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CLINICAL FINDINGS AND HEARING CHANGES IN PEOPLE WITH SICKLE CELL ANEMIA

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ABSTRACT

Introduction: Among the genetic variations encompassed by Sickle Cell Disease, Sickle Cell Anemia stands out as the most severe form. In this pathology, the deformity of red blood cells leads to vaso-occlusive crises that can result in ischemia in the cochlear region, with consequent progressive deterioration of hearing. Objectives: To characterize the degree and type of Hearing Loss; To identify the main Hearing Complaints; To analyze the relationship between having Hearing Complaints and having Hearing Loss; To verify the association between clinical findings and Hearing Loss. Method: This is a cross-sectional, comparative, and analytical study formed by two groups: Case Group (G1) and Control Group (G2), composed of patients from the Hematology Outpatient Clinic of the University Hospital of the Federal University of Sergipe. A total of 212 participants were admitted to the study, 106 from each group. All responded to the Speech-Language Pathology Anamnesis and underwent Meatoscopy, Tonal and Vocal Audiometry, and G1 also responded to the Visual Analog Scale. Results: G1 presented a higher percentage of Hearing Loss compared to G2, with a predominance of mild bilateral Sensorineural Hearing Loss, in addition, G1 had a significantly higher Odds Ratio for having Hearing Loss compared to individuals without Sickle Cell Anemia; There was a correlation between having Hearing Complaints and the presence of Hearing Loss in G1. The Hearing Complaints mentioned were: difficulty understanding speech, tinnitus, and hearing loss. Most patients in G1 were treated with Hydroxyurea; The presence of Pneumonia, Stroke, and Systemic Arterial Hypertension was identified. Conclusion: Patients with Sickle Cell Anemia are more likely to have Hearing Loss. These individuals also presented a higher frequency of hearing complaints, mainly Difficulty understanding Speech. It was also found

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Revista ARACÊ
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that the later the diagnosis of sickle cell anemia, the greater the possibility of hearing loss. It was shown that the presence of comorbidities and vaso-occlusive crises were not associated with the occurrence of hearing loss in the patients evaluated. In the end, no evidence was found to rule out the use of hydroxyurea as a protective factor for hearing in sickle cell patients.

Keywords: Sickle Cell Disease. Sickle Cell Anemia. Hearing Loss.

Revista ARACÊ
ISSN: 2358-2472

INTRODUCTION

Characterized as an autosomal recessive genetic disorder, in Sickle Cell Disease there is a variation in the β-globin gene on chromosome 11 (Abou-Elhamd, 2012). During the mutation, the replacement of the amino acid valine by glutamate in the sixth position of the β chain of hemoglobin results in a hemoglobin HbS (sickle cells) as opposed to the normal hemoglobin HbA in the shape of a disc (Stuart, Preast, 2012). This new cellular conformation can result in the blockage of surrounding microvessels, impairing blood circulation and resulting in ischemia of the affected tissues. (Silva, Nova, Lucena, 2012). The terminology used for Sickle Cell Disease is broad and encompasses a set of hereditary mutations (Abou-Elhamd, 2012; Miguel, 2014; Kiser et al., 2019; Ware et al., 2017; Weigert et al., 2021), manifesting in different hemoglobin genotypes (Lima et al., 2019). Among these variations, Sickle Cell Anemia (SCA) is considered the most serious and presents a serious public health problem in underdeveloped and developing countries (Silva, Nova, Lucena, 2012).

The clinical manifestations of SCA include pain crises; episodes of infection and vaso-occlusion; recurrent acute chest syndrome (symptoms related to pneumonia); priapism and stroke (Abdelmahmuod, 2020; Abou-Elhamad, 2012; Kato et al., 2018; Longoria, 2022).

Pain attacks usually affect the arms, legs, chest, and abdomen; and vaso-occlusions, which result in local ischemia, are a result of the sickle shape of hemoglobins associated with a hard and sticky conformation acquired by this type of red blood cell, making it difficult for them to circulate in the bloodstream, favoring their accumulation in the vessels and capillaries, compromising microcirculation (Abdelmahmuod, 2020; Brazil, 2014; Stuart, Preast, 2012). Fatigue is also a common symptom in people with SCA, although this symptom is not fully understood in research (Ramos, Araújo, 2024). Continuous oxidative stress and vascular inflammation benefit the ischemia-perfusion cycle, causing widespread, chronic, and progressive damage to different organs and tissues (Abdelmahmuod, 2020; Kiser et al., 2019). From this perspective, considering the cochlear sensitivity to hypoxia, the literature proves that in Sickle Cell Anemia (SCA), recurrent cases of vaso-occlusive crises can cause damage to the cochlear microvasculature, resulting in impairment of the central auditory pathways due to hypoxia (Derin et al., 2017; Lago et al., 2019; Strum et al., 2021). The hearing deficit is aggravated because the oxygen supply to the cochlea depends exclusively on the labyrinthine artery,

