ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 08, Issue, 03, pp.19279-19283, March, 2018

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

EVALUATION OF THE IMPLANTATION OF THE NATIONAL NEONATAL SCREENING PROGRAM REGARDING COVERAGE INDEX, DISEASE PREVALENCE AND SICKLE CELL TRAIT IN MATO GROSSO DO SUL - BRAZIL: 2001 – 2015

[1]Berenice A. Kikuchi, [2]Maria Lucia Ivo, [2]Ana Rita Barbieri, [3]Rui A. Camargo , [2]Valter Aragão do Nascimento, [4]Marcos Ferreira Junior, [5]Mayara Bontempo Ferraz, [1]Caroline Neris Ferreira Sarat ,[1]Francine Ramos de Miranda, [6]Abílio Torres, [7]Jorge A. Kikuchi and [8]Márcia Rejane Freire de Oliveira

[1]Postgraduate Program in Nursing and Program in Health and Development in the Middle West Region, Federal University of Mato Grosso do Sul, Brazil
[2] Postgraduate Program in Nursing and Program in Health and Development in theMiddle West Region, Federal University of Mato Grosso do Sul, Brazil
[3]Faculdade de Medicina Veterinária e Zootecnia – Federal University of Mato Grosso do Sul, Brazil
[4]Professor adjunto do Instituto Integrado de Saúde
[5]Postgraduate Program in Nursing
[6]Residente em enfermagem – UFMS
[7]Graduação - Universidade Cruzeiro do Sul – São Paulo, Brasil
[8] Fonaudióloga - Especialização em Serviços de Hemoterapia-University of the Recôncavo of Bahia, Brazil

ARTICLE INFO

Article History:
Received 20th December, 2017
Received in revised form
16th January, 2018
Accepted 24th February, 2018
Published online 30th March, 2018

Key Words:
Neonatal screening,
Sickle cell anemia,
Evaluation.

ABSTRACT

The National Neonatal Screening Program (PNTN) was implemented in Brazil in 2001. This program aims to improve coverage over 15 years and the prevalence of sickle cell disease and sickle cell trait. The objective of this manuscript was to evaluate in the last 15 years the work developed by the National Neonatal Screening Program regarding the coverage index, disease prevalence and sickle cell trait in the state of Mato Grosso do Sul, Brazil. It is a cross-sectional retrospective study carried out with the results of neonatal screening for hemoglobinopathies from 2001 to 2015. The high efficiency liquid chromatography technique was carried out at the Institute of Research, Teaching and Diagnosis of the Association of Parents and Friends of the exceptional in Mato Grosso do Sul. It was observed in the last 15 years that of the total of 612,909 live births, 543,690 were screened, reaching a Coverage index of 88.71%. Sickle cell anemia totaled 67 cases with a prevalence of 0.0127%, and 23 cases of FSC with a prevalence of 0.0046%. Heterozygotes (FAS) totaled 9,200 individuals with a prevalence of 1.6925. PNTN is a consolidated public policy in Mato Grosso do Sul, and its coverage index remained above 80% from 2001 to 2015. There was an increase in the number of cases of sickle cell disease HbSS and HbSC, as well as sickle cell trait.

Citation: Berenice A. Kikuchi, Maria Lucia Ivo, Ana Rita Barbieri, Rui A. Camargo et al. 2018. "Evaluation of the implantation of the national neonatal screening program regarding coverage index, disease prevalence and sickle cell trait in mato grosso do sul - brazil: 2001 – 2015", *International Journal of Development Research*, 8, (03), 19279-19283.

INTRODUCTION

In this study, it stands out the leading role of the Research Institute, Teaching and Diagnostics of the Association of Parents and Friends of the Exceptional (IPED-APAE) of Campo Grande (MS), which included sickle cell disease in neonatal screening in 1997 before the National Neonatal Screening Program (PNTN). Law No. 3,240 of March 29, 1996, for the city of Campo Grande (MS-Brazil) was fundamental for inclusion of sickle cell disease in neonatal screening.

