of response, such agents should be considered only in patients who have SPTCL with a less aggressive biology or as adjunctive treatment. Anthracycline-based combination regimens, in particular, CHOP, represent the most effective type of chemotherapy. Such regimens should be the option of choice when aggressive systemic treatment is considered. In our case, the patient was initially given corticosteroids, however there was recurrence of fever and progression of lesions despite treatment, hence the non-Hodgkin lymphoma-Berlin-Frankfurt-Münster (NHL-BFM) 90 chemotherapy, which is typically used for aggressive pediatric non-Hodgkin lymphomas, was the regimen used. The chemotherapy protocol includes induction phase, consolidation phase, and maintenance therapy courses, composed of prednisone, dexamethasone, doxorubicin, vincristine, cytarabine, 6-mercaptopurine, cyclophosphamide, methotrexate, and L-asparaginase. For relapse and refractory disease, additional strategies include salvage chemotherapy with cladribine, DHAP (dexamethasone, cytarabine, and Cisplatin), ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin), FLAG (fludarabine, cytarabine, and granulocyte-colony stimulating factor), mini-BEAM (carmustine, etoposide, cytarabine, and melphalan), VEPPB (vincristine, etoposide, prednisone, procarbazine, and bleomycin), radiation, and autologous peripheral blood stem cell transplant. The inconsistency in the treatment regimen extends to both the pediatric and adult cases reported in the literature. The rarity of this disease has prevented a unified treatment strategy from being developed. [16,17]

SUMMARY

This is a case report of a 15-year-old female manifesting with indurated, non-tender, erythematous to violaceous subcutaneous nodules on the lower extremities associated with myalgia, intermittent moderate-grade fever, and weight loss over the past 7 months. A combination of clinical presentation, histopathologic examination of the skin lesion and immunohistochemical staining confirmed the diagnosis of Subcutaneous panniculitis-like T-cell lymphoma. Currently, there is no standard treatment regimen for SPTL due to its rarity. The patient is currently on maintenance phase per Berlin-Frankfurt-Münster (BFM) 90 protocol, which is composed of prednisone, dexamethasone, doxorubicin, vincristine, cytarabine, 6-mercaptopurine, cyclophosphamide, methotrexate, and L-asparaginase. There were no infectious or treatment-related complications during chemotherapy. She has had improvement in her systemic symptoms with no recurrence of fever and myalgia, and with the skin lesions subsiding near the completion of chemotherapy. A FDG PET/CT scan is warranted for chemotherapy reassessment and disease prognostication after completing the active treatment.

