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Clinical Profile of Pediatric Patients with Neural Tube Defects in a Tertiary Hospital in Davao City, Philippines: A Five-Year Retrospective Study

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Abbreviations

NTD	Neural Tube Defects
WHO	World Health Organization
DOH-ENHR	Department of Health-Essential National Health Research
UP	University of the Philippines
PGH	Philippine General Hospital
CSF	Cerebrospinal fluid

Abstract
Objectives: The study aimed to describe the clinical profile of pediatric patients with Neural Tube Defects (NTDs) in a tertiary hospital in Davao City from January 2014 – January 2019. **Methodology:** The study used retrospective descriptive research design through chart review in the Medical Records Section of a tertiary hospital in Davao City. Pediatric patients 0 to < 19 years old with final diagnosis of neural tube defects and/or its types admitted from January 2014 to January 2019 were included.**Results:** The main outcome measures of the study were demographic profile of NTD, maternal risk factors, associated congenital anomalies and its outcome. Majority (41%) of NTDs seen from January 2014 to January 2019 were newborns 0-day old presenting with open type of NTDs, 68% of them died before 24 hours of life. The median maternal age upon delivery is between 19 to 34 years old. Its occurrence in both sexes were equally distributed. Maternal infection (24%) followed by poor prenatal check – up (20%) were the identified maternal risk factors for the defect. Teenage mothers have a significant increased risk of having a child with NTD. Cases seen were mostly located in the cranium. Seventy-four percent (74%) of cases reviewed had open type NTDs with myelomeningocoele as the most common subtype. Sixty percent (60%) of the cases were discharged alive but suffered from complications, of which hydrocephalus is the most common. Among the 49 mothers sub-grouped based on history of prenatal intake of folic acid, it revealed that none to poor intake of folic acid is proportional to mothers with poor prenatal check – up. These non - takers of folic acid also have five times chance of bearing anencephalic child. **Conclusion:** This study supported the government's mandate on maternal health and nutrition during pregnancy. With NTDs' high mortality rate and debilitating complications, multidisciplinary management approach and intensification of health prevention strategies are needed to improve the quality of life of every child.
Keywords: Neural Tube Defects, Congenital Anomalies, Folic Acid
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1. Introduction

World Health Organization (WHO) describes birth defects as congenital malformations, deformations, and chromosomal abnormalities that may be structural or functional in origin presenting at birth. Birth defects are life-threatening often ending in long-term morbidity. Affected individuals and their families are burdened by the negative impact on the community, healthcare systems, and society [1]. Currently, more than 7,000 different birth defects were studied. Mostly are genetic or partially genetic in origin occurring pre- or post-conception and more than half of the cases have no identifiable cause. Maternal health such as exposure to infectious disease is also among the crucial factors most especially in low and middle-income countries. Several factors that may cause birth defects are maternal illness, micronutrient deficiencies especially iron and iodine, exposure or illicit drug use, selected environmental chemicals, and high doses of radiation [1].

Yearly, 7.9 million children are born with debilitating birth anomalies accounting for 6% of total births worldwide. In a 2000-2013 WHO report, out of 2.761 million deaths in children, an estimated 276,000 were caused by congenital anomalies. The severity of the impact of this global problem is reflected more in third world countries like the Philippines where birth defects have remained in the top 10 causes of deaths over the last 50 years. [1] A

pilot study was conducted by the Department of Health - Essential National Health Research (DOH-ENHR) with the Institute of Human Genetics - National Institutes of Health in 1999-2000 involving 79 hospitals which showed that Neural Tube Defects (NTD) ranked 6th. A review of records of admitted patients from 1996-2000 at the Philippine General Hospital (PGH) showed that NTDs Ranked 9th [2]. However, there is no formal birth defects registry identified by the national health statistics.

