Sensorineural Hearing affection in Sickle Cell Disease Patients with Chronic Renal Failure and under Dialysis

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Abstract: Objective- To assess the hearing thresholds in patients with sickle cell disease having renal failure and under regular dialysis, and comparing them with other matched groups. **Design;** Cross sectional study. **Methods** – Audiological assessment of patients and controls, with special concentration on the 1 kHz, 2 kHz, and 4 kHz frequencies. **Results**; The overall results show that there is no significant affection of hearing thresholds, at least in the 1000-4000 Hz range between chronic renal failure patients under dialysis between sicklers and non-sicklers, this may be explained by the more severe and permanent metabolic effect of chronic renal failure on hearing that overrides the effect of chronic and repeated sickling on hearing. **Conclusion**; SNHL accompanying RF is apparently not aggravated if associated with SCD, and if any effect would be present, it would only be additive, not synergistic.
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1. Introduction

Patients with sickle cell disease (SCD) are common victims of recurrent attacks of hemolytic and thrombotic crises, these crises are well documented to impair the hearing thresholds of these patients during their crisis attacks, but most of these cases recover most of their hearing abilities within two weeks after recovery, but with long term sensorineural hearing loss (SNHL) over the years.[1-6] The degree of hearing affection reported is variable, but one study reported that 30% of patients had >25dB hearing loss, during childhood, and this increases with age.[5] Farid and Said reported abnormal otoacoustic emission (OAE) responses, especially at higher frequencies, reflecting abnormal cochlear function in 28.6% of children with SCD before the appearance of threshold shift in pure tone audiometry.[6]

Chronic renal failure (CRF) too, has been documented to cause certain degrees of SNHL as a result of the metabolic alterations[7, 8], and the process of dialysis itself was proposed to be an additional contributing factor for the hearing loss, although this is disputed by some.[9]

SCD itself induces several types of renal pathologies, and one study found CRF to be the cause of mortality in about 18%.[10]

The renal syndromes and functional abnormalities in SCD include hematuria, proteinuria, increased glomerular filtration, increased renal plasma flow, acute renal failure, chronic renal insufficiency, decreased concentrating ability, renal tubular acidosis, impaired potassium secretion, increased glomerular perselectivity, and altered ultrafiltration coefficient.[11] The case in the Arabian Peninsula does not differ much, renal abnormalities are present in a significant number of patients with SCD, and proteinuria is the most common abnormality, which eventually leads to renal damage and possible renal failure.[12]

The combination of both diseases SCD and CRF needing dialysis, and the effect of this combined disease status on hearing have not been widely studied due to the relative rarity of surviving patients with sickle cell disease to the age that they actually develop renal failure that necessitates dialysis.

In some parts of Arabian peninsula, where SCD in more common than in other areas of the world, there is a relatively higher survival rate in patients with sickle cell disease one reason that might be responsible for the amelioration of the clinical severity of SCD in the Arabian peninsula is proposed to be the relatively higher levels of HbF that is found in the such patients with the disease [13], which even reduced the incidence of death from sickle related CRF to about 2.5%.[14] This high HbF production in SCD in the Saudi population in genetically determined [15], Both the inherent capacity to produce fetal hemoglobin and the selective survival of F cells contribute to circulating fetal hemoglobin levels in sickle cell anemia. [16, 17] How these influences interact to produce the unusually elevated fetal hemoglobin levels observed in the Saudi population is not known, but classical deletion or non-deletion

hereditary persistence of fetal hemoglobin (HPFH) is not involved since parents do not have elevated circulating hemoglobin F levels. [18]

Furthermore, elevated HbF production is also associated with inheritance of a pattern of DNA restriction enzyme polymorphisms 5' to the β globin gene known as the ++-++ 5' haplotype. [15, 19-22]

Whether SCD, CRF, and dialysis have synergistic effects on inner ear damage, or their effect is merely additive is a question that has not been raised nor addressed in literature up to our knowledge.

The aims of the study were

1. to study the pattern and severity of SNHL in a group of patients with SCD and CFR under dialysis,
2. compare them to patients with SCD alone, with CRF under dialysis alone, and to a control group
3. to determine if SCD had an additive, synergistic, or no effect on SNHL affecting patients with CRF and dialysis

2. Methods;

The study was performed at a secondary referral center at Al-Hasa in the Eastern province of Saudi Arabia. This study was approved by the ethical and moral committee of the facility, and an informed consent was obtained from patients for inclusion in this study.

