Errata

I list of abbreviations fattas: **BCVA = Best Corrected Visual Acuity, VEGF = Vascular Endothelial Growth Factors, LCD = Liquid Crystal Display, LED = Light Emitted Diodes**.

Sid. 4 Fig. 3 & 4 i text **skall vara 4 & 5**

Sid. 4 Fig. 5 i text **skall vara fig. 6**

Sid. 5 Stycke 1.6 rad 20 **by skall vara be**

Sid. 6 Stycke 1.7.7 rad 11 **skall stå: were"black letters"presented…**

Sid. 8 Stycke 1.7.6 Fig. 4 i text **skall vara Fig. 7 och Fig. 5 skall vara 8.**

Sid. 11 Stycke 1.9.1 första meningen skall inledas **"Techniques for"**

Sid. 11 Stycke 1.9.1 von Hoffsten, **skall vara von Hofsten. Samma stavfel i alla referenser**.

Sid. 12 Artikel 4 (p=.003) **skall vara (p=.014)**

Sid. 16 Fig. 6 i text **skall vara Fig. 9**

Sid. 17 Stycke 3.2.4 Fig. 7 i text **skall vara Fig. 10**

Sid. 19 Stycke 4.1 Fig. 8 i text **skall vara Fig. 11**

Sid. 19 Stycke 4.1 Fig. 9 i text **skall vara Fig. 12**

Sid. 21 Stycke 4.1.2 Fig. 10 i text **skall vara Fig. 13**

Sid. 21 Stycke 4.1.4 Fig. 11 i text **skall vara Fig. 14**

Artikel 4. Sid. 10 sista raden. Mean 62.4, D=32.3 och D=39. Skall vara: **Mean 0.12, SD=0.06 och SD=0.08**

Artikel 4. Sid. 19 Tabell 2. Sid. 20 Tabell 3, **se ny uppdaterad artikel 4.**

Tabell 2. Sid. 24 stycke 4.2.9, **se uppdaterad artikel 4.**

Tabell 3. Sid. 29 stycke 5.2.6, **se uppdaterad artikel 4.**

Referens Goldstein sid. 28 artikel 4 fattas i referenslistan skall vara: **Goldstein, M., Öquist, G., and Lewald, I. (2006). Evaluation of PreCodia, a Computerized Reading Aid for Readers Suffering from Dyslexia. In Proceedings of Human Factors in Telecommunication 2006 (Sophia-Antipolis, France), 127-134. Brighton, MA: IGI Group.**

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Analysis of reading eye movements with Tobii 1750 eye tracker in AMD patients pre and post op Ranibizumab (Lucentis) treatment

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Abstract

Background: Reading ability in the elderly means independence, communication, mental agility and quality of life. In age-related macular degeneration (AMD), the main deficit is the loss of reading ability. The neovascular form of age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the developed world among people over 50 years of age. With ranibizumab (Lucentis) a drug treatment has become available and its clinical efficacy has been assessed in several studies. However, despite good outcome of visual acuity, patients often report that their reading ability has been affected. Lately, a new technique to study reading performance and eye-movements has been developed (Tobii eye tracker). The aim of this project was to evaluate, by using the Tobii eye tracker, if patients with neovascular AMD, treated with intravitrial Lucentis, gain a better reading ability.
Material and Methods: Twenty patients, 15 female and 5 male (range 74 – 98 year), with subfoveal neovascular AMD who after clinical examination was assessed for treatment with intravitrial Lucentis, were recruited from the Department of Vitreo Retinal Surgery, St. Erik Eye Hospital. All had, before and after treatment, their reading speed, comprehension, fixations, saccadic eye movements (number of saccades per word and saccade amplitude) and regressions (numbers of regressions per word and regression amplitude) measured with the Tobii Eye tracker while reading two texts with an equal readability rating.
Results: For all eye movement parameters, except the number of regressions per word, there was no statistically significant difference when comparing the results from before and after treatment. However, there was a statistically significant increase in the number of regressions per word after treatment as well as increased visual acuity and comprehension.
Conclusion: As a stand alone measure of visual improvement after, for example Lucentis treatment, evaluation of reading speed and reading eye movements is not sufficient, but can together with other tests, give valuable information about the patients complains and the outcome of a treatment.

