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Review Article

The pituitary in nuclear medicine imaging

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ABSTRACT

The pituitary is an endocrine gland with ability to uptake diverse radiopharmaceuticals and, therefore, susceptible to be investigated by nuclear medicine diagnostic procedures. Although this topic has been scarcely scrutinized, we have data indicating that somatostatin receptor scintigraphy with ^{111}In-DTPA-D-Phe-octreotide or ^{99m}Tc-EDDA/HYNIC-TOC may be of clinical utility in the diagnosis of some pituitary adenomas (PA). Only a few studies have evaluated the diagnostic performance of ^{99m}Tc-MIBI and ^{99m}Tc (V)-DMSA scintigraphy in pituitary disease. Scintigraphy using ^{123}I-methoxybenzamide (^{123}I-IBZM) might be useful in macroprolactinomas expressing dopamine D2 receptors. Pituitary gland does not usually accumulate 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) and, therefore, it is not visualized on positron emission tomography (PET) imaging studies with this radiotracer. The pituitary uptake on^{18}F-FDG PET/CT scans performed in the follow-up of oncological patients are uncommon. However, 60% of these incidental findings are due to PA, mainly non-functioning pituitary macroadenomas, and a small percentage to metastases or other pituitary lesions. Interestingly, ^{18}F-FDG PET/CT may identify hypophysitis induced by different immunotherapeutic agents used in cancer patients. Positive ^{18}F-FDG uptake has been reported in a high percentage of patients with PA, mainly macroadenomas and it seems that there is correlation between tumor size and SUVmax. ^{68}Ga-DOTA-TATE PET/CT may identify functioning and non-functioning PA, although this technique is more useful in the detection of remaining normal pituitary tissue after transsphenoidal adenomectomy, and in the confirmation of recurrence of functioning PA, such as thyrotroph-secreting PA. Furthermore, ^{68}Ga-DOTA-TATE uptake has potential therapeutic implications on molecular-targeted therapy. Lastly, other radiopharmaceuticals that have shown to be taken up in some patients with pituitary disease include ^{18}F-DOPA (prolactinoma), ^{11}C-methionine (residual or recurrent PA), O-(2-^{18}F-fluoroethyl)-l-tyrosine (metastasis), ^{18}F-choline (silent adenoma, ectopic corticotropinoma), and ^{13}N-ammonia (hypopituitarism).

1. Introduction

Nuclear medicine imaging studies have the ability to give anatomic and physiologic information of healthy and neoplastic tissues [1]. They use radioactive material, named radiopharmaceuticals, to diagnose, locate and/or treat different types of diseases, such as gastrointestinal, cardiac, neurological, endocrine disorders, as well as many types of cancers. After its administration, radiotracers accumulate in different tissues of the body and release radioactive energy which is detected in a special camera and through a computer create images of the different tissues, organs or lesions under study.

Pituitary, as any other body organ, may be susceptible to be studied by nuclear medicine techniques. It is necessary to know the physiological uptake of certain radiopharmaceuticals by the pituitary gland in order to make an adequate interpretation of the incidental findings in the functional imaging studies [2–4]. Moreover, there are several pituitary inflammatory pathologies that may be accompanied by pathological uptake [4]. Benign pituitary tumors may also present positive uptake in imaging studies, such as scintigraphy and positron emission tomography (PET) with certain radioisotopes [4]. Finally, aggressive pituitary tumors and pituitary carcinomas can show pathological uptakes in nuclear medicine studies that can be used to establish an adequate therapeutic strategy [5,6].

So far there is not much information about the diagnostic value of different techniques in radionuclide imaging, such as scintigraphy and PET with different radiotracers in pituitary lesions. Therefore, the aim

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of the present work has been to review the most relevant aspects regarding the nuclear imaging not only in normal pituitary gland but also in incidental pituitary lesions, as well as in previously known pituitary lesions, such as hypophysitis and pituitary tumors.

2. Pituitary uptake on ^{18}F-FDG PET

PET/computed tomography (PET/CT) is a diagnostic technique increasingly used in the diagnosis, staging, therapeutic assessment and monitoring cancer progression.

PET provides detailed images of the molecular and cellular functioning of different normal and pathological tissues. It is based on the ability of creating a three-dimensional metabolic image of the distribution of a radiotracer in the organism after its intravenous administration. The combination of PET (functional information) with CT (anatomical information) is able to obtain anatomical and functional details of the different organs and tissues in a single diagnostic image session.