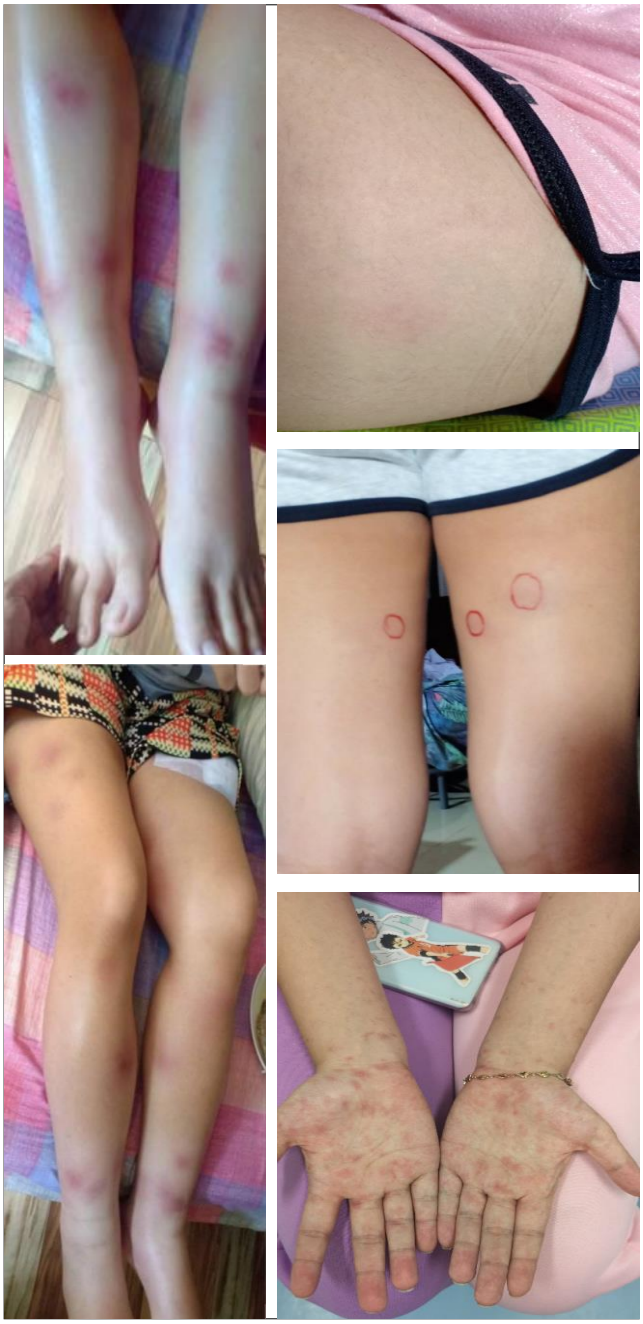

Figure 1. Multiple, indurated, non-tender, erythematous to violaceous colored subcutaneous nodules on the bilateral legs (**A, B**), the thighs (**C**), the popliteal area (**D**) and the hands (**E**).

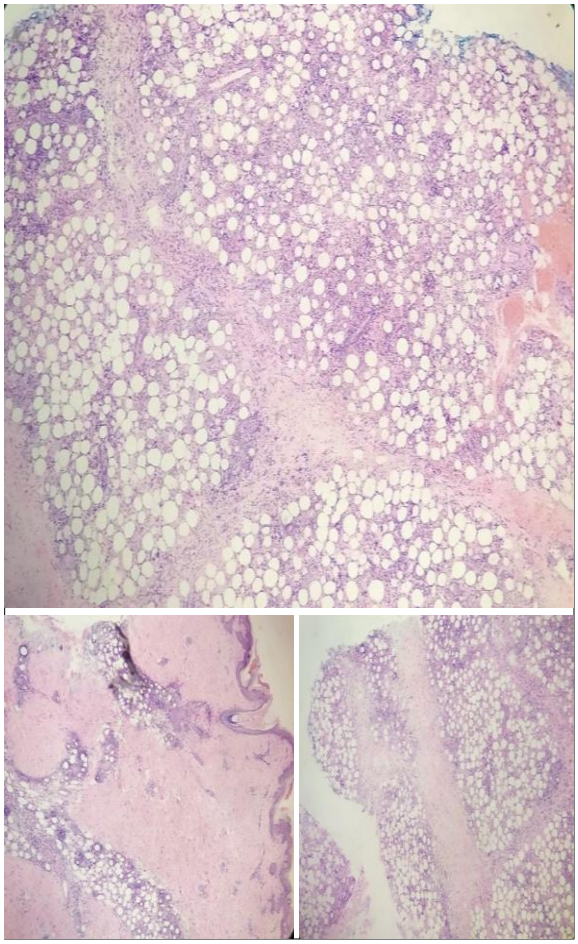

Figure 2. (**A**) Lymphocytic infiltrate primarily in the subcutaneous tissue involving the fibroadipose lobules and with relative sparing of the fibrous septae (Hematoxylin-Eosin (H-E) stain, 4x). (**B**) Area which shows that the epidermis and dermis are relatively spared (Hematoxylin-Eosin (H-E) stain, 4x). (**C**) Dense lymphocytic infiltrate again in the subcutaneous area, sparing the septae for the most part (Hematoxylin-Eosin (H-E) stain, 4x).

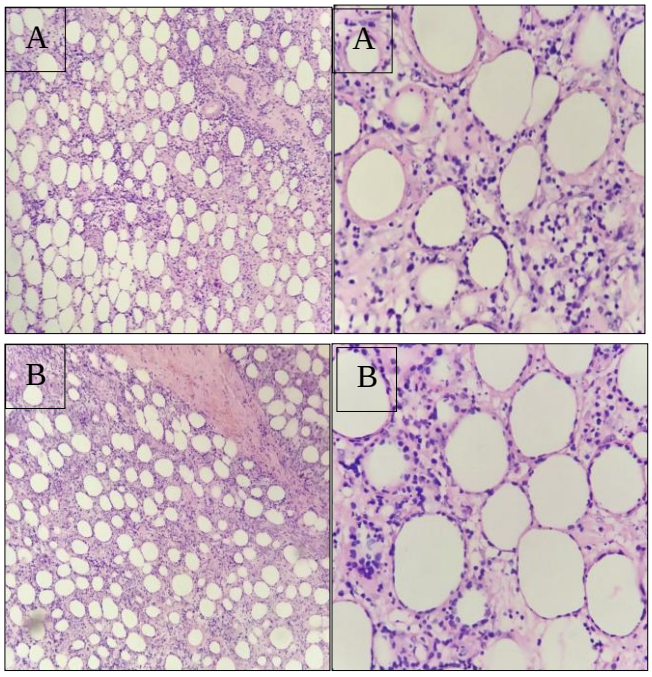

Figure 4. (A, B) Slightly enlarged tumoral lymphocytes with irregular, hyperchromatic nuclei. Some can be seen rimming the adipocytes (Hematoxylin-Eosin (H-E) stain, 40x)

