Running Head: DPOAES IN CHILDREN WITH SICKLE CELL DISEASE

Distortion Product Otoacoustic Emissions in Normal-Hearing Children with Homozygous Sickle Cell Disease

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Abstract

The purpose of this study was to investigate distortion product otoacoustic emissions (DPOAEs) in young normal-hearing children with sickle cell disease (SCD). It was hypothesized that the prevalence of DPOAEs and response amplitudes would be lower than those in children with normal hemoglobin due to suspected compromised cochlear function as a result of vaso-occlusive events characteristic of SCD. Twenty African-American children with SCD and 15 African-American children with normal hemoglobin participated. Distortion product OAEs were evoked by thirteen primary tone pairs with f_2 frequencies ranging from 1000 to 4500 Hz. The primary tones were presented at and L_1 and L_2 levels of 70 and 60 dB SPL (high) and 50 and 40 dB SPL (low), respectively. The findings of this study were completely unexpected and contrary to our original hypotheses. The likelihood of detecting a DPOAE response was not related to the clinical status of the children. Distortion product OAE amplitudes were significantly larger for children with SCD (p = .01).

Educational Objectives: After completing this article the reader will (1) have a basic knowledge of the audiometric complications of sickle cell disease and (2) appreciate the differences in DPOAEs between young normal-hearing children with sickle cell

disease and young normal-hearing children with normal hemoglobin.

KEY WORDS: Audiology, Auditory Thresholds, Otoacoustic Emissions, Sickle Cell Disease.

Sickle cell disease (SCD) is a hereditary genetically determined hemolytic disorder. Of all the hemaglobinopathies, SCD is the most prevalent (Forman-Franco, Karayalcin, Mandel, & Abramson, 1982; Marcus & Lee, 1976). The disease is expressed in descendants of populations from geographical areas with a high incidence of malaria such as Africa, the Mediterranean, and southeast Asia. Sickle cell disease is characterized by arthralgia, acute attacks of abdominal pain, and ulcerations of the lower extremities (Danish & Giordano, 1992; Ranney, 1992; Song, 1971). Sickle shaped erythrocytes are caused by the presence of hemoglobin S. In normal healthy individuals, hemoglobin is genetically coded HbA. In people with SCD, these normal genes have been replaced by a mutated gene, coded for hemoglobin S (i.e., HbSS).

This presence of hemoglobin S has several consequences. First, sickled cells die more rapidly than normal disc shaped red blood cells (c.f. 16 vs. 120 days). Second, sickled red blood cells do not reproduce as rapidly as normal red blood cells, causing a depletion in the number of red blood cells present in the body. Finally, because of their distorted shape and inherent stiffness, sickled cells have difficulty passing through small blood vessels. Inadequate oxygenation of the blood and, ultimately, organs throughout the body results. When the

oxygen reaches a certain level, an increase in the sickling of the blood cells occurs, precipitating "crisis" episodes and causing the individual with SCD intense pain and organ malfunction (Ranney, 1992; Song, 1971).

It has been reported that the prevalence of hearing loss is greater among people with SCD than in the general population. The prevalence of hearing loss has been reported to range from approximately 12% to 41% in the sickle cell population (Adams & Benson, 1991; Ajulo, Osiname, & Myatt, 1993; Ashoor & Al-Awamy, 1985; Atsina & Ankra-Badu, 1988; Crawford et al., 1991; Forman-Franco et al., 1982; Friedman, Luban, Herrar, & Williams, 1980; Gentry, Davis, & Dancer, 1997; Odetoyinbo & Adekile, 1987; Todd, Serjeant, & Larson, 1973). The etiology of hearing losses in individuals with SCD involves conductive (De Virgiliis et al., 1979; Hazell & Modell, 1976), cochlear (Berry, 1975; Elwamy & Kamel, 1988; Gould et al., 1991; Hotaling, Hillstrom, & Bazell, 1989; Schreibstein, MacDonald, Cox, McMahon, & Bloom, 1997; Serjeant, Norman, & Todd, 1975; Sharp & Orchik, 1978; Tavin, Rubin, & Camacho, 1993;) and central (Orchik & Dunn, 1977; Sharp & Orchik, 1978) processes.

