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Original Article

Abnormalities in saccade dynamics in first-episode treatment-naive hyperthyreosis patients with no pre-existing eye damage: a primary exploratory study

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Abstract: Objective: To explore the potential difference of eye saccade dynamics between first-episode treatment-naïve hyperthyreosis patients without pre-existing eye damage and healthy controls by using basic visually guided saccade (VGS). Methods: 15 hyperthyroidism outpatients and 15 healthy controls participated in VGS analysis. Multiple indicators, including amplitude, duration, latency, main sequence analysis was performed to evaluate the differences of peak velocity (PV) and duration between the groups and general linear model was used to find the differences on latency, peak acceleration and peak deceleration between the groups. Results: There was a statistically significant difference in V_{max} values between hyperthyreosis patients and healthy controls (438.47 ± 55.46°/s in control group and 486.10 ± 51.49°/s in hyperthyroidism group, Mann-Whitney U test, Z = -2.053, *P* = 0.040). GLM-based analysis showed that when amplitude = 10.819°, PV = 311.587°/s, duration = 61.94 ms, the saccade latency showed significant differences between hyperthyreosis patients (223.364 ms, 95% confidence interval (CI) = [219.245, 227.482]) and healthy controls (234.601 ms, 95% CI = [230.497, 238.705]); the peak acceleration showed significant differences between hyperthyreosis patients 14127.205°/s^2 (95% CI = [14061.606, 14192.804]) and healthy controls (13959.973°/s^2, 95% CI = [13894.610, 14025.337]); the peak deceleration showed no significant differences between hyperthyreosis patients (-10160.784°/s^2, 95% CI = [-10263.189, -10058.378]) and healthy controls (-10194.008°/s^2, 95% CI = [-10296.046, -10091.970]). Conclusion: Compared to healthy controls, hyperthyreosis patients displayed different dynamics in eye movement during VGS. Saccade tracking examination has a potential value for early detection of thyroid-associated ophthalmopathy.

Keywords: Hyperthyroidism, thyroid-associated ophthalmopathy, visually guided saccade

Introduction

Hyperthyroidism refers to high thyroid function status [1]. Clinical symptoms include varying degrees of enlargement of the thyroid function, proptosis and ocular symptoms [2, 3], an increasing basal metabolic rate[4, 5] and autonomic nervous system abnormalities [6].

Hyperthyroidism can also affect the eyeball, causing exophthalmos and other eye symptoms [7, 8]. Eye diseases caused by hyperthyroidism belong to thyroid-associated ophthalmopathy (TAO). TAO is the most frequent extrathyroidal manifestation of hyperthyroidism. TAO is closely associated with hyperthyroidism and can occur at all stages of hyperthyroidism [9, 10]. Potential consequences of TAO include morphological changes such as exophthalmos, eye motility disturbance, corneal ulceration and optic nerve compression [11]. The exact cause of TAO remains unknown. However, many studies demonstrate that TAO is an organ-specific autoimmune disease involving an imbalance of T lymphocyte subsets. This imbalance is associated with an increase of B lymphocytes, elevated immunoglobulin levels, increased lymphokine production and fibroblast activation, resulting in excessive extracellular material and collagen synthesis [12]. In the early stages of TAO, extraocular muscle fibers may keeps normal, eyeballs' pathological changes showed only tissue edema. Along with the progress of TAO, pathological manifestations of the eye-

