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EFFECT OF FETAL HEMOGLOBIN LEVEL ON AUDITORY DISCRIMINATION IN INDIVIDUALS WITH SICKLE CELL ANEMIA

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Abstract

Introduction: Sickle cell anemia (SCA) is an inherited disorder characterized by hemolysis and vaso-occlusive crises. Hydroxyurea (HDU) is the primary drug available for SCA which increases the concentration of fetal hemoglobin (HbF) and has shown clinically beneficial effects ranging from 15 to 20% on sickle cells. The present study aimed to investigate the impact of HbF level on auditory discrimination ability and speech perception in noise in normal hearing individuals with SCA under HDU treatment.

Material and methods: A between-subject design was used for group comparison. Non-random purposive sampling was used to select participants from a local Hindi-speaking community. A total of 66 normal-hearing adults diagnosed with SCA and under medication with HDU in the age range of 18–40 years were divided into three groups based on HbF%. Auditory discrimination for frequency (DLF), intensity (DLI), and duration (DDT) were evaluated at 500 Hz and 4000 Hz along with SPIN at 0 dB SNR using the MLP toolbox in Matlab.

Results: Comparing the three HbF groups, Kruskal–Wallis tests revealed no significant difference in auditory discrimination based on either DLF, DLI, DDT, or SPIN scores.

Conclusions: The present study indicated no impact on the auditory system of raised HbF level in SCA individuals. The findings suggest that in such individuals not every system in the body is affected equally by raised HbF levels.

Keywords: fetal haemoglobin (HbF) • difference limen for frequency • difference limen for intensity • duration discrimination test • speech perception in noise

WPŁYW POZIOMU HEMOGLOBINY PŁODOWEJ NA DYSKRYMINACJĘ SŁUCHOWĄ U OSÓB Z NIEDOKRWISTOŚCIĄ SIERPOWATOKRWINKOWĄ

Streszczenie

Wprowadzenie: Niedokrwistość sierpowatokrwinkowa (SCA) jest dziedzicznym zaburzeniem charakteryzującym się hemolizą i kryzysami naczyniowo-okluzyjnymi. Hydroksymocznik (HDU) jest podstawowym lekiem dostępnym w leczeniu SCA, który zwiększa stężenie hemoglobiny płodowej (HbF) i klinicznie wykazał korzystny wpływ na krwinki sierpowate w zakresie od 15% do 20%. Niniejsze badanie miało na celu zbadanie wpływu poziomu HbF na zdolność dyskryminacji słuchowej i percepcję mowy w hałasie u osób z normą słuchową z SCA leczonych HDU.

Materiał i metody: Do porównania grup zastosowano model międzyosobniczy. Nielosowy, celowy dobór próby został wykorzystany do wybrania uczestników z lokalnej społeczności mówiącej w języku hindi. Łącznie 66 osób dorosłych ze słuchem w normie, z diagnozą SCA i leczonych HDU, w wieku 18–40 lat podzielono na trzy grupy na podstawie HbF%. Dyskryminacja słuchowa dla częstotliwości (DLF), intensywności (DLI) i czasu trwania (DDT) została oceniona dla częstotliwości 500 Hz i 4000 Hz wraz z SPIN przy 0 dB SNR z użyciem biblioteki MLP (Matlab).

Wyniki: Porównanie trzech badanych grupy z wykorzystaniem testów Kruskala–Wallisa nie wykazało istotnej różnicy w dyskryminacji słuchowej opartej na wynikach DLF, DLI, DDT i SPIN.

Wnioski: Niniejsze badanie nie wykazało wpływu podwyższonego poziomu HbF na układ słuchowy u osób z SCA. Wyniki sugerują, że u takich osób nie każdy układ w organizmie jest w równym stopniu dotknięty podwyższonym poziomem HbF.

