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Case Report

A pheochromocytoma in a patient with neurofibromatosis type 1: A case report

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ABSTRACT

Neurofibromatosis type 1 is one of the most common autosomal dominant disorder characterized by an extreme variability of its manifestations even within the same family. It carries an increased risk of pheochromocytoma. Although rare, recent literature recommend routine screening for symptomatic patients with neurofibromatosis type 1. A 46-year-old man, normotensive, presented a right-adrenal incidentaloma and investigations revealed a pheochromocytoma. We remind the benefit of screening and earlier identification of this affection in patients with neurofibromatosis type 1 to prevent from the morbidity and mortality secondary to an excess of catecholamine secretion.

Key words: Neurofibromatosis type 1; Von Recklinghausen Disease; Pheochromocytoma; Hypertension

INTRODUCTION

Neurofibromatosis type 1(NF1) also known as Von Recklinghausen disease, is a common autosomal dominant disorder due to mutation or a deletion of the NF1gene located at 17q11.2. Affected individuals are at a higher risk for pheochromocytoma and paraganglioma. Its prevalence in patients with hypertension is 0.2-0.6 % but can reach 5.7% in patients with NF1 [1,2]. Recent literature suggests screening for pheochromocytoma (Pheo) in patients with NF1 who develops hypertension or any symptom suggestive of pheochromocytoma and paraganglioma, due to its morbidity and mortality when undiagnosed or when the diagnosis is delayed [3].

We present a case with neurofibromatosis type 1 with an adrenal incidentaloma which turned to be a Pheo after biological investigations and imaging and we remind the benefit of earlier identification.

CASE REPORT

A 46 year-old male presented a progressive asthenia and weight loss (9kg weight loss in 4 years) neglected by the patient with a history of gastrointestinal haemorrhage twelve years ago. He was initially admitted in general surgery department for treatment of his bilio-enteric fistula secondary to a duodenal ulcer. An assessed CT-scan showed two well-defined right adrenal masses measuring each 128x87x86 mm and 60x52x37 mm with central necrosis and calcifications in the biggest one. It suppresses the right kidney and fill in the vertebral foramens D12-L1 and L1-L2 without osteolyses. The magnetic resonance imaging(MRI) showed the same well-defined heterogeneous masses with intense enhancement without spread to adjacent organs (Fig. 1).

So he was referred to our department to explore these masses.

His family history was pertinent for NF1 in his two sisters and two nephews.

He quit smoking for twenty years and he denied any medication, alcohol or drug use. He mentioned headache, palpitations, and sweating for four years without hypertension. His weight was 51 kg height 1,72 meters, body mass index was at 17,23 kg/m^2.

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Vital signs were normal, blood pressure was 120/80 mmHg and hypertension was excluded after assessing a normal 24 hours-blood-pressure monitoring. Palpation of the thyroid gland did not find any nodule or abnormality. Physical exam found multiple café-au-lait macules, axillary inguinal and many cutaneous neurofibromas mostly in the trunk (Fig. 2).

A left-eye-redness was noticed and the presence of Lisch nodule in the left eye was confirmed after ophthalmological examination. No Skeletal abnormalities were noticed. X-ray on tibia and radius were normal. In initial pulmonary CT-scan, centrilobular and paraseptal emphysema, fibrosis and peripheral-apex micro nodules were noticed. Another CT-scan was assessed showed the same bilateral parenchymal lesions mainly in the apex evoking bronchiolitis.

A biochemical tests initiated for his adrenal incidentaloma showed increases in both norephrine 6.3 nmol/l (normal <0.92 nmol/l) and epinephrine 3.15(<1.29 nmol/l). Aldosterone was at 191.15 pg/ml and renin at 85.54 pg/ml suggestive of a secondary hyperaldosteronsim. Bedtime serum cortisol was abnormal and cortisol after 1mg dexamethasone suppressive test was 12.7ng/ml.

11-desoxycortisol and 11-desoxycorticosterone were normal 0.6(0.2-1.1ng/ml) and 114(40-170 pg/ml) respectively.

Pheochromocytoma was highly suspected and functional imaging by ^{131}I-metaiodobenzylguanidine showed only an intense uptake on the right side of the abdomen in the level of L1 super-imposed on the right adrenal gland in the CT. Adrenalectomy was indicated but the patient refused the surgery.

