The Prevalence of Sensorineural Hearing Loss in β-thalassaemia patient treated with Desferrioxamine

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SUMMARY

Objective: This study aimed to evaluate the prevalence of sensorineural hearing loss (SNHL) in β-thalassaemia patients treated with Desferrioxamine (DFO) and determine the correlation of SNHL with average daily DFO dosage, serum ferritin level and Therapeutic index (T.I).

Methods: This is a cross sectional descriptive study carried out for a period of 14 months and 54 patients were recruited. The recruited patients are transfusion dependant β-thalassaemia patient aged 3 years and above treated with DFO. An interview, clinical examination and hearing assessment, which included tympanogram, and Pure Tone Audiometry (PTA) or behaviour alaudiometry were performed. The data on age started on DFO, average daily DFO, duration of DFO intake, serum ferritin past 1 year and Therapeutic Index (T.I) were obtained from patients' case notes.

Results: The prevalence of SNHL was 57.4% and majority has mild hearing loss (93.6%). Fourteen patients (25.9%) have bilateral ear involvement and as many as 17 patients (31.5%) have SNHL in either ear. A total of 23 patients (42.6%) have normal hearing level. Although the prevalence of SNHL was 57.4%, only a small percentage of the patient noticed and complained of hearing loss (11.1%). There is no association between age started on DFO, average daily DFO and duration of DFO intake with normal hearing group and those patients with SNHL. Positive correlation was seen between average daily DFO with 2000 and 4000Hz on PTA in the left ear and between serum ferritin level past 1 year with 4000 and 8000Hz in the right ear and 8000Hz in the left ear. No significant correlation was seen between T.I on PTA.

Conclusion: The prevalence of SNHL from hearing assessment is high in β-thalassaemia patients in this study. However, it is manifested clinically in a smaller percentage. We suggest a baseline hearing assessment should be carried on all β-thalassaemia patients prior to DFO chelation therapy.

KEY WORDS:
Thalassaemia, Pure tone audiometry

INTRODUCTION

β- Thalassaemia is a relatively common disorder in South-East Asia regions caused by genetic defect in the synthesis of β- chain haemoglobin leading to chronic microcytic hypochromic anaemia [1]. Current effective treatment is with regular transfusion aiming to correct the anaemia and to suppress marrow expansion [2]. In the process, regular transfusion results in unwanted accumulation of iron and our body have no physiological system to remove the excess iron [3]. The excess iron deposits in the heart, liver and endocrine organs leading to heart failure, hepatic fibrosis and cirrhosis, diabetes mellitus, hypogonadism, growth failure, sexual immaturity and immunological abnormality[4,5].

Since the introduction of Desferrioxamine, it has been considered the treatment of choice for β-thalassaemia patient with chronic iron overload [6]. Together with regular blood transfusion, the life expectancy dramatically improves to fourth or even fifth decade of life [6-8]. Attention is now shifted towards improving the quality of life in these patients [6]. Despite the advantages and safety of DFO therapy, the chelator is not free of complications. There are reports of sensorineural hearing loss (SNHL) in β-thalassaemia patient treated with DFO [1,5,7-9].

There are also increasing evidences that the hearing loss in β-thalassaemia patients on DFO is asymptomatic clinically. Therefore, detection of any early hearing loss is crucial especially in frequency range that can affect communication[8]. Early detection allows early intervention and improvement in quality of life. The information regarding possibility of hearing impairment can be shared with our haematologists to be used as a guide in adjusting or modify the treatment in these patients. The information can also be used to counsel the patients prior to treatment initiation.