Słowa kluczowe: hemoglobina płodowa (HbF) • granica różnicy częstotliwości • granica różnicy natężenia • test dyskryminacji czasu trwania • percepcja mowy w hałasie

Key for abbreviations	
DDT	duration discrimination threshold
DLF	difference limen for frequency
DLI	difference limen for intensity
Hb	hemoglobin
HbC	hemoglobin C
HBB	β-hemoglobin gene
HbF	fetal hemoglobin
HbS	sickle hemoglobin molecule
HbSC	sickle cell–HbC
HbSS	sickle hemoglobin molecule polymerization
HDU	hydroxyurea
IQR	interquartile range
MLP	maximum likelihood procedure
PTA	pure tone audiometry
RBCs	red blood cells
SIS	speech identification score
SCA	sickle cell anemia
SCD	sickle cell disease
SNR	signal-to-noise ratio
SPIN	speech perception in noise
SPSS	Statistical Package for the Social Sciences
SRT	speech recognition threshold
VOC	vaso-occlusive crises
WHO	World Health Organization

Introduction

Sickle cell anemia (SCA) is an inherited hematological disease affecting humans. SCA is caused by mutations in the β-hemoglobin gene (*HBB*) and its epidemiology, pathophysiology, and clinical complications have been recently reviewed [1]. The two most common genotypes of this disease are homozygosity for the *HBB* Glu6Val mutation (HbS; rs334) called sickle cell anemia (HbSS), and compound heterozygosity for HbS and HbC (Glu6Lys) mutations, called sickle cell–HbC (HbSC) disease. Among all SCD, SCA is the most severe and well-known type of sickle cell disease [1]. Clinically, there is progressive multiorgan failure, including the auditory system, and in severe cases increased mortality. The highest prevalence is in West Africa, India, the Mediterranean region, and the Middle East [2].

The two main features of SCA (an inherited globin chain disorder) are hemolysis and vaso-occlusive crises (VOC). The sickle hemoglobin (HbS) molecule is prone to change into stiff, elongated polymers in a deoxygenated state due to a defect in the *HBB* gene. Initially, sickle erythrocytes go through a cyclical process in which they alternate between their typical biconcave shape and an abnormal crescent shape which they acquire under low oxygen pressure. Eventually, the shift becomes irreversible, and the sickle erythrocytes acquire a permanent sickle shape, promoting hemolysis and VOC [2].

The auditory system is supplied by the labyrinthine artery, a branch of the anterior inferior cerebellar artery. Any VOC incidence before or at this level could affect the entire blood flow in the inner ear (the organ of Corti). Due to microvascular occlusion incidents, which can compromise oxygenation through the labyrinthine artery to the cochlea [3], ischemia of the highly metabolic cochlea and organ of Corti could result in decreased oxygenation of the stria vascularis and failure to maintain the electrochemical gradient of endolymph, which is crucial for inner and outer hair cell function [4]. Vaso-occlusion can also contribute to labyrinthine hemorrhage and labyrinthitis ossificans, which appear to be more common in patients with HbSC and HbSS genotypes, respectively [5]. Also, retrocochlear changes, i.e. functional changes in neural condition of auditory nerves, have been reported in some previous studies [6,7]. VOC has also found to affect the cerebral hemispheres and lead to neurological complications such as strokes, causing possible auditory processing deficits [8]. These multiple-level changes in the auditory system might compromise auditory psychophysical processing, including frequency, intensity, and duration discrimination, as well as ordering-related tasks, which together may result in overall poorer speech understanding.

The pathophysiology of SCA causes multiorgan damage and various acute symptoms. Early therapy with oral medication is useful in reducing the kinetics of HbSS polymerization and chronic complications like pain, acute chest syndrome, acute stroke, aplastic crises, infection with fever, priapism, ocular complications, avascular necrosis, and leg ulcers. A lifelong affliction of hemolytic anemia ultimately requires blood transfusions [9]. Hydroxyurea (HDU) is the primary drug available for SCA and remains the first line of therapy. For SCA patients, changing sickle erythrocyte kinetics is the aim of therapy.

HDU is a ribonucleotide reductase inhibitor which raises fetal hemoglobin (HbF) levels. It raises the quantity of erythrocytes containing HbF as well as its intracellular concentration. Furthermore, HDU decreases leukocyte and reticulocyte counts in circulation, increases red blood cell volume, and decreases deformability. It thus enhances blood flow in capillaries, and modifies adhesion molecule expression, thus averting vaso-occlusive crises.

According to clinical observations, increased HbF concentrations help treat SCA [10]. Laboratory research indicates that fetal hemoglobin levels of at least 15% to 20% may be necessary for a therapeutic benefit [11]. However, in a study of patients not receiving treatment any increase over 4% might be advantageous [12]. The possible beneficial circulatory changes post HDU therapy might have a direct or indirect impact on auditory system function at different levels (retrocochlear or auditory cortical regions). This may provide better overall auditory processing and speech outcomes.