There is, however, a paucity of organized information concerning the manifestation of neuro-otologic and audiologic complications of SCD both in its early and later stages. Given the histopathology findings (Morganstein & Manace, 1969; Pollack

& Lipscombe, 1979) and audiometric data (Urban, 1973; Wilimas, McHaney, Presbury, Dahl, & Wang, 1988), several investigators (Forman-Franco et al., 1982; Friedman et al., 1980; O'Keeffe & Maw, 1991) have expressed surprise that the hearing of individuals with SCD is not more affected than reported in the literature. Friedman and her colleagues (1980) suggested the possibility that cochlear damage may be present but not apparent from pure tone threshold results.

Because SCD is characterized by vaso-occlusive events occurring in a range from microvasculature to large muscular arteries, one would suspect that cochlear function would be particularly vulnerable, considering the delicate nature of cochlear vasculature (Haupt, Scheibe, & Ludwig, 1993; Scheibe, Haupt, & Baumgärtl, 1997; Slepecky, 1996). As a growing body of evidence demonstrates the greater sensitivity of otoacoustic emissions (OAEs) over psychoacoustic and/or standard behavioural testing in the detection of early or subclinical cochlear damage (e.g., Lonsbury-Martin, McCoy, Whitehead, & Martin, 1993; Prieve, Fitzgerald, Schulte, & Kemp, 1997; Schweinfurth, Cacace, & Parnes, 1997), an investigation exploring the otoacoustic emissions in individuals with SCD appeared warranted. To the best of our knowledge, there are no published reports of this to date.

The purpose of this study was to investigate OAEs in individuals with SCD. Specifically, we chose to evaluate distortion product otoacoustic emissions (DPOAEs) in young normal hearing African-American children with SCD. It was felt that DPOAEs may reveal early or subclinical cochlear damage as a result of vaso-occlusive events characteristic of the disease. It was hypothesized that the prevalence of DPOAEs in the children with SCD would be lower than that of the children with normal hemoglobin. It was also hypothesized that any DPOAEs observed in children with SCD would be lower in amplitude than those displayed by children with normal hemoglobin due to the possibility of compromised cochlear function.

Method

Participants

Twenty African-American children with homozygous (HbSS) SCD, ranging in age from 6 to 13 years (M = 8.9 years, SD = 2.2; 11 males and 9 females) participated. They were selected from the East Carolina University School of Medicine Sickle Cell Clinic at Pitt County Memorial Hospital, Greenville, NC. An age- and gender-matched control group (M = 8.4 years, SD = 2.1; 6 males and 9 females) of 15 African-American children with normal hemoglobin also participated. All participants presented with normal otoscopy, normal middle ear function (American Speech-Language-Hearing Association, 1990) and normal hearing

sensitivity defined as having pure-tone thresholds at octave frequencies from 500 to 8000 Hz of ≤ 20 dB HL (American National Standards Institute, 1996). Average pure tone thresholds, for both groups are presented in Table 1.

Apparatus

Distortion product OAEs were measured with a Grason-Stadler GSI-60 DPOAE SYSTEM (Revision 4.2.0) interfaced with a personal computer (Compaq Model Deskpro 2000). Primary tones with an f_2/f_1 ratio of 1.22 were used to evoke DPOAEs. Recordings were obtained from 1000 to 4500 Hz at f_2 frequencies of 1078, 1218, 1359, 1546, 1734, 1921, 2156, 2437, 2718, 3093, 3468, 3890, and 4359 Hz. These frequencies were selected because DPOAE test performance is best in the mid to high frequency range and poorest in the lower and higher frequencies (Gaskill & Brown, 1990; Gorga et al., 1993a, Gorga et al., 1993b; Kimberly, Hernandi, Lee, & Brown, 1997). Two levels of primaries were employed to evoke the DPOAEs. For the "high-level" condition, L_1 and L_2 were set at 70 and 60 dB SPL, respectively. In the "low-level" condition, L_1 and L2 were set at 50 and 40 dB SPL, respectively. Distortion product OAEs were measured using a sequential signal presentation. Averaging the DPOAE data was done in the time domain. Ten averages were obtained on each data point. Sampling rate was 24000 Hz for all conditions.

