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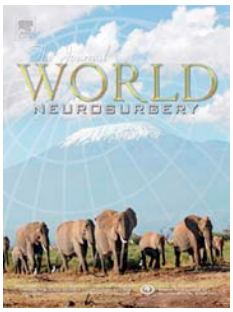

Clinical Usefulness of Coregistered 11C-Methionine Pet/ 3t Mri at the Follow Up of Acromegaly

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PII: S1878-8750(13)01431-9

DOI: 10.1016/j.wneu.2013.11.011

Reference: WNEU 2221

To appear in: *World Neurosurgery*

Received Date: 2 April 2013

Revised Date: 21 October 2013

Accepted Date: 7 November 2013

Please cite this article as: Rodriguez-Barcelo S, Gutierrez-Cardo A, Dominguez-Paez M, Medina-Imbroda J, Romero-Moreno L, Arraez-Sanchez M, Clinical Usefulness of Coregistered 11C-Methionine Pet/ 3t Mri at the Follow Up of Acromegaly, *World Neurosurgery* (2013), doi: 10.1016/j.wneu.2013.11.011.

CLINICAL USEFULNESS OF COREGISTERED ^{11}C-METHIONINE PET/ 3T MRI AT THE FOLLOW UP OF ACROMEGALY

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ABSTRACT:

Objective: To characterize the utility of coregistered 11C-methionine positron emission tomography (MET-PET**)** with 3 Tesla magnetic resonance imaging (3T MRI) in the diagnosis and follow-up of pituitary adenomas in patients with acromegaly and to compare MET-PET and ^{18}F-Fluoro-deoxyglucose emission tomography (FDG-PET) for the evaluation of active or recurrent disease.

Methods. This is a prospective observational study. It included a total of seventeen patients, six patients with a new diagnosis of acromegaly, and 11 patients who had previously undergone resection of a confirmed GH-secreting adenoma. The study protocol consisted of pre-operative and post-operative evaluation with 3T MRI, and both MET-PET and FDG-PET. Co-registration of 3T MRI/MET-PET was accomplished.

Results. In all patients who underwent pre-operative imaging, MET-PET demonstrated increased uptake coincident with location of the pituitary lesion on 3T MRI.

In the postoperative group the coregistered 3T MRI/MET-PET demonstrated evidence of residual tumor in all patients with active disease. MET-PET: sensitivity was 86% and specificity 86% for the diagnosis of recurrence.

Conclusions. MET-PET is a sensitive technique for diagnosing persistent Acromegaly and its coregistration with 3T MRI has demonstrated a better definition of the interface, extension and location of the lesion in the management of active postoperative acromegaly.

Key words: PET, Methionine, 3T MRI, Acromegaly, Pituitary adenoma.

Abbreviations:

MET: 11C-methionine **MET-PET**: 11C-methionine positron emission tomography, **FDG**: 18F-fluorodeoxyglucose **FDG-PET**: 18F-fluorodeoxyglucose positron emission tomography, **SUV_{max}**: Standardized uptake value maximum, **SUV_{max}/SUV_{clgm}**: tumor-to-brain tissue uptake ratio, **SSA treat**: Somatostatin analogue treatment, **3T MRI**: 3 Tesla magnetic resonance imaging, **GH**: growth hormone, **IGF-1**: insulin-like growth factor 1.

INTRODUCTION

The complete surgical removal of GH-secreting tumors results in hormonal control of acromegaly, however, it is not always possible[16]. Approximately 40-60% of invasive macroadenomas are unlikely to be controlled with surgery alone. Removal of more than 75% of the tumor improves control of disease with somatostatin analogues[8,16].

Rarely, magnetic resonance imaging (MRI) can not localize a microadenoma, considering the possibility of ectopic tumor or a GH releasing hormone (GHRH) secreting tumor. Also, at the follow up of the patients who had undergone surgical resection of a GH-secreting pituitary adenoma and continuous with persistent disease, MRI is often unable to distinguish residual tumours from postoperative changes[21].

