

# STUDY OF THE ASSOCIATION OF EXPOSURE TO GENOTOXIC AGENTS AND MYELOYDYSPLASTIC SYNDROME OR SECONDARY ACUTE MYELOID LEUKEMIA IN PATIENTS ATTENDED AT AN AMBULATORY REFERENCE SERVICE IN CEARÁ

João Vitor Araújo Duarte<sup>1</sup>; (ORCID 0000-0002-1473-4043)  
Beatrice Araújo Duarte<sup>1</sup>; (ORCID 0000-0002-8339-5946)  
João Lucas Araújo Morais<sup>1</sup>; (ORCID 0009-0003-6759-6961)  
Matheus Vasconcelos Horta<sup>1</sup>; (ORCID 0009-0004-6715-4634)  
Fernando Barroso Duarte<sup>2</sup>; (ORCID 0000-0001-5170-695X)

<sup>1</sup> *Christus University Center*

<sup>2</sup> *Walter Cantídio University Hospital – HUWC/UFC*

Corresponding author: Beatrice Araújo Duarte (Email: [beatriceaduarte@gmail.com](mailto:beatriceaduarte@gmail.com))

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## INTRODUCTION

Myelodysplastic syndromes (MDS) consist of a heterogeneous group of diseases with comprehensive clinical, laboratory characteristics and pathogenesis but have in common a clonal defect in hematopoietic progenitor cells<sup>1</sup>. MDS is characterized by cytopenia in peripheral blood with normocellular or hypocellular bone marrow with the presence of dysplastic changes (>10%) in one or more hematopoietic lineages. About a third of patients with MDS progress to myeloid leukemia<sup>2,3</sup>. The annual incidence of MDS occurs in 3 to 4/100,000 people in the United States<sup>1</sup>. Advanced age is one of the risk factors for the development of MDS, being rare in childhood<sup>4</sup>, and it is more common in males<sup>1</sup>. Epidemiological studies have demonstrated the association between the occurrence of MDS and factors such as smoking, exposure to benzene and derivatives<sup>2,5-12</sup>. Pesticides, also commonly called pesticides and pesticides, are associated with the occurrence of leukemia, lymphoma and other hematological diseases<sup>13-15</sup>, with a positive association between domestic exposure to pesticides and childhood leukemia<sup>13</sup>. Poynter and colleagues<sup>16</sup> evaluated occupational and residential chemical exposures as risk factors for Acute Myeloid Leukemia (AML) and MDS using population-based data. Associations were verified between SMD and LMA and benzene and vinyl chloride. Exposure to soot, creosote, paints, dyes and tanning solutions, and coal dust have been associated with AML. Al-

though chemical exposures have a clear role in the etiology of myeloid malignancy, these exposures do not represent the majority of cases, with exposures being reported in a small percentage of cases ( $\leq 10\%$ )<sup>16</sup>. The issues of exposure of population groups to risk situations that cause myelotoxicity, which can trigger a hematological disease such as MDS or AML, justifies the relevance of the present study for public health. Understanding the epidemiological behavior of MDS and AML related to the environment and occupation is fundamental for prevention and the establishment of preventive measures. Therefore, the present study aims to associate the various health problems in patients with MDS and AML with the environmental/occupational risk conditions associated with them in a specialized hematology service.

## OBJECTIVES

### General

Associate exposure to genotoxic agents in patients with Myelodysplastic Syndrome and Secondary Acute Myeloid Leukemia in a State reference hospital.