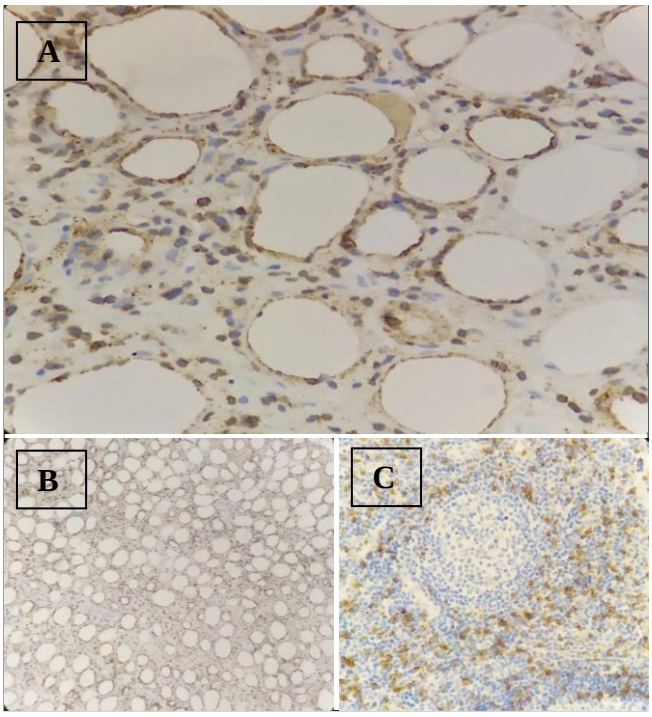

Figure 6. (**A**) CD8 shows reactivity in the tumoral cells, seen in both the stroma and lining the adipocytes (Immunohistochemical stain, 40x). (**B, C**) CD8 shows positivity in the cells of interest (Immunohistochemical stain; 4x, 10X).

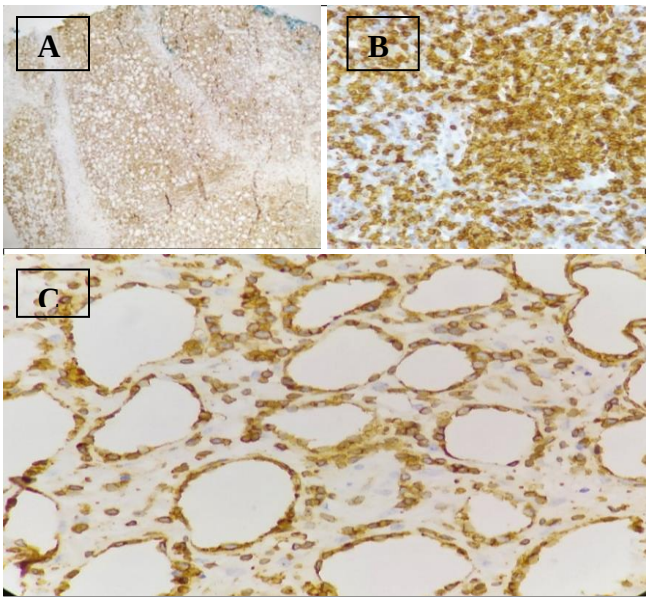

Figure 5. (**A**) Positive membranous staining of CD3 in the tumoral cells in a diffuse pattern (Immunohistochemical stain, 4x). (**B, C**) Atypical lymphocytes express $CD3^{+}$ (Immunohistochemical stain; 10x, 40x).

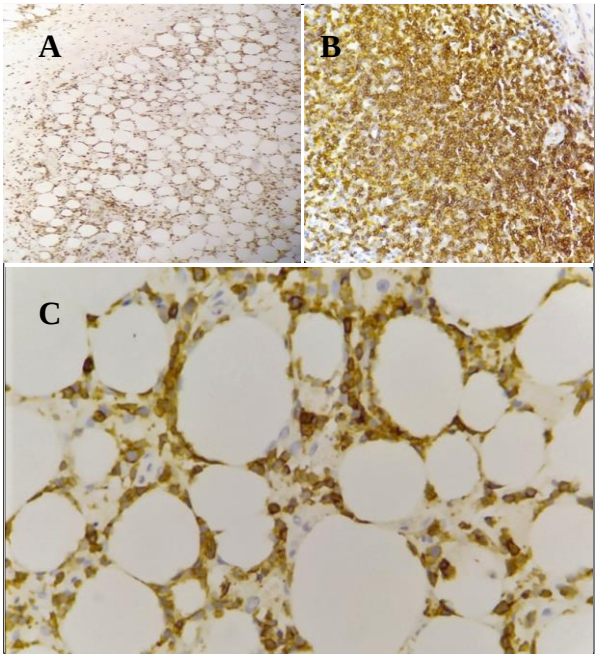

Figure 7. (**A, B, C**) Atypical cells shows CD5 reactivity.

