

ARTICLE

The mortality rate after hospital discharge in patients with myelomeningocele decreased after implementation of mandatory flour fortification with folic acid

Redução da taxa de mortalidade após a alta hospitalar em pacientes com mielomeningocele depois da implementação da fortificação obrigatória das farinhas com ácido fólico

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ABSTRACT

Objective: To evaluate the mandatory folic acid fortification of flour on mortality rates after the hospital discharge of children born with myelomeningocele, the most affected age group and the most frequent cause of death. **Methods:** A retrospective study of 383 children born with myelomeningocele from January 1990 to December 2013 in a high-fetal-risk reference hospital. **Results:** A total of 39 patients died (10.1%), of which 23 (6%) died after discharge. Most children who died were younger than 12 months of age. The most frequent cause of death was infection of the central nervous system, followed by urinary tract sepsis and infections of the respiratory system. Symptomatic Chiari II malformation was the most frequent comorbidity factor. **Conclusion:** Although there was no significant difference in infant mortality before and after folic acid fortification, there was a significant reduction in deaths after hospital discharge in babies born after implementation of mandatory folic acid fortification

Keywords: meningomyelocele; mortality; folic acid.

RESUMO

Objetivo: Avaliar a fortificação obrigatória de farinhas com ácido fólico nas taxas de mortalidade após a alta hospitalar de crianças nascidas com mielomeningocele, a faixa etária mais atingida e a causa mais frequente de morte. **Métodos:** Estudo retrospectivo de 383 crianças nascidas com mielomeningocele de janeiro de 1990 a dezembro de 2013, em um hospital de referência de alto risco fetal. **Resultados:** Um total de 39 pacientes morreram (10,1%), dos quais 23 (6%) morreram após a alta. A maioria das crianças que morreram não alcançaram 12 meses de idade. A causa mais frequente de morte foi infecção do sistema nervoso central, seguido por sépsis, infecções do trato urinário e do sistema respiratório. A malformação de Chiari Tipo II foi a comorbidade mais frequente. **Conclusão:** Apesar de não haver diferença significativa na frequência de mortalidade de recém-nascidos, antes e depois da fortificação obrigatória com ácido fólico, houve uma redução significativa no número de mortes após a alta hospitalar em bebês nascidos após a implementação da fortificação obrigatória das farinhas com ácido fólico.

Palavras-chave: meningomielocelo; mortalidade; ácido fólico.

Myelomeningocele (MMC), or spina bifida cystica, is the most common neural tube defect, developing between days 21 and 28 after fertilization^{1,2}. The lack of a protective lining exposes the neural tissue to gradual destruction due to the deleterious effects of amniotic fluid over the neural plate³.

The prevalence of MMC varies according to the geographic, racial, and ethnic characteristics of the population being

studied, and may differ greatly between different regions of the same continent or country^{4,5}. In Brazil, the prevalence of Chiari II malformation (CMII) is estimated to range between 1.4 and 1.5 per 10,000 births^{6,7}. The cause of MMC is multifactorial, but folic acid (FA) deficiency is the main risk factor. Chromosomal and genetic abnormalities, maternal hyperthermia during the early stages of pregnancy, use of

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antiepileptic drugs (e.g., valproic acid), diabetes mellitus, and obesity may also be involved⁸.

Around 14% of the children born with MMC die before the age of five years, and the mortality rate of children with brain stem dysfunction may exceed 35%⁹. The most frequent causes of death in patients with MMC include CMII-related complications; urinary tract, pulmonary, and cerebrospinal fluid infections; as well as ventricular shunt malfunction¹⁰. In Brazil, fortification of wheat and maize flour and their derivatives with FA became mandatory after 2002.

In 2006, Bol et al.¹¹ reported significantly improved first-year survival after implementation of mandatory folic acid fortification (FAF), compared with the survival rate of children with MMC born before fortification. A significant decline in perinatal and infant mortality was also shown by Sayed et al.¹² in 2008. In 2010, Blencowe et al.² conducted a systematic review of the literature and estimated that FAF reduces the incidence of neural tube defect by 46% and expected neonatal deaths by 13%.

The aim of this study was to evaluate the impact of FAF on the mortality rate of patients with MMC who underwent surgery at a pediatric hospital in Rio de Janeiro, Brazil.

