Clinical note

Extensive hypermetabolic pattern of brown adipose tissue activation on $^{18}$F-FDG PET/CT in a patient diagnosed of catecholamine-secreting para-vesical paraganglioma

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**A B S T R A C T**

The widespread use of $^{18}$F-FDG PET-CT scanning in oncological patients has allowed to demonstrate the existence of metabolically active brown fat, also called brown adipose tissue (BAT), in adult humans, and specifying its anatomical distribution in vivo. As physiological determinants to BAT $^{18}$F-FDG uptake has been identified gender, age, temperature, and body mass index. We have observed extensive activation of the BAT, including the mesenteric region, in a patient with a catecholamine-secreting para-vesical paraganglioma. The extensive BAT activation could be secondary to adrenergic stimulation due to excess of circulating norepinephrine concentration.

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**Extenso patrón hipermetabólico por activación de la grasa parda en un paciente diagnosticado de paraganglioma para-vesical secretor de catecolaminas explorado mediante $^{18}$F-FDG PET/TC**

**R E S U M E N**

El uso generalizado de la exploración $^{18}$F-FDG PET-TC en pacientes de cáncer ha permitido demostrar la existencia de grasa parda metabólicamente activa, también llamada tejido adiposo pardo (TAP), en sujetos humanos adultos, y conocer su distribución anatómica in vivo. Como determinantes fisiológicos de la captación de $^{18}$F-FDG por el TAP se han identificado el sexo, la edad, la temperatura y el índice de masa corporal. Hemos observado una extensa activación del TAP, incluyendo la región mesentérica, en un paciente con un paraganglioma paravesical secretor de catecolaminas. La activación extensa del TAP podría ser secundaria a la estimulación adrenérgica por un exceso de la concentración de noradrenalina circulante.

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**Introduction**

The widespread use of $^{18}$F-FDG PET-CT scanning in cancer patients has allowed to demonstrate the existence of metabolically active brown fat, also called brown adipose tissue (BAT), in adult humans, and specifying its anatomical distribution in vivo. Morphologically, BAT differs from regular white adipose tissue by its rich vascularisation and its high density of mitochondrias. BAT plays a major role in energy expenditure and non-shivering thermogenesis in newborn mammals as well as adults. The presence of BAT in adult humans was confirmed by the experimental $^{18}$F-FDG PET/CT studies for healthy volunteers. BAT-mediated thermogenesis is highly regulated by the sympathetic nervous system. As physiological determinants to BAT $^{18}$F-FDG uptake has been identified gender, age, temperature, and body mass index. Metabolic activity in BAT differs among individuals, being lower in older subjects and in obese ones. In recent years there have been published several case reports of extensive increased $^{18}$F-FDG uptake in BAT in patients diagnosed of catecholamine-secreting adrenal, extra-adrenal and recurrent pheochromocytomas. This BAT uptake decreases or returns to normality after the patient has been prepared or treated with propanolol or after resection of the tumour.

We report a case of extensive activation of BAT cervical, thoracic and abdominal, including the mesenteric area, in a young male patient diagnosed of a para-vesical paraganglioma secretor by $^{18}$FDG PET/CT.

**Case report**

A 22-year-old man is found a blood pressure of 140/100 mm Hg in a medical examination for sports practice. The patient had
night sweating as the only symptom. The plasma norepinephrine values were 25.159 pg/ml (normal 300–650 pg/ml), with normal adrenaline and dopamine levels. MRI scan and 123I-MIBG scintigraphy diagnosed left extra-adrenal retroperitoneal mass in close contact with the left ureter. The patient underwent surgical resection of a retroperitoneal mass of 55 mm in diameter with a pathological diagnosis of paraganglioma with low proliferative index (Ki67: 1–5%). In histopathological analysis there were no signs of capsular invasion, atypia or necrosis. The immunohistochemical analysis reported positivity for chromogranin, neuron specific enolase and S-100 protein. A few days later, it was performed left nephrectomy due to complications in the postoperative period.

The patient has gradually increased the norepinephrine levels up to 6300 pg/ml during follow-up for 3 years. Repeated scintigraphies with 123I-MIBG and ultrasound scans were interpreted as normal so it was performed an 18F-FDG PET/CT scan. This exploration showed a hypermetabolic pelvic mass that produced paravesical protrusion on the dome wall of the bladder with a SUVmax of 15.2 g/ml, right iliac primitive and external, and right obturator lymphadenopathies, with a SUVmax of 15.8 g/ml. In addition, there was an extensive pattern of activation of brown fat nuchal, cervical, subcuticular, axillary, mediastinal, paravertebral, intercostal, perirenal and mesenteric (Fig. 1). The patient underwent surgery, finding the tumour in intimate contact with the bladder dome. Partial cystectomy and right iliac lymphadenectomy were performed, and the histopathology results reported paraganglioma with lymph node metastasis. The definitive immunohistochemical analysis reported in this case positivity for chromogranin and S-100 protein.

