

## Renal vascular hypertension and neurofibromatosis type 1

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### ■ ABSTRACT

Arterial hypertension (HTN) in paediatric patients with type 1 neurofibromatosis (NF1) is usually secondary to stenosis of the renal artery involving the more proximal segments.

The authors present the case of a 9 year-old female patient with NF1. At 3 years of age she was found to have stage 2 HTN blood pressure (BP) 170/95 mmHg; percentile (P) > 99 for age, gender and height). An aetiological study carried out at that time led to a diagnosis of renal vascular hypertension and the exclusion of other secondary causes in the context of NF1. A renal arteriogram revealed multiple stenoses of the aorta and the large vessels: the left renal artery, right renal artery and superior mesenteric artery. A transluminal dilatation of the aorta and the right renal artery was performed, with improved BP control.

The patient left Paediatric Nephrology routine follow-up and was admitted three years later with stage 2 HTN (170/92 mmHg (P > 99)). The angio-MRI and renal arteriogram revealed a worsening of the abdominal aorta stenosis, near total obstruction of the right superior polar artery and an anomalous ascending vascular structure irrigating the left kidney, without indication for surgery. The patient is currently being treated with multiple antihypertensive drugs and her ambulatory BP levels have been in the range of 149-107/70-49 mmHg.

The authors highlight the difficulty of controlling the patient's BP and the severity of the vascular lesions present in this clinical case, which are quite rare in this age group.

### Key-Words:

Renal vascular hypertension; neurofibromatosis type 1; vasculopathy.

### ■ INTRODUCTION

NF1, or von Recklinghausen's disease, is an autosomal dominant genetic disorder that occurs in about 1 out of every 3500 newborns<sup>1,2</sup>. Approximately half of the cases are familial, while the rest are the result of spontaneous mutations. For reasons not entirely understood, these mutations most often occur in the paternal chromosomes<sup>3,4</sup>. While penetration of the mutation is complete, expression of the disease is, however, variable (severity varies between individuals of the same family and between families).

The NF1 gene, located on chromosome 17 [17q11.2], codifies a protein, a neurofibromin (*GTPase-activating protein*) which shows ubiquitous distribution, most notably in the brain, kidney, spleen, thymus and blood vessels<sup>5,6</sup>. Mutations in this protein result in dysplasia of tissues of the mesoderm and neuroectoderm, leading to the various manifestations of the disease<sup>7</sup>, of which multiple *café-au-lait* spots and cutaneous neurofibromas are characteristic. To make a diagnosis of NF1, a minimum of 2 out of the 7 diagnostic criteria established by the *National Institute of Health (NIH) Consensus Conference* in 1987 and later revised in 1997 (Table I) must be met.

NF1 can be associated with several types of vascular dysplasia<sup>7</sup>. This vasculopathy is a significant

**Table 1**

Diagnostic table for NF1 established by the NIH Consensus Conference in 1987 and revised in 1997.

Six or more <i>café au lait</i> spots, measuring greater than 0.5 cm in diameter in prepubescent individuals and measuring greater than 1.5 cm in individuals post puberty.
Two or more neurofibromas or one plexiform neurofibroma
Freckles in the axillary or inguinal areas
Optic glioma
Two or more Lisch nodules (hamartomas) in the iris
Characteristic bone lesions (such as fusion of the radius and the cubitus or pseudoarthritis)
First degree relative with NF1

factor in co-morbidity, considered by some authors to be underestimated<sup>5</sup> and which contributes to the high mortality rate among younger patients<sup>8</sup>. While any vascular segment may be affected, the renal arteries, the aorta, and the cerebral and mesenteric arteries are the vessels most affected<sup>7</sup>. Clinical manifestations include stenosis of the renal arteries, vascular occlusions that result in visceral or cerebral infarctions, aneurysms of the small arteries and spontaneous rupture of the large arteries<sup>5</sup>.

HTN, essential or secondary, is a fairly frequent complication of NF1, with its prevalence reported as being somewhere between 2-15.8%<sup>1,5</sup>. In the majority of paediatric population cases it is caused by stenosis of the renal artery<sup>5,7</sup> or, more rarely, by pheochromocytoma or aortic coarctation.

## ■ CASE REPORT

The patient is a 9 year-old Caucasian female who was diagnosed with NF1 at the age of 9 months. She had 12 *café-au-lait* spots greater than 5mm in diameter. A family history of NF1 was known in her father, grandfather and paternal uncles. The patient's past medical history included mild stenosis of the pulmonary valve diagnosed at the age of one month.

No significant events occurred until the patient was 3 years old. During a routine check-up stage 2 HTN was detected (BP of 170/95 mmHg, P > 99).

