



<b>Title</b>	<b>Distortion product otoacoustic emissions in patients with haemophilia</b>
<b>Author(s)</b>	<b>Leung, Hei-tin; 梁曦田</b>
<b>Citation</b>	
<b>Issued Date</b>	<b>2010</b>
<b>URL</b>	<b><a href="http://hdl.handle.net/10722/173719">http://hdl.handle.net/10722/173719</a></b>
<b>Rights</b>	<b>Creative Commons: Attribution 3.0 Hong Kong License</b>

# Distortion product otoacoustic emissions in patients with haemophilia

Leung Hei Tin

A dissertation submitted in partial fulfillment of the requirements for the Bachelor of Science (Speech and Hearing Sciences), The University of Hong Kong, June 30, 2010.

### **Acknowledgements**

I would like to express my heartfelt gratitude to my dissertation supervisor, Dr. Bradley McPherson, for his inspiring guidance. I would also wish to express my sincere appreciation and thanks to my family and friends for their encouragement and support.

## Distortion product otoacoustic emissions in patients with haemophilia

Leung Hei Tin

### Abstract

This study investigated the cochlear function of 13 haemophilic patients using distortion product otoacoustic emission (DPOAE) assessment techniques. Out of the 26 ears examined, a minority of them produced responses that were considered to be impaired. A positive correlation was found between clotting factor level and DPOAE amplitude, and DPOAE/ noise ratio at high frequencies (4, 6, 8 kHz). Clotting factor level, which is indicative of the severity of haemophilia, may be related to hearing status. It was also revealed that DPOAE amplitude and DPOAE/ noise ratio at low frequencies (1, 2, 3 kHz) were greater than those at high frequencies (4, 6, 8 kHz). Therefore the high-frequency cochlear region may be more sensitive to damage. Intracranial micro-haemorrhage in haemophilic individuals may be linked to an increased risk of cochlear damage. Further studies may use brain computed tomography scan to explore the possible link between intracranial micro-haemorrhage and hearing loss.

## Distortion Product Otoacoustic Emissions in Patients with Haemophilia

### Introduction

Coagulation is an important part of haemostasis, which refers to the process that stops bleeding (McKenzie, 1996). Two common congenital coagulation disorders are haemophilia and von Willebrand disease.

Haemophilia is an x-linked genetic condition in which a clotting factor is partially or completely missing (Canadian Hemophilia Society, 2001). It is more likely to occur in males than females. Most of the females with the defective gene become an asymptomatic carrier of the condition. There are two main types of haemophilia. The most common type is haemophilia A, in which coagulation factor VIII is lacking. It is five times more common than haemophilia B, in which coagulation factor IX is lacking. With the defect of a coagulation factor, a haemophiliac individual bleeds for longer than normal. Complications of the condition may include joint disease, deep internal bleeding, blood-borne infection and intracranial hemorrhage (Canadian Hemophilia Society, 2001). At the end of 2008, Hong Kong had a population of 6 988 900 (Census and Statistics Department, 2008). Based on an incidence rate of about 5 in 100 000 (Nathwani & Tuddenham, 1992), approximately 350 people are affected with haemophilia in Hong Kong.

Von Willebrand disease is more common and usually milder than haemophilia. It is caused by a problem with the von Willebrand factor which is essential for proper blood coagulation. Among the three types of the disease (Type 1, Type 2 and Type 3), Type 3 is the most severe form. Symptoms usually include easy bruising and prolonged bleeding (Page, 2007). The prevalence of clinically significant cases of von Willebrand disease is 1 in 10 000 (Rodrigo, 2004). Hence it could affect as many as 700 Hong Kong people.

Research describing hearing disorders in patients with haemophilia and other congenital coagulation disorders is scarce. Fabiani and colleagues (1985) first observed a non-age linked hearing loss in haemophilic individuals and carried out a more thorough investigation using otological examination, pure-tone audiology, impedance tests and auditory brainstem-evoked responses. The subjects were divided into two groups based on the severity of the congenital coagulation disorder. The 18 patients in the first group had mild haemophilia or von Willebrand's disease, while the 22 patients in the second group had severe haemophilia. From the results, 61% of the ears in the mild group and 40.9% of the severe group were found to have hearing loss greater than 15 dB HL. The pathologies found were mainly cochlear and mixed cochlear-retrocochlear in nature. From the results of the auditory brainstem-evoked (ABR) tests, it was shown that brainstem auditory pathway damage was localized in the rostral brainstem region. This localization was also indicated in the study by Thomas and colleagues, who examined 22 subjects with congenital coagulation disorder (Thomas, McPherson, McWhirter, & McGill, 1992). The patients underwent pure-tone audiometry, tympanometry and acoustic reflex measures, speech audiometry, staggered spondaic word list, synthetic sentence identification test and masking level difference test. The results indicated a predominantly sensorineural hearing loss for high-frequency (>4 kHz) test tones and possible central auditory dysfunction. Fabiani et al. postulated that intracranial micro-haemorrhagic episodes that occur in patients with congenital coagulation disorders are linked to hearing loss. The nature of the dysfunction varies with the site of bleeding. As some areas, such as the stapes footplate, are more susceptible to haemorrhage than the others, high-frequency hearing loss may be more common in these individuals (Fabiani, et al., 1985).