Since pituitary adenomas are characterised by high amino acid metabolism, positron emission tomography (PET) using ^{11}C-Methionine (MET) as a tracer may be a suitable method for the accurate initial detection of these tumours, or the detection of recurrence[5]. The use of ^{18}F-Fluoro-deoxyglucose (FDG) also may offer the potential of monitoring tumor response to therapies in both hormone-producing and non-functioning adenomas, and of differentiating between recurrent tumor and postoperative scarring[10].

The standardized uptake value (SUV) is commonly used to evaluate both MET-PET and FDG-PET tumor metabolism. However, SUV is affected by many factors, which can not be controlled or sometimes even be taken into account. The brain reference index [BRI: regions of interest (ROI) of tumor/ROI of cerebellum] is one of the

approaches to eliminate the variety of factors that affect SUV[20]. We use the tumor-to-brain tissue uptake ratio (SUV_{max}/SUV_{clgm}) in an attempt to eliminate these factors. This ratio has been used as a relative measure of amino acid metabolism in the tumor[5].

We sought to characterize the utility of coregistered MET-PET with 3T MRI in the diagnosis and follow-up of pituitary adenomas in patients with acromegaly. We also compared ^{11}C-Methionine and ^{18}F-Fluoro-deoxyglucose for the evaluation of active or recurrent disease.

METHODS

Patients

This study consisted of two longitudinal cohorts. The first group was composed of six patients with a new diagnosis of acromegaly, and a pituitary lesion visualized on 1.5T MRI. The second group was composed of eleven patients who had previously undergone resection of a confirmed GH-secreting adenoma, and continue to be followed, some of them with evidence of progression or recurrence.

All the patients were diagnosed according to the criteria proposed by the Acromegaly Consensus Group[11,16].

Imaging

The study protocol consisted of pre-operative and/or post-operative evaluation with 3T MRI, and both MET-PET and FDG-PET, performed on the same day. At the time of these metabolic imaging studies, serum samples were drawn for hormonal testing.

All the patients in the first group underwent metabolic imaging studies. Three of them underwent surgery for resection of their pituitary tumor, and were re-evaluated in the post-operative follow-up with hormonal testing and imaging control.

In the second group, all patients underwent hormonal testing and post-operative metabolic imaging.

MRI

MRI examinations were performed using a 3T whole body MR imager (Phillips Giroscan Intera 3 Tesla). The following sequences were acquired in each patient: 3D T1 weighted sequences for coregistration purposes; and high resolution images from the sellar and parasellar regions in sagittal, coronal and axial spin echo T1 weighted sequences with and without gadolinium, and turbo spin echo T2 weighted images. The major criterion used for pituitary adenoma detection on MRI was hypointense lesion with no contrast enhancement after injection of gadolinium.

Metabolic studies with ^{11}C-Methionine and ^{18}F-Fluoro-deoxyglucose

All the PET studies were performed on a GE Discovery STE4 PET-CT scanner in a three-dimensional mode. Data were corrected for scatter, decay and attenuation. Interactive reconstruction was performed with 3D VUE Point. Post-processing was performed on an Advantage Windows 4 workstation.

All patients were examined with both MET-PET and FDG-PET. First, the patient underwent MET-PET, and three hours later underwent FDG-PET. Each patient was thus her/his own control to compare the metabolic activity in the tumor tissue with both tracers.

MET was synthesized according to the following method: METHOD. 4 MBq/Kg bodyweight MET (maximum 555 MBq) were injected intravenously. Tracer accumulation was recorded in the entire brain twenty minutes after the injection during a subsequent twenty minutes. 3 MBq/Kg FDG were injected at least three hours after the MET-PET and data acquisition was accomplished thirty minutes later.

An expert nuclear medicine physician evaluated both MET-PET and FDG-PET separately from the MRI studies. If a focus of visible activity within the sellar or parasellar region was present, the location and laterality of focus was noted, and both the maximum standardized uptake value (SUV_{max}) and the tumor-to-brain tissue uptake ratio (SUV_{max}/SUV_{clgm}) were measured. If the ratio was higher than 1.5 it was

considered a pathological uptake. This ratio was calculated considering the mean value of the SUV in eight to ten voxels with maximum measured activity in the lesion and the mean value of the SUV in six fixed regions of interest (ROIs) in the cortical gray matter of the contralateral hemisphere (SUV_{clgm}) including frontal, temporal, parietal and occipital lobes.