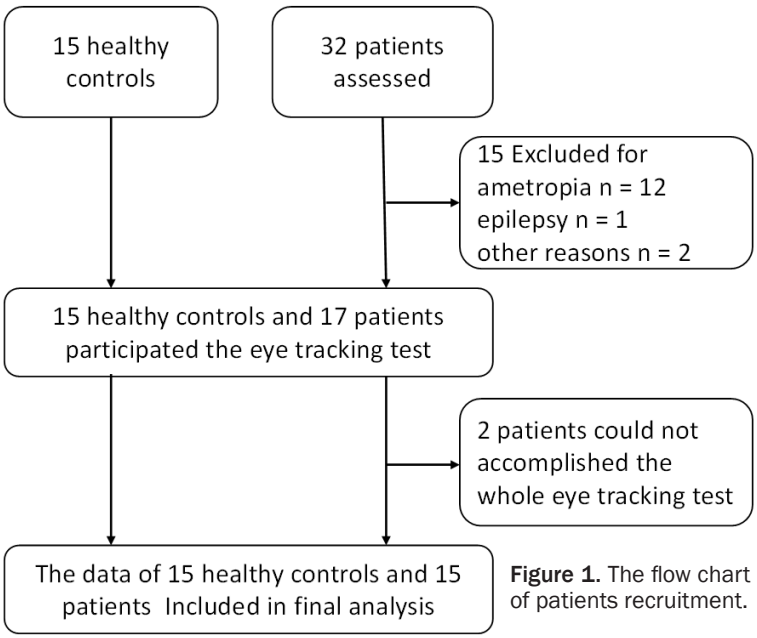

Figure 1. The flow chart of patients recruitment.

balls were hyaline degeneration, glycosaminoglycan (GAG) deposition, hyaluronidase increased, these changes may cause muscle's normal texture disappeared, loosely organized [13]. From one to several years, progression of the disease plateaus. At this stage, acute inflammation subsides while orbital tissue fibrosis develops. Involvement organization of eyeball can't be restored to the former healthy status, as the patient still has residual symptoms and chronic external eye muscle dysfunction [14]. Because there is no specific treatment presently, severe consequence can be mitigated by early administration of anti-inflammatory agents [15]. As a result, there is need of a technique to detect the early stage of TAO. The current diagnosis on TAO is based on standards developed by the NOSPECS classification of American Thyroid Association (ATA). A level reaching greater than 'grade 3' can be diagnosed as TAO. Grade 3 is based on the patient's exophthalmia level. Lower NOSPECS grading (0-2) status based primarily on eyeball symptoms and signs, which is easily ignored by doctors. At present, the lack of sensitive objective examinations for early TAO patients remains a problem [16].

As early as 1986, Klima *et al.* tried to use eye movement tonometry to detect early eye-related symptoms of thyroid [17]. This study described changes in intraocular pressure, using eye movement tonometry, to monitor saccade and detect the ocular symptoms of hyperthyroidism. This study established eye movement tonometry as a useful approach to evaluate the early development of TAO [17]. Despite this, some concerns have been raised in the early assessment on TAO patients using eye movement approach [18, 19]. For example, Traisk *et al.* obtained a negative result on fourteen TAO patients by using eye movement analysis [20]. Patients in these previous studies predominantly had a determined diagnosis of TAO. The current study was designed to explore the early eye damage in patients with hyperthyroidism, which included first-episode hyperthyreosis patients who had no pre-existing eye damage caused by TAO and analyzed the eye movement by using visually guided saccade (VGS).

Materials and methods

Ethics statement

The study was approved by the Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University. According to the tenets of the Helsinki Declaration, all participants enrolled in the study signed written detailed informed consent. Participation was voluntary, and patients were allowed to reject or withdraw at any point.

Participants

15 first-episode treatment-naive hyperthyroidism outpatients (2 males and 13 females) were recruited from the First Affiliated Hospital of Anhui Medical University. The flow chart of patients recruitment was shown in **Figure 1**. Hyperthyroidism is defined as serum T3, T4 higher than the normal range, in combination with lower TSH values. For each participant, serum hormone levels (T4, T3 and TSH) were measured by a chemiluminescence immunoassay performed at the Endocrinology Laboratory of the First Affiliated Hospital, Anhui Medical

Table 1. The basic information and clinic feature of hyperthyroid patients

	The hyperthyroid patients group (N = 15)	The control group (N = 15)	*P* value
Age (Mean ± SD)	39.2 ± 12.7	37.8 ± 9.5	0.787
Sex (Male:Female)	2:13	6:9	0.217
Serum T3 (Mean ± SD)	6.51 ± 4.32 nmol/L	-	-
Serum T4 (Mean ± SD)	248.24 ± 125.50 nmol/L	-	-
Serum TSH (Mean ± SD)	0.013 ± 0.013 IU/mL	-	-
Photophbia	N = 4	N = 0	-
Lacrimation	N = 3	N = 0	-
Fatigue	N = 5	N = 0	-
Diplopia	N = 0	N = 0	-
Ophthalmodynia	N = 1	N = 0	-
Blurred vision	N = 2	N = 0	-
Lyelid contracture	N = 5	N = 0	-
Exophthalmus	N = 0	N = 0	-
Extraocular muscle injury	N = 0	N = 0	-
Optic nerve neuropathy	N = 0	N = 0	-
Hyperemia and edema of the conjunctiva	N = 8	N = 0	-
Scarring of the cornea	N = 0	N = 0	-