****Corresponding author:*** **Berenice A. Kikuchi,**
[1]Postgraduate Program in Nursing and Program in Health and Development in the Middle West Region, Federal University of Mato Grosso do Sul, Brazil

It deals with Combating Racism in the municipality of Campo Grande and provides other measures (CAMPO GRANDE, 1996). It is a claim of the black social movement, with the aim of reducing disparities in health care for the black population in Brazil. In paragraph VII, the Law recommends: "adoption, in the public health system, of procedures for the detection, in the first years of life, of sickle cell anemia" (CAMPO GRANDE, 1996). The actions cited above were of great importance and preceded the creation of the PNTN in 2001 by the Ministry of Health of Brazil. In evaluating the structure, process organization and results of the PNTN in the state of Mato Grosso do Sul, as well as the quality of service and user satisfaction (DONABEDIAN, 1990), it was observed a technical and operational evolution of the IPED-APAE with accreditation in the State Department of Health to perform tests of Phenylketonuria, Primary Congenital Hypothyroidism, Cystic Fibrosis, congenital adrenal hyperplasia, Biotinidase Deficiency, Sickle cell Diseases and other hemoglobinopathies (MATO GROSSO, 2014). According to Cançado and Jesus (2007), it is estimated that there are more than 7,200.000 individuals with sickle cell trait (HbAS) in Brazil, with 200,000 new cases per year. On the other hand, in the homozygous form (HbSS) occurs from 25,000 to 30,000 with 3,500 new cases per year. The term sickle cell disease (DF) is applied to a group of hematological conditions characterized by the presence of hemoglobin S. Changes may be manifested in homozygosis, sickle-cell anemia (HbSS), or in association with other hemoglobins (HbSC, HbSD), as well as interaction with thalassemias (NAOUM; NAOUM 2004; ZAGO; PINTO, 2007). The heterozygous form (HbAS) is considered clinically benign. Among hereditary hemoglobinopathies, HbS has differentiated degrees of severity which leads to evident clinical manifestations, known as sickle cell disease (COSTA, 2004). In view of the foregoing, early diagnosis is fundamental. Due to the importance of the PNTN in the early diagnosis, this manuscript was intended to evaluate the PNTN in relation to the coverage index and to estimate the prevalence of sickness and sickle cell trait in Mato Grosso do Sul from 2001 to 2015.

MATERIAL AND METHODS

This research is a cross-sectional retrospective study that used secondary data contained in the IPED-APAE-MS database.
The data analyzed refer to 612,909 individuals born alive in which they were submitted to the examination for hemoglobinopathies by PNTN, developed in the state of Mato Grosso do Sul, Brazil.

Criteria for inclusion of exams

The results included the exams that presented the diagnosis of sickle cell disease or sickle cell trait proven by High Efficiency Liquid Chromatography (HPLC). This methodology is automated and detects the presence and concentration of normal hemoglobins F, A, variants S, D, C and E on the filter paper (TORRES, 2017). BIO-RAD Laboratories® Kits are used for the confirmation and reconfirmation of the altered cases. Non - sickle hemoglobinopathies were excluded. The variables investigated were the number of live births/year; total screening; occurrence of sickle cell disease and sickle cell trait, and coverage index. Prevalences were calculated per point and 95% CI by the Wald method adjusted using the Z distribution, according to Zar (2010) and considering the finite population. In the coverage, the following formula was used: coverage = (number of triads/number of live births) x 100 (TORRES, 2017). For live births, data from the Information System live births of the Department of Information and Informatics of the Unified Health System of Mato Grosso do Sul (SINASC / DATASUS/MS; 2018) were used. This research was approved by consolidated opinion of the Research Ethics Committee (CEP-UFMS), N°. 1514643/2015. According to Torres *et al*., (2017), after confirming the results for sickle cell disease, the appointment of the child's first consultation with a pediatric hematologist at IPED-APAE is performed. The patient is then followed by a multi professional team until the first year of life, when the diagnosis is confirmed by Hemoglobin Electrophoresis. For the continuity of medical care, it is referred to the Regional Hospital of Mato Grosso do Sul, Brazil.

RESULTS

According to data from Tables 1 and 1-a, it can be seen that the coverage index varied over the 15-year period. In the first five years, since the implantation, the percentages were ascending, in the second one the greater coverage was detected in 2006 (91.66%). The annual coverage of the PNTN decreased from the third five-year period from 2011 to 2015, but there was a recovery of 85.48% in 2015. Totaling in the 15 years 88.71%.

