

Original Research Article

Assessment of Auditory Brainstem Response in Infants Suffering from Congenital Heart Disease

Abstract:

Background: Congenital heart defects are the singular most common congenital anomalies and account for a significant fraction of childhood mortality and morbidity. Hearing impairment was the most frequent sensory deficit. Auditory brainstem response (ABR) was determined to assess the maturation and function of brainstem, and hence, hearing in infants. Therefore, we used ABR for hearing assessment in infants diagnosed with congenital heart disease.

Methods: This observational cross-sectional study was carried out on 60 infants, below or above the age of 12 months, both sexes, with CHD. Infants were further divided into two equal groups: Group A with a cyanotic infant, and group B with cyanotic infants. All patients were subjected to Echocardiography.

Results: 20% of our cases to be affected with varying degrees of hearing loss. No significant difference was found between the cyanotic and a cyanotic infant. However, cyanotic infants below 12 months had higher incidence of hearing loss when compared to those above the age of 12 months; whether the cyanotic or the cyanotic peers.

Conclusions: High prevalence of hearing loss amongst patients with CHD warrants the addition of those patients to the high-risk registry for hearing loss, in order that they may

Comment [HG1]: Infant = 0-12 months, please find another term

Comment [HG2]: Do you mean the single most common congenital anomaly? Or the most common isolated anomaly? Please make it clearer

Comment [HG3]: Please stress out the aim of the study here

Comment [HG4]: Cross sectional is an observational study. No need to stress it twice

Comment [HG5]: Infants, but above 12 months? Please find more suitable terms

Comment [HG6]: Need to introduce the abbreviation first.

Comment [HG7]: Do you mean: the group is divided by age, and further divided (subdivided) by cyanotic/acyanotic status?

Comment [HG8]: Echo for detection of CHD? Please also define the measurement of ABR method here

benefit from early detection and intervention, and ergo protected against the affection of hearing impairment on their neurodevelopment. Routine follow-ups for patients with cyanotic heart disease from the age of 6 months to assess the effect of chronic hypoxemia on the inner ear and monitor the rate of improvement in ABR results, as to establish an accepted rate of improvement, and an appropriate time of intervention, if needed.

Keywords: Auditory Brainstem Responses, Congenital Heart Disease

Comment [HG9]: The conclusion should answer the aim of the study. This conclusion does not relate to background and result. It should reflect the overall research, not just a suggestion or another supporting theory.

Higher incidence in infant below 12 months? Is it somewhat relevant?

Introduction

Congenital heart diseases (CHD) are defined as a structural abnormality of the heart or intra thoracic vessels present at birth that is actually or potentially of functional significance. CHD are the singular most common congenital anomalies and account for a significant fraction of childhood mortality and morbidity, occurring globally in about 1% of livebirths^[1] and has been estimated to be 5-6/1000 live births among Egyptian children ^[2].

Comment [HG10]: Same comments as the above

CHD is a lifelong disease that results from a heart defect or structural anomaly at birth. As CHD impacts the physical, nutritional, and developmental status of children's health, it also may change many aspects of patients and their families' life, as social, psychological dimensions, there by impacting their quality of life ^[2].

Hearing impairment is a pervasive disability affecting nearly 250 million people in the world, and 75% of sufferers live in developing countries. In Egypt there have been no national surveys on the prevalence of hearing loss and deafness. There have been hospital-based and academic studies which give an idea about the magnitude of the problem ^[3].

The current survey shows that the prevalence of hearing loss in Egypt (16.02%) is higher than many other countries, both developed and developing countries. The fact that the age group 0–4 years had a high frequency of hearing loss (22.4%), while the prevalence of hearing loss in school children (6-12 years) was almost 10% (which is higher than rates reported in previous studies in the country of 5.3% and 4.5%) should draw attention to the importance of screening this age group: this should include neonatal screening and preschool screening ^[3].

There were multiple theories about the interconnection between congenital heart diseases and hearing affection in the pediatric age group. From an anatomical and an embryological point of view, preliminary evidence indicates that children with congenital heart disease may be at

increased risk of temporal bone anomalies and hearing loss – basing this theory on the simultaneous chronologic development of the ear and the cardiovascular system, and that may be a predisposing factor to an increased risk of aural anomalies in children with congenital heart disease^[4]. Another theory linked the chronic hypoxemia which patients with cyanotic CHD suffer from to SNHL through hypoxia-driven brainstem maturation retardation^[5]. Moreover, a study went on to propose the possible presence of syndromes not yet known linking hearing loss with congenital heart disease.

Comment [HG11]: This is the key message in the background session. Stress this more in the background. No need for a long background, please make it more concise

Cédric Le Caignec et al. ^[6] studied a family with hearing impairment, congenital heart defects and a congenital opacity of the cornea known as embryotaxan. All participants had congenital heart defects, including tetralogy of Fallot, ventricular septal defect, or isolated peripheral pulmonic stenosis. No individual in this family met the diagnostic criteria for any previously described clinical syndrome. Jagged 1 (JAG1) missense mutation (C234Y) in the first cysteine of the first epidermal growth-factor-like repeat domain of the protein was noted.

Above all, hearing is important for the proper development of every child, especially for those younger than 5 years of age, because it helps in the development of language and speech. Emotional and social problems, as well as issues with academic^[7].

Comment [HG12]: Please state the aim of the study here. Why do you want to conduct the study? Why do you want to analyze the ABR of the CHD patients and further analyze it .

