Original Article

DOI: 10.7860/JCDR/2023/59970.17768

Predictive Utility of Visual Evoked Potentials in Detection of Ocular Changes in Paediatric Sickle Cell Patients: A Cross-sectional Analytical Study

Physiology Section

ARUNITA TUSHAR JAGZAPE[1], VK DESHPANDE[2], TUSHAR B JAGZAPE[3]

ABSTRACT

Introduction: Ocular manifestations are one of the complications of Sickle Cell Disease (SCD) that may occur in various segments of the eye. Optic nerve involvement is under-diagnosed though it can be involved as a sequela to ischemia. Prediction of disease at an early age aids in better diagnosis. Visual Evoked Potentials (VEP) helps to detect abnormalities (silent lesions) in patients with visual complaints who do not present with visible pathological ophthalmological changes. In literature search, no study has been undertaken to assess the predictive utility of VEP regarding subclinical ocular changes in paediatric age group of SCD patients.

Aim: To evaluate predictive utility of VEP to identify subclinical ocular changes in paediatric patients of SCD and to record associated Visual Reaction Time (VRT).

Materials and Methods: In this cross-sectional analytical study, 30 cases (SCD patients) and 30 normal children in age group 3-15 years were evaluated by ophthalmic examination followed by VRT and VEP using Light-emitting diode (LED) goggles (Flash). Statistical analysis included descriptive (percentages) and inferential statistics presented as unpaired t-test, linear regression curve, Pearson's correlation coefficient, coefficient of determination (R^2) and β (regression) coefficient. The analysis was done at 99% confidence interval with significance at $p<0.01$.

Results: There was statistically significant prolongation of P100 latency in both eyes in paediatric cases when compared to normal children ($P<0.01$). N75-P100 amplitude, interocular difference showed no significant changes. When P100 latency was correlated with VRT, there was weak positive correlation ($r=0.207$, $p=0.1278$ for right eye, $r=0.238$, $p=0.0801$ for left eye). Though sensitivity of flash LED goggle VEP was 70%, specificity was high (96.66%). Positive predictive value was 95.45%.

Conclusion: These findings show that VEP can be used as a predictive measure (tool) to detect subclinical changes in absence of ocular complaints and normal ophthalmological findings.

Keywords: Sensitivity, Sickle cell disease, Specificity, Visual reaction time

INTRODUCTION

The SCD is an autosomal recessive genetically transmitted haemoglobinopathy responsible for considerable morbidity and mortality [1]. Sickle cell gene is prevalent in the population of eastern districts of Maharashtra (also known as Vidarbha region). It has also been estimated that Gadchiroli, Chandrapur, Nagpur, Bhandara, Yoetmal and Nandurbar districts would have more than 5000 cases of sickle cell anaemia [2,3]. The pathophysiologic processes that lead to SCD related complications result from a combination of haemolysis and vaso-occlusion which can involve cardiovascular system, renal system, hepatobiliary system, skin, skeleton, lungs, central nervous system; growth and development and eyes [4]. Long-term complications like ocular involvement have emerged in recent years due to an increase in life expectancy of SCD patients [5]. The pathological process of SCD can affect virtually every vascular bed in the eye and its advanced stages has the potential to cause blindness [5,6]. Sickling of erythrocytes within small vessels, causing occlusion of vessels leading to ischemia furthering neovascular proliferation may be the reason for the ocular manifestations of SCD [7]. Another common haemoglobinopathy, thalassaemia, also leads to ocular complications. However, thalassaemia-related changes in Visual Evoked Potentials (VEPs) are caused by iron overload and chelation therapy [8].

In investigation of demyelinating diseases, VEPs are widely used. VEPs are the record of electrical events in cerebral cortex after stimulation of a sense organ [9]. They provide a sensitive indication of visual pathway abnormalities in conduction of impulses; the demyelination of optic nerve detected by measuring the latency and loss of axons in pathway detected by abnormalities of amplitude of VEPs [10]. Pattern Reversal VEP (PRVEP) is the preferred stimulus for most clinical purposes [11]. Flash VEP is done if patient cannot fixate or has a dense opaque media [12] and in young and non cooperative study participants, which circumvents the major limitation of PRVEP [13,14].

Reaction Time (RT) can be defined as the interval between presentation of stimulus and appearance of appropriate voluntary response in a person usually expressed in milliseconds [15]. RT is an indicator for processing rate of sensory stimulation by the central nervous system and the motor response in the form of execution [16,17]. RT equals perception time added to motor time [18]. Documented mean VRT is approximately 180 to 200 milliseconds [19].

