• Clinical Research •

Visual electrophysiological assessment of children with poor response to treatment for functional amblyopia

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Abstract

● **AIM:** To assess the visual electrophysiological outcomes in children with functional amblyopia who exhibited poor response to conventional treatment.

● **METHODS:** Twenty-one children with functional amblyopia, aged 5.7±2.1y (range: 4-10y), underwent comprehensive ophthalmic and refractive evaluations. Spectral domain-optical coherence tomography (SD-OCT) and multifocal electroretinography (mfERG) were conducted to analyze the macular retinal thickness and the first-order response P1 ring of the mfERG in the amblyopic eye (AE) compared to the fellow good eye (GE).

● **RESULTS:** Initially, visual acuity in the AE ranged from 20/800 to 20/40, while the GE exhibited a range of 20/25 to 20/20 (P<0.01). After 6mo of treatment, 17 patients demonstrated improved visual acuity in the AE to 20/50 or better, while 4 children showed no improvement. SD-OCT revealed comparable macular and optic disc structures between the AE and GE. Prior to treatment, the mfERG P1 ring amplitude was significantly reduced in the AE compared to GE (P<0.05). The AE/GE ratio of P1 ring amplitude showed significant improvement post-treatment. However, a smaller AE/GE ratio before treatment was associated with poorer improvement post-treatment.

● **CONCLUSION:** In the management of functional amblyopia, a thorough assessment of amblyopic eye examinations is crucial. Approximately 20% of amblyopic eyes may not achieve significant improvement in visual acuity, despite the absence of detectable organic retinal abnormalities. mfERG may reveal underlying abnormalities. Integrating mfERG into initial assessments or treatment follow-ups can aid in identifying potential hidden retinal defects and predicting the prognosis of the amblyopic eye.

● **KEYWORDS:** functional amblyopia; poor response; optical coherence tomography; multifocal electroretinography; retinal defects

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INTRODUCTION

Functional amblyopia is defined as a decrease in best-corrected visual acuity in one or both eyes caused by abnormal visual experience during visual development without organic pathology on ocular examination[1]. The disruption of normal visual experience during a critical period of visual development leads to alterations in the organization and function of the visual cortex, resulting in a reversible loss of central visual acuity, usually caused by strabismus and/or refractive error[2-3]. Organic amblyopia, on the other hand, is defined as an irreversible loss of vision caused by pathologic changes at the level of the retina or major visual pathways[4-5]. Recent studies have shown that traditional therapies consisting of masking of the non-amblyopic eye are very effective in reversing functional amblyopia[6-8]. However, despite our efforts to optimize treatment compliance in children, not all patients achieve visual improvement. Some studies have shown that up to 25% of patients with functional amblyopia show only partial or no recovery of vision with treatment[9-11]. These findings suggest that children with functional amblyopia who do not respond to treatment may have a mixture of functional and occult organic lesions, but there is still no validated test to assess the relationship between functional abnormalities and occult organic lesions in the child's eye. Therefore, in this study, we compared the visual electrophysiologic findings of children with functional amblyopia after comprehensive amblyopia treatment, and evaluated the ocular function of children with poor treatment response and the associated insidious organic visual loss that may accompany functional

amblyopia in an attempt to explain the failure to achieve treatment outcomes.

PARTICIPANTS AND METHODS

Ethical Approval The study was approved by the Ethical Review Committee of Jiangsu Provincial People's Hospital (No.20210307) and was conducted in compliance with the Declaration of Helsinki. Informed consent was signed by the families (guardians) of all children.

Participants This study was a retrospective study. A total of 21 children with monocular functional amblyopia were included, all from the Department of Ophthalmology, Jiangsu Provincial People's Hospital, and these children were treated with either occlusion therapy or optical and/or pharmacological therapy for the non-amblyopic eye. Inclusion criteria were a diagnosis of unilateral refractive paradox and/or strabismic amblyopia without other ocular abnormalities. Refractive error was defined as an spherical equivalent difference of 1 diopter (D) or more between the eyes without strabismus or an ocular misalignment of 5 prism degrees (Δ) or less. Strabismus and microsaccades were defined as a distance ocular deviation of ≥7Δ in the absence of binocular vision. Exclusion criteria were patients with form-deprivation amblyopia or detectable organic defects.