Patients and Methods

This observational cross-sectional study was carried out on 60 infants, below or above the age of 12 months, both sexes, with CHD. This study was done over the period of a year and a half after approval from ethical committee, Faculty of Medicine Tanta University, Tanta, Egypt.

Comment [HG13]: Please state the inclusion and exclusion criteria. Such as the maximum age (children under 5 years old for example). Do not mix the inclusion criteria with the subdivision of groups

Infants were furtherly divided into two equal groups: Group A with a cyanotic infant, and group B with cyanotic infants. Exclusion criteria were prematurity, surgically corrected congenital heart diseases, other causes of conductive hearing loss, as well as infants with

Comment [HG14]: Is not the infants devided into age group first? And further subdivided into cyanotic & acyanotic?

known risk factors to hearing loss as hyperbilirubinemia, intrauterine infections, exposure to ototoxic drugs, and having family history of hearing loss suggesting congenital hearing loss.

All patients were subjected to: complete history taking (medical, surgical, family, obstetric, medication, and vaccination history), clinical examination (general examination, regional examination, cardiovascular examination and ear examination) and full laboratory investigations including (complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver functions and kidney functions).

Echocardiography: doppler and two-dimensional M-mode echocardiographic evaluation of CHD and pulmonary pressure using (Vivid 7 ultrasound machine, GE Medical system, Horten and Norway) with 7 and 4s MHZ multifrequency transducer).

Hearing assessment: was done through Immittancemetry. High Frequency Tympanometry: (probe tone 1KHz): was done at varying pressure ranging from -400 to +200 mmH₂O. Free field pure tone startle audiometry: Free field PTA was used to assess infants without using headphones; instead, sounds are presented via a speaker placed in front of them.

All the included infants were screened by: Audiometer, Madsen Xeta EN60645 in a suitable room and immittance measures, AT235 Interacoustics. The referred cases were tested by audiometer, AD629 Interacoustics in a sound treated room. Immittancemetry was followed by auditory brainstem response with SmartEPs (TM, Intelligent Hearing system, Miami, USA). Three electrodes were used: a positive electrode high on the forehead, a negative electrode on the ipsilateral mastoid and a ground electrode at the contralateral mastoid. Ipsilateral click stimuli were presented at 90 dBnHL, with alternating polarity, 19.3/second repetition rate and delivered via TDH 49 headphones. The stimulus intensity: started at 90 dBnHL down to 30 dBnHL or to the threshold. Absolute wave latencies (I, III, V) of ABR were recorded and compared between the 4 subgroups. The presence of repeatable wave V at the Intensity of 30

dBnHL was taken as the normal threshold. ABR measures considered for diagnosis of abnormality were: Absent ABR waves, loss of one or more peaks of I–V at 90 dBnHL, and raised threshold at wave V.

Statistical Analysis

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, student t- test, Chi-square, Linear Correlation Coefficient and Analysis of variance [ANOVA] tests by SPSS V20. Quantitative non-parametric data were evaluated using the Mann-Whitney U test and displayed as mean, SD, range, median, and interquartile range. Numbers and percentages were used to present categorical data. Unpaired Student T-test was used to compare between two groups in quantitative data. Linear Correlation coefficient was used for detection of correlation between two quantitative variables in one group. Analysis of variance [ANOVA] tests. According to the computer program SPSS for Windows. ANOVA test was used for comparison among different times in the same group in quantitative data.

Results

Sixty infants were enrolled – their ages ranged from six months to twenty-four months with mean age of 13.217 ± 5.086 SD. Figure (1).

The study enrolled 60 infants with CHD, divided into two groups according to the diagnosis, and 4 subgroups according to the age. Figure (2).

As per our study, ASD was the most encountered congenital a cyanotic heart disease among Egyptian infants in respective age group. Tetralogy of Fallot was found to be the most common cyanotic heart disease. Figure (3).

Only the nine subjects of acyanotic heart groups were on Furosemide with a maximum dose of 2mg/kg PO, whereas none of the cyanotic heart group were on this medication. 11.1% of

Comment [HG15]: It is uncommon to state the details of the statistical analysis here

Comment [HG16]: Is is uncommon to write dthis, since it is a general rule of displaying data

Comment [HG17]: Please rewrite these incomplete sentences

Comment [HG18]: Overall, you need to state which test is used for which parameter. Do not rewrite the theory (e.g for parametric or non parametric data), instead which parameter you want to analyze and with which test

Comment [HG19]: This is only for a normally distributed data. Present it with a statistical calculation in the table

Comment [HG20]: For a demographic data, it is more common to present it in form of table, not diagram,

Comment [HG21]: Same comments, it is more common to present it in form of table

infants on Furosemide had hearing impairment in the left ear only, whilst 9.52% percent of infants not on the same drug were found to have bilateral hearing affection, with P-value of 0.203 on performing t-test. Hence, no correlation was found between using Furosemide and hearing affection in infants suffering from a cyanotic heart defect.

Comment [HG22]: Did not you exclude the patients with exposure to ototoxic drugs? Are these subjects still included? Won't it become bias for the further analysis?

Saturation of peripheral oxygen (SpO₂) in acyanotic group ranged from 94% to 100% with a mean of 97.600 $\pm$ 1.868 SD with P-value of 0.001, whereas in the cyanotic group it ranged from 73% to 86% with a mean of 80.900 $\pm$ 2.998 SD, with P-value of <0.001.

Comment [HG23]: With what test? And compared to what?

Comment [HG24]: Same comment

However, no correlation was found between the saturation of peripheral oxygen and hearing affection in cyanotic infants as the mean SpO₂% in infants with normal hearing was 80.238 + 3.048 SD, while the mean in infants with bilateral hearing impairment was 82.625 + 2.446, with P-value of 0.161 on performing ANOVA test.

