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Full Length Article

The clinical application of critical flicker fusion frequency in demyelinating optic neuritis

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ABSTRACT

Purpose: To investigate the application of critical flicker fusion frequency (CFF) in demyelinating optic neuritis (DON).

Methods: A cross-sectional study. A total of 127 eyes in 69 DON patients and 63 eyes in 33 healthy control (HC) groups were included between January 2021 to September 2021 from Department of Ophthalmology, PLA General Hospital. Patients underwent best-corrected visual acuity (BCVA), visual field, optical coherence tomography (OCT), flash visual evoked potential (F-VEP), and CFF examinations. The affected eyes were divided into aquaporins 4 (AQP4-), myelin oligodendrocyte glycoprotein (MOG-), and double negative DON according to serum antibody; mild, moderate, severe degree visual impairment according to BCVA $\geq$ 0.5, 0.1-0.5, $<$ 0.1; and 4 groups: $<$ 1, 1 ~$<$ 3, 3 ~ $<$ 6 and $>$ 6 months according to time interval from onset to CFF examination. One-way ANOVA was used to perform above subgroup analysis. The correlations between CFF and F-VEP peak time, peak value, BCVA and mean visual filed defect (MD) were analyzed in order via Pearson correlation analysis.

Results: he trichromatic values of red, green, and yellow in DON affected eyes were 21.83 $\pm$ 9.03, 23.66 $\pm$ 10.21, 24.09 $\pm$ 10.77 Hz, respectively, which was significantly reduced compared with the HC group (t = -14.82, -14.22, -14.00; $P < 0.001$). The subgroup analysis showed no significant difference between different antibody subtypes ($P = 0.914 < 0.848 < 0.604$), whereas, a significant decrease of CFF trichromatic value was found in severe visual acuity impairment group ($P < 0.001$). There was a significant difference in CFF- trichromatic values at different time points ($P < 0.001$), to be specific, CFF fluctuated under 20Hz within 3 months after onset and tended to be stable around 24-28Hz. Correlation analysis showed that the peak time of F-VEP (r = -0.486, -0.515, -0.526; $P <$ 0.001), BVCA (r = -0.640, -0.659, -0.642; $P < 0.001$), were negatively correlated with CFF trichromatic values, MD and CFF were positively correlated (r = 0.486, 0.453, 0.476; P = 0.003, 0.006, 0.004).

Conclusions: A significant decrease of CFF value was found in DON-affected eyes, and it has a good correlation with BCVA, MD and latency of F-VEP, and can better reflect the impairment of visual function

1. Introduction

Demyelinating optic neuritis (DON) is an inflammatory demyelinating lesion of the optic nerve, which can cause acute or subacute vision loss, and mainly affects young and middle-aged adults.[1–7] Due to high recurrence rates, blindness, and disability, the effective evaluation of visual function has become a major priority. Currently, clinicians primarily rely on visual field, optical coherence tomography (OCT), and visual electrophysiological examinations. However, due to high costs and prolonged examination periods, timely and effective visual impairment assessments are often not available.

The critical flicker fusion frequency (CFF) detector is a small portable, age-free, and highly repetitive device, based on visual residue phenomenon principles, and reflects temporal aspect of visual function. When flickering light enters the eye, flickering sensations occur, which gradually disappear with increasing flickering frequency, to finally form a

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stable light called light fusion. The critical flicker fusion frequency (CFF) is the minimum intermittent frequency between flicker and stability that induces continuous fusion sensation. In recent years, studies reported a reduced CFF in patients with multiple sclerosis (MS), DON, and diabetic retinopathy, even without visual acuity and field impairment.[8–15] A recent study highlighted the precision of dynamic visual function assessment; it identified a demyelinating attack, and prolonged visual evoked potential (VEP) latencies closely related to CFF values in 23 DON patients.[16,17] The purpose of our study was to explore the clinical application of CFF in Asian patients with DON.