Neural tube defects affect 0.5-2 per 1000 pregnancies worldwide. It occurs because of a defect in the neurulation process that normally occurs during the third to fourth week of fetal life. Defects of the neural tube encompass a wide range of congenital spine and spinal cord defects involving the imperfect development of the neuropore during embryogenesis and the subsequent maldevelopment of the adjacent bone and mesenchymal structures. These lesions can involve any part of the spine, although they most often involve the lumbosacral spine, and range from a simple gap in the lamina of a single vertebral level to an extensive dorsal opening with an exposed spinal cord. [3, 4]

This study aimed to provide an overview of the prevalence of NTDs among pediatric patients seen at a tertiary hospital in Davao City from January 2014 to January 2019. It also aimed to present the profile of pediatric patients with neural tube defects in terms of clinical and demographic characteristics, maternal risk factors and behaviors during pregnancy, other associated congenital anomalies or deficits with the defect, and outcome of the defect. Because birth defects are a major cause of under 5 - mortality, adequate surveillance data are needed for the prevention and evaluation process, particularly for NTDs that have well-established interventions.

2. Methodology

The study was conducted using retrospective descriptive research design. Patients' charts were retrieved from the medical records department of a tertiary hospital in Davao City. Patients' information was gathered and analyzed. Data collected were admissions and cases from January 2014 to January 2019. Patients with discharged final diagnosis of NTD and/or its different types such as: encephalocoele, meningocoele, myelomeningocole, anencephaly, or spina bifida occulta, from the pediatric age group 0 to < 19 years old seen or admitted were included. Purposive sampling in selecting the study participants was used. After all data were collected, these were entered in the Data Collection Sheet. The hospital reference number was used as patient code to protect the patient's personal information. The data collected were encoded in an Excel file and subsequently analyzed.

The clinical and demographic profiles were analyzed using descriptive statistics such as mean and standard deviation for numerical data and, frequency and percent for categorical data. In the presence of other associated congenital anomalies or comorbidities, the same technique was used in the analysis of the demographic profile. The multivariate odds ratio was calculated to determine the associated risk factors with having NTDs. The outcome was reported as frequency and percentage.

3. Results and Discussion

A total of 93 cases were assessed for eligibility of the study. However, only 80 cases were qualified. The remaining 13 charts excluded were cases admitted more than once or charts not retrieved by the medical records.

Table 1. Demographic and Clinical Characteristics of Patients with Neural Tube Defect

Characteristics	Values
Maternal age, Median (IQR)	26 (23-31)
Below 19 yo	8 (10%)
19 yo to 34 yo	42 (53%)
35 yo to 44 yo	9 (11%)
45 yo and above	2 (3%)
Not reported	19 (24%)
Patient's age, Median (IQR)	1 (0-60)
0 days	33 (41%)
1 - 7 days	24 (30%)
8 - 60 days	6 (8%)
More than 60 days	17 (21%)
Patient's sex	
Male	41 (51%)
Female	39 (49%)

Characteristics	Values
Prenatal Intake of Folic Acid	
Yes	26 (33%)
No	23 (29%)
Not reported	31 (39%)
Family History of Neural Tube Defect	
Yes	3 (4%)
No	46 (58%)
Not reported	31 (39%)
Prenatal Illness/Condition	
Maternal infection	19 (24%)
Teenage Pregnancy	8 (10%)
Poor Prenatal	16 (20%)
Multiparity; Elderly Gravid	4 (5%)
Hypertension	3 (4%)
Others	7 (9%)
None	23 (29%)
Maternal Drug Use/Exposure	
Yes	5 (6%)
No	21 (26%)
Not reported	54 (68%)
Type of Neural Tube Defect	
Close	21 (26%)
Open	59 (74%)
Subtype of Neural Tube Defect	
Myelomeningocoele	22 (28%)
Anencephaly	19 (24%)
Meningocoele	14 (18%)
Encephalocoele	10 (13%)
Meningoencephalocoele	8 (10%)
Hydraencephaly	5 (6%)
Spina Bifida Occulta	1 (1%)
Lipomyelomeningocoele	1 (1%)
Location of Neural Tube Defect	
Cranial	48 (60%)
Spinal	32 (40%)

The demographic and clinical profile of pediatric patients with NTDs admitted at a tertiary hospital in Davao City are shown in table 1. It revealed that the median maternal age upon delivery of patients with NTD is twenty-six (26). Fifty-three percent were mothers 19 to 34 years old, 11% delivered at 35 to 44 years old, 8% were teenage mothers less than 19 years old and 3% had their child above 45 years old. The mean age of patients with NTD was 1 day old. Forty-one percent, 41% (n=33) were newborns 0 day old, 30% (n=24) were 1 day to less than 1 week old, 21% (n=17) were aged 60 days old and above, and the remaining 8% (n=6) were infants aged 8 – 60 days old. There was no sex predilection on the prevalence of NTDs, 51% (n=41) were males and 49% (n=39) were females.

