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Original article

Maternal risk factors associated with neural tube defects in Tigray regional state of Ethiopia

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Abstract

Introduction: Unlike developing countries, including Ethiopia the identification of the risk factors in decreasing the burden of neural tube defects (NTDs) is well established in the developed world. Hence, we sought to determine the factors associated with NTDs in Tigray – Ethiopia.

Methods: We undergo a case-control analysis where all NTDs cases were compared to a group of controls derived randomly from the same hospitals where cases were recruited from. The NTDs survey tool which contains a standard questionnaire was prepared. Parental socio-demographic and clinical information such, maternal age, obstetric history, illnesses, drug intake, radiation, occupation, education, history of congenital anomalies, residence, exposure to pollutants such as smoking, chemicals, paternal history, and folic acid utilization was collected and analyzed using SPSS version 20.

Result: This study has shown the maternal age, and residency, birth order 3 and 4, unplanned pregnancy, history of breastfeeding above 2 years, history of stillbirths, history of male gender predominance were found to have a strong association with an occurrence of NTDs ($p = 0.0001$). Though the binary logistic regression analysis showed no significant association in some of the risk factors such as maternal health and drug history, the frequency analysis showed they may have an impact on the incidence of NTDs.

Conclusion: This study has shown the majority of the maternal risk factors and other lifestyle patterns had a significant impact on the occurrence of NTDs. Therefore, efficient monitoring of NTDs in Ethiopia is vital, so our study could be groundwork information in Ethiopia for future programs.

Keywords: Neural tube defects; Risk factors; Maternal health; Drug history

1. Introduction

Neural tube defects (NTDs) occur while the embryonic neural tube fails to close completely, consequently damage the brain and spinal cord [1]. Worldwide, more than 10% of neonatal mortality is caused by embryological malformation of the nervous system [2]. The

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incidence of NTDs in developing countries has been reported to be up to fourfold higher than in developing ones [3]. The most usual NTDs cases are Anencephaly and spina bifida, which usually happens due to lack of the integrity of the brain and spinal cord tissues. Anencephaly is a fatal NTDs type, but babies with spina bifida often survive following surgical intervention [4]. Despite the fact that the incidence of NTDs has decreased recently in the developed nation, it still remains high in the developing world. One scientific review retrieved the incidence of the NTDs from eighteen countries in six world health organization (WHO) regions showed that overall incidence based on live births was 1.67/1000 births for total NTD incidence, 1.13/1000 births for spina bifida, 0.25/1000 for anencephaly and 0.15/1000 for encephalocele in low and middle-income countries [5]. Corresponding estimates based on all pregnancies resulting in live births, stillbirths and terminations were 2.55/1000 births for total NTD burden [5]. The majority of surviving infants require lifelong medical support [6]. In Africa, the reported incidence of spina bifida was variable, for example, in Malawi, it was 0.47/1000 births, in Cape Town, it was 1.74/1000 births, and in Sudan 3.48/1000 births [7,8,9].

It was confirmed that various factors are involved as contributors in the occurrence of the NTDs. These defects are thought to result in part from genetic susceptibility, environmental factors. However, established causative agents, including nutritional deficiency, poverty, obesity, diabetes, and medicinal drugs, account for only a small proportion of occurrence of NTDs, showed that unrecognized causative factors for NTD still remain [10,11]. Studies focused on the identifying possible risk factors involved as contributors in the occurrence of the NTDs are limited in developing countries like Ethiopia. There is no ongoing surveillance system of NTDs in Ethiopia, particularly in Tigray region. Against this background, we sought to determine the possible risk factors associated with NTDs in Tigray regional state of Ethiopia, which could be used to draw attention to the identifiable and avoidable causes. There is an urgent need to conduct this study in Ethiopia as NTDs are highly suspect in the nation.

2. Methods

2.1. Study population and sampling method

The detailed description of the study methodology has been submitted for publication elsewhere. Briefly, study subjects were recruited from the NTDs survey in eight representative hospitals of a Tigray region of Ethiopia. Out of 14,903 pregnancy outcomes assessed for the possible incidence of the NTDs during the study period, a total of 205 mothers who born infants with NTDs were registered during of the study period in October 2016 to June 2017. For the purposes of this study, we used an unmatched concurrent case-control analysis where all cases were compared to a group of controls derived randomly from the same hospitals where cases were recruited from. Accordingly, all mothers who born infants with NTDs (n = 205) were recruited as case and 412 mothers who had a healthy pregnancy outcome recruited as controls (case: control ratio of 1:2).