Coregistered MET-PET/3T MRI

The 3T MRI was then coregistered with the MET-PET, based on the semiautomatic algorithm coregistration implemented in Advantage Windows, reviewed by the nuclear medicine specialist, and evaluated for evidence of increased metabolic activity in areas of the sella and cavernous sinus which appeared abnormal on MRI. We evaluated the results in conjunction with nuclear medicine colleagues.

Verification of the coregistered 3T MRI/MET-PET results was based on the neurosurgeon's surgical findings in the cases from group 1 who underwent surgical treatment, and the pathology results in both group 1 and 2. Matching coregistered 3T MRI/MET-PET features with these findings provided a basis for validation of this technique.

RESULTS

Seventeen patients were entered into the study. The average age was 47 years (range 29-65 yr). The average length of follow up was 22 months (4-80 m).

Preoperative group

In all six of the patients who underwent pre-operative imaging (Table 1), MET-PET demonstrated increased uptake coincident with location of the pituitary lesion on 3T MRI when the coregistration was performed.

Five of the six patients had received somatostain analogue therapy prior to metabolic imaging. There was no difference in the uptake of MET-PET in patients who were on somatostatin therapy whether their GH and IGF-1 levels had normalized or not. The one patient who refused medical therapy demonstrated an elevated uptake of MET in the lesion compared to the other five who were on medical therapy. Although two patients with microadenomas not observed pathological quantitative tumor-to-brain uptake ratios both for MET and FDG, it was possible distinguish visually the lesion when the corigestered MET/3TMRI was performed. This technique has improved evidence of residual tumor instead of performing each test imaging separately (PET or MRI).

We observed an accumulation of FDG in the four patients who presented with macroadenomas.

Postoperative group

In the second group, all were macroadenomas on initial diagnosis with prior surgical resection, including one giant tumor with invasion of the cavernous sinus and temporal fossa.

A total of fourteen patients (the second group, and three of the six from the first group who underwent surgery) were evaluated with post-operative metabolic imaging (Table 2). Of these fourteen, seven had postoperative active disease by biochemical and dynamic testing. All but one were treated with somatostatin analogues. In these seven patients with persistent postoperative disease, 3T MRI demonstrated evidence of

abnormal features in all, but it was unable to differentiate residual tumour from postoperative changes in three of them (Figure 2).

MET-PET

MET-PET demonstrated increased tumor-to-brain uptake ratios ($SUV_{max}/SUV_{clgm} > 1.5$) in six of seven cases of active postoperative disease (Figure 1). Only one of the seven patients cured by surgery demonstrated an increased tumor-to-brain uptake ratio of MET on post-operative metabolic imaging. This resulted in a sensitivity and specificity of 86% for detecting residual tumor in patients who underwent surgical treatment and having persistent disease. In the patients with active disease there was no difference in uptake of MET-PET in those who were on somatostatin therapy regardless of whether they had micro or macroadenomas.

FDG-PET

Only two patients with active post-surgical disease had postoperative FDG uptake on PET (SUVmax / SUVclgm> 0.6) (Figure 1). There was no uptake in any of the seven patients cured by surgery. This resulted in a sensitivity of 28% and specificity of 100% for detecting residual tumor in patients with active postoperative disease.

Coregistered MET-PET/3T MRI

The coregistered MET-PET/3T MRI demonstrated residual tumor in the seven patients with active disease (Figure 1). In the three cases where the MRI could not differentiate between residual tumor and scar tissue, MET-PET was able to show a zone of hypermetabolism. And when coregistration was performed, the residual tumor was diagnosed accurately (Figure 2).

DISCUSSION

MET value

A large number of PET studies[1,2,4,5] have demonstrated the great advantages of both biochemical and functional characterization of pituitary adenomas. Some authors[3,12] have reported MET uptake in the normal pituitary gland, others in normal bone marrow within the sphenoid bone and clivus[7], as well as the physiologic uptake that may occur in the female pituitary gland. The value of MET is its ability to distinguish viable tumor tissue and its high level of discrimination between tumor tissue and normal brain and pituitary tissue[5], as was shown by our three patients with postoperative active disease in which 3T MRI did not clear the doubts as to the location of the residual tumor.