Table 1. Number of live births, total screenings and coverage index of children in the state of Mato Grosso do Sul: 2001-2011

Year	Live births	Total screenings	Coverage index (%)
2001	39,939	32,681	81.83
2002	39,890	36,764	92.16
2003	39,248	34,305	87.41
2004	41,378	37,961	91.74
2005	41,125	37,608	91.45
2006	39,309	37,054	94.26
2007	38,378	34,824	90.74
2008	41,045	37,693	91.83
2009	39,979	36,898	92.29
2010	39,805	35,504	89.19
2011	41,805	36,363	86.98
2012	41,876	35,750	85.37
2013	41,879	35,816	85.52
2014	43,588	36,351	83.40
2015	43,665	38,118	85.48
Total	612,909	543,690	88.71

Source: Information System of Live Births of the Department of Information and Informatics of the Unified Health System in Mato Grosso Sul (BRAZIL, 2017) and Database of the Research Institute, Teaching and Diagnostics of the Association of Parents and Friends of the Exceptional IPED- APAE.

Table 1a. Total screenings and coverage index in children screened at IPED-APAE, live births in Mato Grosso do Sul

Period	Live births	Total Screening	Coverage index(%)
1º- 2001-2005	201,580	179,319	88.95
2º- 2006-2010	198,516	181,973	91.66
3º- 2011-2015	213,739	182,398	85.70
Total	612,909	543,690	88.71

Source: Information System of Live Births of the Department of Information and Informatics of the Unified Health System in Mato Grosso Sul (BRAZIL, 2018) and Database of the Research Institute, Teaching and Diagnostics of the Association of Parents and Friends of the Exceptional IPED- APAE.

According to the data in Table 2, it can be observed that the frequency of the number of sickle cell trait cases increased in the three quinquennia, totaling 9,200 newborns with sickle cell trait during the 15 years, with a prevalence of 1.69 with CI (95%) of 1.6808 – 1.7041.

Table 2. Prevalence of sickle cell trait estimated by point and by 95% confidence interval in children screened at IPED - APAE, Mato Grosso do Sul: 2001-2015

FAS					
Year	Triads	Frequency	Prevalence (%)*	CI (95%)**	
2001	32,681	519	1.5938	1.5350	-1.6517
2002	36,764	540	1.4739	1.4385	-1.5084
2003	34,305	616	1.8011	1.7502	-1.8510
2004	37,961	590	1.5591	1.5224	-1.5950
2005	37,608	596	1.5897	1.5518	-1.6267
2006	37,054	625	1.6917	1.6593	-1.7232
2007	34,824	652	1.8776	1.8332	-1.9210
2008	37,693	598	1.5914	1.5544	-1.6275
2009	36,898	508	1.3818	1.3478	-1.4149
2010	35,504	628	1.7740	1.7280	-1.8192
2011	36,363	638	1.7596	1.7100	-1.8084
2012	35,750	662	1.8569	1.8026	-1.9105
2013	35,816	669	1.8730	1.8188	-1.9265
2014	36,351	676	1.8647	1.8073	-1.9214
2015	38,118	683	1.7967	1.7483	-1.8442
2001-2005	179,319	2,861	1.5965	1.5771	-1.6158
2006-2010	181,973	3,011	1.6557	1.6385	-1.6726
2011-2015	182,398	3,328	1.8256	1.8022	-1.8488
Total	543,690	9,200	1.6925	1.6809	-1.7040

* Estimation of prevalence per point.
** Prevalence estimate by 95% confidence interval. Note: FAS: Sickle trait.
Source: Information System of Live Births of the Department of Information and Informatics of the Unified Health System in Mato Grosso Sul (BRAZIL, 2018) and Database of the Research Institute, Teaching and Diagnostics of the Association of Parents and Friends of the Exceptional IPED- APAE.