The study included 83 patients divided into four groups; Group I; Adult patients with both SCD and CRF under dialysis (18 patients), [they were all the patients with such a combination that underwent dialysis in the center, Group II; Adult patients with CRF only, under dialysis (25 patients), Group III; Adult patients with SCD only (20 patients), and Group IV; Normal adults (20 volunteers) as age and sex matched controls.

Inclusion criteria for a patient to be termed a sickle cell disease patient were; (1) Positive family history of sickle cell disease. (2) Positive documented history of at least 3 attacks of hemolytic crises within the past 10 years necessitating hospital admission. (3) Hemoglobin (Hb) electrophoresis showing high levels of HbS (>60%), and low levels of HbA_1 (<40%), with or without other Hb types (HbF).

Inclusion criteria for a patient to be termed a renal failure patient were; (1) Creatinine clearance less than 20 ml/min. (2) Plasma creatinine more than 600 µmol/L. (3) Plasma urea more 30 mmol/L. (4) Patients being diagnosed as renal failure needing dialysis for at least 5 years. (5) Patients under three sessions of dialysis per week, each session 4 hours at least.

Inclusion criteria for a normal volunteers were; (1) Free from any chronic disease as diabetes, hypertension, renal impairment, rheumatoid diseases, ..etc. (2) Had no history of previous hearing trouble, or ear diseases or surgery. (3) Had no history of ototoxic drug administration.

All patients were subjected to the following; (1) Full history taking for exclusion of any ear troubles other than diminution of hearing, chronic diseases, renal history, to categorize or eliminate the patient from the study groups. (2) Thorough otologic examination, including tympanometry, to exclude middle ear diseases. (3) Full audiological assessment, using the GSI 61® diagnostic audiometer, with special concentration on the 1 kHz, 2 kHz, and 4 kHz frequencies. (4) Speech discrimination levels. (5) Serum creatinine to evaluate renal function.

Additional tests were done to specific study groups as follows; Creatinine clearance, and plasma urea tests for groups I and II, and Hemoglobin electrophoresis for groups I and III.

Statistical Analysis

After verifying the condition of each patient and properly categorizing them, the results of the audiometric testing was tabulated and analyzed using the (t) test for unpaired samples using SPSS software for Windows system (version 12) [SPPS Inc., Chicago, IL] comparing the thresholds of hearing of each frequency and the mean of the sum of frequencies between the different study groups.

3. Results

Comparison of the age and sex between the 4 groups showed no statistically significant difference ($p > 0.05$) i.e. all groups were age and sex-matched. Both sexes were equally endangered with SCD with a male/female ratio of 4:3 in groups 1 and 3.

The hearing threshold for each frequency was measured, the results of the audiological testing were collected, all patients and controls had speech discrimination percentages above 88%, the pure tune audiometric results are shown in table 1, and the means and standard deviations and the mean of the sums were shown in table 2.

Hearing loss was categorized into mild, moderate, severe and profound types. The patients were categorized in one of four categories according to the degree of SNHL and statistical comparison between the four groups was done. In SCD patients most frequently involved frequencies were high frequencies.

Table 1: The audiological thresholds of patients of the different groups, in dB.

Patient no.	1 kHz frequency				2 kHz frequency				4 kHz frequency			
	Gp I	*Gp II*	*Gp III*	*Gp IV*	*Gp I*	*Gp II*	*Gp III*	*Gp IV*	*Gp I*	*Gp II*	*Gp III*	*Gp IV*
1	20	10	10	10	20	15	10	10	25	20	15	15
2	20	10	20	15	25	20	15	10	30	25	25	20
3	15	15	10	15	20	15	10	15	40	20	25	20
4	15	15	15	10	15	20	10	10	30	30	20	15
5	10	20	10	15	15	20	10	10	15	30	15	20
6	15	20	10	10	15	25	10	10	25	40	10	15
7	20	20	10	10	25	20	10	10	40	35	15	15
8	25	25	15	15	35	20	15	15	45	35	20	20
9	10	20	15	20	15	25	20	20	20	30	15	25
10	10	25	15	15	10	25	25	15	20	25	25	20
11	15	20	20	10	10	20	35	20	20	30	30	25
12	15	15	15	10	20	15	25	20	30	25	30	30
13	20	10	15	15	15	10	20	20	25	20	35	20
14	20	15	10	15	25	15	15	15	35	25	35	20
15	20	10	5	10	20	20	10	20	30	25	20	25
16	25	20	10	15	30	25	15	20	50	35	20	20
17	30	25	10	15	35	30	20	20	45	40	30	25
18	25	15	15	15	30	15	10	20	50	20	35	20
19	NA	20	15	10	NA	15	25	20	NA	25	30	25
20	NA	20	10	10	NA	25	20	15	NA	35	25	15
21	NA	20	NA	NA	NA	20	NA	NA	NA	40	NA	NA
22	NA	25	NA	NA	NA	25	NA	NA	NA	45	NA	NA
23	NA	20	NA	NA	NA	25	NA	NA	NA	35	NA	NA
24	NA	25	NA	NA	NA	25	NA	NA	NA	30	NA	NA
25	NA	10	NA	NA	NA	15	NA	NA	NA	25	NA	NA

