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Post audio-visual biofeedback training visual functions and quality of life in paediatric idiopathic infantile nystagmus: A pilot study

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Abstract

Purpose: Biofeedback training (BT) was adapted to idiopathic infantile nystagmus syndrome (IINS) cases to enhance visual functions and quality of life (QoL).

Methods: 10 patients (age 9 ± 3.2 years) treated with the audio-visual BT module of the MAIA microperimeter (Centervue, Padova, Italy) were assessed in two baseline visits and 1 week post-BT (BT 80 min in total). The outcomes were distance and near binocular best corrected visual acuity (BBCVA), fixation stability, reading speed, contrast sensitivity, stereopsis and Children's Visual Function Questionnaire. One-way repeated measured ANOVA and paired *t*-tests were used.

Results: Distance BBCVA improved from 0.46 ± 0.21 and 0.43 ± 0.18 pre-BT to 0.33 ± 0.2 logMAR post-BT (F (2,27) = 13.75, p = 0.0002). Post-BT was better than baseline (p = 0.0001) and pre-BT (p = 0.001). Near BBCVA improved from 0.23 ± 0.09 and 0.21 ± 0.14 pre-BT to 0.04 ± 0.08 post-BT (F (2,27) = 22.12, p = 0.000014), post-BT was better than baseline (p = 0.0001) and pre-BT (p = 0.0006). Stereopsis improved from 283 ± 338″ to 39 ± 32.2″ (p = 0.04), contrast sensitivity from 0.26 ± 0.17 to 0.08 ± 0.12 log units (p = 0.01), and reading speed improved from 74.7 ± 51.2 wpm to 104.7 ± 53.6 wpm (p = 0.0006). Fixation stability improved from 33.6 ± 28.1 to 14.3 ± 10.1 sq. QoL increased from 23.8 ± 2.2 to 26.3 ± 2.3 units (p = 0.001).

Conclusion: BT benefited all visual functions and QoL in this pilot study, heralding a new possibility for Low Vision Rehabilitation in IINS.

Keywords

Nystagmus, biofeedback, quality of life, low vision, vision rehabilitation

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Introduction

Idiopathic Infantile Nystagmus Syndrome (IINS) is responsible for about 10% of all infantile nystagmus cases.[1] IINS refers to a diagnosis of exclusion category in which sensory and neurologic etiologies have been ruled out, resulting in an oculomotor diagnosis with stable, relatively good visual acuity. Differently from CEMAS' classification,[2] which is based on nystagmus waveform type, this study will use the term "IINS" based on the etiologic classification of the nystagmus as described above.[3] IINS has characteristic waveform eye movement patterns with an exponentially increasing velocity slow-phase followed

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by a saccadic fast phase. It is almost always bilateral, conjugate, and occurs in the horizontal plane, in up gaze and downgaze, with little variability.[4]

As a general rule, although the visual acuity is not profoundly decreased in IINS, contrast sensitivity, stereopsis and other visual functions may be significantly affected. Consequently, IINS can still negatively impact quality of life (QoL).[5]

When the patient is functionally asymptomatic, no treatment is required. However, if low vision develops or marked abnormal head posture occurs, interventions are warranted. Current therapies include muscle surgery, the use of optical devices, prisms, drugs and botulinum toxin injections.[6–13] Low vision rehabilitation (LVR) interventions for near reading with stronger additions or magnifiers may be necessary, while abnormal head posture may respond to prismatic glasses and to surgery. However, distance vision is the most difficult to improve in low vision patients, usually requiring the use of telescopes, head worn CCTVs or other electronic magnification methods.

