Article • Visual Evoked Potential in Nepalese Patients with Oculocutaneous Albinism: A Case Series

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ABSTRACT

Purpose: Visual evoked potential (VEP) is an important non-invasive tool used to augment the functions of the visual system. The present study aims to present the VEP recorded among Nepalese subjects with oculocutaneous albinism (OCA) and its correlation with clinical findings.

Methods: In a cross-sectional study, 10 consecutive subjects with OCA and 10 age-/sex-matched normal subjects were selected for a pattern reversal VEP test using the Retiscan Roland electrophysiological diagnostic system. Apart from VEP, OCA subjects' anterior and posterior segments were examined to record clinical findings. Contrast sensitivity with the Pelli-Robson chart, colour vision with the Farnsworth D-15 test, stereopsis with the Titmus vectographic plates, and cycloplegic refraction were also performed. Statistical analysis included paired t-test, independent sample t-test, and multiple linear regression analysis.

Results: Clinical OCA features seen in study patients included horizontal pendular nystagmus in seven subjects, strabismus in four subjects, iris transillumination in seven subjects, disc hypoplasia in two subjects, and macular hypoplasia in four subjects. The mean VEP amplitudes were found to be significantly lower in subjects with albinism than in normal subjects in both right and left eyes for all frequencies. Strabismus ($p<0.001$ for N75-P100, low frequency; $p<0.001$ for N75-P100, high frequency; and $p=0.021$ for P100-N135, high frequency) and nystagmus ($p=0.004$ for P100-N135, high frequency and $p=0.044$ for P100-N135, low frequency) were significantly correlated with the amplitudes of pattern VEP. Mostly, P100-N135 high frequency was associated with clinical findings.

Conclusion: The amplitude of pattern reversal VEP is significantly reduced in albinism, which is correlated with strabismus and nystagmus.

Keywords: contrast sensitivity, nystagmus, oculocutaneous albinism, VEP, visual functions

Introduction

The absence or reduction of melanin in albinism has severe impact in the development of the eye and visual system, especially during the development of the visual pathway. This induces clinical manifestations such as foveal hypoplasia, strabismus, nystagmus, photophobia, and refractive errors,[1-4] resulting in impairment of visual functions and visual disabilities.[5]

Distance visual acuity is significantly affected in these patients, along with the other visual functions. The development of the visual system that occurs in subjects with albinism is different from those with a normal system because of abnormal decussation of optic

nerve fibers at the level of the optic chiasm and subsequent projection to the visual cortex.[6] This leads to subnormal cortical responses to visual stimuli.[7-9]

Evoked potentials are non-invasive studies that measure the electrophysiological response of the nervous system to different sensory stimuli, including visual evoked potentials (VEP).[10] The VEP represents the response of the visual cortex to stimuli presented in the middle of the visual field. For VEP responses to occur, the stimulus must reach the retina, be detected by the photoreceptors, and be transmitted via the optic nerve and optic tract to the thalamus (lateral geniculate nucleus) and further to the visual cortex via the optic radiations. Any disturbance or defect anywhere in this chain of events may change the form and/or latency of the response recorded by the electrodes above the primary visual cortex. Hence, VEP mirrors the function of the visual system up to primary cortex and serves as an important tool for studying the response to visual stimuli.[10,11] A previous study on albinism among Nepalese patients reported a broad spectrum of visual deficits that impair the visual functions.[12] We hypothesized that VEP recordings correlate with clinical findings in subjects with albinism and aim here to present the electrophysiologic recording by VEP among subjects with albinism and the correlation with clinical findings.

Materials and Methods

In a cross-sectional study, 10 subjects with known cases of oculocutaneous albinism (OCA) were recruited between January and December 2015 and were assessed at the B.P. Koirala Lions Centre for Ophthalmic Studies (BPKLCOS). They were referred by the Department of Dermatology, Tribhuvan University Teaching Hospital for detailed ocular examination after the diagnosis of OCA. Subjects with other ocular disorders, such as cataract and corneal disorders disrupting visual function, were excluded from the study.

