Color discrimination assessment in patients with hypothyroidism using the Farnsworth-Munsell 100 hue test

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There is evidence in the literature that hypofunction of the thyroid gland (hypothyroidism) affects color vision in rodents by influencing the production of visual pigment opsin. The effect of hypothyroidism on color vision in humans has not been examined in any great detail. In this cross-sectional study we evaluated color discrimination using the Farnsworth-Munsell 100 hue test (FM-100) in 25 individuals with pre-treatment hypothyroidism (mean age 38±9.2 Yrs), and a control euthyroid group, n=26 (mean age 39.6±8.4 Yrs). There were no statistically significant difference in the total error score (TES) between the groups, but the hypothyroid group had a significantly greater partial error scores (PES) along the blue-yellow (B-Y) axis compared to the red-green (R-G) axis. No statistically significant differences in B-Y and R-G PES were observed in the control group. This study shows that hypothyroidism affects color vision in humans, with impairment being more pronounced in the blue-yellow color subsystem. © 2020 Optical Society of America

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1. INTRODUCTION

Hypofunction of the thyroid gland (hypothyroidism) is a condition in which the thyroid gland is not able to produce enough thyroid hormones. Hypothyroidism can be a serious disorder which affects a large number of individuals depending on age and gender [1,2,3]. It is more common in women than in men however the ratio can vary widely [2,3,4,5]. The effects of thyroid hormones on the brain are most prominent in perinatal development, and the absence or reduction of thyroid hormones limits the normal development of sensory organs [6-9]. However, sensory deficits also occur in adults after acquired hypothyroidism, including changes in visual functions such as prolongation of latency and reduced amplitude of visual evoked cortical potentials (VECP) elicited by achromatic stimuli [10,11], a reduced critical fusion frequency of flicker (CFF) [12] and a prolongation of reaction time [11,13].

Most previous studies investigating color vision in hypothyroidism were conducted in mammals, particularly mice and rats [14-18]. Unlike primates (who are trichromats), mice and rats are dichromats and have only two types of cones, S and M, containing two types of opsin - UV/short-wave-sensitive (S-opsin) and middle- to long-wave-sensitive (M-opsin) [19,20]. Applebury et al. [15], after exposing adult mice to anti-thyroid drug treatment for 2 weeks, did not find any effect on the expression of opsin in the cones. Later Pessôa et al. [16] reported that the expression of S- and M-opsin in mice depends on normal levels of thyroid hormones during perinatal development. Glaschke et al. [17] have analyzed the involvement of thyroid hormones in postnatal development of the cones in mice with congenital hypothyroidism. They have shown that the structural development of the retinal elements has not been affected, but there has been a change in the expression of the opsin, suppressing the expression of M-opsin and activating the expression of S-opsin. It has been found that thyroid hormones in rats participate actively in the synthesis of visual pigment in the retinal cones not only during perinatal development, but also in adult individual's life.

These results have led to the assumption that the color sensitivity in the mature cones is fixed and it cannot be affected by further hormonal regulation. The hypothesis was tested by Glashke et al. [18] by analyzing the cones of adult mice and rats after a state of induced hypothyroidism for 5-7 weeks. No changes in the cone number were found, but the same reverse change in the opsin expression model was observed. The data led the authors to the conclusion that thyroid hormones regulate the production of opsin throughout the individual's life and that adult thyroid hormone deficiency should affect color vision. They suggested that this mechanism exists in all mammals, including humans. The researchers assumed that the difference in the results between their study and that of Applebury et al. [15] is due to the relatively shorter treatment period with an anti-thyroid drug in that study. Navegantes et al. [14] reported that in rats with congenital hypothyroidism, a significant

reduction in the retinal area and a decrease in ganglion cell density was demonstrated compared to the control group, although Glashke et al. [18] did not find morphological changes in the cone number.