Surgical, optical and chemical therapies aim at changing the functional balance among eye muscles, so that fixation stability and the foveation time increases. Active attentional eye movement control training, an old and still most prevalent intervention in LVR, had not been used clinically to treat nystagmus before. The lack of accurate ocular movements monitoring during training was one of the reasons for it. More recently, with the advent of the microperimeters, the audio-visual biofeedback training (BT) module became available.[14] Microperimetric BT has been used for about ten years in LVR and promotes eccentric viewing deployment after central vision loss. It improves near and distance vision for dry-macular degeneration patients.[14–17] These devices display images of the fundus and fixation points on a screen in real time, which allows guidance and biofeedback; therefore, it may help to improve oculomotor control increasing awareness of abnormal eye movements in nystagmus patients. Laboratory studies and a recent retrospective analysis[18] suggested a positive BT effect in reducing the nystagmus amplitude and improving fixation stability.[19–23]

We hypothesize in this study that BT could optimize the visual functions and functional vision in pediatric patients with IINS, as well as QoL, opening a new possibility for treatment of IINS cases.

Methodology

This is a pilot study utilizing an observational case series. The outcomes analyzed in here include visual functions and QoL, comparing control baseline and pre-BT visits to post-BT data. The study was approved by the University Health Network Research Ethics Board and is registered at ClinicalTrials.gov, identifier NCT04142307. All patients and their legal guardians signed an informed consent form.

The children were referred from the Hospital for Sick Children, Toronto, Canada to the LVR service. Inclusion criteria was IINS previously studied in pediatric ophthalmology service accordingly by electroretinogram, brain magnetic resonance imaging, OCT, electronystagmogram, and genetic tests as needed.[1] The exclusion criteria were the presence of other ocular diseases, retinal disease, foveal hypoplasia, both eyes with media opacity, nystagmus cases other than IINS.

During the baseline visit, patients were assessed for Binocular Best Corrected Visual Acuity (BBCVA) for distance with ETDRS charts at 4 meters and BBCVA ETDRS near vision. One week after baseline visit, a pre-BT visit took place. In the pre-BT visit, BBCVA for distance and near measures were repeated. Preferred retinal locus (PRL) was assessed with the MAIA microperimeter and its fixation stability (FS) was calculated by the MAIA software as a 63% and 95% bivariate contour ellipse area (BCEA). In the pre-BT visit, contrast sensitivity was measured with the two levels contrast Colenbrander chart. Reading speed was assessed with the Smith-Kettlewell charts using the best binocular near correction. Stereopsis was assessed with the Frisby Stereo Test. QoL was assessed with the Children's Visual Function Questionnaire (CVFQ), version 3, 2004. Questions 2–34 were suitable for and used in this study.[24] CVFQ is composed by four subsections that describe the visual abilities and biopsychosocial impact of visual functions in the child's life.

All the children in this study were treated with BT after the pre-BT visit. The BT protocol followed involved four consecutive weekly sessions of training. Each session included BT attempts of 20 min (80 min in total), plus resting time, that was also given on demand.

BT procedure involved presentation of a standard LED fixation target consisting of a small red circle of 0.76°. A fixation training target (FTT) was selected on the screen at a fixation point at the foveola. The patient was instructed to stare at the circle and listen to the audio feedback. After that, the patient was guided to try to control the eye movements until the audio feedback became more frequent and then a continuous sound. Continuous sound signalized to the patient that the FTT had been achieved, and at this moment a white dot appeared filling the interior of the circle.

A follow up visit occurred 1 week after the fourth week of BT, when tests performed at the pre-BT visit were repeated. Distance BBCVA continued to be measured during regular follow ups.

Outcome measures selected for analysis were BBCVA for distance and near, fixation stability, reading speed, contrast sensitivity, stereopsis and QoL CVFQ scores. Data analysis was based on descriptive statistics that include frequency distributions, a measure of central tendency (mean) and a measure of dispersion (standard deviation). Statistical comparison between populations was be made by the Wilcox rank sum and t-tests. One-way repeated measured ANOVA analysis was used to compare the measures between baseline, pre-BT and post-BT. Differences were considered statistically significant at a p-value of less than 0.05.