Early stages of the eye conditions are usually asymptomatic and the patient may remain unaware until the disease progresses, often with devastating consequences [7]. Early identification can improve management by paediatricians and better quality of life for patients. VEPs help to detect abnormalities (silent lesions) in patients with visual complaints who do not present with visible pathological ophthalmological changes. In literature search, no study has been undertaken to assess the predictive utility of VEP in regard to subclinical ocular changes in paediatric sickle cell patients.

This study was therefore initiated to measure predictive utility of VEP to detect early ocular changes and changes in VRT in paediatric sickle cell patients. The primary objectives were to identify the changes in latency of P100, N75-P100 amplitude and VRT in patients of SCD and control group; to correlate VEP changes with

VRT and to find out the predictive utility of VEP in early detection of ocular changes. The secondary objective was to determine the sensitivity, specificity, positive and negative predictive value of the tool to detect the changes in P100 latency.

MATERIALS AND METHODS

It was a cross-sectional analytical study with with control group included as per International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines [11] which have suggested that each lab should have its own normative data. The study was conducted in Central Physiology Laboratory under Physiology department of a Rural Medical college of central India. The time period of the study was Jan 2015 to June 2017. The study was conducted after approval from Institutional Ethics Committee (DMIMS(DU)/IEC/2014-15/864).

The participants in the control group consisted of children in the same age group recruited from paediatric department, with normal paediatric assessment, and fulfilling the inclusion and exclusion criteria.

Inclusion criteria:

Sickle cell group:

1. Sickle cell Pattern AS or SS
2. Written informed consent provided
3. Age group from 3-15 years

Control group:

1. Children with absence of SCD
2. Written informed consent
3. Age group 3-15 years

Exclusion criteria:

Sickle cell group:

1. Sickle cell+thalassaemia patients
2. Patients in sickle cell crisis
3. Ocular diseases like congenital glaucoma and cataract
4. Cases with conjunctivitis
5. Any eye injury
6. Refractive errors
7. Known case of sickle cell retinopathy

Control group:

1. Developmental delay
2. Neurologically abnormal child
3. Refractive errors
4. Conjunctivitis, eye injury, optic neuritis, retinitis pigmentosa

Sample size was 60 with 30 participants as cases (SCD group) and 30 participants as control group. Sample size for the main study was calculated by comparing the means of two independent populations for metric data, using the formula:

$N=(r+1)(Z_{\alpha/2}+Z_{(1-\beta)})^2\sigma^2/rd^2$

Substituting 'r' as '1' for equal sample size, $Z_{\alpha/2}$ as 2.58 for 1% level of significance, $Z_{(1-\beta)}$ as 1.28 for 90% statistical power, σ as 15.04 and d as 21.21 (118.07-96.86), the sample size estimated was 15 for cases and 15 for controls. The values of σ and d were computed from the pilot study conducted on 12 participants each in cases and control group as there was inadequate literature pertaining to the present study. In order to increase the precision of the results and in view of availability of adequate clinical material during the study period, we enrolled 30 cases and 30 controls.

Participants in the study group were sickle cell patients (AS or SS patients) recruited from sickle cell clinic run under paediatric department of rural hospital attached to the medical college in central India after verifying inclusion and exclusion criteria. Written informed consent was obtained from both sickle cell patients and control group participants.

The outcome variables were VEP P100 latency right and left eye, amplitude right and left eye, interocular latency difference and VRT. These were collected using Neuron-spectrum NET (version 3), Russia. Discrete variables were the number of crisis episodes in past one year (from history taken from parent), age and gender. Discrete variables were collected using Schedule I which included demographic profile such as name, registration number, age, address and clinical profile like pattern of SCD, age at diagnosis and number of episodes of crisis in past one year.

Ophthalmological examination: Ophthalmological examination was also conducted with the help of a schedule II. Schedule II included detailed ocular examination such as vision, colour vision, head posture, lid margins and lid proper, conjunctiva for conjunctival sickling sign, cornea (size, surface and checking for keratic precipitates), anterior chamber (depth, contents), iris (colour, pattern, rubiosis iridis), pupil, lens, ocular movements, Non Contact Tonometer (NCT), auto-refraction, fundus including media, disc, blood vessels, foveal reflex, macula and background. Fundus examination was performed after dilatation using tropicamide 0.8% with phenylephrine hydrochloride 5%. Data for schedule II was entered by the ophthalmologists.