Table 3. Prevalence of sickle cell disease estimated by point and by 95% confidence interval in children screened at IPED-APAE, Mato Grosso do Sul: 2001-2015

FS					
Year	**Triads**	**Frequency**	**Prevalence (%)***	**CI (95%)****	
2001-2005	179,319	15	0.0094	0.0078	-0.0109
2006-2010	181,973	19	0.0115	0.0099	-0.0129
2011-2015	182,398	33	0.0191	0.0165	-0.0216
Total	543,690	67	0.0127	0.0116	-0.0137
FSA					
Year	**Triads**	**Frequency**	**Prevalence (%)***	**IC (95%)****	
2001-2005	179,319	0	0.0011	0.0004	-0.0016
2006-2010	181,973	0	0.0011	0.0004	-0.0015
2011-2015	182,398	26	0.0153	0.0130	-0.0175
Total	543,690	26	0.0051	0.0044	-0.0058
FSC					
Ano	**Triads**	**Frequency**	**Prevalence (%)***	**IC (95%)****	
2001-2005	179,319	6	0.0044	0.0032	-0.0054
2006-2010	181,973	6	0.0044	0.0033	-0.0052
2011-2015	182,398	11	0.0071	0.0054	-0.0086
Total	543,690	23	0.0046	0.0039	-0.0052
SCF					
Year	**Triads**	**Frequency**	**Prevalence (%)***	**IC (95%)****	
2001-2005	179,319	0	0.0011	0.0004	-0.0016
2006-2010	181,973	0	0.0011	0.0004	-0.0015
2011-2015	182,398	1	0.0016	0.0007	-0.0023
Total	543,690	1	0.0005	0.0003	-0.0007

* Estimation of prevalence per point.
** Prevalence estimate by 95% confidence interval. Note: FAS: sickle cell trait; FS, FSA, FSC, SCF: standard for sickle cell disease
Source: Information System of Live Births of the Department of Information and Informatics of the Unified Health System in Mato Grosso Sul (BRAZIL, 2018) and Database of the Research Institute, Teaching and Diagnostics of the Association of Parents and Friends of the Exceptional IPED- APAE.

According to the data in Table 3, it can be observed that the frequency of the number of sickle cell disease cases increased in the three quinquennia. Of the 543,690 newborns screened, 67 presented sickle cell anemia, resulting in a prevalence of 0.0127 with CI of 0.0116-0.0137 and with FSC 23 cases, resulting in a prevalence of 0.0046, with a CI of 0.0039-0.0052.

DISCUSSION

When evaluating the implementation of the National Neonatal Screening Program (PNTN) from 2001 to 2015, through the results of the database contained in IPED-APAE in Campo Grande, Mato Grosso do Sul, it was observed that of the 612,909 children born alive, 543,690 were screened with a coverage index of 88.71%. These results are above the national coverage parameters of 84% among live newborns (BRAZIL, 2016). In order to report the dynamics of this implantation from 2001, it was necessary to explain the coverage index and the prevalence of sickle cell disease and sickle cell trait in the state of Mato Grosso do Sul, as well as the scientific productions based on the IPED database -APAE. This information was analyzed systematically over different

periods. Coverage index were up in the periods 2000-2005 (HOLSBACH *et al.,* 2008) and 2006-2010 (IVO *et al.,* 2014).
The implementation of the program developed by IPED-APAE for sickle cell anemia between 2000 and 2005, covered satisfactorily the majority of municipalities in the state. In 2002, there was a coverage index of 92.06% (HOLSBACH *et al*., 2008). In these 15 years, the implantation occurred gradually and reached all municipalities of the MS, showing the consolidation of the Program. In 2006, Mato Grosso do Sul with 94.26%, in the second five-year period presented the highest coverage index, when compared to other Brazilian states. In the Federal District, the PNTN evaluated 116,271 newborns from 2004 to 2006, and obtained coverage of 83.4% (DINIZ *et al*., 2009); Santa Catarina in 2011 obtained 89.3% (ELLER; SILVA, 2016); In the period from 2007 to 2009, Bahia reached 88.9% (AMORIM et al., 2010); in 2011, Tocantins reached 84.2% (MENDES; SANTOS, BRINGEL, 2013). The PNTN showed that it is implemented in all Brazilian states. In fact, in 2014 the PNTN reached more than 84% coverage of live births in Brazil (BRAZIL, 2016). The PNTN in the period from 2011 to 2015, although consolidated in the state of Mato Grosso do Sul, presented a decreasing variation from the third quinquennium. That is, with coverage percentage of 83.40% (TORRES *et al*., 2017). Observational studies developed in Mato Grosso do Sul suggest that as of 2006, some factors may be interfering with the good performance of the PNTN. Factors such as the large percentage of collections made early, that is, between the 1st and 2nd day of life, insufficient samples, need for call again patients and difficulty of health services in locating the family. These factors, when grouped together, result in late diagnosis and initiation of treatment, interfering with the prognosis of the disease.

