IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 10 Ser.8 (October. 2020), PP 38-49
www.iosrjournals.org

A Study of VEP Parameters in Infants with History of Neonatal Hyperbilirubinemia

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Abstract: *Infants withhistory of neonatal hyperbilirubinemia candevelopmanyneurological sequelae includingsensory and motordeficits. Visual evokedpotential (VEP) provides a non-invasive and objective method to assess the functionalintegrity of visualpathway. The aim of the studyis to show whetherthereisany VEP parameter changes in infants withhistory of neonatal hyperbilirubinemia compared to agematchedcontrols and whetherthereisany inter-occulardifferences and anydifferences in the differentage groups. An observational, cross-sectionalstudywasundertakenwhere 52 Infants withhistory of neonatal hyperbilirubinemia and 30 controlsweresubjected to mono-ocular Flash VEP testingwith LED gogglesfollowing routine protocolaccording to ISCEV standards(2009).Both cases and controlswere in the age group 0-12 months and wereobtainedfrom Pediatrics OPD. There wasstatisticallysignificant prolongation of N2, P2 latency in botheyescompared to agematchedcontrolsindicatingvisualpathwayabnormality. There was no significantdifferencebetween Right and Lefteye and but therewasdifferencebetweendifferentage groups. Thuswecanseethat VEP canbeused for earlyassessment of functionalintegrity and maturity of visualpathway and CNS function.*

Key Words: *Neonatal Hyperbilirubinemia, Neonatal Jaundice, Visual Evoked Potential, P2 Latency, N2 Latency, N2-P2 Amplitude*

Date of Submission: 08-10-2020 Date of Acceptance: 22-10-2020

I. Introduction

Hyperbilirubinemia is one of the most common pathologies in neonates, and it clinically manifests as jaundice. [1, 2]Jaundice is seen in 60% of term neonate at birth[3]. If not timely managed, hyperbilirubinemia can lead to hyperbilirubinemic encephalopathy, very often followed by neonatal death in case of severe cases. Surviving infants are at high risk of developing sequelae in the form of neurological damage which can manifest as cerebral palsy, epilepsy, sensorineural hearing loss, visual abnormalities or cognitive deficits [4, 5]

The degree of hyperbilirubinemia is a good marker for neurologic manifestations and increase in serum bilirubin level is often associated with increased likelihood of damage to the central nervous system (CNS)[6]. The hyperbilirubinemia induced neurological dysfunction include a wide range of neurological damage. This spectrum includes Kernicterus, acute bilirubin encephalopathy, and isolated neural pathway dysfunction including auditory and visual pathways[4].

Visual Evoked Potential (VEP) is the electrical activity of Occipital Cortex in response to visual stimuli recorded from overlying scalp surface with electrodes. It provides a non-invasive and objective method to assess the functional integrity of visual pathway. VEPs are particularly appropriate for infants and young children who cannot communicate visual symptoms or cooperate for standard vision assessment[7]. In infants the type of VEP that can be used to assess visual function is Flash VEP[8].

The clinical neurological examination of these infants is difficult. VEP can be an important adjunct to the clinical examination and imaging studies. It provides a means for follow up of visual pathway maturation and evaluation of neurological sequelae in infants with perinatal asphyxia.

We intend to undertake a study to evaluate VEP parameters in infants with history of neonatal hyperbilirubinemia. Previous studies provide some data about abnormalities in VEP parameters in the infant[9, 10, 11, 12] . However, the existing data does not show the VEP parameter abnormality in different age groups. They also did not mention anything about inter-ocular difference in infants with history of neonatal hyperbilirubinemia. There is also very little data about VEP parameters among infants with history of neonatal hyperbilirubinemia from Eastern part of India. Present study intends to fill the gap in the knowledge.

In future, a follow up study in a large homogenous population can be undertaken. So, the specific objectives are:

i. To assess the nature of VEP changes in infants with history of neonatal hyperbilirubinemia in our study population.

ii. To assess the nature of VEP changes in different age groups in our study population
iii. Whether there is any correlation of VEP parameters with age in our study population.
iv. To detect whether there is difference between VEP parameter between Right and Left Eyes in infants with history of neonatal hyperbilirubinemia

II. Material And Method

Study was done after getting clearance from Institutional Ethics Committee, R.G.Kar Medical College and Hospital, Kolkata.

1. Study Area

Department of Physiology and Department of Pediatrics at R.G.Kar Medical College and Hospital.

2. Study Population

The study population were the infants, who developed neonatal hyperbilirubinemia (>15mg/dl) due to different causes i.e. ABO incompatibility , Rh incompatibility or G-6 PD deficiency, Exaggerated physiology and other causes which were unknown. (When the infants' discharge certificate did not mention any diagnosis, they were grouped as unknown)

They were referred for VEP test in Department Of Physiology at R.G.Kar Medical College and Hospital.

