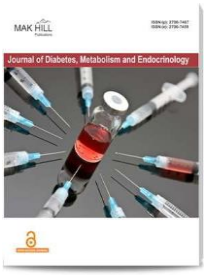

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Research Article

Correlation of Visual Evoked Potential and Optical Coherence Tomography Findings in Adult Patients of Iron Deficiency Anaemia.

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Abstract: Background: Iron deficiency anaemia (IDA) can affect the visual pathway at both a functional (electrophysiological) and a structural (retinal) level. Visual evoked potential (VEP) and optical coherence tomography (OCT) are complementary non-invasive tools, and correlating their findings with each other and with the anaemia/iron profile may clarify how closely functional and structural involvement track together and relate to the severity of iron deficiency. ***Objective:*** To correlate the findings of visual evoked potential and ocular coherence tomography in adult patients of iron deficiency anaemia with haemoglobin less than 10.9 g/dl. ***Methods:*** Forty-four newly diagnosed adult patients of IDA (Hb < 10.9 g/dl, age 18–45 years) and 44 age- and sex-matched healthy controls underwent pattern-reversal VEP (N75, P100, N145 latencies and P100 amplitude, RMS EMG EP MK2 system) and spectral-domain OCT (RTVue, Optovue Inc.; RNFL thickness in four quadrants and average, and central macular thickness) in both eyes, along with haemoglobin and iron-profile estimation (serum iron, TIBC, serum ferritin, transferrin saturation). Pearson's correlation coefficient (r) was calculated between VEP parameters and the anaemia/iron profile, and separately between OCT parameters and the anaemia/iron profile, on SPSS v20; the pattern of VEP and OCT change was then compared to assess concordance between the two modalities. ***Results:*** Both VEP latencies (N75, P100, and N145 in the left eye) and OCT parameters (RNFL thickness in all quadrants and central macular thickness, both eyes) were significantly abnormal in IDA cases compared with controls, indicating that functional (electrophysiological) and structural (retinal) involvement of the visual pathway occurred together in the same cohort of IDA patients. Correlation of VEP latencies with haemoglobin/iron indices was mild to moderate, with a strong positive correlation between right-eye N75 latency and haemoglobin, and between right-eye P100 latency and TIBC. Correlation of OCT parameters with haemoglobin/iron indices was similarly mild to moderate, with the strongest associations seen for haemoglobin with central macular thickness. A direct parameter-to-parameter correlation between VEP and OCT values was not computed in this dataset; concordance between the two modalities was instead evident from the shared direction and statistical significance of change relative to the anaemia/iron profile. ***Conclusion:*** VEP and OCT abnormalities occur together in adult patients of IDA and follow a broadly concordant pattern of worsening with a more deranged iron profile, supporting the combined use of these two non-invasive modalities one functional, one structural for comprehensive early evaluation of visual pathway involvement in iron deficiency anaemia.

Keywords: Iron deficiency anaemia; Visual evoked potential; Optical coherence tomography; Correlation; Retinal nerve fibre layer.

INTRODUCTION

Anaemia is a condition in which the number of red blood cells (RBCs) and, consequently, their oxygen-carrying capacity is insufficient to meet the body's physiological needs.[1] It affects an estimated 2.36 billion individuals globally, especially women and children.[2] The World Health Organization defines anaemia as a blood haemoglobin concentration below 13 g/dl in men and below 12 g/dl in women, and further classifies it as mild, moderate or severe according to the degree of haemoglobin reduction.[3] In India, national guidelines under the Anemia Mukt Bharat programme have adopted similar age- and sex-specific cut-offs to standardise screening and management across the population.[4] According to the National Family Health Survey-4 (NFHS-4), 58.4% of children aged 6–59 months, 53.1% of non-pregnant women, 50.3% of pregnant women and 22.7% of men aged 15–49 years were anaemic in India.[5] The aetiology of anaemia is multifactorial but is, for the most part, preventable, and includes inadequate dietary intake, poor living conditions and a high burden of infections such as malaria and intestinal parasitosis.[6]

Iron deficiency anaemia (IDA), the commonest nutritional cause of anaemia worldwide, is confirmed biochemically by a reduced serum iron and serum ferritin, an increased total iron binding capacity (TIBC) and a reduced transferrin saturation.[7] Because IDA in adults frequently has an insidious onset, the biochemical diagnosis is often delayed by months or years,

allowing time for iron-dependent tissues, including the central nervous system and the retina, to be affected well before the anaemia is recognised clinically.