2.2. Data collection tools

The NTDs survey tool which contains a standard interviewer questionnaire was prepared. The sociodemographic and clinical information on the study participants, for example, maternal age, obstetric history, history of medical illnesses, drug intake, exposure to radiation, occupation, level of education, history of congenital anomalies in the family, history of NTDs, residential area, maternal exposure to pollutants such as smoking, exposure to herbicides or pesticide, paternal history, and history of periconceptional folic acid supplementation were collected But, paternal history was obtained from their wives as secondary information.

2.3. Data collection techniques and quality assurance

To ensure clarity of the prepared questionnaire, our survey tool was pre-tested by the trained research assistants with the minimum academic qualifications of a Diploma in midwifery at general pediatrics wards and pediatric care unit and labor ward in the Ayder Comprehensive Specialized Hospital, which is the main teaching hospital of Mekelle University College of Health Sciences and the tertiary referral hospital for the Tigray region as well as Northern Ethiopia. Each participant evaluated one normal and one NTD patient for which the survey form was completed. Issues of language and comprehension by the examiner and the examinee where collected. As a result, the form was revised in ten questions based on the examiner's observations.

2.4. Statistical data analysis

Subjects were assigned numbers as information was collected. The data collected was sorted, coded and analyzed using SPSS version 20 software for analysis. Bivariate logistic regression analyses were done so as to identify factors associated with neural tube defects. The P-value of less than 0.05 were considered statistically significant.

2.5 Ethical approval

Appropriate consent was obtained from Mekelle University, College of Health Sciences; Health Research

Ethics Review Committee (ERC 0837/2016). For purposes of obtaining an informed consent of the respondents, every mother, on an individual basis, was furnished with detailed information concerning the research, including the research objectives, benefits and the importance of Mothers participation. It was clarified that the choice to participate in the research was completely voluntary and Every mother/caretaker, even after giving consent to participate, shall retain the right to opt out of the research, any time they feel like without repercussion against them. All information obtained was strictly being kept confidential and were only being used for purposes of the said research. A respondent who consents to participate were confirmed by appending her signature or thumbprint on the availed consent Form.

3. Result

3.1. Case series

Out of 14,903 pregnancy outcomes assessed for possible occurrence of the NTDs during the study period, a total of 205 mothers who born infants with NTDs were identified and recorded. The detailed clinical description of NTDs case was submitted for publication elsewhere. Briefly, the overall incidence of NTDs hence was 13.8 per 1000 pregnancy outcome. All of the pregnancy outcomes afflicted with NTDs were assessed. Their diagnoses were anencephaly in 48% (99/205), spina bifida in 47% (96/205) and encephalocele in 5% (10/205) of the cases respectively. The gestational age of the NTDs cases was classified as extremely preterm (<28 weeks) were accounted for 31.7% (65/205), very preterm (28–31 weeks) in 16.1% (33/205), moderate preterm (32–36 weeks) in 19% (39/205), an early term (37–38 weeks) 16.6% (34/205), in full term (39–40 weeks) in 12.7% (26/205), and Post term (>40 weeks) in 3.9% (8/205), of the cases, were identified at delivery rooms soon after their birth (table 1).

3.2. Case-control analysis

The study included mothers' of cases with neural tube defects (n = 205) and their controls (n = 412) (Case: control ratio of 1:2). Socio-demographic characteristics, obstetric history of participant mothers, maternal health and drug history are depicted in Tables 2–4 respectively.

The maternal age of most of the cases was age under 20 years old at 35.1%, followed by age ranging greater than 35 years old at 25.4%, 30–36 years old in 17%, age 25–30 years old in 14.1% and age 21–25 years old in 7.8% of the cases respectively. The majority of the control mothers were classed in an age 21–25 years old in 36.7%, followed by age ranging between 25 and 30 years old in 25.5%, under 20 years old in 16.5% and age ranging greater than 35 years old in 4.9%, of the controls respectively. Most of the cases lived in rural areas, while most of the controls lived in urban areas. Hence, maternal age and residency were found to have a significant association with the risk of having a child with NTDs, and the differences were statistically significant ($p = 0.0001$). The educational status of the cases was illiterately followed by attaining elementary school, high school and college and above respectively. While, most of the controls attained high school, followed by illiteracy, attended elementary school and college and above, respectively. However, the differences were not statistically significant ($p > 0.05$). None of the respondents had a practice of periconceptional folic acid supplementation. Only 4% (9/205) of the cases and 8.7% (36/412) control had taken folic acid supplementation after the second trimester of their pregnancy period. The differences in the mother's marital status, occupational status, and paternal age were not statistically

Table 1
Characteristics of cases with neural tube defects (n = 205) born in eight representative Hospitals of Tigray – Ethiopia, October 2016–June 2017.

