

## SCIENTIFIC LETTERS

### 6-[F18]-Fluoro-dihydroxyphenylalanine positron emission tomography for diagnosis of pheochromocytoma<sup>☆</sup>

#### Tomografía por emisión de positrones marcada con 18-Fluor-dihidroxifenilalanina para el diagnóstico de feocromocitoma

Pheochromocytoma is an uncommon neuroendocrine tumor derived from adrenal chromaffin cells. Pheochromocytoma causes signs and symptoms resulting from catecholamine excess, and its diagnosis may represent a challenge conditioned by the sensitivity and specificity of the diagnostic tests.<sup>1</sup>

We report the case of a 41-year-old woman who reported episodes of palpitations lasting a few minutes, associated with increased blood pressure and occurring in relation to menstruation for the previous two years. There was no associated headache. The patient reported smoking, prior uneventful menses, and two normal term pregnancies. Cardiological study (electrocardiogram, Holter electrocardiogram and blood pressure, and echocardiogram) and chest X-rays were normal, even during symptomatic periods. Physical examination revealed no significant findings. The patient had a weight of 60 kg, a height of 169 cm, blood pressure of 130/60 mmHg, and a heart rate of 80 bpm. Ultrasound gynecological examination was normal.

As part of a differential diagnosis of palpitations and high blood pressure, complete laboratory tests were requested including protein, hormones, and tumor markers. Test results included: blood glucose 89 mg/dL, normal liver profile, beta-2-microglobulin 1.4 mg/L, proteins and immunoglobulins in the normal range, tryptase 7.07 ng/mL (<11.5), TSH 1.45  $\mu$ U/mL, calcium 9.8 mg/dL, calcitonin 2 mg/dL (2–11.5), renin 8 pg/mL (3–33), aldosterone 137 pg/mL (97–626), chromogranin A 0.8 nmol/L (<6). Urinary fractionated metanephrines were normal in two separate measurements. Due to symptom persistence several months later, even during the intermenstrual period, a repeat test was performed, showing a

slight increase: normetanephrine/creatinine ratio 167  $\mu$ g/g (<560), metanephrine/creatinine ratio 333,3  $\mu$ g/dL (<260), and vanillylmandelic acid/creatinine ratio 3.74  $\mu$ g/g (<10), with a chromogranin A level of 12 nmol/L.

A pheochromocytoma or paraganglioma of potential gynecological location was suspected, and an abdominal computed tomography scan (CT) was requested, which showed normal results. A subsequent <sup>123</sup>I-metaiodobenzylguanidine (<sup>123</sup>I-MIBG) scintigraphy showed no pathological uptake (Fig. 1). An additional CT scan of the neck, mediastinum, and chest showed a thyroid nodule, which was found to be benign in nature after ultrasound-guided fine needle aspiration.

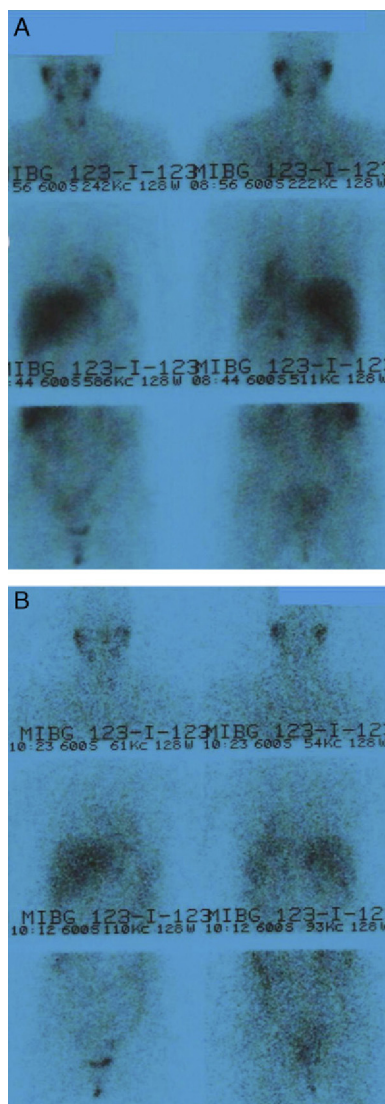
Despite the inconclusive biochemical results and the repeated negative test results, the clinical signs of the patient prompted us to request <sup>18</sup>F-dihydroxyphenylalanine positron emission tomography (<sup>18</sup>F-DOPA-PET-CT), which showed increased uptake in the right adrenal gland (SUVmax 9.59) (Fig. 2) consistent with pheochromocytoma. Alpha-adrenergic blockade was started, with good blood pressure control, followed by beta-blockade before surgery. The pathological laboratory confirmed the suspicion and reported no findings suggesting histological aggressiveness (Ki67 <2% and immunohistochemistry positive for ENE, S-100, chromogranin A, synaptophysin, CD56, PGP 9.5, and vimentin). A genetic study has been requested.