Iron plays a key role in central nervous system (CNS) functions such as myelination, synaptogenesis and the synthesis of neurotransmitters including dopamine, catecholamines, serotonin and possibly GABA, and impulse transmission along the visual pathway may therefore be affected by iron deficiency.[8–10] Delayed myelination and demyelination due to iron deficiency have been shown to increase the latency and decrease the amplitude of the visual evoked potential (VEP) a non-invasive, objective measure of conduction along the optic pathway, recorded as the N75, P100 and N145 waveforms over the occipital cortex in response to a reversing checkerboard stimulus.[9,10] Prior studies, largely in infants and children, have reported prolonged VEP latencies in association with iron deficiency and have proposed VEP as a useful marker of subclinical visual pathway involvement and of response to iron therapy.[11,12]

Iron deficiency has also been linked to retinal dopaminergic dysfunction, thought to alter the receptive area of axons and ganglion cells that constitute the retinal nerve fibre layer (RNFL), and oligodendrocyte dysfunction can similarly compromise axonal and nerve fibre layer integrity.[13,14] Optical coherence tomography (OCT), a light-based, non-invasive imaging technique that provides high-resolution, in-vivo, cross-sectional images of the retina, allows precise, micron-level measurement of RNFL and macular thickness and has been used increasingly to detect and monitor such structural change.[15,16] A number of studies have reported significant RNFL and macular thinning in patients with iron deficiency anaemia, predominantly in children and women, generally in parallel with the severity of anaemia.[17]

VEP and OCT thus assess two distinct but potentially related facets of visual pathway involvement in iron deficiency anaemia one functional and electrophysiological, the other structural and imaging-based. Very few studies have combined VEP and OCT assessment in the same cohort of adult IDA patients, and fewer still have attempted to correlate the two sets of findings with the underlying anaemia/iron profile in a single analysis. Because IDA in adults often has an insidious onset with delayed diagnosis, establishing whether functional and structural markers of visual pathway involvement move together and how closely each tracks the severity of iron deficiency is relevant both for early detection and for using these tests as prognostic or monitoring tools during iron replacement therapy.

AIM AND OBJECTIVE

To correlate the findings of visual evoked potential and ocular coherence tomography in adult patients of iron deficiency anaemia with haemoglobin less than 10.9 g/dl.

MATERIALS AND METHODS

Study design and setting

This was a prospective, case–control study conducted in the Department of Physiology in collaboration with the Department of Medicine and the Regional Institute of Ophthalmology, Pt. B.D. Sharma PGIMS, Rohtak, after approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants in their own language before enrolment.

Study population

Subjects were divided into two groups:

- Group 1 (Cases): 44 newly diagnosed patients of iron deficiency anaemia (IDA) of either sex, aged 18–45 years, with haemoglobin < 10.9 g/dl, confirmed on serum iron studies.
- Group 2 (Controls): 44 age- and sex-matched healthy subjects.

Exclusion criteria: Chronic disorders (diabetes mellitus, cerebrovascular disease, Parkinsonism, multiple sclerosis, neuromuscular disorders, drug-induced neuropathy, smoking, alcoholism, malabsorption syndromes, chronic hepatic or renal disease); history of intake of drugs with known visual or neurotoxicity; history of loss of vision; altered sensorium or psychiatric illness; pregnancy; glaucoma or any macular pathology; and COVID-19-positive status at the time of testing.

Sample size

Sample size was calculated using the standard formula for comparison of means between two independent groups [$N = (Z_{1-}\alpha/2 + Z_{1-}\beta)^2(\sigma1^2 + \sigma2^2)/(\mu1 - \mu2)^2$], with $Z_{1-}\alpha/2 = 1.96$ (95% confidence) and $Z_{1-}\beta = 0.84$ (80% power), yielding a minimum of 44 subjects per group (total N = 88).