Need for the study

Due to circulatory alterations, the pathophysiology of SCA results in a variety of clinical manifestations [13].

Table 1. HbF [%], gender distribution, and age of the SCA participants divided into three HbF groups

Group HbF [%]	HbF [%]				Gender			Age			
	Mean	*SD*	Median	IQR	Male	Female	Total	Mean	*SD*	Median	IQR
Group 1 10–15%	12.37	1.79	13.10	3.5	16	1	17	25.12	6.17	24.11	11.00
Group 2 15–20%	16.92	1.22	16.95	1.8	15	11	26	27.42	7.82	30.50	16.00
Group 3 > 20%	22.93	2.89	21.80	3.0	10	13	23	26.26	7.47	26.00	14.00

As an end-organ system, the auditory system is especially susceptible to VOC events. An SCA crisis could result in stasis of the inner ear's supply channel, so that the organ of Corti and stria vascularis become blocked and outer hair cells die. This can lead to permanent inner ear damage, as reported in previous studies [14]. A fully functioning inner ear and auditory system is crucial for normal hearing and processing of frequency, intensity, and temporal discrimination [15].

SCA individuals under treatment with HDU show varying levels of HbF. Increased HbF levels are reported to be useful in preventing vaso-occlusive crises by reducing the kinetics of HbSS polymerization, raising the volume of RBCs (which reduces their deformability and improves blood flow through capillaries), and altering the expression of adhesion molecules [10]. Thus, studying the effect of HbF level and possible alteration of different auditory discrimination abilities in such individuals might give a better insight into microcirculatory changes in cochlear and retro-cochlear regions. This may also help in understanding target HbF levels.

Studying effects of HbF level might be a tool for forecasting how to safeguard the auditory system from adverse effects of vaso-occlusion events. It might also help in understanding the dose correction for HDU to maintain the required level of HbF% for better outcomes, since reducing vaso-oclusive crisis events lead to a better quality of life in SCA individuals.

Nevertheless, there is no one-to-one correlation between the severity of SCA and HbF percentage. Classification of SCA is therefore not based on HbF, because HbF% could be just one independent variable determining the health of an SCA individual [11]. Thus, it is of some importance to study the impact of HbF% on auditory perception, an aspect that has not yet been explored.

The present study aims to investigate the impact of HbF level on auditory discrimination ability and speech perception in noise in individuals with sickle cell anemia who have normal hearing sensitivity.

Material and methods

A non-experimental standard group comparison method [16] was employed to achieve the aim of studying 66 normal-hearing adults (41 men and 25 women) aged between 18 to 40 years who had been diagnosed with SCA (genotype HbSS) and were taking HDU medication. The episodes of crisis were found to be highly variable among all the participants. To limit the impact of this variable, all individuals needed to document a minimum of 5 crisis reports to be included. Based on their percentage HbF level at the time of the study, the participants were divided into three groups: Group 1 (10–15%), Group 2 (15–20%), and Group 3 (> 20%) (**Table 1**). Categorization was based on the observation that when the HbF level is 15 to 20%, health condition improves.

The inclusion criteria for the participants in the study were a prediagnosed SCA with HbF level < 30% tested within 3 months from the date of audiological evaluation, no prior otological issues, normal hearing sensitivity, and good health on the day of the experimental tests. Formal education up to the 5th standard and A-type tympanograms with reflexes were present in all subjects; their hearing thresholds were ≤15 dB HL at octave frequencies ranging from 250 to 8000 Hz. Additionally, it was determined through a structured interview that the subjects had no prior medical history of severe neurologic or otologic conditions. They did not receive payment for taking part in the study. The institute's ethics committee gave prior approval (ref. no. SH/EC/PhD/AUD-9/2023-24 dated 22-09-2023), and every participant gave written consent to voluntarily participate in the study.

There were two stages to the study. Based on the inclusion and exclusion criteria, phase I involved recruitment and grouping of participants. Phase II involved testing the chosen participants, including auditory discrimination tests and a speech perception in noise (SPIN) test.