Results

Ten patients were treated post two visits 1 week apart. The age ranged from 6 to 15 years old, (average 9 ± 3.2 years). 70% of the patients were male. Results for BBCVA for distance, near vision, and fixation stability (BCEA 63% and 95%) are presented in Table 1. Distance BBVCA improved in average from 20/50+ to 20/40+ in Snellen equivalent. One way repeated measured ANOVA showed a significant effect of BT on distance BBCVA, F (2,27) = 13.75, $p = 0.0002$. Follow up analysis using paired samples t-tests showed that visual acuity post-BT was significantly better than the baseline acuity ($p = 0.0001$) and pre-BT measures ($p = 0.001$). Near BBCVA improved from 20/32 to 20/20 in Snellen equivalent (Table 1). One way repeated measured ANOVA showed a significant effect of BT on near BBCVA, F (2,27) = 22.12, $p = 0.000014$. Follow up analysis using paired samples t-tests showed that visual acuity post-BT was significantly better than the baseline acuity ($p = 0.0001$) and pre-BT measures ($p = 0.001$). The progression of BBCVA measures for distance and near is presented in Figure 1.

The outcomes for stereopsis, reading speed and contrast sensitivity are shown in Table 2. Reading speed assessment was feasible for seven children who were literate and fluent. Table 3 presents all reading speed outcomes, and in parallel near ETDRS binocular near reading letters/continuous print for each patient, which are consistent. The patients who were illiterate still improved significantly the letters critical print size after BT compared to baseline. Figure 2 illustrates the pre-and post-BT contrast sensitivity measurements.

No side effects occurred, besides variable tiredness during the training sessions. Figure 3 illustrates the microperimetry for PRLs obtained from patient # 4 in the baseline visit compared to 1week post-BT. Each point in green in the graph represents one attempt of fixation. The ellipses encircle geographically the PRLs 63% and 95%, respectively, on each test report. The post-BT reduction of this called bivariate contour ellipse area (BCEA) number given by the MAIA in square degrees, when available, demonstrates the BT effect on nystagmus dampening. BT sessions could be registered appropriately by the MAIA, but not all the BCEA baseline or post training could be obtained by the device. For three subjects that MAIA could capture the BCEA measure, the fixation stability improved 42.6% in the BCEA 63% and BCEA 95% equally.

After BT sessions, nystagmus dampening occurred when the patient attempted fixation was told to remember

Table 1. Age, distance BBCVA, near BBCVA, and fixation stability before and after BT.

Patient ID	Age (Years)	BBCVA distance baseline (logMAR)	BBCVA distance pre-BT (logMAR)	BBCVA post-BT (logMAR)	Near BBCVA baseline (logMAR)	Near BBCVA pre-BT (logMAR)	Near BBCVA post-BT (logMAR)	BCEA 63%pre-BT (square degrees)	BCEA 63%post-BT (square degrees)	BCEA 95%pre-BT (square degrees)	BCEA 95%post-BT (square degrees)
1	11	0.3	0.2	0.1	0.3	0.4	0.1	12.7	25.8	37.9	77.2
2	6	0.7	0.6	0.6	0.3	0.2	0.1	N/A	N/A	N/A	N/A
3	10	0.4	0.5	0.4	0.2	0.3	0.2	N/A	N/A	N/A	N/A
4	9	0.5	0.6	0.4	0.3	0.4	0.1	22.5	10.5	67.4	31.6
5	6	0.4	0.3	0.2	0.1	0	0	65.6	6.7	196.6	20.1
6	6	0.9	0.7	0.7	0.4	0.3	0	N/A	N/A	N/A	N/A
10	8	0.4	0.5	0.3	0.2	0.2	0	N/A	N/A	N/A	N/A
12	6	0.5	0.5	0.3	0.2	0.1	0	N/A	N/A	N/A	N/A
13	13	0.3	0.3	0.2	0.2	0.1	0	N/A	N/A	N/A	N/A
14	15	0.2	0.2	0.1	0.1	0	-0.1	N/A	N/A	N/A	N/A
Ave	9	0.46	0.43	0.33	0.23	0.21	0.04	33.6	14.3	100.63	42.96
SD	3.2	0.21	0.18	0.2	0.09	0.14	0.08	28.1	10.1	84.40	30.19
			ANOVA	$p = 0.0002$		ANOVA	$p = 0.0006$	*T*-test	$p = 0.45$	*T*-test	$p = 0.45$

BBCVA: binocular best corrected visual acuity; BCEA: bivariate contour ellipse area, indicating the fixation stability; sq: square degrees; BT: biofeedback training; SD: standard deviation; Ave.: average; N/A: not applicable.
p: one-way repeated measured ANOVA analysis. *T*-test: paired samples analysis.