Physical exam at admission revealed several *café-au-lait* spots on the patient's trunk and extremities as well as grade 1 hypertensive retinopathy. BP was

checked with a suitable cuff, which confirmed values above the 99<sup>th</sup> percentile (right arm 184/96 mmHg, left arm 172/96 mmHg, right leg 173/108 mmHg, left leg 172/112 mmHg). The rest of the examination was normal, including the cardiovascular, pulmonary, neurological and abdominal assessments. Height-weight development was in the 50<sup>th</sup> percentile and psychomotor development appropriate for age.

Haemogram, differential leucocyte count, plasma chemistry (including creatinine, sodium and potassium) and urinalysis data were within the normal range. Chest X-ray revealed a cardiothoracic index at the upper limit of normal, the electrocardiogram met the criteria for hypertrophy of the left ventricle and an echocardiogram showed concentric left ventricular hypertrophy.

Levels of serum cortisol and ACTH as well as levels of vanilmandelic acid and metanephrines in the 24-hour urine collection were normal. Plasma rennin

**Figure 1**

Renal arteriogram shows multiple stenoses of the aorta and large vessels: the superior mesenteric artery and renal arteries, with nearly complete occlusion on the left.

activity, determined by radioimmunoassay (RIA), was elevated (118 pg/ml) at 3 times the normal limit for our institution (3-33 pg/ml). A renal pelvic ultrasound was performed, which showed asymmetry in the size of the kidneys (right kidney 9.1cm; left kidney 8.2cm, both longitudinal diameters), with no adrenal mass. The Doppler study of the renal arteries was inconclusive. A captopril 99mTc-DTPA scintigraphic study showed a marked delay in intraparenchymatous transit on the left side, compatible with left renal artery

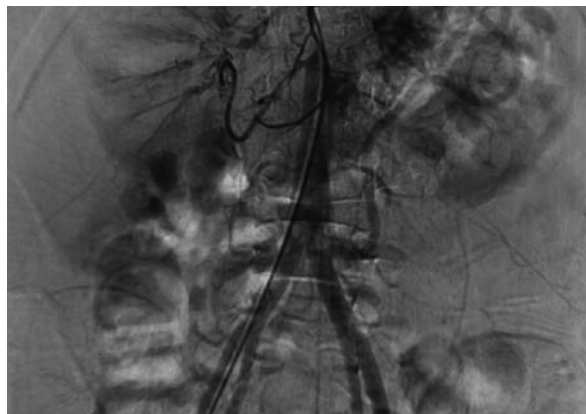
stenosis. Renal arteriogram showed multiple stenosis of the aorta and the large vessels: left renal artery (nearly total), right renal artery and superior mesenteric artery. (Fig. 1).

At the time of admission, the patient started on oral nifedipine (0.5 mg/kg/day), and other antihypertensives were gradually introduced in increasing doses up to the maximum doses for the patient's weight, namely, furosemide 3 mg/kg/day, atenolol 2 mg/kg/day, clonidine 0.2 mg/day and nifedipine was later changed to the retard formulation (1mg/ /kg/day). Reasonable control of BP was achieved (Systolic BP at the 99<sup>th</sup> percentile (P99) and diastolic BP below P99).

Transluminal dilatation of the aorta and the left renal artery was performed, with subsequent improvement in BP control, making it possible to decrease the antihypertensive drugs from four to two. The patient was then discharged. Three years later, the patient was admitted once again, after being referred by her GP due to poor BP control. Her medications at that time were nifedipine (retard formulation; 0.5 mg/kg/day) and atenolol (2 mg/kg/day). BP was 170/92 mmHg (P > 99) and, with the exception of several *café-au-lait* spots, the physical exam was normal and there were no related symptoms. Repeat laboratory tests, including renal function, electrolytes, urinalysis and urine protein/creatinine ratio, were once again within the normal range.

Combination therapy was tried in an attempt to control the patient's BP, with minoxidil (0.2 mg/kg/day) and furosemide (2 mg/kg/day) being added, sequentially, to the previous treatment regimen. As there was no improvement with these treatments, an enzyme conversion inhibitor (enalapril) was started at low doses. The patient developed acute renal failure (maximum plasma creatinine 1.5 mg/dl), which was rapidly reversed once the enalapril was discontinued.

A renal angio-MRI was performed, which showed marked irregular stenosis of the proximal portion of the abdominal aorta, with high grade partial stenosis of the celiac trunk and the superior mesenteric artery and probable complete obstruction of both renal arteries (blood flow appearing to be maintained through collaterals). A new renal arteriogram was performed, which showed that the abdominal aortic stenosis had worsened between the celiac trunk and the right renal polar artery, which had been treat-



**Figure 2**

Renal arteriogram shows a worsening of the abdominal aortic stenosis and nearly complete obstruction of the right superior renal polar artery. An anomalous ascending vascular structure is irrigating the left kidney.

ed by angioplasty (the inferior polar artery showed normal permeability) and the left kidney was being irrigated by an anomalous ascending vascular structure. (Fig. 2).