Auditory discrimination tests (DLF, DLI, and DDT)

This involved three auditory tests for frequency, intensity, and duration discrimination. Difference limen for frequency (DLF), difference limen for intensity (DLI) [17], and a duration discrimination threshold (DDT) were done for 500 and 4000 Hz [18] tones at an anchor duration of 250 ms [19]. Stimuli were sampled at 44.1 kHz. The maximum likelihood procedure (MLP) toolbox in Matlab (MathWorks, USA) was used to evaluate all auditory discrimination tests [20]. Using a large number of candidate psychometric functions, the MLP determines the probability of receiving a response to each presented stimulus. The psychometric function yielding the highest probability determines the stimulus to be presented at the next trial. Within about 12 trials the MLP usually converges on a fairly stable approximation of the most likely psychometric function, which can then be used to estimate

Table 2. Median and IQR for auditory discrimination tests at 500 Hz and 4000 Hz, as well as SPIN at 0 dB SNR, across all three HbF groups

HbF level group		HbF 10–15%		HbF 15–20%		HbF > 20%	
Test parameter	**Test frequency**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
DLF	500 Hz	29.36	62.68	53.70	51.51	48.14	39.61
	4000 Hz	175.10	107.26	186.43	122.41	117.16	124.39
DLI	500 Hz	2.20	2.45	2.95	1.60	2.40	1.26
	4000 Hz	2.90	2.75	3.65	2.75	2.80	2.34
DDT	500 Hz	81.94	42.72	96.64	81.22	76.25	52.25
	4000 Hz	105.77	71.78	100.68	45.85	74.37	40.19
SPIN 0 dB SNR		31.0	6.0	34.5	5.0	34.0	5.0

Table 3. Kruskal–Wallis test statistic (*H*), significance level (*p*), degrees of freedom (*df*), auditory discrimination at 500 and 4000 Hz, and SPIN at 0 dB SNR across all three HbF groups

Test parameter	Test frequency	*H*	*df*	*p*-value
DLF	500 Hz	0.148	2	0.929
	4000 Hz	0.780	2	0.677
DLI	500 Hz	3.612	2	0.164
	4000 Hz	2.207	2	0.332
DDT	500 Hz	2.253	2	0.324
	4000 Hz	4.754	2	0.093
SPIN 0 dB SNR		1.477	2	0.478

threshold [21]. To track a 79.4% correct response criterion, an alternate forced choice method with three trials and MLP was utilized. Each trial consisted of three blocks with a stimulus presented in each; two blocks had the reference stimulus and the third block had the random variable stimulus. The task for the participants was to identify the blocks that held the variable stimulus. The aforementioned protocol was followed in each test, with the MLP toolbox was used to control stimulus presentation and response acquisition [22].

All psychoacoustical tests used a binaural test stimulus presented at 85 dB SPL; subjects were provided with 5 or 6 practice stimuli before the actual tests. A laptop (HP Intel Core i5) with Sennheiser HD449 headphones provided the stimuli for every test. The output of the headphones was adjusted to 85 dB SPL for pure tones at 500 and 4000 Hz in a 6 cc coupler.

Speech perception in noise (SPIN) test

For the SPIN test, the Hindi Sentence Test for Speech Recognition in Noise [23] at 0 dB SNR was utilized. To provide this level, each sentence was digitally combined with speech spectrum-shaped noise in Matlab. Using Sennheiser HD200A headphones, the stimuli plus noise were presented binaurally at 70 dB SPL (since the sentence list was initially standardized at this level [23]). There were 40 keywords in the sentence list. The target sentences needed to be written down or spoken aloud by the participants. The number of accurate keywords identified at 0 dB SNR was noted.

Results

The Statistical Package for the Social Sciences, SPSS (v.26) was used for statistical analyses of the data. A Shapiro–Wilk test showed that the data did not have a normal distribution in all three HbF groups for the three auditory discrimination tests (DLF, DLI, and DDT) at 500 or 4000 Hz or for the SPIN test at 0 dB SNR. Because of the data's non-normal distribution and large differences between mean and median values, median values of all parameters were utilized to compare groups. **Table 2** shows the median and inter-quartile range for DLF, DLI, DDT, and SPIN obtained at 0 dB SNR.

