

Auditory Brain- Stem Responses in Neonatal Hyperbilirubinemia and effect of therapy

Thesis submitted for fulfillment of Ph.D.in Medical Childhood Studies

(Child Health and Nutrition)

**Submitted By**

**Dr. Sanaa Mohamed Tantawy**

M.B.B.Ch ., M.Sc (Pediatrics)

Al-Azhar University

**Supervised by**

|  |  |
| --- | --- |
| **Dr./ Magdy Karam El- din Ali**  Prof. of Preventive Medical and  Epidemiology  Institute of Post- graduate Childhood Studies  Ain Shams University  **Dr./ Safaa El Meneza**  Prof. of Neonatology and Pediatrics  Faculty of Medicine for Girls  Al-Azhar University | **Dr./ Randa Mohamed Kamal**  Prof. of Pediatrics Medical studies Department  Institute of Post- graduate Childhood Studies  Ain Shams University  **Dr./ Mohamed El Gohary**  Prof. of Audiology  Faculty of Medicine for Girls  Al-Azhar University |

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**Abstract**

**Background**: Neonatal hyperbilirubinemia is the most common condition that requires medical attention in newborns**.** The phenomenon of deposited indirect bilirubin in basal ganglia as well as in the vesti­bule-cochlear nucleus causes a neurological syndrome called kernicterus as well as sensorineural hearing loss**.** Currently, the most sensitive means of assessing neurotoxicity may be au­ditory brain stem evoked response (ABR), which shows the predictable early effects of bilirubin toxicity**.**

**Aim:** This study aims to determine the effect of neonatal hyperbilirubinemia on auditory brainstem response (ABR) and evaluate the effect of treatment of hyperbilirubinemia on ABR findings.

**Subjects and Methods:** This case-control study was performed on30 neonates with pathologic hyperbilirubinemia as the jaundiced groupchosen from Neonatal Intensive Care Unit of AL Zahraa Hospital of Al-Azhar University and 20 healthy neonates as the control group chosen from Maternity department of the same hospital during the period from September, 2011 to August, 2012. ABR was performed on both groups. The evaluated variable factors were latency time, inter peak intervals time.

**Results:** The mean latencies of waves I, III and V of ABR were significantly higher in the pathologic hyperbilirubinemia group as compared with the controls and the mean interpeak intervals (IPI) of waves I-III, I-V and III-V of ABR were significantly higher in the pathologic hyperbilirubinemia group as compared with the controls. A total reversibility to normal thresholds ( normal hearing) was displayed by 23 (77.00%) and 25 (83.30%) of jaundiced neonates in the right and left ears respectively, while the remaining 7 (23.00%) and 5 (16.70%) of jaundiced neonates displayed partial reversibility (mild to moderate hearing loss) in the right and left ears respectively (p < 0.001)

**Conclusions**; About 90% of neonates with pathologic hyperbilirubinemia demonstrate ABR changes. Most of these changes (about 77%) revert to normal early after therapy.

**Keywords:** Neonates; Bilirubin; Hyperbilirubinemia; Auditory Brain-Stem Response

**Introduction**

Hyperbilirubinemia is the most common condition that requires medical attention in newborns. The yellow coloration of the skin and sclera in newborns with jaundice is the result of accumulation of unconjugated bilirubin. In most infants, unconjugated hyperbilirubinemia reflects a normal transitional phenomenon. However, in some infants, serum bilirubin levels may excessively raise, which can be cause for concern **(Hansen, 2014).**

Indirect bilirubin, the main cause of neonatal jaun­dice, is strongly neurotoxic for underdevelopment neural system, especially when the indirect bilirubin concentration exceeds the albumin binding capac­ity. Unconjugated bilirubin binds the phospholipids of neuronal plasma membranes as well as the phospho­lipids of subcellular organelles membrane, which leads to cell oxygen deprivation, energy metabolism impair­ment, and cell death. The phenomenon of deposited indirect bilirubin in basal ganglia as well as in the vesti­bule-cochlear nucleus causes a neurological syndrome called kernicterus as well as sensorineural hearing loss. Currently, the most sensitive means of assessing neurotoxicity may be au­ditory brain stem evoked response (ABR), which shows the predictable early effects of bilirubin toxicity **(Thilo& Rosenberg, 2011).**.

