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BRIEF COMMUNICATION

Color vision study to assess the impaired retina-brain cortex pathway in type 2 diabetes: a pilot study in Calabria (Southern Italy)

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Abstract

The present pilot study was undertaken to investigate the impaired acquired color vision on Calabrian male sample showing this parameter as a biological marker in type 2 diabetes. All patients and controls underwent three pseudo-isochromatic clinical test batteries: Ishihara test, Farnsworth test, and City University test. The results show a specific loss of short-wavelength (blue sensitivity) and typical tritan responses in diabetic patients. Generally, in later stages of the disease, the red-green mechanisms are involved. By the impaired color vision study in diabetic patients, we can confirm the impaired retina-brain cortex pathway. We believe that the above not invasive test analysis can support the other instrumental and imaging analysis to study the impaired retina-brain cortex pathway. Moreover, we think that the present clinical method can be useful in terms of preventive medicine.

Keywords Color vision · Type 2 diabetes · Calabrian patients

Introduction

Defective color vision can be acquired as a result of ocular or general pathology, intracranial injury, or by the prolonged use of some therapeutic drugs. The abnormality can originate anywhere in the visual pathway from the retinal receptors to the visual cortex [1, 2]. Changes in color vision provide both evidence of pathology and information about color processing in the visual pathway if the primary site is known. Color disturbance is an early symptom in some pathological conditions and occurs at a recognized stage in others [3]. In diabetes, color function loss can occur before the appearance of clinical diabetic retinopathy [4, 5].

In the retina, short-wavelength (S), middle-wavelength (M), and long-wavelength (L) cones encode the information for red-green and blue-yellow components and luminance through functionally and anatomically distinct retino-geniculo-cortical pathway [6–9]. The ganglion cell axons carry the filtered and encoded visual information as action potentials to the lateral geniculate nucleus. L and M cones mainly project to the parvocellular layers in a smaller part to the magnocellular layers of the lateral geniculate nucleus. Parvocellular layers, important for red-green color vision, respond to the L and M color opponent channel magnocellular respond mainly to luminance information. Ganglion cells that increase their firing rate proportionally to S-cone inactivation project to the koniocellular lateral geniculate nucleus layer responsible for blue-yellow color vision components [10].

According to a disordered metabolism of neural cells [11], diabetes may damage the nerve directly or indirectly through changes in the microcirculation. Retinal functions damaged by diabetes in the first instance by a nutritional deficit which affects the neurons and later by vascular disturbances associated with micro-aneurysms. Blood and exudative masses which may displace tissue, later damage sight and the coagulation of blood vessels used as a treatment can itself affect color and form vision [12].

Lakowski et al. [13] reviewed the history of color vision losses associated with diabetes and gave an analysis of different test methods in many cases; in general, blue losses are most severe. They stressed the fluctuating nature of some color vision difficulties, in the event of variation of blood sugar level. It was seen to be difficult to predict the state of vision or retinal disturbance from either normal or abnormal color vision but a useful approach was found to be a combination of data from different color tests; by such means, there was reasonable prediction of minor retinopathy likely in diabetics in the under 30 and over 60 age groups [12].

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The present pilot study was undertaken to investigate the impaired acquired color vision on Calabrian diabetic type 2 male sample, in order to:

- To compare in the next future the results with those regarding a young diabetic type 1 male sample;
- To show and confirm that diabetes is surely a metabolic disease, but its metabolic defects are regulated by the nervous system which underlies all human organic reactions;
- To consider in the next future these results in views of the mini mental test results on the present sample subject. This, due to the involvement of the hippocampus structure by the effects of neural apoptosis by diabetes;
- To confirm the usefulness of a test battery for the study of color vision, instead only one, to be sure of the real impaired acquired color vision in diabetics.