Discussion

In humans, significant amounts of BAT are presented in newborns and may contribute to body temperature regulation. The BAT seems to disappear rapidly during postnatal periods and in adults it is rather difficult to identify by conventional anatomical examinations. In 18F-FDG PET studies, a pattern of increased 18F-FDG uptake in the neck and supraclavicular areas was initially interpreted as muscular uptake. The metabolic and structural fusion images achievable with PET/CT allowed relating this uptake with fatty tissue. Histological examinations revealed the presence of uncoupling protein-1 (UCP1), a specific biomarker of BAT, in these regions.

The characteristic 18F-FDG uptake location in BAT is neck and supraclavicular region, usually bilateral and symmetrical. It is observed less frequently increased uptake in the mediastinum, around the great vessels, and paravertebral intercostal spaces of the thoracic spine. Subdiaphragmatic uptake is usually limited to adrenal region. The mediastinal and paravertebral BAT uptake is not usually observed in the absence of neck and supraclavicular uptake. The symmetrical pattern of uptake in BAT can be altered by previous surgery that disrupts the sympathetic innervations. It has been described atypical sites of BAT in the posterior neck, axilla, left paratraqueal, paraesophageal, pericardial, retrocrural and perirenal areas and interatrial septum. It is important to recognize these uptake patterns to avoid false-positive results.

It has been observed that physiologic 18F-FDG uptake in BAT increases over time using dual-time point 18F-FDG PET/CT scan. Cypes and colleagues have studied the presence of BAT metabolically active in 3640 consecutive 18F-FDG PET/CT scans performed to 1872 adult patients. Positive 18F-FDG uptake in BAT was seen in 7.5% of the women and 3.15% of the men. The probability of the detection of BAT has been most frequent in young women and inversely correlated with age, outdoor temperature at the time of the exploration, beta-blocker use and body-mass index. The depots of BAT have similar distributions in both sexes, but the mass and activity of BAT are greater in women than men. Cold temperature appears to be the most significant factor in stimulating BAT, so that the incidence of activation of BAT occurs most often in colder
months. In $^{18}$F-FDG PET series of studies carried out in a short interval of time, it was observed that the uptake of BAT disappears when the patient is instructed to avoid exposure to cold temperature.

Additional evidence for the presence of BAT may be seen with $^{123}$I-MIBG, a biomarker of sympathetic stimulation and activation. Okuyama and colleagues have found that $^{123}$I-MIBG uptake, in the nape of the neck related to active BAT, in 12% of children (32/266) explored for evaluation of neuroendocrine tumours after treatment. The observation was limited in the $^{123}$I-MIBG scintographies performed in winter. In a group of 10 healthy volunteers exposed to mild cold ($17^\circ$C) for 2 h, Admiral and colleagues have proven that $^{123}$I-MIBG SPECT/CT and $^{18}$F-FDG PET/CT identify the same anatomic regions as active BAT. It has also been shown BAT uptake of $^{18}$F-6-fluorodopamine in patients evaluated for suspected or proven pheochromocytoma. These findings confirm that the activity of human BAT is influenced by the sympathetic nervous system.

It has been suggested that the incidence of metabolic active BAT is higher in patients with pheochromocytoma that in patients that suffer other types of neoplasms. Ultrastructural and biochemical analysis of intra-abdominal adipose tissue in patients with pheochromocytoma has shown extensive BAT around the adrenal glands and kidneys as well as in the greater omentum. Recently, several case reports have been published illustrating extensive activation of BAT in patients diagnosed of catecholamine-secreting adrenal, extra-adrenal and recurrent pheochromocytomas. In some of these cases a notable increase in $^{18}$F-FDG uptake in subdiaphragmatic, perirenal, mesenteric and omental regions, was detected, in addition to showing activation in the usual locations of BAT. The extensive BAT activation could be secondary to adrenergic stimulation due to excess of circulating norepinephrine concentration.

According to the systematic review performed, we have not found any bibliographic citation on BAT activation in patients with extra-adrenal paraganglioma. The BAT activation pattern is similar to that found in patients with pheochromocytoma, including the mesenteric region. The $^{18}$F-FDG PET/CT scan was performed in the last week of December 2011. According to data from the Basic System of Weather Information in Aragon (SIBICA) minimum temperatures in Teruel, place of origin of the patient, during the six days prior to the test ranged between $-4$ $^\circ$C and $-7$ $^\circ$C, while maximum temperatures ranged between 5 and 12 $^\circ$C. The excess of norepinephrine released by the tumour and the exposure to cold temperature could be determining factors to produce the extensive activation of BAT.

$^{123}$I-MIBG SPECT remains the first choice when a paraganglioma is suspected. The $^{18}$F-FDG PET/CT scan is a suitable alternative when the $^{123}$I-MIBG SPECT is normal or metastatic spread is suspected. In the present patient, bladder activity and not performing a SPECT/CT could be the causes of non-tumour detection in $^{123}$I-MIBG scintigraphy.

In conclusion, we have observed extensive activation of the BAT, including the mesenteric region, in a patient with a catecholamine-secreting para-vesical paraganglioma.

References