Frame rejection occurred if the ambient noise level exceeded 30 dB SPL or if L_1 or L_2 was out of tolerance by +/-5 dB. Test termination occurred if the test time exceeded 32 seconds or 1500 frames, if frame rejection occurred 50 times due to excessive ambient noise, or if frame rejection occurred 20 times due to L_1 or L_2 being out of tolerance for at least 20 frames. The test was accepted when at least 10 frames were averaged, the average noise level was less than -6 dB SPL, and either the DPOAE was 10 dB above the noise floor or the absolute noise level was less than
-12 dB SPL.

Procedure

All testing was conducted in either a double wall sound-treated audiometric suite (Industrial Acoustics Corporation) meeting specifications for permissible ambient noise (American National Standards Institute, 1991) or a quiet clinical examination room. Typical background noise in the clinical examination room was less than 30 dBA. Participants sat quietly while a probe assembly was placed securely in the ear canal. With the probe in place the test was initiated via the computer. Both ears of all participants were tested.

Distortion product OAEs were estimated as the amplitude in the frequency bin for the cubic distortion product $2f_1- f_2$. Noise estimates were obtained from the average amplitude of the three

frequency bins on either side of the cubic distortion product bin (Gorga et al., 1997). The noise floor was set at -6 dB SPL. A DPOAE was determined to be present if its amplitude exceeded the noise floor by at least 3 dB.

Results

Only those DPOAEs with amplitudes greater than the noise floor by at least 3 dB were included in the analyses. Consequently, DPOAE data were not available for all evoking primary pairs for all participants. Table 2 displays the percentage of observed DPOAEs observed as a function of group, ear, primary tone level and f_2 frequency.

A logistic regression analysis was undertaken to ascertain which independent variables were significant predictors of the presence or absence of a DPOAE response (i.e., binary dependent variable). The analysis was performed using SPSS LOGISTIC REGRESSION (Version 8.0.0). Predictor variables of group, ear, level and f_2 frequency were fit in the logistic regression model. The analysis revealed that ear, *Wald statistic* (1) = 4.51, p = .03, and level, *Wald statistic* (1) = 4.51, $p < .0001$, were statistically significant predictors of a DPOAE response. Group, *Wald statistic* (1) = 2.3, p = .13, and frequency, *Wald statistic* (1) = .83, p = .36, were not statistically significant predictors of a DPOAE response. In other words, the presence of a DPOAE response was more likely to be observed in a

participant's right ear and in the high L_1/L_2 condition. The likelihood of a DPOAE response was not dependent on group or frequency.

Mean DPOAE amplitudes as a function of f_2 primary frequency for each group for the low-level and high-level conditions are presented in Figures 1 and 2, respectively. Figures 3 and 4 display individual DPOAE amplitudes for the children with SCD relative to the tenth and ninetieth percentiles of the DPOAE amplitudes from the children with the normal hemoglobin, for the high and low primary tone levels, respectively. A four-factor mixed analysis of variance (ANOVA) was undertaken to investigate differences in mean DPOAE amplitudes as a function of group, ear, primary tone level and f_2 frequency. This and the following ANOVA were performed using the SAS System PROC MIXED (SAS Institute, Version 6.12). This procedure is appropriate for data sets with missing data, as long as the missing data are random (Littell, Milliken, Stroup, & Wolfinger, 1996). The results of the analysis are presented in Table 3. As is evident in Table 3, statistically significant main effects were found for group, frequency and level ($p < .05$). That is, DPOAE amplitudes were significantly larger for children with SCD, larger at the higher stimulus level, and larger for lower f_2 primary frequencies. The findings of significant main effects of frequency and level on DPOAE amplitudes were completely expected. Four statistically

significant interactions also occurred ($p < .05$). These were group by level, frequency by level, ear by level, and group by frequency. Although these interactions attained statistical significance they are not deemed to be clinically significant. All other main effects and interactions were not statistically significant ($p > .05$).

