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Original Article

The prevalence and pattern of neural tube defects and other major congenital malformations of nervous system detected at birth in Barbados

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ABSTRACT

Introduction: Neural tube defects are the commonest major congenital malformation of nervous system. There is paucity of published data on the public health burden of major congenital malformations from the English Caribbean. The objective of this study was to describe the prevalence and pattern of major congenital malformations of the nervous system seen at birth. We also describe the burden of neonatal morbidity and mortality from the neural defects.

Material and methods: This was a retrospective clinical audit of all babies born with major congenital malformations of the nervous system in Barbados. The period of reporting was from 1993 to 2012. Relevant data on the babies with major congenital malformations of the nervous system were obtained from the birth register in the labor ward and the admissions register at the NICU.

Result: The prevalence rate for neural tube defects, congenital hydrocephalus, and other Major Congenital Malformations of the Nervous System was 3.76, 2.66, and 1.25 per 10,000 live births, respectively. Major congenital malformations of nervous system accounted for 10 (1.6%; 95% CI = 0.8%–3.1%) deaths. The prevalence rate of neural tube defects is lower than those reported from most of the countries around the world.

1. Introduction

Major congenital malformations of the nervous system (MCMNS) are reported to be one of the most common major congenital malformations in newborns.[1–4] The prevalence rate of the MCMNS in reports from Asia, Middle-East, Africa, and Europe varies between 23 and 61 per 10,000 live births.[5–8] There is a wide variation in the prevalence of these malformations in different parts of the world.[9] MCMNS are an important cause of mortality and long-term morbidities among children.[8–11] They are becoming relatively more common cause of long-term morbidities and mortalities among children due to the decreasing morbidities and mortalities from causes such as perinatal injuries, infections, and corrective surgeries for most congenital heart diseases. Historically, perinatal injuries, and congenital heart diseases were the common causes of long-term morbidity and mortality among children. Long-term and often disabling morbidities from the malformations of the nervous system poses a serious economic and social burden on the government and the society.[11–13] Many of these malformations of the nervous system such as the neural tube defects, which is the most common of these malformations, can be prevented.[14–17] In others, antenatal detection can help to reduce prevalence, long-term morbidities and mortalities.[16,18]

Barbados, one of the English speaking Caribbean countries, has a total population of 283,000 (2012) including 58,500 (21%) and children under the age of 16. The Under 5 Mortality Rate was 18 per 1000 live births and the life expectancy at birth male/female was 75/81 years.[19] It has a well-organized state run health care infrastructure with free health care for its citizens at the point of delivery.[20] Over 95% of pregnant women having had at least two antenatal visits and over 90% of all deliveries in this country take place at the Queen Elizabeth Hospital.[21] Over one-eighth of all neonatal death in this country is attributed to the major congenital malformations.[22] In this study, we describe the overall prevalence rate and the long-term trends for the MCMNS detected at birth in this population. We also describe the pattern of nervous system

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malformation, the factors associated with these malformations, and the impact of these malformations on the overall neonatal mortality rate in this country.

2. Material and methods

This is a clinical audit of babies born with MCMNS from among all the deliveries in Barbados. The period of audit extends from 1993 to 2012. The stillbirths with MCMNS were excluded from this study. Babies with diagnosis of any of the MCMNS were identified from the admission register maintained in the Neonatal Intensive Care Unit (NICU) at the Queen Elizabeth Hospital (QEH). Relevant data on the babies with MCMCNS were obtained from the birth register in the labor ward and the admissions register at the NICU. These included date of delivery, maternal age, maternal parity, gestational age at delivery, birth weight, and baby's gender. The total number of live births, number of neonatal admissions, total number of babies born with major congenital malformations, death among babies with any major malformations and number of deaths in babies with MCMNS, and overall total number of neonatal deaths during the study period were also collected form these registers. The hospital case records for all the babies with MCMNS were also reviewed to collect additional maternal data such as history of trauma, infection, chronic diseases, medications including over the counter preparations, use of alcohol or drugs in pregnancy. The baby's data such as other associated malformations and outcome in terms of hospital discharge or death were also collected from the baby's case record. Birth statistics for the minority of the births outside the hospital were also collected.

As a routine practice all live born babies were examined after birth by a pediatrician and congenital anomalies, if any, were described in detail. All babies with malformations were appropriately investigated with neuroimaging including ultrasound examination of brain and CT scan of brain. MRI scan and genetic studies were unavailable during much of the study period. Neonatal treatment data and medical complications as recorded by the attending neonatologists at the time of death or discharge from the hospital were also collected.