Prenatal maternal history of folic acid intake is a significant data in this study. It showed 33% (n=26) of mothers were taking folic acid during the first trimester of pregnancy while 29% (n=23) were not. But, 39 mothers have lacking information in terms of prenatal folic acid intake in their record.

Fifty-eight percent, 58% (n=46) of respondents reported no family members having the same defect as the index case, and 4% (n=3) have a family history of NTD. On the other hand, chart reviews of the 39% (n=31) of cases lack data indicating a family history of NTDs.

Predisposing prenatal conditions to bear a child with NTDs identified in this study were the following: prenatal maternal infection (24%), poor prenatal check-up (20%), teenage pregnancy (10%), multiparity (5%), hypertension (4%), and 9% have other associated risk factors such as diabetes, maternal hemorrhage, and oligohydramnios. Among these mothers, 26% (n=21) have no history of intake of teratogenic drugs nor roentgen exposure in contrast to the 6% (n=5) of the population claiming a history of smoking, exposure to fertilizers, and taking oral contraceptives during pregnancy. Seventy percent, 70% (n=56) of mothers; again, did not divulge their history of drug use and exposure on review of charts.

NTDs generally can be an open type or closed type. Results showed 74% (n=59) were open type and 26% (n=21) closed type. Myelomeningocele (28%) was the most common case followed by anencephaly (24%), meningocoele (18%), encephalocoele (13%), meningoencephalocoele (10%), hydraencephaly (6%), spina bifida occulta (1%), and lipomyelomeningocoele (1%). In terms of location, 48 (60%) of the cases were located in the cranium while 32 (40%) were defects of the spine.

Table 2. Demographic, Clinical Characteristics, Maternal Risk factors and Type of Neural Tube Defect

	Type of Neural tube defect		
Characteristics	**Closed**	**Open**	**p-value**
Maternal age, Median (IQR)	23 (17 - 31)	26 (23 - 36)	0.124
19 yo below	4 (31%)	4 (8%)	0.214
19 yo to 34 yo	7 (54%)	35 (73%)	
35 yo to 44 yo	2 (15%)	7 (15%)	
45 yo and above	0 (0%)	2 (4%)	
Not reported	8 (38%)	11 (19%)	
Patient's Age, Median (IQR)	4 (1- 210)	1 (0 - 8)	0.024
0 days	5 (24%)	28 (47%)	0.036
1 - 7 days	8 (38%)	16 (27%)	
8 - 60 days	1 (5%)	5 (8%)	
More than 60 days	7 (33%)	10 (17%)	
Patient's Sex			
Male	12 (57%)	29 (49%)	0.543
Female	9 (43%)	30 (51%)	
Prenatal Intake of Folic Acid			
Yes	6 (29%)	20 (34%)	0.784
No	5 (24%)	18 (31%)	
Not reported	10 (48%)	21 (36%)	
Family History of Neural Tube Defect			
Yes	0 (0%)	3 (5%)	0.651
No	13 (62%)	33 (56%)	
Not reported	8 (38%)	23 (39%)	
Prenatal Illness/Condition			
Maternal infection	4 (19%)	15 (25%)	0.584
Teenage Pregnancy	4 (19%)	4 (7%)	0.0423
Poor Prenatal	3 (14%)	13 (22%)	0.682
Multiparity; Elderly Gravid	1 (5%)	3 (5%)	0.201
Hypertension	1 (5%)	2 (3%)	0.532
Others	3 (14%)	4 (7%)	0.682