The diagnosis of pheochromocytoma is based upon clinical and biochemical data and localization studies. Symptoms are non-specific and show great inter-individual variability. They may mimic many other more common conditions, so that although the presence of pheochromocytoma may sometimes be suspected, the condition is not always diagnosed.<sup>2</sup>

The test of choice for screening a catecholamine-secreting tumor is the measurement of free plasma or urinary fractionated metanephrines.<sup>3</sup> Ideally, both tests should be performed, but urinary measurement is sometimes the only measurement available.<sup>4</sup> Equivocal results may sometimes be achieved, as initially occurred in our patient, raising doubts as to whether the diagnostic algorithm should be continued or whether this should be considered as a false positive.<sup>2</sup>

If the clinical signs and biochemical data are consistent, a localization study is indicated, starting at abdominal levels.<sup>4</sup> Anatomical CT scans or magnetic resonance imaging (MRI) (90–100% sensitivity, but low specificity) usually have to be supplemented with functional nuclear medicine tests,

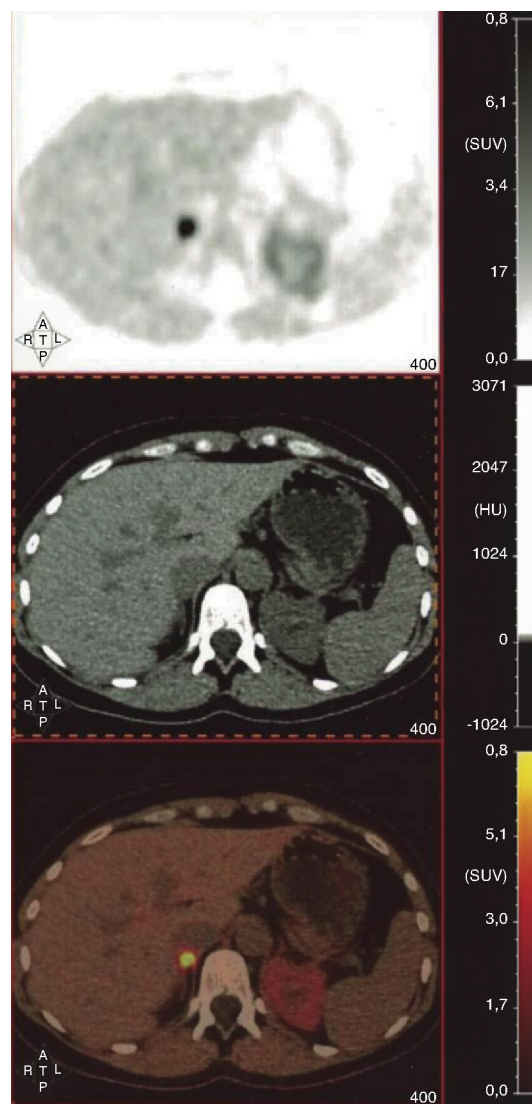
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**Figure 1**  $^{123}\text{I}$ -MIBG scintigraphy (dose of 185 MBq). Anterior and posterior views of neck-chest-abdomen at 24 h (A) and anterior and posterior views of neck-chest-abdomen at 48 h (B). No pathological findings are seen. Images show a distribution of the radiopharmaceutical consistent with physiological distribution from the initial acquisitions.

including scintigraphy with  $^{123}\text{I}$ -MIBG (99% specificity)<sup>5</sup> and the somatostatin analog  $^{111}\text{In}$ -pentetreotide, which is less commonly used because of its lower yield.<sup>6</sup>