Clinical and biochemical assessment

Detailed history, general physical examination, complete haemogram and iron profile (serum iron, serum ferritin, TIBC and transferrin saturation) were recorded for every subject on a pre-designed proforma.

VEP and OCT recording

Pattern-reversal VEP was recorded on an RMS EMG EP MK2 system with standard occipital electrode placement (active Oz, ground Fz, references O1/O2), using a high-contrast (70%) checkerboard stimulus (8 × 8 min checks, reversal rate 1.5 Hz) viewed monocularly from 100 cm. Latencies of N75, P100 and N145, and the amplitude of P100, were recorded for each eye. OCT was performed on a spectral-domain system (RTVue, model RT100, Optovue Inc.) after pupillary dilatation; peripapillary RNFL thickness (superior, inferior, nasal, temporal and average) was recorded using the glaucoma protocol, and central macular thickness (CMT) was recorded using the MM6 macular mapping scan, in both eyes.

Statistical analysis

Data were entered in Microsoft Excel and analysed using SPSS version 20. Continuous variables are expressed as mean ± SD and compared between cases and controls using the unpaired Student's t-test; $p < 0.05$ was considered significant. Pearson's correlation coefficient (r) was calculated separately between (a) VEP parameters and haemoglobin/iron-profile indices, and (b) OCT parameters and haemoglobin/iron-profile indices, for cases and controls in each eye. $r < 0.3$ was taken as mild, 0.3–0.5 as moderate, and $r > 0.5$ as strong correlation. Because VEP and OCT were each correlated with the same haemoglobin/iron-profile dataset, the pattern of correlation for the two modalities could be compared to assess whether functional and structural change in the visual pathway moved in a concordant direction relative to iron status.

RESULTS

Eighty-eight subjects (44 cases, 44 controls) completed the study. The control group comprised 40 males and 6 females, while the case group comprised 13 males and 31 females.

Table 1. Baseline demographic and anthropometric characteristics of cases and controls (Mean ± SD)

Parameter	Cases (n=44)	Controls (n=44)	p-value
Age (years)	33 ± 7.4	32 ± 7.5	0.561
Height (m)	1.657 ± 0.186	1.620 ± 0.091	0.239
Weight (kg)	59.568 ± 6.308	60.602 ± 10.282	0.568
BMI (kg/m²)	21.715 ± 2.135	22.966 ± 2.549	0.015*

Age, height and weight were comparable between groups; BMI was significantly lower in cases than controls ($p = 0.015$).

Table 2. Comparison of haematological indices and iron profile between cases and controls (Mean ± SD)

Parameter	Cases (n=44)	Controls (n=44)	p-value
Haemoglobin (g/dl)	7.246 ± 1.468	13.800 ± 1.295	<0.0001*
Haematocrit (%)	24.674 ± 4.216	41.838 ± 4.169	<0.0001*
MCV (fL)	65.188 ± 9.728	89.125 ± 6.545	<0.0001*
MCH (pg)	18.710 ± 3.647	28.387 ± 2.175	<0.0001*
MCHC (g/dl)	27.255 ± 3.025	34.516 ± 3.768	<0.0001*
Serum iron (µg/dl)	22.685 ± 12.445	100.339 ± 37.989	<0.0001*
TIBC (µg/dl)	472.839 ± 65.20	351.662 ± 59.56	<0.0001*
Serum ferritin (µg/l)	6.297 ± 3.869	86.502 ± 134.459	<0.0002*
Transferrin saturation (%)	6.052 ± 3.383	38.914 ± 11.106	<0.0001*

All haematological indices and iron-profile parameters were significantly reduced in cases compared with controls, confirming the biochemical diagnosis of iron deficiency anaemia, except TIBC, which was appropriately elevated in cases.