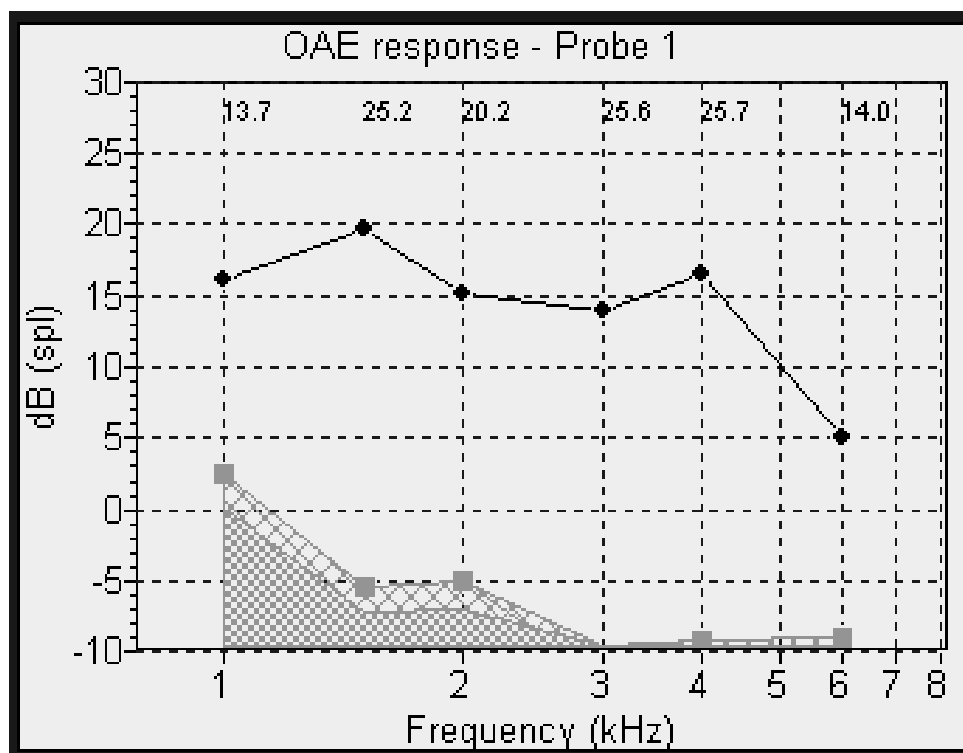
The present study will contribute to the understanding of hearing loss associated with haemophilia by considering otoacoustic emissions (OAEs) in this group. OAE tests have not been carried out in this population. These tests can assess the functioning of the outer hair cells of the cochlea in a non-invasive and rapid manner, thus offering valuable information about the possible pathology in the inner ear. OAEs are acoustical signals that are emitted from the outer hair cells located in the cochlea (Kemp, 1997). Among the three types of OAE, distortion product otoacoustic emissions (DPOAEs) are measured in the current study for two reasons; they allow for greater frequency specificity and they can be used to test at higher frequencies (Gaskill & Brown, 1993).

DPOAEs are generated by the nonlinear mechanism of cochlear activity. Cochlear nonlinearity originates from the outer hair cells of the cochlea. This refers to the cochlea's disproportional output to its input. For low-level auditory inputs, the displacement of the basilar membrane is enhanced so that the output is amplified. However, the response becomes compressive when there is a moderate-level input (Popelka, Osterhammel, Nielsen, & Rasmussen, 1993). DPOAEs are generated as a by-product of this mechanism. When the cochlea is stimulated simultaneously by two pure tone frequencies ( $F_1$ = lower frequency,  $F_2$  =higher frequency), their tonotopic representations along the cochlea might overlap. Distortion is generated if the overlap occurs at a place where the response to one of the tones is nonlinear. As the distortion is a by-product of the nonlinear mechanism that depends on the outer hair cell system, and since the outer hair cells are vulnerable to essentially all cochlear impairments, absent or abnormal DPOAEs are consistent with cochlear impairment.

The measured DPOAE level systematically depends on the four parameters of the stimulus tones, i.e., the levels of the primary tones ( $L_1$ ,  $L_2$ ), the  $L_2$ - $L_1$  level difference, the

absolute stimulus frequencies ( $f_1$ ,  $f_2$ ) and the frequency-separation ratio ( $f_2/f_1$ ). For the intensity-related factors, it is known that the largest DPOAEs are elicited by primary tones at 65 and 55 dB SPL, with the L2-L1 level difference being 10 dB (Gaskill & Brown, 1990; Hauser & Probst, 1991; Whitehead, McCoy, Lonsbury-Martin, & Martin, 1995). For the frequency-related parameters, the most robust of the distortion products occurs at a frequency equal to  $2f_1 - f_2$ , and the frequency ratio of 1.22 results in the largest distortion product (Brown, Sheppard, & Russel, 1994; Gaskill & Brown, 1993). So these settings were followed for the DPOAE measurements in this study.

Figure 1 and figure 2 show two DP-grams generated with the above parameters. The upper line shows the intensity of the distortion product across the stimulus frequencies while the filled area indicates the noise level. The DPOAEs in Figure 1 is more robust than that in Figure 2 as both the DPOAE amplitude and DPOAE/ noise ratio (the difference between DPOAE amplitude and noise floor) are larger.





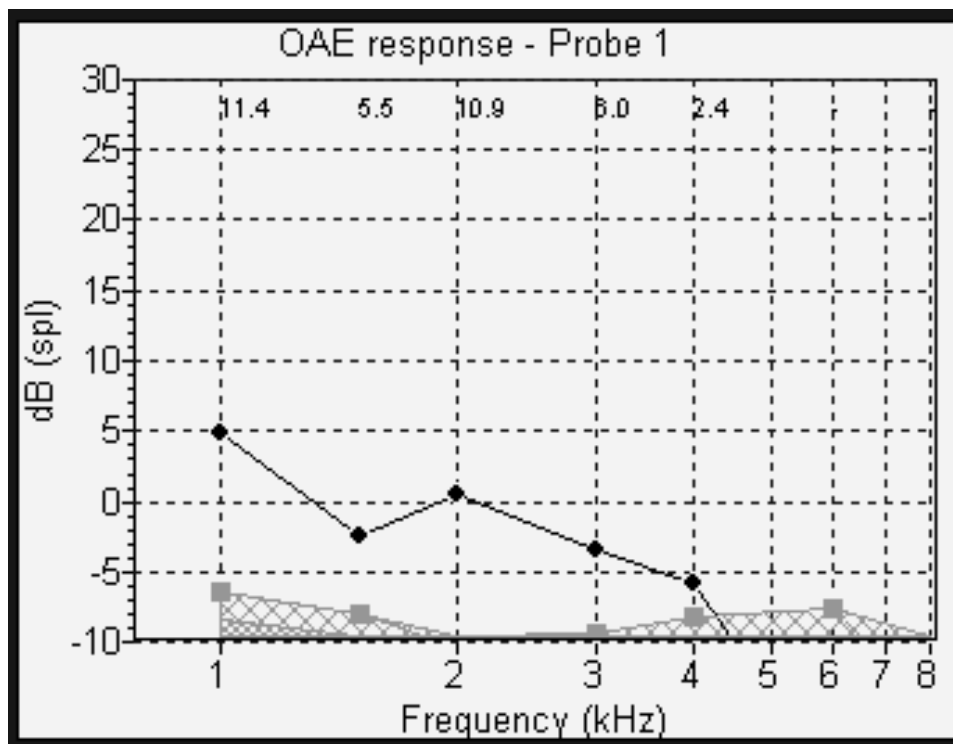


Figure 1 and 2. Two sample DP-grams. DPOAEs were elicited at 2 points per octave from 1-8 kHz ( $f_2/f_1 = 1.22$ ) by primary tones where  $L_1 - L_2 = 10$  dB;  $L_1 = 65$  dB,  $L_2 = 55$  dB. The upper line shows the intensity of the distortion product across the stimulus frequencies while the filled area indicates the noise level. The lower and upper filled area represents the mean noise floor + 1 SD and + 2 SDs respectively.