### Specifics

- Determine the distribution of demographic and clinical characteristics of patients with MDS and AMLs treated at a reference outpatient service in the state of Ceará;

- Correlate personal and family history and occupational/environmental exposure to genotoxic agents with the occurrence and problems related to MDS and/or AMLs;
- Establish a causal relationship between exposure to environmental or occupational hematotoxic risk situations with the occurrence of MDS and AMLs

## MATERIALS AND METHODS

This is an observational, prospective and retrospective study, through research in patient records. The study was carried out in the state's main hematology reference service, located in the onco-hematological diseases outpatient clinic of the Walter Cantídio University Hospital (HUWC), in Fortaleza, Ceará. The population of this study consisted of adults of both sexes, with a diagnosis of MDS and/or AML confirmed by the clinic and laboratory tests, undergoing outpatient follow-up care from July 2021 to July 2022, capturing a total of 50 patients. Those patients who did not reside in Ceará and who were diagnosed with another oncological disease were excluded from the study. HUWC is a reference in the care of people with Myelodysplastic Syndrome and Secondary Acute Myeloid Leukemia located in the Rodolfo Teófilo neighborhood, Fortaleza-CE.

All procedures were carried out in accordance with the ethical guidelines established by resolution 466/12 of the National Health Council. To this end, immediately after the consultation, the patient was informed about the study and after reading and signing the informed consent form (TCLE), the study included the application of a pre-structured questionnaire lasting approximately 20 minutes. From then on, consultation of medical records was possible by signing a trust form. by the hospital superintendent. The data obtained in the study regarding hematological diseases were crossed with data from the literature, aiming to establish a causality criterion with environmental or occupational risk conditions.

The cases were distributed considering individual characteristics, personal, occupational and environmental history. For purposes of comparison between variables (dependent and independent), cases were grouped according to contingency tables. The data collected will be analyzed using the SPSS Program

(Statistical Package for the Social Sciences) version 8.0. The study population characterization data were presented using absolute and relative frequencies and organized in simple tables. Differences were considered statistically significant when  $p < 0.05$ .

### Inclusion criteria

Patients with Myelodysplastic Syndrome and Secondary Acute Myeloid Leukemia treated at the HUWC outpatient clinic were invited to participate in the study consecutively. Informed consent was obtained prior to carrying out any study procedures.

### Exclusion criteria

Patients who did not meet diagnostic criteria for MDS or AML were excluded from the research.

### Risks and Benefits

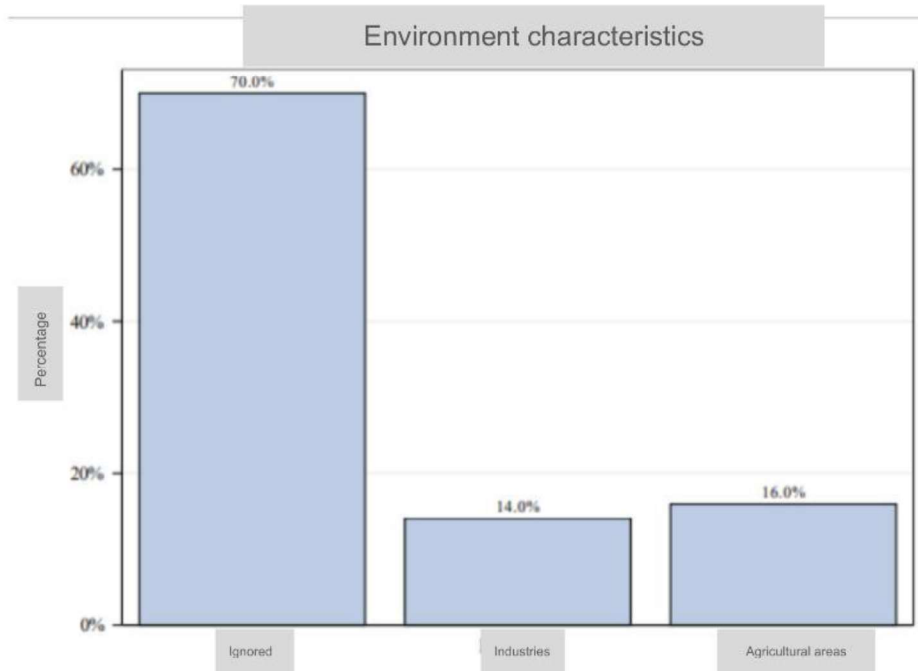
**Risks:** The questionnaires were administered before or after routine consultations at the unit. No extra travel was necessary. The assessment was carried out in the usual way. The risk of the present study was related to the confidentiality of the information and data of the research participants.