2. Methods

This study was approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital (PLAGH) (Grant No.: S2017-093-01) and adhered to the Declaration of Helsinki. Informed consent was obtained from patients and their parents/guardians.

2.1. Patients

Clinical data were prospectively collected from hospitalized patients diagnosed with DON at the Neuro-Ophthalmology Department of the Chinese PLAGH between January 1st and September 30th, 2021.

DON was diagnosed according to evidence-based guidelines for the diagnosis and treatment of DON in China (2021).[18] The detailed inclusion criteria were as follows: (1) Acute impairment of visual acuity, with or without ocular rotation pain. (2) Complication of at least the following two abnormalities: relative afferent pupillary defect (RAPD), visual field defect, abnormal visual evoked potential, dyschromatopsia. (3) Vascular, traumatic, compressive, infiltrative, toxic, metabolic, and hereditary optic neuropathy were excluded. The diagnostic criteria for each subtype are as follows: (1) aquaporins 4 related optic neuritis (AQP4-DON): DON with positive aquaporins 4 (AQP-4) antibody; (2) myelin oligodendrocyte glycoprotein related optic neuritis (MOG-DON): DON with positive myelin oligodendrocyte glycoprotein (MOG) antibody; (3) double negative DON: AQP-4 and MOG antibody were negative, the vision continued to decline for less than 2 weeks, and the vision began to recover about 3 weeks after the onset. Other ocular and systemic diseases that caused visual impairment and visual field defects were excluded, for example, glaucoma, severe cataracts, uveitis, retinal disease, amblyopia, and keratopathy.

In total, 69 DON patients with 98 affected eyes and 29 contralateral eyes, and 33 HC cases (HC group) with 63 eyes were assessed.

2.2. CFF and associated examinations

All patients underwent best-corrected visual acuity (BCVA), color vision, relative afferent pupillary defect (RAPD), intraocular pressure assessment, and other basic ophthalmological examinations, including OCT, Humphrey visual field assessments, and flash-visual evoked potential (F-VEP) before 1 week of the CFF examination. We recorded the following information: thickness of peripheral retinal nerve fiber layer (pRNFL) and macular inner limiting membrane-retinal pigment epithelium (mILM-RPE), F-VEP peak times, VEP peak values, and visual field mean defect (MD) values.

All participants underwent CFF (handheld CFF detector type 2 instrument, NEITZ, Japan) examinations (Fig. 1). Specific inspection steps were: external light was shielded and the test conducted in a relatively quiet environment in a darkroom. All participants were trained in advance to master the operating procedure to avoid errors during the process. The visual target was placed 25 cm in front of the patient's eyes, the deviation angle was $< 2^{\circ}$, and CFF values for monocular red, green, and yellow (rCFF, gCFF, and yCFF) light were recorded, respectively. When adjusting to a particular color, the frequency was gradually increased until the minimum fusion frequency had occurred. Data were then recorded.

Table 1
Comparison of CFF between DON and HC eyes.

group	N	rCFF	gCFF	yCFF
the affected eyes	98	21.83 ± 9.03	23.66 ± 10.21	24.09 ± 10.77
the contralateral eyes	29	34.21 ± 3.18	37.03 ± 4.20	38.24 ± 4.93
the HC eyes	63	36.38 ± 2.90	39.81 ± 3.77	40.71 ± 3.78
t^a		−14.82	−14.22	−14.00
t^b		−11.40	−10.34	−9.96
P		<0.001	<0.001	<0.001

N: number; rCFF, gCFF, yCFF: critical flicker fusion frequency for red, green, yellow; HC: healthy control.
[a] The affected eyes vs HC eyes.
[b] The contralateral eyes vs HC eyes.