Summary of VEP and OCT abnormalities in IDA

Table 3. Summary comparison of VEP and OCT parameters between cases and controls

Modality / Parameter	Eye	Cases vs Controls	p-value
VEP N75 latency	Left	Prolonged in cases	0.0140*
VEP N75 latency	Right	Prolonged in cases	<0.0001*
VEP P100 latency	Left	Prolonged in cases	<0.0001*
VEP P100 latency	Right	Prolonged in cases	<0.0001*
VEP N145 latency	Left	Prolonged in cases	0.0024*
VEP N145 latency	Right	Prolonged in cases	0.0573
VEP P100 amplitude	Both	Lower in cases	0.578 / 0.512
OCT RNFL (all quadrants, avg.)	Both	Thinner in cases	<0.0001*
OCT CMT	Both	Thinner in cases	<0.0001*

Both VEP latencies and OCT thickness parameters were significantly abnormal in IDA cases compared with controls, indicating that functional and structural involvement of the visual pathway occurred together in this cohort.

Correlation of VEP with the anaemia/iron profile

Table 4. Correlation (Pearson's r) of VEP latencies with haemoglobin and iron profile, left eye

Parameter	Group	N75	P100	N145
Hb	Cases	0.275	-0.139	0.134
	Control	-0.400	-0.160	0.166
S. Iron	Cases	0.057	-0.014	0.200
	Control	0.112	-0.161	0.025
TIBC	Cases	-0.247	-0.149	-0.257
	Control	0.015	0.039	0.147
S. Ferritin	Cases	0.028	0.118	0.252
	Control	0.022	0.087	0.290
Trans. Sat.	Cases	0.053	0.096	0.490
	Control	0.153	-0.010	0.059

Table 5. Correlation (Pearson's r) of VEP latencies with haemoglobin and iron profile, right eye

Parameter	Group	N75	P100	N145
Hb	Cases	-0.182	-0.043	-0.037
	Control	0.501	0.129	0.005
S. Iron	Cases	0.031	-0.179	0.034
	Control	0.217	0.002	0.220
TIBC	Cases	-0.037	0.318	0.028
	Control	-0.134	-0.065	0.063
S. Ferritin	Cases	0.153	-0.262	-0.170
	Control	0.020	0.056	-0.116
Trans. Sat.	Cases	0.080	0.052	-0.059
	Control	0.212	-0.099	-0.223

Correlation of OCT with the anaemia/iron profile

Table 6. Correlation (Pearson's r) of OCT parameters with haemoglobin and iron profile, left eye

Parameter	Group	Superior	Inferior	Nasal	Temporal	Average	CMT
Hb	Control	0.125	-0.134	-0.414	-0.283	-0.313	0.398
	Cases	-0.043	-0.095	-0.134	-0.033	-0.126	0.029
S. Iron	Control	0.138	-0.090	-0.100	-0.120	-0.038	-0.110
	Cases	-0.007	0.037	0.064	-0.059	0.004	-0.095
TIBC	Control	0.043	0.071	0.153	0.242	0.137	0.224
	Cases	0.047	0.088	-0.140	-0.097	-0.003	0.030
S. Ferritin	Control	0.050	-0.082	-0.047	-0.081	-0.086	-0.161
	Cases	0.134	0.054	0.138	-0.052	0.092	-0.158
Trans. Sat.	Control	0.074	-0.065	-0.200	-0.184	-0.222	0.069
	Cases	0.334	0.149	0.147	0.087	0.258	-0.278

Table 7. Correlation (Pearson's r) of OCT parameters with haemoglobin and iron profile, right eye

Parameter	Group	Inferior	Nasal	Temporal	CMT
Hb	Control	0.124	0.201	0.149	0.462
	Cases	0.031	0.056	-0.033	0.083
S. Iron	Control	0.053	0.211	0.047	-0.030
	Cases	-0.067	0.055	-0.073	-0.110
TIBC	Control	0.053	-0.030	-0.053	0.163
	Cases	0.014	0.047	0.088	-0.140
S. Ferritin	Control	0.124	0.197	0.149	-0.061
	Cases	-0.164	0.134	0.054	0.138
Trans. Sat.	Control	-0.145	-0.096	-0.073	-0.030
	Cases	-0.002	-0.003	-0.070	-0.308

r < 0.3 = mild correlation; 0.3–0.5 = moderate correlation; r > 0.5 = strong correlation. Positive values indicate a positive correlation, negative values a negative correlation.