All the auditory discrimination tests were done at both 500 and 4000 Hz. The median and interquartile range (IQR) of all tests across HbF groups are depicted in **Table 2**. It can be seen that, for all auditory discrimination tests (DLF, DLI, and DDT), there is a trend for higher median

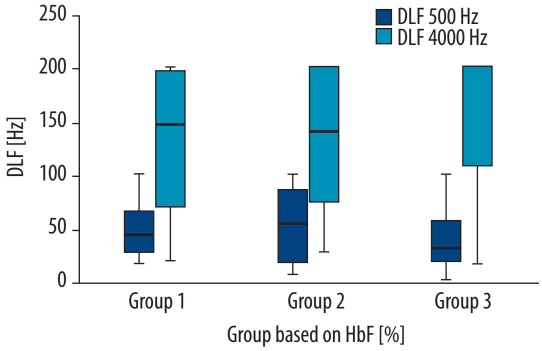

Figure 1. DLF at 500 and 4000 Hz for each of the three HbF groups. There is no statistically significant differences between the groups

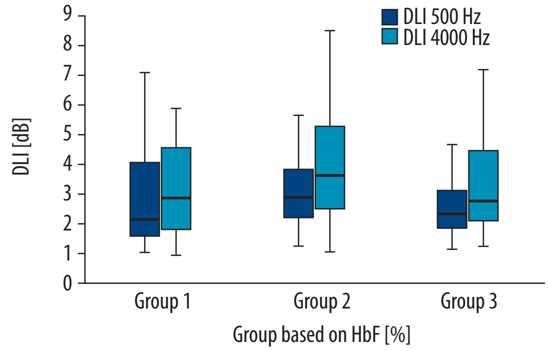

Figure 2. DLI at 500 and 4000 Hz for each of the three HbF groups. There is no statistically significant difference between the groups

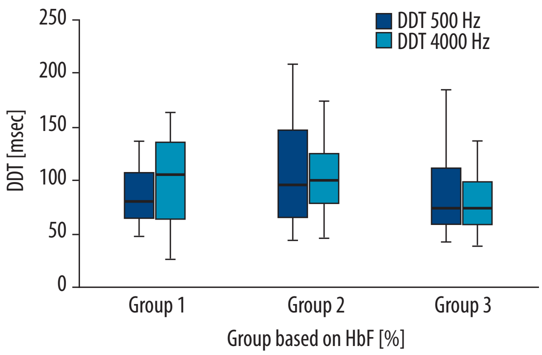

Figure 3. DDT at 500 and 4000 Hz for each of the three HbF groups. There is no statistically significant difference between the groups

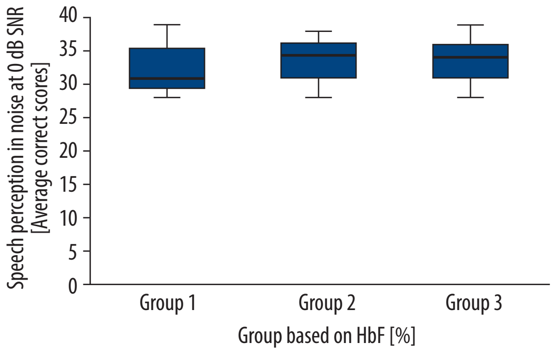

Figure 4. SPIN at 0 dB SNR for each of the three HbF groups. There is no statistically significant difference between the groups

and interquartile ranges with an increase in test frequency. Also, a slightly higher median (reflecting poorer responses) was observed for Group 2 with HbF% between 15–20%. Results of SPIN tests at 0 dB SNR showed poorer response for Group 1, having the lowest HbF% compared to the other two groups. For the SPIN test, the two higher HbF% groups had a similar median and IQR.

A Kruskal–Wallis test was run to assess the significance of differences between all HbF groups on the auditory tests (DLF, DLI, and DDT) in terms of the two tested frequencies (500 and 4000 Hz) and in terms of SPIN at 0 dB SNR (**Table 3**).

The results are shown graphically in **Figures 1, 2, 3, and 4**. There is no significant difference in scores among all three HbF groups in the auditory discrimination tests for each of the tested frequencies and similarly for SPIN scores. Since none of the test parameters were found to have significant differences among groups, correlations (between-group comparisons) were not computed.