MATERIALS AND METHODS

This is a cross-sectional descriptive study where β-thalassaemia patients treated with desferrioxamine (DFO) alone in UKMMC listed in the Thalassaemia Registry (UKMMC) were recruited. This comprised of β-thalassaemia major, β-thalassaemia intermedia and HbE β-thalassaemia patients requiring regular transfusion and treated with desferrioxamine (DFO). Transfusion dependant β-thalassaemia patient aged 3 years and above were recruited in this study. At 3 years and above, the patients would have been started on DFO and able to perform at least behavioural

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Table I: Association between age to start on DFO, average daily DFO dosage, duration of DFO intake, serum ferritin level and Therapeutic Index (T.I) with hearing status

	Hearing status	N	Mean	SD	t	p value
Age started on DFO (year)	Normal	23	9.77	6.38	1.10	0.28
	SNHL	31	8.22	3.92		
Average daily DFO (mg/kg/day)	Normal	23	27.10	7.90	0.32	0.75
	SNHL	31	26.49	6.28		
Duration of DFO intake (year)	Normal	23	9.58	6.27	0.04	0.97
	SNHL	31	9.51	6.16		
Serum Ferritin last 1 year (µg/L)	Normal	23	4700.40	2492.69	-0.57	0.57
	SNHL	31	5263.06	4178.01		
Therapeutic Index (T.I)	Normal	23	0.0081	0.0061	-0.56	0.58
	SNHL	31	0.0092	0.0073		

Table II: The p-value for Pearson correlation between Pure Tone Audiogram (PTA) with average daily DFO, average serum ferritin and TI in the study group for both ears.

	Ear	Frequency (Hz)					
		250	500	1000	2000	4000	8000
Average daily DFO (mg/kg/day)	Right	0.99	0.84	0.65	0.41	0.52	0.13
	Left	0.53	0.38	0.21	0.01**	0.01**	0.23
Serum Ferritin last 1 year (µg/L)	Right	0.42	0.65	0.24	0.06	0.04*	0.02*
	Left	0.87	0.28	0.12	0.56	0.08	0.05*
Therapeutic Index (T.I)	Right	0.41	0.71	0.24	0.22	0.71	0.08
	Left	0.89	0.56	0.18	0.86	0.86	0.68

** Correlation is significant at the 0.01 level (2 –tailed)
* Correlation is significant at the 0.05 level (2 –tailed)

audiometry successfully. Patients with congenital abnormalities of the ear, history of disease which would lead to sensorineural hearing loss such as meningitis, use of ototoxic drug such as gentamicin, previous otological surgery, head trauma, trauma to the ear or suspicious history of noise-induced hearing loss (NIHL) and patient on oral chelator were excluded. A total of 54 patients were recruited.

The recruited patients were interviewed and symptoms of ototoxicity include hearing loss, tinnitus and vertigo were documented. The data for age started on DFO (year), average daily DFO (mg/kg/day), duration of DFO intake (year), serum ferritin past 1 year (µg/L) and Therapeutic Index (T.I) were obtained from patients' case notes. The dosage and duration of DFO therapy were not fixed for all the patients. The DFO was administered by slow subcutaneous infusion into the arm or abdomen lasting 8 till 12 hours per night for 5 to 7 nights per week at a recommended dosage of DFO was between 20 to 40mg/kg/day. The aim of the DFO chelation therapy was to maintain the serum ferritin level below 1000µg/L. Bilateral hearing status was assessed in a sound proof chamber and an audiometer (GSI 61 Clinical Audiometer, Grason- Stadler, Madison, USA) was used to generate auditory signals of different frequencies. The frequencies tested were 250Hz through 8000 Hz. Hearing loss group consisted of patients with threshold worse than 25dBHL for two or more frequencies. All patients were then grouped into either having normal hearing or sensorineural hearing loss (SNHL).The hearing loss group was then subdivided into mild, moderate, severe and profound hearing loss. The age started on DFO, average daily DFO, duration of DFO intake, serum ferritin past 1 year and Therapeutic Index (T.I) were compared with normal hearing group and SNHL group.

The data on average daily DFO, average serum ferritin past 1 year and Therapeutic Index (T.I) were analyzed using Student t-test. Pearson Correlation study was used to calculate the correlation between average daily DFO, average serum ferritin past 1 year and Therapeutic Index (T.I) with PTA at frequencies of 250, 500, 1000, 2000, 4000 and 8000Hz in both ears for patients with SNHL. A p value of less than 0.05 is considered to be statistically significant.