It was reported recently that the mechanism underlying the adverse effect of the thyroid hormone deficit involves the thyroid hormone-activated transcription factor TRβ2. TRβ2 regulates cone differentiation and cone opsin expression. Activation of TRβ2 suppresses the expression of S-opsin and induces the expression of M-opsin [19].

As it was mentioned previously, there is a limited number of studies in humans with hypothyroidism, mainly performed with achromatic stimuli [10-13]. Most of these studies have shown visual deficits such as a slowing in the rate of visual information perception. There are no systematic investigations of color vision in patients with hypothyroidism. Umali et al. [22] did not detect any difference in color discrimination between patients and controls using the D15 color vision test and they concluded that hypothyroidism does not affect human color vision. However, the D15 test has been designed to assess moderate to severe color vision defects and the differences in the pairs of hues are large enough to be flawlessly discriminated not only by color vision normals but also by observers having mild color deficiency [Dain, 2004]. Another study evaluated color contrast sensitivity for letters in hypothyroid patients before and after 3 months of treatment when biochemical euthyroidism has been achieved [23]. The authors apply Chromatest - a software program that analyzes the tritan (B-Y) and the protan (R-G) contrast sensitivity. The color contrast sensitivity was lower in the hypothyroid group relative to controls and it improved after treatment with levothyroxine, more for red and green stimuli, while the difference between thyroid and control group for blue and yellow stimuli still persisted. One of the limitations of this study, as indicated by the authors, is that the color stimuli were generated by a commercial software program which, despite of its suitability for clinical environment, is not the best way to test color vision mechanisms. In addition, the question arises whether longer period of treatment will not lead to a recovery of deficits in the B-Y channel.

In a case study [24], Ricco's area for S-cone incremental (blue) and S-cone decremental (yellow) stimuli was measured in retinal periphery in a patient with hypothyroidism due to autoimmune thyroiditis before and after treatment. It was shown in the first experiment that the area of complete spatial summation for S-cone decrements was enlarged (3 to 10 times) compared to the other participants without thyroid dysfunction. The process seems reversible after a long time of treatment with levothyroxine and reaching biochemical euthyroidism. There were no significant differences for either blue or yellow stimuli for a control subject without hypothyroidism, who participated in both experiments. A shortcoming of this study was the long period between the testing before and after the treatment. In addition, the hormonal status of the patient at the time of the first experiment was not clear, since hypothyroidism was subsequently diagnosed.

The purpose of the present study is to compare color discrimination using the Farnsworth-Munsell 100 hue test (FM-100) of patients with primary hypothyroidism before treatment with levothyroxine with an age- and sex-matched control group of volunteers without thyroid dysfunction.

2. METHODS

A. Subjects

In this cross-sectional study included were 51 female subjects between 18-54 years of age with normal color vision (Ishihara Test For Color Deficiency, 38 Plates Edition and The City University Color Vision Test, Third Edition, 1998). We choose only female subjects to avoid the gender bias. The upper age limit of 54 Yrs of age was used to ensure that normal ageing will not have impacted upon the results in this cohort. The first group consisted of 25 individuals (mean age 38±9.2 Yrs/range 19-53 Yrs) who were patients diagnosed with primary hypothyroidism, including Hashimoto's thyroiditis and postoperative hypothyroidism, but have not received any treatment yet (hypothyroid baseline group). The second group were 26 age- and sex-matched subjects (mean age 39.6±8.4 Yrs/range 18-54 Yrs) without thyroid dysfunction (euthyroid control group). The diagnosis of hypothyroidism was established by measuring free thyroxine (FT4) and thyroid-stimulating hormone (TSH). Additionally is measured free triiodothyronine (FT3), anti-thyroperoxidase (Anti TPO-At) and anti-thyroglobulin (Anti Tg-At) (Table 1). In all participants thyroid ultrasonography was performed by the same physician. All blood serum tests were performed in the same clinical laboratory. Patients with overt hypothyroidism defined as low FT4 (normal range 9–23 pmol/l) with high TSH (normal range 0.3–4 mU/l) levels and patient with subclinical hypothyroidism defined as normal FT4 and high TSH included were in the study.