MET-PET can also accurately discriminate active tumor from fibrosis, cyst, and bleeding, and it is possible to separate pituitary adenoma from neurinoma[5], because the adenoma has high accumulation of tracer.

FDG value

The pituitary gland does not normally accumulate FDG and ordinarily is not visualized on FDG-PET[6,7,9,13]. A recent PET study showed SUV_{max}= 0.74 ± 0.18 (range 0.50-1) for MET and 2.72 ± 0.96 (range 1.3-4.5) for FDG in 10 healthy controls[12]. The pituitary-to-brain ratio was not calculated.

Four of our six patients had a positive uptake in the preoperative FDG-PET, and it could be used for postoperative evaluation of the functional tissue with this tracer if the surgery does not control the disease because the FDG-PET can differentiate between

tumor and post-surgical changes, the latter being hypometabolic while the tumor was hypermetabolic[10,21].

The incidental diagnosis of pituitary adenoma may be occasionally made on FDG-PET imaging[6,14,15,19]. However, a recent multicenter study found focally increased uptake localized to the pituitary gland in 30 of 40,967 patients, leading to a pituitary incidentaloma incidence of 0.073%[13], clearly a rare event. For that reason when we have a patient with active postoperative acromegaly and a positive uptake on FDG-PET imaging, we must suspect that this is the correct location of residual tumor.

MET and FDG

In a review of 165 patients with expansive sellar lesions studied with PET using both tracers (MET and FDG), approximately 90% with pituitary adenoma, the uptake in these tumors was high for MET and moderate to high for FDG. Prolactinomas were metabolically very active, with a higher metabolic rate measured with MET than other types of pituitary adenomas[17].

In some adenomas there is uptake of both MET and FDG, while in others, only MET is high, but it is not yet understood what these different patterns represent[17]. Others have reported that GH adenomas might demonstrate uptake for both MET and FDG[10,15].

Microadenomas can be visualized by PET with several tracers, but most frequently with MET and FDG[9,17,19,21]. Usually, MET will more easily delineate the adenoma than FDG, as the ratio of uptake in the adenoma compared with that in surrounding brain is relatively higher for MET than for FDG in most adenomas[18].

Our results are consistent with the literature[17] that GH adenoma uptake is high for MET (67% in the preoperative group and 85% in the postoperative) and moderate for FDG. In 46% of the cases with active disease was there uptake of FDG (66% in the preoperative group and 28% in the postoperative). In our series, there was no uptake of FDG in patients who had microadenomas, but all were treated with SSA. Francavilla et al[10] demonstrated a mean tumor-to-brain ratio of 1.2 for FDG in 13 GH macroadenomas, and that medical therapy with octreotide decreased adenoma glucose metabolism in TSH and GH adenomas[10].

Although Bergstrom et al.[5] have found that a tumor-to-brain uptake ratio for MET higher than 2 was present in the pituitary adenomas, this level is less when functioning tumors have a good response to medical treatment[4,5,17]. This could explain why our patients with active disease who had received somatostain analogue therapy prior to metabolic imaging had a tumor-to-brain uptake ratios < 2 and the one patient who refused medical therapy demonstrated an elevated uptake of MET (SUV_{max}/SUV_{clgm}= 2.4). Based on these data, we recommend stopping the SSA treatment at least 2-3 month before the PET study, as it is the range recommended by the experts to objectively assess the levels of GH and IGF1, after stopping the treatment[16]

Coregistered MET-PET/3T MRI

The coregistered MET-PET/3T MRI studies were evaluated for evidence of increased metabolic activity in areas of the sella and the cavernous sinus which appeared abnormal on MRI or MET-PET. The 3T MRI abnormality coincided with increased MET uptake in all of the preoperative patients. In the postoperative group, coregistered

MET-PET/3T MRI demonstrated residual tumor in the seven patients with active disease, and it was possible to localize the tumor in three cases where 3T MRI could not differentiate between residual tumor and scar tissue.

It could be used in our clinical practice, enabling better diagnosis and characterization of the tumor before treatment, and, most importantly, in follow up. And it should be included in the armamentarium used to manage patients with acromegaly.