A four-factor mixed ANOVA was also undertaken to examine differences in mean noise amplitude as a function of group, ear, primary tone level and f_2 frequency. The analysis revealed no statistically significant differences for group [F (1, 15) = 1.79, $p = .20$,$\eta^2 = .11$, $\phi = .24$ at $\alpha = .05$] or ear [F (1, 15) = 0.006, Greenhouse-Geisser $p = .94$,$\eta^2 = .00$, $\phi = .051$ at $\alpha = .05$]. Significant main effects of frequency [F (12, 180) = 23.52, Greenhouse-Geisser $p < .0001$,$\eta^2 = .61$] and level [F (1, 15) = 33.79, Greenhouse-Geisser $p < .0001$,$\eta^2 = .69$] were found. All interactions of main effects were not statistically significant ($p > .05$). The significant main effect of frequency reflected, as anticipated, the fact that the noise floor decreased with increasing frequency. During DPOAE recording, the noise floor evidenced with the high primary tone level was significantly louder than the noise floor with low primary tone level by approximately 1.6 dB (c.f. –8.1 and –9.7 dB SPL, respectively). It is believed that this finding reflected the test acceptance criterion of averaging DPOAE responses which were 10 dB above

the noise floor (i.e., more robust responses at the high primary tone level afforded a higher noise floor).

Discussion

The findings of this study indicated that children with SCD have larger DPOAE amplitudes than children with normal hemoglobin and that the prevalence of DPOAEs does not differ between the two groups. These results were completely unexpected and contrary to our original hypotheses. It was hypothesized that any DPOAEs observed in the children with SCD would be diminished in amplitude and the prevalence of DPOAEs would be lower than that of the children with normal hemoglobin due to suspected compromised cochlear function resulting from the vaso-occlusive nature of the disease. It is important first to point out that the DPOAE findings in the control sample were consistent with previous findings of DPOAE amplitudes in normal-hearing children (Owens, McCoy, Lonsbury-Martin, & Martin, 1993; Prieve et al., 1997).

At first glance the findings that children with SCD have larger DPOAE amplitudes than children with normal hemoglobin are difficult to interpret. Considering contemporary models of OAE generation (e.g., Kemp, 1980; 1997), several possibilities for these findings may be offered. First, some dysfunction or reduction in the efferent suppression of outer hair cell activity may be present in the children with SCD. This could be

a consequence of aberrant medial olivocochlear neuron function or a disruption of olivocochlear efferent transmitter function. This is highly speculative, and there is no evidence at this time to indicate that this is the case in individuals with SCD. Second, outer hair cells of children with SCD may be hyper-responsive and the mechanism does not involve efferent system dysfunction. To the best of our knowledge, there is no research to provide insight into this explanation. Third, children with SCD may be on medication regimes that are in some way mediating hyper-responsive activity in outer hair cell function. Some pharmacological agents are known to prevent the inhibition of the OAE response (e.g., Chen, Skellett, Fallon, & Bobbin, 1998; Kujawa, Glattke, Fallon, & Bobbin, 1994). There is also evidence of enhancement of OAEs following drug administration or insult to the olivocochlear efferent system in some individuals (Berlin, Hood, Cecola, Jackson, & Szabo, 1993; Berlin, Hood, Hurley, & Wen, 1994). A test of this hypothesis would involve an investigation of contralateral suppression of OAEs in children with SCD. If the mechanism involves a reduction of efferent system input, it is logical to assume that a stimulus which would normally suppress OAEs would have less, if any, effect on DPOAE suppression in people with SCD. Further, although both groups of children presented with clinically defined normal middle ear function, some undetected differences could have