Comment [HG25]: You did not mention this in methods.

Forty-eight of our subjects were normal. Of the twelve affected, ten of them had bilateral hearing impairment, while 2 of them had only left hearing affection. Seven of the twelve had mild hearing loss, two were moderate and three were moderately-severe, indicated below in figures (4) and (5).

Comment [HG26]: You did not mention the division into left and right ear in the methods. Please state it in the methods if you want to present it

Comparing the incidence of hearing impairment between the cyanotic and a cyanotic infant, our data showed no statistical significance between the two groups in regard to hearing impairment, pure tone audiometry parameters (Hearing threshold at frequencies of 500Hz, 1000Hz, 2000Hz, and 4000Hz, and speech detection threshold), and abnormal auditory brainstem response parameters (wave I, III, V thresholds and latencies). (Figure (1))

Our results displayed statistically significant differences between subgroups (1 and 2) compared to subgroups (3 and 4), regarding the hearing threshold at frequencies of 500Hz, 1000Hz, 2000Hz, and 4000Hz of the pure tone audiometry, as well as wave V latency-

intensity functions of the auditory brainstem response in both left and right ears. The same statistical significance in the same parameters was manifested between subgroup 2 and subgroup 4. (Figures (2), (3), (4), and (5))

Discussion

Congenital heart diseases (CHD) are defined as a structural abnormality of the heart or intra thoracic vessels present at birth that is actually or potentially of functional significance ^[2].

Comment [HG27]: No need to rewrite this. Already on the background

Regarding the distribution of congenital heart diseases among Egyptian infants, ASD was the most encountered congenital a cyanotic heart disease among Egyptian infants in respective age group as per our study. This was in line with Emterres et al.^[2] and Bahiget al.^[8] studies, both of which concluded that ASD is the most common septal defect among Egyptians.

In contrast to Al-Fahham and Ali^[9] who stated that isolated VSD is the most common septal defect among Egyptians. Atwaand Safar^[10] highlighted that the two most frequent diagnoses were ASD (28.8%) and VSD (28.2%). Tetralogy of Fallot was found to be the most common cyanotic heart disease in our study, consistent with Al-Fahham and Ali^[9].

Regarding the incidence of hearing impairment among patients with CHD, our study found 20% of our cases to be affected with varying degrees of hearing loss. Arnold et al.^[4] registered an incidence of hearing loss (16%) among patients with CHD that was not associated with otitis media with effusion. Kindly note that our study excluded patients with otitis media in the beginning of the study as forementioned. Our results may be explained by Keleman, Egami et al. ^{[11][12]} studies, all of whom have established the presence of middle/inner ear anomalies in patients with CHD, and ergo, associated CHD with hearing impairment.

Keleman^[11] reported middle or inner ear anomalies found in 12 out of 15 cases of non-syndromic congenital heart disease on autopsy. Egami et al.^[12] found similar anomalies in 9

out of 10 patients who died of congenital heart disease. **Nadol (1980)** found an increased incidence of middle ear malformations in developmental disorders of structures of mesodermal origin such as the cardiovascular system.

Considering the sex and residence distribution, our study reported no significant difference regarding the prevalence of CHD between the two enrolled groups. This conformed to Al-Fahham & Ali et al.^[9] study that found no sex predilection among Egyptian children with CHD. Worth noting, Females with CHD were more vulnerable to hospitalization due to chest infection than males according to the study by Atwa and Safar^[10]. Sex and residence pattern did not correlate with hearing affection as well as per our study.

Comment [HG28]: Please be consistent with the groups. You stated that there are 4 groups before?

Similarly, neonatal intensive care unit (NICU) admission did not correlate with hearing loss in any of the two groups. This disagrees with Gopinetti^[13] who estimated the prevalence of hearing loss among NICU survivors to be higher than in the general population. However, Gopinetti et al.^[13] did not estimate the prevalence of SNHL among NICU survivors who were affected by CHD.

Comment [HG29]: Please be consistent with groups

Regarding the saturation of peripheral oxygen (SpO₂), there was a significant difference upon comparing our two groups, being higher in the acyanotic group^I. This was consistent with the pathophysiology of the described cardiac lesions.

Comment [HG30]: A table for presentation of these results might help the reader to understand.

However, SpO₂ level did not correlate with hearing loss, abnormal pure tone audiometry parameters (Hearing threshold at frequencies of 500Hz, 1000Hz, 2000Hz, and 4000Hz, and speech detection threshold), nor abnormal auditory brainstem response parameters (wave I, III, V thresholds and latencies). This is in keeping with Aisenberg et al.^[14], who affirmed that there is no significant relationship between level of arterial oxygen saturation, hence cyanosis, and auditory reaction time.

Comment [HG31]: A table for these results might help

Hemoglobin levels were found to be significantly higher in the cyanotic group than those of acyanotic group. This reflects the erythrocytosis frequently encountered in children with CCHD; which is an isolated increase in red blood cells (RBCs), more specifically an increase in RBC mass in response to chronic hypoxemia^[15].

Comment [HG32]: You did not mention this before, in the methods and in the results. It is better to discuss what is written in methods and results here, and compared it to other studies.

A significant difference was found considering Furosemide use between the cyanotic and acyanotic group, being higher in acyanotic group (30% of the cyanotic patients used this drug, versus not being used at all in the cyanotic group). It does not appear, however, that using the drug had an impact on our results, as no correlation was found between Furosemide use and hearing impairment.