Research Methodology All patients underwent a complete ophthalmologic examination including slit lamp examination, funduscopic examination and dilated optometry (cyclopentolate 1% and phenylephrine 2.5%). Comprehensive treatment of amblyopia included eye glasses, correction of refractive error, forcing the amblyopic eye to gaze, and fine work training. The eye is also covered or suppressed with overcorrected or undercorrected lenses and daily doses of atropine.

Routine Inspections Visual acuity was assessed in all patients using a 6-m Snellen visual acuity scale (Es or numbers) and a 1/3 m Rosenbaum near acuity scale. Near visual acuity was recorded in both eyes at the initial visit and in the amblyopic eye (AE) at each follow-up visit. Sensory status was determined by the Worth-4 points test and the Titmus stereotaxic test. Distance of motor alignment was measured with the alternating prism and cover tests.

Central Visual Function Tests Tests to assess central visual function included color vision (Ishihara Plate and Farnsworth Munsell D-15) and imaging of the macula and optic nerve [spectral-domain optical coherence tomography (SD-OCT); Spectralis Heidelberg, Germany], which were performed at the time of the initial visit or subsequent follow-up. After instillation of 5 g/L compound tropicamide eye drops for pupil dilation, images were acquired with the SD-OCT instrument in near-infrared mode (820 nm), with the participants' heads fixed and guided to fixate on a flickering visual target using inner fixation. Initially, the macular cube 512×128 scanning mode was used to obtain information on the macular area of the patients. The fovea was taken as the center, and linear scans with diameters of 1, 3, and 6 mm were performed radiating from the fovea. A total of 6 linear scans were conducted, with two lines forming an angle of 30°, to obtain the retinal thickness of the macular area and generate a pseudo-color macular topographic map. Subsequently, a circular scanning pattern (diameter 12°) was used to measure the retinal nerve fiber layer (RNFL) thickness around the optic disc. The examiner analyzed all scan images of each frame to determine the presence of segmentation errors. The criteria for excluding images were continuous interruptions or distortions of boundaries detected in the same image for 5% consecutively or cumulatively exceeding 20%.

Multifocal Electrophysiologic Examination To assess the functional integrity of the macula and the entire retina, multifocal electrophysiologic (mfERG) examination was performed according to ISCEV standards[12-13]. The mfERG was performed using an Espion visual electrophysiology instrument from Diagnosys, USA. mfERG stimulation units consisted of 61 hexagons increasing in centrifugal degree, all of which were stimulated independently in a pseudo-randomized manner, and were divided into 5 rings from the center of the stimulus to the periphery, with the corresponding visual field degrees of 2.18°, 7.46°, 12.36°, 19.66°, 29.75°, 19.66°, 29.75°, and 2.18° in each ring. The maximum stimulus luminance was ≥1000 cd/m^2, the contrast was >99%, and the amplifier gain was 100 k. The recording electrodes were corneal electrodes placed in the center of the cornea of both eyes, the reference electrodes were placed in the outer canthus of both eyes, and the ground electrodes were placed in the middle of the forehead, and the impedance of the electrodes was <1 kΩ. The distance of the mfERG examination was 28 cm, and the pupils were first dilated to 8 mm after the corrected visual acuity is the best visual acuity, 4% ouabucaine hydrochloride eye drops anesthesia after wearing corneal electrodes, gaze at the center of the stimulator of the red cross-crossing fixed point of vision, with whole body relaxation, to avoid interference. In order to maximize the subjects' ability to complete the recording process, each subject was tested separately in both eyes. An infrared eye fixation monitoring system was used for fixation monitoring during the examination. Conventional first-order response amplitude analysis was performed and first-loop P1 amplitude values in nV/deg^2 were collected for analysis. To better assess the possible effect of amblyopia on mfERG, derivations were made using the ratio of each ring amplitude (rings 1-5) of the amblyopic eye to the healthy eye. This allowed each patient to serve as his or her own control