Procedure for VRT recording: VRT was measured before VEP test using Audio-Visual Reaction time instrument, Medisystems, Haryana, India. There are two sides in the instrument: operator side and subject side. The switch on the operator side was pressed and the subject had to locate the colour which glowed on his/her side and press the button corresponding to that colour. The time taken is measured in LCD meter as the RT in seconds. The participants were explained about the procedure and five trials were given to acquaint them to the procedure. Then three readings were taken and the lowest among them was taken as the VRT reading.

Procedure for VEP recording: Preparation of participants: Parents of the participants were explained about the procedure in detail in local language. The children were also explained the non invasiveness of the procedure in local language to do away with fear and apprehension. The skin of scalp was prepared by proper degreasing and abrading and electrodes were applied after using electrode paste. The LED Goggles were worn over the eyes, in such a way that little or no extraneous light was admitted during the testing.

Electrodes and its placements: Standard disc surface silver chloride electrodes of 1 cm diameter were used for recording and were placed as per the 10-20 electrode system of the International Federation [20]. In 10-20 electrode placement system, the anterior-posterior measurements are based upon the distance between the nasion and the inion over the vertex in the midline. Five points are then marked along this line, namely Frontal pole (Fp), Frontal (F), Central (C), Parietal (P), and occipital (O). The first point (Fp) is 10% of the nasion-inion distance above the nasion; the second point (F) is 20% of this distance back from the point Fp. Hence, the name 10-20 system. The reference electrode was placed at Fp, ground at C and active electrode at O [20].

Machine parameters: VEP was recorded using Neuron-Spectrum NET (version 3), Russia with Band pass of 2 to 100 Hz; Sweeps averaged 50; analysis time of 250 ms; maximum stimuli/ average count: 200. Replication: two responses were recorded. The replicated response measurements with P 100 latency within a 2.5 ms difference and peak to peak amplitude of N75-P 100 within a 15% difference was accepted [21].

Recording of VEP: VEP was recorded using ISCEV guidelines [11]. VEP was recorded using Light Emitting Diode (LED) goggles (Flash VEP). Mono-ocular stimulation was performed with each eye tested separately. The impedance was kept below 5 kilo ohms. Flashes were of red colour at 1 per second. VEP latency and amplitude were evaluated to the prominent wave P wave at 100 ms.

Parameters studied were P 100 latency right and left eye separately, N75-P 100 amplitude right and left eye separately and inter-ocular latency difference.

STATISTICAL ANALYSIS

Statistical analysis was performed using Instat Graphpad and Statistical Package for the Social Science (SPSS) 22 version. Descriptive statistics was presented as percentages. Inferential statistics was presented as unpaired t-test, using two tailed test. The data was expressed as Mean±SD (Standard Deviation). The analysis was done at 99% confidence interval with significance at p<0.01. Effect size i.e., Cohen's 'd' was calculated for significant variables.

Linear regression curve was plotted to find the association between VEP and VRT; number of crisis episodes and VEP; VRT values and P100 latency. Pearson's correlation coefficient was applied based on the linearity of graph. Coefficient of determination (R^2), β (Regression) coefficient was calculated. In order to find out the predictive utility of Flash VEP; sensitivity, specificity, positive and negative predictive value was calculated.

RESULTS

[Table/Fig-1] shows that there was no significant difference between the age groups and gender among cases and controls in paediatric age group in Sickle Cell Disease (SCD).

Age group (years)	Cases	Controls	p-value (Chi-square test)
3-15	8.8±3.30	8.62±2.80	p=0.817, not significant
Gender			
Male	21	18	p=0.416 Not significant
Female	9	12	

[Table/Fig-1]: Gender and Mean±SD of age 3-15 years among cases (n=30) and controls (n=30).

[Table/Fig-2] shows that in both the right eye and left eye, there was significant difference in the mean P100 latency among cases and controls of SCD of paediatric age group [22,23]. The effect size for right eye is 1.570 and for left eye is 1.794 i.e., very large. The above table depicts mean VRT in cases as compared to controls. The difference in values was statistically significant.

Parameters	Cases Mean±SD	Controls Mean±SD	Significance at p <0.01; 99% Confidence Interval	Cohen's 'd'
P 100 latency Right eye (msec)	113.09±12.671	98.47±3.56	t value: 6.081 p<0.01, significant; (8.220, 21.019)	1.570
P 100 latency Left eye (msec)	115.77±12.77	99.00±3.40	t value: 6.949 p<0.01, significant; (10.344, 23.195)	1.794
VRT	0.776±0.25	0.596±0.12	t value : 3.412 p<0.01, significant; (0.037, 0.322)	-

[Table/Fig-2]: Mean±SD of P100 latency, VRT [22,23].
The effect size was determined based on the values given by Cohen J 1988 [22] and expanded by Sawilowsky SS [23] for 'd' as 0.01: very small, 0.2: small, 0.5: medium, 0.8: large, 1.2: very large, 2.0: huge.