Gp= group, NA= Non-applicable, dB=decibel

Table 2: Results of statistical analysis of the study groups. (S.D.= standard deviation)

Frequency	Mean	±S.D.
GROUP I (18 patients)		
1000 Hz	18.33	±5.6
2000 Hz	21.38	±8.1
4000 Hz	31.94	±10.8
Sum of means	23.88	±7.8
GROUP II (25 patients)		
1000 Hz	18.00	±5.2
2000 Hz	20.20	±4.8
4000 Hz	29.80	±7.1
Sum of means	22.67	±5.1
GROUP III (20 patients)		
1000 Hz	12.75	±3.7
2000 Hz	16.50	±7.0
4000 Hz	23.75	±7.5
Sum of means	17.66	±4.9
GROUP IV (20 patients)		
1000 Hz	13.00	±2.9
2000 Hz	15.7	±4.3
4000 Hz	20.5	±4.2
Sum of means	16.4	±3.0

Comparing the different groups with each other for hearing threshold at 1 KHz yielded different results; Comparing groups I & II, and group III &IV showed no significant difference statistically. Comparing groups I &III, group I &IV, groups II &III, and groups II &IV showed a highly significant difference statistically.

In the 2 kHz threshold the following was found comparing the different groups with each other; Comparing groups I &II, and groups III &IV showed no significant difference statistically. Comparing groups I &III and groups II &III showed a significant difference statistically. Comparing groups I &IV and groups II &IV showed a highly significant difference statistically.

In the 4 kHz threshold the following was found comparing the different groups with each other; Comparing groups I and II, showed no significant difference statistically. Comparing groups III &IV showed a significant difference statistically. Comparing groups I & III, groups I & IV, groups II & III, and groups II & IV showed a highly significant difference statistically.

In the sum of mean of the three tested frequencies, the following was found comparing the different groups with each other; Comparing groups I & II, and groups III &IV showed no significant difference statistically. Comparing groups I & III, groups I & IV, groups II &III and groups II & IV showed a highly significant difference statistically.

4. Discussion

Homozygous cases of sickle cell disease were previously considered "early fatalities", this was in part very true due to the severity of the disease and frequency of occurrence of fatal complications, but with recent advances in medicine, a definite cure can be offered to the patient in the form of stem cell transplant.[23] Although this fact is true, it is rarely needed following the precautions of proper prophylaxis from conditions precipitating attacks of sickle crisis, and early treatment of the crisis if it occurs. Also proper genetic counseling has played a role in reduction of the disease severity and number of cases.

The geographical distribution of the disease variants varies from one source to the other, but in the Middle East, and specifically in the Arabian Peninsula, the disease takes a specific pattern, asides from about 1.5% of the population having homozygous SCD, and 20% being sickle cell trait, [1, 24] in the full blown case there is a very low percentage of HbA_1 which may reach zero, with very high levels of HbS, and the remaining usually HbF. This relative high level of HbF may reach 35% [24] (higher than the described 15% maximum in literature) with the specific property of very high affinity to oxygen ameliorates the condition greatly, so that the patient may have Hb levels as low as 6gm/dl and still live a more or less symptom free life [23], and is not considered to be anemic. The amelioration in the clinical picture of the disease with advances in treatment lines has build up a relatively older aged population of sickle cell disease patients, thus making these patients liable to chronic diseases, including renal failure.