Inclusion criteria:

1. Age: 0 – 12 months
2. Either gender
3. Parents who have given consent

Exclusion criteria:

1. Infants who have cataract, vitreous opacities, abnormal pupils
2. Infants with gestational Age < 34 weeks
3. Infants with Birth Weight < 1500 gms
4. Infants with h/o other high risk conditions – perinatal asphyxia, neonatal meningitis, neonatal sepsis.
4. Infants with disorders of optic nerve, chiasma, tract
5. Infants with cerebral white matter disease
6. Infants on Antiepileptic medications
7. Infants with phenylketonuria and other metabolic disorders
8. Infants with congenital anomalies
8. Infants whose mothers have h/o perinatal substance abuse or antenatal infections
9. Age > 12 months
10. Parents who are unwilling to give consent
11. Infant too ill to participate

Appropriate Controls were taken.

3. Study Period

The study will be conducted for 6 months.

4. Sample Size

Total Enumeration method was followed for this study

In this study, 52 infants with Neonatal Hyperbilirubinemia fulfilling the inclusion and exclusion criteria were included.

5. Sampling Design

Purposive sampling

6. Study Design

Cross sectional

Analytical Type

7. Parameters to be studied

1. Age
2. Body Weight
3. Bilirubin Level
4. The wave morphology – whether wave P2 was absent or present
5. Wave Latencies (P2, N2) in mili sec and wave amplitude (N2-P2) in micro volts

8. Study Tool

VEP test was done with Neuro-MEP 4 machine manufactured by Neurosoft Medical Diagnostic Equipment, Ivanovo, Russia.

9. Study Technique

Data collection was done by following method-

Infants with history of neonatal hyperbilirubinemia were taken as study population as per inclusion and exclusion criteria from the Pediatrics OPD in R. G. Kar Medical College. They had no known history of congenital or metabolic anomalies or no history of maternal or fetal infection (as per records). These infants fulfilling the inclusion and exclusion criteria were referred to the Department of Physiology for VEP test.

Before the test was performed, parents of the infant were informed properly about the procedure and informed consent was taken.

The VEP test was done by maintaining proper prerequisite and procedure following the International Society of Clinical Electrophysiology of Vision (ISCEV) 2009 Standard[13]

1. The testing room had minimal electrical noise with background light similar to the luminance of the computer screen.
2. The child was preferably asleep or quiet.
3. Areas for electrode placement were cleaned with cotton and spirit.
4. Silver coated electrodes were applied using electrical paste on -

a) Active electrode – Oz

b) Reference electrode –Fz

c) Ground Electrode –Cz

ISCEV standard montage is Oz–Fz with ground at Cz

5. Impedance was checked. It was below 5 KOhm.
6. Flash light stimulus was delivered by LED goggles.
7. The stimulus parameters are as follows: i) Brief Flash (< 5ms) - to each eye separately.

ii) The Flash should subtend a visual angle of 20°

iii) Stimulus luminance – 3 candela/m^2

iv) Red colored Flash with LED Goggles

v) Frequency – 1 Hz

8. The waveform obtained is analyzed and wave N2 , P2 latencies and N2-P2 amplitude were evaluated.According to International Society of Clinical Electrophysiology of Vision (ISCEV), 2009 standards, there are six recognizable wave peaks in a Flash VEP. Among them P2 peak is the most constant and reproducible wave. An abnormal VEP is

1) The absence of the component waves,
2) Delayed latencies (P2 and N2) [13]

The results were stored as per recommended methods. The final analysis was done by standard statistical method.

10. Statistical analysis plan

The VEP parameter changes of 52 infants were compared with 30 control infants.To compare data of main group and subgroups with control population, Student's t-test was applied and for qualitative parameter (i.e. sex), Chi Square test was done. Then statistical analysis was done with Graph Pad Quick Calc software, California, USA and statpages.info software, USA.

11. There was no conflict of interest

III. Results

I) General Information of cases and controls

1. Sex

Graph 1 *- Pie Chart showing No. of Males and Females in cases*

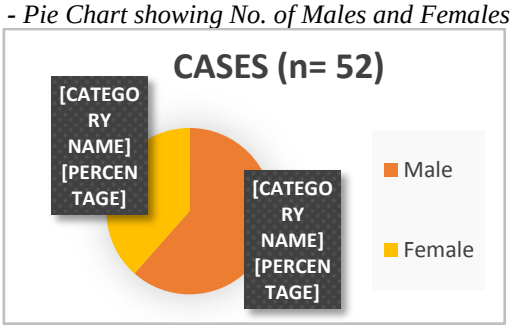


Table 1 *- showing Chi Square test was performed to calculate P value*

	No. of Cases(n=52)	No. of Controls (n=30)	p- value
Males	32	19	.871739
Females	20	11	

Table 1 shows that, with respect to sex, the P values of cases and controls were not significantly different. This shows that the Cases and controls were sex matched.

