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Visual rehabilitation using video game stimulation for Stargardt disease

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Abstract

Background: Stargardt disease, a common form of heredomacular degeneration, leads to severe vision loss. Video game play can act as a positive biofeedback to reinforce visual rehabilitation and fixation training. It can potentially lead to visual improvement. This study was done to explore the possibility of visual improvement using video game stimulation for visual rehabilitation in Stargardt disease.

Methods: We evaluated eight patients with Stargardt disease who had nonatrophic retina surrounding the area of degeneration at the macula. They underwent extensive baseline testing to determine their Snellen visual acuity, pattern visual evoked potentials, retinal sensitivity, and fixation analysis with microperimetry, electroretinography, fundus photography, optical coherence tomography, and autofluorescence. They were given 40 h of training with video game play and re-evaluated on all the tests.

Results: They showed both subjective and objective evidence of improvement in visual functions and vision-related tasks. Visual acuity (from 0.77 ± 0.29 to 0.71 ± 0.32 logMAR, $p = 0.027$), contrast sensitivity (from 1.28 ± 0.25 to 1.46 ± 0.17, $p = 0.002$), and fixation stability (log of bivariate contour ellipse area from 6.67 ± 0.52 to 5.85 ± 0.84, $p = 0.022$) improved significantly. The retinal sensitivity improved by 0.47 ± 3.39 dB ($p = 0.67$). Stereopsis and pattern visual evoked potentials showed improvement. A low vision questionnaire documented subjective improvement.

Conclusion: Visual stimulation by video game play can result in improvement in visual acuity, fixation pattern, and retinal sensitivity with improvement in vision-related tasks. It can serve as a simple rehabilitatory technique for patients with central vision loss due to Stargardt disease.

Keywords: ABCA4 retinopathy, biofeedback, heredomacular degeneration, Stargardt disease, video game stimulation, visual rehabilitation

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Introduction

Stargardt disease is the most common inherited macular disorder. Its prevalence is estimated to be 1 in 8000 to 1 in 10,000.[1] It is caused by a mutation in the *ABCA4* gene and is inherited as an autosomal recessive disorder.[2] It leads to degeneration of the photoreceptors in the central macular area with atrophy of the retinal pigment epithelium and thinning of the small choroidal vessel layer in young age.[3] Children with the disease typically begin experiencing central vision loss between 6 and 12 years of age. The progression of vision loss is variable and can start with a visual acuity of 20/40 and decrease rapidly (especially in children) to 20/200 (legal blindness as per US Social Security definition). So far there are no proven therapies for this disease, and many young adults are resigned to a life of severely impaired vision. Stargardt disease is currently the subject of more clinical trials than any other inherited retinal diseases, including gene therapy, stem cell transplant, and drugs modulating the visual cycle.[4–6] The affected young persons face a lot of difficulties in their daily tasks. Various optical, nonoptical, and assistive devices help the

persons in recognizing faces, watching TV, seeing blackboard, reading fine prints, and performing computer or mobile tasks.

As they lose the central vision, many of these young people use retinal points that are located outside the central area of retinal degeneration for fixation. This point referred to as a preferred retinal locus (PRL) may be at a considerable distance from the atrophic area resulting in eccentric fixation that is often unstable.[7] Poor fixation stability is correlated with poor visual acuity and poor reading speed.[8] One of the methods used to improve the fixation stability in such situations is the biofeedback training using the MP1 microperimeter (Nidek instruments Inc., Padova, Italy). It helps the brain to memorize the fixation location by increasing attention modulation, thereby providing an efficient PRL for visual tasks.[9,10] The hypothesis is that improved fixation in these patients would lead to better visual performance because fixation is an essential prerequisite for visual perception. The cortical neurons located in retinotopic position corresponding to the scotoma do not receive any stimulus. As the extra-scotomatous fixation develops and becomes stable, the healthy neurons from the new fixation begin sending stimulation to this area in the cortex.[11–13] These connections are gradually reinforced leading to a stable system. Adaptive responses in the cortex which lead to these are considered neuronal plasticity.