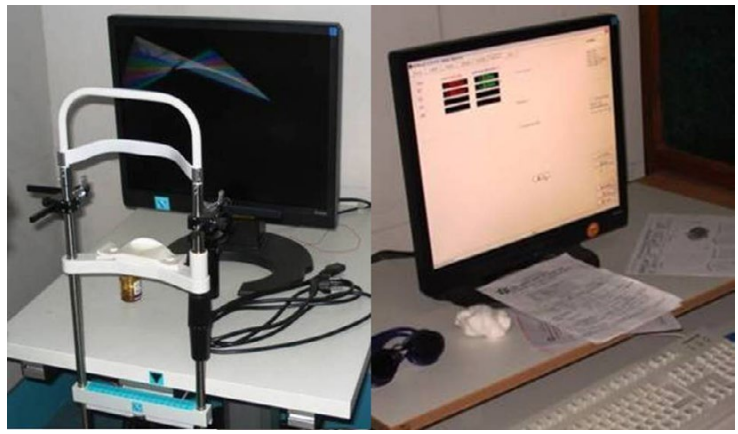

Figure 1. *Instrumentation used for pattern VEP*

All subjects received a detailed explanation of the procedures involved in the study and provided verbal informed consent. Approval for the study was received from the ethics review committee of the Institute of Medicine, Kathmandu. The research protocol adhered to the provision of the Declaration of Helsinki for research involving human subjects.

Unaided and best spectacle-corrected distance visual acuity was measured with an internally illuminated Snellen chart at six meters. Anterior segment examination and fundus examination after pupil dilation using two drops of 0.5% cyclopentolate at an interval of five minutes and a +90D Volk lens were carried out with the slit lamp. Foveal hypoplasia was considered present when there was an absence of foveal or perifoveal reflexes, an irregular distribution of capillary ends, and an absence of macular yellow.[13] Direct, consensual, and afferent pupillary light reflexes were assessed. Cycloplegic refraction was carried out in each subject, and subjective refraction was carried out three days after the cycloplegic refraction. Colour vision was assessed with the Farnsworth D-15 test at 40 cm, with refractive correction if required. Contrast sensitivity was assessed using the Pelli-Robson chart at one meter with refractive correction. For stereopsis, Titmus vectographic plates were used, and results were recorded in seconds of arc.

All subjects were screened for best-corrected visual acuity of 6/60 or better in order to select

for assessment with VEP. In our study, only 10 subjects (55.6%) met the vision criteria and enrolled for VEP examination. Ten emmetropic normal subjects formed the cohort of age- and sex-matched normal subjects and went for the VEP examination. The normal subjects comprised participants who had unaided visual acuity equal to 6/6, contrast sensitivity better than 1.80 on the Pelli-Robson chart, no manifest strabismus on cover test, normal anterior and posterior segments, stereopsis of 60 sec of arc or better, and normal color vision.

VEP was recorded using the RETI-scan Science VEP version 4.8.1 (Roland Consult Electrophysiological Diagnostic System, Brandenburg, Germany) without pupil dilation (Figure 1). Pattern reversal was used to record VEP consecutively in the right eye followed by the left eye, with the untested eye blocked by an occluder placed in the frame attached to the instrument in order to create a barrier between the untested eye and the VEP signal.

Standard silver-gold chloride electrodes were used and were placed according to the International 10/20 system.[14] The stimulation source used was a CRT monitor (17" colour monitor, luminance 80cd/m^2, high-contrast; Roland consult) with a frame frequency of 75 Hz. Stimulation calibration was done as provided by the RETI-scan software (Roland Consult). The pattern reversal stimuli changed phase abruptly: black to white and white to black at a specified number of reversals per second. They were modulated at a frequency of 1.5 Hz. Two pattern element sizes were used: checks of 1° and 0.25° per side.