Nowadays, 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) is the most frequently used PET radiotracer. ^{18}F-FDG, is a glucose analog, that is actively transported into the cells by glucose transporters. Tumor cells have a high capacity to consume glucose; therefore, they accumulate ^{18}F-FDG after its administration. ^{18}F-FDGPET/CT fusion imaging has become one of the main imaging techniques for tumor localization in cancer patients. The images are analyzed qualitatively by comparing those obtained from the lesions with those of healthy tissues, or semiquantitatively by using standardized uptake values (SUVs) [7].

Pituitary gland does not usually accumulate ^{18}F-FDG and therefore, it is not visualized on ^{18}F-FDG PET imaging [8]. This may be due to the small size of the pituitary gland and to the low metabolic rate. However, several benign non-neoplastic and neoplastic pituitary lesions can avidly accumulate ^{18}F-FDG (Fig. 1). Most of these pituitary lesions are incidentally identified in tumor extension studies in cancer patients [3,4,8,9]. Other studies have more specifically evaluated the clinical significance of ^{18}F-FDG uptake in patients with pituitary adenomas [10–12]. More recently, it has been reported a positive correlation between pituitary ^{18}F-FDG uptake and serum TSH in thyroid cancer patients [13]. Lastly, diffuse pituitary ^{18}F-FDG uptake with normal CT or MRI appearance of the pituitary has also been described, suggesting a physiologic uptake in some cases [4,13].

2.1. Incidentally pituitary uptake on ^{18}F-FDG PET/CT

The clinical significance of incidentally pituitary uptake on ^{18}F-FDG PET/CT has been evaluated in the last years [2–4] (Table 1).

In 2010 by Jeong et al., performed a multicenter retrospective study in 40,967 patients who underwent wholebody ^{18}F-FDG PET/CT [2]. The prevalence of focally increased pituitary FDG uptake on PET/CT was 0.073%. The mean SUVmax was 9, being higher in patients with macroadenomas (SUVmax 11.5) than in those with microadenomas (SUVmax 4.8). In this study there was no case of pituitary metastasis.

Hyun et al., [3] analyzed 13,145 consecutive subjects who underwent ^{18}F-FDG PET/CT. They found 107 (0.8%) subjects showing incidental pituitary uptake. These incidental foci of ^{18}F-FDG uptake were correlated with brain MRI findings that were available in 55 (51.4%) subjects. In about half of these patients (29 out of 55, 52.7%), MRI confirmed the diagnosis of pituitary macroadenoma in 21, microadenoma in 5, and malignancy in 3 subjects (lung, breast, and non-Hodgkin lymphoma). A SUVmax of 4.1 showed a diagnostic sensitivity, specificity, and accuracy of 96.6%, 88.1%, and 91.5%, respectively, for detecting pathologic uptake.

In a more recent retrospective study, Ju et al., 2017 [4] reviewed 24,007 ^{18}F-FDG PET/CT whole body scans in last 5 years. After excluding all patients with known history of pituitary disorders, they identified 19 cases (0.08%) with SUVmax > 4.1. The most common pathological diagnosis was primary pituitary tumors (n = 9; 47.4%; 6 non-functioning pituitary adenomas, one lactotroph adenoma, one corticotropoh adenoma, and one somatotroph adenoma; 5 macro- and 4 microadenomas), followed by metastatic malignancy (n = 3; 15.8%; one lung cancer, one melanoma, and one endometrial cancer), Langerhans cell histiocytosis (n = 3; 15.8%), and inflammatory lymphocytic hypophysitis (n = 1; 5.3%). Three cases with negative pituitary MRI were considered as physiologic pituitary uptake.