In general, the presence of normal DPOAE responses across 1-4 kHz, which is the speech frequency range, indicates normal function in both the middle ear and the cochlea (Kemp, 2002). Two common approaches are used to distinguish between normal and impaired DPOAE responses.

The first one is to make the decision based on the DPOAE/ noise ratio. Ears that produce a DPOAE/ noise ratio that is larger than a certain criterion are considered normal. The criterion may be set at 6 dB for clinical purposes and 3 dB for a less stringent standard. However, this rule

may be too simplistic as the DPOAE/ noise ratio depends on the noise level, which is relevant to the surroundings but irrelevant to cochlear status (Robinette & Glattke, 2007). If two persons produce a DPOAE response of 0 dB SPL with a noise level of 0 and -10 dB SPL, respectively, the former case will be considered impaired while the latter will be considered normal. In the latter case, the 10 dB DPOAE/ noise ratio is likely to be inflated by the low level of noise. Therefore, using the DPOAE/ noise ratio criteria may produce inaccurate results due to the inconstant noise level.

There is another approach that only uses the DPOAE response level as the criterion measure. By plotting the normal distribution of DPOAE response amplitude for the normal and impaired population on the same graph, one could argue that responses above the 95th percentile of the impaired population are likely to be coming from an ear with a normal hearing status because so few individuals with impaired hearing could produce DPOAEs of that magnitude or greater. By the same token, any individual who produces DPOAE response amplitudes below the 5th percentile for normal ears would be consistent with having impaired hearing because so few individuals with normal hearing produce DPOAEs that small. The advantage of this approach is that it addresses the overlap between distributions of responses from normal and impaired ears, which is inevitable in reality. But, any responses falling between the 5th percentile for normal ears and 95th percentile for impaired ears will be rendered uninterpretable under this approach.

#### *Hypotheses of current study*

There are two null hypotheses in this study. The first null hypothesis is that there is no significant difference in the prevalence of cochlear hearing loss between patients with haemophilia and normal subjects. Sensorineural hearing loss is indicated by a reduction in DPOAE level due to reduced outer hair cell activity. It is expected that the DPOAE response

level across frequencies will be significantly lower in amplitude in patients with haemophilia

---

Tests

Criteria

---

than in normal subjects. The second null hypothesis is that there is no significant difference in the prevalence of high frequency (4, 6, 8 kHz) and low frequency (1, 2, 3 kHz) cochlear hearing loss in patients with haemophilia. It is expected that the DPOAE response level in the high frequency region will be significantly lower in amplitude than that in the low frequency region, because it was suggested that some areas, such as the stapes footplate, are more susceptible to haemorrhage (Fabiani, et al., 1985)

### **Methodology**

#### *Subjects*

Thirteen young adults with haemophilia were recruited as participants with the help of the Hong Kong Haemophilia Society. An inclusion criterion was that all subjects should be aged between 15 to 35 years of age. This was to avoid any effects of presbycusis. Subjects who were infected with the human immunodeficiency virus (HIV) or suffer from acquired immunodeficiency syndrome (AIDS) were excluded as HIV/ AIDS are proven to be associated with hearing loss (Sooy, 1987). Another exclusion criterion was that subjects with prior occupational exposure to loud noise were not included so as to eliminate the possibility of noise-induced hearing loss. None of the subjects had any pathologic conditions of the external or middle ear, as they passed a hearing screening protocol with the following criteria (see Table 1);

Otoscopic examination	Normal and clear external ear canal and an intact tympanic membrane
Tympanometry	<ol style="list-style-type: none"> <li>1. Jerger Type A tympanogram</li> <li>2. Tympanic compliance between 0.2cm<sup>3</sup> and 2cm<sup>3</sup></li> <li>3. Peak middle ear pressure in the range of +50 and -100 daPa</li> </ol>
Pure-tone audiometry	No threshold greater than 20 dB HL for two or more frequencies, nor any threshold with an air-bone gap of 10 dB or greater

*Table 1.* Passing criteria for the hearing screening

### *Equipment*

All the tests were performed in the Standard Chartered Community Foundation Hearing Centre of the University of Hong Kong. The equipment used included: a Welch Allyn (New York, U.S.A.) fibre-optic otoscope (3.5V nickel-cadmium rechargeable handle); GN Otometrics (Taastrup, Denmark) diagnostic audiometer (Madsen Itera II, model: 1004) calibrated to accepted standards of ANSI s3.22-1996; Grason Stadler (New Hampshire, U.S.A.) middle ear analyzer (GSI 33, model: 1733) calibrated with GSI test cavities (model: 1733-1035) of 2cc for 226 – 678 Hz; and an Otodynamics (Herts, United Kingdom) ILO OAE system (Echoport ILO288 USB-I) with ILO v6 software and general double probe (UGD-USB) calibrated in a 1cc test cavity.

### *Procedures*

After case-history taking and hearing screening which included otoscopic examination, tympanometry and pure-tone audiometry, distortion product otoacoustic emission testing was carried out. Probe fit was checked before otoacoustic emission recording and a stimulus with the properties listed in Table 2 was given. 3 sweeps across the frequency range was taken in each

measurement. DPOAE amplitudes and the noise level were recorded for subsequent data analysis.