Table. 1. Characteristics of hypothyroid and euthyroid control groups

Parameters	Hypothyroid baseline group	Eurothyroid control group	p value
Number	25 female	26 female	—
Age (years)	38±9.2 (19-53)	39.6±8.4 (18-54)	0.937
Mean TSH (0.3-4 mlU/l)	17.3±19.9	2.3±1.1	0.001
Mean FT4 (9-23 pmol/l)	12.4±3.0	15±2.3	0.001
Mean FT3 (3.5-7 pmol/l)	4.7±0.9	—	—
Anti TPO-At positive,%	84.3%	—	—
Anti Tg-At positive,%	87%	—	—

All participants underwent ophthalmic examination which included retinoscopy, intraocular pressure and visual acuity. Information was gathered about each participant's medical history, medications and hypothyroidism diagnosis. The individuals were eligible for the study if they had no ophthalmic disease. Myopia, hypermetropia and astigmatism were corrected using glasses or lenses; no individuals with a self-reported history of ocular disease or of taking medicines known to affect vision were included. Individuals were excluded from the study if they had congenital color vision defects, diabetes or other endocrinological disease apart from hypothyroidism. Spectacles that change color or light intensity were not allowed during the experiment.

This study was approved by the Institute of Neurobiology Bioethics Committee. Prior to the experiments, informed written consent was obtained from all subjects. The study was

performed in accordance with the tenets of the Declaration of Helsinki.

B. Procedure

Color discrimination was evaluated using the Farnsworth–Munsell 100 hue test (FM-100). FM-100 is a sensitive test often used to test for color deficiency or color blindness, including acquired deficiencies. It consists of four boxes containing a total of 85 colored caps. Each box contains two fixed anchor caps, one at the start and one at the end of each box. There are 22 caps in the first box and 21 caps in the other three boxes. The observer's task was to arrange the caps in each box to produce a gradual transition of hue between the two anchor caps. The sequence of the boxes was randomly mixed in advance for each person. The caps in each box were also pre-mixed randomly according to a pre-printed sequence. The participants were encouraged to perform the test quickly and were given about 2 minutes for each box, but they were instructed that the accuracy was also important.

The test illuminance, color temperature of the light source, the procedure and data processing adhered to the original Farnsworth instructions [25]. The FM-100 test was performed using a color vision examination cabinet, specially designed in the Institute of Neurobiology [26]. Briefly, the test was performed under CIE Illuminant 'C' illumination using two Philips MASTER TL-D Super 90 Graphica 36W 965 fluorescent lamps. Color temperature was close to daylight illumination (6350 K). The test illuminance varied between 285 and 295 lux. The chromaticity coordinates were x = 0.32, y = 0.33. The viewing distance was 45-50 cm. The test was performed binocularly with natural pupil, which was about 2-3 mm in diameter. The subjects were dark adapted for 2 minutes and then adapted for 2 minutes to the test illumination. None of the subjects had performed previously FM-100 test.

The total error score (TES) was the sum of scores for the four boxes. In order to evaluate if errors along certain axes are more common i.e. if a bipolarity is present, we also analyzed the partial error scores (PES), where TES were partitioned into scores along the B-Y and R-G axes. The concentration of data along these axes may be related to certain colour vision defects. TES and PES were recorded for both groups using standard testing conditions. B-Y PES (caps 1 - 12, 34 - 54 and 76 – 85) and R-G PES (caps 13 - 33, and 55 - 75) were calculated according to Smith, Pokorny and Pass [27]. Since the error scores have a skewed distribution, a square root transformation has been suggested as providing a distribution closer to normal [28,29]. Hence, the square root of the error scores (√TES and √PES) was used in the statistical analysis.