Table 1 Baseline data of 21 children with amblyopia

Patient No.	Age	Sex	Type of amblyopia	Initial visual acuity in the amblyopic eye (corrected)	Visual acuity after treatment of amblyopic eyes (corrected)
1	4	Female	Refractive error	20/100	20/40
2	5	Male	Refractive error	20/200	20/50
3	5	Male	Refractive error	20/50	20/20
4	6	Female	Refractive error	20/400	20/60
5	9	Female	Refractive error and strabismus	20/100	20/20
6	7	Female	Strabismus	20/50	20/25
7	5	Male	Refractive error	20/70	20/40
8	5	Female	Strabismus	20/150	20/20
9	4	Male	Strabismus	20/50	20/25
10	6	Male	Refractive error	20/100	20/40
11	5	Male	Refractive error	20/300	20/50
12	4	Female	Refractive error	20/200	20/50
13	7	Female	Strabismus	20/90	20/40
14	8	Male	Refractive error	20/80	20/20
15	5	Female	Refractive error	20/60	20/25
16	4	Male	Refractive error	20/150	20/60
17	7	Male	Refractive error	20/90	20/80
18	5	Male	Refractive error	20/50	20/50
19	4	Female	Refractive error	20/100	20/90
20	8	Female	Refractive error and strabismus	20/300	20/300
21	6	Male	Refractive error	20/200	20/150

and minimized the effect of age-related differences in mfERG amplitude. A ratio of 1 (or close to 1) indicates that there is no difference in ring amplitude between the two eyes, whereas a further deviation of the ratio from 1 indicates a greater difference between the two eyes. According to the literature, the difference in mfERG amplitude between the average normal eyes is between 5% and 10%[14]. Therefore, ratios were considered abnormal if they were outside the following range: 0.804≤R≤1.196 (based on a two-sided *t*-test at $P<0.05$).

Statistical Analysis SPSS 21.0 software was used for data processing and analysis. Quantitative data obeyed normal distribution and were expressed as mean±standard, and *t* test was used for comparison between two groups; qualitative data were expressed as the number of cases and composition ratio, and χ^2 test was used for comparison between two or more groups. Logistic regression model was used to analyze the influencing factors. $P<0.05$ was considered as statistically significant difference.

RESULTS

General Data of Patients The clinical baseline data of all patients included in this study were shown in Table 1. Fifteen patients had refractive amblyopia and six patients had strabismic amblyopia. Before treatment, visual acuity ranged from 20/800 to 20/40 in the AE and from 20/25 to 20/20 in the good eye (GE). After 6mo of treatment, visual acuity in the affected eye had improved to 20/50 or better in 17 patients, whereas in the remaining four patients, only one patient had achieved a visual acuity of 20/100 due to poor compliance.

Table 2 OCT findings of the patient's eye

Patient No.	Macular center (AE/GE) μm	Optic disc (AE/GE) μm	Optic disc RNFL (AE/GE) μm
1	219/221	237/241	103/104
2	231/229	248/244	99/97
3	221/225	235/236	107/104
4	218/219	251/248	112/107
5	232/229	243/239	109/110
6	208/211	245/250	104/101
7	210/212	231/228	108/109
8	227/223	229/230	112/111
9	208/206	237/240	101/105
10	213/215	248/251	110/107
11	222/224	237/233	99/99
12	233/229	239/241	98/97
13	223/227	242/239	103/105
14	230/231	251/248	108/107
15	218/215	232/229	103/105
16	238/242	238/241	102/99
17	228/229	241/244	105/104
18	241/237	252/249	109/108
19	221/219	238/231	98/102
20	208/211	234/230	107/105
21	217/216	241/238	106/102

RNFL: Retinal nerve fiber layer; AE: Amblyopic eye; GE: Good eye.