University. For T4, the 'normal' range was 58.10-140.60 nmol/L; for T3, the normal range was 0.92-2.79 nmol/L; and for TSH, the normal range was 0.550-4.780 IU/mL. All patients had higher serum T4 (>140.60 nmol/L) level and T3 (>2.79 nmol/L) and lower TSH (<0.550 IU/mL) at the time of the first visit to the endocrine clinic. The NOSPECS of all patients were grade 3 or less (≤3). All participants in our study did not have myopia, astigmatism, other ametropia, epilepsy, mental retardation, severe physical disease.

15 healthy controls enrolled by advertisements from nearby districts, with no personal history of thyroid or other endocrine-related diseases, no psychiatric disease or family history of psychiatric illness. Participants with a history of head injury or myopia were excluded. Other exclusion criteria were similar to the hyperthyroidism group. The age and gender of two groups were similar. The mean ages and standard deviations (SD) of the hyperthyroidism subjects and healthy controls were 39.2 ± 12.7 and 37.8 ± 9.5 (Mann-Whitney U Test, Z = 0.270, *P* = 0.787). The gender ratio was 2 male, 13 female participants in hyperthyroidism group; 6 male 9 female participants in control group (Mann-Whitney U Test, Z = 1.624, *P* = 0.217). The detailed information and clinic feature of patients see **Table 1**.

Procedures

Stimulus: The experiment was created and analyzed performed using the Experiment Center Software (SensoMotoric Instruments GmbH, Germany). Each participant sat in a chair approximately 60 cm in front of a LCD screen with his or her head fixed comfortably on a chinrest. An IVIEW X HISPEED eye tracker (SensoMotoric Instruments GmbH, Germany) was used to record participants' eye movements while they performed directed tasks, and the sampling rate was set on 1250 Hz with the accuracy rate less than 1 degree with a spatial resolution of approximately 0.01 degree. Patients underwent VGS, in which a single black dot about 1 degree in sight was randomly displayed on gray background. The position of the dot was randomized, and the duration of a dot's display was also randomized between 1000 ms and 1500 ms with no intervals between dots. The participant was told to keep visually fixated on the black dots, and saccades were guided out as the positions of the dots changed. There were 10 practice trials and 100 formal trials, and the practice trials were not included in analyses. Saccade duration was detected with a velocity threshold of 40 degrees per second (°/s) and recorded automatically by computer. The following parameters were recorded during

