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ORIGINAL ARTICLE

High prevalence of elevated blood pressure among children with neurofibromatosis type 1

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Abstract
Background Neurofibromatosis type 1 (NF1) is a common neurocutaneous disease characterized by café-au-lait spots, axillary and inguinal freckling, neurofibromas, and optic gliomas. Increased rates of hypertension (HTN) were reported among NF1 patients, however, the prevalence of HTN and pre-HTN in pediatric NF1 patients has not been clarified.
Methods Blood pressure (BP) measurements, weight, and renal ultrasound were assessed in 224 NF1 pediatric patients followed in a specialized NF1 clinic.
Results The cohort's mean age was 9.1±4.1 years. Overweight and obesity were found in 12.9 and 10.3 % of them, respectively. BP was measured averagely 2.9 times per patient on different occasions. Blood pressure was in the pre-HTN and HTN ranges in 14.9 and 16.9 % of measurements, respectively. BP >95th was detected in 20.5 % at the first measurement. Of 114 children with at least three BP measurements, 18.4 % had two values in the HTN range and 6.14 % had at least three. Overweight was not associated with HTN among children with NF1. Urinary tract ultrasonographic abnormalities were detected in 6.8 % (11/161) of cases.
Conclusions The prevalence of increased BP in pediatric NF1 is much higher than in the general pediatric population. BP has to be regularly assessed and managed in this high-risk population.

Keywords Hypertension · Pre-hypertension · NF1 · Renal ultrasound · Obesity

Introduction

The prevalence of hypertension (HTN) among pediatric patients was reported to reach 3.2–3.6 % [1, 2]. In contrast to adults for whom most cases of HTN are considered primary, a specific etiology can be identified in many pediatric HTN patients for whom HTN is defined as secondary [3, 4]. The most common etiology of secondary HTN among children is renal disease [5–7]. Neurofibromatosis type 1 (NF1), vasculitis, and Takayasu disease are considered the next most common specific etiologies associated with secondary HTN in children [8]. Even though untreated HTN is associated with multiple complications [9], the diagnosis of HTN is commonly overlooked [2]. The 4th Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents of the National High Blood Pressure Education Program [10, 11] defined guidelines for correct measurement of BP. HTN is diagnosed when the measured BP is above the 95th percentile for age, sex, and height percentile on three different occasions at least 1 week apart. Pre-HTN is considered an important predictor for the development of HTN in the near future, and it is defined as at least one BP measurement between the 90th and 95th percentiles [10]. Pre-HTN has been reported to occur in up to 13 % of children and adolescents in the general population [12]. Given the high prevalence of

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HTN, its negative effect on health, and the available effective treatment, efforts to detect HTN in children are crucial.

Neurofibromatosis type 1 (NF1, MIM #162200) is a common dominantly inherited neurocutaneous disease with a birth incidence of about 1:2500 worldwide [13]. The disease is characterized by multiple café-au-lait macules, skin-fold freckling, iris Lisch nodules, and neurofibromas. Less common but potentially more serious manifestations include plexiform neurofibromas, optic nerve and other central nervous system gliomas, and vasculopathy [14].

Vasculopathy is a known feature of NF1 and may affect blood vessels ranging in size from the large proximal aorta to small arterioles, and it may produce vascular deformations, such as stenosis and occlusion [15, 16]. Involvement of renal arteries or the suprarenal aorta has been described in NF1 patients in several small-scale studies, and HTN has been detected in 16 % of children with NF1 using ambulatory blood pressure monitoring (ABPM) [17, 18].

Secondary HTN was reported to be common in NF1 as well. Renal artery stenosis (RAS), the most common site for symptomatic vasculopathy, usually presents with HTN [19] and occurs in approximately 2 % of the NF1 population [20]. Pheochromocytoma, another etiology for secondary HTN, has an increased prevalence of approximately 2 % among individuals with NF1 [21]. Pheochromocytoma typically occurs at an older age compared to RAS [22, 23].

The aim of this study was to estimate the prevalence of abnormal BP values in the pre-HTN and HTN ranges among children diagnosed as having NF1.