Background

The neovascular form of age-related macular degeneration (AMD) is characterized by an abnormal growth of newly formed vessels under the central area of the retina. It is the leading cause of irreversible vision loss in the developed world among people over 50 years of age (Bressler 2004; Congdon et al. 2004). The age-related changes that stimulate the growth of choroidal neovascularizations (CNV) are not yet completely understood. However, the vascular endothelial growth factor A (VEGF-A) promotes angiogenesis and vascular permeability, and has been identified as an important factor promoting CNV, (VIP Study Group 2004; Rakic et al. 2003; Verteporfyrin Roundtable 2000 and 2001 Participants 2002; Otani et al. 2002; TAP Study Group 2001; TAP Study Group 1999; Lopez et al. 1996; Frank et al. 1996; Kvanta et al.1996). With ranibizumab (Lucentis; Novartis, Basel, Switzerland) a drug treatment became available that neutralizes VEGF-A. Its clinical efficacy have been assessed in 3 randomized, double-masked controlled studies (known by the acronyms: MARINA, (Rosenfeld et al. 2006), PIER, (Regillo et al. 2008) and ANCHOR, (Brown et al. 2006) with a total of 1,323 patients with exudative AMD enrolled. Reduced macular thickness and impressive increases in best-corrected visual acuity (BCVA) in a large proportion of eyes have been shown by the MARINA and ANCHOR studies. Results that have been confirmed in a recent study by Rothenbuehler et al. (2009).

However, visual acuity says very little about the entire visual function and can therefore not fully predict the every day functional visual outcome after Lucentis treatment. In order to investigate further aspects of visual function, tests such as colour vision, contrast sensitivity, visual field or maybe more importantly the ability to read should be tested. Reading and writing plays a fundamental role in our culture. Compared with, e.g., speech, written language has an immense impact as it offers the possibility to share information over unprecedented distance in time and space. Reading is a skill that lies deeply imbedded within our mind. Our knowledge on exactly how the reading process is organized within the brain is still to be discovered, but by observing how the eyes move while reading we can obtain knowledge of the recognition process. To enable reading, not only moving the eyes are required, but also a good quality of fixation is essential.

CNV resulting from AMD often leads to scotoma, which is strongly associated with reduced ability to perform everyday activities such as reading (Richter-Mueksch et al., 2006). Measurements of eye movements have been available for several decades. The first precise techniques were based on scleral search coils (which are still used today for certain applications) (Ram-Tsur et al., 2006; Robinson 1963). In recent years, head-mounted and remote camera-based systems have been developed to allow more natural and less cumbersome methods of gaze tracking. But, video-based solutions have either required the use of helmet-mounted equipment or have struggled to deal with head movement. The today commonly used instrumentation for eye movement studies, also struggle with the fact of being time consuming and difficult to use in clinical settings and have primarily been used in experimental studies. There has been a substantial amount of eye-movement research related to reading. Within this field, different research groups have investigated eye-movements in slightly different ways. Their aims have been to understand the mechanics of how the eyes move often in relation to dyslexia and eye-movement anomalies (Ram-Tsur et al. 2006; von Hofsten & Rosander 1996). This leaves very little written on the subject of the functional detection capability in, e.g., eye diseases, measured with these methods.

Tobii eye Tracker

Lately, a new technique to study reading performance and eye-movements has been developed (Tobii eye tracker) (Tobii Technology Inc. 2008). Its primary advantage is its accessibility, in comparison to the video-based and head mounted solutions the subjects only has to sit in front of a computer screen. This ensures a reasonably natural environment for the subject, which provides the most realistic responses to different stimuli. Disadvantages with the system, compared with other eye movement apparatus is the relative low precision when it come to resolution and sampling frequency. In several different applications, however, the Tobii system's accessibility seems to outweigh the lack of precision (Källmark et al. 2008). The Tobii Eye Tracker 1750 (Tobii Technology Inc. 2008) LCD computer screen has an integrated high-resolution camera with a large field-of-view, used to capture images of the patient required for eye tracking. During tracking, the Tobii Eye Tracker uses near infrared diodes (NIR-LEDs) to generate reflection patterns on the corneas of the eyes of the patients. The camera collects these reflection patterns, together with other visual information about the patients. Image processing algorithms in the software identifies relevant features, including the eyes and the corneal reflection patterns. The position in space of each eyeball, and finally the gaze point on the screen, i.e., where the patient is looking are calculated in the Tobii software system. The display is based on a unit with maximum resolution of 1280x1024 pixels. The field of view of the camera for the Tobii is 21 x 16 x 20 cm (width x height x depth) at 60 cm from the screen. The frame-rate is 50 Hz, i.e., 50 gaze data points per second. Each gaze data point is provided with a time stamp in milliseconds, and is describing when each camera image of the eyes is taken. Since each image takes a certain amount of time for exposure, the time-stamp is set to the middle point of exposure. The time-stamp is accurate to about +/- 5 ms. In order to compensate for head movements in the calculation of eye movements, it is enough that one of the eyes are within the field of view. This grant an effective tolerance to head-motion of about 30 x 16 x 20 cm (width x height x depth) which is enough to compensate for head positions, which normally occur when sitting in front of a computer screen. The Tobii Eye Tracker recovers from a complete tracking failure in less than 100 ms, and can track eye gaze in angles up to +/- 40 degrees measured from the camera. By knowing where the eyes are oriented, it is possible to understand what causes reading difficulties, and, e.g., how successful the outcome of treatment is. Further it allows analysis of how reading capabilities varies over time in patients with a variety of diseases. Whilst a person with AMD can suffer from reduced reading ability which can drop to 24/ wpm (Sarah et al. 2006), a normal reader will perform in average 240/wpm (Björnsson 1968). Bearing this in mind, it is important with further investigations of eye-movements to better understand the mechanisms behind the reduced reading and the outcome from the treatment of AMD.