*Table 2.* Properties of the testing stimulus

Sound stimuli	2 pure tones
Frequency	1, 1.5, 2, 3, 4, 6, and 8 kHz
Frequency ratio	1.22
Intensity (dB)	L1= 65dB; L2=55dB
Points per octave	2

#### *Data & statistical analysis*

Statistical analyses were performed using SPSS 15.0 for Windows. Descriptive statistics such as mean and median were used to show the gender and type of haemophilia of the subjects. For the first hypothesis, the amplitude of DPOAEs in patients with haemophilia was compared with two data points (5th percentile for normal ears and 95th percentile for impaired ears) of a large sample of normal subjects (Gorga et al., 1997). No inferential tests could be done due to the small study group sample size. The amplitude of DPOAEs in patients with haemophilia in the high frequency region was compared with that in the low frequency region by paired t-test. The effect of subject ear on DPOAE amplitude and DPOAE/ noise ratio was examined by a paired-sample t-test as it was suggested that DPOAEs tend to be larger for right than for left ears (Stover & Norton, 1993). The effect of age on the two variables was tested by Pearson product-moment correlation to see if the same effect found in Lonsbury-Martin & Martin's study (that DPOAE levels tends to decrease with increase age) would be found (Lonsbury-Martin & Martin,

2007). Pearson product-moment correlation was also computed to examine if there were significant effects of the type of haemophilia and the percentage of clotting factor on DPOAEs.

### Results

Table 3 shows the demographic information of the subjects and Table 4 shows the mean, standard deviation, and 95% confidence interval for the amplitude of DPOAEs and DPOAE/ noise ratio for the subjects.

*Table 3.* Demographic information (age, gender and type of haemophilia) of the subjects

<b>Age in years</b>	<b>Number</b>	<b>Total sample %</b>
15-19	1	8
20-24	6	46
25-29	5	38
30-35	1	8
<b>Gender</b>		
Male	13	100
<b>Type of haemophilia</b>		
Haemophilia A	10	77
Haemophilia B	3	23

*Table 4.* The mean, standard deviation, and 95% confidence interval of the amplitude of DPOAEs and DPOAE/ noise ratio.

	<b>Mean</b>	<b>SD</b>	<b>95% CI</b>
DPOAE	2.68	10.21	-2.87-8.23
DPOAE/ noise ratio	14.37	9.91	8.98-19.76

### *Effect of subject ear*

A paired-sample t-test was used to find if there was any difference in DPOAE amplitude and DPOAE/ noise ratio between left and right ear. No significant difference was found for both DPOAE amplitude ( $t(91) = 1.34, p > .05$ ) and DPOAE/ noise ratio ( $t(91) = 0.61, p > .05$ ).

### *DPOAE amplitude and DPOAE/ noise ratio at high and low frequencies*

In this experiment, response was measured at seven frequencies, 1, 1.5, 2, 3, 4, 6, and 8 kHz.

Among them, 1, 2, 3 kHz were defined as low frequencies while 4, 6, 8 kHz were labeled as high frequencies. The mean DPOAE amplitude at low frequencies (mean= 4.74, SD= 6.27) was greater than that at high frequencies (mean= -0.61, SD= 6.16). Similarly for DPOAE/ noise ratio, responses at low frequencies (mean= 15.70, SD= 7.14) was greater than that at high frequencies (mean= 12.61, SD= 6.26). A paired-sample t-test was used to find if there was any difference in DPOAE amplitude and DPOAE/ noise ratio at high and low frequencies. A significant difference was found for both DPOAE amplitude ( $t(25) = 4.75, p < .01$ ) and DPOAE/ noise ratio ( $t(25) = 2.38, p < .05$ ).

### *Effect of age on DPOAE amplitude and DPOAE/ noise ratio*

A Pearson product-moment correlation was conducted to determine if there is a relationship between age and DPOAE amplitude. There was a small negative correlation between the two variables ( $r(180) = -0.215, p < .01$ ). The same was found for DPOAE/ noise ratio ( $r(180) = -0.218, p < .01$ ).

### *Effects of type of haemophilia*

A Pearson product-moment correlation was performed to examine the relationship between the type of haemophilia (type A and type B) and DPOAE amplitude, and between the type of haemophilia (type A and type B) and DPOAE/ noise ratio. No correlation was found.

### *Effect of the percentage of clotting factor on DPOAEs*

Eight of the thirteen subjects reported their personal level of clotting factor (%). A Pearson product-moment correlation was calculated to investigate the relationship between the percentage of clotting factor and DPOAE amplitude at high frequencies, low frequencies and all frequencies in average. The same was calculated for the DPOAE/ noise ratio. A moderate degree of correlation was found between the percentage of clotting factor and DPOAEs at high frequencies only [DPOAE amplitude: ( $r(14) = 0.684, p < .01$ ); DPOAE/ noise ratio: ( $r(14) = 0.681, p < .01$ )]. Figure 3 shows the scatterplot of DPOAE amplitudes at high frequencies against the percentage of clotting factor.

