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ORIGINAL ARTICLE

Giuliana Lama · Luisa Graziano · Elvira Calabrese · Carolina Grassia · Pier Francesco Rambaldi · Fabrizio Cioce · Michele Adolfo Tedesco · Giovanni Di Salvo · Maria Esposito-Salsano

Blood pressure and cardiovascular involvement in children with neurofibromatosis type1

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Abstract We evaluated blood pressure in a sample of patients with neurofibromatosis type 1 (NF1), using ambulatory blood pressure monitoring (ABPM), to determine whether ABPM, when compared with casual BP recordings, allowed the detection of a higher risk for hypertension. We also evaluated the correlation between BP and vascular abnormalities. We studied 69 NF1 patients (36 males and 33 females) with a mean age of 11±4 years, divided into group A, with 24-h mean systolic blood pressure (SBP) or diastolic blood pressure (DBP) <95th percentile, and group B, with mean SBP or DBP >95th percentile. Standard electrocardiography and M-mode, two-dimensional echocardiography were performed and all patients were in sinus rhythm. ABPM identified 11 hypertensive patients (16%); 5 had a mean SBP >95th percentile, 3 mean SBP–DBP >95th percentile, and 3 a mean DBP >95th percentile. Laboratory and other investigations to exclude secondary hypertension were normal. Cardiac abnormalities were found in 13 of the 69 patients (18.8%) with NF1. There were no significant clinical and cardiac differences between the normotensive and hypertensive group. Our data emphasize the importance of periodic ABPM in NF1 patients to diagnose hypertension early and avoid target organ damage and increased mortality.

Keywords Neurofibromatosis type 1 · Hypertension · Ambulatory blood pressure monitoring

G. Lama (✉) · L. Graziano · E. Calabrese · C. Grassia · M. Esposito-Salsano
Department of Pediatrics,
Second University of Naples,
Via L. De Crecchio 4, 80138 Naples, Italy
e-mail: giuliana.lama@unina2.it
Tel.: +39-81-5665457-58
Fax: +39-81-5665457

P. F. Rambaldi · F. Cioce
Institute of Nuclear Medicine/Radiological Science,
Second University of Naples,
Italy

M. A. Tedesco · G. Di Salvo
Department of Cardiothoracic and Respiratory Sciences,
Monaldi Hospital,
Second University of Naples,
Italy

Introduction

Neurofibromatosis type 1 (NF1) is a frequent autosomal dominant disorder with an incidence of 1 in 3,500 newborns and a prevalence of 1 in 4,500 [1, 2]. About 50% of cases are de novo mutations [3, 4]. NF1 has a broad array of clinical aspects as a result of a dysplasia of mesodermal and neuroectodermal tissues [5]. The NF1 gene is localized on 17q11.2 [6] and produces neurofibromin, a GPTase-activating protein that regulates cell proliferation by inhibiting ras activity [7]. Neurofibromin is a ubiquitous protein [8]. It is also detected in the smooth muscle layer of the aorta [9], and experimental studies indicate that in the absence of this protein mouse embryo hearts develop overabundant endocardial cushions due to hyperproliferation and lack of normal apoptosis [10]. Vascular pathology is an underestimated complication of NF1. Manifestations include renovascular stenosis with associated hypertension, cerebrovascular occlusion, visceral ischemia, aneurysms of smaller arteries, and spontaneous rupture of major arteries [11].

Hypertension is a relatively frequent (2%–15.8%) complication [1, 12]. Few studies have been performed on the incidence of hypertension in NF1 patients; the majority of authors have described only single cases [11, 13, 14]. In NF1 children hypertension is usually caused by renal artery stenosis, which can be intrinsic, arising from arterial dysplasia, or extrinsic, due to neurofibroma or other abdominal mass compression [15, 16]. Pheochromocytoma predominates in adults and occurs at a rate of 1% [7, 17].

Furthermore, office blood pressure (BP) readings are unreliable because of their variability and because the

small number of measurements may not necessarily reflect the habitual BP of an individual [18].

The use of repeated ambulatory blood pressure monitoring (ABPM) allows us to obtain more representative values of BP and to study the behavior of BP during activity and sleep [19, 20, 21, 22]. Studies have suggested the utility of ABPM in a variety of chronic disease, including diabetes mellitus, postoperative monitoring of surgical repair of coarctation of the aorta, and after kidney transplantation. Non-invasive 24-h BP monitoring is useful and reliable for identifying adolescents and children in whom single BP recordings, with manual and/or oscillometric devices, do not allow the detection of hypertension, especially during the resting period. It is accepted that 24-h ABPM is a necessary routine diagnostic test for children and adolescents with elevated BP.