existed. For example, children with SCD may have more efficient backward transmission than children with normal hemoglobin, contributing to greater amplitude DPOAEs (Kemp, 1980; Margolis & Trine, 1997). Finally, one could speculate that larger OAE amplitudes in children with SCD might be a consequence of smaller ear canals relative to those in children with normal hemoglobin. Although we are not aware of any data reporting smaller ear canal volumes, it is well documented that children with SCD are typically smaller than normally developed age-matched children (Ebomoyi, Adedoyin, & Ogunlesi, 1989; Henderson, Saavedra, & Dover, 1994; Phebus, Gloninger, & Maciak, 1984; Platt, Rosenstock, & Espeland, 1984; Stevens, Maude, Cupidore, Jackson, Hayes, & Serjeant, 1986). Smaller ear canal volumes have been hypothesized to account for larger OAE amplitudes (Norton & Widen, 1990). Further investigations are needed to address these speculations.

The clinical applications of these data need to be further explored, as well. Because the literature supports decreased hearing sensitivity in children with SCD (Gentry et al., 1997), one must address what mechanism(s) account(s) for the time course and change in hearing sensitivity that eventually plagues many of these individuals. If normal-hearing children with SCD do have better OAEs than their counterparts with normal hemoglobin, several questions must be addressed. More thorough

attention in case history addressing neurological complications, number of crises, time since last crisis, medication regimes, intravenous treatments, and transfusion history may provide significant insight into the etiology of hearing loss in those with SCD. Additionally, a comprehensive middle ear assessment, including multifrequency tympanometry and acoustic reflexes, would not only identify any middle ear factors contributing to the hearing loss, but would help monitor any effects of SCD in the middle ear. Finally, while this study examined only children with HbSS, there are several other sickle cell hematotypes (e.g., HbSC) which should be examined relative to hearing. Do different types of SCD predispose a greater risk for hearing loss than others? An examination of these factors may provide insight into our understanding of the disease process and its effects.

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Table 1

Mean Pure-tone Audiometric Thresholds and Standard Deviations as a Function of Group, Frequency and Ear

	Frequency (Hz)								
	500	750	1000	1500	2000	3000	4000	6000	8000
Ear									
Right									
Sickle Cell	13.5	10.8	9.2	6.8	4.5	7.2	9.2	9.8	6.8
	(4.9)	(5.4)	(5.4)	(4.7)	(5.1)	(5.7)	(7.5)	(9.7)	(7.1)
Control	7.3	6.7	6.3	4.3	2.3	4.7	7.0	5.7	17.0
	(6.2)	(5.2)	(6.4)	(4.2)	(7.3)	(7.2)	(6.5)	(7.0)	(7.3)
Left									
Sickle Cell	13.7	11.3	9.5	5.3	4.7	8.4	10.3	11.0	8.4
	(5.0)	(4.7)	(3.3)	(5.1)	(3.5)	(5.3)	(6.3)	(5.7)	(5.5)
Control	7.0	6.3	4.7	4.3	3.3	7.3	7.7	9.0	12.3
	(4.1)	(5.2)	(5.8)	(5.3)	(5.2)	(5.6)	(5.6)	(6.3)	(8.6)

Note. For the sickle cell group, n = 20; for the control group, n = 15.

Table 2

Percentage of Observed DPOAEs as a Function of Group, Ear, Primary Tone Level and f_2 Frequency

		f_2 Frequency												
Level	Ear	1078	1218	1359	1546	1734	1921	2156	2437	2718	3093	3468	3890	4359
Low														
	Right													
	Sickle Cell	80	75	85	90	90	85	85	80	90	90	70	90	65
	Control	73	80	80	93	80	93	80	80	73	80	73	60	60
	Left													
	Sickle Cell	70	75	65	80	75	85	70	80	75	70	80	70	65
	Control	93	80	93	93	67	87	93	73	87	80	60	73	60
High														
	Right													
	Sickle Cell	80	85	100	95	95	95	100	100	100	100	100	95	95
	Control	100	100	93	100	100	100	87	93	100	100	100	93	93
	Left													
	Sickle Cell	75	80	85	85	95	95	90	95	95	95	95	95	95
	Control	100	100	100	100	100	93	93	93	93	100	100	93	100

Note. For the sickle cell group, n = 20; for the control group, n = 15.