The points on the skin where the electrodes would be placed were cleaned with the cleaning gel (Electrode PeNu-Prep; Roland Consult) specified for the purpose. The ground electrode was placed on the scalp, a reference electrode was placed on the forehead, and the active electrode was placed slightly above the inion with the help of conductive glue (Ten20 conductive EEG paste; Roland Consult). Less than 5 kΩ impedance was achieved in all cases. VEP measurements for all subjects were performed maintaining the same testing conditions.

All data were entered and analyzed with statistical package for the Social Science (SPSS) version 20. Descriptive variables included frequency, mean, and standard deviation. Paired t-test, independent sample t-test, and multiple linear regression analysis were used for data analysis. P values <0.05 were significant.

Results

Among 10 subjects with oculocutaneous albinism (OCA), there were six male subjects and four female subjects, with a mean age of 16.4±7.9 years (Table 1). Among 10 normal subjects, there were six males and four females with a mean age of 18.3±9.1 years. The mean age was insignificantly different (p=0.27) between albinism subjects and normal subjects. Mean spherical equivalent refractive error was 1.7±4.8 D (range: -8.25 D to +15.50 D). The mean amount of astigmatism was 2.7 D. Eight subjects had with-the-rule astigmatism.

Clinical features such as nystagmus were present in seven subjects, and all of them were horizontal pendular type. Strabismus was present in four subjects: intermittent exotropia in one case, alternate exotropia in another case, and alternate esotropia in two cases. Iris transillumination, disc hypoplasia, and macular hypoplasia were reported in seven, two, and four subjects, respectively (Table 1). A relative afferent pupillary defect was recorded in only two subjects with disc hypoplasia.

The mean contrast sensitivity as measured by the Pelli-Robson chart was 1.37±0.30 log units and 1.37±0.26 log units in the right eye and left eye, respectively, which are highly correlated (r=0.88, p<0.001). Mean contrast sensitivity was insignificantly reduced (p=0.15) in subjects with macular hypoplasia (1.20±0.32) compared to those without macular hypoplasia (1.48±0.25). Color vision was normal in all subjects.

Table 1. Clinical Data of Subjects with Albinism

CN	Age (years)	BCVA in RE	BCVA in LE	Macula	Optic Disc	Iris Trans-illumination	Nystagmus	Cover test	Stereo acuity (sec of arc)	Color Vision	CS in RE (log units)	CS in LE (log units)
1	15	20/30	20/30	normal	normal	absent	normal	AXT	3000	normal	1.70	1.65
2	12	20/120	20/80	hypoplasia	hypoplasia	present	horizontal pendular	no strab	absent	normal	1.65	1.75
3	33	20/40	20/40	normal	normal	present	normal	no strab	200	normal	1.70	1.65
4	5	20/200	20/200	hypoplasia	normal	present	horizontal pendular	IXT	3000	normal	1.05	1.20
5	23	20/120	20/80	hypoplasia	normal	present	horizontal pendular	no strab	800	normal	0.90	1.05
6	16	20/80	20/100	hypopigmented	normal	present	horizontal pendular	AET	absent	normal	1.50	1.35
7	11	20/70	20/70	hypopigmented	normal	present	horizontal pendular	AET	absent	normal	1.35	1.45
8	20	20/40	20/40	hypopigmented	normal	present	horizontal pendular	no strab	400	normal	1.60	1.45
9	19	20/60	20/80	hypopigmented	normal	absent	horizontal pendular	no strab	400	normal	1.05	1.20
10	10	20/100	20/100	hypoplasia	hypoplasia	absent	normal	no strab	3000	normal	1.20	1.00

CN=case number; BCVA=best-corrected visual acuity; AXT=alternating exotropia; IXT=intermittent exotropia; AET=alternating esotropia; CS=contrast sensitivity; RE=right eye; LE=left eye

Table 2. Latency of the Pattern VEP (ms) in Subjects with Albinism and Normal Subjects