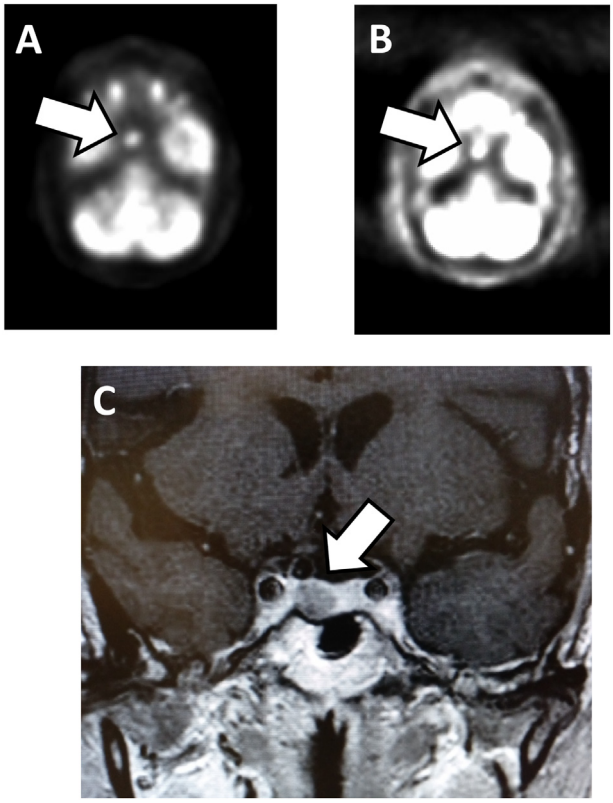

Fig. 1. Incidental focal ^{18}F-FDG uptake in a 56-yr-old woman who underwent PET/CT examination for staging of fusocellular-epithelioid sarcoma of costal wall. Transaxial PET (A) and transaxial PET/CT (B) images showing focus of increased ^{18}F-FDG uptake in sellar region, with SUVmax of 12.9. (C) T1-weighted coronal MRI after administration of gadolinium showing focal area of low signal intensity on right side of pituitary gland. Correlative brain MRI confirmed existence of 7x8x8 mm pituitary microadenoma corresponding to incidental focal ^{18}F-FDG uptake.

In summary, the incidentally pituitary uptake on ^{18}F-FDG PET/CT is an unusual event (0.07–0.8%). It is usually associated with benign pituitary tumors, mainly non-functioning pituitary macroadenomas, although functioning pituitary tumors can also be detected. Metastases, primarily from breast and lung cancer, as well as pituitary affectation of Langerhans cell histiocytosis (LCH) should be considered in the differential diagnosis. Inflammatory pituitary diseases such as lymphocytic hypophysitis can also be detected incidentally on^{18}F-FDG PET. Lastly, we should consider the possibility of incidental physiological pituitary uptake.

2.2. Benign non-neoplastic pituitary lesions

2.2.1. Pituitary cysts

Pituitary cyst lesions are not uncommon. The prevalence of cystic lesions in pituitary incidentalomas has been reported to be about 50% [14]. The most frequent etiology are Rathke's cleft cysts, whose prevalence is estimated to be between 13 and 50% [14,15]. These are benign lesions that usually are not treated by surgical excision. In fact, cystic lesions account for a very small percentage (3–14%) of the pituitary lesions surgically treated [16]. Most cystic lesions do not show

Table 1
Main series that have evaluated the incidental pituitary uptake on ^{18}F-FDG PET.

Author, yr [Ref.]	Study patients	% positive ^{18}F-FDG uptake	Pituitary adenoma MRI	Pituitary macroadenoma	Pituitary microadenoma	Pituitary metastasis	Langerhans cell histiocytosis
	n	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		SUVmax		SUVmax	SUVmax	SUVmax	(SUVmax)
Jeong et al., 2010 [2]	40,967	30 (0.073) 8.9 ± 6.6	18 out of 19 (94.7)	10 (55.5) 11.5 ± 8.4	8 (44.4) 4.8 ± 1.3	0	0
Hyun et al., 2011 [3]	13,145	107 (0.8) 5.3 (range, 2.6-25.6)	29 out of 55 (52.7)	21 (72.4) 10.9 ± 7.0	8 (27.6) 4.7 ± 0.9	3 (5.4) NA	0
Ju et al., 2017 [4]	24,007	32 (0.13)[a] > 4.1	9 out of 19 (47.4)[b]	6 (66.7) NA	3 (33.3) NA	3 (15.7) 16.0 ± 10.6	3 (15.7) 15.0 ± 10.2
Total	78,119	169 (0.21)	56 out of 93 (60.2)	37 out of 56 (66.1)	19 out of 56 (33.9)	6 out of 93 (6.4)	3 out 93 (3.2)

Abbreviations: SUV, standardized uptake value; SUVmax, maximum standardized uptake value; NA, not available.
[a] After excluding all those patients with known history of pituitary disorders.
[b] SUVmax of pituitary adenoma was 13.6 ± 9.8.

^{18}F-FDG uptake. In one series, only 1 out of 8 (12.5%) cyst lesions showed ^{18}F-FDG uptake [12]. In this study mean SUVmax of cyst lesions was around 2.