2. Age –

Graph 2 *-Bar diagram showing Age group in Cases*

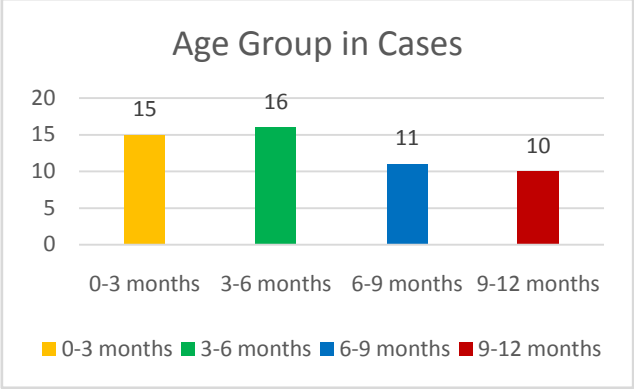


Table 2 *– showing Chi Square test was performed to calculate P value*

Months	**No. of Cases (n=106)**	**No. of Controls (n=30)**	**p- value**
0-3	15	9	.990081
3-6	16	8	
6-9	11	6	
9-12	10	5	

Table 2 shows that, with respect to age, the P values of cases and controls were not significantly different. This shows that the Cases and Controls were age matched.

3. Bilirubin Level

Table 3 *– Showing No. of cases in the two groups divided on the basis of serum bilirubin*

Serum Bilirubin (mg/dl)	15-20	>20	Total
Number	35	17	52
Proportion	67.31 %	32.69%	

4. Causes of Neonatal Hyperbilirubinemia

Table 4 *– showing no. of cases in different etiological groups*

Causes	**No. of Cases (n=52)**	**Proportion (%)**
ABO incompatibility	9	17.31
Rh incompatibility	11	21.15
G6PD Deficiency	8	15.38
Exaggerated Physiology	12	23.08
Unknown	12	23.08

II) All Cases

Graph 5 *- Pie Chart showing Wave P2 presence*

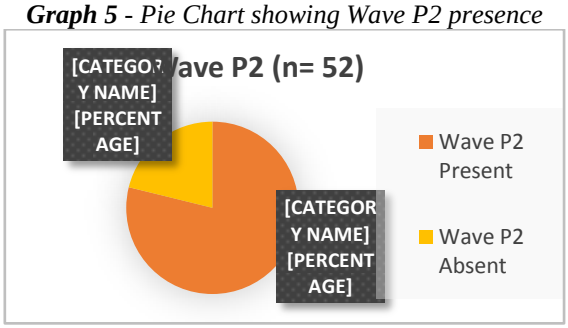


Table 5a *– showing Chi square Test was performed to calculate P value*

	No. of Cases (n=52)	No. of Controls (n=30)	p- value
P2 Wave Present	41	30	0.007*
P2 Wave Absent	11	0	

P value <.05 was considered as statistically significant

b) Mean P2 Latencies of Cases and Controls for both eyes

Table 5 b *– Mean P2 wave latencies of Cases and Controls of right eye with p-value*

VEP Parameter Latency(mS)	CASE Mean(SD) (mS) (n=41)**	CONTROL Mean(SD) (mS) (n=30)	P Value
Wave P2	128.16 (15.89)	98.51 (7.99)	*0.0001**

P value <.05 was considered as statistically significant. * There was statistically significant prolongation of Wave P2 latency compared to control. ** Cases where Wave P2 was present were taken into consideration here.

c) Mean N2 Latencies of Cases and Controls for both eyes

Table 5 c *– Mean N2 wave latencies of Cases and Controls of right eye with p-value*

VEP Parameter Latency(mS)	CASE Mean(SD) (mS) (n=41)**	CONTROL Mean(SD) (mS) (n=30)	P Value
Wave N2	102.89 (11.79)	85.99 (7.34)	*0.0001**

P value <.05 was considered as statistically significant.* There was statistically significant prolongation of Wave N2 latency compared to control. ** Cases where Wave N2 was present were taken into consideration here.

d) Mean P2- N2 Amplitude of Cases and Controls

Table 5 d *– Mean P2- N2 Amplitude of Cases and Controls of right eye with p-value*

VEP Parameter P2- N2 Amplitude (µV)	CASE Mean(SD) (µV) (n=41)**	CONTROL Mean(SD) (µV) (n=30)	P Value
Wave P2	6.10 (2.5)	13.04 (3.41)	*0.0001**

P value <.05 was considered as statistically significant. * There was statistically significant prolongation of Wave P2 latency compared to control. ** Cases where Wave P2 was present were taken into consideration here.