3. RESULTS

Figure 1 presents the √TES values for both hypothyroid and control euthyroid groups as a function of age. The upper panel (a) shows the data for the hypothyroid patients, the bottom panel (b) shows the data for the control group. The open diamonds show our data for both groups, averaged over 18/19-29, 30-39, 40-49, 50-54 years. Our results were compared with the normative range presented in the Verriest, Van Laethem and Uvijis study of FM-100 hue discrimination [30]. It is shown that √TES and RG and BY √PES increased with age [30]. It is seen from Figure 1 that our data do not differ from the normative data in both groups. In these age decades, where we have more subjects (30-50), the average √TES in both groups is consistent with the normative data shown.

Figure 2 presents the individual √PES data as a function of age. The upper panel (a) shows the square root of the B_Y partial error scores and the bottom panel (b) shows the same for the R_G partial error scores for both hypothyroid and control group. The graph demonstrates that most R-G error scores for patients and controls overlap, while a number of B-Y error scores for the patients lie higher than the error scores for the control group. This result is more clearly visible in Fig. 3. where we compare the average results for B-Y and R-G √PES for hypothyroid group and control group.

The descriptive statistics for the square root of total and partial error scores is shown in Table 2. The median of the original error scores is also shown for comparison with previous studies. The hypothyroid group show higher values (√TES=7.51) compared to the control group (√TES=6.79). The statistical analysis showed that the mean √TES for the hypothyroid group were not significantly different from the age matched control group (T-test p=0.51, t=-0.66). Two-way mixed model ANOVA with group (hypothyroid group or control group) and color axis (B-Y, R-G) was performed on the measured PES after applying square-root transformation to deal with violations of normality assumption. The results showed no significant main effect of the group ($F(1,49)=1.345$; $p=0.252$; $\eta_p^2=0.027$) with both hypothyroid group (mean=5.25) and controls (mean=4.67) performing similarly. There was a significant main effect of the color axis tested ($F(1,49)=15.99$; $p<0.01$; $\eta_p^2=0.246$) with more errors along the B-Y axis (mean = 5.387) than along the R-G axis (mean=4.538). There was a significant interaction between the group and the color axis ($F(1, 49= 4.318$; $p=0.043$; $\eta_p^2=0.81$).

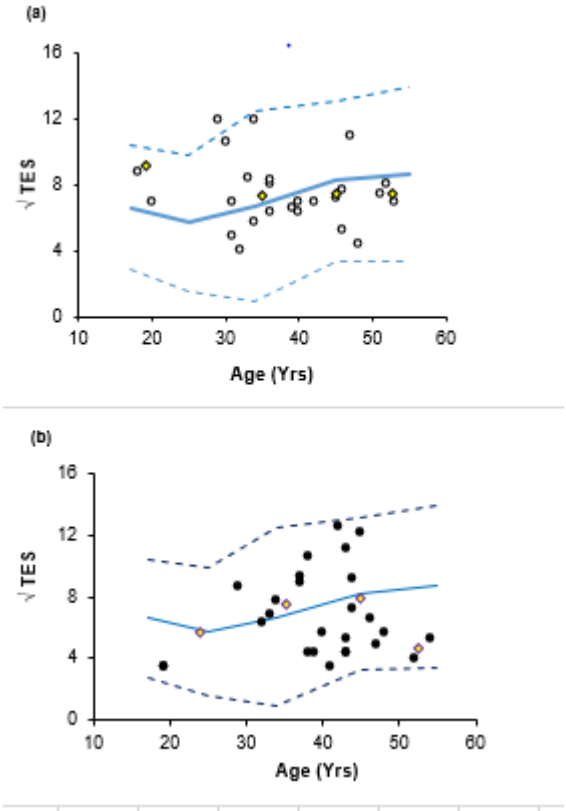

Fig. 1. √TES as a function of age. (a) open circles- individual data for hypothyroid group. (b) closed circles – individual data for control group. Open diamonds indicate the mean data in decades for both groups in the

present experiment. Solid line – mean normative data from Verriest et al. 1982. Broken lines indicate +/- 2 s.d.