RESULTS

Out of the 54 patients recruited, 23 (42.6%) were males and 31 (57.4%) were females. Patients ranged in age from 6 to 33 years with a mean age of 18.37 ± 7.24 years. Majority of the study population were Malays (31 patients, 57.4%) followed by Chinese (23 patients, 42.6%). There was no Indian in our study population or other ethnic group. There were only two symptoms present in the study population. The commonest symptom was tinnitus present in 17 patients(31.5%) followed by hearing loss in 6 patients (11.1%). No patients had vertigo. The majority i.e. 31 patients (57.4%) did not complain of hearing loss, tinnitus nor vertigo.

All the patients underwent tympanogram followed by PTA. None of the patients' required behavioural audiometry. Tympanogram showed that 100% of the ears had a Type A pattern. The prevalence of sensorineural hearing loss among β- thalassaemia patient on regular desferrioxamine was 57.4% (31 patients). The level of hearing loss on PTA in these 31 patients ranged from mild to severe. The commonest level of hearing loss in our study population was mild SNHL with 29 patients (93.6%) followed by 1 patient (3.2%) for moderate and severe hearing loss respectively. None of the study population was diagnosed with profound SNHL. The

association between average daily DFO dosage, average serum ferritin level past 1 year and Therapeutic Index (T.I) was compared in the normal hearing group with SNHL group as summarized in Table I.

The mean age to start on DFO is younger by about 1 year in SNHL group. Statistically, the difference was not significant. There was no fixed dose of DFO that was applicable for all patients. The average daily DFO dosage varied from one patient with another. Mean average daily DFO dosage and duration did not differ much. Based on the results, there was no statistical difference between mean average daily DFO dosage (p value = 0.75) and duration of DFO intake (p value = 0.97) with hearing status.

The level of serum ferritin in our study population was checked during the last 6 months and the mean of all ferritin levels during last year. The mean ferritin levels during the last 6 months for the normal population did not differ much with the mean ferritin levels during last 1 year. Both the ferritin level in 6 months and last 1 year were higher in study population with SNHL. However, the differences in both group was not significant with p value of 0.25 and 0.57 respectively. The mean Therapeutic Index (T.I) in both normal and SNHL group were below the DFO toxicity level of 0.025. There was no significant statistical difference in both groups.

The Pearson correlation coefficient was used to calculate the correlation between daily average DFO, average serum ferritin level for past 1 year and T.I with pure tone audiometry (PTA) at frequencies of 250Hz till 8000Hz in both ears for the 31 patients with SNHL. The p-values for all the above parameters were summarized in Table II.

There was significant positive correlation (p value 0.01) between average daily DFO with frequencies of 2000 and 4000Hz on PTA in the left ear. No significant correlation was shown in the right ear. The other significant correlation was also observed between serum ferritin last 1 year with 4000 and 8000Hz in the right ear and 8000Hz only in the left ear. There is no correlation between PTA with Therapeutic Index (T.I) for both ears in patient with SNHL in all frequencies.

DISCUSSION

A total of 31 patients showed hearing loss that gave the prevalence of SNHL in our study of 57.4%. Our reported prevalence was within the range between 3.8 to 57% as reported in other study [10]. The mechanism of SNHL induced by DFO is still under investigation. The hearing loss was postulated due to the effect of DFO on cochlear ciliated cells at basal turn [11]. An experiment conducted on guinea pig using a regime of DFO at 600mg/kg per day for 30 days showed the cochlear outer hair cells were predominantly missing [10].

The effect of DFO on otological symptoms was studied focusing mainly on tinnitus, hearing loss and vertigo. The commonest symptoms in our series are tinnitus followed by hearing loss and none had vertigo. Tinnitus could be an early sign of DFO ototoxicity. The presence of tinnitus may precede any notable threshold shift and one should not disregard this symptom [12]. Based on the otological symptoms, we concluded that DFO affects the auditory pathway but spare the vestibular system.