Latency in milliseconds	Right Eye			Left Eye			Inter-eye difference		
	Albinism cases	Normal cohort	P value	Albinism cases	Normal cohort	P value	Albinism cases	Normal cohort	P value
N75, low frequency	72.4±10.82	76.2±10.28	0.53	73.8±8.57	77.0±7.31	0.49	-1.4±16.57	0.0±3.86	0.79
N75, high frequency	72.00±8.64	83.6±7.77	0.025*	74.0±10.11	80.60±6.70	0.21	-2.0±14.98	1.0±4.76	0.45
P100, low frequency	103.4±13.83	108±4.32	0.42	109±13.46	106.8±3.42	0.73	-5.6±18.38	1.1±5.63	0.22
P100, high frequency	109.8±10.73	108.8±3.03	0.84	118.6±6.57	109±3.50	0.014*	-8.8±8.74	0.1±5.17	0.007*
N135, low frequency	133.4±10.93	146.6±4.98	0.025*	155±35.65	144.6±5.90	0.54	-21.6±32.89	0.4±6.74	0.035*
N135, high frequency	147.8±22.13	147.8±2.95	1.0	167.3±30.45	142.2±7.16	0.10	-19.5±30.96	2.4±8.38	0.031*

* Significantly different from normal at p<0.05 by paired t-test

Table 3. Amplitudes of Pattern VEP (μV) in Subjects with Albinism and Normal Subjects

Amplitudes (μV)	Right Eye			Left Eye			Inter-eye difference		
	Albinism cases	Normal cohort	P value	Albinism cases	Normal cohort	P value	Albinism cases	Normal cohort	P value
N75-P100, low frequency	4.94±2.46	12.39±8.66	0.022*	4.07±2.95	12.54±8.17	0.01*	0.27±2.02	-0.15±2.12	0.86
N75-P100, high frequency	5.32±1.89	8.27±2.26	0.018*	4.13±2.45	11.91±7.01	0.006*	1.14±2.30	-0.64±4.87	0.09
P100-N135, low frequency	2.14±1.98	8.47±4.97	0.003*	3.37±2.97	8.35±5.63	0.04*	-1.22±3.78	0.13±1.80	0.59
P100-N135, high frequency	2.25±2.18	11.24±8.58	0.007*	3.40±2.24	15.05±12.83	0.013*	-1.16±3.22	-3.82±4.40	0.49

* Significantly different from normal at p<0.05 by paired t-test

VEP findings

Table 2 presents a comparison of the latency of the pattern VEP between OCA subjects and normal subjects. Except for the mean latency of the N75 wave at higher frequency for the right eye (p=0.025) and the mean latency of the P100 wave at higher frequency for the left eye (p=0.014), latencies for other frequencies were statistically insignificant. However, the latency of the inter-eye difference for P100 high-frequency (p=0.007), N135 low-frequency (0.035), and N135 high-frequency (0.031) was significant.