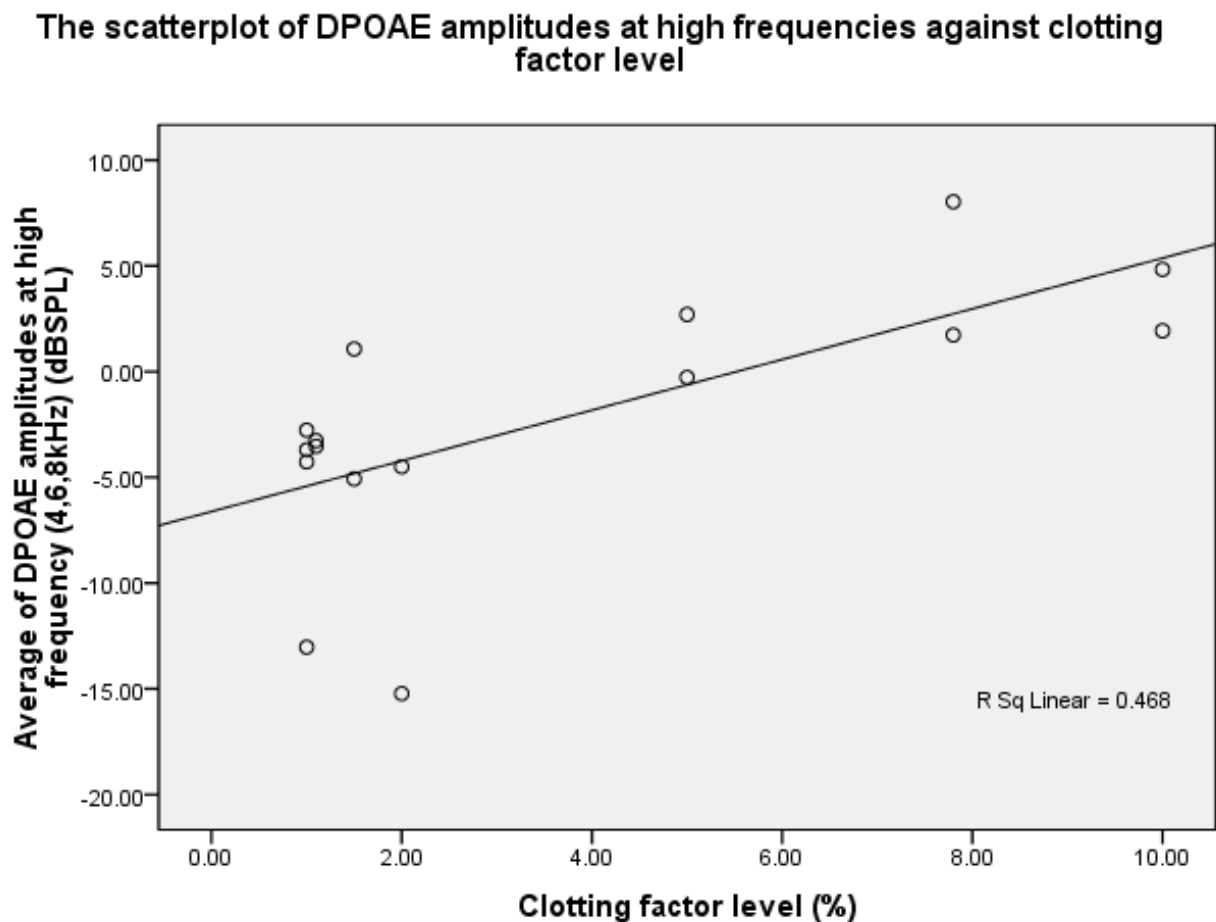
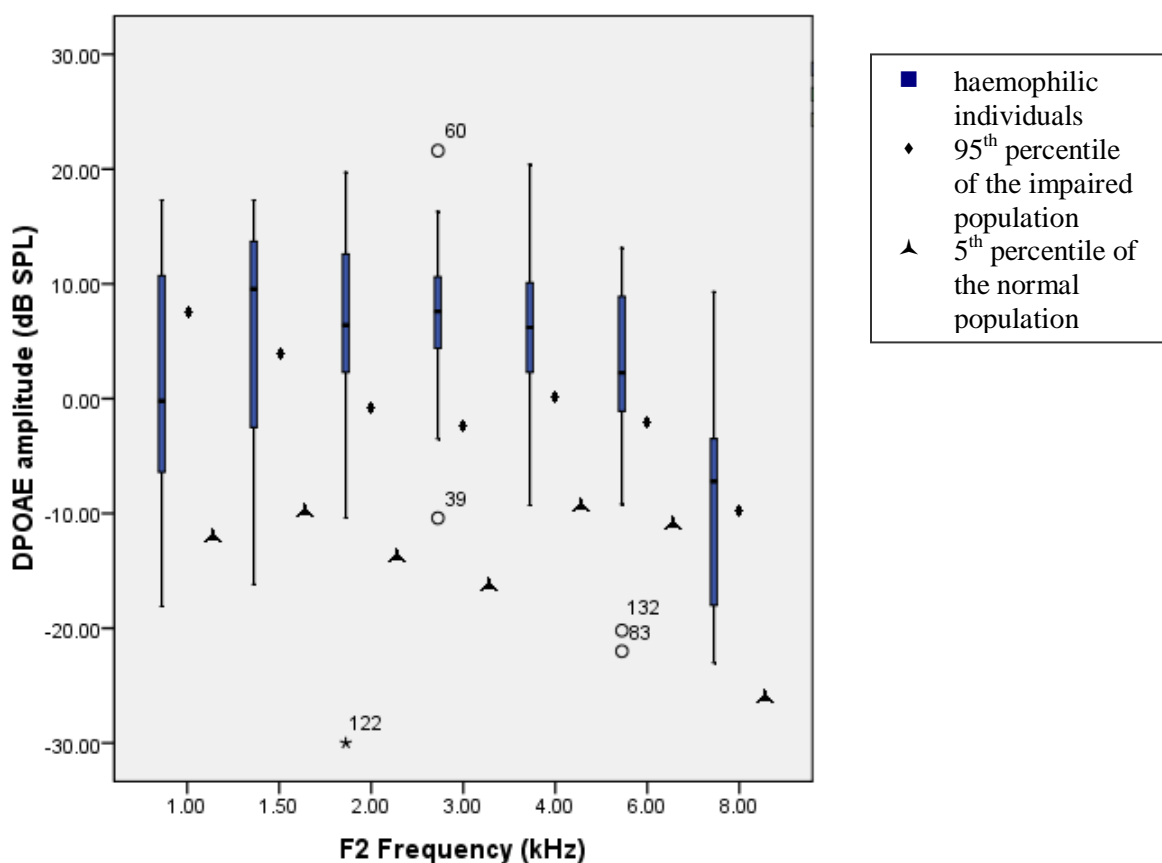


Figure 3 Scatterplot of DPOAE amplitudes at high frequencies against clotting factor level.



*Comparison with a large sample of normal and impaired ears (Gorga, et al., 1997)*

Gorga et al (1997) defined any DPOAE amplitude above the 95<sup>th</sup> percentile of the impaired population as normal hearing because so few individuals with hearing loss can produce DPOAEs of that magnitude or larger. By the same token, DPOAEs below the 5<sup>th</sup> percentile of the normal population are considered to be coming from an ear with impaired hearing as few individuals with normal hearing produce DPOAEs with such a small value. Figure 4 and 5 show the boxplots of DPOAE amplitude and DPOAE/ noise ratio against F2 frequency respectively, alongside with the 95<sup>th</sup> percentile of the impaired population and the 5<sup>th</sup> percentile of the normal population.