Revista ARACÊ
ISSN: 2358-2472

as this artery is classified as terminal and does not have a collateral circulation system responsible for supplying circulation in the event of obstruction, making the inner ear more susceptible to circulatory changes (Kiser et al., 2019; Nelson et al., 2022). Thus, SCD has often been associated with different patterns and degrees of Sensorineural Hearing Loss (SNHL), ranging from profound bilateral losses with partial recovery over time, to mild to moderate unilateral losses, predominantly in high frequencies (Al Jabr, 2016; Lucena et al., 2020; Okbi et al., 2011).

From the perspective of the impact caused by Sickle Cell Anemia on the cochlear organ, studies elucidate the importance of preventive measures, early diagnosis, and continuous monitoring in individuals with this condition. Failure to identify or late diagnosis of SCA can have significant consequences for the central auditory pathways, compromising the auditory development of patients (Oliveira et al, 2022).

In the end, although there are studies addressing the pathophysiology of hearing loss and the auditory profile of individuals with SCA, there is a gap in audiological findings, such as hearing complaints, and their relationship with other clinical findings in this population.

METHODOLOGY

This is a cross-sectional, comparative, and analytical study consisting of two groups: Case Group (G1) and Control Group (G2), matched 1:1 by sex and age, selected for convenience at the Hematology Outpatient Clinic of the University Hospital of the Federal University of Sergipe (HU-UFS).

Individuals aged 7 to 40 years old, diagnosed with Sickle Cell Anemia (SCA) confirmed by hemoglobin electrophoresis, and under medical follow-up were included in G1. Subjects with a history of chronic otological alterations, anatomical alterations in the External Ear (EO) or External Auditory Meatus (EAM), verified by microscopy, and occupational noise exposure were excluded.

For the Control Group (G2), the inclusion criteria considered individuals in the same age range as G1 (7 to 40 years), without hemoglobinopathy or family history of this group of diseases. Participants with HL, a history of chronic otological conditions, and noise exposure were excluded. Occupational noise exposure, changes in the LE or MAE, as evidenced by microscopy, and previous chemotherapy treatment.

Revista ARACÊ
ISSN: 2358-2472

The hearing assessment was preceded by a review of medical records and audiological anamnesis in order to collect clinical and audiological data about the patients. Then, the patients who met the inclusion criteria underwent Meatoscopy, Tonal, and Vocal Audiometry.

The Audiometry was performed at the Audiology Outpatient Clinic of HU-UFS, in a Vibrassom audiometric booth with adequate acoustic insulation, using an Interacoustics audiometer, model Ad 229b, and the descending-ascending method was used (Redondo; Lopes-Filho, 2013). To determine the hearing threshold, the pulsatile stimulus (Warble) was chosen, since the authors above classify it as the most easily identified by subjects undergoing the exam. During the audiometry, the minimum audibility thresholds were investigated for the frequencies of 250, 500, 1,000, 2,000, 3,000, 4,000, 6,000, and 8,000 Hz, separately.

As for the types of hearing loss (HL), the guidance followed the description by Lopes-Filho (2013). In sensorineural hearing loss (SNHL), the structures responsible for conducting sound are preserved, but there is sensory damage to the cochlea. Conductive HL is characterized by changes found in the outer ear (EO*) and/or middle ear (ME). Finally, mixed HL will present conduction and sensory damage factors.

The classification of the degree of hearing loss adopted by the standards of the World Health Organization (WHO, 2020), is one of the diagnostic methods suggested by the System of Speech-Language Pathology Councils (SCF, 2020). Thus, the hearing level was measured based on the quadrivial average of the acoustic frequencies of 500 Hz, 1KHz, 2KHz, and 4 KHz.

The performance of this study was approved by the Ethics and Research Committee of HU-UFS with CAAE: 17045119.6.0000.5546 and consolidated opinion No.: 3,509,379, in compliance with the terms of Resolution No. 466, of December 12, 2012, of the National Health Council of the Ministry of Health of Brazil.