Furosemide (Lasix®), which is a diuretic that is frequently used in the treatment of congenital heart diseases with increased pulmonary flow to alleviate the extra fluid in the pulmonary bed and volume overload (19), was a possible confounding variable in our results.

Many of our subjects were on furosemide at the time of ABR testing. There are numerous reports in the literature of temporary and permanent hearing loss associated with furosemide administration. Most reports of ototoxicity, however, have involved cases of renal insufficiency, very high doses of furosemide, or simultaneous administration of another ototoxic drug^[4].

While several studies have reported permanent hearing loss and cochlear hair cell degeneration after a single diuretic treatment possibly due to autolysis and inadequate fixation, the vast majority of published articles indicate that a single systemic administration of loop diuretics only induces temporary pathological damage or edema to the stria vascularis and cochlear lateral wall. The characteristic features include damage to the marginal cells and swelling of both the intermediate cells and intrastrial space^[16].

Diuretics alone never directly damage the cochlear or vestibular hair cells or the spiral or vestibular ganglion neurons. The pathological changes with edema occur in the stria vascularis approximately 30 min post-treatment; the changes typically completely recover within a day.^[16]

Our subjects received the recommended dosage of either 1 mg/kg intravenously or 2 mg/kg by mouth. This dosage has not been implicated in ototoxicity in controlled studies. Peterson^[17] measured plasma levels of furosemide in premature infants, term infants, and adults following a 1 mg/kg I.V. dosage. The highest plasma level measured--for premature infants--was 6 ug/ml. This level is well below the level associated with reversible ototoxic effects, which is 25 ug/ml. In addition, Santos & Nadol^[18] inferred that those pathological changes, which are dose-dependent, may occur in the absence of a measurable immediate clinical effect.

These drugs are highly bound to plasma protein and subject to hepatic and renal metabolism and excretion. It follows that a patient in hepatic and renal failure would be susceptible to higher concentrations of drug and therefore an increased risk of ototoxicity. Hence, Santos & Nadol^[18] concluded that renal and hepatic insufficiencies are known to potentiate ototoxic effects.

~~To conclude, furosemide~~ Furosemide was found to cause hearing impairment only in high doses, in combination with other ototoxic drugs, or in concurrent renal or hepatic insufficiencies, which did not apply to any of our subjects.

Comparing the incidence of hearing impairment between the cyanotic and a cyanotic infant, our data showed no statistically significant difference between the two groups in regard to hearing impairment, pure tone audiometry parameters (Hearing threshold at frequencies of

Comment [HG33]: Don't write the conclusion here

500Hz, 1000Hz, 2000Hz, and 4000Hz, and speech detection threshold), and auditory brainstem response parameters (wave I, III, V thresholds and latencies).

This is in keeping with Aisenberg et al.^[14], who stated that there is no significant relationship between level of arterial oxygen saturation, hence cyanosis, and auditory reaction time, as mentioned above, furthermore concluded that prolonged hypoxemia in congenital heart disease is not associated with poor performance on all centrally mediated tasks (hearing being from the excluded functions) and that different central nervous system functions vary with respect to their vulnerability to hypoxemia.

This also agrees with Vedat Okutan et al.^[19] that stated no significant difference was found in the ABR parameters between control, cyanotic and cyanotic congenital heart patients aged more than 12 months.

However, our hypothesis is opposed to that of Safabakhsh et al.^[20] who studied miRNAs that are involved in the pathophysiological responses to hypoxia and oxidative stress that result in SNHL. Also found evidence that miR-34a and -29b are involved in hypoxia driven SNHL, and those were the hypoxia-adaptive miRNAs involved in hypoxia driven SNHL. It is worth noting that the forementioned study concluded that further studies are required to determine if these findings are clinically applicable.

Our results disagreed with Gopinetti et al.^[13] as well, whose study supports the etiology of hypoxia as strongly associated with SNHL. However, the patients included in the previously mentioned study were surgically palliated/repaired CHD patients. Hence, acute hypoxia was incorporated among the variables in this study, evidenced by the incorporation of the duration of cardiac arrest as a variable in their results, for instance. These patients were already excluded from our study.

Comment [HG34]: While it is a cross sectional study, please refrain from taking any causality (e.g hypoxia leading to hearing loss). You could not oppose a study for causality with a cross sectional study

Consistent with Sunaga et al.^[5] and Okutan et al.^[19] and our results displayed statistically significant differences between subgroups (1 and 2) compared to subgroups (3 and 4), regarding the hearing threshold at frequencies of 500Hz, 1000Hz, 2000Hz, and 4000Hz of the pure tone audiometry, as well as wave V latency-intensity functions of the auditory brainstem response in both left and right ears. The same statistical significance in the same parameters was manifested between subgroup 2 and subgroup 4.

Sunaga et al.^[5] suggested that chronic hypoxemia in cyanotic infants caused retardation of brainstem maturation, primarily related to progressive retardation of the myelination process of the brainstem in the presence of chronic hypoxemia. They indicated that this retardation had the greatest effect on infants under the age of 12 months, with tolerance to chronic hypoxemia developing with age, as shown by normal brainstem conduction times after 12 months of age.

No significance, however, was found between subgroup 1 and subgroup 3 which matched Sunaga et al.^[5] and Okutan et al.^[19] studies.

Contrasting to Hecox & Cone^[21] who predicted that hypoxemia is the most important factor causing retardation of the brainstem maturation in asphyxiated infants however, recorded and compared auditory brainstem responses after acute asphyxiation, not chronic hypoxemia.