Early di­agnosis and treatment of hyperbilirubinemia is highly important for preventing hearing loss and all newborns with pathologic hyperbilirubinemia must be screened. ABR abnormalities may be transient in majority of pa­tients **(Okhravi et al., 2015)**

**Objective:** This study aims to determine the effect of neonatal hyperbilirubinemia on auditory brainstem response (ABR) and evaluate the effect of treatment of hyperbilirubinemia on ABR findings.

**Subjects and Methods**

**Subjects:**

This case-control study was performed on 30 neonates with pathologic hyperbilirubinemia as the jaundiced groupchosen from Neonatal Intensive Care Unit of AL Zahraa Hospital of Al-Azhar University and 20 healthy neonates as the control group chosen from Maternity department of the same hospital during the period from September, 2011 to August, 2012.

**1-Control group or group of healthy neonates:**

This group included 20 neonates (40 ears were examined), 14 males and 6 females. Birth weight ranged from 2000 to 4000 grams.

They were delivered normally or by cesarean section (CS) at the Maternity Department in Al Zahraa Hospital. They were not considered at risk of hearing impairment, according to the selected criteria of high risk registers (i.e., normal prenatal history, normal bilirubin level, and no history of craniofacial anomalies, congenital infections (TORCH), bacterial meningitis, prolonged mechanical ventilation for >10 days or birth weight <1500 grams).

All the newborns were examined by transcutaneous bilirubin technique and auditory brainstem response (ABR) audiometry between 1st and 7th day of life.

**2-Group of neonates with hyperbilirubinemia:**

It included 30 neonates (60 ears were examined), 13 males and 17 females, selected from the Neonatal Intensive Care Unit (NICU) of Al Zahraa Hospital.

**-Inclusion criteria:**

* Full term, appropriate for date neonates (Gestational age > 37weeks) and near term neonates (Gestational age 35-37weeks) based on New Ballard Score **(Ballard et al., 1991)** with uncomplicated birth history.
* Bilirubin level >13mg/dl.
* Rh incompatibility and fetomaternal blood group incompatibility.
* Onset of jaundice before 24 hours of age.
* History of previous sibling with significant hyperbilirubinemia.
* Infant of diabetic mother.

**-Exclusion criteria:**

* Low apgar scores of 0-4 at 1 min. or 0-6 at 5 mins.
* Birth weight less than 1500 grams**.**
* Conjugated hyperbilirubineamia.
* Congenital infections such as toxoplasmosis, rubella, cytomegalovirus, syphilis, and herpes simplex (TORCSH).
* Bacterial meningitis.
* Neonatal sepsis.
* Birth asphyxia.
* Mechanical ventilation lasting >or= 5 days
* Family history of hereditary childhood sensorineural hearing loss.
* Craniofacial abnormalities.
* Syndromes associated with hearing loss as: Waardenberg Syndrome, Pendred Syndrome, and Usher Syndrome.

**Methods**

-All studied newborn infants were subjected to full medical history, through clinical examination and investigations.

-Auditory brain stem responses ABR test measures the electroencephalographic waves generated by the auditory system in response to clicks via three electrodes placed on the infant's scalp.

***Timing of ABR:***It will be carried out in two phases:

**Phase 1:** ABR examination will be carried out within 24 hrs of the diagnosis of hyperbilirubinemia.

**Phase 2:** repeat examination will be done when total serum bilirubin came down to <13 mg/dL with treatment.

**-Ethical Considerations:** according to theInstitutions' Ethical Com­mittee.

**-Statistical analysis:** using spss (statistical package for social science) version 12

**RESULTS**

Of 50 newborns that met the enrolment criteria and participated in the study, the case group included 30 new­borns (13 males and 17 females) and there were 20 new­borns (14 males and 6 females) in the control group. In the case group, the mean age of newborns was 3.97 ± 3.28 days.