*Figure 4. Boxplot of DPOAE amplitude against F2 frequency.*

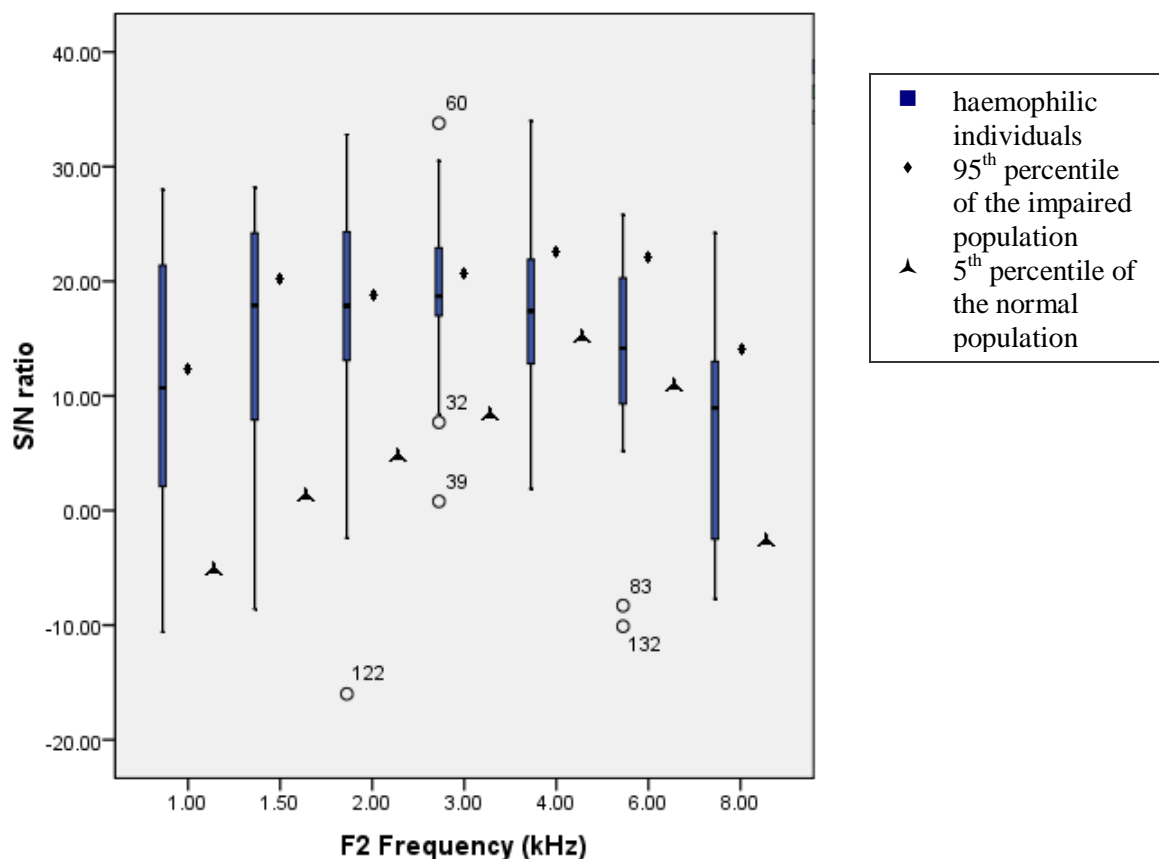


Figure 5. Boxplot of DPOAE/ noise ratio against F2 frequency.

Only DPOAE amplitudes were considered when judging the normality of the 26 ears across the 7 frequencies. Amplitudes above the 95<sup>th</sup> percentile of the impaired population were viewed as normal. The results are shown in Table 5.

Table 5. Number of impaired ears (out of a total of 26 ears) across 7 frequencies based on the criteria of Gorga et al. (1997).

Frequency (Hz)	1000	1500	2000	3000	4000	6000	8000	Average <sup>a</sup>
Number of impaired ears	2	1	1	0	1	2	0	1

<sup>a</sup> Refers to the mean of the 7 frequencies

## Discussion

### *Effect of subject ear*

Stover and Norton (1993) found that DPOAEs tend to be larger for right than for left ears. This was not observed in the present study. The reason may be that the sample size is too small to detect the slight effect previously noted. As no significant difference was found, subject ear was not considered as a variable in the analysis that followed.

### *DPOAE amplitude and DPOAE/ noise ratio at high and low frequencies*

Thomas et al. (1992) suggested that high-frequency hearing loss is more common in haemophilic individuals because some areas, such as the stapes footplate, are more susceptible to bleeding. This same trend was also found in the current study—that DPOAEs at low frequencies were higher than those at high frequencies. However, brain computed tomography (CT) scans may be required if one wants to identify the sites and extent of the intra-cranial hemorrhage (Kinney, Zimmerman, Butler, & Gill, 1977). With that information, the link between hearing loss and intra-cranial bleeding can possibly be established.

### *Effect of age on DPOAE amplitude and DPOAE/ noise ratio*

In this study, only individuals aged between 15 to 35 years were recruited so as to eliminate the possible effects of presbycusis. A negative correlation was found between age and DPOAE amplitudes. This echoes the result reported in a recent study (Lonsbury-Martin & Martin, 2007). However, Stover and Norton (1993) found that the influence of age on DPOAEs is negligible, given that the influence of age and hearing level on DPOAEs were analyzed separately. Future studies have to be better controlled with respect to the individuals' hearing level in addition to age before a reliable conclusion can be drawn.

### *Effects of the type of haemophilia*

No effects of the type of haemophilia were found. But due to the small sample size, the results may be inconclusive as slight effects may not be detected.

### *Effect of percentage of clotting factor on DPOAEs*

Thomas et al. (1992) found that the extent of hearing loss was greater in patients with mild congenital coagulation disorders than those with moderate and severe disorders. The current result contradicts their work, as a positive correlation was found between the percentage of clotting factor and DPOAEs at high frequencies. The higher the clotting factor level (and hence the milder the disorder), the greater the amplitude of DPOAEs recorded. However, as the correlation was only of a moderate level and was only shown in the high frequency region, this may be related to the suggestion that some regions (such as the stapes footplate) may be more susceptible to damage than the others (Thomas et al., 1992).

### *Comparison with a large sample of normal and impaired ears*

Although both DPOAE amplitudes and DPOAE/ noise ratios were recorded in the study, only the DPOAE amplitudes were considered when judging the normality of the ears because the DPOAE/noise ratios depend on the noise level of the environment, which is irrelevant to the individual's hearing status (Robinette & Glatke, 2007). Based on the criteria of Gorga et al. (1997), ears with DPOAEs below the 5<sup>th</sup> percentile of the normal population were considered impaired. Out of the 26 ears examined, only one of them was regarded as impaired when the average result of the 7 testing frequencies was considered. Less than 3 ears produced responses that were considered to be impaired in any of the 7 test frequencies.