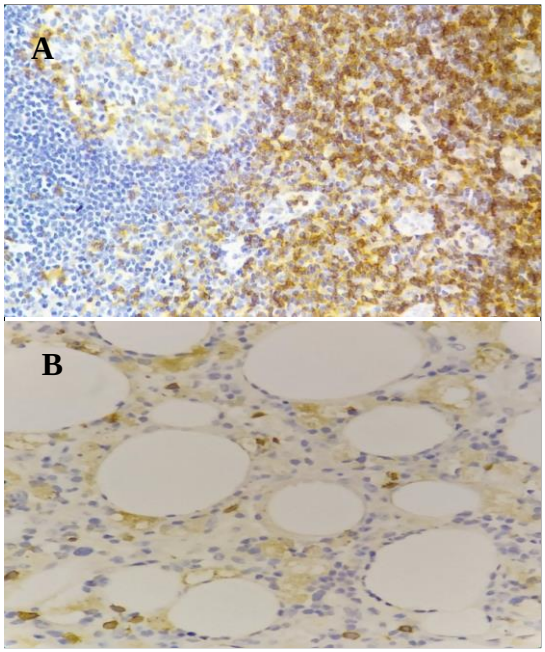

Figure 8. (**A, B**) CD4 Staining is not reactive in the cells of interest, though there is positivity scattered lymphocytic cells.

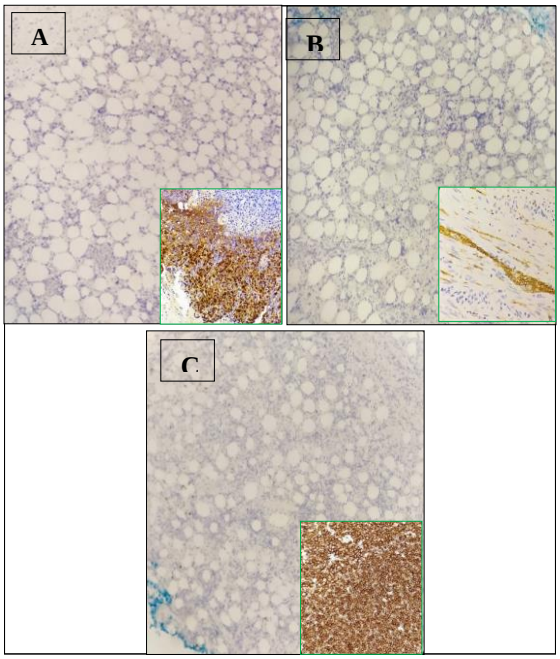

Figure 9. Immunohistochemical staining: (**A**) Epstein-Bar Virus-encoded small RNA (EBER) negative, (**B**) CD56 negative, (**C**) CD20 negative. (*Compared with the controlled inset showing positivity in EBER, CD56, and CD20)

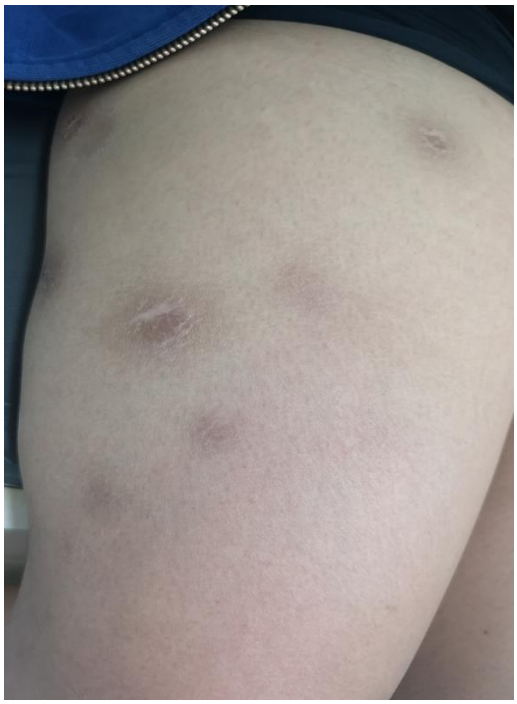

Figure 10. Multiple hyperpigmented subcutaneous nodules on the thighs after 10 days of treatment with Dexamethasone