* There was no significant statistical difference regard­ing gender, postnatal age, gestational age, type of delivery, feeding, anthropometric measurements and vital signs between the two groups. The average total serum bilirubin level (TSB) was 22.35 ± 3.72 and 10.57 ± 1.55 mg/dL before and after the phototherapy, respectively in the case group.
* The mean latencies of waves I, III and V of ABR were significantly higher in the pathologic hyperbilirubinemia group compared with the control group.
* The mean interpeak intervals (IPI) I-III, I-V and III-V of ABR waves were significantly higher in the pathologic hyperbilirubinemia group compared with the control group.
* **Table (1)** Comparison between jaundiced group and control group regarding absolute and interpeak latencies before treatment

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Absolut &Interpeak Latencies** | | **Control group** | | **Jaundiced group** | | **Independent t-test** | |
| **Mean±** | **SD** | **Mean±** | **SD** | **t** | **p-value** |
| Right | I (ms) | 1.54 | 0.13 | 1.84 | 0.30 | 4.103 | 0.002 |
| III (ms) | 3.68 | 0.28 | 4.41 | 0.28 | 8.245 | 0.000 |
| V (ms) | 5.86 | 0.40 | 7.01 | 0.52 | 7.839 | 0.000 |
| I-III (ms) | 2.14 | 0.24 | 2.57 | 0.41 | 4.048 | 0.002 |
| III-V (ms) | 2.18 | 0.34 | 2.46 | 0.28 | 2.843 | 0.007 |
| I-V (ms) | 4.32 | 0.37 | 5.03 | 0.17 | 7.798 | 0.000 |
| V at 40 Db | 7.33 | 0.46 | 8.06 | 0.79 | 3.571 | 0.001 |
| Left | I (ms) | 1.64 | 0.15 | 1.85 | 0.32 | 2.657 | 0.011 |
| III (ms) | 4.09 | 0.29 | 4.41 | 0.41 | 2.850 | 0.007 |
| V (ms) | 6.32 | 0.38 | 6.85 | 0.67 | 3.077 | 0.004 |
| I-III (ms) | 2.45 | 0.25 | 3.00 | 0.43 | 4.945 | 0.000 |
| III-V (ms) | 2.23 | 0.32 | 2.58 | 0.39 | 3.101 | 0.004 |
| I-V (ms) | 4.68 | 0.41 | 5.03 | 0.50 | 2.421 | 0.020 |
| V at 40 dB | 7.61 | 0.47 | 8.32 | 0.23 | 6.068 | 0.000 |

This table shows that there is a highly statistically significant difference between jaundiced group and control group in absolute and interpeak latencies before treatment in the right and left ear.

**Table (2)** Comparison between jaundiced group and control group regarding wave morphology before treatment

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Wave morphology** | | | **Control group** | | **Jaundiced group** | | **Chi-square test** | |
| **No.** | **%** | **No.** | **%** | **X2** | **P-value** |
| Right | I | Well defined | 15 | 75.0% | 4 | 13.3% | 24.022 | 0.000 |
| Ill defined | 5 | 25.0% | 8 | 26.7% |
| Absent wave | 0 | 0.0% | 18 | 60.0% |
| III | Well defined | 15 | 75.0% | 4 | 13.3% | 22.953 | 0.000 |
| Ill defined | 5 | 25.0% | 10 | 33.3% |
| Absent wave | 0 | 0.0% | 16 | 53.3% |
| V | Well defined | 16 | 80.0% | 3 | 10.0% | 26.316 | 0.000 |
| Ill defined | 4 | 20.0% | 15 | 50.0% |
| Absent wave | 0 | 0.0% | 12 | 40.0% |
| V at 40 dB | Well defined | 15 | 75.0% | 3 | 10.0% | 31.771 | 0.000 |
| Ill defined | 5 | 25.0% | 3 | 10.0% |
| Absent wave | 0 | 0.0% | 24 | 80.0% |
| Left | I | Well defined | 16 | 80.0% | 4 | 13.3% | 23.704 | 0.000 |
| Ill defined | 4 | 20.0% | 14 | 46.7% |
| Absent wave | 0 | 0.0% | 12 | 40.0% |
| III | Well defined | 15 | 75.0% | 3 | 10.0% | 25.694 | 0.000 |
| Ill defined | 5 | 25.0% | 10 | 33.3% |
| Absent wave | 0 | 0.0% | 17 | 56.7% |
| V | Well defined | 16 | 80.0% | 4 | 13.3% | 23.333 | 0.000 |
| Ill defined | 4 | 20.0% | 16 | 53.3% |
| Absent wave | 0 | 0.0% | 10 | 33.3% |
| V at 40 dB | Well defined | 17 | 85.0% | 3 | 10.0% | 33.125 | 0.000 |
| Ill defined | 3 | 15.0% | 3 | 10.0% |
| Absent wave | 0 | 0.0% | 24 | 80.0% |

There is a highly statistically significant difference between jaundiced group and control group in all categories of wave morphology in right & left ear before treatment.