According to a study developed by Ivo *et al*. (2014), 75% of the collections in Mato Grosso do Sul occurred early. Torres (2017) points out that only 25.5% of the collections were performed between the 3rd and 5th day of life, as recommended by the Biological Neonatal Screening Technical Manual (BRASIL, 2016). Both cited studies were performed in the IPED-APAE database (Ivo *et al*., 2014 and Torres, 2017), although in different periods they presented aspects already detected that need to be improved in the PNTN to reach the goal of 100% coverage of live births. As a suggestion arise actions that should be considered in education and health. That is, to guide the pregnant woman and/or the mother about the importance of the exams done in neonatal screening, to seek or access the result. Explanations should be given to pregnant women and/or mothers, which is an examination done only once in a lifetime and that should be guarded carefully. It is necessary to instruct health professionals about the accuracy of blood samples for analysis. The health posts of collection must consider the recommended period of the 3rd and 5th days of life. Agility in patient call cases again for sample collection, active search and early treatment. For diagnosed patients, it is necessary to provide informative material with language understandable to the lay public. It is observed that HbSS is prevalent in the state of Mato Grosso do Sul with 67 newborns detected, followed by FSC with 23 cases. In general, these two variations of sickle cell disease are prevalent in the world and even in Brazil (PIEL *et al*., 2013). When assessing the number of HbAS cases per quinquennium, there were a total of 2,624 cases in the period from 2000 to 2005 (HOLSBACH *et al*., 2008); in the period from 2006 to 2011, 3.040 cases were obtained (IVO *et al*., 2014), and 3,399 cases in the period from 2011 to 2015 (TORRES *et al.,* 2017). The two pathologies had a gradual increase in the state of Mato Grosso do Sul, however, in the last five years the number of cases almost doubled. In relation to the sickle cell disease group, sickle cell anemia (HbSS) is clinically more severe and has high morbidity and mortality. In view of the above, it is essential the early detection with guarantee of medical care and support to the family. Such factors are necessary for the family, as well as the patient to coexist in a positive way with this chronic disease. In fact, it is important to stimulate the organization of patients and their families to guarantee rights already won, such as the free distribution of medicaments in the Public Health System. Hydroxyurea is a social achievement that is part of the medicaments of the high cost pharmacy. In fact, hydroxyurea proved to be essential for the quality of life of people with this disease (BISPO *et al*., 2017). Neonatal screening turned into a consolidated Public Policy, whose action was directed to early diagnosis, starting in 2001 with 12 states of the federation, reaching in 2014, the 26 states and the federal district. Once the condition was established to reverse the late diagnosis of sickle cell disease, there was a need for medical assistance to this population. In response to the pilgrimage of family members and especially the mother who have their children affected by the disease, the Ordinance 822/2001 (BRASIL, 2001) resolved this question. Thus, this Ordinance was implemented and completes 15 years on June 6, 2015 (BRAZIL, 2016).

Conclusion

PNTN is a consolidated public policy in Mato Grosso do Sul, Brazil. As shown in this manuscript, there was a small reduction in coverage over the 15 years, but with signs of recovery in 2015. The number of cases of sickle cell anemia (HbSS) and sickle cell trait increased in the state. To ensure the effectiveness of the PNTN, some health education measures should be implemented, such as the dissemination of information about the disease and, above all, the sickle-cell trait, production of informative and educational material with language that is easy for the lay public. The qualification of the health professionals about the quality of the samples is necessary so that they do not collect samples early. Thus, it is necessary to highlight how these factors may compromise the treatment.

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