	Type of Neural tube defect		
Characteristics	**Closed**	**Open**	**p-value**
None	5 (24%)	18 (31%)	0.714
Drug use/Exposure			
Yes	1 (5%)	4 (7%)	0.1453
No	3 (14%)	18 (31%)	
Not reported	17 (81%)	37 (63%)	
Location of Neural Tube Defect			
Cranial	11 (52%)	37 (63%)	0.4208
Spinal	10 (48%)	22 (37%)	

Note: p-value <0.05 means significance

Results of this study showed that patient's sex, family history of NTD, maternal age, prenatal intake of folic acid, drug use/exposure, and the clinical location of the NTD, all do not affect either type of NTD. However, the patient's age at birth (0 day old) was statistically correlated with open type NTD. According to maternal illness or condition, teenage mothers have 0.115 times more likely to have open type NTD, signifying statistical relevance.

Table 3. Associated Congenital Anomalies or Deficits with the Defect

Common Congenital Anomalies	**n (%)**
Hydrocephalus	24 (30%)
Musculoskeletal Problems	16 (20%)
Agenesis of Corpus Callosum	11 (14%)
Seizures	10 (13%)
Genitourinary Problems	9 (11%)
Microcephaly	9 (11%)
Arnold Chiari Malformation	9 (11%)
Facial Anomalies	6 (8%)
Subependymal nodules	5 (6%)

Same with most of the studies 30% of the cases have associated hydrocephalus. Others manifest with musculoskeletal problems (20%) like inability to walk, seizures (13%), genitourinary problems (11%) presenting as neurogenic bladder, microcephaly (11%), and facial anomalies (8%) including cleft lip/palate or low set ears. On imaging, 14% were noted with associated agenesis of corpus callosum, 11% with Arnold Chiari Malformation and 6% have subependymal nodules.

Among these cases, 48 (60%) were discharged alive, 20 (25%) succumbed to death and 12 cases (15%) went home against medical advice after appraisal for neurosurgical intervention.

Table 5. Demographic, Clinical Characteristics, Material Risk factors and Intake of Folic Acid

	Prenatal intake of folic acid		
Characteristics	**Yes**	**No and Not mentioned**	**p-value**
n (%)	26 (33%)	54 (68%)	
Maternal age, Median (IQR)	28 (20 - 41)	22 (18 - 30)	0.012
19 yo below	1 (4%)	7 (13%)	0.142
19 to 34 yo	12 (46%)	30 (56%)	
35 to 44 yo	3 (12%)	6 (11%)	
45 yo and above	1 (4%)	1 (2%)	
Not reported	9 (35%)	10 (19%)	
Patient's age, Median (IQR)	1 (0- 60)	1 (0 - 60)	0.165
0 days	10 (38%)	23 (43%)	0.142
1 - 7 days	9 (35%)	15 (28%)	
8 - 60 days	0 (0%)	6 (11%)	

	Prenatal intake of folic acid		
Characteristics	**Yes**	**No and Not mentioned**	**p-value**
More than 60 days	7 (27%)	10 (19%)	
Patient's sex			
Male	12 (46%)	29 (54%)	0.176
Female	14 (54%)	25 (46%)	
Family History of Neural Tube Defect			
Yes	0 (0%)	3 (6%)	0.265
No	20 (77%)	26 (48%)	
Not reported	6 (23%)	25 (46%)	
Prenatal Illness/Condition			
Maternal infection	7 (27%)	12 (22%)	0.542
Teenage Pregnancy	1 (4%)	7 (13%)	0.494
Poor Prenatal	3 (12%)	13 (24%)	<0.01
Multiparity; Elderly Gravid	1 (4%)	3 (6%)	0.142
Hypertension	2 (8%)	1 (2%)	0.163
Others	3 (12%)	4 (7%)	0.162
None	9 (35%)	14 (26%)	0.341
Maternal Drug Use/Exposure			
Yes	2 (8%)	3 (6%)	0.142
No	15 (58%)	6 (11%)	
Not reported	9 (35%)	45 (83%)	
Type of Neural Tube Defect			
Close	6 (23%)	15 (28%)	0.775
Open	20 (77%)	39 (72%)	
Subtype of Neural Tube Defect			
Myelomeningocoele	9 (35%)	13 (24%)	0.251
Anencephaly	2 (8%)	17 (31%)	0.021
Meningocoele	5 (19%)	9 (17%)	0.529
Encephalocoele	5 (19%)	5 (9%)	0.193
Meningoencephalocoele	3 (12%)	5 (9%)	0.769
Hydraencephaly	1 (4%)	4 (7%)	0.494
Spina Bifida Occulta	1 (4%)	0 (0%)	0.921
Lipomyelomeningocoele	0 (0%)	1 (2%)	0.962
Location of Neural Tube Defect			
Cranial	13 (50%)	35 (65%)	0.152
Spinal	13 (50%)	19 (35%)	