**Benefits:** The information collected in the questionnaire contributed to the understanding of the association between genotoxic agents and MDS and AMLs. Participation in the study is voluntary.

## RESULTS

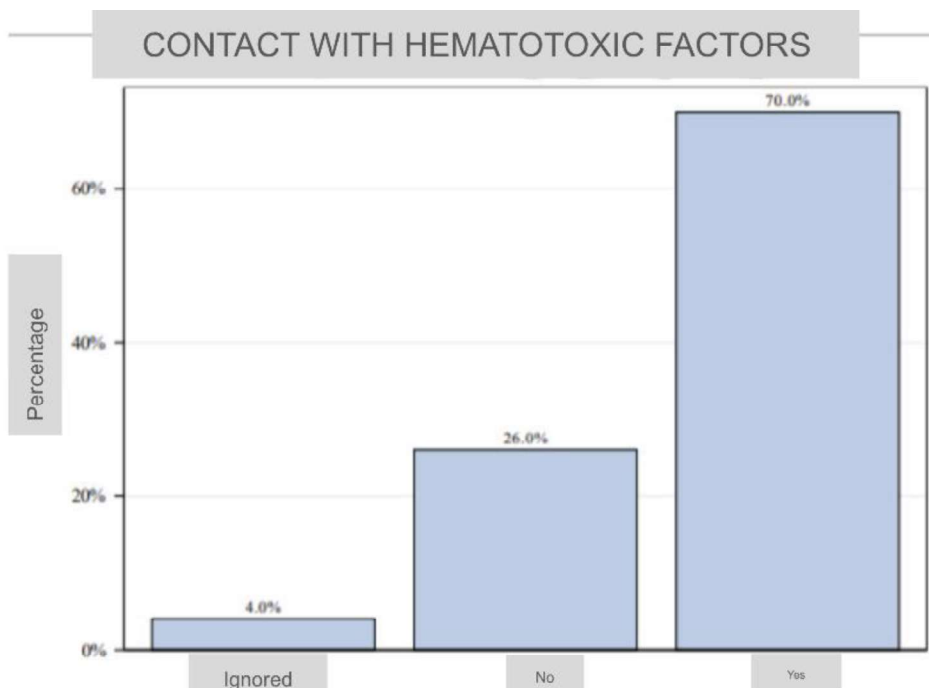
The sample collected consists of 50 patients who were undergoing therapeutic activities at the HUWC Hematology Service, with an average age of 67.8 years. Among these, 14 patients (28%) were male, while 36 patients (72%) were female. With regard to race, a numerical superiority was noted in mixed/brown indigenous individuals and Caucasian/white individuals; which, together, accounted for 90% of the patients interviewed. Regarding the patients' level of education, a diverse range was found, in which 7 patients (14%) were illiterate and 43 patients (86%) had some level of education. Regarding domicile situation, 6 patients (12%) live in rural areas, while 44 patients (88%) live in urban areas. In this sense, it was reported that 30% of these patients live in residences close to industries (14%) and agricultural areas (16%) (Figure 1).

**FIGURE 1 – Environment characteristics**



Of the patients interviewed, 47 were diagnosed with myelodysplastic syndrome; while 3 - have a diagnosis of acute myeloid leukemia. Of these, 11 patients reported having reports of similar hematological disease in the family. Of the 50 patients, 35 patients (70%) stated that they had contact with factors hematotoxic; of these: pesticides (30%), metals (6%), solvents (38%), paints and varnishes (38%) and ionizing radiation (40%) (Figure 2).

**FIGURE 2 – Contact with hematotoxic factors**



When it comes to lifestyle habits, it was reported that 42 patients (84%) were using medications, such as: antihypertensives (46%), antibiotics (5%), cardiotonics (6%), hypoglycemic drugs (15%), centrally acting drugs (26%), gastroprotectors (14%) or anti-inflammatory drugs (4%). In social history, 15% of patients reported smoking or having a previous history of smoking. With regard to alcohol consumption, 14% reported drinking or having a previous history of alcoholism. Regarding the consumption of illicit drugs, only 1 patient (2%) reported using or having a previous history of dependence.