No information is available about the prevalence of cardiovascular abnormalities in patients with NF1, because echocardiography has been performed in only a small percentage of the study population. Therefore, there is some disagreement about the validity of this technique for patients with NF1 [23].

The aim of this study was to determine, in patients with NF1, whether ABPM, compared with casual BP recordings, allowed the detection of a higher risk for hypertension. We also sought to evaluate the correlation between BP and vascular abnormalities.

Patients and methods

We studied 69 neurofibromatosis patients (36 males and 33 females) with a mean age of 11 years (range 5–25 years) (Table 1). The diagnosis of NF1 in all patients was made according to the guidelines of the 1987 NIH Consensus Statement Conference [24]. All patients were classified according to four levels of severity established by the Baylor program [25].

At the time of enrolment, informed consent was obtained from each child and/or parents. Each NF1 patient underwent a complete physical examination with BP measurement and a biochemical analysis. Serum creatinine (Cr) levels were measured by the Jaffé method and creatinine clearance (C_{Cr}) was calculated according to the formula of Schwartz et al. [26], using K values of 0.55 for all subjects other than males over 13 years, in whom a value of 0.70 was used. Microalbuminuria (Ma), on two 24-h urine samples, was measured by an enzyme immunoassay (normal range 2–20 mg/l). Plasma renin activity (PRA) was evaluated after a 1-h supine rest using a radioimmunoassay for the quantitative determination of PRA (Biochem Immuno System, Italia, normal range 75–150 ng/ml per hour). Before ABPM, we measured BP three times consecutively, using a mercury sphygmomanometer, after a sitting rest of at least 5 min. The cuff size complied with the criteria of the Task Force for Blood Pressure Control in Children [27]. For systolic BP (SBP) Korotkoff phase I was used; for diastolic BP (DBP) phase IV was used in children under 13 years and phase V in children above 13 years. The mean measurements were taken as the casual BP.

Table 1 Characteristics of patients with neurofibromatosis type 1 and controls (*BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure)[a]

	Patients	Controls	*P**
n	69	30	
Gender (M/F)	36/33	17/13	NS
Age (years)	11±4	11±3	NS
Age range (years)	5–25	5–23	NS
Weight (kg)	45±17	42±11	NS
Height (cm)	145±18	147±15	NS
BMI (kg/m^2)	20±4	19±2	NS
Casual SBP	107±7	98±10	<0.1
Casual DBP	73±10	69±7	<0.1
Heart rate (beats/min)	85±15	82±10	NS

*P=Student's t-test for paired/unpaired data: $P<0.05$ was considered statistically significant

[a] Values are expressed as means±SD

For ABPM we used a SpaceLabs model 90207 monitor (SpaceLabs, Redmond, Wash., USA) weighing 340 g (including batteries). This device employs an oscillometric method with a deflation rate of 8 mmHg/s. The proper cuff was selected from among three sizes supplied by the manufacturer (10×13, 13×24, and 24×32 cm), according to the arm length of the subject. The cuff wrapped completely around the non-dominant upper arm with the bladder covering at least two-thirds of it. A difference within 5–10 mmHg was accepted as accurate for both systolic and diastolic BP, when a comparison between the methods was made.

ABPM was performed on regular school days with normal recreational activities. No patients played sports or took medication during the study. Recording began between 8:30 a.m. and 9:00 a.m. The reading frequency was programmed for every 20 min from 8:00 a.m. to 10:00 p.m. (daytime) and every 60 min from 10:00 p.m. to 8:00 a.m. (night-time). We chose these time intervals because these periods corresponded closely to activity and sleep in the majority of the subjects. The mean time studied by ABPM was considered satisfactory for analysis if more than 20 h of data were obtained, with a minimum of 30 recordings during the day and with almost 10 measurements during the night-time. This was considered as the cut-off minimum for all patients studied.

When interference or error in the reading occurred, the process was automatically repeated after 2 min while retaining the pre-established sequence. During the daytime period, an acoustic signal before the measurement was automatically programmed to remind the children to relax their arms. Blood pressure measurements were rejected automatically, or after visual inspection, if SBP was >220 or <70 mmHg, DBP >140 or <40 mmHg, or a reading was higher than double the previous or subsequent reading.

