Thyroid Gland ^{18}F -FDG Uptake in Neurofibromatosis Type 1

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Keywords

Thyroid gland · Incidentaloma · Neurofibromatosis type 1 · Positron emission tomography/computed tomography

Abstract

Purpose: To investigate thyroid gland characteristics on ^{18}F -FDG positron emission tomography/computed tomography (PET/CT) imaging in patients with neurofibromatosis type 1 (NF1). **Subjects and Methods:** Thyroid gland characteristics of patients with a clinical diagnosis of NF1 who underwent ^{18}F -FDG PET/CT imaging for the first time to distinguish benign neurofibroma from malignant peripheral nerve sheath tumor (MPNST) at our institution ($n = 69$) were compared to PET/CT imaging of sarcoidosis ($n = 25$) and early stage lung cancer ($\text{T}_1\text{N}_0\text{M}_0$ tumors, $n = 15$) patients. **Results:** Two NF1 patients (3%) showed a diffuse ^{18}F -FDG uptake in the thyroid gland, 2 patients (3%) had an irregular uptake, and 7 patients (10%) had a focal uptake. Among the sarcoidosis patients, 1 showed a diffuse uptake (4%) and 1 had an irregular uptake (4%). In the early stage lung cancer group, 1 patient showed a diffuse uptake (7%) and 1 had a focal uptake (7%). NF1 patients had larger mean thyroid volume and mean SUV_{max}

compared to sarcoidosis patients but not compared to early stage lung cancer patients. Four NF1 patients were diagnosed with multinodular goiter, 2 patients were diagnosed with benign chronic lymphocytic thyroiditis, 1 patient had metastasis to the thyroid, and 1 patient had medullary thyroid cancer. **Conclusion:** Even though NF1 patients did not show an increased risk of thyroid incidentaloma on PET/CT compared to previous studies on non-thyroid cancer patients, the incidence shows that awareness of possible thyroid disease is important.

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Introduction

Neurofibromatosis type 1 (NF1) is a common neurocutaneous disorder that predisposes affected individuals to developing benign and malignant tumors [1]. NF1 has an autosomal dominant inheritance and is due to muta-

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Table 1. Overview of the current literature on NF1 with concurrent thyroid disease

Study	Subjects (<i>n</i> = 1)	Methods	Outcome
Gorgel et al. [11]	NF1 + GIST + pheochromocytoma	Thyroid US Fine needle aspiration biopsy	Multifocal papillary thyroid carcinoma Cervical lymph node metastases
Kim et al. [12]	NF1	Thyroid US FNA biopsy	Papillary thyroid carcinoma
Koksal et al. [13]	NF 1	Thyroid US Total thyroidectomy	Follicular papillary thyroid carcinoma Neurofibroma
Gkaliaghkhoui et al. [14]	NF1 + pheochromocytoma	Investigation for other pheochromocytoma-related syndromes	Hyperparathyroidism Medullary thyroid cancer (MEN 2A) Germline mutation for NF1 but not RET
Hashiba et al. [15]	NF1 + papillary thyroid cancer + pheochromocytoma	Head CT + MRI + angiography Histologic examination	Skull metastasis from papillary thyroid cancer
Yoshida et al. [16]	NF1 + lung metastasis of malignant schwannoma	Autopsy	Carcinoid tumor in duodenum Medullary thyroid carcinoma Diffuse adrenal medullary hyperplasia
Faraz et al. [17]	NF1	Laboratory investigation	Autoimmune hypothyroidism
Nabi et al. [18]	NF1	Thyroid US FNA Laboratory investigation	Hashimoto thyroiditis
Nanda [19]	NF1	–	Autoimmune thyroiditis
Bolko et al. [20]	NF1 + Noonan	Laboratory investigation Thyroid US Radioisotope scan Thyroid iodine uptake	Graves disease
NF1, neurofibromatosis type 1; US, ultrasonography; CT, computed tomography.			

tions in the NF1 gene located at chromosome 17q11.2 [2, 3]. The protein product encoded by the gene called neurofibromin is expressed in many tissues [4].

The characteristic lesions of NF1 are neurofibromas, i.e., benign peripheral nerve sheath tumours [5]. Patients with NF1 have an increased risk of developing soft tissue sarcomas, such as malignant peripheral nerve sheath tumours (MPNST), which have a poor prognosis due to a high occurrence of metastases [6]. Positron emission tomography (PET) imaging with ¹⁸F-FDG (fluorodeoxyglucose) may be helpful in distinguishing MPNST from benign plexiform or nodular neurofibromas [7].

NF1 is also associated with other malignant cancer types such as pheochromocytoma or breast cancer [8, 9]. In addition, significantly higher risks have been reported for other malignancies [10].