## DISCUSSION

In the present study, it is possible to observe a higher number of female patients (72%) compared to male patients (28%), one of the factors possibly related to the increased prevalence of MDS and AML would be the exposure of some women to hematotoxic products from dyes used in hair, as the female public is exposed in greater quantities to these factors compared to the male public. According to the study Hair Dye Ingredients and Potential Health Risks from Exposure to Hair Dyeing. In the American and European population, around 33% of women over 18 and around 10% of men over 40 dye their hair. Permanent hair dyes penetrate the hair to change the natural hair color, and are more often associated with adverse reactions and pose a greater risk to human health. Two population-based case-control studies related<sup>3,17</sup> that patients subjected to the use of hair dye had a higher prevalence of primary myelodysplastic syndrome when compared to individuals who did not have such exposure<sup>18</sup>.

The predominance of patients living in urban locations (88%) in our study is notable, however patients living in rural locations (12%) may have been exposed to pesticides that are toxic to the bone marrow, especially pesticide agents. The relationship between occupational exposure to pesticides in high doses and the occurrence of several diseases is well established, notably in hematological malignancies, recently reported in AML<sup>19,20</sup>.

According to the study Low-Dose Pesticides Alter Primary Human Bone Marrow Mesenchymal Stem/Stromal Cells through ALDH2 Inhibition<sup>21</sup>, the risk of developing a myeloid disorder (MDS or AML) for individuals exposed to such components is increased compared to the general population, however the contribution of pesticide products to the development of such hematological disorders in the exposed individual is low, thus suggesting a multifactorial pathophysiology that may include environ-

mental impact. This hypothesis is supported by the observation that there is an underexpression of aldehyde dehydrogenase 2 (ALDH2), with an increased concentration of acetaldehyde in the stromal and mesenchymal cells of patients exposed to pesticides who developed primary MDS<sup>21</sup>.

(ALDH2) is known to be a cytosolic enzyme responsible for the intracellular oxidation of aldehydes, which is involved in the oxidation of retinol to retinoic acid during the initial stages of differentiation of hematopoietic stem cells (HSC). This enzyme is crucial for the protection of HSCs against endogenous and exogenous toxic aldehydes, as well as for the ability of these cells to differentiate into distinct lineages<sup>21</sup>.

In the sample collected, it was seen that 11 patients (22%) had similar hematological diseases in the family. Currently, approximately 7 loci of a single gene are known that, when mutated, predispose to an increased risk of developing primary MDS and AML. Table 1 summarizes the 7 single-gene loci that predispose to hereditary MDS, as well as the two most common pediatric bone marrow failure diseases that increase the risk of adult incidence of MDS.<sup>25</sup>

Therefore, clinicians should be aware of the signs and symptoms of hereditary predisposition to hematologic malignancies and should obtain a family history and careful history in all patients with MDS and AML to identify patients who may be appropriate for additional genetic counseling and testing. Since, individuals with such inherited genes need additional consideration regarding the appropriate therapeutic choice, especially with regard to allogeneic stem cell transplantation<sup>22</sup>. In our study, there was a numerical predominance of mixed/brown individuals and Caucasian/white individuals; which, together, accounted for 90% of the patients interviewed. Findings from the study The incidence, risk factors, and survival of acute myeloid leukemia secondary to myelodysplastic syndrome: A population-based study indicate that race does not alone contribute to the increased risk of developing AML and/or MDS, but when other variables are attributed such as: Married marital status, female sex and black race demonstrated a better prognostic impact on survival when compared to single, white, male individuals who demonstrated a worse prognostic impact on survival<sup>23</sup>.