Table 2. Descriptive statistics for the square root of total (√TES) and partial (√PES) FM 100 error scores for the hypothyroid and control group. The median values of the original error scores are also shown.

Hypothyroid baseline group

Parameters	TES	√TES	B-Y PES	B-Y √PES	R-G PES	R-G √PES
Mean		7.51		5.90		4.61
Median	48	6.93	34	5.83	19	4.36
SEM		0.41		0.30		0.27
N	25	25	25	25	25	25

Eurothyroid control group

Parameters	TES	√TES	B-Y PES	B-Y √PES	R-G PES	R-G √PES
Mean		6.79		4.88		4.47
Median	36	5.99	23	4.79	15.5	3.94
SEM		0.45		0.44		0.29
N	26	26	26	26	26	26

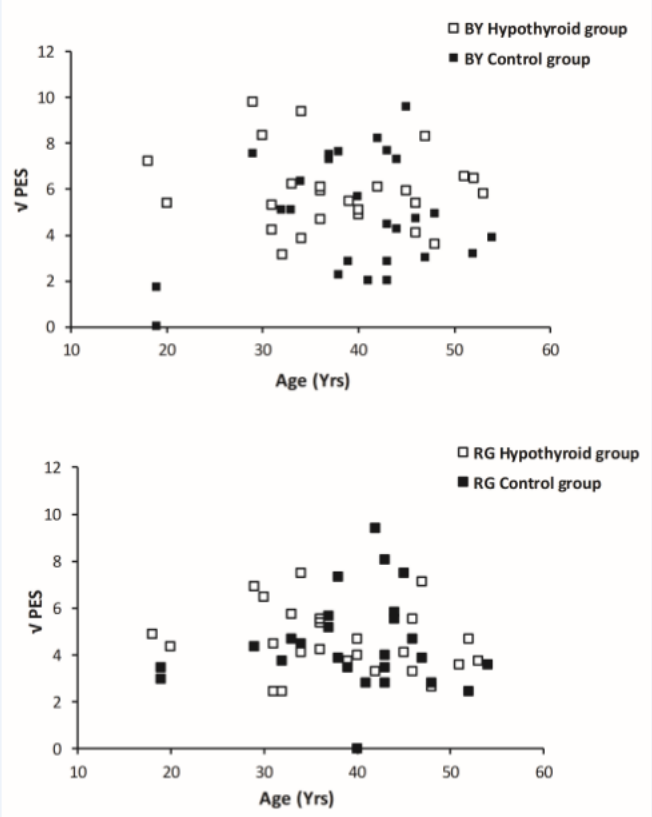

Fig. 2. Square roots of B-Y partial error scores (a) and R-G partial error scores (b) for the hypothyroid group (open squares) and the control group (closed squares) as a function of age.

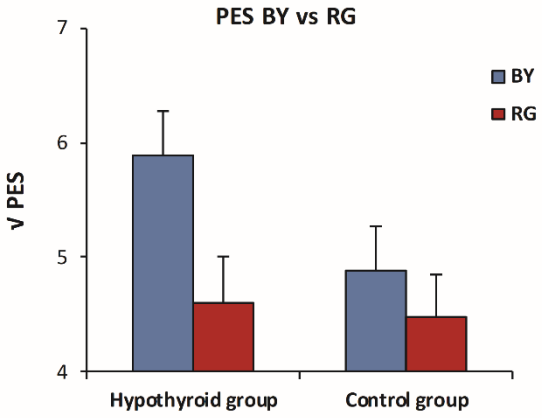

Fig. 3. B-Y and R-G √PES comparison for both hypothyroid and control group. Vertical bars represent standard error of the score.