Methods

Subjects

The medical charts of all pediatric patients (aged 2–17 years) who were referred to The Israeli Gilbert Neurofibromatosis Center from January 2004 through January 2014 were reviewed. Only patients with NF1 diagnosed clinically based on the National Institute of Health (NIH) criteria [20, 23] that had complete follow-up records which included age, gender, height, weight, and BP measurements were included. A single BP measurement was carried out at each routine follow-up visit. Intervals between visits were 6–12 months, and BP values were measured for the first three visits. In addition, the distribution of BP values according to existing percentiles was calculated for the first three visits as well. Body mass index (BMI) percentiles were calculated based on the Centers for Disease Control and Prevention growth charts, and definition of BMI status was determined accordingly: normal= <85th percentile, overweight 85th≤BMI <95th percentile), percentile, and obese ≥95th percentile [24].

BP measurements were performed using the Vital Signs Monitor (Welch Allyn 300 Series. Model: 53NTO; Welch Allyn Inc, Skaneateles Falls, NY) according to the standards defined by the 4th Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents of the National High Blood Pressure Education Program [10]. The measured BP values were classified according to existing percentiles for sex, age, and height percentile: normal=<90th percentile, pre-HTN range = >90th percentile but <95th percentile, and HTN range = >95th percentile for systolic and/or diastolic BP. A patient was defined as being HTN if the BP was ≥95th percentile on ≥3 different occasions. Assessment of the kidneys and urinary tract was performed by abdominal ultrasonography (US).

Determination of blood pressure in the general population

The subjects' BP measurements were compared to the rate of elevated BP in the general pediatric population as defined by the Task Force Report criteria for HTN [10]. In addition, given the possibility that the prevalence of HTN in children had increased during the past few years due to a higher prevalence of obesity and other factors, an additional comparison was performed with a recently described large-scale cohort of 199,513 healthy children aged 3–17 years [12], in which BP was measured at the initial well-child visit.

Statistical methods

The data were analyzed using BMDP Statistical Software (1993, Chief Editor: W.J. Dixon, University of California Press, Los Angeles, CA). Continuous variables were compared using analysis of variance (ANOVA). Discrete variables were compared using Pearson's Chi-squared test. A p value of <0.05 was considered significant.

Results

A total of 269 children and adolescents (age 2–17 years) with a clinical diagnosis of NF1 were followed in The Israeli Gilbert Neurofibromatosis Center, of whom 224 patients had sufficient data on height, weight, and BP values. Of these, 53% of them were males. The mean age of the study participants was 9.1±4.1 years (Table 1).

Overall, 646 BP measurements were performed in this cohort, amounting to an average of 2.9 measurements per subject (range, 1–8). BP values were in the pre-HTN and HTN range in 14.9 % (96/646) and 16.9 % (109/646) of these measurements, respectively. A total of 29 patients (12.9 %) were overweight and 23 (10.3 %) were obese.

Table 1 Patient characteristics

Number of cases	224
Age, years (mean±SD)	9.1±4.1 (range, 2–17)
Gender, *n* (%) (M/F)	119 (53.1)/105 (46.9)
Familial NF1, *n* (%)	106 (47.3)
Sporadic NF1, *n* (%)	117 (52.2)
Unknown, *n* (%)	1 (0.4)
Height, percentile (mean±SD)	34±31.5
Weight, percentile (mean±SD)	31.2±14.5
BMI percentile (%)	
<85th, *n* (%)	173 (77.2)
85th–94th, *n* (%)	28 (12.5)
95th–98th, *n* (%)	18 (8.0)
≥99th, *n* (%)	5 (2.2)
≥95th+20 %, *n* (%)	4 (1.8)

BMI body mass index, *NF1* neurofibromatosis type 1

First-visit measurement

At the first visit, 149/224 (66.5 %) of the children were normotensive, 29/224 (12.9 %) had BP values in the pre-HTN range, and 46/224 (20.5 %) had BP in the HTN range (Fig. 1). When these results were compared to the expected rates of pre-HTN and HTN (5 % for each, by definition), the differences were highly significant ($p<0.001$). Increased BP among the NF1 patients was observed when tested for each gender separately as well ($p<0.001$ for each). In comparison to recent BP data, our NF1 cohort had significantly higher BP values at the first record, with 20.5 vs. 5.4 % in the HTN range ($p<0.001$). These significantly higher BP values observed in our NF1 cohort remained after stratification according to age ($p<0.05$) for all age groups (Table 2). The difference in the pre-HTN 12.9 vs. 12.7 % was not significant.