Four outliers with particularly low DPOAE amplitudes were observed in Figure 4. Further investigations were made to reveal any trends present. However, it was found that the four points

had little in common as they occur at different frequencies (2, 3 and 6 kHz, respectively); they were from four different individuals and the clotting level of two of the four individuals were unknown (see Table 6).

*Table 6.* Information of the four outliers observed in Figure 4

Subject number	F2 frequency (kHz)	DPOAE amplitude (dB SPL)	Clotting factor level of the subject
122	2	-30.00	unknown
39	3	-13.30	unknown
139	6	-20.20	2%
83	6	-22.00	1%

#### *Limitations of the present study and future study*

The sample size of this study was quite small and reliable inference often could not be made. For example, the prevalence rate of hearing loss between patients with haemophilia and normal subjects could not be compared. Also, subtle trends may have been missed due to the reduced sensitivity of the small sample. Future studies should include a larger number of subjects so that valid conclusions can be drawn. Female carriers of the defective gene and patients of von Williebrand's disease should also be included so as to study the effects of gender and type of congenital coagulation disorder on DPOAEs. Besides, only 8 of the 13 subjects reported their level of clotting factor. Meaningful conclusions could not be made due to the incompleteness of the data. As the percentage of clotting factor was by self-report only, the reliability of the data is debatable due to possible memory flaws.

## **Conclusion**

The current study offers some preliminary data about the hearing status of patients with haemophilia. DPOAE tests were used as they could examine functioning of the outer hair cells of the cochlea in a non-invasive and objective manner. Out of the 26 ears examined, only a minority of them produced DPOAEs that were lower than those of the impaired population. A positive correlation was found between the percentage of clotting factor and DPOAEs at high frequencies. The test results also revealed that DPOAEs at low frequencies were significantly greater than those at high frequencies. Although no definite conclusion can be drawn from this small-scale study, it appears that clotting factor level may be related to hearing status, and that the high-frequency region of the haemophilic individuals may be more sensitive to damage. This topic should be explored more fully by involving a larger sample pool. Brain computed tomography (CT) scans may also be carried out if one wants to identify the sites and extent of the intra-cranial hemorrhage. With that information, the link between hearing loss and intra-cranial bleeding can possibly be established.

## References

- Brown, A. M., Sheppard, S. L., & Russel, P. T. (1994). Acoustic distortion products (ADP) from the ears of term infants and young adults using low stimulus levels. *British Journal of Audiology*, 28, 273-280.
- Canadian Hemophilia Society. (2001). *All about hemophilia: a guide for families*. Quebec: Canadian Hemophilia Society
- Census and Statistics Department. (2008). Hong Kong 2008 population. Retrieved November 1, 2009, from [http://www.censtatd.gov.hk/hong\\_kong\\_statistics/statistics\\_by\\_subject/index.jsp?subjectID=1&charsetID=1&displayMode=T](http://www.censtatd.gov.hk/hong_kong_statistics/statistics_by_subject/index.jsp?subjectID=1&charsetID=1&displayMode=T)
- Fabiani, M., Di Girolamo, A., Mariani, G., Casini, A., Giacomini, P., & Chistolini, A. (1985). Hearing disorders in haemophilia and von Willebrand's disease. *Advances in Audiology*, 3, 161-181.
- Gaskill, S. A., & Brown, A. M. (1990). The behavior of the acoustic distortion product,  $2f_1 - f_2$ , from the human ear and its relation to auditory sensitivity. *Journal of the Acoustical Society of America*, 88, 821-839.
- Gaskill, S. A., & Brown, A. M. (1993). Comparing the level of the acoustic distortion product  $2f_1 - f_2$  with behavioural threshold audiograms from normal-hearing and hearing-impaired ears. *British Journal of Audiology*, 27, 397-407.
- Gorga, M. P., Neely, S. T., Ohlrich, B., Hoover, B., Redner, J., & Peters, J. (1997). From laboratory to clinic: a large scale study of distortion product otoacoustic emissions in ears with normal hearing and ears with hearing loss. *Ear and Hearing* 18, 440-455.

- Hauser, R., & Probst, R. (1991). The influence of systematic primary-tone level variation L2-L1 on the acoustic distortion production emission 2f1-f2 in normal human ears. *Journal of the Acoustical Society of America*, 89, 280-286.
- Kemp, D. T. (1997). Otoacoustic emissions in perspective. In M. S. Robinette, Glatke, T.J. (Eds.), *Otoacoustic emissions: clinical applications* (3 ed., pp. 1-21). New York: Thieme Medical Publishers, Inc.
- Kemp, D. T. (2002). Otoacoustic emissions, their origin in cochlear function, and use. *British Medical Bulletin*, 63, 223-241.
- Kinney, T. R., Zimmerman, R. A., Butler, R. B., & Gill, F. M. (1977). Computerized tomography in the management of intracranial bleeding in hemophilia. *The Journal of Pediatrics*, 91(1), 31-35.
- Lonsbury-Martin, B. L., & Martin, G. K. (2007). Distortion-product otoacoustic emissions in populations with normal hearing sensitivity. In M. S. Robinette & T. J. Glatke (Eds.), *Otoacoustic emissions: clinical applications* (3rd ed., pp. 107-130). New York: Thieme Medical Publishers, Inc.
- McKenzie, S. B. (1996). *Textbook of hematology* (2nd ed.). Baltimore: Williams & Wilkins.
- Nathwani, A. C., & Tuddenham, E. G. (1992). Epidemiology of coagulation disorders. *Baillière's Clinical Haematology*, 5, 383-439.
- Page, D. (2007). All about von Willebrand disease...for people with von Willebrand disease and their families Available from <http://www.hemophilia.ca/files/AllAboutVWDRRevisedEng.pdf>