2.3. Statistical analysis

Data were statistically analyzed by SPSS Ver. 26 (IBM Corporation, NY, USA). If measurement data were normally distributed, they was expressed as the mean ± standard deviation, while categorical data were described as the number of cases and percentages. Based on the time interval from condition onset to CFF examination, patients were divided into four groups: < 1 m (within 1 month), 1~< 3 m (between 1 and 3 months), 3~< 6 m (between 3 and 6 months), and >6 m (more than 6 months). We defined BCVA ≥0.5, 0.1~< 0.5, and <0.1 as mild, moderate, and severe visual impairment, respectively. CFF trichromatic values were compared between different antibody subtypes, different degrees of visual impairment, and different check intervals, using one way analysis of variance (ANOVA) *post hoc* tests. The Student-Newman-Keuls (SNK) method was used for comparisons between groups. Correlations between CFF and other ophthalmologic examination: F-VEP peak times, peak values, BCVA and MD were analyzed, respectively. The correlation coefficient was r and $P < 0.05$ was considered statistically significant.

Fig. 1. Handheld CFF detector type 2 machine (NEITZ, Japan).

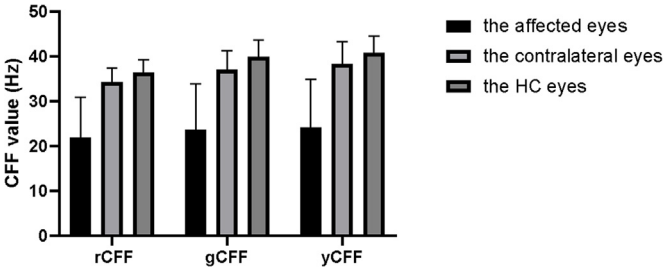

Fig. 2. Comparison of CFF value between DON and HC eyes.

Table 2
Comparison of CFF at different subgroups in DON affected eyes.

	N	rCFF	*P*	gCFF	*P*	yCFF	*P*
subtype			0.914		0.848		0.604
AQP4	39	21.77 ± 8.51		24.00 ± 9.59		23.97 ± 9.99	
MOG	25	21.28 ± 9.23		22.64 ± 10.60		22.52 ± 11.32	
Double negative	34	22.29 ± 9.69		24.03 ± 10.86		25.38 ± 11.37	
BCVA			<0.001		<0.001		<0.001
mild	48	27.17 ± 6.87		29.94 ± 7.60		30.69 ± 8.07	
moderate	18	20.61 ± 8.07		22.11 ± 8.30		22.11 ± 8.80	
severe	32	14.50 ± 6.87		15.13 ± 7.97		15.31 ± 8.51	
Check interval			<0.001		<0.001		<0.001
<1 m	25	17.00 ± 7.87		17.56 ± 8.67		17.84 ± 9.27	
1~<3 m	16	18.25 ± 8.51		20.06 ± 9.09		19.88 ± 9.16	
3~<6 m	16	24.25 ± 6.65		26.44 ± 7.60		27.88 ± 7.50	
>6 m	41	25.22 ± 9.10		27.71 ± 10.34		28.07 ± 11.11	

N: number; rCFF, gCFF, yCFF: critical flicker fusion frequency for red, green, yellow; AQP4: aquaporins 4-antibody; MOG: myelin oligodendrocyte glycoprotein antibody; BCVA: best-corrected visual acuity; <1 m: within 1 month; 1~<3 m: between 1 to 3 months; 3~<6 m: between 3 and 6 months; >6 m: above 6 months.

3. Results

3.1. Demographics and ophthalmological examination results

In total, 69 DON patients with a mean age of 34.19 ± 12.45 years and 33 HC cases with a mean age of 35.18 ± 10.96 years were assessed, respectively. We observed a female predominance in the DON group; 51 (73.9%) were female, while only 16 (48.5%) were female in the HC group. The median logarithm of the minimum angle of resolution (logMAR) visual acuity was 0.22 (interquartile range (IQR): 0.00, 1.27) for the 98 affected eyes in the DON group. Seventy-three affected eyes in this group underwent optic disc OCT examination, and 70 eyes underwent macular OCT examination. The median thickness of pRNFL and mILM-RPE was 67.50 μm (IQR: 61.00, 96.25) and 234.00 μm (IQR: 224.00, 247.25), respectively. The mean MD value was −12.40 ± 7.79 dB in 35 affected eyes. The mean peak values and peak times for F-VEP were 15.26 ± 7.67 μV and 115.60 ± 24.60 ms, respectively, in 50 affected eyes.

