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Renovascular disease and hypertension in children with neurofibromatosis

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Abstract Neurofibromatosis type 1 (NF1) is associated with vascular lesions, such as renal artery stenosis, and secondary hypertension. The real prevalence is largely unknown, particularly in children. We observed 27 patients with NF1, mean age 12.8 years (range 4.2–24 years), for 2–10 years to assess the association of NF1 with vascular abnormalities and secondary hypertension. Patients were studied with angiography, 24-h blood pressure monitoring, a captopril test, and Doppler ultrasonography of aorta and renal arteries. The prevalence of hypertension was 18.5%; 61.5% of patients studied with angiography had vascular lesions, half of whom were apparently normotensive. However, they had abnormal 24-h blood pressure monitoring, which was a first sign of poor blood pressure control. Those patients with severe hypertension (11.1%) were successfully treated with percutaneous transluminal angioplasty (PTA); stenosis recurred in 2 of 3 patients after a 2-year follow-up period, and was responsive to drugs. We conclude that hypertension is a frequent complication of NF1 in pediatric patients, it is usually secondary to typical vascular lesions, and requires careful follow-up. Ambulatory blood pressure monitoring (24-h) is a sensitive method for detecting initial alterations of the blood pressure pattern. PTA may be an effective treatment in this condition.

Key words Hypertension · Renal artery stenosis · Percutaneous transluminal angioplasty · Neurofibromatosis type 1 · Ambulatory blood pressure monitoring

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Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with an incidence of approximately 1:3,000 [1, 2]. This disorder is characterized by various clinical manifestations as a result of dysplasia of neuroectodermal and mesodermal tissues. Café-au-lait spots, cutaneous neurofibromas, and tumors of the central and peripheral nervous system, as well as other systems may be involved. NF1 may be associated with various vascular dysplasias [3–7]: vascular changes may affect vessels of all calibers, but they are most common in the renal arteries, aorta, mesenteric and cerebral arteries [2].

Secondary hypertension may develop in NF1 as a result of pheochromocytoma; while it is a common etiology in adult patients, in pediatric patients elevated blood pressure is usually due to renal artery stenosis [8–11], generally involving the origin or the proximal tract of the vessel [3, 5, 6], and is associated in 25% of patients with coarctation of the abdominal aorta [5]. Several patients with NF1 and hypertension have been reported in the literature, showing the extreme variability in anatomical lesions [4, 6], in clinical features, and in the different opinions concerning diagnostic procedures and management [3–5, 9, 12–15].

Studies have examined pediatric patients with hypertension secondary to renovascular disease. The prevalence of NF1 in this group ranged between 11% and 26% [16–19], but the real incidence of secondary hypertension in patients with NF1 and its incidence in different age groups is unclear.

Treatment of secondary hypertension involves antihypertensive drugs, percutaneous transluminal angioplasty (PTA), or surgical reconstruction of the stenotic arterial tract if needed [17–18, 20–22]. However, several studies have reported poor efficacy of PTA in NF1 [13, 19, 22, 23].

The aim of this study was to assess the association of NF1 with vascular abnormalities and secondary hypertension, to examine the efficacy of PTA, and provide indications for diagnosis of hypertension in these patients. We describe a group of children and adolescents with NF1.

Patients and methods

We studied 27 patients with a diagnosis of NF1, 11 males and 16 females, aged 4.2–24 years (mean age 12.8 years), who were followed for 2–10 years by at least annual ambulatory controls (at the pediatric hospital "Clinica De Marchi", University of Milan, Italy). All patients were Caucasian. Eleven patients had familial NF1, and 3 patients had a family history of essential hypertension; there was no preferential distribution of these patients in the different groups.

Patients underwent basal blood pressure measurements, renal function assessment, venous digital subtraction angiography, Doppler ultrasonography of renal artery, 24-h blood pressure monitoring, captopril test, eye examination (fundus oculi), and echocardiography.

We studied 13 patients with venous digital subtraction angiography. The other 14 patients did not undergo angiography, either because they did not agree to the procedure or because of a lack of clinical indications. Aortography with selective catheterization of the renal arteries was performed only in patients with pathological venous digital subtraction angiography or overt hypertension (3 patients), in order to utilize PTA if stenosis was confirmed.