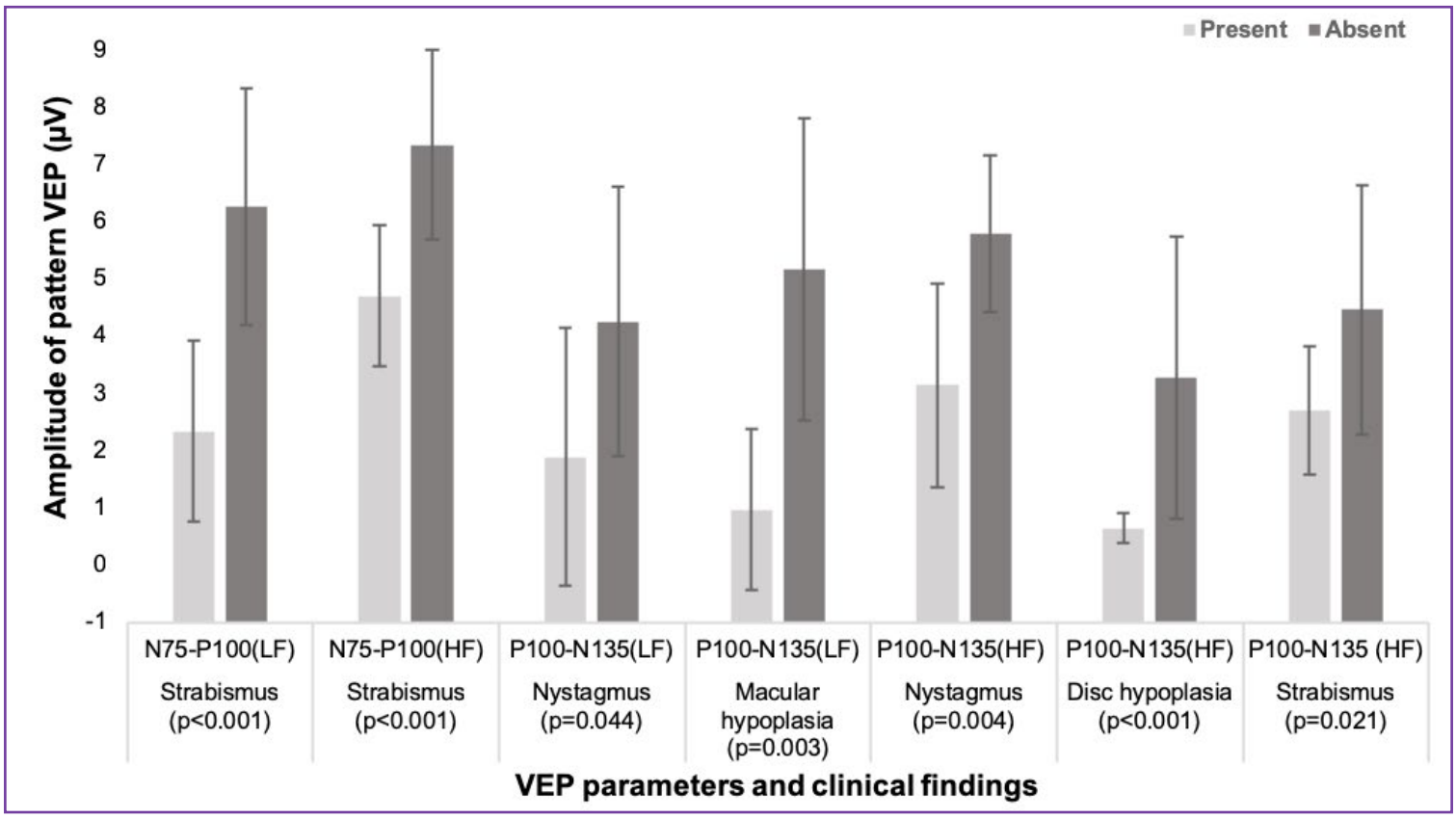

Figure 2. *Amplitude of pattern VEPs (μV) shows significant difference by independent t-test at p<0.001 for N75-P100, low frequency; p<0.001 for N75-P100, high frequency; and p=0.021 for P100-N135, high frequency in cases with strabismus; p=0.004 for P100-N135, high frequency and p=0.044 for P100-N135, low frequency in nystagmus; p=0.003 for P100-N135, low frequency in macular hypoplasia; and p<0.001 for P100-N135, high frequency in disc hypoplasia.*

Table 3 presents the amplitudes of the pattern VEP in subjects with albinism and normal subjects. The mean amplitudes of the N75-P100 wave at lower frequency, the mean amplitudes of the N75-P100 wave at higher frequency, the mean amplitudes of the P100-N135 wave at lower frequency, and the mean amplitudes of the P100-N135 wave at higher frequency were found to be significantly lower in subjects with albinism than in normal subjects in both the right and left eyes. However, the inter-eye difference compared between albinism and normal subjects was insignificant for all amplitudes.

