Image fusion analysis of ^{99m}Tc-HYNIC-octreotide scintigraphy and CT/MRI in patients with thyroid-associated orbitopathy: the importance of the lacrimal gland

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Received: 18 February 2003 / Accepted: 28 March 2003 / Published online: 13 June 2003

Abstract. The aim of this study was to describe the anatomical structures that show uptake of the somatostatin analogue octreotide in patients with thyroid-associated orbitopathy (TAO). The study population comprised a series of 20 TAO patients attending the out-patient thyroid clinic and 12 patients presenting head or neck tumours. Scintigraphy was carried out with our newly developed tracer, technetium-99m labelled EDDA-HYNIC-TOC (^{99m}Tc-TOC). Morphological imaging was done with either magnetic resonance imaging or X-ray computed tomography without contrast medium. Both imaging procedures were done within an interval of 3–4 weeks. For the image fusion procedure, specific external reference markers were used for each imaging modality. The markers were screwed onto a reference frame, which was held in place via a vacuum-fixed mouthpiece. The anatomical structure showing tracer uptake that was most frequently recognised was the lacrimal gland, followed by the retronasal area, cervical lymph structures, salivary glands, the anterior insertion points of the extra-ocular muscles and discrete areas of the neck extensor muscles. The lacrimal gland and the retronasal area showed the highest and most frequent uptake of ^{99m}Tc-TOC in TAO patients, whereas such uptake did not occur in the retrobulbar space. In spite of knowledge of these results of image fusion, no changes in the involved structures could be detected on morphological imaging. It is concluded that binding of ^{99m}Tc-TOC is more frequently localised to the anterior compartment of the eye and to the neck. The previously used term "orbital" uptake should be abandoned and replaced by a descriptive term relating to the anatomically recognised structure showing tracer accumulation, i.e. the lacrimal gland. The uptake of octreotide by lymphoid and salivary glands opens a new field of investigation related to the physiology of somatostatin.

Keywords: Octreotide – ^{99m}Tc-EDDA-HYNIC-TOC – Thyroid-associated ophthalmopathy – Image fusion – Lacrimal gland

Eur J Nucl Med Mol Imaging (2003) 30:1155–1159
DOI 10.1007/s00259-003-1207-0

Introduction

Thyroid-associated ophthalmopathy (TAO) has been recognised as a clinical entity for more than 150 years [1]. The basic clinical picture of TAO has not changed since these initial descriptions. Morphological imaging techniques, e.g. computed tomography (CT) and magnetic resonance imaging (MRI), can document involvement of the extra-ocular muscles as well as anterior displacement of the lacrimal gland [2, 3]. Functional imaging methods using octreotide have suggested the involvement of immunological mechanisms in the orbital region. Tracer uptake has been shown to be amenable to modulation by immunosuppressive therapy. In addition, probable involvement of the lacrimal gland has been described [4]. In spite of these results, several recent reviews have pointed out the need for further investigation into the pathophysiology of this disease [5]. Recent technical developments have paved the way for a new analysis of this situation. The first improvement was the development of a technetium-99m labelled octreotide tracer [6]. The second improvement was the development of a

The individual results of the first 18 patients with thyroid-associated orbitopathy have been analysed as part of a doctoral thesis (H. Kainz, University of Innsbruck, 2002).

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highly reproducible method for image fusion analysis based on an external reference frame [7]. The aim of this study was to identify the anatomical structures depicted with ^{99m}Tc-EDDA-HYNIC-TOC (^{99m}Tc-TOC) in patients with early-stage TAO by means of image fusion analysis.

Materials and methods

External reference frame for image fusion. The system (Medical Intelligence, Schwabmünchen Germany) consists of the SIP Laboratory, Innsbruck reference frame, reproducibly connected to the Vogele-Bale-Hohner (VBH) vacuum mouthpiece. The methodology of image registration has been described previously [7]. For different imaging modalities, identical reference frames are equipped with modality-specific markers (americium-241 for nuclear medicine, nitroglycerin for MRI and glass beads for CT) placed at identical positions. Based on the external markers, the resulting datasets are manually registered using commercially available software (Framelink/Cranial; Stealth navigation system, Medtronic, Boulder, Colo., USA).

Radionuclide and morphological imaging. The imaging procedures were carried out according to the previously published methods for ^{99m}Tc-TOC [4, 6]; 370 MBq of tracer was administered intravenously. Free ^{99m}Tc accounted for a maximum of 3%. Whole-body imaging was done at 4 h p.i., followed by single-photon emission tomography (SPET) imaging of the head (60 steps, 35 s/step, 128×128 matrix). Conventional tomographic imaging was done with either MRI (Magneton Vision, 1.5 Tesla, Siemens) or computed axial tomography (GE Advance CT) without contrast media.