Throughout the study period discharge/death diagnosis was recorded using the clinical approach for the classification of the major malformations of the nervous system. Major congenital malformations included defects present at birth, which may be fatal and/or handicap the patient throughout life. Based on the review of the neuroimaging studies and other investigations we classified these malformations based on those proposed by Van der Knapp.[23] Prevalence was calculated by dividing the number of newborns with the MCMNS (numerator) by the total number of live newborns for the given time period (denominator) and expressed as per 10,000 live births. Proportion of neonatal deaths attributed to MCMNS was calculated by dividing the number of death attributed to MCMNS during the first month of life by the total number of all deaths during the first 28 days of life expressed as percentage. Case fatality rate for the MCMNS was calculated by dividing the number of deaths during the first 28 days of life by the total number of live born babies with MCMNS requiring admission to the NICU. Prematurity was defined as: delivery less than 37 complete weeks of gestation. Small for Gestational Age (SGA) was defined as the birth weight below the 10th percentile for the given gestational age.

Ethical approval was obtained from the ethics committee at the Queen Elizabeth Hospital and Institutional Review Board for ethics in study involving human subjects of the University of the West Indies and the Ministry of Health, Barbados. All precautions were taken to protect the personal information of the patients, only the investigators have access to the database.

Data were entered and stored in a specially created Microsoft Access spreadsheet, Microsoft Excel was used for data tabulation and generation of graphs. The results were analyzed by simple statistical techniques and tests of significance including Chi-square tests were applied. The online statistical calculator Vassar Stats was used for calculation of 95% Confidence Intervals (CI) with continuity and the Relative Risk (RR).

3. Results

Over the 20 years study period, there were 63,827 live births in Barbados and there were 49 cases of MCMNS. The overall prevalence rate for the MCMNS during the 20 years study period was 7.68 per 10,000 live births. The relative proportion of the main category of MCMNS based on the discharge/death diagnosis is shown in Fig. 1. Neural tube defects with or without hydrocephalus were the commonest (49%; 95% CI = 34.6–63.5%) malformation seen. It was followed by congenital hydrocephalus (34.7%; 95% CI = 22.1–49.7%) not associated with neural tube defects. Congenital hydrocephalus not associated with neural tube defects consisted of Chiari Malformations (13 cases), Dandy Walker malformation (2 cases), and Congenital hydrocephalus not associated with any other malformation on CT scan (2 cases). The prevalence rate for the neural tube defects and the congenital hydrocephalus was 3.76 and 2.66 per 10,000 live births, respectively. Trend in the prevalence rates of various types of MCMNS are shown in Fig. 2. The overall prevalence rate for all MCMNS increased from 6.99 per 10,000 live births during the 1993–2002 to 8.40 per 10,000 live births during the 2003–2012. However, this difference in the prevalence rate over the time period was statistically not significant (RR = 1.21 and $P = 0.512$). Over the same time period, the prevalence rate for the neural tube defects increased from 3.47 to 4.04 per 10,000 live births. This difference in the prevalence rate too was statistically not significant ($P = 0.708$). The risk ratio for the neural tube defect during the latter ten-year period compared to former ten year period was 1.16 (95% CI = 0.52–1.16).

The details of the pattern of MCMNS seen in this population, based on the Van der Knapp classification system, are shown in Table 1. Disorder of dorsal induction resulted in 75.5% (95% CI = 60.8–86.2%) of all MCMNS, with neural tube defects accounting for 49% (95% CI = 34.6–63.5%) of all MCMNS. Myelomeningocele was the commonest (62.5%; 95% CI = 40.8–80.4%) of the neural tube defects, accounting for 30.6% (95% CI = 18.7–45.6%) of all MCMNS. Of the 15 cases of Myelomeningocele, hydrocephalus, and Chiari type 1 malformation was detected on CT scan of brain in 10 (66.7%; 95% CI = 38.7–87.0%). Anencephaly was the least common

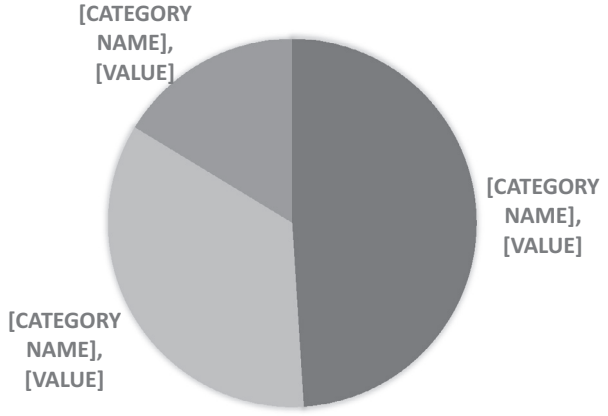

Fig. 1. Distribution of the clinical diagnosis categories of the major congenital malformations of the nervous system in Barbados, 1993–2012.