RESULTS

The sample profile of the study included 212 individuals divided between two groups, G1 (Case) and G2 (Control), with 106 participants each. The median age was 17 years for each group, with an Interquartile Range (IQR) of [11-23]. There was no significant difference (p=0.950) between the frequency of men (49.1%) and women (50.9%).

Revista ARACÊ
ISSN: 2358-2472

A significantly higher proportion of Hearing Loss (HL) was observed in G1 (34.9%), compared to G2 (16%). Regarding the distribution of HL, G1 presented higher proportions of bilateral HL (19.8%) and sensorineural HL, both in the Right Ear (RE) (0.9%) and in the Left Ear (LE) (0.9%). There was also a predominance of mild HL in the RE (1.9%) in G1 and, although the difference did not reach significance, G1 (24.5%) had a slightly higher proportion of mild HL, compared to G2 (15.1%), in the LE ($p > 0.005$).

Table 1 shows non-significant associations between patients in G1, considering the presence or absence of Hearing Loss (HL) with the variables gender, education, and clinical findings. Higher medians, in addition to significance, were observed for the time of diagnosis and time of treatment initiation among individuals with HL.

Table 1 – Association between age and clinical variables by absence or presence of Hearing Loss in G1.

Hearing Loss	No	Yes	p-value
Age (years), Median [IQR]	16 [11-20]	18 [11-24]	0.375 M
Age Group			
7-18 years	41 (59.4%)	19 (51.4%)	0.538 F
18-40 years	28 (40.6%)	18 (48.6%)	
Total	69 (100%)	37 (100%)	
Sex			
Male	36 (52.2%)	16 (43.2%)	0.420 F
Female	33 (47.8%)	21 (56.8%)	
Total	69 (100%)	37 (100%)	
Education Level			
Illiterate	0 (0%)	1 (2.7%)	0.104 Q
Incomplete Primary	37 (54.4%)	14 (37.8%)	
Primary	0 (0%)	3 (8.1%)	
Incomplete High School	16 (23.5%)	9 (24.3%)	
High School	12 (17.6%)	9 (24.3%)	
Incomplete Higher Education	2 (2.9%)	1 (2.7%)	
Higher Education or more	1 (1.5%)	0 (0%)	
Sickle Cell Disease Diagnosis Time			
Median [IQR]	11.5 [7.4-16]	17 [9-22]	0.008 M
Sickle Cell Disease Treatment Time			
Median [IQR]	11 [7-15.5]	17 [9-22]	0.003 M
Diagnosis-Treatment Time			
Median [IQR]	0 [0-0]	0 [0-0]	0.695 M
Use of Hydroxyurea			
No	22 (31.9%)	10 (27%)	
Yes	47 (68.1%)	27 (73%)	0.662 F
Total	69 (100%)	37 (100%)	
Hospitalization			
No	21 (30.9%)	9 (24.3%)	0.508 F
Yes	47 (69.1%)	28 (75.7%)	
Pain Crises			
No	7 (10.3%)	3 (8.1%)	1.000 F
Yes	61 (89.7%)	34 (91.9%)	
Self-Perception of Pain (VAS), Median [IQR]	9 [8-10]	9 [8-10]	0.592 M

Legend: IQR – Interquartile Range. n – absolute frequency. % – relative percentage frequency. M – Mann-Whitney Test. F – Fisher's Exact Test. Q – Pearson's Chi-Square Test.
Source: The author (2024).

Revista ARACÊ
ISSN: 2358-2472

Table 2 – Association between comorbidities reported by absence or presence of Hearing Loss in G1.

Hearing Loss	No	Yes	p-value
Comorbidities			
No	52 (75.4%)	21 (56.8%)	
Yes	17 (24.6%)	16 (43.2%)	0.077 F
Total	69 (100%)	37 (100%)	
Hypertension (HTN)			
No	69 (98.6%)	35 (97.2%)	1.000 F
Yes	1 (1.4%)	1 (2.8%)	
Stroke (CVA)			
No	61 (88.4%)	32 (86.5%)	0.765 F
Yes	8 (11.6%)	5 (13.5%)	
Pneumonia			
No	59 (85.5%)	26 (70.3%)	
Yes	10 (14.5%)	11 (29.7%)	0.078 F
Total	69 (100%)	37 (100%)	

Legend: IQR – Interquartile Range. n – absolute frequency. % – relative percentage frequency. F – Fisher's Exact Test.
Source: The author (2024).