[Table/Fig-3] also depicts mean inter-ocular difference values in cases as compared to controls that were statistically not significant. Mean N75-P100 amplitude right eye and left eye in cases as compared to controls were statistically not significant.

Parameters	Cases Mean±SD	Controls Mean±SD	Significance at p<0.01
Inter-ocular difference	3.250±2.23	2.25±1.54	p=0.091 Not significant
N75-P100 amplitude (μV) Right eye	18.445±9.103	18.012±4.58	p=0.810 Not significant
N75-P100 amplitude (μV) Left eye	17.421±9.053	18.293±5.01	p=0.541 Not significant

[Table/Fig-3]: Mean±SD of inter ocular difference and amplitude in cases as compared to controls (Mann-Whitney U test).

Pearson's correlation coefficient was applied to find the association between P100 latency of right eye and left eye and number of episodes of crisis. There was a weak positive correlation between P100 latency of right eye with number of episodes of crisis and P100 latency left eye with number of episodes of crisis (1.76±1.47) [Table/Fig-4].

Response variable (y)	Predictor variable (x)	Pearson's correlation	Correlation coefficient	Interpretation
P100 latency right eye	Number of episodes of crisis	Pearson's Correlation	R=0.26 p=0.1685	Weak positive correlation
P100 Latency left eye	Number of episodes of crisis	Pearson's Correlation	R=0.26 p=0.1726	Weak positive correlation

[Table/Fig-4]: Correlation of VEP with number of episodes of crisis in cases.

Pearson's correlation coefficient was applied to find the association between VRT and P100 latency of right eye and left eye and VRT and number of episodes of crisis. There was a weak positive correlation between VRT and P100 latency of right eye and VRT and P100 latency left eye. There was also weak positive correlation between VRT and number of episodes of crisis [Table/Fig-5].

Response variable (y)	Predictor variable (x)	Pearson's correlation	Correlation coefficient	Interpretation
VRT	P100 latency right eye	Pearson's correlation	R=0.207 p=0.1278	Weak positive correlation
VRT	P100 latency left eye	Pearson's correlation	R=0.238 p=0.0801	Weak positive correlation
VRT	Number of episodes of crisis	Pearson's correlation	R=0.368 p=0.0584	Weak positive correlation

[Table/Fig-5]: Correlation of VRT with number of episodes of crisis and VEP for cases.

[Table/Fig-6] depicts the regression coefficient that shows the increase in P100 latency with increase in number of episodes of crisis.

Response variable (y)	Predictor variable (x)	Correlation coefficient (R)	Coefficient of Determination (R^2)	β (Regression) coefficient	Interpretation
P100 latency right eye	Number of episodes of crisis	0.26	0.066	2.212	P 100 latency will increase 2.21 times per unit episode of crisis
P100 Latency left eye	Number of episodes of crisis	0.26	0.065	2.209	P 100 latency will increase 2.209 times per unit episode of crisis

[Table/Fig-6]: Coefficient of determination and β (Regression) coefficient.

[Table/Fig-7] shows that the tool is more specific (96.66%) which means that it is less likely that an individual with positive test will be free from disease. Positive predictive value of 95.45% shows the probability that patient with a positive (abnormal) test actually has the disease.

[Table/Fig-8] is a linear regression graph VRT with P100 latency right eye. X-axis or predictor variable is the P100 latency right eye and Y-axis or response variable is the VRT.

[Table/Fig-9] shows ''Area Under Curve'' or "AUC" as 0.835 i.e., 80% chance that Flash VEP will distinguish between positive class and negative class since AUC near to 1 is good measure of separability.