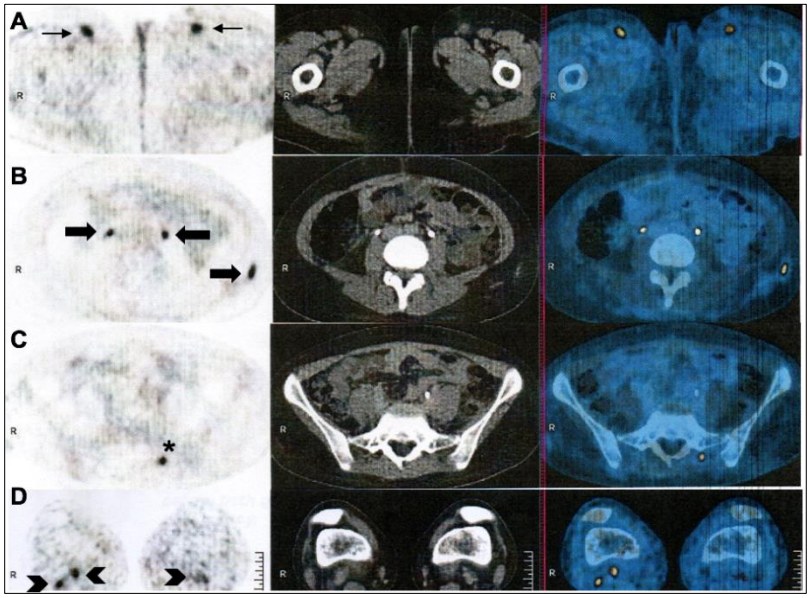

Figure 11. FDG-PET image of the (**A**) abdomen shows prominent-sized lymph nodes seen in the left inguinal/proximal thigh region, measuring 0.9 cm. Smaller lymph nodes are also seen in both inguinal regions. There is increased FDG uptake in the prominent left inguinal and small bilateral inguinal lymph nodes (thin arrows). (**B**) Musculoskeletal, FDG-avid diffuse subcutaneous thickening, haziness, and stranding densities in the left upper arm, right epigastric, bilateral posterolateral lumbar region, both pelvic, both gluteal, and both lower extremities (thick arrows). (**C**) A focus of increased FDG uptake is also noted in the left paraspinal (sacral) muscle, likely an intramuscular node (asterisk). (**D**) Another FDG-avid focus is noted in the proximal tibia and a smaller focus in the left proximal tibia. FDG-avid bilateral popliteal nodes are also noted, more prominent on the right (arrow heads).

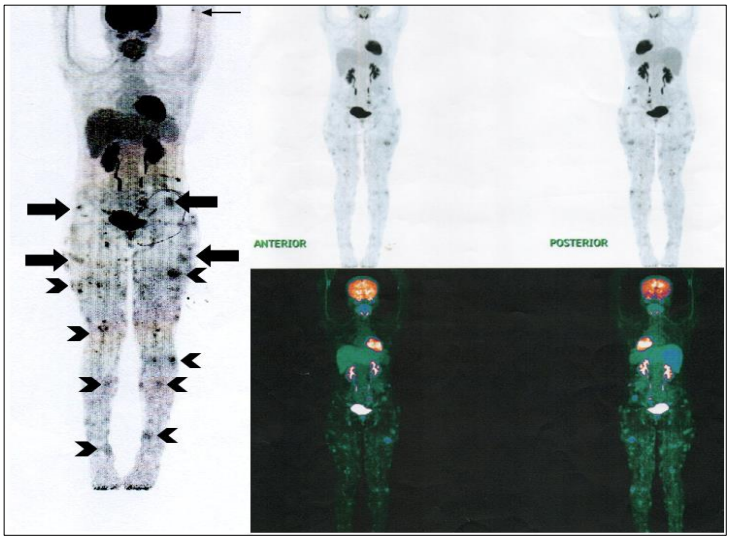

Figure 12. FDG-PET images show hypermetabolic diffuse subcutaneous thickening, haziness and stranding densities in the left upper arm (thin arrow), right epigastric, bilateral posterolateral lumbar regions, both pelvic, gluteal (thick arrows) and both lower extremities in keeping with known malignancy; hypermetabolic bilateral inguinal, popliteal and left paraspinal intramuscular lymph nodes are consistent with active lymphomatous disease (arrow heads); hypermetabolic foci in the tibia are suspicious for metastasis.

Figure 13. Brown-tinted, post-inflammatory hyperpigmentation of the subcutaneous nodules (**A**) 5 days after initiation of treatment and (**B**) near completion of induction treatment.