TAO patients. A series of 20 consecutive patients referred to the out-patient thyroid unit of the Department of Nuclear Medicine of the University of Innsbruck were included in the study. The investigational protocol was approved by the local Ethics Committee. The majority of patients were studied at an early stage of the disease owing to the awareness of the clinicians involved (Thyroid Unit). This awareness has arisen from our initial observations, which revealed "orbital" uptake even in patients without clinically evident TAO [4]; thus, patients with peri-orbital swelling were studied early in the course of the disease. Only three patients were referred after having had signs and symptoms of TAO for more than 6 months. All patients were euthyroid at the time of the examination.

Controls. A series of 12 patients undergoing the same diagnostic procedure for brain tumour or paraganglioma were included. In one patient with a paraganglioma, who presented a tumour mass at the right carotid artery, a dual-tracer study was carried out. First a ^{99m}Tc-SPET study was done, followed later by the ^{99m}Tc-TOC study and by CT with contrast media. In this special case, exact localisation of the paraganglioma in relation to the right lobe of the thyroid was required.

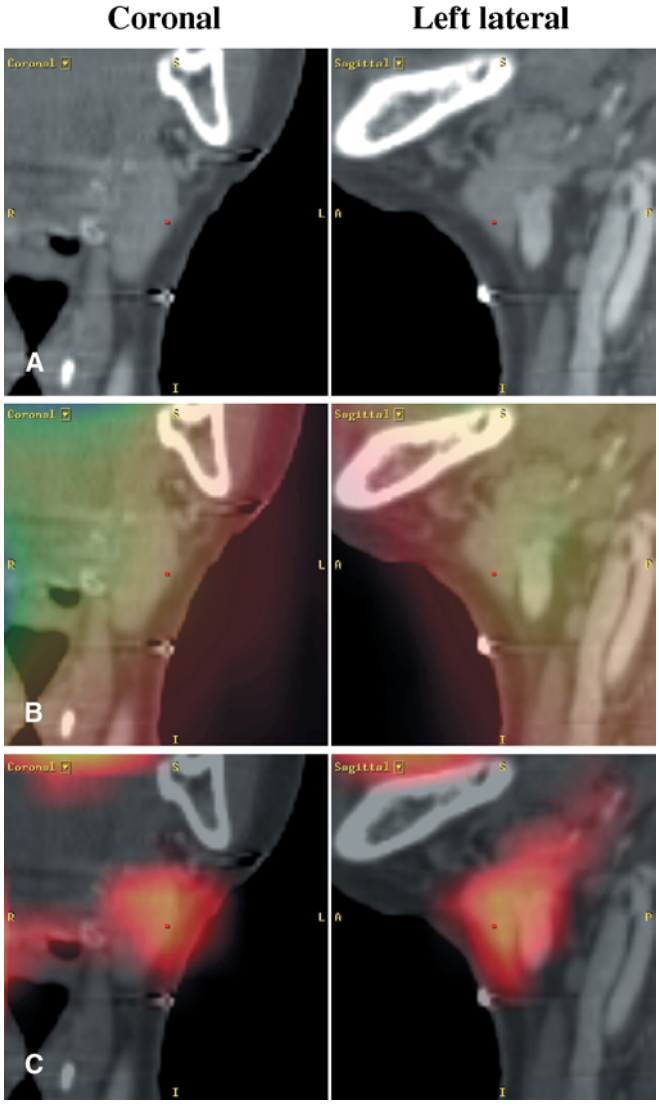

Fig. 1A–C. Distribution of pure ^{99m}Tc and ^{99m}Tc-TOC in the only patient studied with contrast-enhanced CT. **A** CT with contrast medium: The left mandible is easily recognisable on all images. The right image clearly shows arterial and venous vessels. **B** ^{99m}Tc-SPET: Tracer distribution is rather faint and homogeneous in the neck region. **C** ^{99m}Tc-octreotide SPET: uptake of ^{99m}Tc-octreotide is clearly localised to the submandibular gland, as well as to the sublingual salivary glands

Results

Controls

This group of patients revealed rather faint uptake of ^{99m}Tc-TOC in the nasal area as well as along the lacrimal gland. The dual-tracer study on the patient with a paraganglioma allowed us to differentiate "unspecific" uptake of pure ^{99m}Tc, equivalent to free ^{99m}Tc, from that of ^{99m}Tc-TOC (Fig. 1). The paraganglioma on the right side of the neck showed intense uptake of both tracers. The