An advantage of the coregistered MET-PET/3T MRI is that it can precisely show spatial information within a clear image[12]. It can also add anatomical precision in the target for gamma knife radiosurgery procedures[21].

CONCLUSIONS

Although these results must be considered as preliminaries, we have shown that **MET-PET** is a technique with high sensitivity (86%) and specificity (86%) for the detection of recurrence, and its coregistration with 3T MRI has demonstrated improved definition of the margins, extension and location of the residual lesion.

FDG-PET is highly specific (100%) in detecting patients who are correctly identified as not having residual tumor; if there is a positive result in the FDG-PET study, the patient has a high probability of having residual GH adenoma.

The combination of these three techniques is a valuable tool in the diagnosis of recurrent GH-secreting pituitary tumor.

ACKNOWLEDGMENT

We want to express our deepest and sincere thanks to Professor Edward Laws Jr. MD, FACS for enlightening discussion, reviewing the language and encouraging us to complete our investigation.

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FIGURE LEGENDS

Figure 1. Residual GH adenoma in the left cavernous sinus (arrow). a. 3T MRI imaging show residual tumor involving left ICA. b. Coregistered MET-PET/3T MRI allows accurate identification of residual tumor with high uptake of MET. c. MET-PET and d. FDG-PET show a zone of hypermetabolism but it is difficult to establish a exact location.

Figure 2. Recurrence of microadenoma, GH+, in the left cavernous sinus (arrow). a. The existence of previous surgical changes makes it difficult to assess the 3T MRI imaging. b. Coregistered MET-PET/3T MRI was able to show a zone of high uptake of MET and the residual tumor was diagnosed accurately.

Table 1. Pre-operative group

№	Tumor size	MET-PET SUV_{max}	MET-PET SUV_{max}/ SUV_{clgm}	FDG-PET SUV_{max}	FDG-PET SUV_{max}/ SUV_{clgm}	SSA treat at the time of PET	3T MRI	GH IGF-1
1	< 10 mm	2.8	1.4	3.3	0.46	Yes	Visible	N
2	< 10 mm	2.4	1.1	3.3	0.43	Yes	Visible	N
3	> 10 mm	4.5	2.4	7.2	0.75	No*	Visible	↑↑
4	> 10 mm	2.1	1.6	3.9	0.65	Yes	Visible	↑
5	> 10 mm	2.7	1.8	3.3	0.66	Yes	Visible	N
6	> 10 mm	3.3	1.88	3.8	0.63	Yes	Visible	↑

Cases 1 and 2 had microadenomas pretreated with SSA and presented with non pathological tumor-to-brain uptake ratios both for MET and FDG. Cases 3-6 had macroadenomas and presented with increased tumor-to-brain uptake ratios both for MET and FDG. *Case 3, who refused medical therapy, demonstrated an elevated uptake of MET in the lesion compared to the other five who were on medical therapy.

№: Patient n°, **MET-PET**: 11C-methionine positron emission tomography, **FDG**: 18F-fluorodeoxyglucose positron emission tomography, **SUV_{max}**: Standardized uptake value maximum, **SUV_{max}/SUV_{clgm}**: tumor-to-brain tissue uptake ratio, **SSA treat**: Somatostatin analogue treatment, **3T MRI**: 3 Tesla magnetic resonance imaging, **GH**: growth hormone, **IGF-1**: insulin-like growth factor 1, **N**: hormone level in normal ranges, ↑: high hormone level, ↑↑: very high hormone level.