III) Right Eye

A) All Cases

Graph 6 *- Pie Chart showing Wave P2 presence in Right Eye for cases*

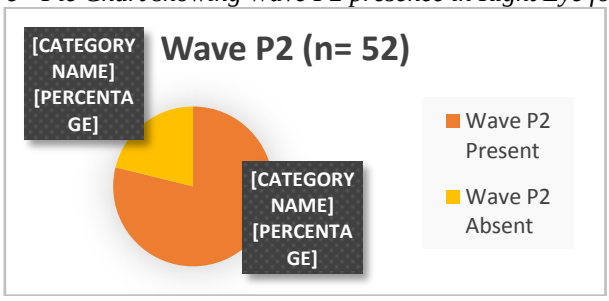


Table 6a - Chi square Test was performed to calculate P value

	No. of Cases (n=52)	No. of Controls (n=30)	p- value
P2 Wave Present	41	30	0.0058*
P2 Wave Absent	11	0	

*Statistically Significant

b) Mean Latencies of Cases and Controls

Table 6b *– Mean P2 wave latencies of Cases and Controls of right eye with p-value*

VEP Parameter Latency(mS)	**CASE Mean (SD) (mS) (n=41)****	**CONTROL Mean (SD) (mS) (n=30)**	**P Value**
Wave P2	128.45 (15.85)	98.51 (7.99)	*0.0001**

Table 6c *– Mean N2 wave latencies of Cases and Controls of right eye with p-value*

VEP Parameter Latency(mS)	**CASE Mean (SD) (mS) (n=41)****	**CONTROL Mean (SD) (mS) (n=30)**	**P Value**
Wave N2	102.96 (12.4)	85.41 (8.12)	*0.0001**

*Statistically Significant

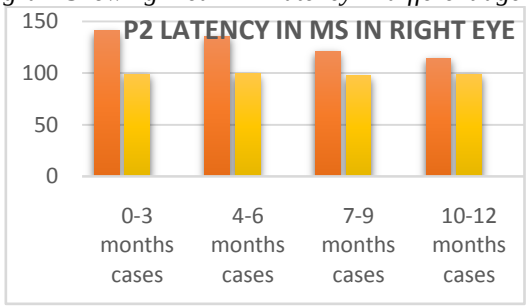
B) For Different Age Groups

Table 7a *- Showing Mean P2 latency in different age groups in Right Eye*

VEP Parameter Latency(mS)	**CASE Mean(SD) (mS)**	**CONTROL Mean(SD) (mS)**	**P Value**
0 – 3 months	141.19 (11.53) *(n = 11)***	98.9 (8.2) (n=9)	*0.0001 **
4-6 months	134.54 (14.23) *(n = 11)***	99.12 (8.18) (n = 8)	*0.0001 **
7-9 months	121.1 (10.82) *(n = 9)***	97.42 (7.86) (n = 6)	*0.0003**
10 – 12 months	114.34 (9.41) (n = 10)**	98.6 (7.7) (n = 5)	*0.0001**

*** No of cases with Wave P2 present*

Graph 7a *- Bar Diagram Showing Mean P2 Latency in different age groups in Right Eye*



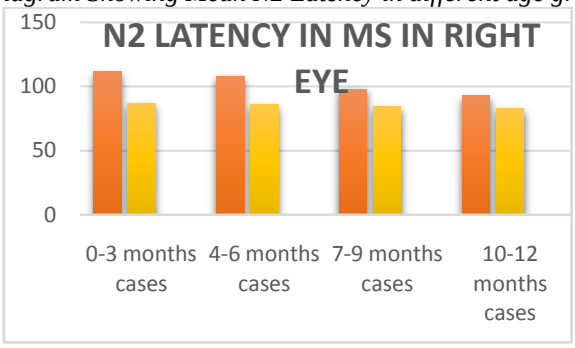
P value <.05 was considered as statistically significant * There was statistically significant prolongation of Wave P2 latency compared to control

Table 7b *- Showing N2 Latency between Different Age Groups in Right Eye*

VEP Parameter Latency(mS)	**CASE Mean(SD) (mS)**	**CONTROL Mean(SD) (mS)**	**P Value**
0 – 3 months	111.39 (10.17) *(n =11)***	86.72 (7.23) (n=9)	*0.0001 **
4-6 months	108.02 (13.58) *(n = 11)***	85.67 (8.33) (n = 8)	*0.0007 **
7-9 months	97.97 (8.05) *(n = 9)***	84.23 (8.43) (n = 6)	*0.0072**
10 – 12 months	92.6 (4.39) (n = 10)**	82.61 (3.98) *(n = 5)*	*0.0009 **

*** No of cases with Wave N2 present*

Graph 7b *- Bar Diagram Showing Mean N2 Latency in different age groups in Right Eye*