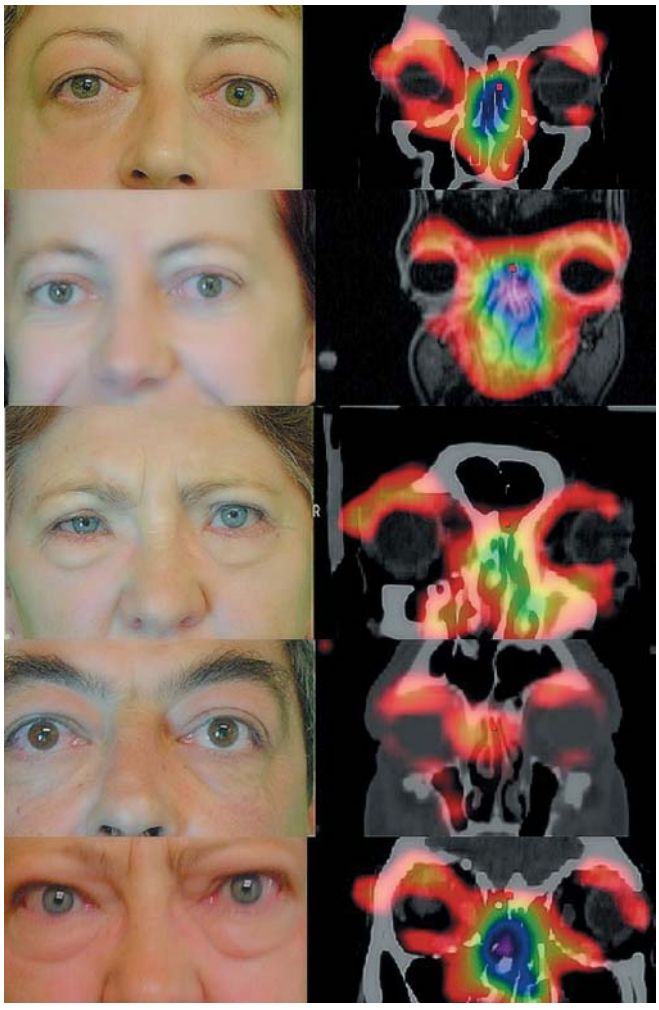

Fig. 2. Comparative presentation of the clinical signs in relation to the image fusion results. The patterns of "eyelid swelling" correspond to the distribution of ^{99m}Tc-TOC. The intensity of the scintigrahic images has been chosen in order to stress the relation of the lacrimal gland to the bony structures of the orbit. At the upper lateral orbit, the area showing ^{99m}Tc-TOC uptake corresponds to the lacrimal gland in the fossa lacrimalis. In the midline, both the nasolacrimal ducts as well as the nasal area can be recognised