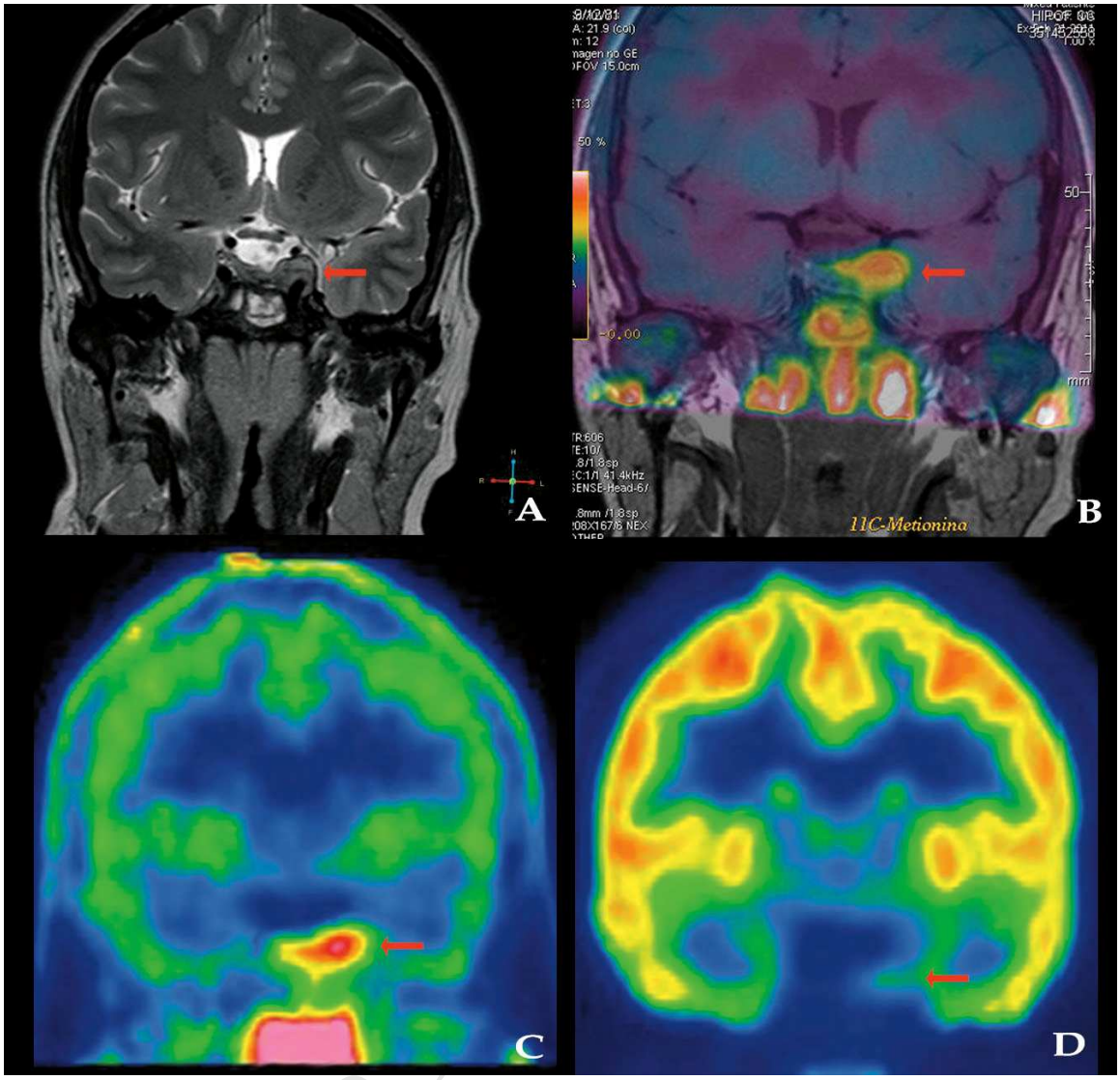
Table 2. Post-operative group

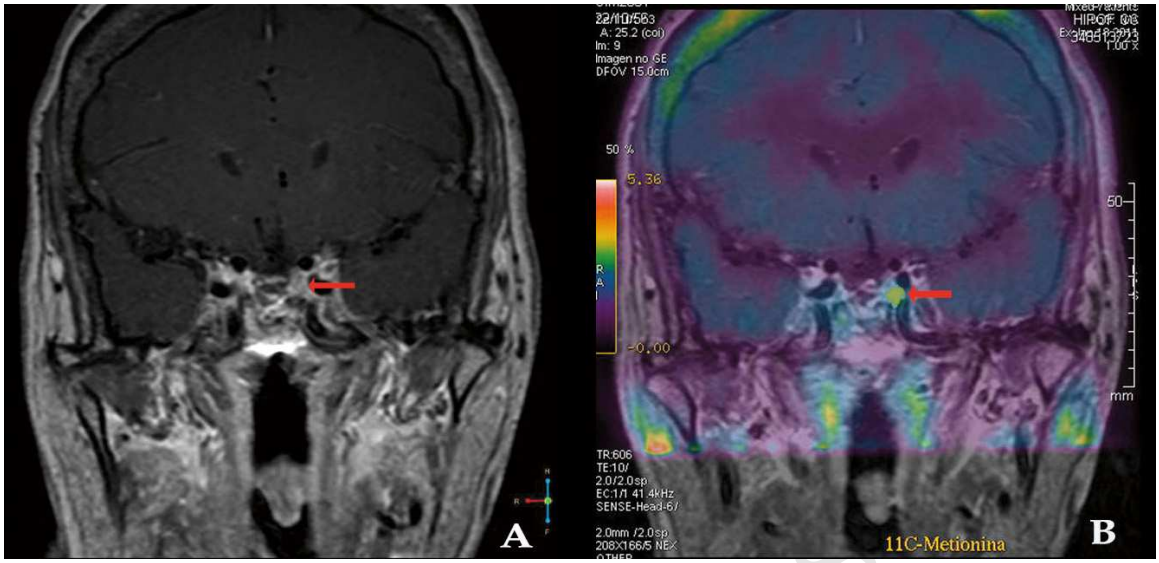
№	Acrom	Tumor size	MET-PET SUV_{max}	MET-PET SUV_{max}/ SUV_{clgm}	FDG-PET SUV_{max}	FDG-PET SUV_{max}/ SUV_{clgm}	treat	3T MRI	GH IGF1
1	Control	-	2.1	1.4	3.4	0.33	No	Gland	N
2	Control	-	3.8	2.1	3.3	0.2	No	Gland	N
3	Control	-	1.3	0.76	2.5	0.24	No	Empty sella 2°	N
4	Control	-	2.5	1.39	3.5	0.27	No	Post-surg. changes	N
5	Control	-	2.4	1.26	2.6	0.39	No	Empty sella 2°	N
6	Control	-	1.7	1	2.6	0.38	No	Post-surg. changes	N
7	Control	-	2.6	1.4	4.5	0.4	No	Empty sella 2°	N
8	Active	> 10 mm	3.8	2	6.5	0.77	No	Left CS	↑
9	Active	> 10 mm	3.6	1.6	6.1	0.67	SSA+ SRT	Left CS-temp fossa	↑
10	Active	< 10 mm	3.8	1.6	3.9	0.4	SSA	Post-surg. changes	↑
11	Active	< 10 mm	3.8	1.9	2.1	0.29	SSA	Post-surg. changes	N
12	Active	< 10 mm	3.1	1.08	4.1	0.51	SSA	Left CS	↑
13	Active	< 10 mm	3.2	1.8	3.1	0.4	SSA	Pituitary stalk	↑
14	Active	< 10 mm	2.4	1.53	5	0.4	SSA	Post-surg. changes	↑

Cases 1-7: Control disease, defined as a normal IGF-1 for age and gender and a GH < 1 ng/ml during an OGTT. One of these seven cases (Case 2) demonstrated an increased tumor-to-brain uptake ratio of MET and none had FDG uptake. Cases 8-14: Active disease. All but one (Case 12) demonstrated pathological MET uptake. Two cases had macroadenomas (cases 8 and 9) and presented with increased tumor-to-brain uptake ratios for both MET and FDG. The highest value of MET and FDG uptake ratio was in Case 8 who had not received medical therapy. In three cases (10, 11 and 14) MRI could

not differentiate between residual tumor and scar tissue in the sellar and parasellar region.

№: Patient n°, **Acrom**: Acromegaly state, -: Non tumor, **MET-PET**: 11C-methionine positron emission tomography, **FDG**: 18F-fluorodeoxyglucose positron emission tomography, **SUV_{max}**: Standardized uptake value maximum, **SUV_{max}/SUV_{clgm}**: tumor-to-brain tissue uptake ratio, **treat:** treatment, **SSA**: Somatostatin analogues, **SRT**: stereotactic radiation therapy, **3T MRI**: 3 tesla magnetic resonance imaging,, **GH**: growth hormone, **IGF-1**: insulin-like growth factor 1, **N**: hormone level in normal ranges, ↑: high hormone level, ↑↑: very high hormone level.





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