When compared with HC eyes, we observed a significant decline in DON eyes ($P < 0.001$), especially in affected eyes of DON patients, and the mean CFF values for red, green, and yellow were 21.83 ± 9.03, 23.66 ± 10.21, and 24.09 ± 10.77 Hz, respectively in affected eyes, and 34.21 ± 3.18, 37.03 ± 4.20, and 38.24 ± 4.93 Hz, respectively in contralateral eyes (Table 1, Fig. 2).

3.2. Subgroup analyses of CFF values

We observed no statistically significant differences in CFF tricolor values between AQP4-DON, MOG-DON, and double-negative DON ($P > 0.05$) (Table 2, Fig. 3).

We observed that rCFF, gCFF, and yCFF values varied across different impaired vision groups ($P < 0.001$). Values were lower in severely impaired vision eyes; 14.50 ± 6.87, 15.13 ± 7.97, and 15.31 ± 8.51 Hz for rCFF, gCFF, and yCFF, respectively (Table 2, Fig. 4).

Subgroup analyses revealed a significant drop of CFF values fluctuated under 20 Hz within 3 months, but gradually increased and stabilized to 24–28 Hz after 3 months ($P < 0.001$) (Table 2). A statistical difference was observed before and after 3 months of onset ($P < 0.05$). (Table 3, Fig. 5).

3.3. Correlation analyses between F-VEP, BCVA, visual field, and CFF values

Strong negative correlations were identified between F-VEP peak times and CFF trichromatic values in affected eyes ($P < 0.001$); correlation coefficients were −0.486, −0.515, and −0.526, respectively. However, we observed no statistical correlations between F-VEP peak value and CFF values ($P > 0.05$) (Table 4).

We also analyzed correlations between BCVA, visual field, and CFF values. Strong negative correlations were observed between logMAR visual acuity and CFF values in affected eyes ($P < 0.001$); correlation coefficients were −0.640, −0.659, and −0.642, respectively. Furthermore, positive correlations were identified between the visual field and rCFF ($r = 0.483$), gCFF ($r = 0.453$), and yCFF ($r = 0.476$) in affected eyes ($P < 0.05$) (Table 4).

Correlations were not evident between F-VEP, BCVA, visual field, and CFF values in contralateral healthy eyes ($P > 0.05$) (Table 4).

4. Discussion

Generally, visual function refers to the ability to acquire visual information. This consists of static visual function and temporal acuity; the former includes visual acuity, visual field, color perception, brightness, contrast sensitivity, and spatial resolution, whereas the latter reflects visual system responses to variations in light over time, as measured by CFF.[19] CFF is a psychophysical test of visual temporal resolution and has

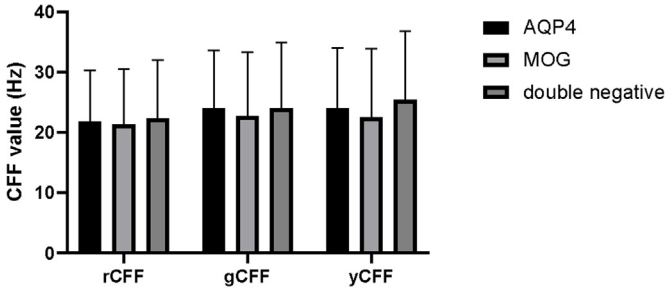

Fig. 3. Comparison of CFF value between different antibody subtypes in DON affected eyes.

