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ORIGINAL PAPER

^{99m}Tc-HYNIC-TOC scintigraphy in evaluation of active Graves' ophthalmopathy (GO)

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Abstract
Objective A promising radiopharmaceutical ^{99m}Tc-HYNIC-TOC (^{99m}Tc-HYNIC-Octreotide) can be applied for somatostatin receptor scintigraphy with the potential to replace Indium-111 labeled somatostatin analogus. Here we evaluate whether orbital ^{99m}Tc-HYNIC-TOC scintigraphy can be used as a Graves' ophthalmopathy (GO) activity parameter to predict the retrobulbar irradiation response.
Methods Orbital ^{99m}Tc-HYNIC-TOC scintigraphy was performed on 14 consecutive patients demonstrating moderated to severe Graves' ophthalmopathy. The patients were treated with retrobulbar irradiation following the octreoscan and the response to this therapy was assessed at 3 months after the start of treatment. The orbital ^{99m}Tc-HYNIC-TOC uptake was calculated to assess the effects of treatment.
Results Among the 14 GO patients, eight (57.1%) responded to retrobulbar radiotherapy; six (42.9%) showed no change. We compared the eight responders and six non-responders in terms of orbital ^{99m}Tc-HYNIC-TOC uptake, using the orbital/occipital ratio. On the 4-h ^{99m}Tc-HYNIC-TOC scintigraphy, responders had a higher orbital/occipital uptake ratio than the no-responders ($P = 0.001$). A significant correlation was found between the orbital/occipital ratio and the clinical activity score (CAS) ($P = 0.034$). The Receiving-Operator-Characteristic curve showed the best threshold for discriminating active and inactive disease was 1.40 (sensitivity, 100%; specificity, 83.3%). In the responders group, all these eight patients had positive scintigraphy. While there were five patients who had negative scintigraphy in the non-responders group.
Conclusion Orbital ^{99m}Tc-HYNIC-TOC scintigraphy can be a useful method for the estimation of disease activity and prediction the response to subsequent radiotherapy in GO patient. And the patients with positive octreoscan were more likely to respond to irradiation.

Keywords Graves' ophthalmopathy (GO) · Somatostatin receptor scintigraphy (SRS) · Radiotherapy

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Introduction

Graves' ophthalmopathy (GO) is a disorder of extraocular muscles and retrobulbar tissues associated with autoimmune thyroid disease. It is one the most frequent complication of Graves' disease. The main clinical manifestations of the disease include exophthalmos, periorbital swelling, venous congestion and involvement of cornea and optic nerve. Patients afflicted with GO may experience not only pain and visual loss, but also disfigurement. Current therapeutic modalities are less than satisfactory with only two-thirds of patients having a favorable response. The emphasis is on early detection and treatment during the active phase of the disease [1]. Disease activity is probably the prime determinant of response and it is a challenge for the future to develop reliable parameters of disease activity on the basis of which patients can be selected for further medical treatment, or can be subjected to rehabilitative surgery without prior immunosuppression. Various methods to evaluate disease activity have been proposed. The most widely used method in clinical studies is the clinical activity score (CAS) (see "Methods").

Somatostatin receptor scintigraphy (SRS), with different types of radiopharmaceuticals, has been recently shown able to reveal the presence of activated lymphocytes in inflammatory foci of several autoimmune diseases [2]. Indium-111 labeled SRS has been recommended for the detection of somatostatin receptor positive tumors. Sites with increased numbers of activated lymphocytes may also show In-111 labeled somatostatin analog with Graves' ophthalmopathy (GO). However, indium-111 as a radiolabel has several drawbacks, including limited availability, suboptimal gamma energy and high-radiation burden to the patient. There are some reports that orbit scintigraphy methods were applied in GO patient with different agent of somatostatin [3, 4]. The scintigraphy with ^{99m}Tc-HYNIC-TOC (^{99m}Tc-HYNIC-Octreotide) has been used to visualize somatostatin receptor-expressing tumors, such as medullary thyroid carcinoma, pulmonary nodules, carcinoid syndrome, pancreatic cancer, and pituitary tumor [5, 6, 7]. The goal of this study was to evaluate whether orbital ^{99m}Tc-HYNIC-TOC scintigraphy can be used a disease activity parameter that predicts the response to retrobulbar irradiation therapy.