2.2.2. Hypophysitis

Biopsy-proved primary lymphocytic hypophysitis has been recently detected in a patient with ^{18}F-FDG with SUVmax of 4.7 [4]. ^{18}F-FDG PET not only is able to uncover primary lymphocytic hypophysitis but also secondary hypophysitis, such as immunotherapy-induced hypophysitis in cancer patients [9,17–20]. In 2013, ^{18}F-FDG PET/CT revealed for the first time an ipilimumab-induced hypophysitis in a 77-year-old man with advanced melanoma. After 4 weeks of prednisolone therapy a normalization of the uptake of ^{18}F-FDG in the pituitary gland was reported [9]. Moreover, ^{18}F-FDG may also identify hypophysitis induced by anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA4) such as ipilimumab, but also by anti-programmed cell death 1 (anti-PD1) antibodies, such as nivolumab [19,20]. The characteristic image is a homogenous and intense enhancement and intense pituitary uptake of ^{18}FDG (Fig. 2).

2.2.3. Pituitary uptake and primary hypothyroidism

Pituitary ^{18}F-FDG uptake positively correlates with thyroid stimulating hormone (TSH) levels in subjects with diffuse thyroid ^{18}F-FDG uptake [21]. Other authors have observed diffuse pituitary uptake on ^{18}F-FDG PET scan in patients with differentiated thyroid cancer (DTC) after withdrawal of levothyroxine (L-T4), which also correlates with serum TSH [13]. This uptake is associated with normal CT or MRI appearance of the pituitary indicating a physiologic pituitary uptake. It can be hypothesized that a hyperfunction of thyrotroph cells induced by an increase in the hypothalamic secretion of thyrotropin-releasing hormone (TRH) would result in a high glucose metabolism that would increase the pituitary^{18}F-FDG uptake on PET scan. Therefore, ^{18}F-FDG uptake in the pituitary gland should make us rule out the presence of primary hypothyroidism for not to misinterpret a pathological uptake due to a pituitary adenoma or pituitary metastasis.

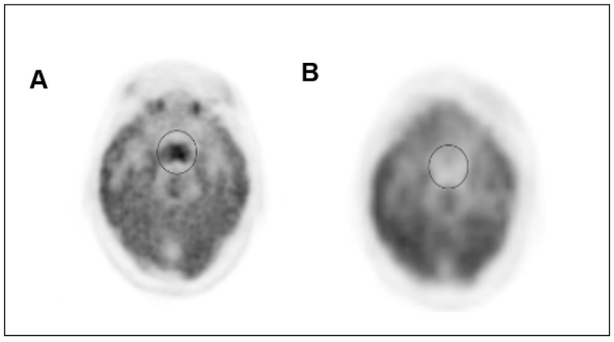

Fig. 2. ^{18}F-FDG image in a 65-yr-old woman diagnosed with hypophysitis with local compressive symptoms and deficiency of thyrotropin and corticotropin. Increased ^{18}F-FDG PET pathological uptake in sellar region compatible with the diagnosis of hypophysitis (A, circle). ^{18}F-FDG image PET showing an absence of uptake after therapy with glucocorticoids (B, circle).

2.3. Neoplastic pituitary lesions

2.3.1. Pituitary adenomas

The usefulness of ^{18}F-FDGPET scan for patients with pituitary tumors was evaluated in 2013 in a cohort of 24 patients with PA (14 non-functioning and 10 functioning tumors) [12]. Nineteen out of 24 (79.2%) showed increased pituitary uptake of ^{18}F-FDG on PET scan. Positive ^{18}F-FDG uptake was shown in all pituitary macroadenomas (n = 14) while in only 50% of the microadenomas (n = 10). The percentage of patients with positive uptake of ^{18}F-FDG was similar in patients with non-functioning (11 out of 14, 78.6%) than in those with functioning (8 out of 10, 80%) pituitary adenomas. A SUVmax of > 2.4 had 94.7% sensitivity and 100% specificity for positive ^{18}F-FDG uptake. Tumor size was positively correlated with SUVmax, showing macroadenomas a mean SUVmax significantly higher than that of microadenomas. A maximal diameter of 8.5 mm of pituitary tumor had 78.9% sensitivity and 72.7% specificity for positive ^{18}F-FDG uptake.

The prevalence of positive ^{18}F-FDG uptake in functional pituitary microadenomas has been reported in 60% (12 out 20 microadenomas; 10 Cushing's disease (CD) and 2 acromegaly) [10]. However, other more recent studies have described increased ^{18}F-FDG uptake in all patients with hormone-producing pituitary microadenomas [22]. It could be hypothesized that a functioning PA has increased glucose metabolism which accounts for increased ^{18}F-FDG uptake on PET scan.