The chronic effects of renal failure on hearing have previously been studied [7, 8] and it has been shown that there is an increase in the hearing thresholds, especially in the higher frequencies, in these patients. Studies have also failed to demonstrate any long term affection on hearing by the process of dialysis itself. [9]

On the other hand, the chronic effects of attacks of hemolytic crisis's in sickle cell disease patients has also been studied, showing acute hearing loss with the acute attack, especially in the higher frequencies, followed by amelioration of the condition, with a cumulative effect over the years with repeated attacks of crisis. [1, 2, 4, 5] Several reasons have been proposed for the varying SNHL prevalence results among sickle cell patients. These include age, locality and type of hemoglobin gene of the patient. Previous studies have noted that SNHL becomes more severe with increasing age and increasing number of sickle cell crises of patients, but Friedman et al. (1980), could not confirm this statement in their study. [25] In this study, increasing patient's age in the 38 patients with SCD was associated with increased incidence of hearing loss in patients with and without renal failure. Farid and Said (2009) found a correlation between cochlear function detected using OAEs and the number of heamolytic crises and compliance to hydroxyurea treatment. [6]

Histopathologic changes in the inner ear in cases of SCD were studied by Morgenstein and Manace (1969), they demonstrated expansile and diffusely hyperplastic petrosal marrow accompanied degeneration of the organ of Corti, consistent with ischemia. [26] Whitehead *et al.* (1998), reported labrynthine hemorrhage too, but this was reported to be the cause of sudden but reversible SNHL. [27]

The combined effect of a patient being a sickler, and having end stage renal failure needing dialysis has not been widely studied, if studied at all. The idea of our study was to find if the affection of a patient with both conditions would lead to a simple additive effect on hearing or there is a synergistic effect on hearing, comparing the results with those of other groups of patients in the same environment and within the same age group where the study was carried out.

The results showed that in comparing the normal control group (IV) to the sickle cell disease group patients (III), a significant difference was found only in the 4 kHz frequency, this finding agrees with most of the previous studies that demonstrated an affection of hearing in chronic sickle cell patients with hearing impairment reported to range from 0 to 66% (Table 3). Different patterns and degrees of hearing loss are reported, ranging from profound bilateral losses with partial recovery over time, to mild to moderate unilateral losses predominately in the high frequencies. Our results coincides with the results of Friedman *et al.* [25] and Todd *et al.* [28] who found that sickle cell disease is complicated initially by a high frequency hearing loss and later on by a generalized endocochlear hearing loss, but the limitation of affection in our study to the 4 kHz frequency may be due to the amelioration by the high HbF levels, so only the higher frequencies (most sensitive) were affected. Both sexes were equally endangered in our study with a male/female ratio of 4:3 which agrees with the findings of Todd *et al.* [28]

Also when comparing the patients with chronic renal failure (group II) with the control group (IV), a significant hearing loss was found in all frequencies, agreeing with most previous studies. [7, 8]

When comparing our target group (I) with the control group (IV), a significant difference in all hearing thresholds tested was found, and the same highly significant statistical difference in all thresholds was found when comparing them with the

sickle cell disease group (III), but interestingly enough no statistical difference in any level was found when they were compared with group (II) patients having renal failure only.

The overall results show that there is no significant affection of hearing thresholds, at least in the 1000-4000 Hz range between chronic renal failure patients under dialysis between sicklers and non-sicklers, this may be explained by the more severe and permanent metabolic effect of chronic renal failure on hearing that overrides the effect of chronic and repeated sickling on hearing.

Table 3: Review of the literature and summary of group studies.

Investigator(s)	Year	N	Procedure [a]	Hearing loss
Todd *et al.* [28]	1973	83	PT	22%
Sharp and Orchik[29]	1978	09	HE	1/9
Friedman *et al.*[25]	1980	43	HE	12%
Odetoyinbo and Adekile[30]	1987	56	HE	21%
Elwany and Kamel [31]	1988	10	HE, ABR	Abnormal
Wiliams *et al.* [32]	1988	22	CAP	0%
Crawford *et al.* [2]	1991	75	HE	41%
Gould *et al.* [33]	1991	34	HE, ABR	13/34, 6/25
MacDonald *et al.* [34]	1999	84	PT	21.4%
Chiodo *et al.* [35]	1997	75	PT	57%
Downs, Stuart and Holbert [36]	2000	20	DPOAE Amplitudes	significantly larger
Koussi *et al.* [37]	2001	24	HE, ABR	4.6%
Mgbor and Emodi [38]	2004	50	PT	13.4%
Burch-Sims and Matlock [39]	2004	113	HE, ABR	21%
Farid and Said [6]	2009	28	PT, TEOAE, DPOAE	Normal PT, and abnormal TEOAE & DPOAE in some

[a] Pure tone thresholds (PT); hearing evaluation (HE); auditory brainstem response (ABR); central auditory processing (CAP); distortion product otoacoustic emissions (DPOAE).

Conclusion

The SNHL accompanying chronic renal failure is apparently not aggravated if associated with sickle cell disease, and if any effect would be present, it would only be additive, not synergistic.

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