Discussion

Individuals suffering from SCA sometimes report adverse effects on their auditory system, perhaps due to vaso-occlusion and hemolysis pathophysiology caused by stasis of the labyrinthine artery supplying the inner ear. This can involve hypoxia, ischemia, and organ cell death, leading to permanent inner ear damage and hearing loss [14] together with poor auditory processing ability and speech perception [15]. Ischemia of the highly metabolic cochlea and organ of Corti results in decreased oxygenation of the stria; vaso-occlusion can also contribute to labyrinthine hemorrhage and labyrinthitis ossificans causing sensorineural hearing loss [24].

SCA individuals who are under treatment with hydroxyurea (HDU) show varying levels of HbF. HDU is reported to be beneficial in preventing vaso-occlusive crises, probably by reducing the kinetics of HbSS polymerization and raising the volume of RBCs (reducing their deformability and improving the flow of blood through capillaries) and altering the expression of adhesion molecules [10].

In the present study, no significant effect was noticed across the three groups in any auditory processing test. This could be due to clinical absence or negligible raised HbF levels at the cochlear level, since unequal distributions of HbF across different organ systems has been reported [2]. It might also indicate no beneficial impact of raised HbF level upon the pathophysiological process of vaso-occlusion [12], at least at the level of the cochlea.

Further, though there were differences in HbF% across groups no significant difference suggests that even the HbF level below 15% and above 10% may be sufficient to increase blood flow. Data on HbF% before the assessment was not acquired, so this limits the study's conclusion and suggests further longitudinal investigation.

For all auditory discrimination tests, the high-frequency test frequency was found to give larger figures than the low-test frequency, but there was still no significant difference across HbF groups. The higher value with the 4000 Hz test frequency for discrimination tasks may be due to the asymmetrical anatomical distribution of blood supply throughout the length of the cochlea [25].

The SPIN scores were found to be slightly poorer for Group 1, although they were not statistically significant. Group 1 had HbF levels below the reported clinically beneficial level (i.e., < 15%). In the present study, participants were under HDU medication to boost HbF levels, and all had HbF levels between 10 and 30%, similar to previous findings [26]. The literature suggests a HbF level of > 15% is beneficial in reducing the overall impact of SCA-related pathophysiology. Although Groups 2 and 3 had HbF levels ≥ 15%, there was still no significant difference to the other groups; this probably supports the idea that even an HbF level of 10–15% may be sufficient to increase blood flow and provide similar functioning of the auditory system. This suggests that varying HbF levels did not change the functioning of the auditory system (either auditory discrimination or speech perception in noise).

Possibly, differences in speech perception seen in people with SCA may be related to the number of crises they have suffered. A larger number of crises might lead to poorer auditory processing difficulties or speech perception issues. In the present study, participants reported a large variability in the total number of crises, so this issue can be seen as one requiring further research. Finally, the timing of the tests administered to these individuals might be important, and this aspect also requires further investigation.

Conclusions

HbF levels of up to 15–20% have been reported to reduce clinical symptoms such as vaso-occlusion and hemolytic processes in SCA patients. The present study has found a negligible impact of raised HbF levels on auditory acuity. The explanation could involve unequal HbF distribution, negligible impact of improved HbF levels, and in general no direct link of HbF level with auditory performance. It seems that in SCA individuals every system in the body does not benefit equally or show a difference with raised HbF levels. Since the number of crises, which was highly variable among the participants, might play a major role, the outcomes of this study may not reflect the HbF level and its impact on auditory processing and speech perception outcomes.

Clinical implications

- The present study underlines the need for better understanding of the link between HbF level and the auditory system.
- There is a need for further studies on the impact of HDU and dose levels in SCA individuals to avoid its side effects on different organ systems, including the auditory system.
- Studying different auditory processing abilities in these individuals will give a better insight into microcirculatory changes in the cochlear and retro-cochlear regions after treatment.
- Choosing appropriate rehabilitative options for SCA individuals is still difficult.

Limitations and future directions

The present study evaluated the effect of HbF level on auditory processing at a specific point in time. Longitudinal studies might be the more effective way to understand the consequence of HDU treatment and HbF level in SCA individuals. Another limitation is the inability to measure the HbF level at the time of experimental test administration. Having knowledge of HbF levels at the same time as other variables like frequency of vaso-occlusive crises will give a better insight into impacts on the auditory system. Case controlled studies should be conducted in the future.

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