ABPM with 85% or more likely readings was analyzed and recordings with erroneous measurements exceeding 30% were excluded from the analysis. As reference values for ABPM in 0- to 17-year-olds, we used data from a sample of 241 healthy Mediterranean children [28]. In contrast, we considered those 17 years or older as adults and we used ABPM reference values from the Pamela study [29]. For each subject the following parameters were calculated: mean SBP, DBP and SBP–DBP load, defined as the percentage of BP readings during a 24-h period that exceeded the age- and sex-specific 95th percentile. The acceptance of diagnostic procedures was determined using a visual analogue scale with a 10-cm line ranging from "very annoying" on the left to "not annoying at all" on the right [30]. Patients with a mean SBP and/or DBP above the age- and sex-specific 95th percentile underwent a second ABPM within 10 days.

We considered hypertensive patients as those who showed two sessions of ABPM with 24-h mean SBP and/or 24-h mean DBP above the age- and sex-specific 95th percentile. Normal dipping was defined as a fall in the mean systolic and diastolic BP during the night-time of 10% or more of the corresponding mean daytime BP. We then divided the patients into group A, with 24-h SBP or DBP <95th percentile, and group B, with mean SBP or DBP >95th percentile.

In all children, standard echocardiograms and electrocardiograms were performed, and all showed sinus rhythm. In hypertensive patients we performed more-specific investigations to exclude secondary hypertension (Table 2). 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

Table 2 Investigation protocol for hypertension in patients with neurofibromatosis type 1 (*VMA* vanillylmandelic acid, *CT* computed tomography, *NMR* nuclear magnetic resonance, *PRA* plasma renin activity, *ACE* angiotensin converting enzyme)

Suspected pheochromocytoma
Urinary VMA or metanephrine
Urinary catecholamines
Meta-I-benzilguanidine nucleotide scan
Abdominal CT scan or NMR
Suspected renovascular hypertension
PRA and aldosterone
ACE inhibitor challenge test
Echo-color Doppler flow of the renal arteries
Tc-DTPA renal scan

flow distribution was studied by color Doppler ultrasonography. During the performance we found no aortic or renal arterial thrombus or increased blood flow velocity through the renal artery. Therefore, patients with hypertension had angiotensive converting enzyme (ACE) inhibition scintigraphy. Scintigraphic provocative studies based on the effect of ACE inhibitors on renal function were used to diagnose renal ischemia and renal vascular hypertension. The scintirenographic study was divided into two phases, the baseline phase (BSL phase) and the ACE inhibition phase (ACE-I phase). Patients were well hydrated p.o. For the ACE-I phase, ACE inhibitors (captopril 0.2–0.4 mg/kg p.o.) were administered. The scintigraphy was performed 1 h after captopril. The studies were performed without sedation in the supine posterior projection. A large field-of-view camera, with a low-energy/high-efficiency collimator for 99m technetium (99mTc) studies, was used. Data were recorded on a computer to obtain images or to generate renograms. Each phase of the study included scintigraphic sequential imaging and a simultaneous renograph using 99mTc-Mercapto-Acetyl-Triglycine (MAG3) [31].

In hypertensive children standard M-mode, two-dimensional echocardiograms and color Doppler scans were performed. Left ventricular mass (LVM) was calculated from the left ventricular internal dimension at end diastole, interventricular septal thickness, and left ventricular posterior wall thickness [32]. LVM was normalized for height$^{2.7}$ using an allometric approach, as suggested by De Simone et al. [33].

In addition, 30 normal subjects (17 boys and 13 girls) selected from the outpatient clinic were the control group, chosen for comparable age (mean age of 11±3 years) and body surface area. They had no evidence of systemic or renal disease from their history and physical examination.

Statistical analysis

Statistical analysis of ABPM, weight, height, and BP values was performed using Student's *t*-test for unpaired data; $P<0.05$ was considered statistically significant. The data were expressed as mean±SD.

Results

Table 1 shows the clinical data and BP parameters of the NF1 patients and the control group. The groups were well matched with respect to mean age at the time of study and no significant differences were noted for gender, mean body mass index, and for casual measurement of BP, either between boys and girls or between groups. Only 1 patient was excluded from the study because she presented with 24-h DBP values >95th percentile on the first ABPM, but the second ABPM showed a number of readings <60%. On casual measurement, 15 patients showed BP values between the 90th and 95th percentile and 5 BP values >95th percentile. Three have a family history for hypertension and 3 for NF1.

The 24-h ABPM identified 58 patients in group A (84%) with 24-h SBP or DBP <95th percentile and 11 in group B (16%) with 24-h SBP or DBP >95th percentile for age and sex. Five patients in group B were at grade III of the Baylor Program, 4 at grade II, and 2 at grade I.