IV) Left Eye

A) All Cases

Graph 8 *- Pie Chart showing Wave P2 presence in Left Eye for cases*

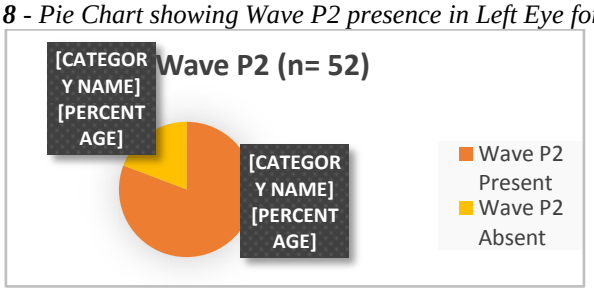


Table 8a - Chi square Test was performed to calculate P value

	No. of Cases (n=52)	No. of Controls (n=30)	p- value
P2 Wave Present	42	30	0.0114*
P2 Wave Absent	10	0	

*Statistically Significant

b) Mean Latencies of Cases and Controls

Table 8b *– Mean P2 wave latencies of Cases and Controls of left eye with p-value*

VEP Parameter Latency(mS)	**CASE Mean (SD) (mS) (n=42)****	**CONTROL Mean (SD) (mS) (n=30)**	**P Value**
Wave P2	127.89 (14.71)	98.82 (4.74)	*0.0001**

*Statistically Significant

Table 8c *– Mean N2 wave latencies of Cases and Controls of left eye with p-value*

VEP Parameter Latency(mS)	**CASE Mean (SD) (mS) (n=42)****	**CONTROL Mean (SD) (mS) (n=30)**	**P Value**
Wave N2	102.83 (11.17)	86.45(6.44)	*0.0001**

*Statistically Significant

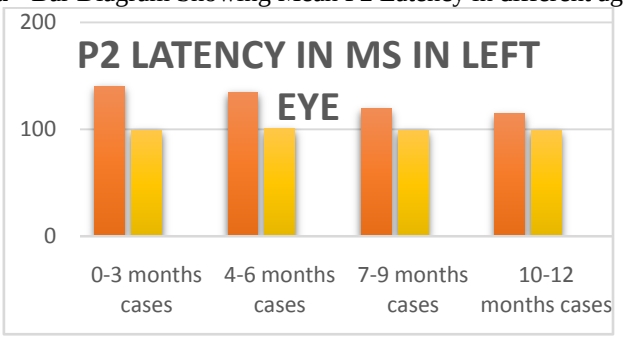
B) For Different Age Groups

Table 9a *- Showing Mean P2 latency in different age groups in Left Eye*

VEP Parameter Latency(mS)	**CASE Mean(SD) (mS)**	**CONTROL Mean(SD) (mS)**	**P Value**
0 – 3 months	140.24 (10.23) *(n = 11)***	98.81 (4.49) (n = 9)	*0.0001 **
4-6 months	134.6 (8.84) *(n = 12)***	100.2 (7.33) (n = 8)	*0.0001 **
7-9 months	119.12 (12.0) *(n = 9)***	98.89 (8.3) (n = 6)	*0.0034**
10 – 12 months	114.13 (9.49) (n = 10)**	99.1 (7.37) *(n = 5)*	*0.0087**

*** No of cases with Wave P2 present*

Graph 9a - Bar Diagram Showing Mean P2 Latency in different age groups



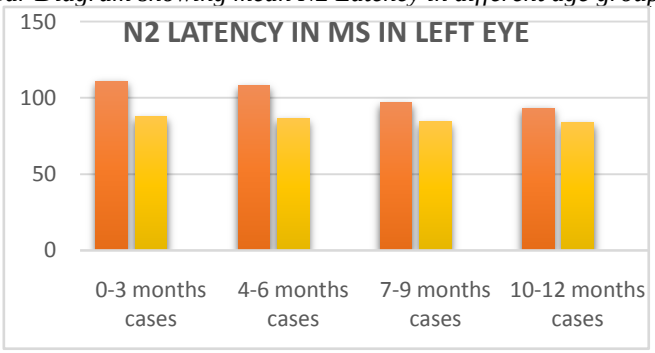
P value <.05 was considered as statistically significant * There was statistically significant prolongation of Wave P2 latency compared to control

Table 9b - *Showing N2 Latency between Different Age Groups in Left Eye*

VEP Parameter Latency(mS)	**CASE Mean(SD) (mS)**	**CONTROL Mean(SD) (mS)**	**P Value**
0 – 3 months	110.85 (10.39) *(n = 11)***	87.56 (7.11) (n = 9)	*0.0001* *
4-6 months	108.01 (8.97) *(n = 12)***	86.43 (6.93) (n = 8)	*0.0001* *
7-9 months	96.71 (7.96) *(n = 9)***	84.23 (8.43) (n = 6)	*0.0122**
10 – 12 months	93.29 (4.89) (n = 10)**	83.65 (3.78) *(n = 5)*	*0.0020**