Amblyopia, a developmental anomaly that results from physiological alterations in the visual cortex, causes impaired vision due to abnormal binocular interaction during the sensitive period of visual development early in life.[14] Recent studies have shown that even after the critical period, vision can be improved in adults with amblyopia by intensive training of the amblyopic eye with noninvasive stimulation of the visual cortex.[15,16] Video games are attention-demanding tasks which are preferred by the young population. Action video games (also called as first-person or third-person shooter games) are classified as those games which have extraordinary speed; perceptual, cognitive, and motor load; unpredictability; and peripheral processing.[17] Many studies have shown visual improvement in amblyopic eyes by reduction of suppression and perceptual learning with the use of video games.[14,16,17] Video game play induces plasticity in amblyopia, which improves lower and higher levels of visual processing indicating several neural mechanisms which probably involve recalibration of the distorted retinotopic cortical mappings.[18]

This plasticity can be made use of by training with action video games, thereby improving the person's visual performance. Action video game playing is associated with improved visuomotor performance. But the underlying neural mechanisms associated with this increased performance are not well understood. In an amblyopic eye, the video game play stimulates the dormant fovea to result in increased sensitivity and improved visual acuity.[18]

We propose that aggressive training with action video games can be tried in patients with Stargardt disease, to stimulate the PRL because their peripheral retina is uninvolved. We attempted the video game stimulation technique in patients with Stargardt disease to improve the visual functions.

Methods

A feasibility study was carried out. It conformed to the tenets of the Declaration of Helsinki and was approved by the institutional review board (Study no 544-2016-P). Written informed consent was obtained from all the participants.

Patients with Stargardt disease and no other health issues were recruited. The diagnosis of Stargardt disease was clinical and was confirmed by fundus photo, autofluorescence, optical coherence tomography, and full-field electroretinography. The fundus showed a well-demarcated area of degeneration at the macula with beaten bronze appearance and hypoautofluorescence. The surrounding retina was nonatrophic and the optic nerve head was normal. Optical coherence tomography revealed thinning of the retina with atrophy of the photoreceptors at the fovea. The electroretinography showed normal photopic and scotopic responses in all the patients.

The patients underwent baseline tests, which included logMAR visual acuity recording, visual evoked potentials, stereopsis (assessed by Randot Stereo test, Stereo Optical Co, Inc., Chicago, IL), and contrast sensitivity measurements for distance (1 m) and near (33 cm; assessed by Pelli-Robson test). The visual acuity was tested by an independent optometrist who was not part of the study and was unaware of the patients' participation in the study. The retinal sensitivity and fixation were analyzed with microperimetry

on scanning laser ophthalmoscopy optical coherence tomography (Optos PLC, Washington, DC). The polar 5-210 program was used, which tested 52 points in the macular area with 4-2 strategy. The fixation stability was measured by calculating the bivariate contour ellipse area values using the following formula:

$$BCEA = 2.28\,\sigma H\,\sigma V\left(1-\rho^2\right)^{1/2}$$

where σH and σV are the standard deviations of the horizontal and vertical fixation position and ρ is the product-moment correlation of these two components.[10,19]

All patients were advised to play action video game (Call of Duty 4 Modern Warfare, developed by Infinity Ward and published by Activision) for 1 h daily in each eye with alternate patching. None had any previous experience in playing video games such as this. The compliance was monitored by weekly video conversations over the Skype app. The patients were asked a set of questions during the video chat to confirm that their training sessions are going on as scheduled. The number of sessions completed and the level of game reached were confirmed. Assessment of the video game levels currently played by the patient was done by asking the patient to play the game for 10 min during the video chat. Apart from this, each patient was also asked to maintain a logbook of the training sessions and to email the logbook to the study coordinator.

At the end of 40 h (20 h each eye), all patients were reassessed in the office and all the tests were repeated. All patients were administered a previously validated low vision questionnaire before and at the end of the training (Appendix 1). We report here the cases who completed the training and returned for follow-up.