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A CASE REPORT ON GELASTIC SEIZURES

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ABSTRACT

Gelastic seizure is a rare seizure type, with laughter as the main ictal manifestation. In the presence of a hypothalamic hamartoma, laughing seizures are referred to as gelastic epilepsy which is seen in less than 5% of epilepsies [1]. These seizures begin during infancy with a progressive course and may present with precocious puberty and cognitive decline. In the absence of a hypothalamic hamartoma, gelastic seizures have a later onset and are more seldom encountered. These are seen in less than 1% of all epilepsies and occur as part of a frontal or temporal lobe epilepsy [1]. For gelastic seizures not associated with this lesion, prognosis is good since they are more responsive with AEDs and may be controlled by a single AED.

This is a case report of a 7-year-old male who presented with recurrent attacks of spontaneous, mirthless, and inappropriate laughter associated with hyperkinetic movements. Workup did not show a hypothalamic hamartoma. Interictal EEG showed bilateral frontal lobe discharges in prolonged runs. He was given carbamazepine which provided adequate seizure control. This is the second case reported in this institution from 1992 until present.

INTRODUCTION

Gelastic seizure, coined by Daly and Mulder in 1957, was derived from the Greek word "gelos" which means laughter [1]. Gelastic seizure, classified under focal emotional seizures, is a rare type of seizure that manifests as laughter-like vocalization [2]. According to the PPS ICD registry, there have been 74 out of 4 million reported cases of other epilepsy types including gelastic seizure among others, since 2010. In the Philippines, there were two reported cases both associated with a hypothalamic lesion, one of which was seen in our institution in 1992.

The laughter in gelastic seizures has been described as unnatural, mechanical, mirthless, bubbling, and sometimes mimicking a normal one [3]. Gelastic epilepsy, on the other hand, is often differentiated from gelastic seizure through the presence of an epileptogenic lesion called hypothalamic hamartoma. In the absence of this lesion, seizures are said to arise from frontal and temporal lobes [3]. The onset of seizure is in the first year of life in approximately 85% of cases. Some cases can begin in early to mid-childhood. There is no sex predilection, and most cases are sporadic [2].

CASE REPORT

A 7-year-old right-handed male, who was initially seen at the Telemedicine OPD of our institution, came in with a chief complaint of uncontrollable and inappropriate laughing spells. The history

started six weeks prior to consult, when the patient was observed to exhibit brief episodes of laughter usually occurring three to five times daily, lasting for five to ten seconds. He was reported to be aware during the episodes since he could communicate with his mother while attacks were ongoing. The mother also reported that there were no triggers or events preceding these bouts of laughter and would occur anytime during the day while doing his daily activities. The episodes were initially regarded as attention-seeking behavior since the patient was naturally mischievous as described by the mother.

Five weeks PTC, the sudden outbursts of laughing episodes would now occur more frequently around five to ten times per day and were longer in duration, lasting for ten to twenty seconds. The episodes are now also seen to occur in sleep. The parents were still able to talk to him during these episodes, hence they still attributed it to his naughty behavior, and no consult was done. When asked, the patient verbalized that he cannot control the said outbursts of laughter but is aware that the laughter was happening.

Four weeks prior to consult, the laughing spells were followed by left versive gaze, and head deviation to the left, occurring for ten to twenty times per day with the same duration. The episodes were noted to occur more frequently in wakefulness than in sleep. During this time, the patient started to have complaints of dizziness after each episode but would resolve spontaneously after fifteen to twenty minutes.

Two weeks prior to consult, there was a further increase in the frequency of the episodes, occurring twenty to forty times per day of the same duration. The left versive gaze and head deviation to the left were now accompanied by truncal rotation towards the left, and insuppressible body movements such as rolling on the floor, bipedal kicking, and throwing hand movements. He had preserved consciousness on all the attacks and there was no post laughter confusion or dysphasia. Somatosensory symptoms such as numbness or prickling or tingling sensations were also noted.

The increase in frequency of the episodes and its occurrence even in sleep prompted consult at our institution via telemedicine. During the consult, the patient had approximately 10 brief episodes of sudden outbursts of laughter with hyperkinetic movements which prompted referral to Neurology service for proper evaluation and management. The patient was seen by the Neurology fellow on the same day via video call and was noted to have another two episodes of the same laughing spell and associated body movements. Based on the clinical presentation of the patient, gelastic seizure was considered. The seizure episodes occurred in a stereotypic fashion in the absence of any triggers. He was started on carbamazepine at 10 mg/kg/day and an EEG and cranial MRI were advised. Seizures decreased from 48 to 35 times per day during the one-week medication. Follow-up was done after, and seizures were noted to occur in clusters, with 10 seizure episodes in 1 cluster. Due to this, carbamazepine dose was increased to 15 mg/kg/day with note of

decreasing episodes each day. After another week, the patient attained a seizure-free status.