*** No of cases with Wave N2 present*

Graph 9b - *Bar Diagram showing mean N2 Latency in different age groups in Left Eye*



V) Comparison between right and left eye

Table 10 a– *Mean P2 latency in cases where P2 wave is present in cases*

VEP Parameter Latency(mS)	**Right Mean (SD) (mS) (n=41)****	**Left Mean (SD) (mS) (n=42)**	**P Value**
Wave P2	128.45 (15.85)	127.89 (14.71)	*0.8679**

* Not statistically insignificant. **** Cases where Wave P2 is present

Table 10 b– *Mean N2 latency in cases where N2 wave is present in cases*

VEP Parameter Latency(mS)	**Right Mean (SD) (mS) (n=41)****	**Left Mean (SD) (mS) (n=42)**	**P Value**
Wave N2	102.96 (12.4)	102.83 (11.17)	*0.9601**

* Not statistically insignificant. **** Cases where Wave N2 is present

Table 11a *- showing Comparison of mean P2 wave latencies between the different age groups (Inter group ANNOVA)*

P2 Latency	GROUPS (AGE IN MONTHS) Mean (SD)				P Value
	0-3	4-6	7-9	10-12	
Right Eye	141.19 (11.53)	134.54 (14.23)	121.1 (10.82)	114.34 (9.41)	0.001*
Left Eye	140.24 (10.23)	134.6 (8.84)	119.12 (12.0)	114.13 (9.49)	0.001*

*Statistically significant

Table 11b *- showing Comparison of mean N2 wave latencies between the different age groups (Inter group ANNOVA)*

P2 Latency	GROUPS (AGE IN MONTHS) Mean (SD)				P Value
	0-3	4-6	7-9	10-12	
Right Eye	111.39 (10.17)	108.02 (13.58)	97.97 (8.05)	92.6 (4.39)	0.001*
Left Eye	110.85 (10.39)	108.01 (8.97)	96.71 (7.96)	93.29 (4.89)	0.001*

*Statistically significant

Analysis of results

Out of 52 infants with history of Neonatal Hyperbilirubinemia, 32 (61.54%) were males and 20 (38.46 %) were females (Graph 1).

15 (28.85 %) of the infants belonged to the age group of 0-3 months, 16(30.77%) in the 4-6 months age group, 11(21.15%) in 7-9 months age group and 10(19.23 %) in the 10-12 months age group. (Graph 2) 30 controls were taken. Chi square test was performed and it was found that with respect to age and sex, the cases and controls were not very different. The cases were properly matched with controls with respect to age and sex.

35 (67.31 %) infants had serum bilirubin level between 15-20 mg/dl and 17 (32.69%) infants had serum bilirubin level > 20 mg/dl (Table 3)

9(17.31%) infants had ABO incompatibility, 11 (21.15%) infants had Rh incompatibility, 8 (15.38%) infants had G6PD deficiency, 12 (23.08%) infants had exaggerated physiology and 12 (23.08%) infants had Hyperbilirubinemia due to unknown causes. (Table 4)

Out of the 52 infants, 47 (90.38%) showed some degree of visual dysfunction in one or both eyes (absence of P2 or prolongation of P2 latency)

Wave P2 was absent in 11 (21.15%) in one or both eyes in cases (Graph 5). The P value is 0.007, so, there is statistically significant association between Wave P2 presence of Case and Controls (Table 5a). Among the cases where Wave P2 was present (n=41), there was statistically significant prolongation of Wave P2 latency (Table 5b), Wave N2 latency (Table 5c) and reduction of N2-P2 Amplitude (Table 5d) compared to controls. This indicates a dysfunction of visual pathway.

Wave N2, P2, changes with respect to right eye –

Wave P2 was absent in 11 (21.15%) in one or both eyes in cases (Graph 6). The P value is 0.007, so, there is statistically significant association between Wave P2 presence of Case and Controls (Table 6a). Among the cases where Wave P2 was present (n=41), there was statistically significant prolongation of Wave P2 latency (Table 6b), Wave N2 latency (Table 5c). This indicates a dysfunction of visual pathway.

In the age group **0-3 months**, 4 (26.67%) infants showed absent Wave P2. Out of the 11 (73.33 %) infants in whom the wave P2 was present, there was statistically significant prolongation of Wave P2 latency and Wave N2 Latency (Table 7a, 7b). This indicates a dysfunction of visual pathway.

In the **4-6 months**, 5 (31.25%) cases had absent wave P2. Out of the 11(68.75 %) infants in whom Wave P2 was present, there was statistically significant prolongation of Wave P2 latency and Wave N2 Latency (Table 7a, 7b). This indicates a dysfunction of visual pathway.