^{18}F-FDG uptake rate in pituitary adenoma is 30% higher than that in the whole brain [11]. Moreover, ^{18}F-FDG uptake is higher in non-functional pituitary adenomas compared with functioning adenomas, which displayed similar levels of glucose metabolism. Recurrent macroadenomas displayed metabolism similar to adenomas not surgically treated, whereas glucose uptake was lower in the irradiated tumors *versus* non-irradiated adenomas. Lastly, medical therapy with DA or somatostatin analogs (SSA) decrease glucose utilization by the tumor [11].

It has been reported that corticotropin-releasing hormone (CRH) stimulation leads to delayed, selective glucose uptake in corticotropinomas [23]. In this setting, it has been demonstrated the utility of

CRH stimulation in improving ^{18}F-FDG-PET detection of adenomas in CD, suggesting that some MRI invisible adenomas may be detectable by ovine CRH-stimulated FDG-PET imaging [24].

2.3.2. Pituitary metastasis

The pituitary gland is a very uncommon place for pituitary metastases. In fact, they only represent 0.4% of all intracranial metastases and about 1% of pituitary lesions surgically treated [25]. The most frequent responsible primary tumors are lung (36.8%), followed by breast (22.9%) and kidney (7.0%) cancer. Other malignancies are colon cancer, melanoma, non-Hodgkin lymphoma, and plasmocytoma [3,25]. More recently, metastasis to the sellar/suprasellar region from endometrial carcinoma revealed by ^{18}F-FDG PET and confirmed by subsequent CT and MRI of the brain in a 77-year-old woman, has been reported [26].

Most patients have hypopituitarism (83%), diabetes insipidus (75%) and defects of the visual fields (67%) at diagnosis [27]. Metastasis to the pituitary can be detected by ^{18}F-FDG PET. The prevalence of pituitary metastasis in pituitary lesions with ^{18}F-FDG uptake is very low (~6%), *i.e.*, approximately one-tenth of the prevalence of pituitary adenomas (Table 1).

2.3.3. Pituitary involvement in Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) is a rare multisystemic disease secondary to an abnormal proliferation of Langerhans cells or histiocytes with infiltration in one or several organs. In central nervous system, LCH can affect the pituitary stalk and hypothalamus which can develop panhypopituitarism and central diabetes insipidus [28]. In a recent study, LCH has been the responsible etiology for positive pituitary ^{18}F-FDG uptake in about 16% of patients, with a SUVmax of 15.0 ± 10.2 [4]. However, a detailed analysis of > 78,000 patients from three studies showed a much lower prevalence (~3%) (Table 1).

3. Pituitary uptake on somatostatin receptor scintigraphy

Receptors for somatostatin (SSTRs) are expressed in both normal pituitary gland and pituitary tumors. Therefore, the somatostatin receptor scintigraphy (SRS) should be able to identify pituitary adenomas (PA) on the basis of the presence of these SSTRs (Fig. 3).

^{111}In-DTPA-D-Phe-octreotide (^{111}In-pentetreotide) scintigraphy (Octreoscan®) has shown to be a useful tool to confirm the presence of SSTRs in selected patients with PA, although the percentage of uptake is different according to the type of tumor [29,30]. In fact, tumor uptake of ^{111}In-pentetreotide has been reported in 12 out of 13 (92.3%), 2 out of 4 (50%) and 2/12 (16.7%) of growth hormone (GH)-, thyrotropin (TSH)-secreting and non-functioning PA (NFPA), respectively [29].

A single photon emission computed tomography (SPECT) imaging with technetium-99 m-labeled hydrazinonicotinyl-tyr^3-octreotide (^{99m}Tc-EDDA-HYNIC-TOC; Tektrotyd), a semiquantitative analysis of increased focal tracer uptake in the sellar area, has shown as a highly sensitive and reliable method for detecting PA [31].

This pituitary uptake may have therapeutic implications since the demonstration of the presence of *in vivo* SSTR is a necessary requirement for the use of therapy with somatostatin analogs (SSA) or even peptide receptor radionuclide therapy (PRRT). Small series of patients have not been able to demonstrate a clear predictive value of PA uptake in SRS on the therapeutic effect of SSA [32,33]. More recently, a prospective case-control study performed 39 patients with NFPAs not cured by surgery showed a lower percentage (19% *vs* 53%) of patients with increase in tumor size of the remnant in those patients with positive Octreoscan® and chronic therapy with long acting octreotide (octreotide LAR) compared to those patients with negative Octreoscan and, therefore, not treated with SSAs [34].