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS), version 20.0 (IBM Corp, Armonk, NY). Wilcoxon signed-rank test was done to compare the pre- and post-training parameters. A p value <0.05 was considered as significant. This being a feasibility study, the sample size was limited.

Results

The study was conducted between September 2016 and September 2017. A total of 15 patients in the age range of 13–30 years (mean = 18.5 ± 3.2 years, median = 16 years) were included. Eight patients completed the study and came for follow-up tests. These were included in the analysis. There were six males and two females. All the patients were diagnosed clinically to have Stargardt disease. Healthy paracentral and peripheral retina was confirmed on fundus examination, autofluorescence, and electroretinography. A few patients showed flecks surrounding the macular lesion. The pre-training mean visual acuity was 0.77 ± 0.29 logMAR (range, 0.20–1.0 logMAR). After training, it improved to 0.71 ± 0.32 logMAR ($p = 0.027$). There was significant improvement in contrast sensitivity (1.28 ± 0.25 to 1.46 ± 0.17, $p = 0.002$) and in fixation stability measured by the log of bivariate contour ellipse area (6.67 ± 0.52 to 5.85 ± 0.84, $p = 0.022$). The retinal sensitivity improved by 0.47 ± 3.39 dB ($p = 0.67$) but did not reach statistical significance. There was improvement in stereopsis. The 1-degree checker size pattern visual evoked potentials showed mild improvement in amplitudes as well as latencies ($p = 0.21$, $p = 0.96$). The 15-degree checker size also showed improvement. There was statistically significant improvement in the amplitude ($p = 0.029$). The improvement in latency was not significant ($p = 0.15$). Subjectively, patients noted some improvement in daily tasks with improvement in questionnaire scores. The details of pre- and post-training are given in Table 1.

A change in the location of PRL was seen. The fixation point was measured from the center of the screen. The mean displacement was 12.56 ± 13.88 degrees across X axis and 9.79 ± 6.41 degrees across Y axis. Out of eight cases, three had equal baseline vision in both the eyes, four showed more improvement in the better eye, and one showed more improvement in the worse eye. One eye of one patient showed more than two lines of visual improvement, and both eyes of one patient showed more than one line of visual improvement.

Discussion

In Stargardt disease, the central point of the retina, which is normally used for fixation, is degenerated leading to poor visual acuity. However, the retina just outside the area of degeneration is nonatrophic. In the process of adaptation, many patients develop preferred retinal loci outside the area of degeneration which are used for various tasks such as reading. In an experimental setup, a monkey developed PRL in both the eyes within days of creating macular burns in both the eyes

Table 1. Visual acuity and other parameters before and after training with video game stimulation in patients with Stargardt disease.

	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7		Case 8	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
VA (LogMAR)-RE	0.5	0.34	0.24	0.18	0.54	0.44	1	1	0.9	0.86	1	0.92	1	1	1	0.9
VA (LogMAR)-LE	0.92	0.6	0.3	0.12	0.5	0.44	1	0.94	0.92	0.84	1	0.9	0.94	0.96	1	0.9
VA (LogMAR)-BE	0.42	0.34	0.2	0.12	0.38	0.34	0.98	0.94	0.9	0.8	1	0.9	0.94	0.94	0.9	0.8
Contrast Sensitivity-RE	1.65	1.65	1.5	1.65	1.5	1.65	1.05	1.35	1.05	1.35	1.05	1.2	1.35	1.5	1.05	1.35
Contrast Sensitivity-LE	1.5	1.65	1.5	1.65	1.6	1.85	1.35	1.65	1.2	1.35	1.2	1.35	1.65	1.5	1.05	1.35
Stereopsis (arc sec)	NM	70	80	50	70	70	>500	>500	>500	200	>500	200	>500	400	>500	200
Worth Four dot test-Distance	LE-Sup	Uncrossed diplopia	Fusion	Fusion	Varying	Varying	LE-sup	LE-sup	RE-sup	RE-sup	Fusion	Fusion	RE-sup	RE-sup	Fusion	Fusion
Worth Four dot test-Near	LE-sup	Fusion	Fusion	Fusion	Fusion	Fusion	LE-sup	LE-sup	RE-sup	RE-sup	Fusion	Fusion	Fusion	Fusion	Fusion	Fusion
RE-Retinal sensitivity (dB)	8	9.12	15.23	16	18.46	19.04	14.96	17.46	13.2	NA	19.1	15.27	17.46	18.12	19.15	14.08
LE-Retinal sensitivity (dB)	8.04	9.05	15.88	16.27	18.49	19.31	16.15	17.46	17.3	NA	15.08	16.3	16.45	17.12	19.25	19.12