Despite the increased risk of endocrine tumors in NF1, the current literature on thyroid cancer in this population mainly consists of case reports as summarized in Table 1 [11–20]. Diazz et al. [21] found nodular goiter in 59% of a population of 17 NF1 patients who underwent ultrasonography (US) and thyroid cancer in 2 out of 10 NF1 patients (20%), indicating that thyroid disease may be underestimated in the context of NF1.

This study analyses thyroid gland abnormalities in a population of NF1 patients who underwent ¹⁸F-FDG PET/CT. We selected 2 other non-thyroid cancer patient populations without a known predisposition to or diagnosis of thyroid disease who underwent ¹⁸F-FDG PET/computed tomography (CT) as “control” groups: (1) patients with sarcoidosis and (2) patients with early stage lung cancer. We hypothesized that patients with NF1 show a higher incidence of thyroid disease.

Table 2. Demographics, visual category numbers, mean volume, and mean SUV_{mean} and SUV_{max} of thyroid glands on PET/CT for each patient group

Demographics	NF1 (n = 69)	Sarcoidosis (n = 25)	T1 lung cancer (n = 15)
Males	34 (49)	15 (60)	9 (60)
Age (range), years	37±17 (7–80)	45±11 (22–64)	58±4 (48–63)
<i>Thyroid gland</i>			
Not visible	58 (84)	23 (92)	13 (87)
Diffuse	2 (3)	1 (4)	1 (7)
Diffuse	2 (3)	1 (4)	–
Focal	7 (10)		1 (7)
Volume, cm ³	14.7±5.3 ^a	12.0±5.6 ^a	14.9±5.7
Goiter	8 (12)	2 (8)	2 (13)
SUV _{mean}	1.2±0.5	1.1±0.4	1.3±0.4
SUV _{max} (range)	2.7±3.5 ^a (0.8–28.6)	1.7±0.8 ^a (0.9–4.8)	2.1±0.6 (1.2–3.3)

Values are presented as means ± SD or numbers (%) unless otherwise stated. PET/CT, positron emission tomography/computed tomography; SUV_{mean}, mean standardized uptake value; SUV_{max}, maximum standardized uptake value. ^a Statistically significant difference.

Materials and Methods

Subjects

Patients with a clinical diagnosis of NF1 were selected from the Maastricht Neurofibromatosis Centre, which serves as a tertiary referral center for neurofibromatosis patients in The Netherlands. Scans between December 2006 and September 2016 at the Department of Radiology and Nuclear Medicine in the Maastricht University Medical Centre were analyzed (*n* = 71). All ages were included. Only the first PET/CT scan was used to analyze thyroid gland uptake. Patients were excluded from this study if the thyroid gland could not be analyzed adequately (*n* = 2).

Control groups included patients with sarcoidosis and patients with early stage lung carcinoma (T₁N₀M₀) from previous research databases in our department. Twenty-five and 15 control patients, respectively, were selected to form the best possible age-matched group.

Imaging Protocol

Patients fasted 6 h before the examination. The blood glucose in all of the patients was below 10 mmol/L. ¹⁸F-FDG (GE Health Care Radiopharmacy; Eindhoven, The Netherlands) was injected intravenously. The injected total activity of FDG depended on the weight of the patient (i.e., weight × 2; MBq). After a resting period of 60 min, PET and CT whole body images were obtained on Gemini TF64 slice PET/CT (Philips, Best, The Netherlands). A low-dose CT scan (tube voltage, 120 kVp; effective tube current, 30 mAs; slice thickness, 4 mm) was performed without intravenous contrast and used for attenuation correction of the PET images and for thyroid volume measurements.

Thyroid Gland Analysis

Visual interpretation of the ¹⁸F-FDG uptake of the thyroid gland was categorized as follows: (1) no increased uptake or thy-

roid gland not visible, (2) diffuse increased uptake, (3) irregular increased uptake, and (4) focal increased uptake. The PET/CT scans of NF1 patients and controls with an increased thyroid uptake were analyzed for other remarkable regions in order to identify a possible pattern.

PMOD software (version 3.0, 2008; PMOD Technologies) was used for quantitative analysis of the volume (mm³) and ¹⁸F-FDG uptake in the thyroid, measured as a mean and maximum standardized uptake value (SUV_{mean} and SUV_{max}).

Goiter on PET/CT imaging was defined according to radiological references as a calculated total thyroid volume of more than 18 cm³ for female and more than 25 cm³ for male adult patients [22]. Age-specific reference values were used for patients under 16 years of age, since the thyroid gland volume does not increase after the age of 16 years [23].