Above Table (Table 5) was subcategorized to depict the proportion of the population (49 mothers) who declared their history of intake or no intake of prenatal folic acid based on the clinicodemographic characteristics and the distinguished maternal risk factors.

The study showed that intake of folic acid during pregnancy is not related to patient's age, sex, family history of NTDs, maternal drug use and exposure, and the clinical characteristics of NTD. Among the mothers, the median maternal age implied a statistically significant value indicating younger mothers tend not to take folic acid during pregnancy. This is also reflected by the statistically significant value of <0.01 on maternal poor prenatal check–up, connoting that mothers who do not take folic acid also had poor prenatal check–up. Lastly among the NTD subtypes, it revealed non-takers of folic acid have a 5.013 times or higher chance to have a child with anencephaly.

The Philippine Birth Defects Registry Project concluded in a study in 1999-2000 that anencephaly and its similar malformation belong to the top 10 leading congenital anomalies in the Philippines [39]. This data is supported by a records review in UP– PGH in 1996-2000 declaring NTDs ranked 9th [2]. Despite this gathered information, the journey in creating a baseline monitoring system for birth defects in a developing country such as the Philippines has been a challenge because data became individualized and may not be reflective of the real score. Moreover, prevention strategies in health, policies, and program implementation reached a low coverage, especially in far-flung areas. Indeed, the outcome of this research will be instrumental in addressing urgent public health concerns and will pave the way for more research and promising output.

The prevalence of neural tube defects in a tertiary hospital in Davao City is estimated at two to three cases per 1000 population [40]. As the only government tertiary hospital, majority of the patients reside in low-income communities and are dependent in the government's medical and social assistance. A similar study in Lagos mentioned 73% of the mothers of NTD patients belong to the low socioeconomic class [41]. In an urbanized area like Davao region where 58% of the study population lives, the result is alarming thus must be given immediate regard. Although 38% of the cases were rural settlers, the variation in prevalence carries the same burden in our healthcare system.

Majority of study participants were first seen and diagnosed in less than 30 days old, with a median age of 1 day old. This is similar to a study by Venkatesh K. L. in 2017 where 73% presented in the neonatal age group [42]. Contrary to many worldwide studies that showed female predominance, this study and that of Basma et al. from Sudan and LoTilla from UP-PGH showed no significant gender difference between males 51% and females 49% [16, 17]. However, it supported the study among Sudanese linking maternal age younger than 35 as the high-risk age group for NTD. This is ascribed to defective hyaluronate metabolism resulting to vertebral failure [16].