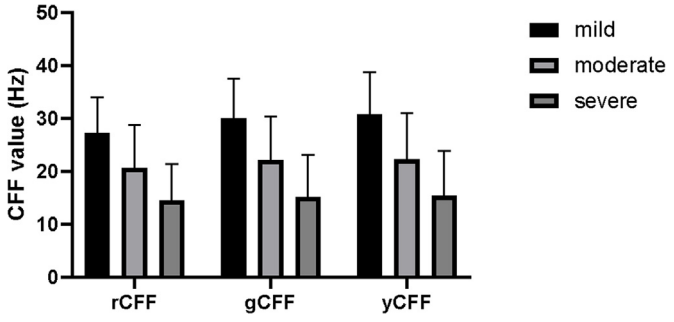

Fig. 4. Comparison of CFF value between the different impaired vision groups in DON affected eyes.

Table 3
Comparison of CFF results at different check intervals using the SNK method.

check interval	N	rCFF (Hz)		gCFF (Hz)		yCFF (Hz)	
		1[a]		1[a]	2	1[a]	2
<1 m	25	17.00		17.56		17.84	
1~<3 m	16	18.25		20.06		19.88	
3~<6 m	16		24.25		26.44		27.88
>6 m	41		25.22		27.71		28.07
P		0.628	0.707	0.784	0.659	0.503	0.948

N: number; rCFF, gCFF, yCFF: critical flicker fusion frequency for red, green, yellow; <1 m: within 1 month; 1~<3 m: between 1 and 3 months; 3~<6 m: between 3 and 6 months; >6 m: above 6 months.
[a] BetweenColumns 1 and 2 subsets of alpha = 0.05.

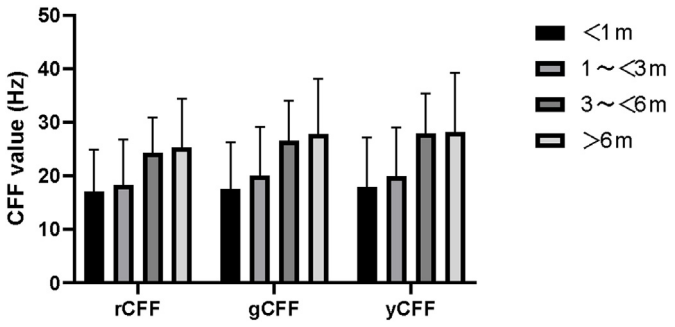

Fig. 5. Comparison of CFF value between different check intervals in DON affected eyes.

been widely used as an analytical tool for retinal diseases, e.g., chloroquine toxic retinopathy, diabetic retinopathy, central serous retinopathy, age-related macular degeneration, and predicting postoperative visual outcomes in subjects with cataracts.[20–22] In 1957, Brenton included several optic nerve diseases, including ischemic, compression, demyelinating, and glaucoma optic neuropathy,[23] and the results showed that CFF was more sensitive and specific than RAPD or color vision in the assessment of optic neuropathy. Daniel et al. reported impaired CFF in 13 recovered ON patients, and proposed the involvement of axonal projections of magnocellular retinal ganglion cells.[24] Due to limited equipment, the clinical application of CFF to ON has been neglected and there are few clinical studies on CFF in optic nerve diseases.

Our study included 69 DON patients and 33 HCs and demonstrated a significant decrease in CFF values in DON eyes when compared with HC eyes, which is more noteworthy in the affected eyes. It is hypothesized that axons posterior to the lamina cribrosa are segmentally wrapped with myelin sheaths composed of oligodendrocytes, therefore, visual information is transmitted by leaps. During acute disease phases, the myelin sheath may be attacked by inflammatory cells, inducing massive disintegration and delayed visual transmission. Therefore, it is not difficult to understand prolonged F-VEP peak times and decreased CFF values in DON patients.