Table 3 – Odds Ratio for G1 having Hearing Loss.

Hearing Loss	**OR (95% CI)**	**p-value**
G1 – Case Group	2.85 (1.48-5.49)	0.002
Adjusted for: Case Group and Sex	2.85 (1.48-5.49)	0.002
Adjusted for: Case Group, Sex, and Age	2.99 (1.53-5.87)	0.001
Adjusted for: Case Group, Sex, Age, and Hearing Complaint	2.76 (1.40-5.45)	0.004
Adjusted for: Case Group, Sex, Age, Hearing Complaint, and Sensation of Hearing Loss	2.72 (1.37-5.39)	0.004
Adjusted for: Case Group, Sex, Age, Hearing Complaint, Sensation of Hearing Loss, and Difficulty Understanding Speech in Noise	2.71 (1.37-5.39)	0.004
Adjusted for: Case Group, Sex, Age, Hearing Complaint, Sensation of Hearing Loss, Difficulty Understanding Speech in Noise, and Tinnitus	2.64 (1.32-5.26)	0.006

Legend: OR – Odds Ratio. CI 95% – 95% Confidence Interval.
Source: The author (2024).

Table 4 – Analysis of the Hearing Complaint variable in the evaluated groups.

Group	G1	G2	p-value
Hearing Complaints (HC)			
No	68 (64.2%)	83 (78.3%)	0.033 F
Yes	38 (35.8%)	23 (21.7%)	
HC: Tinnitus			
No	88 (83%)	97 (91.5%)	<0.003 Q
Yes	18 (17%)	9 (8.5%)	
HC: Difficulty Understanding Speech			
No	86 (81.1%)	92 (86.8%)	0.350 F
Yes	20 (18.9%)	14 (13.2%)	
HC: Hearing Loss			
No	98 (92.4%)	104 (98.1%)	0.005 Q
Yes	8 (7.6%)	4 (1.9%)	

Legend: n – absolute frequency. % – relative percentage frequency. F – Fisher's Exact Test.
**Q – Pearson's Chi-Square Test.
Source: The author (2024).

Revista ARACÊ
ISSN: 2358-2472

DISCUSSION

Sickle Cell Anemia, the homozygous form of Sickle Cell Disease, is widely recognized for its various pathophysiological disadvantages, including HL (ANVISA, 2022; Brasil, 2022; Santos et al., 2020; Stuart and Preast, 2012).

When analyzing the results, it was identified that the presence of Hearing Loss was significantly higher in G1 participants, with Odds Ratio indicating greater susceptibility of this population to having hearing deficit. There was a predominance of mild bilateral Sensorineural Hearing Loss, this finding corroborates other studies carried out in a population with the same hemoglobinopathy, even when the research analyzed a different age group than the one studied here (Al Jabr, 2001; Piltcher et al., 2000; Rissatto-Lago et al., 2018; Sarac, Boke, Okuyucu, 2018; Strum et al., 2021). As investigated in other studies, no significance was observed in the distribution of Hearing Loss by sex (Rissatto-Lago et al., 2019; Taiaple et al., 2012; Weigert et al., 2021).

Studies demonstrate a relationship of compatibility between Vocal Audiometry and the hearing thresholds found in Tonal Audiometry in patients with Sickle Cell Disease. Desai, Brewer, and Ballas (2015), when describing three cases of deafness associated with this genetic condition, observed normality in the Speech Reception Threshold (SRT). Likewise, Lucena et al., (2020) reported, in their evaluation, the occurrence of an unaltered Speech Recognition Index (SRI) in all their patients, corroborating the results of the present study in which the results of the speech test were consistent with the tonal thresholds.

Regarding the influence of the variables Time of Diagnosis and Time of Treatment of Sickle Cell Anemia on the occurrence of Hearing Loss, a significant difference was observed between the medians in sickle cell patients with and without Hearing Loss, being higher among patients with Hearing Loss. These data show that the delay in diagnosis and at the beginning of treatment of this hemoglobinopathy favors a greater predisposition to have said loss. The difference between these periods indicated that the treatment was started soon after diagnosis for most patients, demonstrating the effectiveness of early intervention by the Hematology outpatient clinic of HU-UFS.