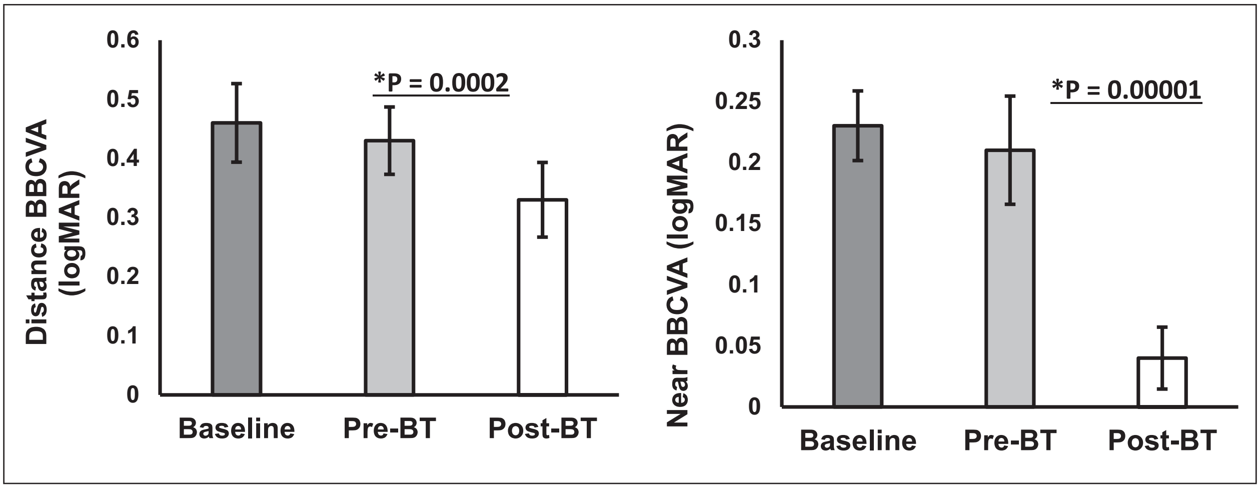

Figure 1. Binocular best corrected visual acuity measures comparing baseline, pre-and post-BT for distance and near vision.
BBCVA: binocular best corrected visual acuity measured in ETDRS for distance (left) and near (right); BT: biofeedback training; Pre-BT: baseline visit; Post-BT: 1 week Post training; *p*: one-way repeated measured ANOVA analysis.

Table 2. Stereopsis, reading speed and contrast sensitivity pre-BT and post-BT.

Outcome	Pre – BT	Post – BT	*p* value
Stereopsis (seconds of arc)	283 ± 338.1	39 ± 32.3	0.04
Reading speed (words/minute)	74.7 ± 51.2	104.7 ± 53.6	<0.0006
Contrast sensitivity (logMAR)	0.26 ± 0.17	0.08 ± 0.12	0.01

BT: biofeedback training (Average ± SD).
p value: *t*-tests, paired samples analysis.

the BT sound. Furthermore, in all daily activities, this effect occurred naturally during conversations, playing videogames or improving psychological behavior, as related by the parents. CVFQ scores of QoL (available for nine patients) increased from 23.8 ± 2.2 to 26.3 ± 2.3 (p=0.001). CVFQ subsections outcomes are analysed in Figure 4. General vision, visual competence, personality, and family impact of the IINS improved after BT.

Figure 5 shows the BBCVA measurements for the participants until the present. Five subjects have completed more than 3 months of follow up so far, and a trend for maintenance of the results post-BT is evident.