Aim of the experiment

The Tobii 1750 eye tracker can be regarded as more clinically accessible and less cumbersome than most other eye movement equipment and results from previous studies show that the Tobii system, despite its relative low resolution and sampling frequency, is suitable for evaluation of reading performance in clinical settings (Källmark et al. 2008). The aim of this project was therefore to evaluate if patients with neovascular AMD, treated with Lucentis, gain a better reading ability after treatment.

Methods and Material

Patients and clinical investigation

Twenty patients, 15 female and 5 male were recruited from the Department of Vitreo Retinal Surgery, St. Erik Eye Hospital, Stockholm, Sweden. Their mean age was 81.8 year (range 74 – 98 year). Inclusion criteria's were: Patients (50 year or older) with subfoveal neovascular AMD who after clinical examination with fluorescein and Indocyanin green (ICG)-angiography and coherence tomography (OCT), and who had (1) VA 20/200 or better; (2) classic or predominantly choroidal neovascularisation (CNV); and (3) occult CNV with an extension < = 4 disc areas with ongoing or a recent exposition of the disease. Exclusion criteria were lesions characterized of sub retinal fibroses with widespread geographical atrophies. Before examination of the reading eye-movements, all patients were refracted to best visual acuity (BVA) and consideration to the reading distance were taken for optimal glasses during the reading test.

Apparatus

A Tobii 1750 eye tracker was used for the experiment (Tobii Technology Inc. 2008). Subjects were seated in a comfortable chair approximately 60 cm from the screen. Before each recording the system was calibrated using a nine-point calibration pattern. The texts were presented left justified in a 24-pt sans-serif font over six pages (figure 1).

Texts

Each subject read two texts, from now on called text A and B. Both were editorials from a Swedish newspaper of equal difficulty measured using LIX (Björnsson 1968) (see www.lix.se for a calculator) (LIX = 48). Each text was 35 sentences long and of similar word length (A=501, B=518) (Table.1).

Procedure

The patients included, were scheduled for three Lucentis injections over a three month intravitrial. Half of the subjects read text A before text B and vice versa. The subjects were instructed to read normally as they would in any everyday situation. They were informed that they would be asked questions about the text afterwards. After reading a text, the subject was asked five multiple-choice questions on the content. The questions were designed so that the options were ambiguous and could only be answered if one had read certain passages spread over the whole text. The complete experiment took approximately 15 minutes to perform.

Analysis

Reading speed was measured in words read per minute (wpm) from the onset of the first page to the conclusion of the last. Comprehension was enumerated as the ratio of correct answers (%). Eye movements were recorded as time stamped coordinates of how the eyes moved over the screen. The recordings were analysed in two steps. First fixations were detected; next the movements between fixations were categorized. Any period when the eye remained within 1.5 degrees from its centre of gravity for at least 100 ms was considered a fixation. During a fixation, the centre of gravity was continuously re-weighted to the horizontal and vertical mean position. In the event of larger movements or blinks the fixation was considered finished. Movements between fixations were categorized depending on amplitude and direction. Movements shorter than 6.3 degrees would be classified as saccades if they were directed in a forward/downward direction (between 45 and 225 degrees); otherwise they were

categorized as regressions. Movements larger than 6.3 degrees were categorized as forward/backward/down/up sweeps depending on orientation (figure 2).
Eye movements were independently analyzed for the left and right eye and the results were averaged over both eyes. The number of fixations, saccades, and regressions were normalised into occurrences per word. The duration of fixations, the amplitude of saccades and regressions, and the ratio between saccades and regressions were used as comparison measures for the statistical analysis.

Statistics

The Wilcoxon signed-rank test was used for comprehension whereas paired Student's t-tests were used for all other measures. All tests were two-sided and the alpha level was set to 95 % ($p = .05$).

