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Cezar D.S. Souza , Clea S. Almeida , Pamela V. Andrade , Joilson M. Santos , José L.G. Amaral , Helga C.A. Silva

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BJAN-D-23-00526_Letter to The Editor

Retrospective analysis of 20-years of activity of the Brazilian malignant hyperthermia hotline service

Cezar D.S. Souza, Clea S. Almeida, Pamela V. Andrade, Joilson M. Santos, José L.G. Amaral, Helga C.A. Silva*

Universidade Federal de Sao Paulo, Departamento de Anestesiologia, Dor e Terapia Intensiva, Unidade de Hipertermia Maligna, São Paulo, SP, Brazil

*** Corresponding author.**
E-mail: halsilva@uol.com.br (H.C.A. Silva).
ORCID ID:
Cezar Daniel Snak de Souza: 0000-0002-0464-3332
Pamela Vieira de Andrade: 0000-0002-1095-4807
Joilson Moura dos Santos: 0000-0002-0850-5893
José Luiz Gomes do Amaral: 0000-0003-2177-5174
Helga Cristina Almeida da Silva: 0000-0002-9372-7019

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Dear Editor,

Malignant Hyperthermia (MH) is a pharmacogenetic syndrome with autosomal dominant inheritance manifested as a crisis of hypermetabolism associated with anesthesia. This syndrome has significant clinical variability, ranging from abortive forms, such as isolated masseter spasm, to fulminant forms.[1] Typical forms are commonly characterized by hypercapnia, tachycardia, muscle rigidity, hyperthermia, metabolic acidosis, and rhabdomyolysis, and can evolve with death in 11%–25% of cases.[1,2] MH is caused by exposure of genetically susceptible individuals to halogenated anesthetic agents and/or depolarizing neuromuscular blocker succinylcholine.[1] The frequency of MH is estimated at 1:50,000 anesthesia in adults and 1:10,000 in children, occurring in all ethnic groups, and more frequently in men than women.[1] Mutations in the Ryanodine Receptor Gene (RYR1) are present in 50% to 70% of families, followed by mutations in the

dihydropyridine receptor gene (CACNA1S) in 1% of cases and isolated cases of mutations in the STAC3 gene. To date, the gene locus has not been identified in the remaining MH cases.[1] The clinical diagnosis is based on the history of exposure to triggering agents associated with clinical and laboratory findings, while the definitive diagnosis is based on the in Vitro muscle Contracture Test (IVTC). Alternatively, genetic tests can be used to search for pathogenic variants linked to MH. The main differential diagnoses are Neuroleptic Malignant Syndrome (NMS), Serotonin Syndrome (SS), thyrotoxicosis, sepsis, pheochromocytoma, iatrogenic hyperthermia, ischemic encephalopathy, ascending generalized tonic-clonic seizures following intrathecal use of contrate and overdose of 3,4-Methylenedioxymethamphetamine (MDMA/ecstasy).[1]

In Brazil, since 1991 there has been a telephone service to guide the diagnosis and treatment of anesthetic complications related to MH. The MH Hotline is available 24 hours a day, seven days a week, and has a single and exclusive telephone line (+55-11-55759873) to guide Brazilian health professionals in managing MH and its differential diagnoses.[3] The primary objective of the present study was to analyze the characteristics of calls to the Brazilian MH Hotline between 2001–2019.

The present observational and retrospective study was approved by the Institution's Ethics and Research Committee (CEP nº 1050/2006, 0970/2008, and 0979/2017), and is part of the Brazilian Multidisciplinary Study of Malignant Hyperthermia (Database: https://hdl.handle.net/20.500.12682/rdp/GAB9EH). This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The primary material consists of all service forms from the Brazilian HM Hotline between 01/01/2001 and 31/12/2019. This form has the following fields: name of the consultant, date of phone call, telephone, profession, specialty, place of call, e-mail, patient's name/age/sex/mother's name, problem, and solution presented. The secondary study material consisted of the medical records of patients who, after being notified to the MH Hotline, were referred for evaluation at the service after signing the free and informed consent form. Patients and family members treated on an outpatient basis and with an indication for additional investigation were referred for IVCT and genetic testing when indicated. Each form was analyzed by two independent researchers (CDSS and HCAS). Categorical variables were expressed as frequency and percentage.

The Brazilian hotline service for MH received 363 calls from 01/01/2001 to 12/31/2019 (19.1 ± 6.90 calls/year), with most calls coming from the South and Southeast

states of Brazil (Table 1). If we compare the percentage of calls with the percentage of the population living in each region, there is evidence of underreporting in the Northeast, Central West, and North regions. The consultants were mainly physicians (72.5%), followed by patients/family members (9%), pharmacists (3.3%), and nursing staff (2.7%). The majority of calls were for evaluation of suspected MH acute crises (45.7%), followed by NMS (9.6%), and SS (0.3%). The other calls aimed to obtain information on how to perform safe anesthesia (12.9%), refer families for investigation (12.9%), obtain dantrolene (9.3%) and scientific information about HM (7.7%). Eight families with crises considered compatible with MH were evaluated at the MH service; four were investigated for susceptibility to MH. In two families, IVCT was performed on two patients with a personal history of acute malignant hyperthermia crisis (index cases: one positive and one negative), while in two other families, IVCT was performed on three individuals related to the index case (negative results).

The Hotline for MH had a lower-than-expected number of calls, given the continental dimensions of Brazil. Riazi et al.[4] and Larach et al.[5] reported an annual average number of MH cases of 19.6 and 31.4, respectively, with 6.78 confirmed by IVCT by the Canadian group and 15.05 with clinical MH score $\geq$ 35 in the American group. Although a potentially fatal condition, MH remains possibly underreported to the Brazilian MH Hotline by professionals from part of the Brazilian territory. Most of the calls were from the South/Southeast regions of the country, suggesting the need for greater dissemination of information related to MH and the hotline service in the other regions of Brazil. Furthermore, less than five percent of suspected cases were returned to our service for investigation. To reverse this situation, in 2010, an email service was implemented to guide health professionals and family members (cedhima@hotmail.com), and in 2016, a website was created (cedhima.unifesp.br) for guidance of family members, patient referral, and general scientific dissemination. The present disclosure of information about calls to the MH Hotline is another crucial step towards recognizing the gaps in the fight against MH in our country, increasing the degree of suspicion and amplifying educational actions for health professionals in Brazil.

Ethical approval

The present study was approved by the Institution's Ethics and Research Committee (CEP nº 1050/2006, 0970/2008 e 0979/2017).

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Conflicts of interest

The authors declare no conflicts of interest.

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Table 1 Number of calls (2001-2019) versus population from the five Brazilian regions.

	2001–2019		Population (2022 census)[a]	
Regions of Brazil	**n**	**%**	**n**	**%**
Southeast	252	69.4	84 847 187	41.8
South	57	15.7	29 933 315	14.7
Northeast	25	6.9	54 644 582	26.9
Midwest	17	4.7	16 287 809	8
North	3	0.8	17 349 619	8.5
Not informed	9	2.5	–	–
Total	**363**	**100**	**203 062 512**	**100**

n, absolute number, %, percentage.

[a] Brazilian Institute of Geography and Statistics, available at https://sidra.ibge.gov.br/tabela/4714.