In the sample of the present study, it was proven that 11 patients had contact with pesticide agents. In a 2021 study, Foucault et al evaluated exposure to pesticides and the relationship with changes in the mesenchymal stroma of the bone marrow, altering the production of cell activity. ALDH2 enzyme, which



**TABLE 1 – Familial myelodysplastic syndromes (MDS)/acute leukemia (AL) predisposition syndromes**

Syndrome	Gene	Inheritance	Heme Malignancy	Other Associated Abnormalities	Reference
Familial platelet disorder with propensity to myeloid malignancies	<i>RUNX1</i>	AD	MDS/AML/T-cell ALL	Thrombocytopenia, bleeding propensity, aspirin-like platelet dysfunction	[3]
Thrombocytopenia 2	<i>ANKRD26</i>	AD	MDS/AML	Thrombocytopenia, bleeding propensity	[4]
Familial AML with mutated <i>DDX41</i>	<i>DDX41</i>	AD	MDS/AML, CMML	None	[5]
Thrombocytopenia 5	<i>ETV6</i>	AD	MDS/AML, CMML, B-cell ALL, multiple myeloma	Aplastic anemia	[6]
Familial MDS/AML with mutated <i>GATA2</i>	<i>GATA2</i>	AD	MDS/AML/CMML	Neutropenia, monocytopenia, MonoMAC syndrome, Emberger syndrome	[7]
Familial aplastic anemia with <i>SRP72</i> mutation	<i>SRP72</i>	AD	MDS	Aplastic anemia	[8]
Familial AML with mutated <i>CEBPA</i>	<i>CEBPA</i>	AD	AML	None	[9]
Fanconi anemia	Complementation Groups	AR, X-linked	MDS, AML	Pancytopenia, macrocytic anemia, congenital malformations	[10]
Telomeropathies (dyskeratosis congenita)	<i>TERC, TERT, others</i>	AD, AR	MDS/AML	Macrocytosis, aplastic anemia, oral leukoplakia, dysplastic nails, lacy skin rash	[11]

AD, Autosomal dominant; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CMML, chronic myelomonocytic leukemia; AR, autosomal recessive.

induces accumulation of acetaldehyde and damage to DNA, causing defects in primitive hematopoiesis. Therefore, the genotoxicity of these components and the need for appropriate preventive measures are reaffirmed.

In a study carried out in 2016 involving exposure to polycyclic aromatic hydrocarbons and other metals<sup>24</sup>, 41 studies were analyzed, in which, in 4, significance was seen between aluminum, iron and steel smelting industries and the occurrence of leukemias and lymphomas not hodgkin. In the present study, an association of 6% with metals and 38% with solvents was seen, lacking more relevant studies.

In a systematic review carried out in 2022, it is reported that 2 population studies determined that the use of hair dye is a risk factor for MDS<sup>3,17</sup>, although a large number of studies have found no significant association between hair dye and an overall increased risk for leukemias, NHLs or myelomas. Therefore, given the presence of conflicting data, further studies are necessary.

In a study that evaluated radiation exposure in children in 2012<sup>25</sup> an association was seen between brain tumors and leukemia in children who underwent more CT scans. In addition to this finding, 40% of the patients studied had some exposure to radiation.

Tobacco remains an important risk factor associated with neoplasms, despite a reduction due to awareness campaigns over the years, in a 2021 study, it was proven that leukemias still constitute 13% of malignancies caused by smoking.mar<sup>26</sup>. We observed in our sample an exposure of 15% of patients among smokers and ex-smokers.

**CONCLUSION**

The biases in the study were the number of patients, as it is a rare disease, and the failure to monitor patients longitudinally, which makes an analysis of cause and consequence impossible.

Lack of knowledge about this pathology combined with its low incidence makes early diagnosis

difficult, increasing morbidity and mortality, making it necessary to focus more on this disease in the training of primary care doctors. Knowing the main risk factors can help in the screening and diagnostic suspicion of myelodysplastic syndrome, mitigating its complications, such as acute myeloid leukemia.

In short, it has been demonstrated that the main factors involved in the genesis of Myelodysplastic Syndrome are family history and exposure to hepatotoxic factors, such as pesticides, paints, varnishes and radiation. Demonstrating the need for guidance from the health system to the population with the aim of primary prevention of a disease with a high rate of morbidity and mortality and treatments that are difficult to access.

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