Variable	Frequency (n)	Percentage (%)
Gestational age of the identified neural tube defects (NTDs) cases (n = 205)		
Extremely preterm (<28 weeks)	65	31.7
Very preterm (28–31 week)	33	16.1
Moderate preterm (32–36 week)	39	19
Early term (37–38 week)	34	16.6
Full-term (39–40 week)	26	12.7
Post-term (>40 weeks)	8	3.9
Type of neural tube defects (NTDs) identified (n = 205)		
Anencephaly	99	48
Encephalocele	10	5
Spina bifida	96	47
The pregnancy outcome of the identified neural tube defects (NTDs) cases (n = 205)		
Live	45	22
Stillbirth	160	78

Table 2
Socio-demographic characteristics of cases with neural tube defects (n = 205) and their controls (n = 412).

Characteristics	Frequency: n (%)		OR and (CI) 95%	P-value
	Cases (n = 205)	Controls (n = 412)		
Maternal age (years)				
<20	72 (35.1)	68 (16.5)		
21–25	16 (7.8)	151 (36.7)	0.1 (0.054–0.185)	0.001
26–30	29 (14.1)	105 (25.5)	0.261 (0.154–0.442)	0.001
31–35	36 (17.6)	67 (16.3)	0.507 (0.301–0.856)	0.011
>35	52 (25.4)	20 (4.9)	2.456 (1.330–4.533)	0.004
Marital status				
Married	188 (91.7)	376 (91.3)		
Divorced	17 (8.3)	36 (8.7)	0.944 (0.517–1.726)	0.853
Residence				
Rural	88 (42.9)	115(27.9)	1.942 (1.368–2.758)	0.0001
Urban	117 (57.1)	297 (72.1)		
Educational status				
Illiterate	70 (34.1)	109 (26.5)	2.569 (0.7–9.428)	0.155
Elementary school	53 (25.9)	78 (18.9)	2.718 (0.732–10.097)	0.135
High school	52 (25.4)	119 (28.9)	1.748 (0.473–6.455)	0.402
College and above	3 (1.5)	12 (2.9)		
Occupational status				
Housewife	139 (67.8)	217 (52.7)	1.708 (0.851–3.429)	0.132
Labor	25 (12.2)	69 (16.7)	0.966 (0.432–2.163)	0.933
Merchant	27 (13.2)	93 (22.6)	0.774 (0.351–1.705)	0.525
College educated Professional	12 (5.9)	32 (7.8)		
Took folic acid supplement prior to conception				
No	205 (100)	412 (100)		
Took folic acid supplement at any time				
Yes	After the first trimester	9 (4)	36 (8.7)	
No	196 (95.6)	376 (91.3)	2.149 (1.016–4.543)	0.045
Paternal age (years)				
<25	10 (4.9)	22 (5.3)		
26–35	94 (45.9)	227 (55.1)	0.911 (0.415–1.998)	0.816
36–45	53 (25.9)	95 (23.1)	1.227 (0.541–2.786)	0.624
>=45	22 (10.7)	25 (6.1)	1.936 (0755–4.965)	0.169
No response	26 (12.7)	43 (10.4)		

CI: confidence interval, n: number, OR: odds ratio, P value < 0.05 – considered as statistically significant.

significant between cases and controls ($p > 0.05$) (Table 2).

The maternal obstetric history, such as birth order 3 and 4, unplanned pregnancy, history of breastfeeding above 2 years, history of stillbirths, history of male gender predominance were strongly associated with risk of having pregnancy outcome afflicted with NTDs, the differences were statistically significant ($p = 0.0001$) as compared with controls. The differences in the history of the birth order below 3, history of breastfeeding not more than 2 years were not statistically significant between cases and controls ($p > 0.05$) (Table 3).