The patient was born to a 22-year-old, gravida 1 parity 1, with regular pre-natal check-up at a lying-in clinic and regular intake of ferrous sulfate and multivitamins. He had no illness, infection, bleeding, or any feto-maternal complications during the perinatal and post-natal course. He was delivered full term via normal spontaneous delivery at a lying-in clinic assisted by a midwife. The labor lasted for 3 hours without difficulty in delivery. There was no cord coil, meconium-stained amniotic fluid, or premature rupture of membrane. He had good cry and activity at birth, with a birthweight of 3 kilograms. Physical examination was unremarkable with no note of dysmorphism, cyanosis, pallor, jaundice. Newborn screening was normal. Hearing screening was not done. The patient had an unremarkable neonatal course. The developmental history was unremarkable as well. At present, he is a Grade 2 student on modular type of learning and adapted well with this new type of learning modality. However, there was a note of hyperactivity and inattentiveness during his previous school years described as inability to complete tasks and follow instructions.

In the succeeding month, the patient was seen by the Neurology service for follow-up. Seizures were controlled at 15 mg/kg/day. EEG revealed focal epileptiform discharges coming from the right frontal region which appear to evolve and spread to the right frontopolar, frontocentral parietal and the midline frontal and central regions lasting for 32 to 50 seconds in duration seen during sleep. No clinical event was seen. The EEG was consistent with a focal epilepsy coming from the right frontal hemisphere. Carbamazepine assay revealed normal results (22.7 umol/L) (NV16.9-50.8 umol/L). He had good compliance with medications and seizures were controlled. No adverse reactions were noted.

After another month, the patient came in for clearance prior to MRI. He was seen awake and comfortable with stable vital signs. Physical examination was unremarkable. There were no signs of early maturity such as change in body habitus, appearance of axillary, facial, and pubic hair, and deepening of voice. Sexual maturity is appropriate for age (Tanner stage 1). Neurologic examination was unremarkable as well. The patient was kempt at the time of the examination, dressed appropriate for age and sex. He had good eye contact and normoproductive speech. He had euthymic mood and appropriate affect with no disturbance in though content, good insight, judgement, and abstract thinking. The cranial nerves were intact. There were no sensorimotor or cerebellar deficits. Reflexes were 2+ on all extremities and there were no meningeal signs of irritation. The cranial MRI revealed unremarkable results and no hamartomas were seen. Seizures were controlled in the succeeding months, and he was able to do his usual activities.

DISCUSSION

Laughter is a normal physiologic response. It becomes pathologic when it is

inappropriate to the emotional context. In this manner, laughter can be deemed as seizure equivalent and are referred to as gelastic seizures. A seizure is considered as gelastic in the presence of the following criteria: stereotyped recurrence, absence of external precipitants, concomitant manifestations accepted as epileptic, interictal EEG findings, and absence of conditions that can cause pathologic laughter. In our patient, all the mentioned conditions were evident hence a gelastic type of seizure was entertained.

Gelastic seizures are most seen in association with benign malformations arising from the hypothalamus. This lesion is called hypothalamic hamartoma which was first described by Berkovic et al. in 1988, calling it "early-onset gelastic epilepsy, hypothalamic hamartoma, and precocious puberty syndrome." This syndrome frequently causes a severe epileptic encephalopathy resistant to antiepileptic treatment [4]. Seizures originating from hypothalamic hamartoma typically begin in infancy with an average of 10 months at presentation [5]. The clinical course is often progressive and evolves into a more complex seizure disorder. Cognitive regression or behavioral abnormalities such as impulsiveness and aggression may ensue. Precocious puberty is also a significant finding in majority of cases. On imaging studies, T2-weighted MRI scans would show a hypointensity in the presence of a hypothalamic hamartoma, while T1-weighted images would show hyperintensity [5]. EEG findings are associated with an ictal discharge originating from the hamartoma itself. The seizures in the setting of this tumor are intractable by nature but may improve significantly with surgical intervention. In more than 50% of patients, the excision of the lesion has been found to control seizures and improve behavior and cognition [6]. In our patient, the MRI scan did not show hypothalamic hamartoma or any other possible structural lesion. The patient had no pertinent examination that would reveal precocious puberty, and developmental history was also at par with age.