The development of the neural tube is a systematic process with significant genetic component modulated by a host of environmental factors. It can present as gene-gene, gene-environment, and gene–nutrient interaction [18]. Several studies mentioned the role of genetics and family history in the pathophysiology of the disease [12, 18, 42]. In this study, three parents gave history of a relative with NTD but none on a previously affected child. Hence genetic correlation was not assessed. Opposition to the PGH study linking maternal history of smoking, intake of various therapeutic drugs, and roentgen exposure to NTD [17, 20], 26% of the mothers of affected children denied smoking during pregnancy and were not taking anti-seizure drug. However, this part in the results is inconclusive of the population because a significant 68% did not declare their history. Literature also discussed the association of maternal fever and hyperthermia in the first trimester of pregnancy with NTD [18, 43, 44, 45]. Yet only one study by Golalipour et al. in Northern Iran mentioned an association of maternal infection specifically helicobacter pylori and NTD [46]. Studies on maternal respiratory and urinary tract infections manifested by mothers in this study are an open book for further investigation as limited data are linking these infections with NTD except for one study in Sudan relating the defect with UTI [16]. Chronic maternal diseases such as diabetes, overweight, and obesity were also established to cause a manifold increase in the incidence of NTD [18, 19]. This is in contrast to the study result where only 1 mother declared maternal diabetes, while maternal pregnancy body mass indexes were not extracted in patients' history. Albeit its multifactorial causes, it is apparent that 70% of open neural tube defects can be prevented by periconceptional folic acid [47]. The outcome of this preventable anomaly is reflective mostly on teenage mothers who tend not to take folic acid and had poor prenatal check–ups. They likewise have five times risk of having a child with anencephaly.

Cranial defects account for 60% of the location of NTD. This supported the Philippine data in UP-PGH but defied most of the international studies [16-17]. Neural Tube Defects are broadly categorized based on whether the cranium or spinal cord is covered or not. Identical to literature in Sudan, United Arab Emirates, and India, [16, 18, 42, 48] open type cases were regarded in 74% of the reported NTD, of which myelomeningocoele sac (28%) was the most common subtype followed by anencephalic newborn (24%) delivered in the hospital's delivery room. The result is in contrast to the 2017 Philippines study where nasoethmoidal meningocoele was more common. There is paucity of data on the incidence of spina bifida occulta to 1% considering it as the most common closed type NTD. Similar to the results of several researches on the most common location of spinal defects, [16, 42, 48] 54% were located in the lumbosacral area, followed by the sacral and thoracolumbar. Cerebrospinal fluid (CSF) leakage complicated the overlying skin of some patients predisposing them high risk to acquire infection. [16, 48] CSF leakage was reported in 54% of the study cases.

Clinical and/or imaging findings of hydrocephalus were the most common associated congenital anomaly in 30% of cases. Result is similar to the literature gathered from international and national sources [16, 17]. Fifty – nine percent of the myelomeningocoele cases in this study were accompanied by hydrocephalus. For caudal defect, motor weakness in the form of clubfoot presents in 20% and neurogenic bladder with associated recurrent urinary tract in 11%. Fourteen percent of the cases had associated corpus callosum agenesis and findings related to Arnold Chiari Malformation in 11%. The rest of the complications mainly involved the central nervous system. Accompanying anomalies increases the risk for mortality to a significant level. Mortality was highest among

anencephalic newborns (95%) who were all delivered in the said hospital but immediately died in 24 hours of life. The same findings were noted in the 2007 study in the Philippines where 33% of the mortality was anencephaly [17]. The outcome of NTD is poorly reflective of the actual patients' status since most of the patients did not go back for follow up and 15% refused operative treatment and went home against medical advice. 60% of the open NTD otherwise were discharged alive.

Regardless of both international and national mandates in decreasing neural tube defects through maternal diet and supplementation, cases are still high, unmonitored, and not followed [27, 30]. This holds in this study, 44 (68%) of the study population revealed no intake or part of their history did not mention any. These facts thereby connote that the United Nations Millennium Development Goal 4 of reducing child mortality was not reached. The alarming results then call for review and re-emphasis of Philippines government's policy statement on the importance of folic acid intake to reduce child mortality and morbidity [30].

Globally, it is estimated that approximately 300,000 babies are born each year with NTDs, [6] resulting in approximately 88,000 deaths and 8.6 million disability-adjusted life years [7, 8]. In low-income countries, NTDs may account for 29% of neonatal deaths due to observable birth defects [9]. The burden of this worldwide dilemma is highest among South East Asian countries.

