

Type 1 neurofibromatosis and pheochromocytoma: Focus on hypertension

Sir,

Neurofibromatosis 1 (NF1) or von Recklinghausen disease, is an autosomal condition caused by heterozygous mutations of the NF1 gene. This genetic disorder occurs in approximately 1 of every 3,000 live births. Clinically, the disease presents with café-au-lait spots, freckles near the axilla and groin, and benign tumors of the peripheral nerve sheath, that are called neurofibromas. Lisch nodules, represented by small hamartomas of the iris, are also often present. Moreover, patients affected by NF1 frequently present learning disabilities and may develop skeletal abnormalities, vascular disease, central nervous system tumors, or malignant peripheral nerve sheath tumors.^[1,2]

It is an autosomal dominant disorder; anyhow 50% of the cases are sporadic. NF1 infact is caused by a mutation of the NF1 gene, that has been mapped on chromosome 17. The gene encodes for a protein called neurofibromin, which is involved in the inhibition of cell proliferation processes.

NF1 is characterized by a wide clinical variability, also in the same patient at different times in life. Many people with NF1 have only mild manifestations of the disease, such as pigmentary lesions, Lisch nodules, or learning disabilities; however elder patients have got an higher probability of more serious complications.^[1-3]

The average life expectancy of these individuals is reduced by about 15 years. Malignant peripheral nerve sheath tumors and vascular diseases represent the most frequent causes of early death in people affected by NF1.^[4]

The criteria mentioned in a National Institutes of Health (NIH) Consensus Conference document developed in

1987 are still widely used in the routine clinical practice. These criteria are satisfied when a patient presents two or more of the following features, in the absence of another diagnosis:

- Six or more café-au-lait spots >5mm in the greatest diameter in the prepubertals, and >15 mm in the postpubertals;
- Two or more neurofibromas of any type or one plexiform neurofibroma;
- Freckling in the axillary or the inguinal regions;
- Optic glioma;
- Two or more Lisch nodules;
- A typical osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis; or
- A first degree relative affected by NF1 as defined above. These criteria are usually recognized as highly specific and sensitive in adults, but sometimes diagnosis may be more problematical.^[5]

Concerning NF1 induced vasculopathy, it's worthwhile to stress that the prevalence of hypertension is higher in NF1 patients towards general population and this can develop at any age. Hypertension may be caused by renal artery stenosis, coarctation of the aorta and by pheochromocytoma^[6] or it may be "essential".^[3]

Pheochromocytoma is a catecholamine secreting tumour arising from chromaffin cells of the adrenal gland and represents a rare cause of secondary hypertension. In the 85-90% of cases it is located in the adrenal medullary, while 10% derives from sympathetic ganglia and paraganglia, being so called paraganglioma. The most typical extra-glandular location are Zuckerkandl's organs which are located between aortic bifurcation and lower mesenteric artery. The main secretion products of pheochromocytoma are catecholamines (noradrenaline, adrenaline, dopamine); signs and symptoms are therefore due to the direct catecholamines action. Arterial hypertension, tachycardia, pallor, headache, panic attacks represent the principal clinical manifestations. Moreover, catecholamines may exert direct and indirect effects on glucose metabolism causing hyperglycaemia, lactic acidosis and weight loss. Hypertension is often paroxysmal and may be so severe to cause hypertensive emergencies. Indeed, pheochromocytoma diagnosis is important, since hypertension is reversible following tumor resection.^[3,4]

In 1910, Suzuki for the first time described the association between pheochromocytoma and type I neurofibromatosis.^[7] Pheochromocytoma and ganglia neuroblasts arise from a common precursor deriving from the primitive neuroectoderm or the neural crest. Type I neurofibromatosis is also a displastic disease of

the neuroectoderm. Therefore an association between neurofibromatosis type I and pheochromocytoma has been described, even though its incidence is very low. Pheochromocytoma presentation and clinical course are similar to those of the isolated disease.^[8]

Furthermore, the presence of arterial hypertension has been described in the 1.5-2.5% of the patients suffering from neurofibromatosis type I; however, from a careful evaluation of the literature, pheochromocytoma is diagnosed only in 20-50 % of the cases of hypertension which happened in type I neurofibromatosis.^[9]

Particularly, the importance of a careful and accurate evaluation of the patient suffering from neurofibromatosis and hypertension must be underlined, although it is a rare association. Therapy will infact consist of adrenal mass resection, with complete recovery.

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