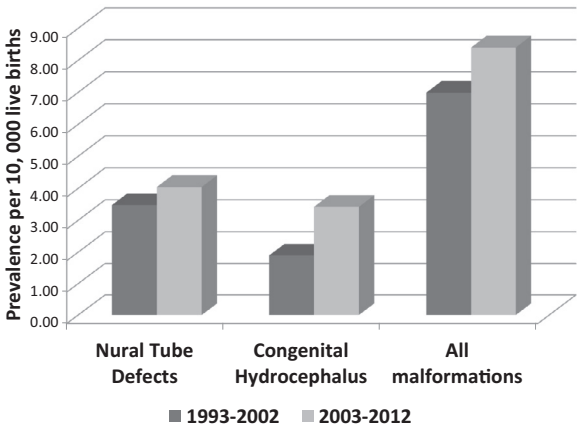

Fig. 2. Time trend in the prevalence rate of major congenital malformations of nervous system in Barbados, 1993–2012.

(8.3%; 95% CI = 1.5–28.5%) of the neural tube defects, accounting for just 4.1% (95% CI = 0.7–15.1%). Of the two cases of Chiari type 2 malformations, one was detected because of CT imaging for splayed sutures and increased head circumference soon after birth and the other one was diagnosed by antenatal ultrasound and confirmed by postnatal CT imaging.

Fetal and maternal characteristics associated with open neural tube defects are shown in Table 2. Open neural defects were more common among babies with low birth weight (<2500 g) compared to babies with birthweight > 2500 g (RR 2.64; 95% CI = 0.98–7.1; $P = 0.098$) and among pre-term babies compared to term or post-term babies (RR = 1.77; 95% CI = 0.35–3.96; $P = 0.791$). Also, it was more common among babies born to mothers aged > 35 years compared to those born to mothers younger than 35 years (RR = 1.81; 95% CI = 0.72–4.61; $P = 0.300$). History of chronic alcohol intake was recorded for the mother of one of the two cases of microcephaly and baby was diagnosed to have fetal alcohol syndrome. None of the mothers reported any history of using illegal drugs or taking medications known to predispose to neural tube defects.

Additional malformations involving other systems were seen in 5 babies with MCMNS (3 babies with neural tube defects, 1 with lyssencephaly, and one with hydrocephalus). Two babies with neural tube defects had an additional congenital heart disease (one ASD and one VSD) while another has bilateral talipes equinovarus deformity. The baby with the lyssencepahly additionally had a VSD while the baby with hydrocephalus had multiple congenital anomalies including skeletal dysplasia, cleft lip and palate, and hypo plastic lungs.

During the 20 years study period, there were a total of 11,842 neonatal admissions to the intensive care unit and of these 49 (0.4%; 95% CI = 0.3–0.5%) were from the MCMNS. Over the same period there were 617 neonatal deaths and MCMNS accounted for 10 (1.6%; 95% CI = 0.8–3.1%) deaths. The case fatality rate for the MCMNS during the neonatal period was 20.4% (95% CI = 10.7–34.8%). Among the neural tube defects there were only two deaths and both these babies had anencephaly.

Table 1
Pattern of major congenital malformations of the nervous system in Barbados, 1993–2012.

Pattern of malformations	*N* (%)
Disorders of dorsal induction	37 (75.5)
Neural tube defects	24 (49.0)
Anencephaly	2 (4.1)
Encephalocele	3 (6.1)
Myelomeningocele	15 (30.6)
Meningocele	4 (8.2)
Chiari malformations with hydrocephalus	13 (26.5)
Type 1	10 (20.4)
Type 2	3 (6.1)
Disorders of Ventral induction	4 (8.2)
Dandy walker with hydrocephalus	2 (4.1)
Holoprocencephaly	1 (2.0)
Septo-optic dysplacia	1 (2.0)
Disorders of neuronal proliferation and histeogenesis	4 (8.2)
Hydranencephaly	2 (4.1)
Porencephaly	2 (4.1)
Disorder of migration and dysgenesis	4 (8.2)
Lyssencephaly	1 (2.0)
Sciezencephaly	1 (2.0)
Microcephaly and craniosynostosis	2 (4.1)

Table 2
Factors associated with the neural tube defects in Barbados, 1993–2012.