Clinical Records

In case of an abnormal thyroid gland uptake, the electronic patient files were reviewed for additional clinical information on possible thyroid disease. Reports on thyroid US were collected, as were fine-needle aspiration cytology, histology after (hemi) thyroidectomy, and FT4 and/or TSH levels that were measured closest to the time of the first PET/CT scan when available.

Statistical Analysis

To test the significance of differences between continuous data, an independent samples *t* test was used. *p* < 0.05 (*α* = 0.05) was considered statistically significant. The Fisher exact test was used to test the significance of categorical data. The correlation between thyroid volume and age was measured with the Pearson correlation. Statistical evaluations were carried out with SPSS 21.0 for Windows (SPSS Inc.).

Table 3. Outcome of thyroid investigations and other remarkable PET/CT regions

Case No.	Thyroid uptake	Thyroid US	FNA	Histology	Increased uptake on PET/CT
1	Focal	MNG max 1.2 cm MNG max 1.3 cm No progression	Bethesda I	–	Pharyngeal tonsils and bone marrow
2	Diffuse	–	–	–	Nasopharynx, tonsils, and bone marrow
3	Focal	MNG	Follicular oncocyctic lesion / papillary thyroid cancer	Benign CLT	Focal lesion in the right lung (SUV _{max} = 10.0)
4	Focal	Follow-up elsewhere	–	–	Parotid glands and bone marrow
5	Focal	1 large node (R), 2 small nodes (L)	Possible medullary thyroid carcinoma	Undifferentiated thyroid carcinoma (primary or me-tastasis to the thyroid)	Focal lesion in the right lung apex (primary focus or double tumor)
6	Focal	Node (1 cm) No progression	Follicular (possibly oncocyctic) lesion	Normal thyroid hormone levels and Tn scan	Left (SUV _{max} = 1.9) and right (SUV _{max} = 2.6) adrenal glands
7	Irregular	MNG MNG maximum 9 mm (R) MNG (L)	Bethesda I MNG/follicular lesion Bethesda II	2. Multinodular hyperplasia, no malignancy 3. Medullary thyroid carcinoma Pheo-chromocytoma screening: negative	Cervical lymph nodes and bone marrow
8	Diffuse	–	–	–	Pharyngeal tonsil (compression by neurofibroma) and bone marrow
9	Focal	Node (2 cm) No progression	Bethesda II	–	Pharyngeal tonsils, cervical lymph nodes, and bone marrow
10	Irregular	–	–	–	Pharyngeal tonsils and bone marrow
11	Focal	– MNG Stable	Bethesda I Bethesda II Bethesda III	Benign CLT	Pharyngeal tonsils

Case numbers correspond to Clinical Records. MNG, multinodular goiter; US, ultrasonography; PET/CT, positron emission tomography/computed tomography; CLT, chronic lymphocytic thyroiditis.

Results

Demographics

A number of 69 patients were analyzed. For 33 (48%) NF1 patients, a genetic mutation was found at our institution and recorded in their clinical genetics file. The sarcoidosis patient group consisted of 25 patients who underwent a PET/CT scan between March 2009 and September 2011. The group of patients with early stage lung cancer consisted of 15 patients who underwent a PET/CT scan between February 2007 and August 2008. The number of male patients and the mean age are summarized in Table 2 for each patient group.

Thyroid Gland

The results of PET/CT imaging are summarized in Table 2. No significant difference was found between patient

groups in terms of the number of patients with diffuse, irregular, or focal uptake, respectively.

Patients with NF1 showed significantly higher thyroid gland volumes than patients with sarcoidosis ($p = 0.02$). There was no significant difference in thyroid volume between patients with NF1 and patients with early stage lung cancer or between patients with sarcoidosis and patients with early stage lung cancer.

No significant differences between groups were found in the number of patients meeting the criteria for goiter. The correlation between thyroid volume and age was low for each patient group ($r < 0.25$) and scatter plot graphs did not show any trends or notable outliers.

NF1 patients had a significantly higher mean SUV_{max} compared to sarcoidosis patients ($p = 0.03$). This difference remained significant when only patients with normal visual interpretations of the thyroid gland were in-

cluded in the analysis ($p = 0.04$). No significant difference was found for SUV_{mean} between patients with NF1 or sarcoidosis and patients with early stage lung cancer, respectively.

Clinical Records

Table 3 provides an overview of the additional endocrine investigations in the eleven NF1 cases with increased thyroid gland uptake on ^{18}F -FDG PET/CT. Seven patients underwent thyroid US following the PET/CT scan. One patient was referred elsewhere for follow-up. In the remaining 3 patients, thyroid uptake did not trigger a recommendation for further follow-up. Thyroid US was suggestive of multinodular goiter in 4 patients and showed 1 focal lesion in 2 patients and one large focus and 2 smaller foci in 1 patient.