- Popelka, G.R., Osterhammel, P.A., Nielson, L.H., & Rasmussen, A.N. (1993). Growth of distortion product otoacoustic emission with primary-tone level in humans. *Hearing Research, 71*, 12-22
- Robinette, M. S., & Glatke, T. J. (2007). *Otoacoustic emissions: clinical applications* (3rd ed.). New York: Thieme Medical Publishers, Inc.
- Rodrigo, E. (2004). Molecular basis of von Willebrand disease and its clinical implications. *Haematologica, 89*(9), 1128-1133.
- Sooy, C. D. (1987). The impact of AIDS on otolaryngology, head and neck surgery. *Advances in Otolaryngology, Head and Neck Surgery, 1*, 1-28.
- Stover, L., & Norton, S. J. (1993). The effects of aging on otoacoustic emissions. *Journal of the Acoustical Society of America, 94*, 2670-2681.
- Thomas, K., McPherson, B., McWhirter, W., & McGill, J. (1992). Hearing loss in patients with congenital coagulation disorders. *Journal of Audiological Medicine, 1*, 176-184.
- Whitehead, M. L., McCoy, M. J., Lonsbury-Martin, B. L., & Martin, G. K. (1995). Dependence of distortion-product otoacoustic emissions on primary tones in normal and impaired ears: I. effects of decreasing L2 below L1. *Journal of the Acoustical Society of America, 97*, 2346-2358.

## Appendix A

### Informed Consent Form

You are cordially invited to participate in a research study titled ‘Distortion product otoacoustic emissions in patients with haemophilia.’ Distortion product otoacoustic emissions (DPOAEs) test is a standard audiological test that evaluates the functioning of outer hair cells of the inner ear. This study aims at evaluating the auditory system of patients with haemophilia by testing distortion product otoacoustic emissions. Distortion products (DP) are faint sounds, produced by normal cochlea when two pure tones, slightly different in frequency, are simultaneously presented to the ear. The result of the distortion product otoacoustic emissions test will help to identify patients who are at risk for hearing impairment.

In this study, hearing screening (20 mins) which includes pure tone audiometry and tympanometry will be carried out. Pure tone audiometry identifies the hearing threshold levels of an individual; while tympanometry measures the aural acoustic immittance as a function of the ear canal pressure. Upon passing the screening, you will be invited to have a DPOAE test for both ears (15 mins). The DPOAE test is conducted by inserting a soft silicone probe with miniature microphone into the entrance of external ear canal. The cochlea will be stimulated simultaneously by two tones of different frequencies. The responses from the cochlea will then be recorded. No potential risks or discomfort will be caused.

All the information obtained in this study will remain strictly confidential and will be used for research purposes only. Your participation in this project is voluntary. This means that you can withdraw from this project at any stage, for any reasons, without negative consequences. If you want to know more about the rights as a research participant, please contact the Human Research Ethics Committee for Non-Clinical Faculties, the University of Hong Kong (Tel: 2241 5267).

If you have any questions or concerns about the research, please feel free to contact the investigator Alice Leung Hei Tin (Tel: 6220 4624).

-----  
I, \_\_\_\_\_ (Name of Participant) understand the procedures described above and agree to participate in the study.

Signature : \_\_\_\_\_

Date : \_\_\_\_\_

Contact number : \_\_\_\_\_

## Appendix B

### 同意書

香港大學言語及聽覺科學部誠意邀請閣下參與一項名為「血友病人士的耳聲發射」的研究。

「耳聲發射」是常規的聽力檢查，主要測試耳蝸內毛細胞的功能。這項研究是透過「耳聲發射」來測試血友病病人的內耳系統的狀況。研究的結果有助於確認可能患有聽力障礙的病人。

研究期間，參加者須要接受簡單的聽力篩檢(約20分鐘)。篩檢包括「純音測試」和「中耳聲阻抗測驗」。「純音測試」可以評估參加者雙耳在各頻率的聽力表現，而「中耳聲阻抗測驗」則可提供耳膜及中耳系統狀況的資料。通過篩檢者將會被邀請參加這項「耳聲發射」研究(約15分鐘)。研究員會把已接駁電腦的軟矽膠探嘴放進耳朵的外耳道口，探嘴會發放兩個頻率不同的音，然後量度耳蝸的反射聲音。本測試不會構成不良或不適的反應。研究收集之所有資料只供香港大學作研究用途，並會絕對保密。此為自願的研究項目，參加者可隨時終止測試，有關決定將不會引致任何不良後果。如閣下想知道更多有關研究參與者的權益，請聯絡香港大學研究操守委員會(電話:2241 5267)。

如對此項研究有任何疑問，請聯絡香港大學言語及聽覺科學部本科生梁曦田 (電話:6220 4624)。

本人 \_\_\_\_\_(參加者姓名)明白測試的程序，並願意參加此項研究。

參加者簽名 : \_\_\_\_\_

日期 : \_\_\_\_\_

聯絡電話 : \_\_\_\_\_

## Appendix C

## Distortion product otoacoustic emissions in patients with haemophilia

Case History Form

Name: \_\_\_\_\_

Date of Birth: \_\_\_\_\_

Sex: M/F

Haemophilia A Haemophilia B von Willebrand's disease Others 

Clotting factor level (%): \_\_\_\_\_

Severity: mild/ moderate/ severe

Have you ever

- |   |   |     |    |          |       |
|---|---|-----|----|----------|-------|
| 1 | had hearing loss?                       | Yes | No | Details: | _____ |
| 2 | had middle ear infection?               | Yes | No | Details: | _____ |
| 3 | had an ear surgery?                     | Yes | No | Details: | _____ |
| 4 | had regular exposure to loud noise?     | Yes | No | Details: | _____ |
| 5 | had a history of familial hearing loss? | Yes | No | Details: | _____ |
| 6 | been tested positive for HIV/AIDS?      | Yes | No | Details: | _____ |

Hearing Screening Recording Form

	Otosopic Examination		Tympanometry		
	Ear debris/ wax	Other abnormalities	Peak Compliance (ml)	Peak Pressure (daPa)	Jerger Type
Right ear					
Left ear					

CNE = cannot evaluate    ✓ = Pass    X = Fail

Pure-tone Audiometry – AC						
Frequency	250 Hz	500 Hz	1 kHz	2 kHz	4 kHz	8 kHz
Right ear						
Left ear						
Pure-tone Audiometry – BC						
Frequency	250 Hz	500 Hz	1 kHz	2 kHz	4 kHz	8 kHz
Right ear						
Left ear						

✓ = Pass at 20dB HL    X = Fail at 20dBHL