Subjects and methods

Subjects

A total of 14 patients (seven males and seven females, aged 25–50 years) with moderately severe GO were studied. We recruited untreated, consecutive patients with at least NOSPECS class 3 b–c, or class 4 b–c [8]. A 2-month screening period before baseline assessment ensured that thyroid status was stable and that GO was not spontaneously improving. Only patients with euthyroid (normal serum free T4 and T3 with normal or suppressed serum TSH) for at least 2 months who had not been treated with I-131, immunosuppressive therapy, orbital surgery, or orbital radiotherapy within the previous year, or with corticosteroids in the previous 6 months, were eligible for recruitment. They were examined thyroid hormone and TSH levels at the beginning of the study and after 3 months, respectively. Six subjects without any history of ophthalmic, thyroid, or autoimmune disease were studied as controls with normal serum free T4, T3, and TSH level. SRS was performed in all subjects, and subsequently retrobulbar irradiation therapy was started in GO patients. A careful clinical examination of orbits disease was executed in all patients before and 3 months after irradiation treatment. The severity of the ophthalmopathy was assessed by the intensity of proptosis (as measured with a Hertel exophthalmometer), lid width, and the presence or absence of diplopia during analysis of ocular mobility. To assess the activity of the ophthalmopathy, we employed a clinical activity score (CAS) [9, 10] by assigning one point to each of the following seven manifestations and summing the points: spontaneous retrobulbar pain, pain on eye movement, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle, and eyelid edema or fullness. The response to this therapy was evaluated at 3 months after start of treatment. Progression or improvement of ophthalmopathy was defined by changes in at least two major criteria (variations in proptosis and lid width of 2 mm or greater, appearance, disappearance, or change in the degree of diplopia, changes in the activity score 2 points or more, and changes on one tenth or more in visual acuity) and one minor criterion (soft tissue changes, self-assessment evaluation) [11]. Informed consents were obtained from GO patients and control subjects and the study was approved by the Ethics Committee of RuiJin Hospital, Shanghai JiaoTong University School of Medicine.

Methods

^{99m}Tc-HYNIC-Octreotide was purchased from Yuanpu Isotope (Shanghai China). Quality controls were performed on labeled peptide before the injection. More than 95% of the radioactivity was peptide bound in injectable preparations. SPECT images were obtained 4 h after the iv injection of approximately 20 mCi of ^{99m}Tc-HYNIC-Octreotide. A dual-detector SPECT camera (Vertex, ADAC, USA) with VXGP collimator, matrix $128 \times 128 \times 8$, were conducted in this study. Reconstruction was performed using a butterworth filter on back-projected images. No attenuation correction was applied. A total of ten images (5 mm apart) in the transverse plane were obtained and from these ten, the six slices with maximal orbital uptake were selected, using the pituitary gland as anatomical reference. Thus, per patient 12 orbital images were analyzed. The measurement of orbital uptake was done using a fixed (1,154 pixels) rectangular region of interest (ROI). The numbers of counts in the 12 orbital images were averaged. In each of the six slices the nonspecific, background uptake was determined in an occipital area. Per area, the counts in the six slices were measured using the same fixed ROIs and the means of the six slices were calculated. To correct orbital uptake for nonspecific background uptake, we calculated the ratio of orbital to occipital uptake.

Orbital irradiation was performed using a 4 MeV linear accelerator. A computer-assisted tomography of the orbit was performed in all patients before treatment to define the radiation field. All patients were treated bilaterally. A total of 20 Gy was delivered to each eye in ten fractionated doses over a period of 10 days.

Statistical analysis

In all three groups (Responders, non-Responders, and control groups) the octreotide uptake (orbital/occipital ratio) was expressed as mean ± SD. The comparison of ^{99m}Tc-HYNIC-TOC uptake (orbital/occipital ratio) was performed using the Kruskall–Wallis test. The correlations between the orbital/occipital ratio and CAS before treatment were investigated with Spearman's correlation test. Receiving Operator Characteristic (ROC) curve test was assessed using the area under the ROC curve as an index performance. ROC curve-based best threshold value between responders and non-responders was defined as the cutoff that resulted in the best sensitivity for the detection of cases that was presumed to give a response to immunosuppressive treatment with an associated specificity of 85% or more. All data were analyzed using the SSPS 11.5 for Windows package (SPSS Inc, Chicago, IL). The level of statistical significance was determined as $P < 0.05$.