Table 1. (Continued)

	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7		Case 8	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Visual evoked potential																
RE (1-degree checker size)																
Latency (ms)	109.37	93.75	95.48	95.48	95.48	97.22	86.14	104.16	114.5	105.9	76.38	71.1	104.6	125	92.01	79.38
Amplitude (mV)	2.84	3.3	2.75	3.18	4.69	4.69	3.12	3.65	2.09	4.14	1.53	3.78	3.12	1.54	1.56	2.04
RE (15-degree checker size)																
Latency (ms)	81.59	85.54	85.06	85.06	111.11	88.54	105.9	111.11	100.69	109.37	107.6	90.27	112.1	98.96	98.96	71.18
Amplitude (mV)	2.11	3.39	2.93	3.64	4.18	4.18	2.53	3.41	3.19	3.34	3.07	4.52	2.53	2.12	2.09	3.61
LE (1-degree checker size)																
Latency (ms)	112.84	86.8	90.27	90.27	95.48	99.22	83.33	107.63	79.86	72.91	71.18	92.01	107.8	88.33	88.54	107.65
Amplitude (mV)	2.21	3.62	5.44	5.44	6.81	7.65	3.46	1.89	2.45	1.79	3.61	3.93	1.89	4.56	1.56	3.71
LE (15-degree checker size)																
Latency (ms)	104.16	71.18	79.56	81.59	92.01	104.16	88.54	90.27	NA	116.3	93.75	118.05	100.9	102.43	111.11	93.75
Amplitude (mV)	1.55	4.05	2.12	2.12	3.71	4.23	2.24	4.93	NA	1.6	3.85	1.98	4.93	5.31	3.86	4.42
LogBCEA-RE	7.34	5.25	6.44	4.56	6.39	5.83	6.5	5.89	5.68	5.3	7	6.05	7	6.95	7	7
LogBCEA-LE	7.93	6.11	3.34	3.04	6.29	6.04	7.12	7.3	6.72	5.5	8.5	7.12	7.3	7.11	8.52	8.12
VRQoL score	60	65	59	67	62	65	55	63	45	49	55	55	55	61	55	57

BCEA, bivariate contour ellipse area; BE, both eyes; LE, left eye; RE, right eye; sup, suppression; VA, visual acuity; VRQoL, vision-related quality of life.

with laser.[20] However, this locus can be eccentric, situated much farther away from the central fovea. Also, it is often associated with unstable fixation. Both eccentric location and stability of fixation have been seen to correlate with visual acuity in Stargardt disease.[8] The location of the PRL and stability of fixation can be improved with viewing training. The biofeedback technique, performed using the biofeedback module available with the older version of the Nidek microperimeter, MP1 uses auditory feedback to reinforce the fixation stability. The retinal locus chosen according to the best retinal sensitivity and a convenient location is stimulated. Auditory reinforcement encourages the patient to fix with this point. We did a pilot study using the biofeedback technique in Stargardt disease and could demonstrate visual improvement after 10 sessions of training.[10] However, this software module is no longer available.

Our hypothesis is that aggressive action video game can exercise a similar purpose of selection, and stimulation of PRL can be achieved in Stargardt disease which would lead to visual improvement. The action video game helps the brain in improving its plasticity, attention, and learning. It requires split second decisions and action. When the target of the level in the game is achieved, it can work as a positive feedback, encouraging the patient to maintain the fixation. Progressively increasing difficulties in the levels of the game can help in refining the stimulation process. Thus, playing action video game can help a patient with Stargardt disease, develop an appropriate PRL, help maintain steady fixation with it, and lead to improvement in visual acuity along with improved contrast sensitivity.