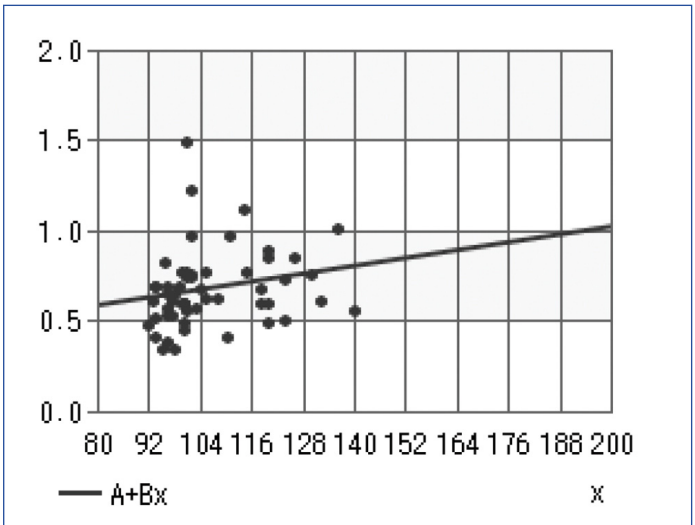
DISCUSSION

In this study, significant difference between latency of P100 of right eye and left eye among cases and control group was seen. N75-P100 amplitude did not show any significant changes. VRT showed significant difference between cases and control group.

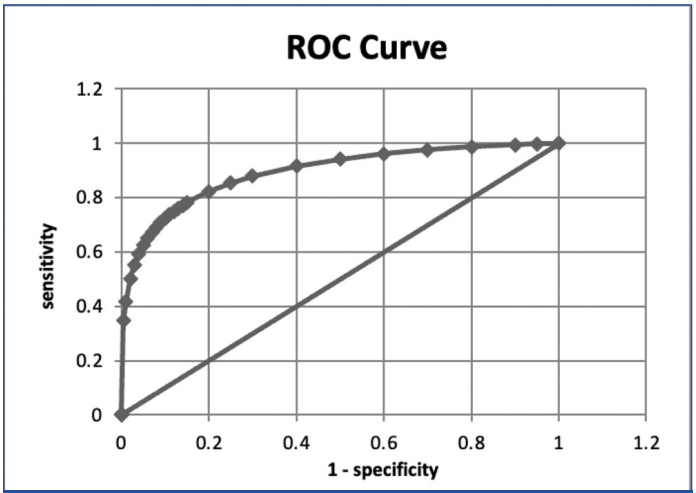
VEP test was conducted in the age group of 3-15 years. This age group was selected as final stages of maturation of the visual

Latency test	Present		Absent
Present	21 (a)		1 (b)
Absent	9 (c)		29 (d)
Total	30		30
Parameter	Values		99% Confidence Interval
Sensitivity	70%		(0.442, 0.958)
Specificity	96.66 %		(0.857, 1.06)
Parameter	**Values**	**99% Confidence Interval**	**Interpretation**
Positive predictivity of the test	95.45%	(0.847, 1.053)	This is good diagnostic tool for identifying the patients of Sickle Cell Disease (SCD) with Visual Evoked Potentials (VEP) changes as positive predictive value is 95.45% but it is not good for ruling out patients.
Negative predictivity of the test	76.31%	(0.54, 0.98)	

[Table/Fig-7]: Sensitivity and specificity for detecting changes in P 100 latency; Positive predictive value and negative predictive value.



[Table/Fig-8]: Linear regression graph of Visual Reaction Time (VRT) with P100 latency right eye.



[Table/Fig-9]: Receiver Operating Characteristic (ROC) curve. Area Under Curve (AUC): 0.835.

pathways is at 3-5 years [24] and that after 6-12 months of age, only little maturational change occurs in LED VEPs [25]. The difference in N75-P100 amplitude for right and left eye was statistically insignificant [Table/Fig-1], even though the amplitude was reduced. When the N75-P100 amplitude in controls is compared with normal subjects of other studies, it is increased, since the LED goggles flashed red coloured flashes, which is mentioned to produce amplitude of flash VEP which is up to twice than that produced by flashing white light [14,26]. The mean values of control group are consistent with the findings of Kothari R et al., (97.7±5.61 Right eye, 97.67±4.51 left eye) and Al Sadik FNA (98.5±4.65 right eye, 98.3±4.77 left eye) [27,28].

The VER is the averaged electrical response of the visual cortex. It is evoked by repetitive visual stimulation. Its use is to utilise as an indicator of retino-cortical conduction and the degree of synchronous conduction at the visual cortex. Due to the cortical magnification factor, the occipital lobe receives a disproportionately large projection from foveal retina representing the reception of message arising from the central retinal zone [29].