Results

In our study, there were eight (57.1%) responders who demonstrated clinical improvement according to the mentioned criteria and the remaining six (42.9%) patients comprised the non-responders. Subsequently the responders and non-responders were defined as two groups. The demographic data of the patients are given in Table 1. There was no statistical difference between the age and gender spectrums of groups ($P > 0.05$). No clear difference was found in smoking habits between the two groups. The duration of thyroid disease and ophthalmopathy was comparable between two groups ($P > 0.05$). There were no differences in the severity of the ophthalmopathy and thyroid function between the two groups. However, the mean value of CAS in responder group was significantly higher than that in non-responders ($P = 0.026$).

In a patient with disease activity in the left orbit, ^{99m}Tc-HYNIC-TOC intensively accumulated in the left orbital area (Fig. 1). And in the image of normal control, there were no obvious ^{99m}Tc-HYNIC-TOC accumulation in both orbit (Fig. 2).

We compared the eight responders, the six non-responders and controls in terms of orbital ^{99m}Tc-HYNIC-TOC uptake, using the orbital/occipital ratio. On the 4-h ^{99m}Tc-HYNIC-TOC scintigraphy, the mean ± SD orbital/occipital ratio was 1.57 ± 0.11 in responders and 1.27 ± 0.17 in non-responders. This ratio was 1.07 ± 0.06 in the control group. The responders had a significantly higher orbital/occipital uptake ratio than non-responders ($P = 0.001$) (Fig. 3). A significant difference between controls and non-responders were observed ($P = 0.024$).

We found a significant correlation between octreotide uptake and the CAS of the disease ($r = 0.568$, $P = 0.034$). However, there was no significant correlation between octreotide uptake and severity of the disease, smoking status, the duration of disease, or thyroid function.

The efficiency of the orbit ^{99m}Tc-HYNIC-TOC uptake to assess disease activity and predict a response to radiotherapy was evaluated by ROC curve analysis. The ROC curve for 4-h orbital/occipital uptake ratio showed a large area under the curve (AUC) that was 0.958. The best

Table 1 Clinical and biochemical features of the 14 patients with GO

	Responders	Non-responders	*P*	control
No. (patients)	8	6	–	6
Gender (M/F)	4/4	3/3	0.704	4/2
Mean age (year)	39.1 ± 10.0	39.0 ± 5.4	0.978	41.8 ± 10.7
Smokers (*n*)	2	2	0.594	–
Duration of hyperthyroidism (*m*)	43.3 ± 39.9	23.8 ± 28.1	0.339	–
Duration of ophthalmopathy (*m*)	35.5 ± 37.6	21.5 ± 29.1	0.464	–
FT3 (pmol/L)	5.0 ± 2.1	6.3 ± 1.8	0.258	4.1 ± 0.8
FT4 (pmol/L)	15.7 ± 5.5	15.5 ± 3.2	0.960	13.9 ± 1.6
TSH (uIu/ml)	3.1 ± 2.0	1.0 ± 0.8	0.051	2.2 ± 0.9
TRAb	32.9 ± 26.0	62.8 ± 28.3	0.108	6.7 ± 4.1
Proptosis (mm)	20.2 ± 2.8	19.6 ± 5.0	0.778	–
Diplopia (*n*)	5	3	0.529	–
Lid width (mm)	9.9 ± 2.5	11.4 ± 1.9	0.283	–
CAS	3.9 ± 1.0	2.8 ± 1.0	0.026*	–

*The mean value of CAS in responder group was significantly higher than that in non-responders ($P = 0.026$)