For a clearer illustration of the results, we subtracted √PES for RG from √PES for BY (Figure 4). The data for the hypothyroid group are presented in the upper graph (a) and the data for the control group are presented in the bottom graph (b). It could be seen that the points for the controls lie on both above and below of the zero line, indicating that the number of errors are almost equally distributed between the R-G or B-Y axis. The hypothyroid group data lie almost completely above the zero line of the graph. This result shows a higher number of errors along the B-Y color axis.

To further check the presence of bipolarity in the distribution of error scores, we presented

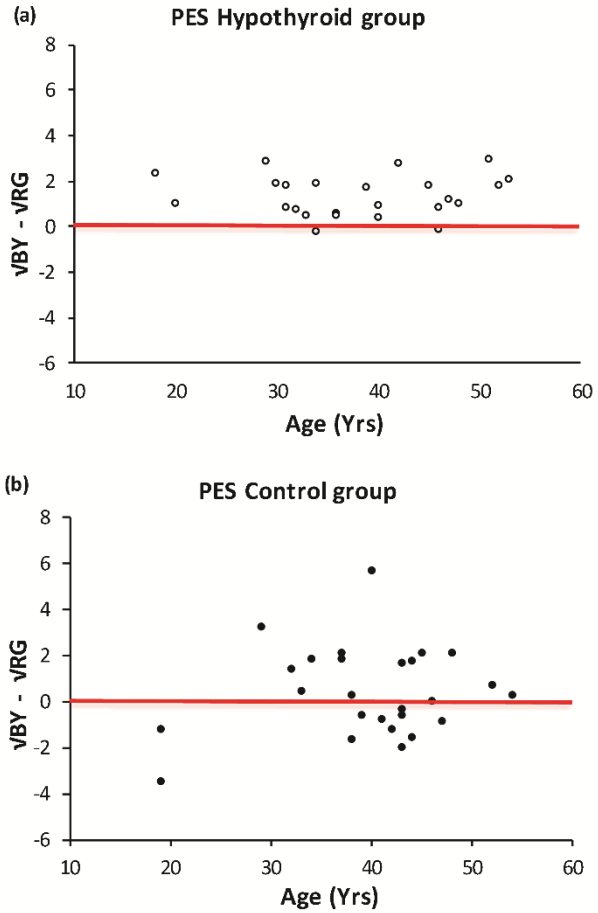

Fig. 4: √B-Y - √R-G for hypothyroid group (a) and control group (b) vs age.

3. DISCUSSION

The results in the present experiment suggest that hypothyroidism affects color vision in humans with greater impact on B-Y compared to the R-G discrimination errors, opposite to the expectations based on opsin expression in adult hypothyroid rats and mice. Hence, "the mouse model" is not applicable to humans. We could not be confident that the observed changes in color discrimination in hypothyroid group is related to the opsin expression as seen in rodents, because of the substantial differences between mouse and human retina. In mice and rats, which are dichromats, the retina contains a small number of S-opsin cones and majority of M-opsin cones. It has been reported that after induced hypothyroidism, S-opsin expression has been elevated in all cones while M-opsin expression has been reduced significantly [19]. If a similar process occurs in the human retina, and if it is associated with impaired color discrimination in the B-Y axis, then we would expect the hypothyroidism to be associated with decreased S-opsin production. No statistical significant elevation in the R-G color discrimination was observed in both groups in our study. This probably shows that the reversible mechanism in the opsin production observed in mice and rats does not appear to occur in humans.

It is known that the S-cone system is more vulnerable to certain diseases that affect vision and color vision in particular. It has been found that the blue sensitivity is reduced in glaucoma and high intraocular pressure [31-33]. The results in the case study showed that Ricco's area for S-cone decrements is enlarged in patient with hypothyroidism [24]. Patients with high intraocular pressure who do not show visual loss when tested with standard W/W perimetry, very often show deficits when tested with blue-on-yellow perimetry. In many cases, this is an indicator of glaucoma development [32]. Greenstein et al. [34] have found decreased S-cone pathway sensitivity in retinitis pigmentosa, diabetes and glaucoma.