The intensive video game training in our patients improved the lower and higher levels of visual functions to some extent. There was improvement in visual acuity, stereopsis, contrast sensitivity, and fixation stability. We took care to avoid any possible bias by getting the visual acuity checking by a third person, blind to the study details. Also, we feel the results we saw are beyond the normal intersession variability reported for microperimetry.[21,22] There were both subjective and objective evidence of visual improvement. The mean retinal sensitivity did show improvement in six patients; however, it did not reach statistical significance probably due to small sample size. Also, the margin of increase in the retinal sensitivity is less on account of the degeneration of the photoreceptors in the central area, which we feel would restrict the statistical significance. The pattern visual evoked potentials also showed improvement. Therefore, we propose the possibility of using action video game play as a means to improve visual acuity in Stargardt disease. However, sustainability of these improvements would need to be tracked. The possibility of unacceptable diplopia does exist and needs to be borne in mind while advising this training. It is likely to be more beneficial in young children in whom the PRL are still not established and the fixation is unstable.

However, our study has limitations due to its small sample size and lack of a control group. A larger study needs to be done to check this hypothesis. A longer follow-up is also essential to determine whether the benefits seen are sustained for a long time or not.

Conclusion

Video game play may be useful as a low vision rehabilitation tool in patients with macular degeneration due to Stargardt disease. It can lead to stimulation of a PRL, improved fixation, and quality of vision. It can also act as a positive biofeedback to the patient. Thus, it may help patients to improve the performance of vision-related tasks.

Availability of data

Data are given in the table included in the manuscript.

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Appendix 1

LV Prasad-Functional Vision Questionnaire.[23]

S no			None	A little	Moderate	Great	x	n/a
		Yes /No/ Not applicable If yes, how much difficulty do you have?	4	3	2	1		
1	Do you have any difficulty in making out whether the person you are seeing across the read is a boy or a girl, during the day?							
2	Do you have any difficulty in seeing whether somebody is calling you by waving his or her hand from across the road?							
3	Do you have difficulty in walking alone in the corridor at school without bumping into objects or people?							
4	Do you have any difficulty in walking home at night (from tuition or a friend's house) without assistance when there are streetlights?							
5	Do you have any difficulty in copying from the blackboard while sitting on the first bench in your class?							
6	Do you have difficulty in reading the bus numbers?							
7	Do you have any difficulty in reading the other details on the bus (such as its destination?)							
8	Do you have any difficulty in reading your textbooks at an arm's length?							
9	Do you have any difficulty in writing along a straight line?							
10	Do you have any difficulty in finding the next line while reading when you take a break and then resume reading?							

Appendix 1. (Continued)

S no			None	A little	Moderate	Great	x	n/a
		Yes /No/ Not applicable If yes, how much difficulty do you have?	**4**	**3**	**2**	**1**		
11	Do you have any difficulty in locating dropped objects (pen, pencil, eraser) within the classroom?							
12	Do you have any difficulty in threading a needle?							
13	How much difficulty do you have in distinguishing between 1 rupee and 2 rupee coins (without touching)?							
14	Do you have difficulty in climbing up or down stairs?							
15	Do you have difficulty in lacing your shoes?							
16	Do have difficulty in locating a ball while playing in the daylight?							
17	Do you have difficulty in applying paste on your toothbrush?							
18	Do you have difficulty in locating food on your plate while eating?							
19	Do you difficulty in identifying colors (e.g. while coloring)?							
20	How do you think your vision is compared with that of your normal-sighted friend? Do you think your vision is	As good as your friend's		A little bit worse than your friend's		Much worse than your friend's		
If they can no longer perform the task because of their vision, they are to circle 'x', and if they do not perform the task for nonvisual reasons, to circle 'n/a'.								