**Table (3)** Comparison between jaundiced group and control group regarding hearing threshold before treatment

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Hearing threshold** | | | **Control group** | | **Patients group** | | **Chi-square test** | |
| **No.** | **%** | **No.** | **%** | **X2** | **P-value** |
| **Before ttt** | RT.ear | Normal hearing | 20 | 100.00% | 5 | 16.70% | 33.333 | 0.000 |
| Mild to moderate  hearing loss | 0 | 0.00% | 19 | 63.30% |
| Severe to profound  hearing loss | 0 | 0.00% | 6 | 20.00% |
| LT.ear | Normal hearing | 20 | 100.00% | 6 | 20.00% | 30.769 | 0.000 |
| Mild to moderate  hearing loss | 0 | 0.00% | 15 | 50.00% |
| Severe to profound  hearing loss | 0 | 0.00% | 9 | 30.00% |

There is a highly statistically significant difference between jaundiced group and control group regarding hearing threshold before treatment in both ears.

**Table (4)** Comparison between jaundiced group before and after treatment

regarding absolute and interpeak latencies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Absolut &Interpeak Latencies  Before Treatment** | | **Before** | | **After** | | **Independent t-test** | |
| **Mean** | ±**SD** | **Mean** | ±**SD** | **t** | **P-value** |
| Right | I (ms) | 1.84 | 0.30 | 1.63 | 0.23 | 3.043 | 0.004 |
| III (ms) | 4.41 | 0.28 | 3.81 | 0.24 | 8.911 | 0.000 |
| V (ms) | 7.01 | 0.52 | 6.01 | 0.35 | 8.738 | 0.000 |
| I-III (ms) | 2.57 | 0.41 | 2.18 | 0.29 | 4.254 | 0.000 |
| III-V (ms) | 2.46 | 0.28 | 2.2 | 0.34 | 3.233 | 0.002 |
| I-V (ms) | 5.03 | 0.17 | 4.38 | 0.40 | 8.191 | 0.000 |
| V at 40 Db | 8.06 | 0.79 | 7.58 | 0.34 | 3.057 | 0.003 |
| Left | I (ms) | 1.85 | 0.32 | 1.55 | 0.17 | 4.534 | 0.000 |
| III (ms) | 4.41 | 0.41 | 4.26 | 0.29 | 4.362 | 0.000 |
| V (ms) | 6.85 | 0.67 | 6.43 | 0.41 | 2.929 | 0.005 |
| I-III (ms) | 2.65 | 0.43 | 2.71 | 0.42 | 2.643 | 0.010 |
| III-V (ms) | 2.44 | 0.39 | 2.17 | 0.42 | 2.962 | 0.004 |
| I-V (ms) | 5.00 | 0.50 | 4.88 | 0.53 | 2.847 | 0.006 |
| V at 40 dB | 8.32 | 0.23 | 7.97 | 0.49 | 3.542 | 0.001 |

This table shows that there is a highly statistically significant difference between jaundiced group before and after treatment in all absolute and interpeak latencies in the right and left ears.