Patients and methods

Eleven Calabrian male patients (mean age 70.72 ± 7.79; mean duration's disease 10.81 ± 7.27; mean glucose 153.22 ± 128.66) admitted to the Istituto Nazionale Riposo e Cura per Anziani (INRCA), Cosenza (Calabria, Southern Italy) were enrolled. Twelve controls were matched for age and sex (mean age 65.25 ± 27.82; mean glucose 104.10 ± 30.1). Patients and controls signed their informed consent. An ophthalmologist examined all patients and controls in order to rule out cataracts, senile maculopathy, or ocular fundus anomalies. One inherited colorblindness subject was excluded by the analysis. The analyzed sample was 23 subjects. Fixed sampling of males allowed us to avoid the genetic Lyon [14] which is present in the heterozygous females for X-linked diseases such as the inherited red-green color vision deficiency. Females' exclusion allowed us to avoid those heterozygous colorblind females who would be "false positives" for the acquired red-green color vision deficiency caused by diabetes, altering the result analysis. If we had not considered 8% of red-green inherited colorblindness frequency in Calabrian people [15], we would have found a relatively significant high number of "false positive" subjects showing a red-green color vision trend which as in a Gaussian curve can carry a minimum value (normal color vision) to a maximum value miming the inherited red-green colorblindness, passing for different anomalous color vision levels. We should not comprehend if homozygous female status is really inherited or acquired; and in heterozygous status, we miss all those females miming the normal color vision. Acquired color vision deficiency is real in the male cohort because they have not the compensation presence by second X chromosome, and the anomaly has not hidden.

All patients and controls underwent Ishihara test [16] which is the most reliable among the pseudo-isochromatic tests to identify colorblind subjects (inherited red color vision deficiency, protanopy or protanomaly; inherited green color vision deficiency, deuteranopy or deuteranomaly). Farnsworth dichotomous D-15 test [17] identified both the greatness of color vision deficiency by the high number of errors (maximum value, n. 15) and the type (deutan, protan, or tritan). The City University test [18] identified (both binocularly and monocularly) people with different types and degrees of the acquired red-green deficiency (maximum value of errors number, n. 6) and blue-yellow color vision deficiency (maximum value of errors number, n. 3).

Results

The results of this pilot work on the effects by diabetes on color vision are provided in Table 1. No correlation existed between duration of diabetes and number of errors by tests. The positive polarity of the abnormal error scores (range, 226.6–390.0) in six out of 11 patients was determined by a no any ambiguity in the axis of color confusion that was distinguished sharply by the City University test. Furthermore, this test supported greatly the other two utilized tests for a better investigation during the acquired color vision screenings. The error scores do not correlate with duration of disease. Sensibility resulted to be 72.7%. Accuracy resulted to be 86.9%. Specificity resulted to be 100%.

Discussion

Diabetes also induces morphological changes in neuros, including synaptic vesicle depletion in massy fiber nerve terminals [19], dendritic atrophy of caspase 3 pyramidal neurons [20], and increases the expression of the presynaptic synaptophysin [21]. Caspase 3 has been demonstrated to be a downstream effector of phosphorylated p38MAPK (pp38) which causes neuronal death induced by high glucose [22]. Retinal neurons may also be affected by diabetes, even before the detection of microvascular dysfunction. Diabetes increases apoptosis in neural cells in human retina early in the course of the disease. Further, there may be a primary neurodegenerative process which contributes to loss of vision in diabetic retinopathy. Neuroprotection in diabetic may be a valuable therapeutic target.

Conventionally, pigment epithelium and cone receptor disorders have long been associated with tritan defects. While

Table 1 Number of errors made by patients and controls reading clinical color vision tests