Discussion

Our preliminary results for BT in IINS show that it benefits all visual functions and widely the quality of life estimates as compared to baseline control measures. BT for Nystagmus was described as early as 1980.[15–19] The results obtained in previous studies found increasing of foveation time, visual acuity improvement and nystagmus intensity reduction during the sessions. The protocols were not reproductible clinically, exception for Ciuffreda,[18] who used a special device for simulating BT. No methodology was developed before to follow the long-term efficiency of the method or BT benefits for other visual functions and QoL in children with IINS. It is obvious that the core of the BT method is based on improving oculomotor control centrally through increased attention, but still its mechanisms of action remain not fully understood.[25]

Recently, Caputo studied retrospectively 12 children between 6–12 years old and obtained significant fixation stability and BBCVA improvement using MAIA BT for 100–240 min in total.[18] In our pilot study there was a strong correlation of improvement not only in distance but near BBCVA concomitant to an improvement in stereopsis, contrast sensitivity, QoL, and fixation stability (when available) post-BT.

Distance vision

Distance vision, a challenge in the LVR, was markedly impacted by BT. The natural progression of BBCVA for IINS children has been described as 0.04 to 0.06 logMAR (3 letters of Snellen) of improvement as the age doubles.[26] This is insignificant compared to the BT effect in this study, 0.1 logMAR/1 week after BT. Accompanied by the other visual functions improvement, the improvement of 1 ETDRS line for visual acuity as obtained inhere can be the difference for being eligible for a driver's license, psychological comfort for social conversations, reading menus in restaurants, and can never be overemphasized. Furthermore, this visual improvement from the nystagmus dampening can theoretically boost the visual development in early age children, impacting decisively this cohort's prognosis.[27,28] The improvement in distance vision has been maintained after the therapy up to 5 months so far.

Table 3. Reading speed and near BBCVA pre- and post-BT.

Patient ID	Age (Years)	Reading speed pre-BT (words/minute)	Reading speed post-BT (words/minute)	Near BBCVA pre-BT (logMAR)	Near BBCVA Post-BT (logMAR)
1	11	64	120	0.4	0.1
2	6	N/A	N/A	0.2	0.1
3	10	48	91.4	0.3	0.2
4	9	41.7	64	0.4	0.1
5	6	N/A	N/A	0	0
6	6	16	36	0.3	0
10	8	64.2	96	0.2	0
12	6	N/A	N/A	0.2	0
13	13	128	150	0.1	0
14	15	161	192	0	−0.1
Ave/Sd	9 ± 3.2	74.7 ± 51.2	104.7 ± 53.6 $p < 0.0006$	0.21 ± 0.14	0.04 ± 0.08 $p < 0.0006$

Reading Speed as measured with the Smith-Kettlelwell Test.
BT: biofeedback therapy; N/A: not applicable.
p: *p* value using *t*-test paired samples analysis.

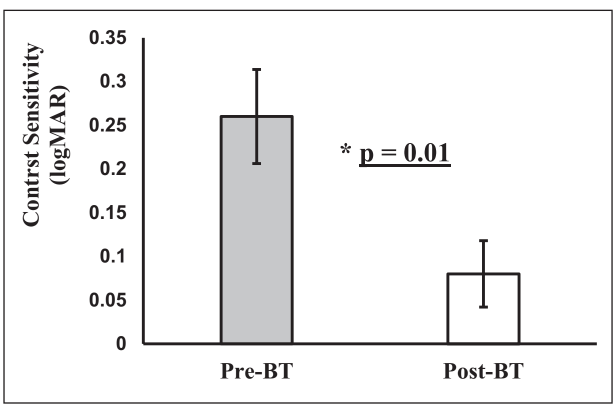

Figure 2. Contrast sensitivity pre-and post BT.
Contrast Sensitivity: Colenbrander Charts Contrast Sensitivity in LogMAR; BT: biofeedback training; Pre: visit before training; Post BT: > 1 week visit after training; *p*: paired samples *T*-test.