In a five–year review of cases referred to the Genetics Clinic, PGH for findings of congenital anomalies on prenatal ultrasound by Abarquez, Conchita et. al in 2009, CNS abnormalities contributed almost half of all cases. Neural tube defects, particularly anencephaly and encephalocele, were the next most commonly detected CNS malformation after hydrocephalus. Many are invariably lethal with about half of the cases dying in utero, and the remainder either die in the newborn period or live to undergo several surgeries or suffer various neurologic sequelae [10]. In general, there are no available local data on the prevalence and profile of neural tube defects in Davao City. This hospital in Davao City is a good venue to review these cases because of its large population. It a government hospital under the Department of Health of the Republic of the Philippines [11].

3.1 Etiology and Risk factors

According to the National Institute of Child Health and Human Development, the exact cause of neural tube defects is not known. Genetics plays a role in some cases; the risk increases by 2% to 5% after having one child with the defect [12]. Consanguinity was suggested to contribute to the high incidence of NTDs in most Middle Eastern countries. [13]. Studies in India and Turkey suggest female over male preponderance while data from Sudan and Philippines revealed no significant sex distribution and family history failed to reveal recurrence of the same malformation among siblings [14, 17]. Case reports and epidemiologic studies have mentioned many chemicals, various therapeutic drugs, environmental contaminants, pollutants, infectious agents, and solvents as risk factors of the defect. Maternal infection and hyperthermia, use of valproic acid during pregnancy, nutrient deficiency and excess, and chronic maternal diseases such as diabetes mellitus are implicated to cause a manifold increase in the incidence of NTD [18].

Gedefaw, Abel et. al mentioned in his article that women who had a normal or an underweight pre-pregnancy BMI were 51% less likely to have NTDs than those who were overweight or obese which has a twofold increase [19]. While in a prospective case-control study on 46 participants with NTDs, the results revealed that prenatal surveillance ($p<0.002$), multivitamin consumption ($p<0.001$), history of having a child with NTD ($p<0.001$), alcohol drinking ($p<0.014$), and passive smoking were risk factors of NTDs ($p<0.001$). [20] Neural tube defects among Filipinos in a retrospective study of 141 cases in UP PGH in May 2007 revealed maternal intake of teratogenic drugs (20%), illness during the first trimester (3%) and roentgen exposure during pregnancy (2%) are risk factors of the defect [17].

3.2 Types and Location

The neural tube is formed from the migration and fusion of the neural plate; hence, the type and severity of malformation vary based on the location of the defect. It ranges from a defect in the brain, spine, or spinal cord. Nir Shimoni classifies NTDs based on embryological considerations and the presence or absence of exposed neural tissue. It is divided into either "open" or "closed". Open NTDs representing 80% of all NTD's frequently involve multiple aspects of the CNS. It is due to failure of primary neurulation; thus, the neural tube fails to appropriately close along the dorsal midline completely exposing the neural tissue, or may be covered by a membrane, with associated cerebrospinal fluid (CSF) leakage [21]. Most common examples include meningocele (spina bifida), myelomeningocele, encephalocele, and anencephaly. On the other hand, closed NTDs are localized and confined to the spine and result from a defect in secondary neurulation. Neural tissue is not exposed and the defect is fully covered by dysplastic skin covering. [22].

Retrospective studies in India and Turkey had similar findings of myelomeningocoele and the lumbosacral spine as the commonest type and location of NTD [15,16]. This differs from the local Philippines data showing 31% of cases presenting with meningocoele and 73% of them presents as cranial defects [17].

3.3 Prognosis and Complication

The disabilities among survivors with neural tube defects are determined by the location and extent of the lesion and the presence of comorbidities. In general, lesions in the distal area will manifest interruption of neural function; and the higher the lesion, the greater is the neurologic deficit. Luckily if a patient survives, the major morbidities are developmental delay and the normal ambulation, and genitourinary control. Later outcome relies on perinatal management and availability of support services. In a study by Althouse and Wald in UK between 1965 to 1972, 213 patients with spina bifida were randomly selected. The 5-year survival differs among the lesions giving 36% for those with open lesions and 60% for those with closed lesions. Closed cranial lesions were further associated with severe handicap in 75% [23].