**Table (5)** Comparison between jaundiced group before and after treatment regarding wave morphology

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Wave morphology** | | | **Before** | | **After** | | **Chi-square test** | |
| **No.** | **%** | **No.** | **%** | **X2** | **P-value** |
| Right | I | Well defined | 4 | 13.3% | 21 | 70.0% | 29.619 | 0.000 |
| Ill defined | 8 | 26.7% | 9 | 30.0% |
| Absent wave | 18 | 60.0% | 0 | 0.0% |
| III | Well defined | 4 | 13.3% | 21 | 70.0 % | 22.978 | 0.000 |
| Ill defined | 10 | 33.3% | 7 | 23.3% |
| Absent wave | 16 | 53.3% | 2 | 6.7% |
| V | Well defined | 3 | 10.0% | 19 | 63.3% | 24.252 | 0.000 |
| Ill defined | 15 | 50.0% | 11 | 36.7% |
| Absent wave | 12 | 40.0% | 0 | 0.0% |
| V at 40 dB | Well defined | 3 | 10.0% | 14 | 46.7% | 21.687 | 0.000 |
| Ill defined | 3 | 10.0% | 10 | 33.3% |
| Absent wave | 24 | 80.0% | 6 | 20.% |
| Left | I | Well defined | 4 | 13.3% | 21 | 70.0% | 24.647 | 0.000 |
| Ill defined | 14 | 46.7% | 9 | 30.0% |
| Absent wave | 12 | 40.0% | 0 | 0.0% |
| III | Well defined | 3 | 10.0% | 21 | 70.0% | 27.944 | 0.000 |
| Ill defined | 10 | 33.3% | 8 | 26.7% |
| Absent wave | 17 | 56.7% | 1 | 3.3% |
| V | Well defined | 4 | 13.3% | 23 | 76.7% | 26.892 | 0.000 |
| Ill defined | 16 | 53.3% | 7 | 23.3% |
| Absent wave | 10 | 33.3% | 0 | 0.0% |
| V at 40 dB | Well defined | 3 | 10.0% | 15 | 50.0% | 24.218 | 0.000 |
| Ill defined | 3 | 10.0% | 10 | 33.3% |
| Absent wave | 24 | 80.0% | 5 | 16.7% |

This table shows that there is a highly statistically significant difference between jaundiced group before and after treatment regarding wave morphology (marked improvement is noticed in wave's identifiability).

**Table (6)** Comparison between jaundiced group before and after treatment regarding hearing threshold

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Hearing threshold** | | **Before** | | **After** | | **Chi-square test** | |
| **No.** | **%** | **No.** | **%** | **X2** | **P-value** |
| RT.ear | Normal hearing | 5 | 16.70% | 23 | 76.00% | 23.111 | <0.001 |
| Mild to moderate hearing loss | 19 | 63.30% | 7 | 23.00% |
| Severe to profound hearing loss | 6 | 20.00% | 0 | 00.00% |
| LT.ear | Normal hearing | 6 | 20.0% | 25 | 83.30% | 25.645 | <0.001 |
| Mild to moderate hearing loss | 15 | 50.0% | 5 | 16.70% |
| Severe to profound hearing loss | 9 | 30.0% | 0 | 0.00% |

This table shows that there is a highly statistically significant difference between jaundiced group before and after treatment regarding hearing threshold (marked improvement of hearing is noticed).

**Discussion**

Hyperbilirubinemia is a common problem and one of the most important problems in newborns **(Okhravi et al., 2015).** ABR has been an effective method of assessing the audi­tory pathway and brainstem function in newborns and infants, recently recognized as a useful diagnostic tool in newborns **(Picton et al., 2012).** In the present study, according to the results of ABR, latencies of almost all the waves and intervals were significantly prolonged in jaundiced neonatal group com­pared with healthy control group, The mean laten­cy time of ABR waves I, III, V and the mean latency time of waves V at 40 dB in right and left ears were significantly higher in the studied group than that of the control group (P < 0.01). Also the mean inter-peak-interval (IPI) time of waves I-III, III-V, I-V in right and left ears of the studied group were significantly higher than that in control group (P < 0.01) **(Table 1)**.The results of the present study were in agreement with the studies done by **Okhravi et al., (2015),** **Sobhy et al., (2015), Liang and Xie (2011), Baradaranfar** **et al., (2011**), **Saluja et al,.(2010)**, **Jiang et al., 2007), Sharma et al**., **(2006) and EL Meneza et al., (2005).**

Also in the present study a comparison was done between jaundiced neonates group before and after treatment regarding absolute and inter-peak latencies, waves morphology, and hearing threshold **(Tables 4, 5, 6)**.The results of this comparison revealed that, most of the ABR tests showed a marked improvement in the mean laten­cy time of waves I, III, V, wave V at 40 dB and the mean inter-peak-intervals (IPI) of waves I-III, III-V, I-V of ABR in right and left ears of the studied jaundiced group after treatment (p < 0.001) **(Table 4**) which indicate an improvement of transmission time in the brainstem. Also a marked improvement in waves identifiability was noticed in waves I, III, V, and wave V at 40 dB in both right and left ears as regarding waves morphology (p = 0.000) **(Table 5**). Also hearing threshold was considered in this comparison as the presence of wave V in ABR with the minimum stimulus intensity which indicate a marked improvement in hearing where, total reversibility to normal thresholds