Selected demographic characteristics	Numbers (*N* = 23)	Total live births	Prevalence/10,000 live births
Infants gestational age			
<37 weeks	3	7213	4.16
37–40 weeks	20	56,614	3.53
Infants birth weight			
<2500	5	6047	8.27
2500–4000	17	54,901	3.10
>4000	1	2879	3.47
Infants gender			
Female	10	31,587	3.17
Male	13	32,040	4.06
Maternal age			
15–24	5	22,932	2.18
25–34	12	30,576	3.92
35–44	6	10,192	5.89
Gestational order			
Gravida 1	8	19,982	4.00
Gravida >2	15	44,310	3.39

4. Discussion

Congenital malformations of the nervous system are extremely complex and are best studied by correlating with embryological development.[23,24] Basic events in normal brain development includes the following four stages: (a) the dorsal induction which involves the formation and closure of the neural tube and failure of which leads to the various neural tube defects (Anencephaly, Encephalocele, Myelomeningocele, and Meningocele) and Chiari malformations; (b) the ventral induction which involves formation of brain segments and face, failure of which causes Holoprosencephalies, Dandy Walker malformation, Cerebellar hypoplasia/dysplasia (Chiari-IV); (c) neuronal proliferation and histeogenesis, and the problems which lead to various neurocutaneous syndromes, hydranencephaly, and porencephaly; and (d) the migration of neurons the disorders of which result in Lyssenencephaly, scizenencephaly, and microcephaly.

The overall prevalence rate of the MCMNS in this population during the study period was 7.68 per 10,000 live births. This prevalence rate is much lower than those reported in most studies from other parts of the world. Studies from Asia, Middle-East, Africa, and Europe have reported prevalence rate varying between 23 and 61 per 10,000 live births.[5–8] Neural tube defects and congenital hydrocephalus were the two most common MCMNS seen in this population. Similar pattern of nervous system malformation have been reported in many studies from around the world.[1,6–8,10] The prevalence rate of 3.76 per 10,000 live births for the open neural tube defects seen in this study is also lower

than those reported in recent studies from around the world which varied between 4.0 and 12.1 per 10,000 live births.[6,11,25] Wide geographic variation in the prevalence of neural tube defect is a well-recognized fact. Lower prevalence rate of neural tube defects seen in this study may have been due to the mandatory fortification of several food items especially flour in this country since the early nineties. Studies have shown that folic acid fortification of food items leads to reduction in the prevalence of neural tube defects.[17,25,26] The overall lower prevalence of MCMNS in this population was due to the lower prevalence rate of the open neural tube defects. However, it is interesting to note that a significant number of women still had babies with neural tube defect despite the folate supplementation of all types of flours consumed in this country. This reinforces the findings form a study in the USA where folate dietary folate supplementation is mandatory and which clearly showed that folate only prevents a certain proportion of neural tube defects.[27] Further studies are necessary to identify other risk factors in neural tube defect and to identify women with those risk factors.

In this population, myelomeningocele with or without hydrocephalus was the commonest diagnosis accounting for two-thirds of all neural tube cases and anencephaly was least common accounting for less than a tenth of all neural tube defect cases. This pattern of neural tube defect is different from those reported in other studies. Many studies have reported a much higher proportion of anencephaly.[25,28,29] However, in this country abortion for medical reason is legal and is often carried out in the public hospital free of any charges. Many of the cases of anencephaly detected by ultrasound examination in the antenatal period undergo termination of pregnancy. The two cases of anencephaly reported in this study were from 1993 and 1995 when antenatal ultrasound examination was not universal. The neural tube defects were more prevalent among male, premature, and low-birth weight babies. However, in none of these cases, the difference in the prevalence rate was statistically significant. Gender preponderance of neural tube defects have been variously reported. While many studies have reported female preponderance,[28,29] some have reported male preponderance. Some studies have reported increasing prevalence of neural tube defects in mothers over 35 years.[25,28,29] In this study, we did not find any significant difference in the prevalence of neural tube defects among babies born to mothers younger than 35 years and those 35 years or older.

One of the major limitations of this study was that the stillbirths were excluded from the study due to the incompleteness availability data on these babies. This study has all other limitation of a retrospective audit study of this type. Lack of regional studies for comparisons compromises the interpretation of study findings and recommendations.

In conclusion, neural tube defects are the commonest MCMNS. The prevalence of neural tube defects in this population is lower than those reported from several regions of the world and it may have been due to the universal fortification of food items like baking flours in this country. There have been no significant changes in the prevalence of neural tube defects or other major congenital malformations of nervous system over the twenty-year study period. Although we recorded no mortality among the cases of neural tube defects other than the deaths form anencephaly, these conditions are known to result in long lasting physical and psychological morbidity and social and economic challenges. There is a need for establishing a congenital malformation registry with prospective data entry. Periodic review of information gathered from such a registry will help us in monitoring time trend, resource allocation for future health care needs and it may help us identify factors linked to the causation and prevention of neural tube defects.

Conflicts of interest

The authors have none to declare.

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