Although the pathogenesis of hearing alterations in Sickle Cell Anemia is not yet fully elucidated, the use of Hydroxyurea (HU) appears to have neuroprotective potential, minimizing the inflammatory effect of this hemoglobinopathy in the cochlear region (Longoria et al., 2022; Rissatto-Lago et al., 2019). This variable was also considered in the present study, but, as in another study, no significant difference was found between

Revista ARACÊ
ISSN: 2358-2472

patients with Sickle Cell Anemia with and without Hearing Loss who used the medication in question (Rissatto-Lago et al., 2018). These findings do not allow us to recognize or deny the protective cochlear effect of this medication in the patients evaluated, and further studies are needed for this purpose.

In addition, the presence of pneumonia, Stroke, and Systemic Arterial Hypertension (SAH) was identified, in this order of occurrence and with no difference between patients with and without Hearing Loss, that is, the presence of comorbidities did not influence the occurrence of Hearing Loss. The results found in this study differ from those found in previous studies, when the influence of comorbidities on the presence and extent of hearing damage resulting from Sickle Cell Disease was mentioned, mainly recurrent infections and stroke (Kapoor et al., 2021; Towerman et al., 2019).

In G1, no difference was found in the influence of pain crises as potentializers of hearing alteration, and such crises were intense for both patients with and without Hearing Loss, according to the results of the Visual Analog Scale, reinforcing the absence of influence of pain on the occurrence of Hearing Loss.

In this research, a greater number of individuals who mentioned having Hearing Complaints were observed in G1 compared to G2. However, what was unexpected for G1 was having Difficulty Understanding Speech as the most recurrent complaint. This difficulty seems to be related to the presence of deficits in cognitive functions, such as attention and/or memory. Authors also report that there is a worsening of cognitive performance in pain crises and there is a greater risk of cognitive decline with age in this population (Longoria et al, 2022). Another factor to be considered in Speech Understanding Difficulty is the low level of education of the sample, in addition to the lack of knowledge of the time of onset of Hearing Loss, since the population studied had not undergone auditory monitoring. Carvalho, Novelli, and Colella-Santos (2015) point to the existence of ontogenetic issues involved in the relationship between auditory functions and the adequate development of a subject's language. Thus, according to these researchers, the development of Precise engagement of the peripheral and central auditory systems is essential for the execution and understanding of oral and written language.

Studies also draw a parallel between Hearing Loss caused by Sickle Cell Disease and its likely impacts on linguistic development (Taipale et al., 2012; Towerman et al., 2019). It is worth noting that no studies were found that discussed Difficulty in Understanding Speech, associated or not with Hearing Loss in people with Sickle Cell

Revista ARACÊ
ISSN: 2358-2472

Anemia, for this reason, it is important to conduct research that evaluates this relationship more accurately.

The literature describes that vaso-occlusive crises also promote recurrent anomalies in the physiological mechanisms of hearing. These would lead to an increase in neuronal discharges, causing asynchrony in the central auditory pathways, resulting in Tinnitus (Abdelmahmuod et al., 2020; Kiser et al., 2019; Longoria et al., 2022; Martins, Moraes-Souza, Silveira, 2010; Nascimento et al., 2019; Nelson et al., 2022), which was the second most reported Hearing Complaint in this research.

Regarding hearing loss, it is understood that this Hearing Complaint needs to be further investigated to understand its characteristics. It is believed that its reference may be related to Hearing Loss or otorhinolaryngological aspects such as the occurrence of allergic processes close to the date of the interview of the individuals or due to Eustachian tube dysfunction.

CONCLUSION

It was found that patients with Sickle Cell Anemia are more likely to have Hearing Loss compared to individuals who do not have this condition. It was found that treatment began immediately after diagnosis. Furthermore, the longer it takes to diagnose Sickle Cell Anemia and consequently to start treatment, the greater the predisposition of these individuals to hearing loss. In addition, the findings of this study do not allow us to deny the protective effect of cochlear use with Hydroxyurea. In the group of patients with Sickle Cell Anemia, those with Hearing Loss had a higher frequency of Hearing Complaints. Since Difficulty Understanding Speech was the most reported complaint, it is clear that more detailed studies are needed to assess whether its occurrence is related to Hearing Loss, cognitive aspects specific to people with Sickle Cell Anemia, or whether it is related to both situations. Finally, the presence of comorbidities is not associated with Hearing Loss in the patients evaluated, as well as pain crises, although they were reported as intense.

Revista ARACÊ
ISSN: 2358-2472

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