However, these procedures do not always allow for the identification of tumor location because of their limited spatial resolution. In such cases, PET imaging may be more useful.<sup>7</sup> Different radiotracers have been used for this purpose, including  $^{18}\text{F}$ -dopamine ( $^{18}\text{F}$ -FDA),  $^{18}\text{F}$ -DOPA, and  $^{18}\text{F}$ -deoxyglucose ( $^{18}\text{F}$ -FDG), based respectively on the ability of these tumors to incorporate and subsequently decarboxylate amino acids and on cell incorporation of glucose through the GLUT-1 pathway. Other recently designed radiotracers based on the presence of somatostatin receptors ( $^{68}\text{Ga}$ -DOTA-Tyr3-octreotide [ $^{68}\text{Ga}$ -DOTATOC] and DOTA-Nal-octreotide [ $^{68}\text{Ga}$ -DOTANOC]) have given encouraging results, but adequate comparative studies are not available yet.<sup>6</sup>



**Figure 2**  $^{18}\text{F}$ -dihydroxyphenylalanine positron emission tomography ( $^{18}\text{F}$ -DOPA-PET-CT). Axial sections at abdominal level (SPECT, CT, and fusion). A markedly increased uptake by the right adrenal gland (SUVmax=9.59) is seen in the absence of structural gland enlargement in the CT scan, which is consistent with pheochromocytoma. Activity of the left adrenal gland is normal. No focal deposits suggesting paraganglioma and/or metastases are seen in the neck, chest, abdomen, or pelvis.

Several authors have concluded that  $^{18}\text{F}$ -DOPA-PET has a higher yield and, if implemented as a routine procedure, would condition patient management and treatment.<sup>7</sup> Some series report false positive rates of 0% and sensitivity values up to 100%, higher than those of other functional tests, even if metanephrine levels are not very high,<sup>5,6,8</sup> as occurred in our patient. An additional advantage over  $^{123}\text{I}$ -MIBG is that, since  $^{18}\text{F}$ -DOPA has a shorter half-life, it allows for a higher dose and earlier image acquisition.<sup>9</sup> In addition, differentiation from normal adjacent tissue is enhanced, because healthy adrenal medulla does not take up the radiotracer,<sup>6,9</sup> a feature that some authors have proposed optimizing by prior treatment with carbidopa.<sup>10</sup>

It should be noted, however, that the best diagnostic test in each case is difficult to establish because of the heterogeneity and low prevalence of pheochromocytoma and paraganglioma, and will depend on the individual patient characteristics in terms of the secretory profile, suspected location, the histological characteristics of cell differentiation, biological behavior, and potential association with a genetic mutation.<sup>6,11</sup>

An adaptation to advances in imaging procedures is required, which includes the possibility that in hospitals where <sup>18</sup>F-DOPA-PET is available, it may replace <sup>123</sup>I-MIBG, at least partly, because of its greater precision, convenient performance, and less adverse effects for patients, although cost-effectiveness studies assessing its use will be required.

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## Acute severe hyponatremia induced by aceclofen in a male patient with central diabetes insipidus

### Hiponatremia aguda grave inducida por aceclofeno en un paciente varón con diabetes insípida central

#### Introduction

The side effects of desmopressin are headache, lethargy, obtundation and seizures all of which are due to severe and rapid hyponatremia caused by water intoxication. These symptoms have been described in patients treated with this drug for central diabetes insipidus, primary nocturnal enuresis and nocturnal polyuria.

Non-steroidal anti-inflammatory drugs (NSAIDs) in combination with desmopressin can induce symptomatic hyponatremia, though this effect is very rare and has seldom been described in the literature.

In this report, we describe the case of a 46-year-old man with central diabetes insipidus undergoing long-term

treatment with a constant dose of desmopressin who developed acute severe symptomatic hyponatremia when desmopressin was combined with aceclofen.

#### Case report

A 46-year-old man was admitted to the Emergency Department of the Dr. Peset University Hospital (Valencia, Spain) with lethargy, obtundation and loss of consciousness. He had been diagnosed with central diabetes insipidus at the age of 28 and was being treated with desmopressin at a dose that he denied having altered. Three days prior to admission the patient had experienced dizziness, headache, nausea and vomiting.

A physical examination revealed normal blood pressure (130/80 mmHg), pulse rate of 90 bpm and body temperature of 36.9 °C. A neurological examination gave a Glasgow coma score of 14 (E4 V4 M6) and otherwise normal results.

On admission, the most relevant laboratory parameters were as follows: sodium (Na) 113 mequiv./L (reference value 135–145 mequiv./L); potassium (K) 4.3 mequiv./L (reference value 3.5–5 mequiv./L); creatine phosphokinase (CPK) 3576 UI/L (reference value 30–200 UI/L); creati-