Association between clinical findings and pattern VEP is presented in figures 2 and 3. Regarding amplitude of pattern VEP in albinism, strabismic subjects (p<0.001 for N75-P100, low frequency; p<0.001 for N75-P100, high frequency and p=0.021 for P100-N135, high frequency) and subjects with nystagmus (p=0.004 for P100-N135, high frequency and p=0.044 for P100-N135, low frequency) had lower amplitudes of pattern VEP. Mostly, P100-N135 (low-frequency) and P100-N135 (high-frequency) were associated with clinical findings. Regarding the latency of pattern VEP, P100 high-frequency was significantly associated with strabismus (p=0.003), nystagmus (p=0.017), and macular hypoplasia (p<0.001).

Discussion

The present study shows the association between OCA and VEP findings. Patients can be referred for electrophysiological testing upon clinical suspicion or a family history of albinism when clinical signs are less definitive. However, in the present study, all subjects were clinically confirmed cases of OCA. In the study, the sample size is small. However, these patients represent a clinical cross-section of patients with OCA as they were total hospital attendees during the entire year of 2015.

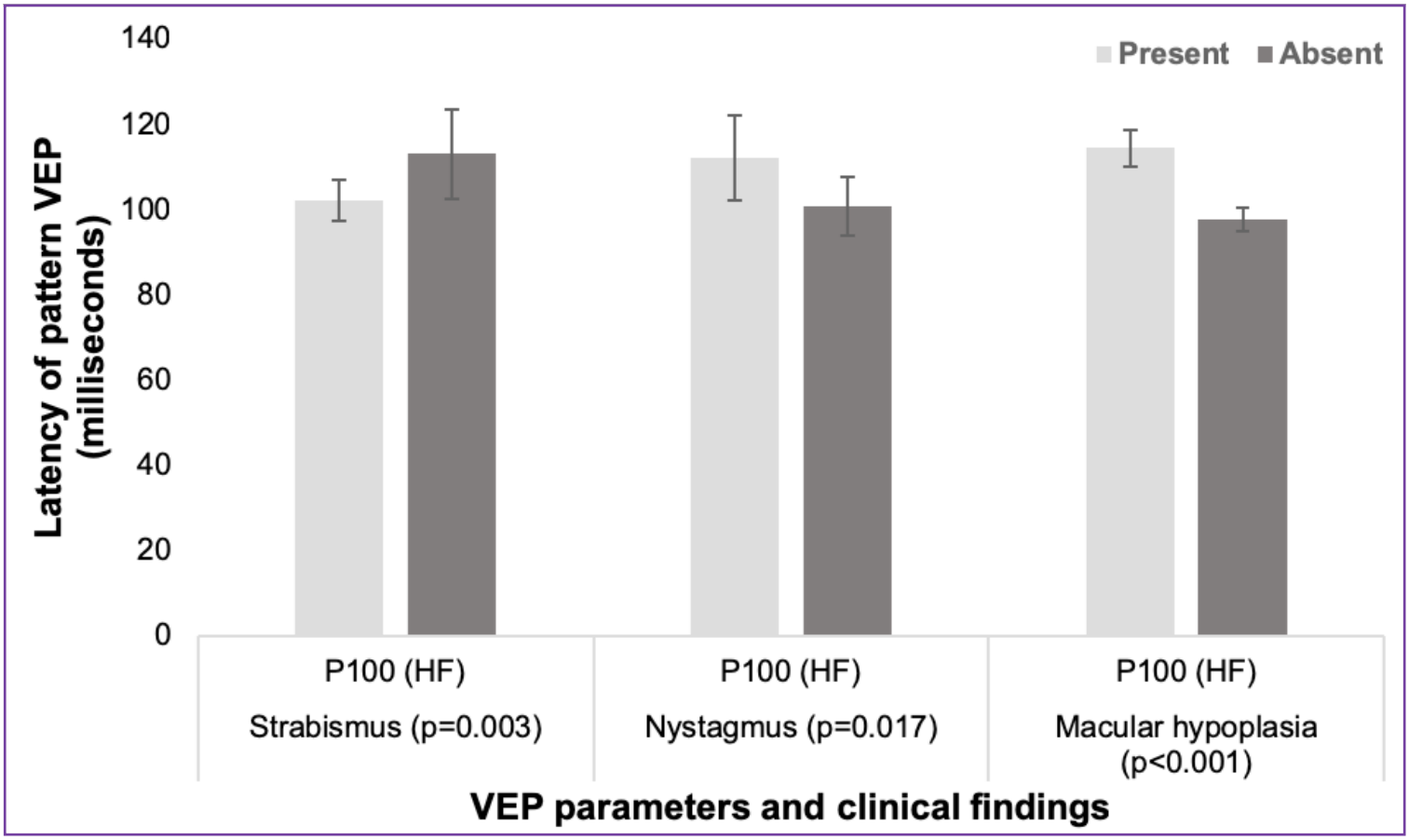

Figure 3. *Latency of pattern VEPs (ms) shows a significant difference by independent t-test at p=0.017 for nystagmus; p<0.001 for macular hypoplasia; and p=0.003 for strabismus.*

The VEP data presents reduced amplitude of pattern reversal VEP in OCA, with significant correlation between the VEP amplitude and clinical findings. Likewise, the inter-eye difference in the latency of pattern VEP above P100, high-frequency is the only significant difference between OCA and normal subjects (Table 2). However, the amplitude of pattern VEP for all frequencies is significantly different between OCA and normal subjects (Table 3). Regarding correlation between clinical findings and VEP, strabismus, followed by nystagmus, delivered the highest correlation with VEP as it was compared to individual clinical features (Figures 2 and 3). Regarding the proportion of cases with iris transillumination combined with strabismus, three out of four cases with strabismus were also noted to have iris transillumination. However, the proportion was similar for subjects without strabismus and iris transillumination as well; among six cases without strabismus, four cases reported iris transillumination. Similarly, six subjects had both nystagmus and iris transillumination, and two subjects had none (Table 1). The findings further confirm that amplitude measurement was more sensitive