(normal hearing) was displayed by 23 (77.00%) and 25 (83.30%) of jaundiced neonates in the right and left ears respectively, while the remaining 7 (23.00%) and 5 (16.70%) of jaundiced neonates displayed partial reversibility (mild to moderate hearing loss) in the right and left ears respectively (p < 0.001) **(Table 6**). These results of the comparison were in agreement with **Sobhy et al., (2015), Wong et al., (2006)** and **Sharma et al**., **(2006).**

**-Conclusions**; About 90% of neonates with pathologic hyperbilirubinemia demonstrate ABR changes. Most of these changes (about 77%) revert to normal early after therapy, indicating need for aggressive therapy in this subgroup of neonates.

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**الملخص العربي**

**دراسة استجابة جذع المخ فى حالات ارتفاع نسبة الصفراء فى الاطفال حديثى الولادة و تأثير العلاج**

**المقدمة**

يعد ارتفاع نسبة الصفراء (اليرقان الوليدى) في الاطفال حديثي الولادة هو من اكثر الأمراض شيوعاويحتاج الى رعايه طبية. هى ظاهرة انتقالية حميدة و مؤقتةIn a few infants, however, serum bilirubin may rise to hazardous levels that pose a direct threat of brain damage. ، ولكن ارتفاع نسبة الصفراء التي قد تصل إلى المستويات الخطرة هي التي تشكل تهديدا مباشرا بتلف في المخ. ان ترسب مادة البيليروبين (المادة المسببة لليرقان الوليدي) فى بعض اجزاء المخ يتسبب فى حالات التأثر المخى الحاد بالبليروبين ( كرنيكترس) و كذلك يؤدى الى تاثر الجهاز السمعي.

يعتبر جهاز رسم السمع بالجهد المثار لقياس استجابة جذع المخ السمعية من اهم الادوات لتقيم حالات التأثر المخى بالبىليروبين .

**الهدف من الدراسة**

تهدف هدة الدراسة التى تقيم القدرات السمعيه للاطفال حديثي الولادة و المصابين بارتفاع نسبة الصفراء و تأثير العلاج عليهم**.**

**المنهجيه :**

تمت هده الدراسة علي 30 طفل يعانون من ارتفاع نسبه الصفراء (اليرقان الوليدي) كمجموعة الدراسة و قد تم اختيارهم من وحده الرعايه المركزة لحديثي الولادة بمستشفي الزهراء الجامعي بجامعة الازهر وأيضا 20 طفل حديثي الولادة لا يعانون من اى مرض كمجموعة مقارنة و قد تم اختيارهم من قسم النساء و الولادة بمستشفي الزهراء الجامعي بجامعة الازهر. وخضعت المجموعتين للفحوصات الاكلينيكيه والمعمليه الكاملة و تم اختبارهم لقياس استجابة جدع المخ السمعية قبل و بعد العلاج.

**نتائج الدراسه**

90% من حالات الاصابة بالصفراء اظهرت تغير في نتائج الاختبار حيث اظهرت النتائج ان 19(63.3%) حاله كانوا يعانون من فقدان بسيط لمتوسط للسمع و 5(20 %) حالات يعانون من فقدان شديد للسمع في الأذن اليمنى و15(50%)حاله و9(30%) حالات كانوا يعانون من فقدان بسيط لمتوسط للسمع وفقدان شديد للسمع في الأذن اليسري علي التوالي قبل العلاج. معظم هده التغيرات (77%) عادت الي التحسن بعد العلاج مباشرة حيث اصبحت 7 حالات فقط هي التي تعاني من فقدان بسيط لمتوسط للسمع فقط في الاذن اليمنى و5 حالات تعاني فقط من فقدان بسيط لمتوسط للسمع في الأذن اليسري .

اى ان ضعف السمع نتيجة ارتفاع نسبه الصفراء فى الاطفال حديثة الولادة قابل للتحسن بعد العلاج .