The VEP amplitude changes are due to axonal pathology without demyelination and that a pure delay without amplitude reduction is a characteristic of a demyelinating optic neuropathy [30,31]. Neurophysiological tests have proven to be objective and sensitive tools for the detection of even subclinical central nervous system impairments [32,33]. Even in absence of any symptoms or signs of clinical optic nerve involvement, VEP can detect optic nerve conduction delay. In some studies, VEPs showed conduction delay but less marked changes in amplitude [31,34].

The mean VRT (in sec) in cases was 0.77±0.25 and in controls it was 0.59±0.12, the difference being statistically significant. In a paediatric study, mean VRT was reported as 0.26±0.067 [35]. In study by Kiselev S, mean VRT in five-year-old children were 580 ms±144 and six-year-old were 467 ms±85 [36]. In the present study, there were four colour switches to be operated, any one at a time. It is not just a single key to be pressed every time. In this study, when the operator/researcher pressed a red-light button, the light on the subject's side would be on, but the subject had to recognise the colour and then switch off the light by pressing the corresponding switch below the colour switch.

The mean VRT of 590 ms can be hence explained on the mechanism of ventral and dorsal visual processing stream [37,38]. There are two processing streams in visual cortex: the ventral stream (vision for perception) which looks after the identification of an object and a dorsal stream (vision for action) which takes care of relative special position of the eye. The dorsal and ventral pathways have different latencies, but comparable differences in latencies between different areas. As we move through visual pathways from retina to primary visual cortex to visual association area, there is a change in the response characteristics of the neurons. Higher up in the pathway, neurons have larger receptive fields and they respond to more complex stimuli and possess greater response latencies. The properties of having larger receptive fields and response to more complex stimuli result from the processing and integration of visual information in the preceding areas. The increased response latencies are due to the time for transmission of information through the brain and the time for some degree of processing at each stage. Visual stimuli are selective for specific stimuli and show this specificity at the initial stage, so that the cells at the previous stage carry out some degree of processing before passing information to the next stage. It seems that a neuron continuously passes on information as it processes it, instead of completing the processing and then passing on the information. At a synapse, different factors could influence this processing of information. The feed-forward information (incoming information from the preceding areas) may involve feed-back mechanisms playing a modulating role, in the form of lateral inhibition, followed by intracortical feedback and feedback also from higher centres. In this mechanism, simple stimuli detection would take 200 ms, whereas, the activity of recognition and discrimination of patterns would lengthen the RT to 400-500 ms [37].

When P100 latency right and left eye was correlated with VRT, the graph was linear and there was weak positive correlation which shows that as P100 latency increases, VRT increases. This is explained by the fact that in VRT, firstly light has to pass from rods and cones

to relay in optic nerve, through visual pathway to the striate cortex and then through series of impulses to result in motor response of contraction of muscles and pressing of the off switch [37-39].

In order to provide justification for the predictive utility of VEP and VRT to detect early subclinical eye changes in paediatric patients of SCD, following points are put forward: In guidelines 9B, it is mentioned that p<0.01 as a stringent measure of abnormality must be followed. In the present study, significance was determined with p<0.01 [21]; also mentioned that the values of latency or amplitude measured should be well beyond the normal data collected on age matched normal subjects in the laboratory. In this study, there is statistical difference between latency of right and left eye in cases and controls. Amplitude showed no statistical difference between cases and controls; the upper limit of normal for latencies, amplitudes and interside differences is 2.5 to 3 SD above the control mean value, left-sides being tested separately and interside differences were labelled as a criterion for abnormality [40]. In this study, the upper limit is well beyond the limit of 3 SD of mean value. Regression coefficient was 2.212 which means that P 100 latency of right eye will increase 2.21 times per unit episode of crisis and 2.209 means P100 latency will increase 2.209 times per unit episode of crisis. The tool is more specific (96.66%) which shows that it is less likely that an individual with positive test will be free from disease and positive predictive value shows the probability that patient with a positive (abnormal) test actually has the disease. AUC was 0.835 i.e., 80% chance that Flash VEP will distinguish between positive class and negative class since AUC near to 1 is good measure of separability.

The paediatric patients of SCD also did not report any complaints and ophthalmological examination was normal. Children are not always accurate observers in change in visual perception and there is a need to monitor disease progression and/or effects of any therapy, for which VEPs play an important role [25]. The positive correlation between P100 latency and VRT suggest that as P100 latency increases, VRT also increases. The common factor in these two variables is the path through which it travels to reach its destination, involving the optic nerve. Since both these variables have increased the optic nerve is involved subclinically.