Maternal health and drug history, such as a history of herbal medicine usage, smoking, alcohol consumption, exposure to pesticide or herbicide, chronic disease, exposure to parasitic infection, exposure to radiation and source of drinking water during pregnancy showed no significant difference as compared with controls ($p > 0.05$) (Table 4).

4. Discussion

Neural tube defects (NTDs) are more prevalent in developing countries as compared to the developed world [5]. The reason being pregnant women in these countries is more likely to be at risk from potential causative agents such as infection, poor maternal nutrition, lower socioeconomic and educational status, low environmental protection programs and low access to medication [11,13]. Many scientific Studies reported that parental socio-demographic status, such as Age, race, education, and economic status, access to health care; maternal dietary habit, exercise habits, and other lifestyle patterns, both before and during pregnancy had

Table 3
The obstetric history of mothers of cases of neural tube defects (n = 205) and their controls (n = 412).

Characteristics	Frequency n (%)		OR and (CI) 95%	P-value
	Cases (N = 205)	Controls (N = 412)		
Parity				
Prime to 2	134 (65.4)	217 (52.6)		
Birth order 3 and 4	43 (21)	135 (32.8)	0.513 (0.342–0.770)	0.001
Birth order above 4	28 (13.6)	60 (14.6)	0.752 (0.457–1.237)	0.262
Use planned pregnancy				
Yes	143 (69.8)	222 (53.9)		
No	62 (30.2)	190 (46.1)	1.974 (1.383–2.817)	0.0001
The previous period of breastfeeding for each child				
Prime (no previous child)	78 (38.5)	87 (21.1)		
<=2 years	99 (48.3)	321 (77.9)		
>2 year	27 (13.2)	4 (1)	21.886 (7.477–64.061	0.0001
An outcome of previous pregnancy				
Stillbirth	14 (6.8)	2 (0.5)	19.125 (4.279–85.483)	0.0001
Live birth	112 (54.6)	306 (74.3)		
Prime (no previous child)	79 (38.5)	104 (25.2)		
Sex of the previous child				
Female	50 (24.4)	156 (37.9)		
Male	66 (32.2)	152 (36.9)	0.507(0.339–0.760)	0.001
Prime (no previous child)	89 (43.4)	104 (25.2)		

CI: confidence interval, n: number, OR: odds ratio, P value < 0.05 – considered as statistically significant.

Table 4
Maternal health and drug history of cases of neural tube defects (n = 205) and their controls (n = 412).

Characteristics	Frequency n (%)		OR and (CI) 95%	P value
	Cases (N = 205)	Controls (N = 412)		
Use herbal medicines during pregnancy				
Yes	1 (0.5)			
No	204 (99.5)	412 (100)		
Smoke during the pregnancy				
Yes		1 (0.2)		
No	205 (100)	411 (99.8)		
Consume any alcohol during pregnancy				
Yes	5 (2.4)	1 (0.2)	10.275 (1.192–88.5)	0.34
No	200 (97.6)	411 (99.8)		
Suffered from chronic disease during pregnancy				
Yes	4 (2)	1 (0.2)		
No	201 (98)	411 (99.8)		
Exposed to pesticide or chemicals				
Yes	5 (2.4)	2 (0.4)	5 (0.150–166.6)	0.368
No	200 (97.6)	410 (99.6)		
Suffered from parasitic infection during pregnancy				
Yes	1 (0.5)			
No	204 (99.5)	412 (100)		
Exposed to radiation during pregnancy				
Yes	5 (2.4)	2 (0.4)	5 (0.150–166.6)	0.368
No	200 (97.6)	410 (99.6)		
Source of drinking water				
City water	170 (82.9)	359 (87.1)		
A local river water	35 (17.1)	53 (12.9)	1.355 (0.849–2.163)	0.203

CI: confidence interval, n: number, OR: odds ratio, P value < 0.05 – considered as statistically significant.

a significant impact on maternal health and their pregnancy outcome [15,16].

Our study has shown the maternal age above 35 years was found to have a strong association with high risk of having a child with NTDs, the difference was statistically significant ($p = 0.0001$). This study is comparable to other studies which showed a direct relationship between the incidence of NTDs and increasing maternal age [17,18]. Our finding also showed that the maternal age under 20 years and parental residence were found to have a strong association with high risk of having a child with NTDs, the difference was statistically significant ($p = 0.0001$). This may be associated with a low nutritional habit of the adolescent age women and a shortage of demand or supply to healthy foodstuff selection [2]. Thus, this finding indicated that there is a need for providing health education in rural area and improvement of dietary counseling to the population, which is a key to prevent NTDs and other birth defects. Enhancement of nutritional habit in adolescent age is a critical time, because habits that are formed during the adolescent age may continue throughout their reproductive years.