CAS: clinical activity score

TRAb: TSH receptor antibody

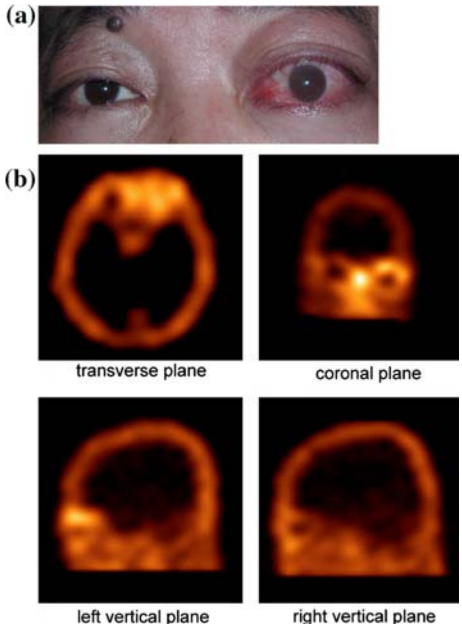

Fig. 1 The GO patient complained left eye pain, redness, swelling, and impairment. (**a**) The SPECT images of the case in the transverse, coronal, and vertical planes. The images showed markedly elevated 99mTc-HYNIC-TOC uptake in left orbit compared with right orbit (**b**) Note that the apparent orbit findings of inflammation (such as pain, redness, swelling, impairment) are synonymous with the increased ^{99m}Tc-HYNIC-TOC uptake in the 4-h scintigraphy

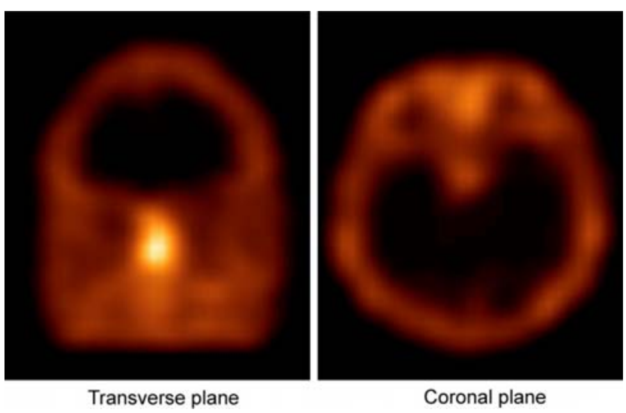

Fig. 2 No ^{99m}Tc-HYNIC-TOC accumulation was observed in both orbits in the subject without ophthalmopathy

threshold for discriminating active and inactive disease was 1.40 (sensitivity, 100%; specificity, 83.3%), which yielded a positive predictive value of 88.9%, and a negative predictive value of 100%.

Discussion

Graves' ophthalmopathy undergoes two phases of early active stage and later inactive stage [12]. The definition of

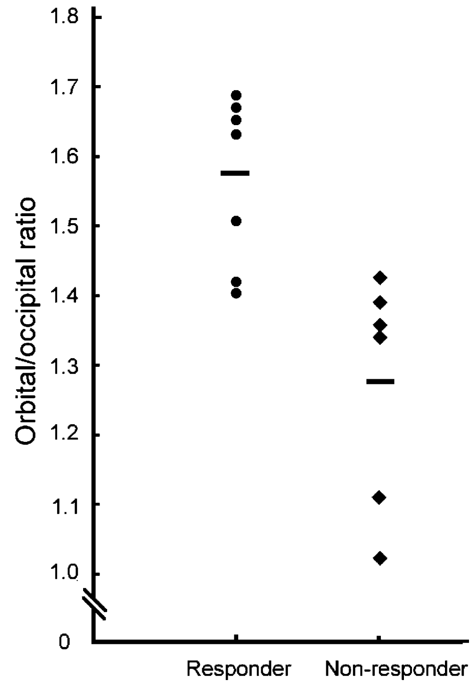

Fig. 3 On the 4-h ^{99m}Tc-HYNIC-TOC scintigraphy, responders had a higher mean ± SD orbital/occipital uptake ratio: 1.57 ± 0.11 versus 1.27 ± 0.17 (P = 0.001)

the phase of ophthalmopathy plays a pivotal role in prognosis and timing of therapeutic interventions [13]. Some parameters have been sought to assess the orbital disease activity. The Clinical Activity Score (CAS) is based on the classical signs of inflammation, which is fast, cheap, and requires no other measurement. But its negative predictive value is relatively low [9, 14]. Magnetic Resonance Imaging (MRI), include T2 weighted MRI and Short Tau Inversion Recovery, could be used to assess disease activity according to detecting edema and inflammation in the extraocular muscles [15, 16]. But larger studies should be performed to further assess this modality. A mode ultrasonography can be used to show intramuscular structural differences and this ability has been used to make the distinction between active and inactive ophthalmopathy. However this method is operator-dependent and a lager study of 56 patients demonstrated it is insufficient as a test [17].