Bamforth and Baird likewise conducted a population-based study among patients with both spina bifida and hydrocephalus. They compared the life expectancy between the cases in 1962-1970 to the group from 1970-1986. At least 60% of patients showed serious disabilities. The group of patients belonging to the years between 1970 and 1986 had a striking improvement in survival until one year of age. While in between ages of 7 and 16 years, there was no difference in survival between the two cohorts [24].

The best outcomes were reported by Hunt. In the years 1963 and 1971, 117 consecutive infants with open spina bifida who had surgical repair within 48 hours of life were followed to their 16th birthday. The survival rate was 60%. Of them, fifty percent could ambulate more than 50 yards, 25% were continent, and 70% had an IQ of more than 80. On those patients with lesions at L3 or below, 75% of patients survived. Among the survivors, ambulation was not affected in 90%, 45% had intact genitourinary, and 80% had normal IQ [25].

Among Filipinos, the major additional abnormalities secondary to the NTD present in a study of 82 patients were (58%) hydrocephalus (41) and seizure (12) on patients with cranial defect while neurogenic bladder (15) and hydrocephalus (12) were seen with caudal defects. About 27% (19) patients also showed severe developmental delay. Of these cases, hydrocephalus (62%), encephalocele (37%), and microcephaly (14%) were present. Mortality was 6%, 3 (33%) were anencephalic and the remaining (66%) died of infection [17].

3.4 Role of Folic Acid

Though the etiology of NTD is multifactorial, reports show that an estimated 50-70% of these birth defects could be prevented with adequate maternal intake of folic acid [26]. The US Public Health Service and the Institute of Medicine recommended that women in their reproductive age consume 400 mcg of folic acid daily, to minimize the risk of an NTD-affected pregnancy [27]. Meanwhile, the US Food and Drug Administration intensified its goals in March 1996 on fortification of the US flour and enriched the grain supply with 140 mcg of folic acid per 100 g of grain [28]. A systematic review on the impact of flour fortification with folic acid on the neural tube by Castillo-Lacelotti et al in 2012 was thereafter made after this public health recommendation. Twenty-seven studies showed a significant reduction of NTD by 60% after fortification of flour in areas of Chile, Brazil, Argentina, Canada, Costa Rica, and USA from 1999 to 2009 [29].

In a local study, Filipino pregnant women were shown to be folate deficient and its prevalence was found to be higher in the first trimester compared to the second or third trimester. This suggests that a significant number of the subjects entered pregnancy with insufficient folate stores in their bodies. The study also reported that maternal diets were found to meet only 33.7 percent of the Recommended Daily Allowance for folate. In addition to consuming diets rich in folate, women of childbearing age in the Philippines are also encouraged to take folic acid supplements in the form of multivitamins. A daily intake of 0.4 mg of folic acid supplements is currently being recommended. This policy statement emphasizes the importance of adequate folic acid intake prior to pregnancy to reduce morbidity and mortality due to neural tube defects and presents recommendations to various sectors of society [30].

Expanding global neural tube defects prevention initiatives can support the achievement of the United Nations Millennium Development Goal 4 of reducing child mortality, a goal which many countries in South East Asia are currently not poised to reach.

4. Conclusion

Majority of neural tube defects seen and admitted at a tertiary hospital in Davao City were newborns 0 day old delivered at the hospital's delivery room and presented with open type of NTDs. Maternal infection followed by poor prenatal check-up were the identified maternal risk factors for the defect. Teenage mothers have a significant increased risk of having a child with NTD. This is associated with poor prenatal check-up and societal stigma. NTDs in this study were mostly seen in the cranium. Most cases reviewed had open-type. Myelomeningocoele is the most common subtype, followed by anencephaly.

Neural Tube Defects are preventable anomalies given adequate pre-conceptional and antenatal folic acid supplementation. Due to the weak campaign efforts in achieving NTD free Philippines, the study results call for intensification of policies on awareness of NTD prevention and improvement of the maternal and child health standards. To attain a better outcome and improve the quality of life of these children, a multidisciplinary approach

must be addressed through early detection, medical and surgical management, rehabilitation and long-term follow-up.

Declaration of conflict of interest
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