This is a pioneer study to utilise VEP as a prediction tool and associated VRT for the early detection of subclinical eye changes in paediatric patients of SCD. The present study deals with sickle cell patients right from 3-15 years so that subclinical changes if any can be picked up and the patients can be monitored for eye changes and the health care providers can '**catch them young**' regarding the ocular changes.

Limitation(s)

There was unequal availability of SS (n=24) and AS (n=6) pattern of sickle cell patients due to which the correlation of P100 latency with pattern could not be established.

CONCLUSION(S)

The present study showed prolongation of P100 latency with no significant changes in inter-ocular difference and N 75-P100 amplitude. VRT was also prolonged in SCD cases. Based on the findings of sensitivity, specificity, PPV and NPV, Beta coefficient, VEP can be used as predictive tool for early eye changes in sickle cell patients in the absence of evident symptoms and ocular findings. This point toward a subclinical derangement in the visual pathway which should be monitored.

Acknowledgment

We would like to acknowledge the Head of department of ophthalmology Dr. Sachin Daigavane for his cooperation in evaluation of eye changes. We also like to thank the nursing staff, social worker Mr. Vishal Lokhande and statistician for all the logistic support provided for the conduction of study.

REFERENCES

[1] Kamble M, Chaturvedi P. Epidemiology of sickle cell disease in a rural hospital of central India. Indian Paediatrics. 2000;37:391-96.
[2] Colah RB, Mukherjee MB, Martin S, Ghosh K. Sickle cell disease in tribal populations in India. Indian J Med Res. 2015;141:509-15.
[3] Kate SL, Lingojwar DP. Epidemiology of sickle cell disorder in the state of Maharashtra. Int J Hum Genet. 2002;2(3):161-67.
[4] The management of sickle cell disease. National Institutes of Health. National heart, Lung and Blood Institute. Division of Blood Diseases and resources. NIH publication No 02-2117. 2002. Cited on Jan 2015. Available from: https://www.nhlbi_nih.gov/files/docs/ guidelines/sc_mngt.pdf
[5] Fadugbagbe AO, Gurgel RQ, Mendonca CQ, Cipolotti R, dos Santos AM, Cuevas LE. Ocular manifestations of sickle cell disease. Ann Trop Paediatr. 2010;30:19-26.
[6] Popma SE. Ocular manifestations of sickle hemoglobinopathies. Clin Eye Vis Care. 1996;8:111-17.
[7] Jackson H, Bentley CR, Hingorani M, Atkinson P, Aclimandos WA, Thompson GM. Sickle retinopathy in patients with sickle trait. Eye. 1995;9:589-93.
[8] Negi B, Bhardwaj P, Sharma S, Sharma M, Thakur P. Visual evoked potential in children with thalassaemia. IJRR. 2020;7(1):439-42.
[9] Misra UK, Kalita J. Visual evoked potential-Anatomical basis of visual evoked potential. Clinical Neurophysiology. 1st Edition. Elsevier. New Delhi; 1998.250-251.
[10] Walsh P, Kane N, Butler S. The chemical role of evoked potentials. J Neurol Neurosurg Psychiatry. 2005;76(suppl II):ii16-ii22
[11] Odom JV, Bach M, Brigell M, Holder GE, McCulloch DL, Mizota A, et al. ISCEV standard for clinical visual evoked potentials (2016 update). Doc Ophthalmol. 2016;133:01-09.
[12] Bhatt D. Electrophysiology for ophthalmologist (A practical approach). J Clin Ophthalmol Res. 2013;1(1):45-53.
[13] Abdelkar M. The effect of change of check size and wavelength of stimulus on visual evoked potential parameters. Delta J Ophthalmol. 2016;17(2):779.
[14] Subramanian SK, Gaur GS, Narayan S. Low luminance/eye closed and monochromatic stimulation variability of visual evoked potential latency. Ann Indian Acad Neurol. 2013;16:641-48.
[15] Balakrishnan G, Uppinakudru G, Singh GG, Bangera S, Raghavendra AD, Thangavel D. A comparative study on Visual choice reaction time for different colors in females. Neurol Res Int. 2014;2014:301473.
[16] Bhabhor MK, Vidja K, Bhanderi P, Dodhia S, Kathrotia R, Joshi V. A comparative study of visual reaction time in table tennis players and healthy controls. Indian J Physiol Pharmacol. 2013;57(4):439-42.
[17] Solanki J, Joshi N, Shah C, Mehta HB, Gokhale PA. Study of correlation between auditory and visual reaction time in healthy adults. Int J Med Pub Health. 2012;2:36-38.
[18] Lupp U, Hauske G, Wolf W. Different systems for the visual detection of high and low special frequencies. Photogr Sci Eng. 1978;22:80-84.
[19] Shelton J, Kumar GP. Comparison between auditory and visual simple reaction times. Neuroscience and Medicine. 2010;1:30-32.
[20] Jasper HH. The ten-twenty electrode system of the international federation. Electroenceph Clin Neurophysiol. 1958;10:371-75.
[21] Epstein CM. American Clinical Neurophysiology Soceity. Guideline 9B: Guidelines on Visual evoked potentials. Recommended standards for Visual evoked potentials. J Clin Neurophysiol. 2006;23(2):138-56.
[22] Cohen J. Statistical power analysis for the behavioural sciences. 2nd Ed. USA. Lawrence Erlbaum Associates; 1988. 20-23.
[23] Sawilowsky SS. New effect size rules of thumb. JMASM. 2009;8(2):597-99.
[24] Voitenkov V, Andrey K, Skripchenko N. Flash visual evoked potentials in healthy infants. Int J Ophthalmol. 2016;16(4):614-16.
[25] Taylor MJ, McCulloch DL. Visual evoked potential in infants and children. J Clin Neurophysiol. 1992;9(3):357-72.
[26] Givre SJ, Arezzo JC, Schroeder CE. Effects of wavelength on the timing and laminar distribution of illuminance evoked activity in macaque V1. Vis Neurosci. 1995;12:229-39.
[27] Kothari R, Singh R, Singh S, Jain M, Bokariya P, Khatoon M. Neurophysiologic findings in children with spastic cerebral palsy. J Pediatr Neurosci. 2017;5:12-17.
[28] Al-Sadik FNA. Visual evoked potential in children with spastic cerebral palsy. Medical Journal of Babylon. 2012;9(2):379-84.
[29] Ikeda H, Tremain KE, Sanders MD. Neurophysiological investigation in optic nerve disease: combined assessment of the visual evoked response and electroretinogram. Br J Ophthalmol. 1978;62:227-39.
[30] Bass SJ, Sherman J, Bodis-Wollner I, Nath S. Visual evoked potentials in macular disease. Invest Ophthalmol Vis Sci. 1985;26:1071-74.
[31] Holder GE. Electrophysiological assessment of optic nerve diseases. Eye. 2004;18:1133-43.
[32] Verrotti A, Blasetti A, Chiarelli F. Visual evoked potentials and diabetic polyneuropathy. Neurol Sci. 2006;27:299-300.
[33] Han HS, Kim H, Lee SS. A 5-year follow-up visual evoked potentials and nerve conduction study in young adults with type I diabetes mellitus. Neurology Asia. 2016;21(4):367-74.
[34] Halliday AM, Mc Donald WI, Mushin J. Visual evoked response in diagnosis of multiple sclerosis. BMJ. 1973;4:661-64.