METHODS

We performed a retrospective study of a cohort of 383 children diagnosed with MMC who were surgically repaired from January 1990 to December 2013. There were 39 deaths, and our focus was on the children who died after hospital discharge, which accounted for 23 out of the 39 (58.97%) deaths.

This study was approved by the institution's Committee of Ethics in Research.

The relationship of mortality to the following variables were evaluated: age, cause of death, risk factors, postoperative complications, and gender. Data were analyzed using Epi Info, ver. 7.1.4.0 software (Centers for Disease Control and Prevention, Atlanta, USA). Results with p values < 0.05 were considered significant. The period of implementation of flour fortification was calculated according to the model used by Orioli et al.⁶, and consisted of the sum of the 18 months elapsed from the time of publication of the decree, the three-month period for the implementation of fortified flours, and the nine months of gestation.

RESULTS

Demographics

Of the 21,310 live births between 1994 and 2013 at the Insitituo Fernandes Figueira, 10,894 (51.1%) were boys and 10,299 (48.3%) were girls (male/female ratio of 1.05:1). Gender-related information was not found for 0.5% ($n = 117$) of the children. Analysis of the 330 cases of MMC showed

that the proportion of female children with MMC was 56.6% ($n = 187$) and that of male children with MMC was 43.3% ($n = 143$, $p = 0.0038$).

The frequency of MMC before mandatory flour fortification was 1.34% ($n = 172$), while the incidence after implementation of FAF was 1.81% ($n = 158$), which was a significant increase in the incidence rate ($p = 0.0055$).

Surgical technique

For all 383 MMC cases, the initial treatment was correction of the MMC according to the usual 5-layer technique. Among the 23 patients who died after hospital discharge, five patients also underwent simultaneous placement of a ventriculoperitoneal shunt.

Surgical complications

There were 28 surgical complications; the most common were infections of cerebrospinal fluid and shunt hardware (78.5%, $n = 22$), as well as ventriculoperitoneal shunt malfunction. The complications and incidence rates are shown in Table 1.

Risk factors and causes of death

Neurogenic bladder, recurrent urinary tract infections, lower-limb paralysis; recurrent respiratory infections, chronic constipation, chronic renal failure, hydronephrosis, apneic crises, and gastroesophageal reflux disease were risk factors for mortality.

The most common causes of death were central nervous system (CNS) infections, occurring in eight of the 23 (34.7%) fatalities after hospital discharge. Respiratory infections and sepsis of urinary tract origin were the second most common cause of death, each being a major contributing factor in 21.7% ($n = 5$) of the 23 deaths. Respiratory tract infections were also an aggravating factor in eight cases. All the cases of urinary sepsis had kidney failure. Intracranial hypertension and CMII were major contributing factors in two of 23 (8.69%) patients. Chiari II malformation was also present and associated with death in four other cases. The cause of death of one patient was septic gastroenteritis complicated by kidney failure.

Table 1. Complications of surgical treatment.

Variable	N	%
Surgical procedure	6	21.4
Wound Infection	3	10.7
Intracranial hypertension*	3	10.7
Ventriculoperitoneal shunt (VPS)	22	78.5
CNS Infection	8	28.5
VPS Infection	7	25
VPS Malfunction**	6	21.4
VPS Shortening***	1	3.5

CNS: central nervous system; VPS: ventriculoperitoneal shunt; *Intracranial hypertension occurred in three children not derived at MMC correction; **Three children have resultant intracranial hypertension; ***Resulting in intracranial hypertension

Nine of 23 (39.1%) children died in the first year of life, five between the ages of two and three years, and four between the ages of one and two years. Five children died between the ages of three and 11 years (Figure). The highest number of deaths after hospital discharge occurred in female children, 60.8% (n = 14), but this rate was not significant (p = 0.981).

At a given moment, five live births presenting with signs and symptoms of CMII were identified, and accounted for 21.7% of the 23 children analyzed.

Correlation of deaths with hospital discharge and FAF

Of the 383 operated children, the total number of deaths was 39 (10.1%). The deaths were classified as occurring before hospital discharge (BHD) or after hospital discharge (AHD). The BHD group, composed of 16 of the 383 (4.1%) cases of MMC, included the children who died at younger than 30 days and those who, despite surviving the first month of life, were not discharged. The AHD group included 23 of 383 (6.0%) children who died after hospital discharge. The mean survival period was 2.8 years, ranging from two months to 11 years.