Recommendations: high prevalence of hearing loss amongst patients with CHD warrants the addition of those patients to the high-risk registry for hearing loss, in order that they may benefit from early detection and intervention, and ergo protected against the affection of hearing impairment on their neurodevelopment. Routine follow-ups for patients with cyanotic heart disease from the age of 6 months to assess the effect of chronic hypoxemia on the inner ear and monitor the rate of improvement in ABR results, as to establish an accepted rate of improvement, and an appropriate time of intervention, if needed.

Comment [HG35]: Just before the conclusion, please write the limitations of the study

Conclusion:

Presence of concurrent hearing loss of varying degrees in 20% of patients suffering from congenital heart disease. No statistically significant difference between patients suffering from a cyanotic heart disease when compared to those suffering from cyanotic heart disease in terms of hearing loss. Cyanotic infants below the age of 12 months had higher incidence of hearing loss when compared to those above the age of 12 months.

Comment [HG36]: This conclusion is better than in the abstract session.

Additional Disclosures:

Human subjects: All authors have confirmed that this study did not involve human participants or tissue.

Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

References:

Comment [HG37]: If possible, use the latest reference. More than half of your reference is older than 5 years

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UNDER PEER REVIEW

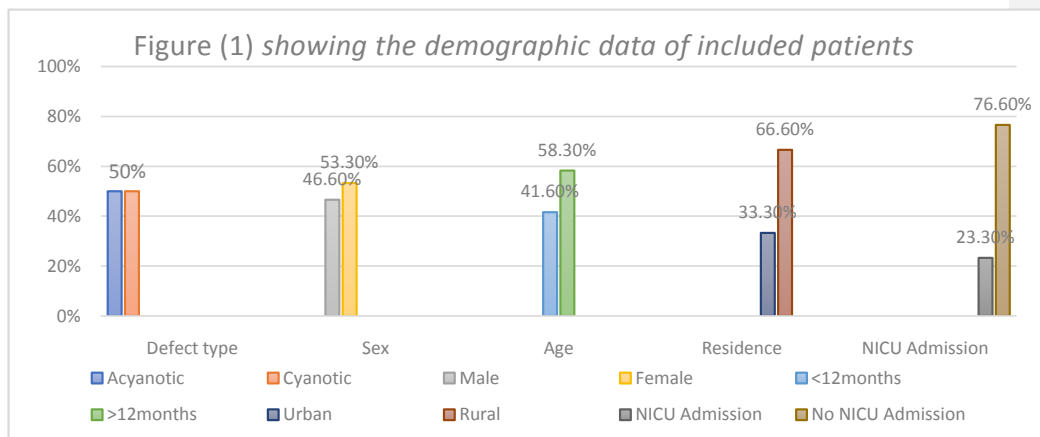


Figure 1: demographic data of included patients

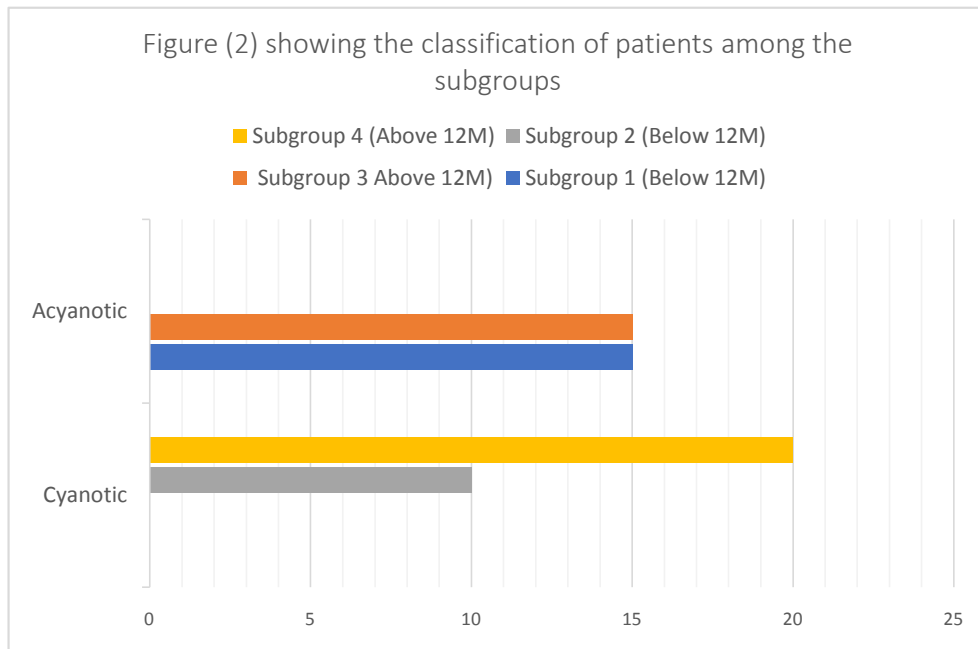


Figure 2: classification of patients among the subgroups

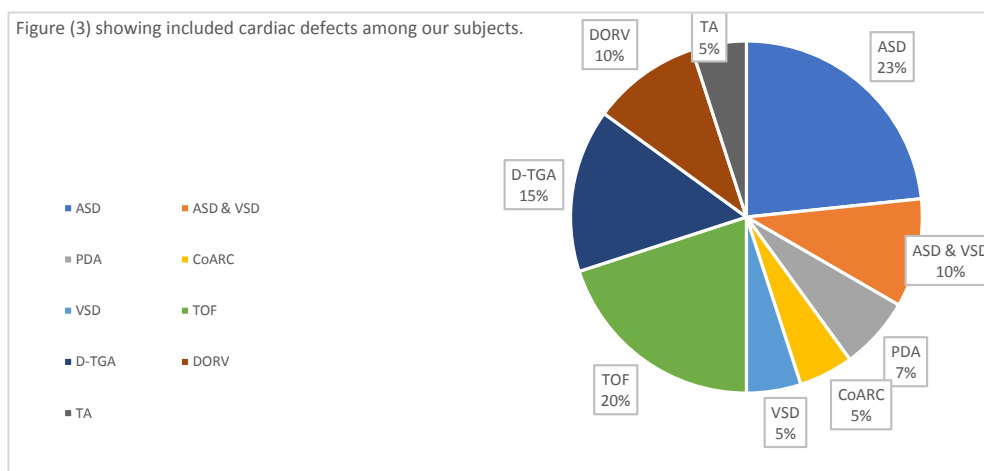


Figure 3: cardiac defects among our subjects

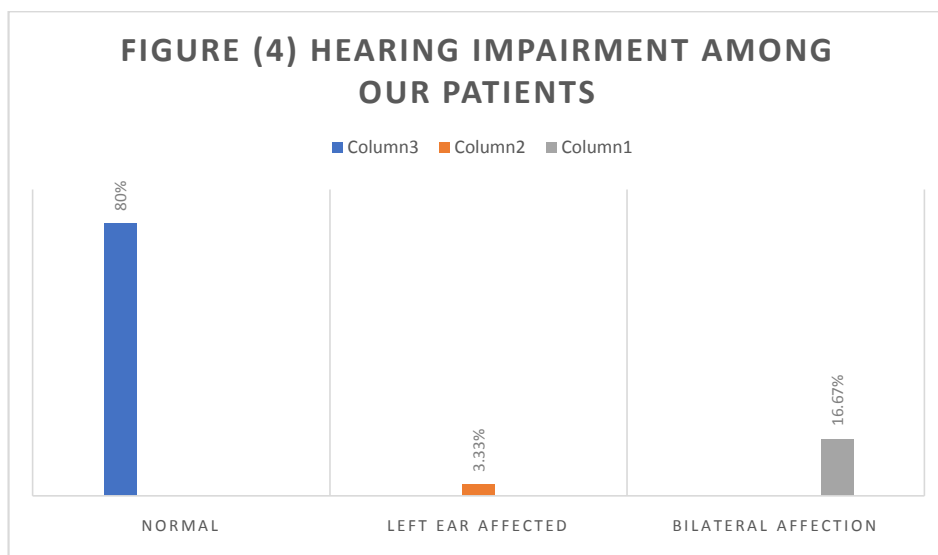


Figure 4: hearing Impairment among our patients

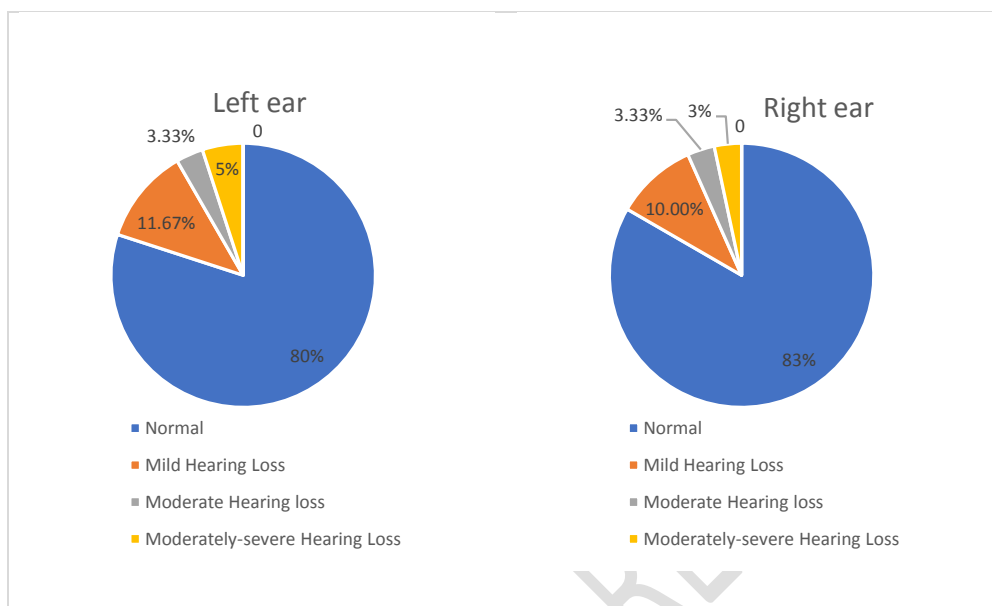


Figure 5: hearing impairment and degree of hearing impairment in each ear

Table (1): showing the comparison between patients with a cyanotic heart disease compared to patients with cyanotic heart disease in relation to number of cases with hearing affection per group, pure tone audiometry frequencies and auditory brainstem response intensity-threshold and latencies.