The mean values of 24-h SBP and DBP were significantly higher in group B than in group A (123±6 vs. 116±9 mmHg, $P<0.001$ and 76±7 vs. 69±5 mmHg, $P<0.01$). Respectively, the load mean SBP was 28±26% vs. 12±13%, $P<0.0005$ and the load mean DBP was 35±25% vs. 19±12%, $P<0.0002$. Among these patients, 5 (3 boys and 2 girls) had a mean SBP >95th percentile, 3 (1 boy and 2 girls) a mean DBP >95th percentile, and 3 (2 boys and 1 girl) SBP–DBP >95th percentile. There were no differences between groups for the number of patients or for the values of increased SBP or DBP load. Again, there were no differences between groups and controls for values of C_{Cr} and Ma.

Of these 11 patients, 1 had plexiform cervical neurofibroma and another had pulmonary valve stenosis. All 11 patients had normal urinary and plasma values of cathecolamines, vanillylmandelic acid, and PRA. Tests to exclude secondary hypertension, such as the ACE inhibitor challenge test and echo-color Doppler flow of the renal arteries, were normal.

Comparing casual BP recordings with the data obtained by ABPM, only 5 patients had BP values >95th percentile by both methods. The acceptance score of diagnostic procedures ranged from 7 to 9 cm. ABPM had the lowest acceptance, while office BP measurements and electrocardiography were the highest. When we analyzed mean daytime and night-time SBP–DBP, we found some significant differences between hypertensive and normotensive groups, with mean readings being significantly higher in group B than A (Table 3). Systolic and diastolic mean day and night-time BPs were closely correlated in group B ($P<0.007$, $r=0.83$ for SBP and $P<0.0001$, $r=0.83$ for DBP), while the correlation was weaker for group A ($r=0.73$ for SBP and $r=0.67$ for DBP). The nocturnal fall of BP was normally distributed in group A (SBP–DBP dipping >10%) with systolic and diastolic dipping being closely correlated (r=0.55). In group B, we observed dipping averaging <10% in 7 of 11 patients only for SBP readings.

In group B values of PRA were higher, but not significantly so (2.3±1 vs. 2.7±0.9 ng/ml per hour, $P<0.1$), than in group A. In both groups, PRA decreased normally with chronological age ($r=-0.17$) and there was no direct correlation between PRA and mean load SBP–DBP ($r=0.01$ and $r=-0.01$, respectively).

All patients were in sinus rhythm and no significant difference was noted between groups for LVM/height$^{2.7}$ values (33±6 g/m$^{2.7}$ vs. 35±7 g/m$^{2.7}$). Cardiac abnormalities were found in 13 (7 males, 6 females) of the total 69 young patients (18.8%) with NF1; 7 were normotensive

Table 3 Characteristics of normotensive and hypertensive patients with neurofibromatosis type 1

	Normotensive	Hypertensive	*P*
No. of patients	58/68 (84%)	11/68 (16%)	<0.001
Gender (M/F)	30/28	7/4	NS
Age (years)	10±4	12±4	NS
Weight (kg)	44±16	49±24	NS
Height (cm)	146±16	146±23	NS
BMI (kg/m^2)	21±4	22±5	NS
PRA (ng/ml per hour)	2.3±1	2.7±0.9	<0.1
Aldosterone (pg/ml)	132±25	144±34	<0.1
Casual SBP (mmHg)	105±15	114±15	<0.01
Casual DBP (mmHg)	73±7	76±9	<0.01
24-h SBP (mmHg)	116±9	123±6	<0.01
24-h DBP (mmHg)	69±5	76±7	<0.01
SBP load (%)	11±12%	25±22%	<0.01
DBP load (%)	17±13%	32±15%	<0.01
24-h heart rate (beats/min)	95±11	97±11	NS
Daytime SBP (mmHg)	111±8	120±10	<0.001
Daytime DBP (mmHg)	65±7	73±9	<0.001
Night-time SBP (mmHg)	105±6	113±9	<0.001
Night-time DBP (mmHg)	61±5	63±8	<0.001

Table 4 Cardiac abnormalities of the 13 patients with neurofibromatosis type 1

	Normotensive	Hypertensive	*P*
Secundum atrial septal defect	1	1	NS
Left pulmonary artery stenosis		1	NS
Coarctation thoracic aorta	1		NS
Mitral valve prolapse	1		NS
Mild mitral regurgitation	1	1	NS
Mild aortic regurgitation	1	1	NS
Atrial septal aneurysm	1	1	NS
Hypertrophic cardiomyopathy	1	1	NS
No. of patients	7 (53.9%)	6 (46.1%)	NS

and 6 hypertensive patients (Table 4). There were no significant clinical and cardiac differences between the normotensive and hypertensive patients, but the prevalence of cardiac defects was more common in hypertensive (6 of 11, 55%) than normotensive (7 of 58, 12%) patients. However, neither group showed obstruction of the left ventricular outflow or a family history of hypertension.