The mortality rates before and after fortification of the BHD group and AHD and group were compared. Before fortification there were 11 BHD deaths and 20 AHD deaths. After fortification, five BHD patients and three AHD patients died. The total number of deaths was 31 before and eight after mandatory fortification. The reduction in total number of deaths after mandatory fortification was significant (p = 0.00919) and the reduction in the number of AHD deaths after fortification was significant (p = 0.0088), but not the number of BHD deaths (p = 0.568). The results are shown in Table 2.

Of the 23 children who died AHD, the highest prevalence was observed in the lumbosacral region, followed by thoracolumbar. The locations and frequencies are presented in Table 3.

DISCUSSION

There have been few studies related to late mortality in patients with MMC, particularly regarding etiology and age ranges.

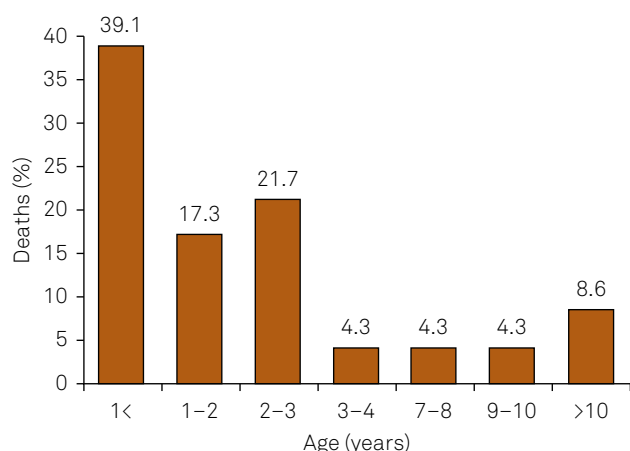


Figure. Distribution of deaths by age group.

The decrease in the incidence of MMC at our institution before and after mandatory FAF was not significant. There are several possible explanations for this finding: a) FAF of flour alone was not sufficient for promoting a significant decrease in MMC rates, because the FA concentration in Brazilian flours is 1.5 mg/kg, which is lower than the FA concentration adopted by other Latin American countries, such as Argentina and Chile where the FA concentration is higher and where they have experienced a significant decrease in neural tube defects and MMC^{6,7,13}; b) the Brazilian public health system nowadays provides easier and faster access to prenatal diagnostic tools, thereby increasing the frequency of early MMC diagnosis and directing these cases to reference centers such as the Insitituo Fernandes Figueira; c) our institution is a tertiary reference center for a low-income population, which is much more frequently affected by neural tube defects; d) Brazil is a multiracial country with an ethnic profile different from other Latin-American countries⁷. Moreover, in some countries, the prevalence of MMC was not substantially reduced by FAF of flours, and in some countries the prevalence has even increased¹⁴. These findings might be a result of heterogeneous supplementation policies and lack of flour fortification. Also, educational and social interventions regarding folic acid supplementation are needed¹⁴.

In our series, of the 383 live births with MMC, 23 (6%) died after hospital discharge; most of the deaths occurred before five years of age (n = 20), corresponding to 86.9% of the total number of AHD deaths. Analysis of deaths by age range showed that 39.1% (n = 9) of the children died during the first year of life. Ten deaths occurred from the ages of one to four, as follows: four (17.3%) between one and two years, five (21.7%) between two and three years, and one (4.3%) between three and four years. The remaining four deaths occurred at the ages of seven (n = 1), nine (n = 1), and 11 years (n = 2). The highest death rates occurred in the lowest age ranges.

A Brazilian study of 36 cases of MMC found a mortality rate of 16.6% (n = 6), with all the deaths occurring before two years of age¹⁵. Another study followed 84 patients after discharge, and most of the deaths (74%) occurred during the first

Table 2. Deaths before and after mandatory flour fortification.

Variable	DBF n (%)	DAF n (%)	pc	Fisher exact
Total	31 (13.7)	8 (5)	0.00919	0.00569
BHD	11 (4.8)	5 (3.1)	0.568	0.450
AHD	20 (8.8)	3 (1.8)	0.0088	0.0040

DBF: Deaths before fortification; DAF: Deaths after fortification.