Ethical considerations

Ethical approval was given by the local ethical committee and the study adhered to the declaration of Helsinki.

Results

Of twenty recruited patients, six had to discontinue due to reasons beyond our control. All patients ($N = 14$) completed the experiment and had no problems with understanding what to do or how to do it. All results for visual acuity (VA), reading speed, comprehension and eye movements are presented below and summarised in table 2. For analysis of reading speed, comprehension and eye movements, texts A and B were regarded as one test which then was compared with the results of both texts after treatment.

Visual acuity

On average there was a significant improvement in visual acuity ($p = .036$). The patients read significant more ETDRS letters after treatment with a mean (M) increase of 8.85 letters ($SD = 14.19$). However, four patients had a decreased visual acuity while all other patients had an increased visual acuity.

Visual acuity

There was a significant difference in number of ETDRS letters read before and after treatment ($p = .036$). The mean number read before was $M = 29$ ($SD = 13.84$) and $M = 38$ ($SD = 11.28$) after treatment.

Reading speed

There was no significant difference in reading speed before and after treatment ($p = .25$). The reading speed was $M = 181.2$ wpm, ($SD = 34.3$) before treatment and $M = 171.6$ wpm, ($SD = 41.3$) after. Only two patients had an increased reading speed after the treatment.

Comprehension

There was as significant difference in comprehension of the texts before and after treatment ($p = .031$). The mean correctly answered questions for the texts were $M = 50\%$, ($SD = 20\%$) before treatment and $M = 60\%$, ($SD = 22\%$) after.

Eye Movements

The eye movements analysed was the number of fixations per word, the duration of fixations (i.e., in time), the number of saccades per word, the saccadic amplitude, the number of regressions per word, and the amplitude of the regressions. For all eye movement parameters, except the number of regressions per word, there was no statistically significant difference when comparing the results from before and after treatment (see table 2). However, there was a statistically significant increase in the number of regressions per word after treatment ($p = .046$), with a mean of 0.12 (SD = 0.06) before and 0.14 (SD = 0.08) after treatment.

Discussion

The treatment with Lucentis was effective in significantly increasing mean BVCA for the majority of the patients, which is in accordance with recently published reports (Rosenfeld et al. 2006; Brown et al. 2006; Regillo et al. 2008; Rothenbuehler et al. 2009; Kiss et al. 2009; Bressler et al. 2009).

The average values for reading speed found in this study M = 181.2 wpm before treatment and M = 171.6 wpm after, gives no significant changes that could be explained by the treatment. Both before and after treatment our AMD patients on average read slower than what we found examining normal subjects (Källmark et al. 2008).

In recent studies, opposite to expectations, reading speed was found to be significant different between two texts having an equal readability rating (Källmark et al. 2008). The same texts were used in this study and regardless of the outcome from the treatment, similar findings could be seen in which text A was red significantly slower compared with text B. When conducting analyzes of the data the texts were therefore analyzed together. Hence, texts used for studying reading performance should be chosen carefully since even texts of similar linguistic difficulty, due to the nature of the text content, can yield the differences found in reading performance. When analyzing the two texts together, no significant improvement or change in reading speed could be seen after the treatment. Although no improvement in reading speed could be found, a significant improvement in comprehension could be seen from M = 50% before treatment and M = 60%) after. The reason to this might be the increased visual acuity, but could also be a result of the strive to achieve as well as possible since the patient were aware of the questionnaires they were about to get after the tests. The improved comprehension could also be a result of the learning effects since the same texts were read at both occasions. However, this is unlikely for two reasons, firstly since the texts were read three months apart and secondly since one would expect reading to be faster the second time if the patients recognised the texts.

When looking at individual data, the subjects can be divided into two groups: A) Patients that had an increased visual acuity with 10 or more letters after treatment (n=5) (i.e., equivalent to two lines or better on the chart) and B) Patients who had an increased visual acuity less then 10 letters (n=9). When separating these groups, a clear difference in reading eye movement performance can be seen for those who had an increased visual acuity with 10 letters or more (table 3). They displayed, not only as the whole group, a significant increased comprehension but also a significant slower reading speed ($p = .014$), which could be explained with a more in-depth reading when also having an increased visual acuity. Furthermore, a significant number of more fixations per word could be seen ($p = .030$), this is also probably due to a more thorough reading.