The Ethiopian demographic and health survey has reported that the women who live in rural areas were more likely to be underweight than those from cities [19]. The young age of first marriage, poor dietary intake, and low meal frequency were found to be significant factors in a study of the Kunama population in Northwest Tigray [20]. Though many studies have been reported for the link between poor intake of FA and the incidence of NTDs [12], it is disappointing that most of our study participants are unaware of the role of FA use and its magnificent means of declining the occurrence of the NTDs which is regularly a social problem in our environment. None of our study participants were consumed folic acid during the preconception period, which may contribute to a higher prevalence rate of NTDs (13.8 per 1000 births) suspected in Tigray – Ethiopia. Hence, an epidemic of this size calls for emergency intervention consisting of mandatory folic acid fortification of a centrally processed food as an emergency public health intervention and a program to get all women of reproductive age to consume a supplement with 400 μg of folic acid [2,12]. Though our binary logistic regression analysis showed no significant association between maternal educational status and the occurrence of NTDs, the frequency analysis showed most of the NTDs cases were classed below elementary school as compared to controls; this could have an impact on the issue of the NTDs.

Studies have been reported an association between advanced paternal age and several congenital anomalies, including NTDs and hydrocephalus [21], which is in contrast to our finding that showed no significant association was found between paternal age and the occurrence of neural tube defects. Associations of congenital anomalies and advanced paternal age above 50 years have also been reported in Egypt [22]. The difference with our finding may be due to the difference in the culture of the population towards an age of paternal marriage and other factors. Paternal history or information was obtained from their wives as secondary information in our study; this may have an impact on the result.

This study has also shown the maternal obstetric history, such as birth order 3 and 4, unplanned pregnancy, and previous history of breastfeeding above 2 years was found to be significant factors in the risk of having pregnancy outcome afflicted with NTDs. Taken together, these might suggest extended lactation could be contributors to the occurrence of NTD in this study. A double-blind randomized control trial study has found that the maternal folate level was diminished during extended lactation [14]. Similarly, Indian studies showed that the birth defects were more common in women with fourth gravid and above [23,24]. The higher incidence of birth defects with a high range of gravidity could be caused by a higher maternal age. Studies have shown that there is an increased rate of mutation after the 3rd birth order compared to the first and second birth order [23]. Moreover, our study showed the previous history of stillbirths was strongly associated with the risk of having pregnancy outcome afflicted with NTDs. A similar pattern was reported from Riyadh City, Saudi Arabia [16]. Likewise, our finding showed that the history of male gender predominance was found to be significant factors for incidence of NTDs, which is comparable with many African studies that reported male gender predominance had an association with the occurrence of the congenital anomalies [25,26,27]. The male gender predominance for birth defects was thought to be caused by the fact that, male embryos are more liable to oxidative stress [28,29]. This could be due to the biological fragility of the male embryo, other causes are not well established [28,29,30]. Oxidative stress has a significant role in the development or occurrence of several congenital anomalies such as NTDs, limb defects, cardiovascular defects, orofacial clefts and other structural birth defects. Oxidative stress formed as an effect of the imbalance between the production of oxygen free radicals and the antioxidant defense mechanism of cells and tissues of our body. This pattern can generate irreversible oxidation of DNA, protein, and lipids with cell death due to enzyme inactivation [27,30].

5. Conclusion

This study has shown the majority of the maternal risk factors such as maternal age, residency, birth order above three, unplanned pregnancy, history of breastfeeding, history of stillbirths, history of male gender predominance and other lifestyle patterns had a significant

impact on the occurrence of NTDs. Determining its incidence in a certain region and population, and in the same way, the finding of secular trends will be of the important essence in investigating or identification of the risk and protective factors. The benefit of determining the possible factors and maternal lifestyle adjustment in decreasing the burden of NTDs is well established in developed and some developing countries. But an expanded program or campaign for prevention of NTDs has not been conducted in Ethiopia instead. Surveillance data are useful for developing prevention or intervention programs. Efficient monitoring of NTDs in Ethiopia is vital, so our study could be groundwork information in Ethiopia for future programs.

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