In the age group **7-9 months**, 2 (18.18 %) cases had absent wave P2. Out of the 9 (81.82%) infants in whom Wave P2 was present, there was statistically significant prolongation of Wave P2 latency and Wave N2 Latency (Table 7a, 7b). This indicates a dysfunction of visual pathway.

In the age group **10-12 months**, 0(0 %) cases had absent wave P2. Out of the 10 (100%) infants in whom Wave P2 was present, there was statistically significant prolongation of Wave P2 latency and Wave N2 Latency (Table 7a, 7b). This indicates a dysfunction of visual pathway.

Wave P2 changes with respect to left eye-

Wave P2 was absent in 10 (19.23%) cases (Graph 8). The P value is 0.0114, so, there is statistically significant association between Wave P2 presence of Case and Controls (Table 8a). Among the cases where Wave P2 was present (n=42), there was statistically significant prolongation of Wave P2 latency (Table 8b), Wave N2 latency (Table 8c). This indicates a dysfunction of visual pathway.

In the age group **0-3 months**, 4 (26.67%) infants showed absent Wave P2. Out of the 11 (73.33 %) infants in whom the wave P2 was present, there was statistically significant prolongation of Wave P2 latency and Wave N2 Latency (Table 9a, 9b). This indicates a dysfunction of visual pathway.

In the **4-6 months**, 4 (25%) cases had absent wave P2. Out of the 12(75 %) infants in whom Wave P2 was present, there was statistically significant prolongation of Wave P2 latency and Wave N2 Latency (Table 9a, 9b).This indicates a dysfunction of visual pathway.

In the age group **7-9 months**, 2 (18.18 %) cases had absent wave P2. Out of the 9 (81.82%) infants in whom Wave P2 was present, there was statistically significant prolongation of Wave P2 latency and Wave N2 Latency (Table 9a, 9b).This indicates a dysfunction of visual pathway.

In the age group **10-12 months**, 0(0 %) cases had absent wave P2. Out of the 10 (100%) infants in whom Wave P2 was present, there was statistically significant prolongation of Wave P2 latency and Wave N2 Latency (Table 9a, 9b).This indicates a dysfunction of visual pathway.

There is no statistically significant difference between the P2 and N2 latency of right and Left Eye (Table 10a, 10b).

Inter group ANNOVA

Inter group one way ANNOVA for different age groups (Table 11a, 11b) show that there was statistically significant relation of Wave P2 and N2 latency between the different age groups in both eyes.

IV. Discussion

This cross sectional and observational study was carried out with 52 infants with history of neonatal hyperbilirubinemia and 30 age and sex matched control. All the infants belonged to the age group of 0-12 months. They were subjected to VEP testing according to International Society of Clinical Electrophysiology of Vision (ISCEV), 2009 standards[13] and the VEP findings of the cases were analyzed with respect to the controls. The parameters studied was the presence of waveform, latency of Wave P2 and N2, N2-P2wave amplitude of each eye. These parameters were used to assess the presence of visual pathway abnormality in the infants with h/o neonatal hyperbilirubinemia.

Elevated serum levels of unconjugated bilirubin are considered toxic for the central nervous system. It is a risk factor for neonatal deafness, visual abnormalities and encephalopathies. A high concentration of serum bilirubin is treated with phototherapy and/or exchange transfusion (in severe hyperbilirubinemia and cases which are resistant to repeated phototherapy)[14,15].

Unless it is managed in a timely manner, hyperbilirubinemia can lead to encephalopathy, various neurological sequelae like cerebral palsy, epilepsy, sensorineural hearing loss, visual abnormalities or cognitive deficits[7,16]. Early identification of those who have sustained insult to the immature nervous system is essential to instigate effective remedial action without delay [17] and to reduce the severity of neurological injury [18]. Visual evoked potentials (VEPs) are potentially valuable prognostic tools in high-risk newborn infants. The test objectively evaluates the functional integrity of ascending pathways of the nervous system which are vulnerable to injury[7, 19, 20]. A number of studies show that VEPs are sensitive to acute alteration of CNS function and provide information for long term prognosis[21, 22, 23].

Bilirubin is highly toxic to neuron. Bilirubin binds avidly to cell membranes, especially myelin-rich membranes, making neurons the principal target of bilirubin toxicity. Exposure of neurons to unconjugated bilirubin in vitro is often accompanied by macroscopic changes, including reduced dendritic and axonal arborization, reduced neurite extension and ramification[24], reduced cell proliferation[25], and increased death by apoptosis[26] and cell-cycle arrest[27,28]. Biochemical changes induced by bilirubin include protein oxidation, lipid peroxidation, reduced cellular glutathione content[29], increased lactate dehydrogenase levels, and nitric oxide release[30].