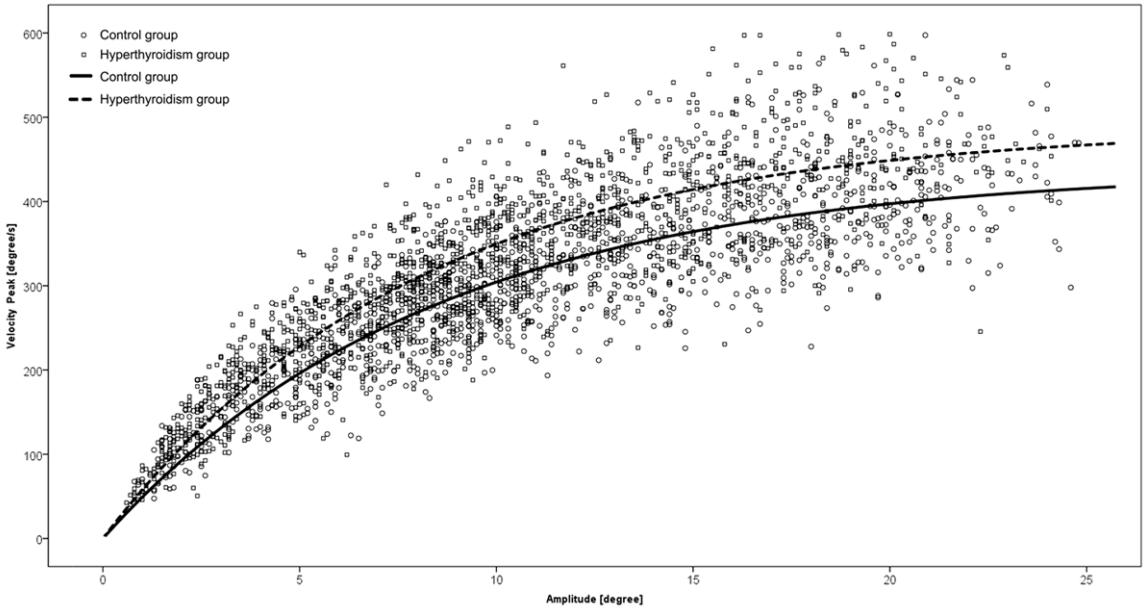

Figure 2. Typical saccadic main sequences for amplitude and peak velocity. Curve fitted according to the main sequence equation: Peak Velocity = V_{max}*(1-e^(-Amplitude/c)). The V_{max} values of control group and hyperthyroidism group were 438.47 ± 55.46°/s and 486.10 ± 51.49°/s. The V_{max} values showed significant differences between two groups.

each saccade: amplitude, duration, latency, peak velocity (PV), peak acceleration and peak deceleration.

Statistical analysis

Statistical analysis was carried out with SPSS for Windows (SPSS 19.0, SPSS Inc., Chicago, IL, USA).

Main sequence analysis

Saccade PV and amplitude can be fitted in main sequence equation (equation-1), Peak Velocity = V_{max} * (1-e^(-Amplitude/c)) equation-1 in this equation, V_{max} is the asymptotic value of the PV of the saccades of big amplitude, c is the amplitude constant. The nonlinear regression procedure was used on each group to estimate the V_{max} and constant c to fit the main sequence.

General linear model (GLM) was used to find the differences on latency, peak acceleration and peak deceleration between the groups. Saccade latency, peak acceleration and peak deceleration were set as the dependent variables, the PV, duration, amplitude as covariates, pair wise comparisons between groups was using the Bonferroni correction method.

Results

Main sequence analysis

The V_{max} values of control group and hyperthyroidism group were 438.47 ± 55.46°/s and 486.10 ± 51.49°/s, the V_{max} values were found to be significantly different between two groups (Mann-Whitney U test, Z = -2.053, P = 0.040), the fitting curves are shown in **Figure 2**.

Results of the GLM-based analysis at amplitude of 10.819°, PV value of 311.587°/s, and in a time duration of 61.94 ms, indicated that the saccade latency of the control group and hyperthyroidism group was 234.601 ms (95% CI = [230.497, 238.705]), and 223.364 ms (95% CI = [219.245, 227.482]), respectively, a significant difference was found between the saccade latency of both groups (P<0.001). Similarly, the peak acceleration in control group and hyperthyroidism group was 13959.973°/s^2 (95% CI = [13894.610, 14025.337]), and 14127.205°/s^2 (95% CI = [14061.606, 14192.804]), respectively, peak acceleration was also found to be significantly difference between the two groups (P<0.001). The peak deceleration in control group and hyperthyroidism group was -10194.008°/s^2

Table 2. The general descriptions of saccades

	The hyperthyroid patients group (n = 15)	The control group (n = 15)
Saccade latency (Mean ± SD)	223.26 ± 80.99 ms	234.30 ± 68.51 ms
Amplitude (Mean ± SD)	10.23 ± 5.41°	11.41 ± 5.64°
Peak velocity (Mean ± SD)	322.55 ± 115.29°/s	300.56 ± 94.56°/s
Saccade duration (Mean ± SD)	57.12 ± 19.23 ms	66.79 ± 21.96 ms
Acceleration peak (Mean ± SD)	14747.42 ± 5468.56°/s^2	13297.69 ± 4224.44°/s^2
Deceleration peak (Mean ± SD)	-10819.69 ± 3817.90°/s^2	-9526.93 ± 3016.26°/s^2

(95% CI = [-10296.046, -10091.970]), and -10160.784°/s^2 (95% CI = [-10263.189, -10058.378]), respectively, and no significant difference was observed between in the peak deceleration of the two groups (P = 0.662), detailed information was shown in **Table 2**.