[35] Bhakare P, Vinchurkar A. Study of visual reaction time in autism. IJMRPS. 2015;2(7):49-51.
[36] Kiselev S. Age-related differences in processing speed in preschool children. The Open Behavioral Science Journal. 2015;9(Suppl 1-M4):23-31.
[37] Tovee MJ. How fast is the speed of thought? Curr Biol. 1994;4(12):1125-27.
[38] Merigan WH, Maunsell JHR. How parallel are the primate visual pathways? Annu Rev Neurosci. 1993;16:369-402.
[39] Oram MW, Perrett DI. The time course of neural responses discriminating between different views of the head and face. J Neurophysiol. 1992;68:70-84.
[40] Oken BS, Phillips TS. Evoked potentials. Clinical Encyclopedia of Neuroscience. 2009;4:19-28.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Physiology, AIIMS, Raipur, Chhattisgarh, India.
2. Ex-Provice Chancellor, DMIMS, Nagpur; Exprofessor, Physiology, Department of Physiology, JNMC Sawangi (M), Wardha, Maharashtra, India.
3. Additional Professor, Department of Pediatrics, AIIMS, Raipur, Chhattisgarh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Arunita Tushar Jagzape,
Department of Physiology, 3rd Floor, AIIMS, Raipur, Gate No. 5, Medical College Building, GE Road, Raipur, Chhattisgarh, India.
E-mail: arunitaj4@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 17, 2022
- Manual Googling: Nov 18, 2022
- iThenticate Software: Dec 15, 2022 (12%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 31, 2022**
Date of Peer Review: **Oct 31, 2022**
Date of Acceptance: **Dec 16, 2022**
Date of Publishing: **Apr 01, 2023**