Concordance between VEP and OCT findings

A direct parameter-to-parameter Pearson correlation between VEP latency/amplitude values and OCT RNFL/CMT values was not computed in this dataset; the correlative analysis was performed separately for VEP versus the anaemia/iron profile and for OCT versus the anaemia/iron profile. Comparing the two sets of results, both VEP latencies and OCT thickness parameters were significantly abnormal in the same cohort of IDA patients relative to controls, and both showed a similar overall pattern mild-to-moderate, often inconsistent correlation with individual iron indices, but a shared direction of worsening (longer VEP latency, thinner RNFL/CMT) as the iron profile became more deranged. This concordance in the direction and statistical significance of change, occurring in the same patients undergoing both tests, supports the interpretation that functional (electrophysiological) and structural (retinal) involvement of the visual pathway occur together in adult IDA, even though the magnitude of correlation with any single biochemical marker was not strong for either modality.

DISCUSSION

The present study is among the first to evaluate VEP and OCT together in adult patients of IDA and to correlate the findings of both with the anaemia/iron profile within the same cohort. Most previous work has examined either VEP or OCT in isolation, or has been conducted in infants and children rather than adults.

VEP acts as a dependable electrophysiological marker of CNS involvement in IDA: prolongation of N75 and P100 latencies (and N145 in the left eye) in the present study is consistent with reports by Sayorwan et al.,[18] Algarín et al.,[12] Monga et al.[11] and Sarici et al.,[19] all of whom linked prolonged VEP latency in iron deficiency to demyelination and impaired oligodendrocyte function.[9,10] In parallel, OCT demonstrated significant reduction in RNFL thickness across all quadrants and in central macular thickness, consistent with Koca et al.,[20] Cikmazkara et al.,[17] Basset et al.,[21] El-Gamal et al.[22] and Samant et al.,[23] who similarly reported RNFL and macular thinning in IDA and, in several cases, a relationship between the degree of thinning and the severity of anaemia.

Correlation analysis in the present study showed that neither VEP latency nor OCT thickness correlated strongly and consistently with any single iron-profile parameter across both eyes and both groups a finding also noted by several of the cited authors and attributable to the multifactorial determinants of both tests (for VEP: pattern size, contrast, luminance, refractive error, fixation; for OCT: axial length, disc size, individual anatomical variation) beyond iron status alone. Nonetheless, the direction of change for both VEP and OCT parameters was congruent with the underlying biological model iron deficiency impairing CNS myelination and retinal dopaminergic and structural integrity and both tests were abnormal in the same set of patients. This concordance is the practically important finding: it suggests that VEP and OCT are not detecting unrelated or discordant processes, but complementary functional and structural facets of the same underlying pathophysiological process, and that combining the two tests can strengthen confidence in early, subclinical detection of visual pathway involvement in adult IDA compared with either test used alone.

VEP and OCT, used together, are also potentially useful as prognostic and monitoring tools during iron supplementation, since variations in VEP latency and OCT-measured RNFL/CMT could each independently track treatment response even where they do not correlate strongly with each other or with a single biochemical index.

CONCLUSION

In adult patients of iron deficiency anaemia with haemoglobin less than 10.9 g/dl, both visual evoked potential and optical coherence tomography abnormalities were present together, each correlating mildly to moderately, and largely independently, with individual components of the anaemia/iron profile. The concordant direction of functional (VEP) and structural (OCT) change in the same patients supports the combined use of these two non-invasive tools for comprehensive early detection and monitoring of subclinical visual pathway involvement in adult iron deficiency anaemia.

Limitations

- A direct parameter-to-parameter correlation between VEP and OCT values was not computed in the original dataset; concordance was assessed indirectly through the shared direction and significance of change relative to the anaemia/iron profile.
- The sample size, though adequate as per a priori calculation, was relatively small; a larger cohort would allow more reliable correlation analysis.
- This was a case–control study; a longitudinal, pre- and post-treatment cohort design would better establish whether VEP and OCT changes track each other, and iron status, over time.

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