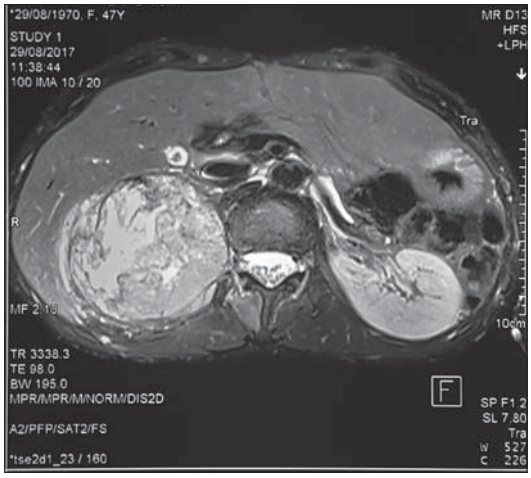

Figure 1: MRI showing the right adrenal masses.

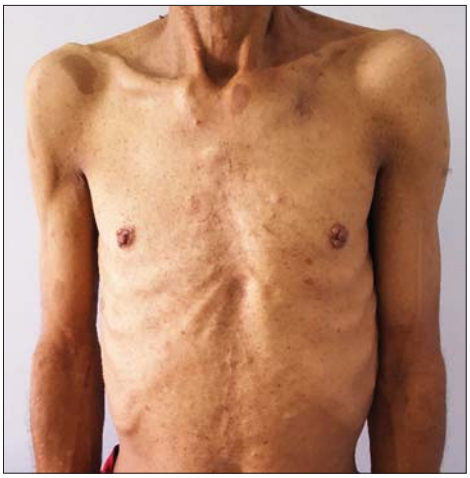

Figure 2: Cutaneous neurofibroma and café-au-lait patches of the trunk.

DISCUSSION

NF1 is a common autosomal dominant disorder due to mutation or a deletion of the NF1 gene, a tumour suppressor gene located at 17q11.2 which codes for neurofibromin that is a GTPase-activating protein involved in the inhibition of renin-angotensin system. Neurofibromatosis can be diagnosed if two or more criteria are found according to National Institute of Health which are [4]:

1. Six or more cafe au lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals.
2. Two or more cutaneous/subcutaneous neurofibromas of any type or one plexiform neurofibroma.
3. Freckling in the axillary or inguinal regions.
4. Optic pathway glioma.
5. Two or more Lisch nodules (iris hamartomas seen on slit lamp examination).
6. Bone dysplasia such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis.
7. A first-degree relative (parent, sibling, or offspring) with NF-1.

In our case 5 criteria were fulfilled. The differential diagnoses of NF1 include other forms of neurofibromatosis. One or two café-au-lait patches occur in 10% of the general population(5). And the lack of other criteria should suggest a follow up in a specialised center because it might be a mosaic form of NF1 or neurofibromatosis type2. In neurofibromatosis type2 café-au-lait patches are less numerous and

shwannomas occurs in vestibular, spinal cranial or peripheral nerves. Subcutaneous schwannomas can be confused with neurofibromas and biopsy can be necessary in some cases to distinguish neurofibromas from lipomas and schwannomas [5].

Neurofibromas can be cutaneous or subcutaneous, their number and size can increase in the adolescence or adulthood and can reach even thousands. When it impairs function or affect self-image, surgery is recommended. Spinal neurofibroma may develop in any level of the spinal cord and can compromise its function in addition of the risk of malignant transformation into malignant peripheral nerve sheath tumours (8-13%) [5,6]. Batista et al. [6] proposed an algorithm for treatment of neurofibroma. This cancer has bad prognosis and that's why patients affected with NF1 should be educated about unusual symptoms or those suggesting those complications. It seems to be more important than the periodic medical examination [7].