Comparison of Spectral Domain-Optical Coherence Tomography Findings As shown in Table 2, we performed SD-OCT of the macula and optic nerve in all patients. The results showed that the mean macular center thickness in the amblyopic eyes was 213.41±16.32 μm compared to 212.89±18.61 μm in the healthy eyes ($P>0.05$). Similarly, the

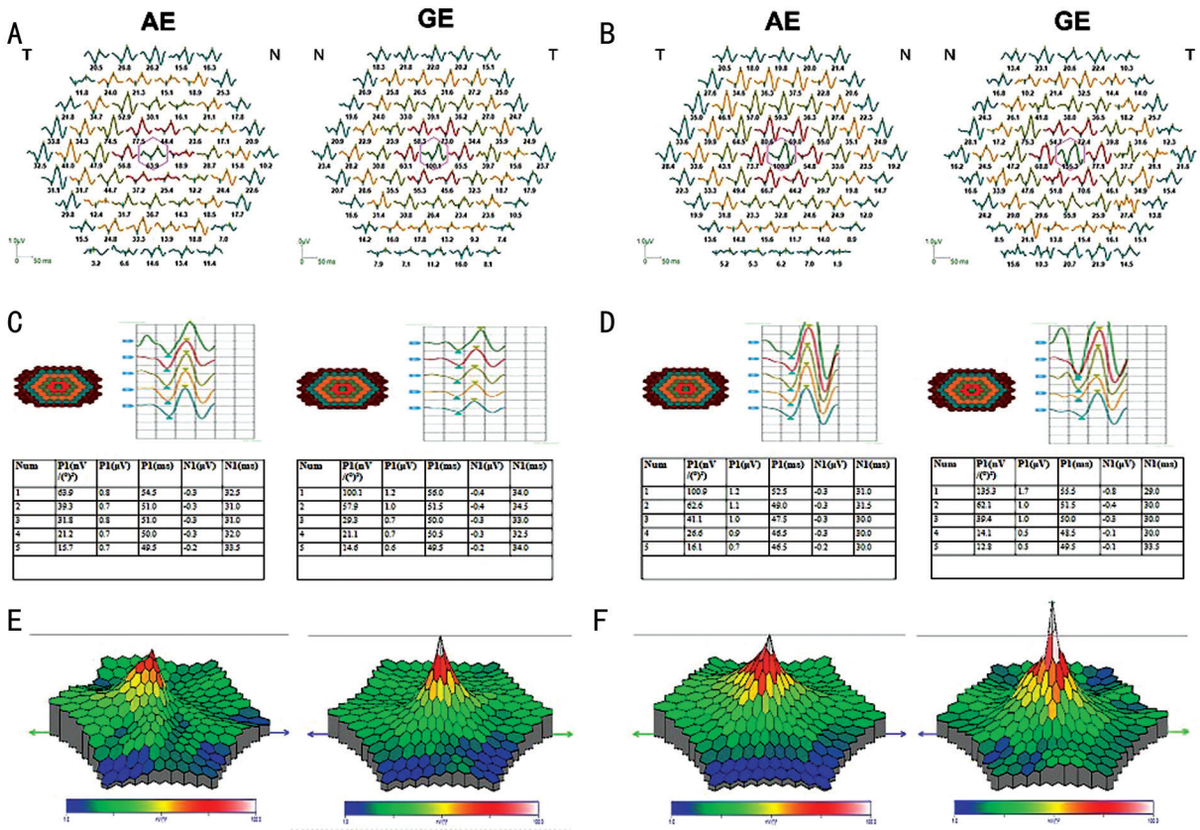

Figure 1 Results of mfERG before and after amblyopia treatment in patient 18 A: Waveforms obtained from each eye before treatment; B: Waveforms obtained from each eye after treatment; C: Analysis results of each ring before treatment (rings 1 to 5, with the patient's data for each ring indicated in form); D: Analysis results of each ring after treatment; E: 3D reconstruction of the parameters of each eye before treatment; F: 3D reconstruction of the parameters of each eye after treatment. MfERG: Multifocal electroretinography; AE: Amblyopic eye; GE: Good eye; T: Temporal side; N: Nasal side.