A. Number of errors by 9 patients with color vision deficiency										
Patients	Age years	Disease years	Ishihara test errors	Farnsworth test errors (error scores)*	The City University test errors					
					Red/green			Blue/yellow		
					RE	LE	Both	RE	LE	Both
1	77	6	2/17	0/15 (117.0)	0/6	0/6	0/6	0/3	0/3	0/3
2	78	5	0/17	7/15 (230.4)	0/6	1/6	0/6	1/3	1/3	1/3
3	67	7	4/17	6/15 (261.1)	2/6	3/6	1/6	0/3	1/3	0/3
4	78	18	12/17	6/15 (226.6)	1/6	0/6	0/6	1/3	0/3	0/3
5	69	10	0/17	3/15 (164.7)	0/6	0/6	0/6	0/3	0/3	0/3
6	80	3	0/17	5/15 (180.2)	1/6	0/6	0/6	1/3	0/3	1/3
7	71	3	1/17	8/15 (256.7)	4/6	2/6	1/6	1/3	1/3	1/3
8	71	21	1/17	7/15 (390.0)	5/6	5/6	3/6	1/3	1/3	0/3
9	62	9	1/17	0/15 (117.0)	0/6	0/6	0/6	0/3	0/3	0/3
10	71	23	4/17	12/15 (253.3)	0/6	1/6	0/6	2/3	2/3	2/3
11	54	14	2/17	4/15 (142.3)	0/6	0/6	0/6	0/3	1/3	1/3
B. Number of errors by 12 normal controls with normal color vision										
Patients	Age years		Ishihara test errors	Farnsworth test errors (error scores)**	The City University test errors					
					Red/green			Blue/yellow		
					RE	LE	Both	RE	LE	Both
1	59		0/17	0/15 (117.0)	0/6	0/6	0/6	0/3	0/3	0/3
2	50		2/17	4/15 (146.3)	0/6	0/6	0/6	0/3	0/3	0/3
3	74		1/17	0/15 (117.0)	0/6	0/6	0/6	0/3	0/3	0/3
4	59		1/17	4/15 (142.6)	0/6	0/6	0/6	0/3	0/3	0/3
5	56		2/17	4/15 (154.4)	0/6	0/6	0/6	0/3	0/3	0/3
6	69		0/17	2/15 (128.6)	0/6	0/6	0/6	0/3	0/3	0/3
7	62		1/17	0/15 (117.6)	0/6	0/6	0/6	0/3	0/3	0/3
8	66		1/17	5/15 (152.1)	0/6	0/6	0/6	0/3	0/3	0/3
9	67		1/17	4/15 (161.1)	0/6	0/6	0/6	0/3	0/3	0/3
10	71		2/17	2/15 (140.6)	0/6	0/6	0/6	0/3	0/3	0/3
11	70		0/17	6/15 (148.1)	0/6	0/6	0/6	0/3	0/3	0/3
12	80		0/17	4/15 (161.8)	0/6	0/6	0/6	0/3	0/3	0/3

$t = 0.98$, d.f. 20, $p < 0.1$

RE, right eye; LE, left eye

*Range 117.0–390.0; mean 215.97 ± 85

**Range 117.0–161.8; mean 140.6 ± 5.04

"outer" neurons frequently induce protanomalous defects, disorders of the "inner" neurons frequently give rise to deutan-acquired defects. Tritan defects are often classically associated with outer layers of the retina and red-green defects with inner layers. Such findings are supported by Grützner [23], while Marré [24] showed early loss of blue sensations in retinal disease followed by red-green disturbances [4].

Acquired type 3 (tritan) color deficiency, or blue-yellow deficiency, in diabetes was described in 1954 by Dubois-Poulsen and Cochet [25], and also prior to the onset of visible retinopathy. This occurs in association with reduced sensitivity in the short-wavelength (S cone) pathway. Pseudo-isochromatic clinical test battery shows a specific loss of short-wavelength (blue sensitivity) and typical tritan responses. Generally, in later stages of the disease, the red-green mechanisms are involved. This differentiation can be based on the different answers by our brain when some insults or diseases are present. The brain analyzes and thus determines the color of a surface by determining the color of every point in it by an additive mechanism, that is, by gauging the amounts of long, middle, and short wave light reflected from each point. The reason is to be found in the anatomical connections between the eye and the brain. These are organized topographically, with every point in the primary visual cortex which, until the last two decades, was considered to be the sole visual perceptive cortex and remains perhaps, even today, the more extensively studied part of the visual cortex [1].

Conclusion

Color vision testing may potentially provide a cost-effective tool for diagnosing the diabetes and can support the other instrumental and imaging analysis to study an impaired retina-neuron visive areas pathway.

Moreover, the present clinical method can be useful in terms of preventive medicine.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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