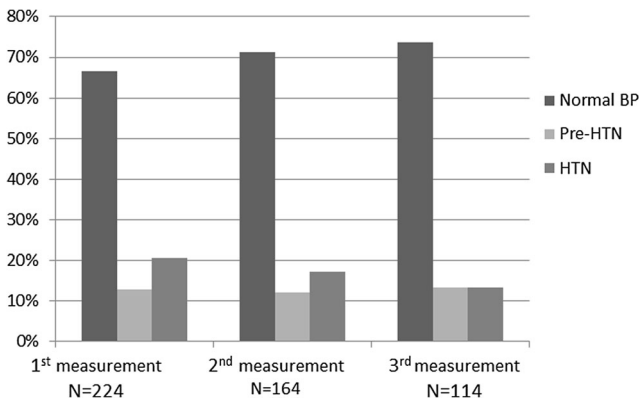

Fig. 1 Blood pressure ranges for different measurements. Percentage of individuals with blood pressure in the normal range (*Normal BP*), in the pre-hypertension range (*PreHTN*), and in the hypertension range (*HTN*) as derived from the first three BP measurements. *N* represents the number of individuals in each group

Second-visit measurement

At the second visit, 117/164 (71.3 %) of the children were normotensive, 19/164 (11.6 %) had BP values in the pre-HTN range, and 28/164 (17.1 %) had BP in the HTN range (Fig. 1). When these results were compared to the expected rate of pre-HTN and HTN (5 % for each, by definition), the differences were highly significant ($p=0.002$).

Third-visit measurement

At the third visit, 84/114 (73.7 %) of the children were normotensive, 15/114 (13.2 %) had BP values in the pre-HTN range, and 15/114 (13.2 %) had BP in the HTN range (Fig. 1). When these results were compared to the expected rate of pre-HTN and HTN (5 % for each, by definition), the differences were highly significant ($p=0.009$).

Prevalence of HTN

Hypertension is defined by having at least three BP measurements within the HTN range on three different visits (either sequential or not sequential). Seven of the 114 children (6.1 %) with at least three BP measurements on different visits were found to have HTN. Since Lo et al. [12] defined HTN when BP was in the HTN range during the index visit and at two subsequent consecutive visits, we followed a similar strategy, looking for individuals with increased BP in the first three consecutive measurements. Four NF1 cases (3.5 %) had such findings, which is about ten times higher than in a HTN detection rate among healthy pediatric population based on Lo et al.'s report (0.3 %) [12].

The effect of BMI

Twelve percent of the individuals with NF1 (18/149) who had normal BP at the first measurement were overweight (85th≤BMI <95th percentile), and 10.7 % (16/149) were obese (BMI >95th percentile). Among the children with BP measurements within the pre-HTN range in the first measurement, 10.3 % (3/29) were overweight and 10.3 % (3/29) were obese. Of the children whose BP measured within the HTN range, 17.4 % (8/46) were overweight and 8.7 % (4/46) were obese. Altogether, there was no significance difference between weight categories of children with NF1 and normal and pre-HTN ranges of BP (N=178) and these with HTN range BP (N=46) (Table 3). Moreover, none of the children with NF1 and HTN were overweight or obese.

Table 2 First blood pressure measurement (range) by age groups compared to the normal control group

Age group, years		*n*	Normal BP	%	PreHTN	%	BP ≥95th	%	*p* value
≤5	Sample	57	39	68.42	7	12.28	11	19.30	<0.001
	Control	48,469	41,355	85.32	4017	8.29	3097	6.39	
8–11	Sample	101	64	63.37	14	13.86	23	22.77	<0.001
	Control	68,917	60,921	88.40	4505	6.54	3491	5.07	
12–14	Sample	39	30	76.92	4	10.26	5	12.82	=0.022
	Control	43,478	34,460	79.26	6668	15.34	2350	5.41	
15–17	Sample	27	16	59.26	4	14.81	7	25.93	<0.001
	Control	38,649	26,559	68.72	10,180	26.34	1910	4.94	