mean optic nerve thickness in the AE group was 103±15.49 μm, which was not significantly different from 101.54±16.87 μm in the GE group (P>0.05). Even the retinal nerve fiber layer thickness, *etc*., in the amblyopic eyes of the four patients who responded poorly to amblyopia treatment did not show any significant abnormality.

Comparison of Multifocal Electrophysiologic Examination Analysis A traditional first-order response first-ring amplitude analysis of the mfERGs showed that the patients had significantly lower ring 1 amplitude ratios and that the post-treatment amplitude ratios of the affected and healthy eyes were significantly higher than the pre-treatment ratios (P<0.05; Tables 3 and 4). However, in four children with poor response to amblyopia treatment we found that the pre-treatment AE/GE ratio was less than 0.75 and the increase in the AE/GE ratio after treatment was not significant. Among them, patient 18 had a preoperative AE/GE of only 0.53, and the AE/GE improved to 0.8 after treatment, but no significant improvement in visual acuity was observed (Figure 1).

DISCUSSION

Studies have shown that the human macular sulcus is the first area of the eye to develop from 14wk of fetal life, but

Table 3 Results of mfERG examination of patients' eyes

Patient No.	Pre-treatment mfERG P1 ring amplitude density (AE/GE)	Post-treatment mfERG P1 ring amplitude density (AE/GE)
1	0.97	0.96
2	0.93	0.91
3	0.94	0.96
4	1.04	1.01
5	0.87	0.91
6	1.03	1.12
7	1.02	1.06
8	0.96	0.97
9	0.87	0.91
10	1.01	1.06
11	0.90	0.91
12	1.02	1.04
13	0.87	0.91
14	1.01	0.97
15	1.05	1.03
16	0.95	0.93
17	0.77	0.78
18	0.53	0.80
19	0.73	0.79
20	0.67	0.72
21	0.73	0.80

AE: Amblyopic eye; GE: Good eye.

Table 4 Comparison of patients' examination results

Program	Average value	Standard deviation	Standard error mean	Difference 95% confidence interval		*t*	*P* (bilateral)
				Lower limit	Upper limit		
Macular center	-0.190	2.857	0.623	-1.491	1.110	-0.306	0.763[a]
Optic disc	0.905	3.477	0.759	-0.678	2.488	1.192	0.247[a]
Optic disc RNFL	0.619	2.500	0.545	-0.519	1.757	1.135	0.270[a]
Pre-treatment mfERG P1 ring amplitude density (AE/GE) *vs* Post-treatment mfERG P1 ring amplitude density (AE/GE)	-0.03048	0.05757	0.01256	-0.05668	-0.00427	-2.426	0.025

[a]AE *vs* GE. RNFL: Retinal nerve fiber layer; AE: Amblyopic eye; GE: Good eye.