Venous digital subtraction angiography was performed using a Philips V2 digital unit, equipped with an isocentric rotating arc and a high-resolution matrix television display (512×512 pixels). A non-ionic low-osmolality contrast medium (LRAVIST 370, Shering, Berlin or IOPAMIRO 370, Bracco, Milan) was injected into a vein, as bolus of 2 mg/kg, followed by 20 ml of 0.9% saline solution [16]. Aortography, selective catheterization of the renal arteries, and any supernumeraries were performed using pigtail and Cobra 1-, 4-, or 5-F preformed catheters (Cordis Europa, The Netherlands). The angiographic guide wires were hydrophilic (M. Radifocus, Engled Type, Terumo, Tokyo, Japan). The flushes and checks with a non-ionic low-osmolality contrast medium (LOCM, ioxaglate) were performed using a closed-circuit system (two-port disposable manifold, Cordis). The saline used for flushing the catheters was heparinized (2,000 units/250 ml). The necessary intestinal hypotonia was induced by an intravenous injection of 20–40 mg of *N*-butyl scopolamine hydrobromide (Buscopan, Boeringer Ingelheim-Italia, Regello, Italy). General anesthesia was used in patients 4–9 years of age, but the others were sedated with appropriate intravenous doses of diazepam (Valium-Roche Spa, Milan, Italy).

After selective renal angiography, the guide wire was advanced into a peripheral arterial branch. The diagnostic catheter was replaced with a dilating catheter with a 4.5-F shaft and a balloon of the caliber deemed appropriate for each patient (3–7 mm), which would permit a maximum inflation pressure of 10 atm (Usci Bard, Bilerica, Mass., USA). The balloon was inflated to working pressure for approximately 30 s using a 50% solution of saline and ioxaglate 320. The entire dilatation procedure was monitored fluoroscopically. Results were evaluated angiographically. Patients were admitted for dilatation treatment when therapy could not be postponed following a lack of response to common antihypertensive treatment. The case evaluation team included a pediatrician, a vascular surgeon, and an interventional radiologist. In all patients, renal PTA was performed during the same session.

Doppler ultrasonography was performed with the patient in the supine and lateral decubitus position, with a 3- or 5-MHz transducer, according to age. Blood flow distribution was studied by color Doppler ultrasonography; 24-h blood pressure monitoring was performed with Space Labs 90202-Tecno System (Milan). The captopril test was performed by collecting blood samples before administration of the drug and at 60 min. Arterial pressure was measured prior to the test and every 15 min thereafter. The dose of captopril administered was 12.5 mg in children aged less than 10 years and 25 mg in older children. A captopril test was considered positive according to diagnostic criteria proposed by Muller et al. [24], i.e., post-captopril plasma renin activity (PRA) >12 ng/ml per hour, absolute PRA increase >10 ng/ml per hour, and a 150% PRA increase or more, or 400% or more if the baseline PRA was <3 ng/ml per hour.

Results

We divided the patients into four groups on the basis of angiographic results and the presence of hypertension. We found no relevant difference in the distribution of age among the different groups of patients; in particular, the frequency of vascular alterations and the development of hypertension were not related to age. All patients had normal renal function, echocardiography, and ocular fundi. The results are shown in Table 1.

Group I (4 patients): vascular lesions and hypertension

Three patients in this group had symptomatic hypertension, and blood pressure remained consistently elevated despite antihypertensive medication. They underwent selective arteriography [in all cases the stenosis was revealed with venous digital subtraction angiography (Table 1)] and PTA. The immediate post-angioplasty aortogram did not show a complete resolution in every case. Despite the radiological findings, blood pressure returned rapidly to normal values, and antihypertensive therapy could be stopped. One patient maintained normal blood pressure values (with normal 24-h blood pressure monitoring and a normal captopril test) for the 9 years of follow-up, without other therapy. In the other 2 children, blood pressure remained under control without therapy for 2 years; antihypertensive medication was then required and proved effective. The fourth patient in this group developed borderline hypertension during follow-up; venous digital subtraction angiography showed narrowing of the abdominal tract and bilateral stenosis of the renal arteries (middle aortic syndrome).