Naively one would expect that increased or stable (i.e., not further reduced) visual acuity after Lucentis treatment would result in an ability to read faster and make fewer eye movements. However, this seems not to be the case. On the other hand, comprehension improved after treatment something that might indicate that reading becomes easier even though it is not directly related to the reading speed. However, Carver (1990) found that reading speed and comprehension were correlated in normally sighted people. A finding that might lead to predict poor reading comprehension abilities on the basis of slow reading speed. On the other hand, Watson et al. (1990) found such a prediction inappropriate if the patient is an adult low vision patient with maculopathy who presumably had good comprehension ability before vision loss. Low vision patients with rehabilitation training showed no correlation between reading speed and measured comprehension. Furthermore, the significant number of more fixations per word found in this study after treatment is likely to be due to a more thorough reading since a higher level of VA allows more rechecks or double check confirmation (Ciuffreda & Tannen 1995) without "getting lost" in the text.

Conclusion

Reading is fundamental in our modern society and should be tested in order to fully understand a patient's complaints; however, reading performance cannot be used as a stand alone measure of visual improvement after, e.g., Lucentis treatment.

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Legends

Figure 1. Graphic presentation showing an example of how a page was displayed with screen dimensions

Figure 2. Graphic presentation showing the categorization of eye movements depending on amplitude and orientation.

Table 1. Text A and B word, sentence and LIX composition

Table 2. Summary for the whole group of patients with the ETDRS and eye movement variables for the read texts.

Table 3. Summary for the group of patients with an increased visual acuity of 10 ETDRS letters or more and the eye movement variables for the read texts.

	Text A	Text B
Sentences	35	35
Words	501	518
Long Words (>6 characters)	170	174
Average Sentence Length (ASL)	14.3	14.8
Long Word Ratio (LWR)	33.9 %	33.6 %
LIX (ASL + LWR)	48.2	48.4
Lexical Density (types/tokens)	55.9 %	55.8 %
Word Variation (log(types)/log(tokens))	90.6 %	91.3 %

Table 1. Text A and B word, sentence and LIX composition.

	Before treatment		After treatment		
	M	*SD*	*M*	*SD*	*P*
ETDRS nr. of letters	29	13.84	38	11.28	.036*
Reading speed	181.2	34.3	171.6	41.3	.25
Comprehension (%)	50	20	60	22	.031*
Fixations per word	0.92	0.13	0.95	0.17	.36
Fixation duration (ms)	297.4	48.4	300.1	54.5	.82
Saccades per word	0.61	0.11	0.62	0.14	.62
Saccade amplitude (°)	2.94	0.41	2.91	0.39	.62
Regressions per word	0.12	0.06	0.14	0.08	.046*
Regression amplitude (°)	2.47	0.34	2.50	0.33	.60
Saccade/regression ratio	6.10	3.34	5.48	2.30	.21

Table 2. ETDRS, reading speed, comprehension and eye movements for the whole group of patients

	Before treatment		After treatment		
	M	*SD*	*M*	*SD*	*P*
ETDRS nr. of letters	21	11.52	45	6.38	.002*
Reading speed	173.1	34.2	149.0	31.7	.014*
Comprehension (%)	44	15	64	22	.031*
Fixations per word	0.93	0.12	1.01	0.10	.030*
Fixation duration (ms)	309.2	55.6	325.3	59.2	.61
Saccades per word	0.59	0.06	0.64	0.10	.059
Saccade amplitude (°)	2.91	0.36	2.84	0.41	.35
Regressions per word	0.17	0.08	0.18	0.10	.35
Regression amplitude (°)	2.38	0.26	2.40	0.36	.70
Saccade/regression ratio	4.27	1.79	5.00	3.13	.21

Table 3. Reading speed, comprehension and eye movements for the group of patients with an increased visual acuity of 10 letters or more.

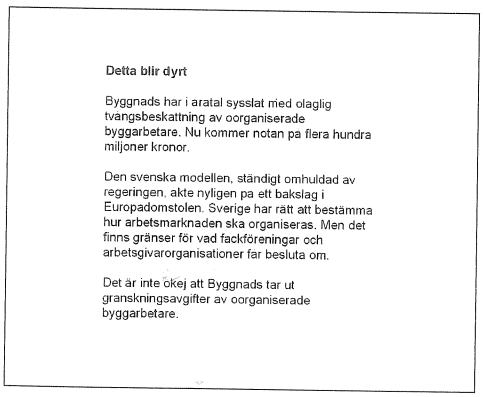

Figure 1. Example of how a page was displayed with screen dimensions.

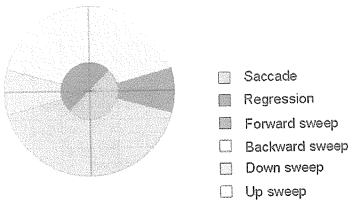

Figure 2. Categorization of eye movements depending on amplitude and orientation