Comment [HG38]: Please see the format of the table for academic purposes

				Defect type		X ²	P-value
Group				A cyanotic	Cyanotic		
Affected				2	8	4.350	0.114
PTA	500 Hz	Range	10 - 35	10 - 65	-1.484	0.143	
		Mean $\pm$ SD	18.333 $\pm$ 5.307	22.500 $\pm$ 14.429			
	1000 Hz	Range	10 - 35	10 - 65	-1.426	0.159	
		Mean $\pm$ SD	18.500 $\pm$ 5.277	22.500 $\pm$ 14.429			
	2000 Hz	Range	10 - 35	10 - 65	-1.426	0.159	
		Mean $\pm$ SD	18.500 $\pm$ 5.277	22.500 $\pm$ 14.429			
	4000 Hz	Range	10 - 35	10 - 65	-1.078	0.285	
		Mean $\pm$ SD	19.667 $\pm$ 5.074	22.667 $\pm$ 14.368			
	SDT Hz	Range	10 - 35	10 - 65	-1.426	0.159	
		Mean $\pm$ SD	18.500 $\pm$ 5.277	22.500 $\pm$ 14.429			
ABR	Threshold	I	Lt	90.000 $\pm$ 0.000	90.000 $\pm$ 0.000	0.000	1.000
			Rt	90.000 $\pm$ 0.000	90.000 $\pm$ 0.000	0.000	1.000
		III	Lt	78.667 $\pm$ 10.080	79.333 $\pm$ 10.148	-0.255	0.799
			Rt	75.333 $\pm$ 8.996	76.000 $\pm$ 9.322	-0.282	0.779
		V	Lt	33.667 $\pm$ 8.899	38.000 $\pm$ 12.149	-1.576	0.120
			Rt	32.000 $\pm$ 5.509	36.667 $\pm$ 12.411	-1.882	0.065
	Latency	I	Lt	1.521 $\pm$ 0.286	1.620 $\pm$ 0.177	-1.545	0.128
			Rt	1.612 $\pm$ 0.227	1.643 $\pm$ 0.181	-0.575	0.568
		III	Lt	4.075 $\pm$ 0.332	3.933 $\pm$ 0.288	1.771	0.082
			Rt	4.160 $\pm$ 0.297	4.004 $\pm$ 0.344	1.886	0.064
		V	Lt	6.055 $\pm$ 0.375	6.201 $\pm$ 0.567	-1.176	0.245

			Rt	6.190 ± 0.525	6.169 ± 0.564	0.149	0.882
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Table (2): The comparison between patients with a cyanotic heart disease below the age of 12

months (subgroup 1) compared to patients with cyanotic heart disease below the age of 12 months

(subgroup 2) in relation to number of cases with hearing affection per subgroup, pure tone

audiometry frequencies and auditory brainstem response intensity-threshold and latencies.

Comment [HG39]: Please see the format of the table for academic purposes

			Below 12 months						X2	P-value	
Group			A cyanotic			Cyanotic					
Subgroup			1			2			8.362	0.004*	
Affected			2			7					
PTA	500 Hz	Range	10	-	35	10	-	65	-2.507	0.020*	
		Mean + SD	20.000	±	5.976	33.000	±	18.886			
	1000 Hz	Range	10	-	35	10	-	65	-2.452	0.022*	
		Mean + SD	20.333	±	5.815	33.000	±	18.886			
	2000 Hz	Range	10	-	35	10	-	65	-2.452	0.022*	
		Mean + SD	20.333	±	5.815	33.000	±	18.886			
	4000 Hz	Range	10	-	35	10	-	65	-2.311	0.030*	
		Mean + SD	21.000	±	6.036	33.000	±	18.886			
	SDT Hz	Range	10	-	35	10	-	65	-2.452	0.022*	
		Mean + SD	20.333	±	5.815	33.000	±	18.886			
ABR	Threshold	I	Lt	90.000	±	0.000	90.000	±	0.000	0.000	1.000
			Rt	90.000	±	0.000	90.000	±	0.000	0.000	1.000
		III	Lt	79.333	±	10.328	80.000	±	10.541	-0.157	0.877
			Rt	74.000	±	8.281	78.000	±	10.328	-1.072	0.295
		V	Lt	34.667	±	7.432	49.000	±	15.239	-3.147	0.005*
			Rt	33.333	±	7.237	49.000	±	15.239	-3.464	0.002*
	Latency	I	Lt	1.616	±	0.146	1.660	±	0.171	-0.644	0.527
			Rt	1.613	±	0.194	1.657	±	0.152	-0.598	0.295
		III	Lt	4.120	±	0.277	3.798	±	0.243	2.980	0.007*
			Rt	4.113	±	0.335	3.912	±	0.340	1.464	0.556
		V	Lt	6.047	±	0.425	6.415	±	0.540	-1.903	0.157
			Rt	6.273	±	0.561	6.439	±	0.538	-0.735	0.470

UNDER PEER REVIEW

Table (3): The comparison between patients with a cyanotic heart disease above the age of 12 months (subgroup 3) compared to patients with cyanotic heart disease above the age of 12 months (subgroup 4) in relation to number of cases with hearing affection per subgroup, pure tone audiometry frequencies and auditory brainstem response intensity-threshold and latencies.