Subgroup analyses indicated little impact of CFF values on differentiating DON subtypes. The main differences between ON subtypes involve different antibody-mediated immune responses. Hence, CFF as a functional indicator cannot easily distinguish between DON subtypes. Additionally, we divided affected eyes into four groups according to the time interval from condition onset, we find a prominent difference of CFF exists before and after 3 months of condition onset. CFF fluctuated under 20 Hz within the first 3 months, whereas CFF trichromatic results were stable around 24–28 Hz, although they continued to improve slowly after 3 months. In accordance with these findings, Daniah et al.[25] performed multifocal VEP assessments on ON evolution and observed that amplitude recovery and latency shortening were fastest within the first 3 months, and continued to improve slowly after 3 months, but changes were not significant. Latency shortening after ON is primarily due to remyelination which occurs during early post-acute stages, where cells form new myelin sheaths.[26] These observations suggest that prompt and effective treatments are necessary to restore myelin integrity during the first 3 months. However, remyelination is often incomplete, as significant residual CFF even 12 months after acute ON.

The severe visual impairment group had lower CFF values. Correlation analyses demonstrated a strong negative correlation between logMAR visual acuity and CFF values, F-VEP latent times and CFF values in affected eyes; correlation coefficients were more than 0.4. Similarly, a correlation was identified between MD and CFF values in affected eyes. These results indicated a consistency in visual functional indicators in DON affected eyes. CFF was sensitive to changes in visual function and F-VEP, although these conclusions may be slightly biased due to the unequal and small cohort size.

However, despite this and absent longitudinal follow-up data, we demonstrated that CFF examinations were valuable for patients with DON. We observed significant decreases across different parameters in DON patients, especially during acute disease phases, and it will gradually recover and stabilize after 3 months. In conclusion, CFF better reflected the visual function of affected eyes, and was closely associated

Table 4
Correlation analysis of BCVA, visual field, F-VEP, and CFF in DON patients.

	N	rCFF		gCFF		yCFF	
		r	*P*	r	*P*	r	*P*
the affected eyes							
BCVA	98	−0.640	<0.001	−0.659	<0.001	−0.642	<0.001
MD	35	0.483	0.003	0.453	0.006	0.476	0.004
Peak value	50	0.210	0.142	0.253	0.077	0.298	0.036
Peak time	50	−0.486	<0.001	−0.515	<0.001	−0.526	<0.001
the contralateral eyes							
BCVA	29	−0.206	0.285	−0.222	0.248	−0.314	0.097
MD	9	0.393	0.295	0.285	0.458	0.269	0.484
Peak value	10	0.146	0.686	−0.123	0.736	−0.051	0.889
Peak time	10	0.420	0.226	0.180	0.619	0.246	0.494

N: number; rCFF, gCFF, yCFF: critical flicker fusion frequency for red, green, yellow; BCVA: best-corrected visual acuity; MD: mean defect.

with BCVA, MD, and VEP peak times.

Study Approval

This study is approved by National Key Research and Development Program (2018YFE0113900)(2018YFE0113900).

This study was reviewed and approved by the Ethics Committee of PLA General Hospital (Approval No.: S2017-093-01).

Author Contributions

All authors had full access to all the data in the study and were responsible for the integrity and accuracy of data.

Study concept and design, acquisition of data, analysis and interpretation of data, drafting and revision of manuscript:JXF; Acquisition of data, analysis and interpretation of data:YPW; Critical revision of manuscript for intellectual content:SYT; Acquisition of data:GCX, HFZ; Study supervision: QGX; Study concept and design, study supervision, and critical revision of manuscript for intellectual content: SHW.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

CFF	critical flicker fusion frequency
rCFF	critical flicker fusion frequency for red
gCFF	critical flicker fusion frequency for green
yCFF	critical flicker fusion frequency for yellow
DON	demyelinating optic neuritis
HC	healthy control
BCVA	best-corrected visual acuity
OCT	optical coherence tomography
VEP	visual evoked potential
F-VEP	flash visual evoked potential
MS	multiple sclerosis
RAPD	relative afferent pupillary defect
AQP4	aquaporins 4
AQP4-DON	aquaporins 4 antibody related demyelinating optic neuritis
MOG	myelin oligodendrocyte glycoprotein
MOG-DON	myelin oligodendrocyte glycoprotein antibody related demyelinating optic neuritis
MD	mean defect
mILM-RPE	macular inner limiting membrane-retinal pigment epithelium

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