The utility of SRS has been shown to be effective in the imaging diagnosis not only for conventional but also for aggressive PA (Fig. 4). The potential role of Octreoscan® in the localization and extension

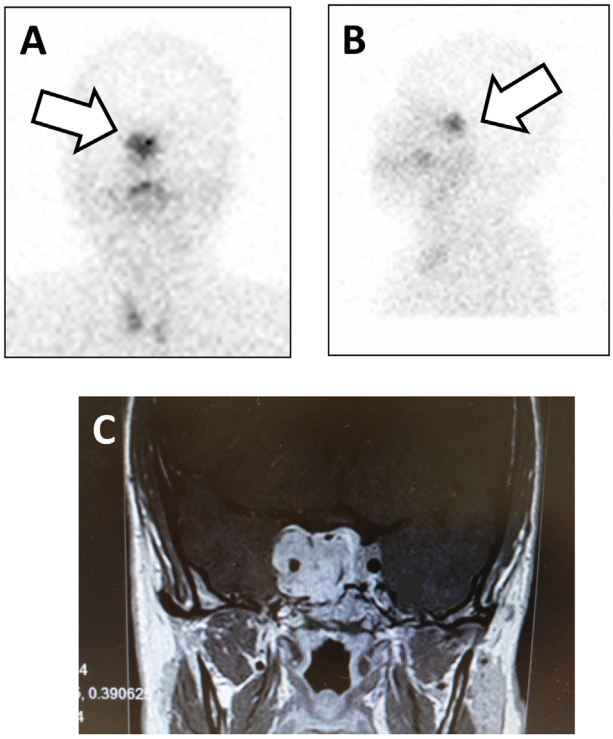

Fig. 3. Coronal (A) and sagittal (B) planar images of Tektrotyd scintigraphy showing a high uptake at the base of the skull in relation to pituitary mass. (C) T1-weighted coronal MRI after administration of gadolinium showing the presence of a non-functioning pituitary macroadenoma.

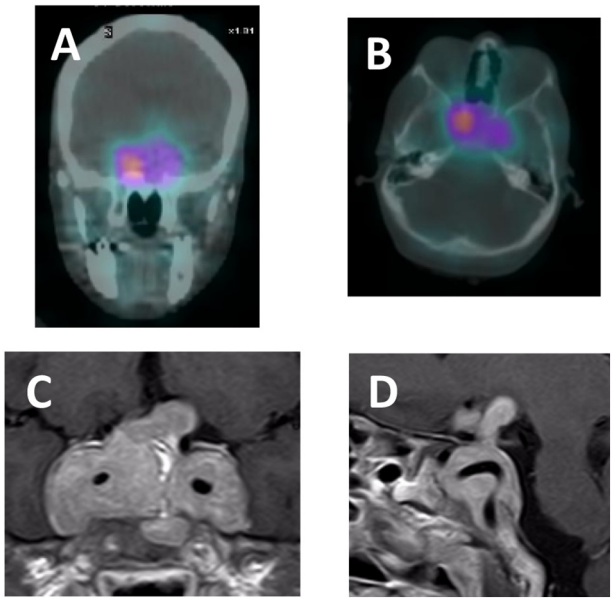

Fig. 4. Coronal (A) and axial (B) ^{111}In-pentetreotide SPECT CT images showing a hypercaptant lesion located in the suprasellar region. T1-weighted coronal (C) and sagittal (D) MRI images showing the presence of an aggressive lactotroph adenoma.

study in aggressive dopamine agonist (DA) resistant prolactinomas has been recently reported [5,6].

4. Pituitary uptake on ^{68}Ga-DOTA-TATE PET

The analysis of the biodistribution of ^{68}Ga-1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid-D-Phe,Tyr3-octreotate

(DOTA-TATE) uptake in normal tissues has shown that pituitary gland is the fourth organ with the highest uptake (SUV_{max}, 9 to 10), only after the spleen, kidneys and adrenal glands [35,36].^{68}Ga-DOTA peptide PET imaging has several advantages over conventional SRS, such as better image resolution, less time-consuming procedure, and semiquantification of the lesions.^{68}Ga-DOTA-TATE uptake has potential therapeutic implications on molecular-targeted therapy using SSA and PRRT targeting the SSTRs.