than latency in our study using pattern reversal VEP. Contrary to our findings, Dorey et al[5] reported that VEP latency is more sensitive than amplitude asymmetry index. They also reported a high correlation between VEP latency differences between hemispheres and clinical features, with foveal hypoplasia showing the highest correlation. There are many differences between our study and the Dorey et al. study. In our study, pattern reversal VEP was used, and no hemispheric assessment was performed, whereas pattern appearance VEP and flash VEP were used in the Dorey et al study, along with the hemispheric assessment. We have a significantly lower number of cases than the other study, and we are also aware that pattern reversal VEP is reported to be a weaker predictor than pattern

onset VEP, especially in nystagmus.[15-17] It has been a notable limitation of our study because pattern reversal VEP is the only available technique in our clinical set up. Thus, based on our study, careful observation and prediction is necessary to interpret the findings of VEP, especially in nystagmus. It is clear that VEP is particularly valuable to the clinician in cases where clinical signs are less evident, such as intracranial misrouting in albinism, which is depicted by the magnitude of VEP asymmetry.[7-9,18] Lack of hemispheric assessment in our study has been a severe limitation to the judgment of intracranial misrouting in our subjects. The present study implies that all of the patients with albinism have recorded significantly reduced amplitudes compared to the normals and that VEP amplitudes have been well correlated with contrast sensitivity and stereopsis (among visual functions) and strabismus (among clinical findings).

In the study, most of the subjects (nine cases) were below the age of 25 years. There was only one patient with albinism who was aged 33 years and had apparently normal clinical findings except iris transillumination. Thus, the effect of age on VEP findings may be less conclusive in our study for reduced VEP recording.[19] There are other several limitations that hinder the generalization of the findings. They are inconsistently having small samples, clinical tests like optical coherence tomography findings to quantify macula- and optic nerve head-related clinical findings, and perimetry to detect any defects in optic nerve and visual pathway.

Conclusion

The amplitude of the pattern reversal VEP is significantly reduced in albinism, which is correlated with contrast sensitivity, stereopsis, and strabismus.

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