Pulmonary complications are often associated with NF1 and has been reported in few series. The prevalence of parenchymal lung disease in patients with NF1 was 7 to 23% [8,9]. Several manifestations were described in the literature such as interstitial fibrosis, obstructive neurofibromas, infiltrative lesions, cysts, bubbles (50%), emphysema (25%) or bibasilar reticulations (50%) [10]. Even pulmonary hypertension has been described which can be due to parenchymal lesions or the involvement of pulmonary arteries. CT-scan shows Emphysema, scattered cystic spaces, peripheral ground-glass and reticular densities, ground-glass opacities [11]. Emphysema and interstitial fibrosis are two different disorders, their association can occur more importantly in smoking-patients[10], even though it remains controversial in some studies [9]. Our patient was a tobacco user had no symptoms and his thoracic CT-scan showed a bilateral-upper-paraseptal emphysema, peripheral nodules suggestive of bronchiolitis with reticular densities and linear fibrosis.

As for gastro-intestinal manifestations, described in 25% of patients with NF1 [14,15], they can be the first manifestation of the disease. The clinical, radiographic and histological findings are not specific to NF1. The most common symptoms are diarrhoea or constipation, abdominal pain, intestinal obstruction and palpable abdominal masses but also dyspepsia and haemorrhage who can be related to intestinal neurofibroma. Gastro-intestinal tumours were found in one-third of autopsy series of patients with NF1 [16]. Gastrointestinal stromal tumours are the most common mesenchymal tumours of the gastrointestinal system [5]. The manifestations can be only anaemia and bleeding. Our patient presented a gastro-intestinal bleeding with anaemia but no images suggestive of intestinal tumours were seen in the CT.

The prevalence of Pheo in patients with NF1 is more important in patients with hypertension in general population, 1.0%–5.7% versus 0.2-0.6% and even higher rates are in those with NF1 and hypertension at 20%–50% [1,9-22]. Two prospective studies showed higher prevalence of Pheo in which patients with NF1 were screened for Pheo (7.7% [3] and 14.6% [22]). It can be explained by the fact that routine screening for PPGLS is not recommended by the guidelines in normotensive or asymptomatic patients [20].

Pheo in NF-1 can be entirely asymptomatic suggesting that its true prevalence is unknown but clinicians should not ignore the possibility of the presence of Pheo in the lack of hypertension. The commonest clinical signs besides the hypertension includes, palpitations, headache, dizziness or sweating were found in more than half patients in Gruber et al. study [20]. NF1 patients should undergo screening for this affections especially when associated with catecholamine-symptoms or hypertension [25]. The mean age at the moment of diagnosis was reported between the age of fourty and fifty in some studies [19,20].

In patients with NF1, Pheo usually produces epinephrine and norepinephrine [21,23,24]. The best diagnostic test is serum metanephrines and diagnosis is established if plasma metanephrines are increased [9,21]. Our patient, aged 46, presented paroxysmal symptoms such as palpitations, wetting and headache without hypertension and the biochemical assessment confirmed the catecholamine secretion of epinephrine and norepinephrine.

An adrenal mass can be discovered accidentally in patients with NF1, and must be evaluated to exclude Pheo. Those masses can be mistaken for non-functional gonglioneuroma or a gastrointestinal mass in CT-scan and biopsy could be fatal [25]. In most cases it is unilateral intra-adrenal mass, bilateral or multifocal in 10% to 15% of patients [21,23] and can be also extra-adrenal in 0-6% [23].

Malignancy occurs in 3 to 12 % [20, 25]. Myrick et al. reported that the size of adrenal tumours in NF1 patients

is almost half the size of patients non-NF1 [28]. But our patient had huge masses similar to non-NF1 patients.

Treatment in patients with Peo associated with NF1 seems to be similar in patients without NF1 [28]. Surgical removal is the effective treatment [21].

Currently, studies did not establish a genetic-clinical association between NF1 and Pheo due to the variability of the expression of this disease, the large size of the gene, the lack of hot spots and the high rate of de novo mutations [19,25]. But some studies reported that loss of heterozygosity was observed in Pheo associated with NF1 and it seems to be that Pheo is considered as a true component of NF1 [26].

CONCLUSION

To summarize, annual examination and screening for NF1 in adulthood include blood pressure measurement, ophthalmological exam, physical exam for the skin and the skeleton and other tests or imaging according to the symptoms reported by the patients. Screening for PPGLs is recommended for symptomatic or hypertensive patients but others support a routine screening regardless of the age or the symptoms [20]. This affection can be potentially malignant [17] and increase the morbidity and mortality secondary to catecholamine secretion when the diagnosis is delayed. Special health care and education should be provided to those patients.

Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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