Recently, several studies have claimed that [111In-DTPA-D-Phe1]-octreotide scintigraphy was able to assess disease activity [18, 19]. These studies demonstrated increased 111In octreotide accumulation in patients with active orbital disease than in those with inactive disease and emphasized that a positive orbital octreotide scintigraphy indicated clinically active disease in which immunosuppressive treatment might be beneficial. Compared to [111In-DTPA-D-Phe1]-octreotide, ^{99m}Tc-HYNIC-TOC is a promising new radiopharmaceutical with the potential to replace [(111)In-DTPA-D-Phe(1)]-Octreotide for SRS due to the advantage of improved image quality, lower radiation dose for the patient, and daily availability. Our study supplied the clinical results about the application of 99mTc-HYNIC-TOC scintigraphy in Chinese patients with GO.

In our present open, prospective study, SPECT images were obtained 4 h after the iv injection of approximately 20 mCi of ^{99m}Tc-HYNIC-TOC. We used the orbital/occipital uptake ratio to reflect the orbit ^{99m}Tc-HYNIC-TOC uptake and found a good correlation with the Clinical Activity Score, which was also reported by earlier studies although a different time interval after injection was used for SPECT image formation [18, 19].

Although performed in a small number of patients, still, we can observe the orbital uptake of ^{99m}Tc-Octreotide was significantly elevated in the responder group compared to the non-responder group. Similar to 111-In octreotide scintigraphy [20], this study also shows that measurement of orbital ^{99m}Tc-HYNIC-TOC uptake might be of use in predicting the outcome of immunosuppressive treatment of patients with GO.

The best cut-off point orbital/occipital ratio for discriminating active and inactive disease was 1.40 with a sensitivity of 100% and a specificity of 83.3% based on ROC analysis (Positive predictive value 88.9%, negative predictive value 100%). This is in agreement with a small study with 12 patients, finding a positive predictive value of 84%, and with a recent study in selected (active) patients with Graves' ophthalmopathy (positive predictive value: 90%) [21, 22]. The high negative predictive value is favorable in clinical practice to choose patients with inactive disease who will not benefit from immunosuppression therapy and to avoid the side-effects of the therapy. SRS results could predict the therapeutical outcome in patients with GO treated with orbital Radiotherapy.

Therefore these preliminary results of the current study demonstrated that ^{99m}Tc-HYNIC-TOC orbital/occipital uptake is well correlated with the disease activity. Histological finding is the gold standard for disease activity which indicated that lymphocytic infiltration, edema and fibroblast activation in specimens of patients with ophthalmopathy of recent onset, and fibrotic changes and fat accumulation in patients with longstanding eye disease. But it is very difficult to collect the orbit specimen of each GO patient. In the absence of histology, orbital ^{99m}Tc-HYNIC-TOC scintigraphy is able to determine the pathological phase of Graves' disease, giving a high positive scan in the active early phase and a low positive or negative scan in the stable end phase of the disease. It was confirmed by the case in Fig. 1, which showed that scintigraphy images were consistent with the apparent orbit findings of inflammation. Also, we found this is a potentially useful technique to predict the response to retrobulbar radiotherapy in GO. It might be that a combination of activity parameters are needed to accurately predict response to treatment and further studies are required in large series to determine its roles as a guide for therapeutic strategy in GO.

One limitation of the present study has to be addressed is that TSH level was close to being significant between the two groups. It seemed that TSH level could be regarded as a predictor of radiotherapy response in this study. Few studies focus on the relationship between TSH level and radiotherapy response. It is mainly because the thyroid associated ophthalmopathy could occur in the patient with low TSH level (Graves' hyperthyroidism), high TSH level (hypothyroid Hashimoto's thyroiditis), or in euthyroid subjects with no current or past evidence of thyroid hyper or hypofunction [23, 24]. In contrary, there is some evidence that TSH levels could be recognized as risk factors for the deterioration of eye disease after radioiodine in Graves' hyperthyroidism patients [25, 26]. Therefore, the TSH level on the effects of treatment of GO remain unclear. Our result might indicate an indirect correlation between TSH level and treatment response of GO. Further study is needed to elucidate the precise role of TSH level in the treatment response of GO.

In conclusion, orbital ^{99m}Tc-HYNIC-TOC scintigraphy can be a useful method for the estimation of disease activity and prediction of the response to subsequent radiotherapy in GO patient.

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