Thyroid hormones regulate neurotransmitter levels and key neurotransmitter in the retina is dopamine [Djamgoz et al, 1997,35, 36, Brandiers, 2008, Carravaggio, 2018]. There is a correlation between thyroid function and dopamine levels [37-41], so it can be expected that hypothyroidism can cause low levels of dopamine. Dopamine is released by retinal dopaminergic amacrine cells and has an important role as a chemical messenger for light adaptation of the visual system, has a retinal trophic function and affects eye growth [35]. The reduction in retinal dopamine results in reduced visual contrast sensitivity, spatial and temporal vision, as well as absolute sensitivity control and color vision. [e.g. Djamgoz et al, 1997,35, 36]. Witkovsky and Derry reports that dopamine or its antagonists change the balance of ON and OFF discharges. However, they are not relevant to responsiveness and do not cause a significant change in the organization of the receptive field (Witkovsky and Dearry, 1992).

According to the retinal dopaminergic hypothesis, the decreased amount of dopamine in the central nervous system in hyperactivity and attention deficit disorder, may cause low hypodopaminergic levels in the retina, which in turn would have a deleterious effect on the S-cones that are highly susceptible to dopamine levels [41]. However, the data obtained in children with hyperactivity and attention deficit disorder are controversial [42,43]. Blue-yellow deficits have also been observed in other conditions causing dopaminergic hypoactivity, such as Parkinson's disease (Djamgoz et al, 1997, 44, Brandies, 2008) or cocaine withdrawal (Djamgoz et al, 1997, 44, Brandies, 2008). but it's not so clear in schizophrenia [e.g. 45]. Later Fernandes et al. demonstrated reduction in thresholds for short, medium and long wavelengths in patients with schizophrenia (Fernandes et al., 2018).

The FM-100 test is a sensitive test to detecting color anomalies in diseases which damage the optic nerve such as demyelinating optic neuritis (DON). Patients with acute DON revealed a significant elevation at B-Y axis PES using FM-100 test. The deficit gradually improves during the patient recovery [40]. There is no data that hypothyroidism in humans causes demyelination of the optic nerve. We can speculate that demyelination is an additional factor for impaired color discrimination in patients with hypothyroidism along the B-Y axis, as observed in DON. An important role of thyroid hormones for the recovery of myelin is observed in multiple sclerosis in rats [42].

FM-100 test is suitable for the study of color discrimination in cataract patients. Age-related cataracts significantly affects the color vision which is effectively restored after surgery. Cataract patients tested with FM-100 preoperatively exhibit worse discrimination than the control group at photopic and mesopic condisions, which corresponding to the 470–580 nm range of the visible light spectrum. This worse color discrimination responds Y-GY, GY-G, G-BG and BG-B color bands under photopic condition and YR-Y under mesopic conditions [Ao et al. 2019]. These results are close to the data obtained in our study with

hypothyroid patients, in which the deficits affected in great impact the G-BG color band.

Cranwell et al. (2015) demonstrated that FM-100 scores depend not solely on the chromatic discrimination ability, but also on non-verbal intelligence. There is data that the latter might be affected in patients with hypothyroidism [Dugbartey (1998), Dietzel [12]. TES in our study was lower for hypothyroid group related to controls, but the results were not statistically significant. So we cannot maintain for certain that hypothyroidism has affected significantly the non-verbal abilities of hypothyroid subjects in the present study.

The data in this study showing worse color discrimination along the B-Y axis in hypothyroid patients are consistent with the results obtained from Cakir et al. [23] for persistent B-Y deterioration in color contrast sensitivity in hypothyroid individuals. In addition, the present results are consistent with the results obtained in the case study [24] for impairment in B-Y chromatic mechanism in a patient with hypothyroidism. The question remains how color deficits in hypothyroid group obtained in the present study with FM-100 test would change after treatment with levothyroxine for an extended period of time.

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