Comment [HG40]: Please see the format of the table for academic purposes

			Above 12 months							X ²	P-value
Group			A cyanotic				Cyanotic				
Subgroup			3				4			0.802	0.670
Affected			1 (Left only)				2 (Left and Bilateral)				
PTA	500 Hz	Range	10	-	20	10	-	45	-0.262	0.795	
		Mean + SD	16.667	±	4.082	17.250	±	7.860			
	1000 Hz	Range	10	-	20	10	-	45	-0.262	0.795	
		Mean + SD	16.667	±	4.082	17.250	±	7.860			
	2000 Hz	Range	10	-	20	10	-	45	-0.262	0.795	
		Mean + SD	16.667	±	4.082	17.250	±	7.860			
	4000 Hz	Range	10	-	25	10	-	45	0.380	0.706	
		Mean + SD	18.333	±	3.619	17.500	±	7.864			
	SDT Hz	Range	10	-	20	10	-	45	-0.262	0.795	
		Mean + SD	16.667	±	4.082	17.250	±	7.860			
ABR	Threshold	I	Lt	90.000	±	0.000	90.000	±	0.000	0.000	1.000
			Rt	90.000	±	0.000	90.000	±	0.000	0.000	1.000
		III	Lt	78.000	±	10.142	79.000	±	10.208	-0.288	0.775
			Rt	76.667	±	9.759	75.000	±	8.885	0.527	0.602
		V	Lt	32.667	±	10.328	32.500	±	4.443	0.065	0.949
			Rt	30.667	±	2.582	30.500	±	2.236	0.204	0.839
	Latency	I	Lt	1.419	±	0.363	1.604	±	0.181	-1.939	0.062
			Rt	1.612	±	0.267	1.637	±	0.197	-0.309	0.759
		III	Lt	4.031	±	0.383	4.001	±	0.290	0.261	0.796
			Rt	4.207	±	0.256	4.050	±	0.345	1.484	0.147
		V	Lt	6.063	±	0.334	6.095	±	0.563	-1.190	0.850
			Rt	6.107	±	0.490	6.035	±	0.539	0.411	0.684

Table (4): The comparison between patients with cyanotic heart disease below the age of 12 months (subgroup 2) compared to patients with cyanotic heart disease above the age of 12 months (subgroup 4) in relation to number of cases with hearing affection per subgroup, pure tone audiometry frequencies and auditory brainstem response intensity-threshold and latencies.

Comment [HG41]: Please see the format of the table for academic purposes

				Below 12 months			Above 12 months			X ²	P-value
Group				Cyanotic							
Subgroup				2			4			14.491	0.001*
Affected				7*			2 (Left and Bilateral)				
PTA	500 Hz			33.000	±	18.886	17.250	±	7.860	3.250	0.003*
	1000 Hz			33.000	±	18.886	17.250	±	7.860	3.250	0.003*
	2000 Hz			33.000	±	18.886	17.250	±	7.860	3.250	0.003*
	4000 Hz			33.000	±	18.886	17.500	±	7.864	3.198	0.003*
	SDT Hz			33.000	±	18.886	17.250	±	7.860	3.250	0.003*
ABR	Threshold	I	Lt	90.000	±	0.000	90.000	±	0.000	0.000	1.000
			Rt	90.000	±	0.000	90.000	±	0.000	0.000	1.000
		III	Lt	80.000	±	10.541	79.000	±	10.208	0.250	0.804
			Rt	78.000	±	10.328	75.000	±	8.885	0.826	0.416
		V	Lt	49.000	±	15.239	32.500	±	4.443	4.541	<0.001*
			Rt	49.000	±	15.239	30.500	±	2.236	5.407	<0.001*
	Latency	I	Lt	1.660	±	0.171	1.604	±	0.181	0.758	0.455
			Rt	1.657	±	0.152	1.637	±	0.197	0.288	0.775
		III	Lt	3.798	±	0.243	4.001	±	0.290	-1.902	0.068
			Rt	3.912	±	0.340	4.050	±	0.345	-1.037	0.308
		V	Lt	6.415	±	0.540	6.095	±	0.563	1.489	0.148
			Rt	6.439	±	0.538	6.035	±	0.539	1.938	0.063

Table (5): The comparison between patients with a cyanotic heart disease below the age of 12 months (subgroup 1) compared to patients with a cyanotic heart disease above the age of 12 months (subgroup 3) in relation to number of cases with hearing affection per subgroup, pure tone audiometry frequencies and auditory brainstem response intensity-threshold and latencies.

Comment [HG42]: Please see the format of the table for academic purposes

				Below 12 months			Above 12 months			X ²	P-value
Group				A cyanotic							
Subgroup				1			3			3.037	0.219
Affected				2			1 (Left only)				
PTA	500 Hz			20.000	±	5.976	16.667	±	4.082	1.784	0.085
	1000 Hz			20.333	±	5.815	16.667	±	4.082	1.999	0.055
	2000 Hz			20.333	±	5.815	16.667	±	4.082	1.999	0.055
	4000 Hz			21.000	±	6.036	18.333	±	3.619	1.468	0.153
	SDT Hz			20.333	±	5.815	16.667	±	4.082	1.999	0.055
ABR	Threshold	I	Lt	90.000	±	0.000	90.000	±	0.000	0.000	1.000
			Rt	90.000	±	0.000	90.000	±	0.000	0.000	1.000
		III	Lt	79.333	±	10.328	78.000	±	10.142	0.357	0.724
			Rt	74.000	±	8.281	76.667	±	9.759	0.807	0.426
		V	Lt	34.667	±	7.432	32.667	±	10.328	0.609	0.548
			Rt	33.333	±	7.237	30.667	±	2.582	1.344	0.190
	Latency	I	Lt	1.616	±	0.146	1.419	±	0.363	1.870	0.073
			Rt	1.613	±	0.194	1.612	±	0.267	0.015	0.988
		III	Lt	4.120	±	0.277	4.031	±	0.383	0.731	0.471
			Rt	4.113	±	0.335	4.207	±	0.256	-0.864	0.395

		v	Lt	6.047	±	0.425	6.063	±	0.334	-0.115	0.910
			Rt	6.273	±	0.561	6.107	±	0.490	0.863	0.396

UNDER PEER REVIEW