Group II (4 patients): vascular lesions with normal basal blood pressure

This group comprised patients with vascular abnormalities without hypertension. They were asymptomatic, and basal blood pressure was normal. One child had narrowing of the aorta in the abdominal tract distal to the origin

Table 1 Pediatric patients with neurofibromatosis type 1 (*BP* blood pressure, *US* ultrasonography, *PTA* percutaneous transluminal angioplasty, *Hypert* hypertension, *BL* borderline hypertension, *mas* middle-aortic syndrome, *N* normal, *P* pathological, / not performed)

Group	Patient	Age	Sex	Basal BP	24-h BP monitoring	Captopril test	Venous digital subtraction angiography	Doppler US	Standard angiography and PTA
I	1	6.3	F	Hypert	P	P	Renal artery stenosis in mas	P	Yes, 2 years cured
	2	10.4	F	Hypert	P	P	Renal artery stenosis in mas	P	Yes, 2 years cured
	3	10	M	Hypert	P	P	Proximal renal artery stenosis	/	Yes, cured
	4	13.8	M	BL	/	P	Renal artery stenosis in mas	P	/
II	5	11.6	F	N	P	P	Renal artery stenosis	N	/
	6	15.8	F	N	/	P	Coarctation of abdominal aorta	/	/
	7	14.5	F	N	P	P	Ostial stenosis of renal artery	N	/
	8	15.8	F	N	P	N	Renal artery stenosis	N	/
III	9	11	M	N	N	N	N	N	/
	10	24	M	N	N	P	N	N	/
	11	13.3	M	N	N	N	N	N	/
	12	19.8	F	N	N	P	N	N	/
	13	11.4	F	N	N	N	N	N	/
IV	14	11.2	F	N	N	P	/	N	/
	15	22.7	F	BL	P	N	/	N	/
	16	6.5	M	N	N	N	/	/	/
	17	4.2	F	N	N	P	/	N	/
	18	19.6	F	N	N	N	/	N	/
	19	7.6	M	N	N	N	/	N	/
	20	8.7	M	N	P	P	/	/	/
	21	15.6	M	N	N	N	/	N	/
	22	10	F	N	/	N	/	N	/
	23	9	F	N	/	/	/	N	/
	24	5.7	F	N	/	/	/	N	/
	25	15	M	N	/	/	/	N	/
	26	11.1	F	N	N	N	/	N	/
	27	23	M	N	/	/	/	N	/

of the renal arteries. In the other patients venous digital angiography demonstrated renal artery stenosis with an ostium stenosis in 1 child. Three patients had a positive captopril test, with elevated basal PRA values. When performed (3 of 4 patients), 24-h blood pressure monitoring was abnormal, while color echodoppler results were normal (not in agreement with findings of venous digital subtraction angiography). Selective angiography was not performed because of blood pressure values and no indications for PTA.

Group III (5 patients): normal angiography and normal basal blood pressure

Patients in this group were normotensive, with normal angiographic findings; 24-h blood pressure monitoring was normal; 2 of these patients had a positive captopril test.

Group IV (14 patients)

Two patients in this group had abnormal 24-h blood pressure monitoring, and 1 had borderline basal blood pressure. We could not assess their vascular condition because they did not agree to the procedures and were lost to follow-up. Clinical data of the other patients who could not be studied with angiography are presented in Table 1.

Discussion

The prevalence of hypertension detectable by basal blood pressure measurement was 18.5% in this study. This is elevated compared with the prevalence of 1%–5% generally reported in young patients with NF1 [8], but it remains within the range observed in an Italian study of 57 children and adolescents with NF1 [6].

In our series, 8 of 13 (61.5%) young patients with NF1 had radiologically demonstrated renal vascular abnormalities; half of these developed severe or borderline hypertension (group I, Table 1). Some children (group II) with vascular lesions had normal basal blood pressure values, but those who underwent 24-h blood pressure monitoring showed abnormal values, particularly nocturnal values. These findings are similar to the results of other studies, which have demonstrated reduced circadian blood pressure fluctuations and a predominance of nocturnal hypertension in patients with renovascular lesions [25–27]. Initial vascular lesions are not sufficient to produce a stable elevation of blood pressure, but can be the cause of hypertensive events and alter the circadian blood pressure profile. The overall high incidence of alterations of blood pressure pattern (33.3%) may be related to the use of continuous 24-h blood pressure monitoring, which is likely to be a more-sensitive indicator of the initial signs of altered arterial pressure regulation in patients with vascular abnormalities.