In some cases, such as in our patient, a hypothalamic hamartoma was not seen on workup. Gelastic seizures not associated with this lesion present as part of a frontal or temporal lobe epilepsy. They are said to originate from the anterior lobe, particularly from the basal temporal cortex, the lateral temporal convexity, the cingulate gyrus, and the mesial frontal lobe. [1]. Semiological studies have shown that gelastic seizures arising in the temporal lobe are mirthful in quality whereas those of frontal lobe origin are mirthless [7]. In addition to this, temporal lobe seizures are described to have slower onset and progression. Associated automatisms and post-ictal confusion are also common and are often longer in duration [8]. Frontal lobe seizures, on the other hand, occur in brief episodes with abrupt and explosive onset and rapid progression. The attacks are also associated with hyperkinetic movements, bipedal automatisms, somatosensory symptoms, and loud vocalization [8]. Our patient presented with hyperkinetic movements with interictal EEG findings consistent with a focal epilepsy coming from the right frontal lobe, supporting our diagnosis of a gelastic

seizure associated with frontal lobe epilepsy. A similar case was reported by San Martin et al. in 2002 describing a 35-year-old man who had daily spells of sudden unmotivated laughter attacks which were occasionally complicated by forced head version towards the right. The cranial imaging did not show a structural lesion while EEG results illustrated ictal patterns arising from the left anterior lobe and left frontal lobe implying that there are symptomatogenic areas for ictal laughter present in the frontal and temporal lobes.

The diagnosis of gelastic seizures is made based on the character of the seizure and confirmed by cranial imaging and EEG. Cranial MRI is the imaging of choice and reveals the presence of a lesion on the hypothalamus. Although some epileptogenic lesions in the form of cavernous hemangioma or focal cortical dysplasia have been reported, the exact incidence of the occurrence of these lesions in association with gelastic seizures is not well established [1]. Electroencephalogram (EEG), on the other hand, confirms whether the pathological laughter has an epileptic basis. In the presence of a hypothalamic hamartoma, it is used to evaluate the degree of epileptic progression. However, studies have shown that it has little benefit in distinguishing between patients with and without hypothalamic hamartoma [7].

The management of gelastic seizures, like any other disease, is directed at the underlying condition or syndrome. In confirmed cases of hypothalamic hamartoma, resection usually has good control of seizures. In the absence of this lesion, seizures are commonly benign in course and are typically controlled with one to three anti-epileptic drugs used in focal seizures including Carbamazepine, Lamotrigine, Clobazam, Lacosamide, Levetiracetam, Oxcarbazepine, and Topiramate [12]. There is currently no established report that states the individual efficacy of the mentioned AEDs used in gelastic seizure. In our patient, seizures were controlled using a single AED, namely carbamazepine at 15mg/kg/day.

Thorough investigation using imaging and electrophysiological methods is required to obtain a diagnosis and develop a treatment plan. The main goal of treatment is to liberate the patient from seizures so that he can live a normal social life, and avoid tumor progression, recurrence, and possibly permanent neurological sequelae [9]. In the presence of a hypothalamic hamartoma, prognosis for seizure control and social adaptation is poor unless complete surgical resection is performed. The transcallosal anterior interforniceal technique is currently the most effective surgical approach. Other novel approaches such as endoscopic technique and gamma knife have also been employed with success. Surgical complications are uncommon but may result to third nerve paresis, hemiparesis, appetite stimulation and weight gain, transient hypersomnolence and hyperthermia, and transient endocrine abnormalities such as hypothyroidism and diabetes insipidus. Surgery should be performed as early as possible to minimize long-term cognitive impairment and behavioral disturbances associated with potentially catastrophic condition [11]. According to Zenteno et al.,

in patients who underwent complete resection of hypothalamic hamartoma, 52% to 54% become seizure free and 24% to 35% have more than 90% seizure reduction. On the other hand, for patients without a hypothalamic hamartoma, prognosis is more favorable since seizures follow a benign course and are more responsive with AEDs. Most cases of pure gelastic seizure achieve a seizure free status despite being off from AEDs for an average of 3 to 5 years [13].

SUMMARY

This case presented a 7-year-old male with recurrent attacks of inappropriate and unprovoked laughter with preserved consciousness and no associated autonomic dysfunction. Diagnosis was established with the clinical and EEG findings results typical for gelastic seizure. Cranial MRI failed to demonstrate a lesion denoting that the seizure is part of an anterior lobe epilepsy and not gelastic epilepsy that is associated with a hypothalamic hamartoma. Physical and neurologic examination were unremarkable. Findings of poor prognosis such as intractable seizures, precocious puberty, and cognitive and behavioral impairment were not seen. The patient is currently on carbamazepine at 5.14 mg/kg/day with seizure control for 6 months now.

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