FNA was performed successfully in 6 out of 7 patients who underwent thyroid US after PET/CT imaging, and 1 patient's biopsy was successful after follow-up US (case 11). Cytology was benign (Bethesda II) in 2 patients, 1 of whom was referred elsewhere for follow-up (case 9), and another patient eventually showed thyroid cell atypia on subsequent biopsies (case 11). (Hemi)thyroidectomy was performed in 4 patients, including case 7 with inconclusive cytology and a progressive goiter. No malignancy was found although a completed thyroidectomy during follow-up revealed medullary thyroid carcinoma. Histology showed benign chronic lymphocytic thyroiditis (CLT) in 2 patients. The fourth patient who underwent total thyroidectomy was diagnosed with undifferentiated thyroid carcinoma of doubtful origin, with either metastasis to the thyroid from primary lung cancer or a double tumor.

Eight patients showed a notably increased uptake in the nasopharynx and/or pharyngeal tonsils, and/or cervical lymph nodes and/or bone marrow, including 3 patients who did not undergo further endocrine investigation and 1 patient who was lost to follow-up. One patient was eventually diagnosed with CLT.

The 3 NF1 patients with an abnormal uptake on PET/CT imaging without ultrasound follow-up did not present with clinical symptoms of thyroid disease at our institution.

Both the sarcoidosis group and the early stage lung cancer group each included 2 patients with an increased thyroid gland uptake on PET/CT. During the follow-up at our institution, no thyroid-related problems were mentioned in the electronic patient file.

Discussion

In this study of 69 NF1 patients, the percentages of patients who showed an increased uptake in the thyroid gland on PET/CT were comparable to the control groups. The total number of thyroid incidentalomas on PET/CT in NF1 patients was 11 (15%), among which 7 patients (10%) had focal lesions. Demir et al. [24], Bae et al. [25], and Adas et al. [26] showed lower percentages in non-thyroid cancer patients with a range between 1 and 3%. However, the most recent study with the largest population by Barrio et al. [27] reported a comparable percentage of focal incidentaloma compared to this study (13.6%). Karantanis et al. [28] reported a diffuse increased uptake in 2.9% of 4,732 non-thyroid cancer patients, which is comparable to our results.

No significant difference was found in the number of patients with goiter between groups. Previous studies have shown that CT imaging is also qualified to measuring thyroid gland volume, with median volumes between 8.1 and 26.7 cm³, but validated reference values have not been provided [29–32]. Tunbridge et al. [33] investigated the epidemiology of thyroid disorders in a general community and found a comparable prevalence of 15.5% palpable and/or visible goiters, with a male:female ratio of 1:4.

The NF1 patients showed significant increased ^{18}F -FDG uptake in the thyroid gland compared to sarcoidosis patients but not compared to early stage lung cancer patients. Even though sarcoidosis patients have a risk of developing autoimmune thyroiditis [34], no such cases were found in our control group. An increased uptake in the head and neck region and bone marrow was noticed in both NF1 patients (73%) and controls, with an increased uptake in the thyroid gland. It is possible that this pattern is due to a (concurrent) infectious process [35–37]. A causative association or possible underlying mechanism of thyroid disease in NF1 is difficult to adjudicate and beyond the scope of our study.

Our retrospective analysis of clinical records showed a comparable incidence of thyroid malignancy or other thyroid disease in NF1 patients compared to previous studies in non-thyroid cancer patients [24–27]. Only one study by Ferner et al. [7] described a case of FDG-PET-positive thyroid cancer in a population of NF1 patients ($n = 105$; 1%) discovered through PET/CT.

Limitations

Population-based limitations regard the small and relatively younger population of NF1 patients and the fact

that only patient control groups could be used. The retrospective design of this study with inherent incomplete thyroid data, nonexclusion of possible preexisting primary (autoimmune) thyroid disease, and the numbers lost to follow-up make our conclusions not firm but only indicative.

Conclusions

In the present form our study did not show an increased risk of thyroid pathology in NF1 patients. Active clinical surveillance and systematic prospective research on thyroid pathology in a large population of NF1 patients is needed to determine the exact implications for clinical management.

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Statement of Ethics

Our retrospective study does not contain any studies involving animals performed by any of the authors. This article does not contain any identifiable personal data and therefore does not require informed consent of the participants. This was reported to and confirmed by the Medical Ethics Committee and the Board of Directors of our institution.

Disclosure Statement

The authors declare that they have no conflict of interests.

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