it is also the last area to fully develop between the ages of 2 and 4y, with the peripheral optic cones completing their development before that[15-16]. Because the human macular plexus is relatively immature at birth and develops rapidly in the early postnatal period, this makes it more susceptible to environmental influences. In order to determine whether functional amblyopia in one eye may be poorly responding to amblyopia training because of possible insidious structural abnormalities, the present study was designed to evaluate the relationship between structural abnormalities in the macular and optic nerve regions of the affected eye and poor vision correction in poorly responding children, in terms of the structural and functional examination of the macula and optic disc. Our findings suggest that out of 21 children with monocular amblyopia, 17 were effective for comprehensive amblyopia treatment with mean visual acuity improvement ranging up to 20/50, but 4 children with amblyopic eyes responded poorly to the treatment. Detailed analysis of the intraocular structures of all children revealed no difference in the central retinal thickness of the macula in all children with amblyopia compared with the healthy eye, and no significant differences in optic disc and RNFL thickness. In addition, by analyzing the first-order response first-loop amplitude of the mfERGs we found that the P1 amplitude of the children with amblyopic eyes was significantly lower than that of the normal eyes, and the difference was statistically significant, and after amblyopic treatment, the P1 of the amblyopic eyes improved significantly compared with the previous one. However, it is worth noting that in children with poor response to amblyopia treatment their amblyopic eye P1 was lower, and the magnitude of improvement after treatment was lower than in children with better response to treatment.

Approximately 30% to 35% of the retinal thickness at the macula is made up of ganglion cells and the RNFL, and it is here that ganglion cells are most densely packed[17-18]. There are three forms of retinal ganglion cells: X cells, Y cells, and W cells. X cells are found primarily in the central recess and provide high visual acuity. Refractive amblyopia occurs when the retinal image is blurred by refractive errors at a critical stage of visual development, resulting in insufficient stimulation of the X ganglion cells in the macular center recess, impaired development of the X cells of the visual pathway, and low spatial resolution[19-20]. Reduced X-cells are also found in animal amblyopia tests[21], so we can speculate that the thickness of the retina in the macular center pits of amblyopic eyes is reduced compared to normal eyes. In this study, we used SD-OCT to measure the retinal thickness in the macular center recess of amblyopic eyes and found that the difference in the retinal thickness in the center recess of amblyopic eyes was not statistically significant compared to that of healthy eyes (P>0.05). In normal subjects, the thickness of the RNF varies in all directions around the optic disc, being thicker above and below the optic disc and relatively thinner nasally and temporally, which is in accordance with the anatomical curved course of the RNFL in the posterior pole. Lekskul *et al*'s[22] study of the quadrants around the optic disc and the mean RNFL thickness of monocular amblyopia including strabismic amblyopia and refractive amblyopia, as well as strabismic amblyopia did not find such a change. However, Kasem and Badawi[23] found that mean RNFL thickness was significantly thicker in patients with monocular amblyopia compared to normal, and this significant difference between refractive error and refractive error amblyopia persisted after grouping the types of amblyopia. Nishikawa *et al*[24] also found that unilateral amblyopia eyes had a reduced density of macular blood vessels and a thicker inner retinal layer compared to the contralateral eye. Other studies suggested that refractive amblyopia may affect the postnatal ganglion cell reduction process, resulting in a thicker RNFL than in normal eyes[25-26]. We need to further expand the sample size and analyze the study subjects stratified by refractive status, as well as conduct histological studies to further confirm the effect of amblyopia on the thickness of the retina in the central recess. However, we found that there was no significant change in the peripapillary RNFL thickness in all directions in amblyopic eyes compared with healthy eyes, and the difference was not statistically significant. This may be due to the fact that we included a small sample size and did not perform a stratified analysis. In subsequent studies, we need to further expand the sample size and stratify the classification for poor responders to further elucidate the presence of anatomical abnormalities in poor responders with amblyopia.