However, Doppler ultrasonography was negative in patients apparently normotensive with vascular lesions

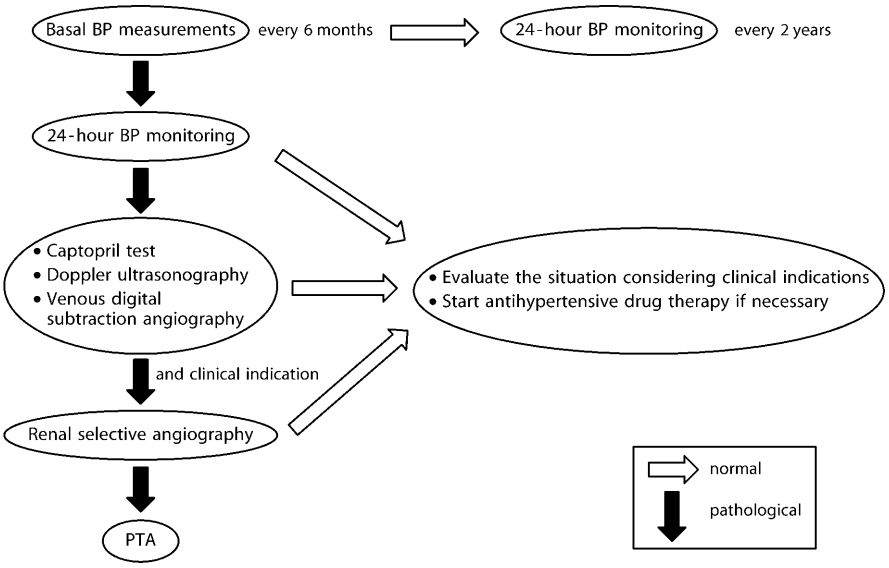

Fig. 1 Diagnostic algorithm for secondary hypertension in neurofibromatosis type 1 (*BP* blood pressure, *PTA* percutaneous transluminal angioplasty)

(group II). This is consistent with the fact that, despite a reported sensitivity of 84%–100% for renal artery stenosis [10, 22, 28, 29], this technique can diagnose stenotic lesions only when they are sufficient to cause hypertension [10, 30]. Doppler ultrasonography may be helpful in diagnosing the underlying presence of vascular abnormalities in patients with overt hypertension [10].

A captopril test may also be useful, even in children [31]. In our series the captopril test was positive in the majority of patients from group II. However, other patients with a positive captopril test are likely to be false positive, since blood pressure and radiological findings were normal (Table 1). The captopril test appears to have a good sensitivity, and a reasonable specificity, and may be used as an indicator of renovascular hypertension [21]. However, the diagnosis should always be confirmed by angiography. We suggest that venous digital subtraction angiography be employed initially, while selective standard contrast angiography could be reserved for a selected number of patients. A diagnostic algorithm is shown (Fig. 1).

The management of renovascular hypertension remains controversial. Antihypertensive drug therapy is generally used, and PTA or surgical treatment (reconstructive vascular surgery, embolization, autotransplantation, partial or total nephrectomy) if necessary and feasible [17, 18, 20, 22, 33]. It is generally accepted that NF lesions respond poorly to PTA, presumably because of the tough fibrotic tissue involved that is refractory to dilatation [13, 19, 22, 23]; poor results are sometimes obtained by PTA in middle-aortic syndrome and in ostial lesions [22, 32]. Nonetheless, some authors have used this method in NF1 [3, 5, 9, 15, 16], and encouraging results (67% success rate) or at least temporary benefits were obtained. Our results, in accordance with other reports, suggest the use of this technique in patients with NF1 and vascular lesions. The benefit obtained may be transitory and restenosis may occur, but in our patients hypertension after PTA was responsive to pharmacological treatment. None of the hypertensive patients in our study showed alterations of hypertension target organs. PTA in NF appears as a reasonable alternative to surgery (less invasive, lower cost, shorter hospital stay) and can be safely performed in children [16, 33]. Moreover, this treatment may be repeated if necessary. Surgical revascularization could be reserved for the more-complex cases, or those in which PTA fails or complications occur.

We conclude that vascular lesions and hypertension are frequent in young patients with NF1. Alterations in blood pressure pattern, moreover, may be present in a consistent percentage of patients who are apparently normotensive, as a first signal of vascular affection. It appears important to evaluate adequately blood pressure values and vascular status, in order to detect developing hypertension in this predisposing condition. The longitudinal follow-up of this group of patients will permit clarification of the evolution and prognosis of the vascular alterations.

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