A thrombotic tendency study was performed, including Factor V Leiden assay, to screen for the presence of a mutation in the methyltetrahydrofolate reductase gene - MTHFR, antithrombin III, protein C and protein S levels; screening for activated protein C resistance, lupus anticoagulant, antiphospholipid antibodies and  $\beta$ 2-glycoprotein I; homocysteine and lipoprotein levels and a lipid panel. All these tests came back negative.

The patient is currently followed in the outpatient nephrology clinic and is asymptomatic, with ambulatory BP in the range of 149-107/70-49 mmHg, under treatment with multiple antihypertensives (nifedipine retard 40 mg/day, atenolol 50 mg/day, clonidine 0.15 mg/day, minoxidil 6mg/day and furosemide 40 mg/day).

## ■ DISCUSSION

Arterial hypertension associated to NF1 among the paediatric population is usually secondary to renal artery stenosis, which generally involves the ostium or the most proximal segment to the vessel and in 25% of the cases is associated to aortic coarctation<sup>7,9</sup>.

Greene *et al*, 1974, describe two types of stenosis. One involves primarily the large vessels (aorta, carotid and proximal segments of the renal arteries), which become embraced by ganglioneurofibromas, in which the consequent proliferation of the intima, thickening of the media and fragmentation of the internal elastica can lead to stenosis and aneurism. The second type affects the smaller vessels. This type is not directly related to neurofibromas and it reflects a vascular dysplastic process. Histologically, the authors have identified clusters of smooth muscle cells and concluded that it was a dysplasia of the mesoderm<sup>9,10</sup>.

Several authors<sup>8</sup> have speculated on this dysplasia pathogeny, with reference made to some mechanisms of Schwann (Sayer) cells proliferation or smooth muscle cells, changes in the regular vascular histogenesis secondary to a dysfunctional protein, or changes in the normal process of vascular maintenance and reparation.

This case report, the aetiology of the arterial hypertension, which is thought to be renovascular, corresponded to the main cause of HTN associated to NF1 for this age group. In terms of diagnosis, renal arteriography remains the diagnostic test of choice and it should be performed in patients strongly suspected to be suffering from renovascular disease. The initial screening tests, Doppler ultrasonography, captopril scintigraphy, angio-CT or renal angio-MRI, should be selected according to the patient's profile and to the availability and reliability of each technique in the place where the tests are performed.

In this case report, the asymmetry of the renal dimensions and the high rennin dosage suggested an HTN of renovascular aetiology or intraparenchymatous, confirmed by the captopril scintigraphy and later by the arteriography. The latter plays a role in diagnosis and also allows therapeutic intervention. On a second evaluation the first choice test was the angio-MRI, which is less invasive.

The diffuse and progressive character of the vasculopathy of NF1 is strongly present in this case report: among the vascular territory analysed (chest-abdominal) multiple stenosis of the aorta and its main vessels (left renal artery, right renal artery, and superior mesenteric artery) were evident. These multiple stenosis developed strongly over a 3-year period:

severe worsening of the abdominal aorta stenosis between the celiac trunk and the polar renal, almost total obstruction of the superior right polar renal artery, which had undergone angioplasty and left kidney irrigated by an anomalous ascendant vascular structure.

The therapeutic approach to renovascular disease in these patients is complex. It is made out of the association of drug therapeutic with revascularisation techniques, such as percutaneous transluminal angioplasty (PTA) and surgery (vascular reconstruction, embolisation, renal autotransplant and partial or total nephrectomy)<sup>9</sup>.

PTA is a less invasive technique than surgery, involves less hospitalisation time and can be repeated if necessary. However, the vascular lesions have a weak response to angioplasty, probably due to the fibrous tissue resistance to dilatation, and also due to the diffuse character of the vasculopathy. Vascular lesions also tend to reappear sooner than expected. Ostial lesions have even worst results. However, despite the limited success, most authors defend that this technique should be the first choice approach in primary stenotic lesions, as well as in the recurrent ones, leaving surgical vascularisation for more complex cases or cases where no practical results are seen after PTA<sup>9</sup>.

In this patient, transluminal dilatation of the left renal artery stenosis led to improved blood pressure control allowing a reduction in the number of anti-hypertensive drugs, although this effect proved to be temporary. On admission three years later, the extent of the lesions (stenosis of the abdominal aorta between the celiac trunk and the renal polar artery and stenosis of both renal arteries) did not allow a repetition of the angioplasty. No other revascularisation technique has been undertaken to date.

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