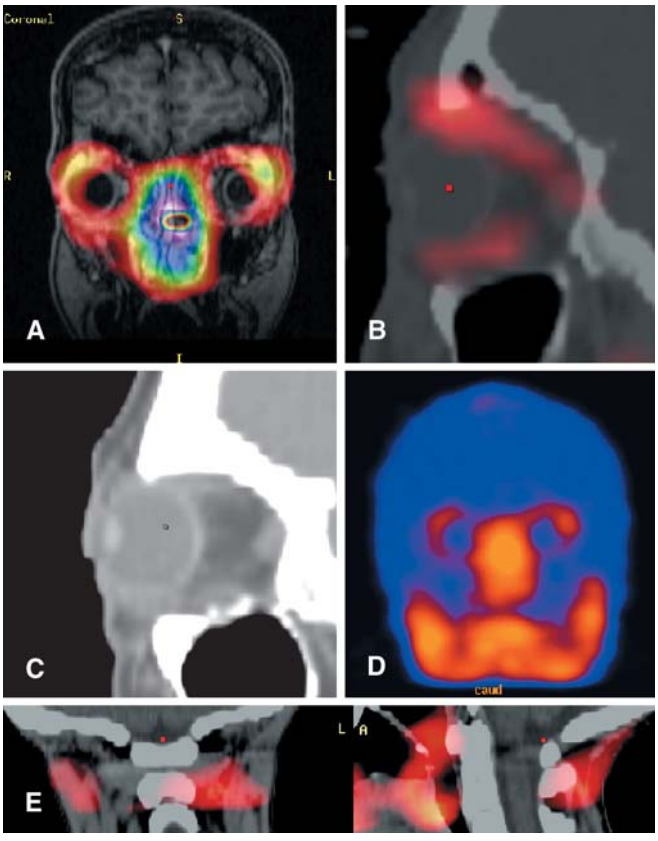

Fig. 3A–E. Summary of the most frequent patterns of uptake of ^{99m}Tc-TOC. **A** Eye glass and hot nose signs: uptake in the lacrimal gland, the accessory lacrimal glands, the lacrimal ducts, the lacrimal sac, the naso-lacrimal ducts and the nasal area. **B** "Scissors" sign delineating eye muscles that show tracer uptake. The retrobulbar soft tissues show no uptake. **C** Eye muscle displacement without tracer uptake.**D** W and omega (Ω) signs of the joint demonstration of salivary and lymphoid glands. The 'W' appears as a continuous line of demarcation between the head and the neck. **E** Nuchal uptake located to muscular structures

thyroid showed normal uptake of ^{99m}Tc, and only the left thyroid lobe showed preferential uptake of ^{99m}Tc-TOC; in this lobe an ultrasound control revealed a pattern consistent with autoimmune changes. In the nasal and orbital regions, faint but homogeneous distribution of ^{99m}Tc, but not of ^{99m}Tc-TOC, could be seen, while submandibular glands and lymphoid structures only showed ^{99m}Tc-TOC uptake (Fig. 1C).

Evaluation of SPET images in TAO

Image fusion analysis revealed that the following anatomical structures showed tracer uptake: (1) the lacrimal gland, (2) the retronasal region, (3) neck lymphatics and (4) the salivary glands. Tracer uptake in the retro-orbital space or in the extra-ocular muscles was seen in very few cases. A special uptake pattern in TAO patients was located in nuchal muscles. In the three cases of long-standing TAO without clinical signs of activity, ^{99m}Tc-TOC uptake was low and comparable to the level seen in the control group.

The majority of the patients showed uptake in the lacrimal gland corresponding to the clinical expression of the disease, i.e. the side presenting soft tissue swelling also revealed tracer uptake in the lacrimal gland (Fig. 2). Coronal slices were the most adequate in showing this involvement. Together with the lacrimal gland, the area of the lower eyelid also showed tracer uptake. The presence of both patterns represents the "eye glass sign" (Fig. 3A). In some cases, a typical pattern was found when both the superior and inferior recti muscles were

depicted, forming the so-called scissors sign (Fig. 3B). In some cases, displacement of retro-orbital muscles was seen only on the morphological images, without a correlation on functional imaging (Fig. 3C). Quite often an interwoven uptake was found in the ventral area of the orbit, i.e. in the area of ventral muscle insertion; this was especially evident in the upper part of the eye bulb, where the lacrimal gland is located. The image fusion analysis revealed that the uptake seen in the retronasal space corresponded to the area where the nasal mucosa is expected. In TAO patients, this uptake was usually asymmetrical, i.e. preferential uptake was seen on either the left or the right side. Adjacent SPET slices showed a connection between the retronasal space and the lacrimal ducts (Fig. 3A). Besides these structures, we were also able to identify tracer uptake in neck lymphatic structures as well as salivary glands. The lymphatic glands that were recognised were the palatine, lingual, pharyngeal and tonsillary structures. In one case we were able to recognise a pattern suggestive of tonsillitis (confirmed by ENT examination). The optical sum of all of these structures resembled a "W" beginning with the parotids and continuing with the submandibular glands, lymphoid glands and sublingual glands (Fig. 3D). When the uptake in the parotids was low, the central part resembled an omega (Ω). Finally, we were able to identify tracer uptake in nuchal muscles. These areas of uptake were usually very small and discrete (Fig. 3E).

Morphological imaging did not reveal any pathological changes in the lacrimal glands, the retronasal area, the neck lymphatics, the salivary glands or the nuchal muscles.

Discussion

A large number of studies have revealed the imaging capability of the octreotide analogue ^{111}In-OctreoScan (Mallinckrodt, Petten, The Netherlands) in patients with TAO. In this study, however, we used a newly developed octreotide analogue, ^{99m}Tc-TOC [6], in combination with precise image fusion procedures [7]. In order to eliminate any doubts about the specific uptake of this octreotide analogue, we showed in a sequential dual-tracer study that the distribution of ^{99m}Tc-TOC differs from that of pure ^{99m}Tc. Thus, even considering the small amount of free ^{99m}Tc in ^{99m}Tc-TOC, it will surely not produce confounding images. This approach allowed us to clearly recognise the anatomical structures in the head and neck that present somatostatin receptors. Among these, the salivary and lymphoid glands have not previously been described as being somatostatin receptor positive.