Near vision

Reading speed is typically benefited by BT in adults with central vision loss.[16,17] In this study, this also occurred significantly for IINS children. For illiterate patients, a proportional improvement was obtained for near BBCVA. This was consistent with the reading speed improvement from the literate children. Reports of better school performance were frequent.

Contrast sensitivity and stereopsis

These two visual functions correlated to the ETDRS letters visual acuity also improved significantly. There were reports of better orientation and mobility from the children and their parents, due to the greater contrast sensitivity, and better definition to see and play video games, probably from both functions' improvement.

Quality of life

QoL CVFQ scores increased significantly post-BT, improving in all the subsections general vision, visual competence, personality, and family impact of the nystagmus. During the study, more than one participant exemplified this through an improved behavior at school and home post-BT. Enjoying traveling with the family, fine near vision tasks as drawing, painting and reading books are a few of the items studied in CVFQ that disclose the impact of BT in the patient's quality of life.

Many previous studies could not demonstrate a stable increase of the visual acuity post-BT for nystagmus treatment. These studies used electrical nystagmography connected to audio BT, while our cases were trained with the MAIA microperimeter BT module. This difference in methodology can itself explain the better outcomes found. The younger age of our patients was possibly an important differential factor.[29] The inclusion criteria was also a differential in the present study. Only IINS children were included, not INS patients in general.[18] IINS has a better potential for improvement, since the anatomical ocular and neurological structures are normal. Further investigations should be conducted for the other INS cases.

The BT protocol used was feasible for application in a clinical setup, although requires specialized staff training. Only four sessions of 20 min each, 80 min in total, were used. This protocol is shorter, thus more comfortable for the family compared to the common 10 sessions (100–240 min) protocol. This may have contributed to the good

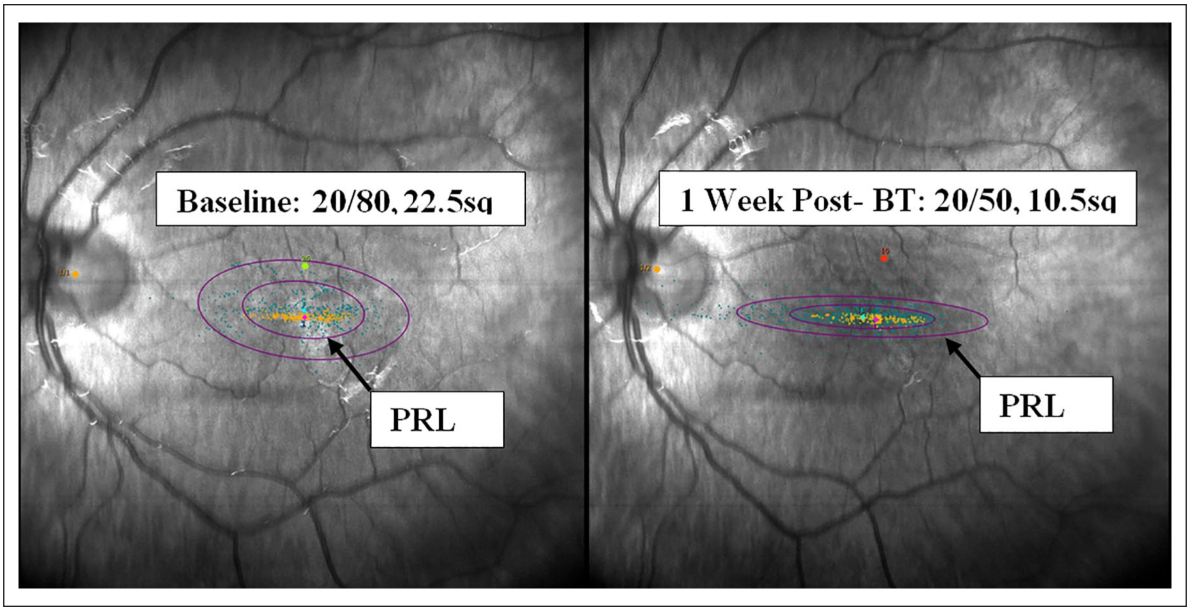

Figure 3. MAIA microperimetry PRLs pre- and post - BT for patient # 4.
PRL: preferred retinal locus; BT: biofeedback training; Binocular best corrected visual acuity: 20/80 pre- and 20/50 post-BT. 63% BCEA: bivariate contour ellipse area (PRL fixation stability calculated by MAIA microperimeter) 22.5 sq pre- and 10.5 sq post-BT; sq: square degrees.