Table 3. MMC frequency according the site of the defect.

Site	n	%
Lumbosacral	9	39.1
Thoracolumbar	8	34.8
Lumbar	5	21.7
Thoracic	1	4.3

month of life¹⁶. Another case series reported that most deaths occurred between the neonatal period and preschool age^{9,17,18}. Mortality rates in MMC do not stabilize as the patients become older. An analysis of long-term studies showed that 240 (71.2%) of 337 reported deaths occurred in patients up to 16 years of age^{9,16,17,18}. The main cause of death in patients older than 16 years was unrecognized ventriculoperitoneal shunt dysfunction^{18,19}. A cohort study that followed patients for more than 40 years found that there were 56% of patients who survived to around 20 years of age, but the mortality rate continued to increase with age, and the last evaluation showed that there were 33.3% of patients of the initially observed population who were still alive^{9,20}. These results are very different from those presented by Talamonti et al., who reported only five deaths among 202 patients followed over 25 years²¹.

The total number of deaths in our study was 39 (10.1%). During the period before FAF (January 1990 - December 2005), there were 225 cases of MMC, with a mortality rate of 13.7% (n = 31). Considering only the cases in which AHD deaths occurred, the mortality rate was 8.8% (n = 20). After implementation of FAF, there were 158 cases of MMC, and the total death rate for this period was 5.0% (n = 8). There were five neonatal deaths (3.1%) during the same period. These data show a significant reduction in the total number of deaths during the years after FAF implementation. However, regarding neonatal mortality, that is, the live births not discharged from the hospital, the mortality rate was not significantly reduced after FAF. This result differs from the findings of others on the protective role of FAF against neonatal mortality^{2,11,12}. There was a significant decrease in AHD deaths 1.8% (n = 3) after implementation of mandatory FAF versus 8.8% (n = 20) before implementation. A series of 304 children with MMC, who were born in Ireland before FA supplementation, showed that only 33% of the children survived to their first birthday, and just over 27% survived to the age of five years²². However, after mandatory FAF, there was a significant increase in the survival rate of children with MMC, leading to the hypothesis that FA, in addition to preventing MMC, might also play an important role in reducing the severity of MMC among live births¹, as well as

malformations in other organs or systems²³ and the resulting neonatal mortality²⁴.

The most common cause of death detected in our study was CNS infections, particularly those related to the cerebrospinal fluid (34.7%), followed by urinary sepsis and respiratory infections (21.7%). Cerebrospinal fluid infections were mostly caused by shunt infections and these are regarded as a highly significant predictor of mortality²⁵. Children with shunts are at high risk of cerebrospinal fluid infection, ranging from 5.5% to 25% of cases²⁶, and shunts are thought to be the cause of death in 33% to 50% of children with MMC^{15,16}.

Urinary tract infections resulting from neurogenic bladder and vesicoureteral reflux, in some cases, have led to urinary sepsis, kidney failure, and ultimately death²⁷.

Chiari II malformation was the third most common cause of death, acting either as a determining or contributory factor. The signs and symptoms of this malformation are protean and may be transient, making it difficult to estimate its real prevalence among neonates and infants. It is assumed that, at some time, 6% to 32% of individuals with MMC will have neurological manifestations related to CMII²⁸. The mortality is higher and may be the main cause of death among neonates with CMII, affecting more than 40% of MMC patients^{18,29,30}.

Discontinuing the follow-up of patients with MMC has a dramatic impact on the number of deaths^{21,22}. The most common cause of discontinuation is the lack of multidisciplinary centers for spina bifida treatment. Since most families have a low income and live on the outskirts of large cities, regular follow-ups are reduced or even neglected, since most patients have severe limitations in ambulation and need special requirements for transportation, which is not always available³¹.

In conclusion, the mortality rate of patients with MMC after they were discharged from the hospital was 6%. Most children died before their first birthday. The most common causes of death were CNS infections, respiratory infections, and urinary sepsis. Symptomatic CMII was the most common comorbidity factor. The mortality rate after hospital discharge decreased after implementation of mandatory flour fortification with folic acid.

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