We consider the uptake in the lacrimal gland to be the central result of our study. We feel that recognition of this phenomenon enables us to explain the real mechanism underlying the classical sign of upper and lower "lid swelling", which is clinically evident in some patients in the form of the "eye glass sign". In accordance with our initial hypothesis that an immune mechanism is involved in the pathophysiology of TAO [4], we tend to interpret the uptake in the lacrimal gland area as an expression of an immunological reaction. The lacrimal gland system is an immunocompetent system which is summarised in the term mucosa-associated lymphoid tissue (MALT) [8, 9, 10]. Lymphatic flow from the lacrimal gland, as well as from the orbit, can be followed into the cervical lymphatic areas [11]. The uptake in the nuchal area is puzzling since it does not correlate to any known sign or symptom of TAO. We explain this uptake as a focal inflammatory reaction of the neck extensors due to the postural changes corresponding to myofascial pain syndrome [12].

In conclusion, a wide range of structures in the head and neck area show uptake of ^{99m}Tc-TOC in patients with TAO. The most relevant site appears to be the lacrimal gland, which clinically corresponds to eyelid swelling. The identification of octreotide uptake in the lymphatic and salivary glands reveals a new aspect of the physiology of these organs as well as that of somatostatin. The role of the neck lymphatics and the salivary glands in relation to the diagnosis and therapy of TAO remains to be elucidated.

Acknowledgements. This study was made possible by the expert contributions from Thomas Lang and Martin Knoflach, SIP Laboratory, Department of Radiology I, University of Innsbruck, who carried out the image fusion procedures. We also wish to thank the technical assistants of the Departments of Nuclear Medicine and Radiology I who were involved in the imaging procedures. Their expert technical work is deeply appreciated.

References

1. von Basedow K. Exophthalmus durch Hypertrophie des Zellgewebes in der Augenhöhle. *Woch ges Heilkunde* 1840; 13:197–204.
2. Murakami Y, Kanamoto T, Tuboi T, Maeda T, Inoue Y. Evaluation of extraocular muscle enlargement in dysthyroid ophthalmopathy. *Jpn J Ophthalmol* 2001; 45:622–627.
3. Nugent RA, Belkin RI, Neigel JM, Rootman J, Robertson WD, Spinelli J, Graeb DA. Graves orbitopathy: correlation of CT and clinical findings. *Radiology* 1990; 177:675–682.
4. Moncayo R, Baldissera I, Decristoforo C, Kendler D, Donnemiller E. Evaluation of immunological mechanisms mediating thyroid-associated ophthalmopathy by radionuclide imaging using the somatostatin analog^{111}In-octreotide. *Thyroid* 1997; 7:21–29.
5. Weetman AP. Graves' disease. *N Engl J Med* 2000; 343: 1236–1248.
6. Decristoforo C, Mather SJ, Cholewinski W, Donnemiller E, Riccabona G, Moncayo R.^{99m}Tc-EDDA/HYNIC-TOC: a new ^{99m}Tc-labelled radiopharmaceutical for imaging somatostatin receptor-positive tumours; first clinical results and intra-patient comparison with ^{111}In-labelled octreotide derivatives. *Eur J Nucl Med* 2000; 27:1318–1325.

7. Sweeney RA, Bale R, Moncayo R, Seydl K, Trieb T, Eisner W, Burtscher J, Donnemiller E, Stockhammer G, Lukas P. Multimodality cranial image fusion using external markers applied via a vacuum mouthpiece and a case report. *Strahlenther Onkol* 2003; 179:254–260.
8. Dua HS, Gomes JA, Jindal VK, Appa SN, Schwarting R, Eagle RC, Jr., Donoso LA, Laibson PR. Mucosa specific lymphocytes in the human conjunctiva, corneoscleral limbus and lacrimal gland. *Curr Eye Res* 1994; 13:87–93.
9. Knop E, Knop N. Lacrimal drainage-associated lymphoid tissue (LDALT): a part of the human mucosal immune system. *Invest Ophthalmol Vis Sci* 2001; 42:566–574.
10. Knop N, Knop E. Conjunctiva-associated lymphoid tissue in the human eye. *Invest Ophthalmol Vis Sci* 2000; 41:1270–1279.
11. Gruntzig J, Schicha H, Huth F. Eye and lymph drainage. *Z Lymphol* 1979; 3:35–45.
12. Adler E. Die Schmerzdruckpunkte an der Halswirbelsäule, Chap XVIII. *Allgemein-Erkrankungen durch Störfelder. Diagnose und Therapie, 3. edn.* Heidelberg: Verlag für Medizin Dr. Ewald Fischer; 1977; 305–308.