The percentage of patients with hearing loss on PTA was 57.4% but only 11.1% of study population complaint of hearing loss. Most of the patients did not notice any hearing loss probably due to the slow progression. These patients had adapted or compensated for the hearing loss. This information highlights the need for routine hearing assessment despite no complaint of hearing loss.

In the 1980s, there were reports of ototoxicity induced by DFO. Albera *et al* [1] showed that there was a uniform trend of high frequencies hearing loss in association with higher DFO dosage. Therefore, a safe therapeutic level of DFO dosage was investigated. In 1989, Porter *et al* [11] studied 47 patients with β-thalassaemia major revealed that high dose of DFO therapy was not the sole risk factor for DFO ototoxicity. The investigators concluded that the high dose of DFO therapy in association with low serum ferritin level (<2000µg/L) is the risk factor for DFO toxicity. The investigators introduced the Therapeutic index (T.I) that was obtained by dividing the mean daily DFO dose (mg/kg) with serum ferritin (µg/L). A ratio of less than 0.025 is apparently safe to avoid DFO toxicity [11]. Therapeutic Index (T.I) was used as a predictor of ototoxicity and visual toxicity [13].

In our study, the Therapeutic Index (T.I) for all our patients was notably below the safe level of 0.025 (0.0092 ± 0.0073). Despite the low Therapeutic Index (T.I) level, we reported a 57.4% of the patients with abnormal audiogram. In another study, the T.I was below the critical level yet hearing loss developed in 48.7% of their patients [5]. We concluded that SNHL occurred even at a low level of Therapeutic Index (T.I). We postulated that SNHL in β- thalassaemia patient on DFO may not be influenced by high dose of DFO or low level of serum ferritin but might be related to genetic factor. Recent study showed that the presence of certain genotypes were more susceptible to noise induced hearing loss [14]. Genetic factors might play a role in modifying the susceptibility of β-thalassaemia patients to DFO ototoxicity. We do not recommend relying on T.I to avoid DFO toxicity but recommend annual hearing assessment or whenever patients are symptomatic (tinnitus or hearing loss).

Pure tone audiometry (PTA) is the main method of detecting hearing loss in β-thalassaemia patients [8]. Since we are unsure regarding the effect of DFO on hearing threshold, we used pure tone audiogram (PTA) as the instrument for audiologic assessment. We found positive correlation between average daily dose of DFO with 2000 and 4000Hz in the left ear with p value of < 0.01 on PTA. The other significant correlation was seen between serum ferritin for the past 1 year with frequency of 8000Hz in both ears with addition of 4000Hz in the right ear only. The high frequencies involvement could be due to the effect of DFO on the cochlear ciliated cells at basal turn [11]. Our study concurred with other investigator that revealed a high frequency involvement mainly at 4000 and

8000Hz [15]. However, we did not expect asymmetrical involvement of hearing loss. Medical literature search showed other investigators reported similar asymmetrical SNHL in their work [16]. On the other hand, there was study that showed no preponderance of hearing loss for either ear [5]. The predilection of hearing loss in either ear could be by chance and has no preference for either right or left ear.

The lack of statistical differences was attributed to the few limitations we encountered in our study. The DFO dosage was not standardized and differs from one patient to another based on individual requirements. It was not possible to standardize the DFO dosage for all the patients. The compliance of daily DFO infusion was questionable especially in the younger patients who needed to endure the pain from the needle prick and DFO infusion.

CONCLUSION

The prevalence of SNHL in β- thalassaemia patients on DFO was 57.4% and only a small percentage of these patients noticed the hearing loss (11.1%). Tinnitus is the commonest otological symptoms and may be the early symptom suggesting possible threshold shift and a PTA should be used to confirm any threshold shift. The average daily DFO dose affects high frequency SNHL significantly in the left ear as shown on PTA. Despite the Therapeutic Index (T.I) of DFO was less than 0.025 to avoid DFO ototoxicity, we demonstrated high percentage of SNHL on PTA. It is imperative that all β- thalassaemia patients should undergo a baseline audiological test prior to starting DFO and during chelation therapy if tinnitus or hearing loss were present.

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Conflict of interest

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