Chen, Y., Kang, W. et al conducted serial VEPs in infants with hyperbilirubinemia and found the wave latencies were significantly prolonged in infants in the severe and moderate groups than in the controls. The amplitudes of VEPs were lower in severe and moderate groups than in the control group only initially[9].

Hou C, Norcia AM et al found abnormal VEP parameters including decreased wave amplitude in full term infants with history of neonatal hyperbilirubinemia. The infants were evaluated between 14-22 weeks of age[10].

Chen WX, Wong V et al found that out of the 16 infants with history of neonatal hyperbilirubinemia, 4 infants showed VEP abnormalities within 1 year of age but no abnormality was found after repeat testing after 1 year of age[11].

Good WV, Hou C. et al showed that children who had jaundice with TB levels between 10 and 25mg/dL, but who did not have kernicterus, have measurable changes in visual function as evaluated by VEP parameter abnormality, when compared to control infants who did not have jaundice[12]

The aim and objectives of our study was to assess the nature of VEP changes in infants with history of neonatal hyperbilirubinemia and to find out whether there is any difference between the findings of right and left eye.

Out of the 52 infants, 47 (90.38%) showed some degree of visual dysfunction in one or both eyes (absence of P2 or prolongation of P2 latency). Chen, Y., Kang, W. et al[9], Hou C, Norcia AM et al[10], Good WV, Hou C. et al[12] has showed similar findings though the percentage of abnormal findings are more in this current study. Chen WX, Wong V et al has found though that the VEP wave abnormalities can be transient[11].

In our study, we also attempted to analyze the VEP parameters separately in both eyes.

In Right eye, P2 wave was absent in 21.15% cases and out of the ones where wave P2 was present, there was statistically significant prolongation of P2 and N2 wave, indicting visual pathway dysfunction. Similar findings were obtained from left eye. There was no statistically significant difference between findings of right and left eye.

So, from our study we see that neonatal hyperbilirubinemia does not contribute to any change in inter ocular VEP difference and affects both eyes equally.

In our study we divided the infants into 4 age groups :- 0-3 months, 4-6 months, 7-9 months and 10-12 months. The P2 wave latencies, N2 wave latencies and N2-P2 wave amplitudes were analyzed in two eyes separately in these age groups.

There is statistically significant prolongation of P2 and N2 wave latencies in all the age groups in both the eyes in infants with history of neonatal hyperbilirubinemia compared to control.

We find that both the mean N2 and P2 latency is maximum in infants in the age group 0-3 months for both the eyes with gradual decrease in latency in the higher age groups.

Intergroup annova shows that there is statistically significant changes among the different age groups. This is consistent with findings by Chen WX, Wong V et al who found on serial testing that latencies decrease with increasing age[11].

In our study, we found that the wave amplitude N2-P2 is reduced in infants with history of neonatal hyperbilirubinemia in both the eyes. This is consistent with the findings of Chen, Y., Kang, W. et al[9] and Hou C, Norcia AM et al[10].

The decrease in wave amplitude could be due to either a decrease in the number of active neurons, or decrease in their degree of synchronous activation. Postmortem analysis of cortex from survivors of severe jaundice showed a general sparseness of cells throughout cortex, but especially in the frontal and occipital lobes[29].

A number of studies have reported that exposure to hyperbilirubinemia also affects the retina[30,31].

From the above discussion we see that there are significant VEP changes in infants with history of neonatal hyperbilirubinemia in our population. There is no interocular difference in the VEP findings implying that hyperbilirubinemia affects both sides similarly. Our study shows that there is statistically significant age related P2 , N2 wave latency prolongation. The age related VEP changes in these infants have to be further explored with analysis of the effect of serum bilirubin level and the different etiological causes on VEP parameters at different ages.

Thus, based on the above findings we can say that VEP can serve as an early objective and non-invasive test to assess the neurological status and visual pathway in infants with history of neonatal hyperbilirubinemia. This early diagnosis can help us initiate early rehabilitative and therapeutic measures and limit the socio-developmental adverse outcomes associated with hyperbilirubinemic CNS changes.

Limitations of my study include the lack of assessment of bilirubin level and etiology specific wave changes. No follow up was done so the long term VEP changes could not be assessed.

V. Conclusion

VEP can be used for early assessment of the functional integrity and maturity of visual pathway and CNS function in infants with history of neonatal hyperbilirubinemia. This helps in early initiation of rehabilitation process. Further follow up studies with larger sample sizes can be undertaken to strengthen the knowledge gained from this study.

Acknowledgements

The authors will like to thank all the faculties of R.G. Kar medical College and Hospital and Calcutta National Medical College and Hospital for their encouragement and support.

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Chattopadhyay MunMun, et. al. "A Study of VEP Parameters in Infants with History of Neonatal Hyperbilirubinemia." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(10), 2020, pp. 38-49.