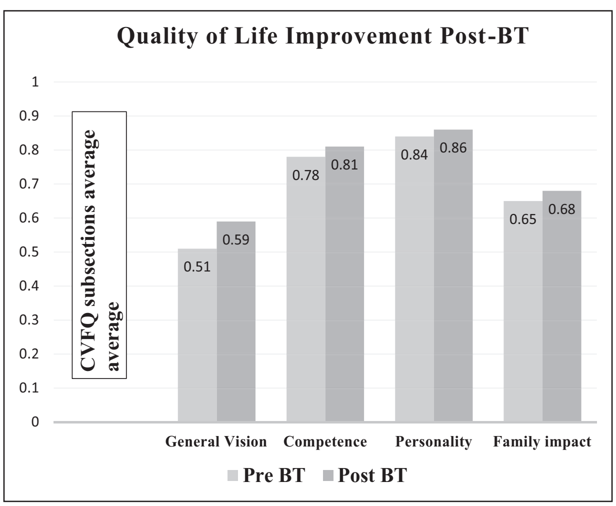

Figure 4. CVFQ QoL subsections pre-and post BT.
CVFQ: children's visual function questionnaire; BT: biofeedback training; Pre: visit before training; Post BT: >1 week after training.
The average of the answers for each subsection is represented above pre- and post- BT.

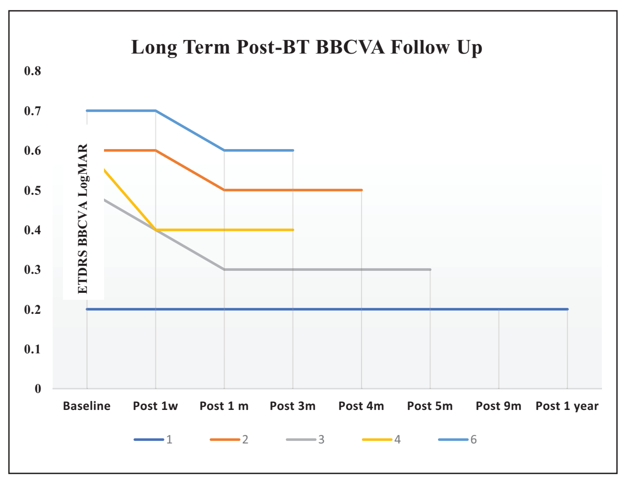

Figure 5. Long term follow up for BBCVA post-BT.
BBCVA: binocular best corrected visual acuity in LogMAR as measured with ETDRS charts; Post 1 w: 1 week post-biofeedback training; Post 1 m: 1-month post-biofeedback training and so consecutively; Post 1 year: 1-year post-biofeedback training.

adherence to the treatment. The BT has been a harmless, inexpensive and non-surgical therapy. BT can be repeated as needed, although we still do not know if repetition of the sessions can achieve higher results.

Limitations

An important limitation of this study was the absence of an accurate method to measure FS, which could not be determined in most of the subjects. This can be attributed to the high frequency IINS cases also included in this study. It was clear that the MAIA instrument, which has a 25 Hz registration frequency, although much valuable for BT, was not able to study the nystagmoid ocular movements for comparison. Infrared video nystagmography becomes necessary for further research. Another limitation in this study was that the number of patients we had so far was not ideal for statistics analysis. Therefore, the continuation of this study is mandatory.

Authors' note

None of authors have any propriety interest related to this study.

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