Discussion

Hypertension, both essential and secondary, is relatively frequent in NF1, and we have found a higher incidence (16%) of hypertension with 24-h ABPM than in both the general pediatric population and NF1 children with casual BP measurement. The detection of 5 positive hypertensive patients using casual BP measurements emphasizes that a small number of measurements may not necessarily reflect the habitual BP of an individual. The difference between ABPM and casual BP measurements seems to be associated with the degree of physical activity during ABPM, which furnishes a reliable profile in these small patients. This finding is in agreement with the data from other ABPM studies of healthy children [22, 34]. The acceptance of ABPM was good and without side effects, even though it had a lower acceptance score than other diagnostic procedures. Only Virdis et al. [12] found a 15.8% incidence of hypertension in 57 NF1 children using casual BP measurement. In only 2 patients, the authors demonstrated an organic cause (renal artery stenosis). Riccardi [1] hypothesized an association between hypertension and large plexiform neurofibroma or numerous neurofibromas, explaining this by increased catecholamine production by the neurofibroma. These findings derive from a few studies all based on casual BP measurement [11, 18, 35, 36]. Among our patients, a 16-year-old boy had hypertension and a large cervical plexiform neurofibroma, but he did not have increased urinary catecholamine levels. No patient had renal artery stenosis or pheochromocytoma. Hence the reason for the high frequency of hypertension is still unknown. Reubi [37, 38] reported the occurrence of NF1 vasculopathy in 1945. This author characterized three different vascular anomalies according to blood vessel diameter as the pure intimal type with concentric growth of intima, the nodular-aneurysmatic type with disruption of the elastica, and the periarterial-nodular type with nodular proliferation. Greene et al. [39] described two histological appearances of affected vessels in neurofibromatosis, the first in larger affected vessels and the second mainly in smaller and more peripheral affected vessels. In the former, the vessels are surrounded by neurofibromatous or ganglioneuromatous tissue in the adventitia. In the latter, there is a dysplasia of the small vessels with multiple nodules histologically and nodular aggregates of smooth muscle ultrastructurally. Salyer and Salyer [40] categorized NF1 vasculopathy into four histopathological varieties: pure intimal, advanced intimal, intimal aneurysmal, and nodular. In all of these forms, proliferation of spindle cells occurred within arterial walls and was thought to be responsible for the associated arterial disruption and degeneration. These observations could explain the involvement of the cardiovascular system in NF1. Other authors described an NF1 vasculopathy that may be widespread and involved arteries, arterioles, and veins [41]. In our study we found no renal artery stenosis or pheochromocytoma. None of the hypertensive children had a family history of hypertension; 3 patients had familial NF1. In the absence of other causes, the elevated BP values may be due to low-grade vasculopathy. Recently, we suggested the presence of vascular abnormalities in NF1 patients, irrespective of casual BP and age [42, 43]. The cardiovascular involvement in NF1 may be progressive and requires long-term follow-up. Periodic monitoring of BP values should be carried out to diagnose precocious hypertension, which is significantly associated with increased mortality [44], and to avoid target organ damage. In our patients, cardiac abnormalities were found in 13 of the total 69 patients with NF1. We observed a

higher prevalence of abnormalities in hypertensive than normotensive patients.

Therefore, patients with NF1 are at increased risk for a variety of cardiovascular disorders, but the natural history and pathogenesis of these abnormalities are poorly understood. The report of the NF1 Cardiovascular Task Force summarizes the current understanding of vasculopathy, hypertension, and congenital heart defects that occur in association with NF1 [45]. Recommendations are made regarding routine surveillance for cardiovascular disease and diagnostic evaluation and management of cardiovascular disorders in individuals with NF1.

In conclusion, our data emphasize the importance of periodic ABPM in NF1 patients to diagnose hypertension early and avoid target organ damage and increased mortality. Our understanding of the natural history and pathogenesis of cardiovascular disease in NF1 has improved substantially in the past few years, but many clinically important questions remain unanswered. Patients need continuing follow-up with cardiovascular evaluation.

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