The mfERG can be categorized into first-order and second-order responses, which can comprehensively record the electrical responses occurring in different retinal regions. Beneish *et al*[27] found that the mfERG maps of amblyopic eyes exhibited a reduced amplitude compared with those of normal eyes, indicating the possibility of functional abnormalities in ganglion cells. In addition, Feng and Zhao[28] found that the response amplitude density in the mfERG maps of monocular amblyopic patients was lower than that of healthy eyes and normal standard values, suggesting that there is an abnormality in the second-order response of the mfERG in amblyopic eyes, which is a preliminary confirmation of the possible damage to retinal ganglion cells. Recent studies have also shown that conditions such as optical defocus, inattention, and poor fixation during the examination may lead to a decrease in the amplitude of the N1 and N2 waves in the mfERG map, especially in the central region, and a shortening of the latency of the P1 and N2 waves[29]. Because of the large degree of mfERG amplitude variability, the effects of the subject's age, sex, eye type, refractive error and its degree on the first- and second-order responses of mfERG should be considered in mfERG studies of amblyopia. mfERG first-order response of the P1 wave has the same cellular origins as that of b-wave under bright adaptation of the full-field ERG, and it is now more uniformly recognized that the first-order response of the P1 wave of the mfERG is predominantly originates from retinal bipolar cells, and the decrease in the mean amplitude density of the P1 wave is suggestive of retinal bipolar cell abnormality, whereas the change in latency is suggestive of an alteration in the transmission of neural information in the visual pathway[30]. In the present study, we found a decrease in mfERG first-order response amplitude density in amblyopic eyes, suggesting an abnormal retinal function in amblyopic eyes, which may be due to a decrease in retinal bipolar cell function. However, with the improvement of visual acuity in amblyopic eyes after amblyopia treatment, the mfERG P1 wave amplitude density increased, and the visual function was significantly recovered compared with before. Studies have shown that there are precise synaptic loops in the mammalian visual system, and visual experience plays an important role in the formation and modification of synapses during the transition from immature to mature circuits[31-32]. Amblyopic children are at a critical stage of visual development. Refractive correction removes the abnormal visual environment, and amblyopia treatment removes the competition of the gaze eye for the visual input of the amblyopic eye, which leads to the enhancement of the cellular function of the inhibited visual pathway, improvement of the synaptic circuit function, and gradual restoration of retinal function. Although multifocal ERG center amplitudes have been reported to be affected by unstable fixation, the results reported herein were collected by binocular mfERG, in which stable ocular fixation and corneal monitoring corroborate the reliability of the results. Al-Hadad *et al*[33] used a similar monitoring technique in their binocular mfERG recordings. Even in the presence of small ocular deviations, mfERG tested under binocular conditions is acceptable as long as the patient has binocular vision. In addition, as mentioned above, the binocular method of mfERG testing was more feasible in our cohort of young children. This not only facilitated their cooperation with the test, but also made them more willing to undergo subsequent follow-up examinations.

There are some limitations in our study, mainly due to the small sample size included and the even lower percentage of children with poor amblyopia response, so the examination parameters for children with poor response could not be categorized and stratified for analysis. In addition, the follow-up period was relatively short, and we will further expand the sample size, and extend the follow-up period and increase the follow-up nodes in order to further clarify the problems of children with poor responders to functional amblyopia treatment, so as to provide a reference for subsequent improvement of the effectiveness of amblyopia treatment and to help children with poor responders to improve their visual function. Furthermore, all patients included in our study were diagnosed with unilateral amblyopia. However, there were no detectable ocular structural abnormalities in the amblyopic eyes, particularly through fundus examination and OCT imaging, where the eye structures appeared normal. Therefore, in the discussion section, we have emphasized this phenomenon. We believe that despite the normal appearance of the patients' eye structures as assessed by current diagnostic methods, their visual functions remain impaired. This could potentially be due to some subtle structural damage or functional impairment that is not detectable by current means. Hence, there is a need for supplementary multifocal visual evoked potential examinations, and even the development of more precise diagnostic instruments and methods that can detect the source of the pathology at a more microscopic level.

In conclusion, this study suggests that we need to comprehensively evaluate the examination results of the affected eyes when treating functional amblyopia, and that there may be about 20% of affected eyes that fail to achieve a cure, and that in these patients there may be no detectable organic retinal structural abnormalities, including the structure of the macula and optic disc, but there may be abnormalities in their functional assessments such as mfERG. And mfERG is added to the initial evaluation of functional amblyopia or subsequent follow-up during treatment to rule out possible occult retinal defects, which can be an important reference for

determining the prognosis of the affected eye.

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