Table 3

Summary Table for the Four-Factor Mixed Analysis of Variance Investigating Mean DPOAE Amplitude as a Function of Group, Ear, f_2 Frequency, and Level

Source	*df*	SS	*F*	*p*
Group	1	4741.14	6.73	.01*
Ear	1	4.79	0.24	.63
Frequency	12	8186.83	34.48	<.0001*
Level	1	40381.65	2040.73	<.0001*
Ear x Frequency	12	92.64	0.39	.97
Level x Ear	1	195.00	9.85	<.0001*
Level x Frequency	12	1000.73	4.21	<.0001*
Level x Ear x Frequency	12	162.84	0.69	.77
Group x Ear	1	0.91	0.05	.83
Group x Frequency	12	481.30	2.03	.02*
Group x Level	1	280.77	14.19	<.0001*
Group x Ear x Frequency	12	108.45	0.46	.94
Group x Level x Ear	1	13.56	0.69	.41
Group x Level x Frequency	12	77.15	0.32	.98
Group x Level x Ear x Frequency	12	56.72	0.24	.99

Note. *$p < .05$

Continuing Education Questions

1. Sickle cell disease is:
   a. Found only in African-American populations
   b. Hereditary and genetic
   c. Carried by all African-American
   d. All of the above.
   e. None of the above.
2. Hearing loss in individuals with sickle cell disease is:
   a. Conductive
   b. Cochlear
   c. Central
   d. Conductive or cochlear
   e. Conductive, cochlear or central
3. According to this study, DPOAE amplitudes in children with homozygous sickle cell disease are:
   a. Larger than those in children with normal hemoglobin at low L_1 and L_2 levels
   b. Smaller than those in children with normal hemoglobin at low L_1 and L_2 levels
   c. Larger than those in children with normal hemoglobin at high L_1 and L_2 levels
   d. Larger than those in children with normal hemoglobin at both low and high L_1 and L_2 levels

e. Smaller than those in children with normal hemoglobin at high L_1 and L_2 levels

4. It was thought that children with sickle cell disease would have poorer DPOAEs than children with normal hemoglobin because:
   a. All people with sickle cell disease have a hearing loss
   b. Children with sickle cell disease are generally smaller than children with normal hemoglobin
   c. Cochlear function may be compromised due to impaired vascularization
   d. All of the above
   e. None of the above
5. The larger DPOAE amplitudes in children with SCD than children with normal hemoglobin was hypothesized to be a result of:
   a. Reduced efferent suppression of outer hair cell activity
   b. Hyper-responsive outer hair cells due to a mechanism that does not involve efferent system dysfunction
   c. Medication regimes that are in some way mediating hyper-responsive activity in outer hair cell function
   d. Children with SCD may have more efficient middle ear backward transmission than children with normal hemoglobin
   e. All of the above

Answer key:

1. B
2. E
3. D
4. C
5. E

Figure Captions

Figure 1. Mean DPOAE amplitudes (dB SPL) as a function of group, ear, and f_2 frequency at the high-level condition (i.e., L_1 and L_2 of 70 and 60 dB SPL, respectively). The open circles and squares represent the right and left ears of the children with normal hemoglobin and the and the closed circles and squares represent the right and left ears of children with sickle cell disease.

Figure 2. Mean DPOAE amplitudes (dB SPL) as a function of group, ear, and f_2 frequency at the low-level condition (i.e., L_1 and L_2 of 50 and 40 dB SPL, respectively). The open circles and squares represent the right and left ears of the children with normal hemoglobin and the and the closed circles and squares represent the right and left ears of children with sickle cell disease.

Figure 3. Scatter plot representing individual DPOAE amplitudes for the children with SCD relative to the 10th and 90th percentiles of the DPOAE amplitudes from the children with the normal hemoglobin for the high primary tone level.

Figure 4. Scatter plot representing individual DPOAE amplitudes for the children with SCD relative to the 10th and 90th percentiles of the DPOAE amplitudes from the children with the normal hemoglobin for the low primary tone level.