Discussion

Since Klima G studied TAO by using eye trackers in 1986 [17], some evidences have demonstrated that the eye movement functional damage could be found in the severe and late fibrotic TAO [21, 22]. However, contradictory results could be found among the early findings, Schworm *et al.* reported that no clinically relevant saccadic changes were found in early active Graves' ophthalmopathy [18]. In another study, Schworm *et al*., also reported that the hyperthyroid patients with or without TAO had different vertical eye movement velocity compared with the controls [23]. Wouters *et al*., reported that the saccades in Graves' disease patients without active eyeball symptoms and injury of extraocular muscles showed lower maximum main sequence velocities [24].

Patients with hyperthyroidism have different symptoms of eyeballs. The absence of an early detection system for eye damage in patients with hyperthyroidism remains a diagnostic challenge. The current diagnosis on TAO is based on standards developed by NOSPECS. Currently, assessment of early TAO patients in NOSPECS is based primarily on the eyeball symptoms and signs, which is lack of objectivity and sensitivity. Anti-inflammatory, anti-edema and immunosuppressive therapy in the early inflammatory phases of fibroblast proliferation can improve the condition of the eye, and may even restore normal anatomy and function of the eyelids [25-27].

In our study, patients with hyperthyroidism exhibited a higher velocity and peak acceleration, which might be attributed to the increased excitability of the sympathetic nervous system caused by hyperthyroidism. The widespread manifestations of increased sympathetic activity in patients with hyperthyroidism include faster heart rates, irritability, heat intolerance, nystagmus, and faster neural system reactions [28]. These reasons may lead to the changes in the eye movements in patients with hyperthyroidism. In clinical practice, prescription of β-blockers in hyperthyroid patients could improve the symptoms of sympathetic activation as well as ocular symptoms. Tian *et al*., demonstrated that the increased active eye muscle tension may represent an adaptational mechanism of the saccade system to overbear the eye movement restriction in TAO, furthermore this may cause the higher velocities of TAO [29].

The major pathological changes associated with the TAO are inflammation of the outer orbital soft tissue and eye muscles [7, 30]. Early pathological changes are lymphocytes and plasma cells infiltration into the extraocular muscle tissue [31]. Gopinath *et al*., has demonstrated that the prevalence of antibodies against the eye-muscle antigens could be detected in the patients with early Graves' disease (the course of disease <12 months) with and without ophthalmopathy [28, 32], but the early course of the disease could hardly be mentioned. Generally, the reason of change of V_{max} was mainly due to the physical structure of the eyeballs, such as ocular muscles or orbital resistance. In the current study, we have reported that the V_{max} values changed, which indicates that the physical changes have occurred in the ocular structure (such as ocular muscles), but more evidences should be collected to define the related early inflammatory course of TAO.

In our study, we also found that the patients group had shorter latencies. Catz *et al*., have reported that the adaptability of central neural

saccade generator changed in the patients with hyperthyroidism [33], and this may cause the inability in patients to effectively control the initializations of saccades.

Compared with the previous studies, our study has two characteristics: first, enrolled patients had no serious signs of eyeball damage, including: extraocular muscles, corneal or optic nerve damage, and most patients did not complain any ocular discomfort in endocrinology clinic. Moreover, all patients were first-episode treatment-naive hyperthyreosis patients. Our results suggest that the eye damage caused by hyperthyroidism may be earlier than expected, and fortunately, eye saccade tracking technique may assist in its early detection of the disease. To further strengthen the findings of this study, it is necessary to carry out additional research in other populations and inclusion of larger sample sizes.

Conclusion

As an exploratory study, we found that hyperthyreosis patients showed a significant difference in the dynamics of saccades during VGS relative to normal healthy controls. Saccade tracking examination may have a potential value for the early detection of TAO.

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Disclosure of conflict of interest

None.

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