Both non-functioning and functioning pituitary micro- and macroadenomas have been detected with ^{68}Ga-DOTA-TATE PET/CT [22,37–39]. However, compared to ^{18}F-FDG, ^{68}Ga-DOTA-TATE usually seems more useful in the detection of remaining normal pituitary tissue after transsphenoidal adenomectomy, whereas ^{18}F-FDG shows a greater ability to detect recurrent or residual pituitary adenomas [22,40]. In some occasions, ^{68}Ga-DOTA-TATE PET has been useful in the confirmation of recurrence of functioning pituitary tumor, such as TSH pituitary adenoma [41].

Some authors have used ^{68}Ga-DOTATATE PET and MRI for cyberknife radiosurgery planning in GH-secreting pituitary adenomas [38].

^{68}Ga-DOTA-TATE PET seems to have potential clinical applications in the diagnosis and monitoring in pituitary carcinoma. Interestingly,^{68}Ga-DOTA-TATE showed advantage in the detection of brain metastases from a pituitary carcinoma compared with ^{18}F-FDG PET/CT and enhanced MRI [42]. Moreover, ^{68}Ga-DOTA-TATE PET/CT has been used not only for diagnostic assessment but also for monitoring of ^{177}Lu-DOTATATE therapy in pituitary carcinoma [43].

5. Pituitary uptake on ^{99m}Tc-MIBI scintigraphy

Technetium-99 m-labeled hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-MIBI) is a radiopharmaceutical agent used in nuclear medicine to evaluate cardiac perfusion and localize pathological parathyroid glands in primary hyperparathyroidism. Uptake and retention of this radiopharmaceutical are related to perfusion and the number of mitochondria and, therefore, is associated to a high metabolic activity. Few studies have evaluated ^{99m}Tc-MIBI uptake by PA. A strong affinity for PA but not for normal pituitary gland has been reported [44–46]. Accordingly, the incidental pituitary uptake of ^{99m}Tc-MIBI in studies of parathyroid SPECT might be a hint for the presence of a silent PA [46]. Lastly, some authors have reported that ^{99m} Tc-MIBI SPECT may be a highly sensitive and specific method in differentiating hormone secreting pituitary tumors [31].

6. Pituitary uptake on ^{18}F-DOPA PET

Pituitary uptake on ^{18}F-DOPA PET has been positive in some pituitary adenomas, mainly prolactinomas [47,48]. Medical treatment with DA is the treatment of choice for prolactinoma. This therapy is effective in normalizing serum prolactin (PRL) levels in 73–96% of patients, decreasing tumor size in 50% and 100% [49].^{18}F-DOPA pituitary uptake has also been associated to multiple endocrine neoplasia type 1 in one patient harboring a microprolactinoma [48]. In this patient, ^{18}F-DOPA uptake reflected the efficacy of DA therapy on prolactinoma throughout the follow-up. In fact, 6 months after the beginning of cabergoline administration, prolactin plasma levels returned to normal and the^{18}F-DOPA pituitary pathological uptake completely regressed, suggesting a possible relationship between uptake and clinical response to the DA. Different mechanisms in the uptake of ^{18}F-DOPA in prolactinomas have been considered. Among them are the presence of L-type amino acid transporter system in prolactinomas and the overexpression of D2 dopamine receptors (D2R) on the lactotroph cell membrane [48].

7. Pituitary uptake on ^{18}F-choline PET

Normal pituitary gland ^{18}F-labeled fluoromethylcholine (^{18}F-FCho) uptake is usually moderately intense (SUVmean, 1.90 ± 0.21) [50]. The first pituitary adenoma disclosed at ^{18}F-FCho PET/CT was reported in 2016. It was a silent mixed mamosomatotropic macroadenoma (silent adenoma type 3) incidentally discovered (SUVmax, 6.6) in a 67-year-old man with recurrent prostate cancer [51]. More recently, a ectopic adrenocorticotropic hormone-secreting pituitary adenoma localized in the left maxillary sinus was visualized with ^{18}F-FCho PET/CT in a 49-year-old man with persistent hypercortisolemia after an unsuccessful attempt of surgical resection in which previous imaging study with ^{18}F-FDG PET/CT and ^{68}Ga-DOTA-NOC PET/CT was not diagnostic [52].

8. Pituitary uptake on ^{11}C-methionine PET

Radiolabeled amino acids have emerged as valuable molecular probes for imaging in Oncology because tumors tend to have high amino acid metabolism. It has been known for many years ^{11}C-methionine (^{11}C-MET) can be used for *in vivo* quantitative studies of amino acid metabolism of pituitary adenomas [53]. ^{11}C-MET PET/CT is a sensitive technique complementary to MRI for the detection of pituitary adenomas and residual or recurrent pituitary adenomas after surgery [54–57]. Moreover, ^{11}C-MET PET/CT can provide valuable diagnostic information when MRI and ^{18}F-FDG PET/CT are negative, especially in microadenomas [58,59].

9. Pituitary uptake on ^{99m}Tc (V)-DMSA scintigraphy

^{99m}Tc-labeled dimercaptosuccinic acid ^{99m}Tc(V)-DMSA is another radiopharmaceutical agent used for the evaluation, imaging, and management of many types of cancers. About 95% of benign and malignant primary brain tumors are detected by ^{99m}Tc(V)-DMSA SPECT scans, including PA [31,60,61]. Some studies have reported a sensitivity of 81% for detecting PA, which increases to 95% for lesions > 10 mm in size and to 100% for NFPAs [60,61]. ^{99m}Tc(V)-DMSA may also be useful not only for detecting PA, but also for the differentiation of non-functioning PA from other sellar and parasellar lesions [60].

10. Pituitary uptake on ^{123}I-methoxybenzamide scintigraphy

In vivo visualization of D2R expression detected by pituitary scintigraphy using ^{123}I-methoxybenzamide (^{123}I-IBZM) has been evaluated in PA [62–64]. ^{123}I-IBZM is a ligand for *in vivo* imaging of DA-sensitive macroprolactinomas, but not for microprolactinomas or GH-secreting adenomas [62]. An intense ^{123}I-IBZM uptake in NFPA patients was predictive of a good response to a chronic treatment with DA, such as quinagolide and cabergoline [64].

11. Pituitary uptake on O-(2-18F-fluoroethyl)-l-tyrosine PET

The first clinical case of incidental pituitary disease found on O-(2-^{18}F-fluoroethyl)-l-tyrosine (^{18}F-FET) PET imaging was reported in 2014 [65]. She was a 54-y-old woman with breast cancer treated with mastectomy, chemotherapy, and radiation therapy with metastatic spread to the bone and brain. An incremental increase in ^{18}F-FET pituitary uptake (SUVmax, 5.8) compared with ^{18}F-FDG, and a rapid growth on pituitary MRI was suggestive of pituitary metastasis.

12. Pituitary uptake on ^{13}N-ammonia PET

Dynamic ^{13}N-ammonia (^{13}N-NH_3) PET can provide information on blood perfusion and metabolism of the pituitary gland. ^{13}N-NH_3PET is considered as a new imaging method for identifying pituitary tissue.

It has been shown useful in early diagnosis of damage to the pituitary gland and in diagnosing hypopituitarism [66]. In this setting, it has been reported that the first-pass uptake rate of ^{13}N-ammonia in the pituitary gland is significantly lower in patients with hypopituitarism

than in healthy volunteers, suggesting that ^{13}N-ammonia could be a good indicator of pituitary blood flow and a reflection of the metabolic integrity of pituitary tissue [66].

^{13}N-NH_3PET/CT imaging has been shown as a sensitive tool for locating and distinguishing pituitary tissue from pituitary adenomas, particularly those with tumor maximum diameter < 2 cm [67]. It is due to ^{13}N-ammonia shows a higher uptake in the normal pituitary tissue than in PA, indicating that it is a good indicator of adequate pituitary tissue blood flow [66]. In fact, it has been suggested that combining ^{18}F-FDG and ^{13}N-ammonia PET/CT scans could increase the accuracy of PET in detecting location of pituitary tissue [67].

13. Conclusions

The available data on the techniques of nuclear medicine in pituitary conditions are abundant in the literature, although the information is poorly systematized. The knowledge in this field appears scattered in some original prospective and retrospective studies, case reports or case series. We herein bring the first extensive and updated review on the clinical utility of radiotracers and nuclear medicine imaging in pituitary disease.

The pituitary gland has the ability to uptake different radiopharmaceuticals and, therefore, is susceptible to be investigated with several imaging techniques used in nuclear medicine. Several pituitary inflammatory conditions, pituitary metastases, and pituitary tumors may also show positive uptake in functional imaging studies. Pituitary uptake on ^{18}F-FDG has shown useful in detecting several non-neoplastic and neoplastic pituitary lesions; most of them incidentally identified in tumor extension studies in cancer patients. Radiotracers based on SSTRs are able to identify PA on the basis of the presence of SSTRs with possible therapeutic implications. Lastly, many other radiotracers available in nuclear medicine could be helpful in identifying different pathologies susceptible to be studied with complementary imaging tests.

Declaration of Competing Interest

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