BP blood pressure, *PreHTN* pre-hypertension

Neurological findings related to increased blood pressure

Neurological findings were compared between the 23 NF1 children who had elevated BP on at least two measurements, and the 276 NF1 children with no elevated BP or a single abnormal measurement. While four of the 23 children (17.4 %) with elevated BP on at least two measurements were reported to have developmental delay, only ten out of the 276 (3.6 %) children with one or less elevated BP measurements were reported to have that finding ($p<0.001$). The frequency of hyperintensities detected on T2-weighted brain MRIs was similar in both groups: 48 % (11/23) and 42 % (116/276) among those with elevated BP on at least two occasions compared to those with less than two abnormal BP values, respectively.

Renal abnormalities

A urinary tract US study was available for 161/224 (71.9 %) subjects. Twelve US abnormalities (7.5 %) were detected in 11 (6.8 %) cases. These findings included small/underdeveloped kidneys (2/161, 1.2 %), dilated renal pelvis (3/161, 1.9 %), double collecting system (3/161, 1.9 %), hydronephrosis (2/161, 1.2 %), renal cyst (1/161, 0.6 %), and distended bladder (1/161, 0.7 %).

Of the 15 children with an increased BP on ≥2 BP measurements that underwent renal US, two (13.3 %) had abnormal US findings with dilated renal pelvis in both. This difference did not, however, reach a level of significance ($p=0.3057$), possibly due to the small number of renal US total abnormal findings. The results of further imaging (including Doppler US) and nephrological evaluation for the cause of HTN in these patients were absent from the available files.

Discussion

The current study evaluated the prevalence of elevated BP during childhood and adolescence in a population recognized as having a higher prevalence of HTN [17, 18, 20, 21, 25, 26].

Table 3 Characteristics of patients according to blood pressure percentile on first measurement

N	BP <95 % on first measurement 178	BP ≥95 % on first measurement 46	*p* value
Age, years (mean±SD)	9.1+4.1 (range, 2–17)	9.1+4.2 (range, 2–17)	NS
Gender, *n* (%) (M/F)	93 (52)/85 (48)	27 (59)/19 (41)	NS
Familial NF1, *n* (%)	82 (46)	24 (52)	NS
Sporadic NF1, *n* (%)	95 (53)	22 (48)	NS
Unknown, *n* (%)	1 (0.56)	0	
Height, cm (mean±SD)	127.7±22.2	128.7±24.3	NS
Weight, kg (mean±SD)	30.7±14.1	33.0±15.8	NS
BMI (mean±SD)	17.8±3.2	18.6±3.3	NS
BMI percentile (%)			
<85th	139 (78)	34 (74)	NS
85th–94th	21 (11.8)	8 (17.4)	NS
95th–98th	16 (9)	2 (4.34)	NS
≥99th	3 (1.69)	2 (4.34)	NS

BMI body mass index, *NS* not significant, *BP* blood pressure, *NF1* neurofibromatosis type 1

Our results showed that elevated BP is more prevalent in pediatric NF1 patients compared to the statistical expectation and reported data in an age-adjusted population [12]. We found that 12.9 and 20.5 % of these patients had BP values in the pre-HTN and HTN range, respectively, on their first BP measurement. Similar results were detected on further measurements. While the detected frequency of pre-HTN was similar to that of the general population, the HTN values detected in the NF1 cohort were about four times higher than expected. The prevalence of HTN, as defined by three consecutive HTN BP measurements, was 3.5 %, a value that was much higher than expected and ten times higher than the findings of a large-scale study on a healthy pediatric population [12].

A large proportion of our study children underwent renal US (71.9 %, 161 individuals), but Doppler US was not routinely carried out and the data on any further evaluations they may have undergone were not available. Notably, urinary tract US abnormalities were detected in 6.8 % (11/161) of NF1 patients, but they were present twice as often in children with elevated BPs. This difference, although not reaching a level of significance, may hint to a possibly renal origin of HTN in the NF1 population. These findings warrant universal use of abdominal imaging, including kidney US along with Doppler examination of the renal arteries as well as the abdominal aorta, both in the initial evaluation and during follow-up in these high-risk patients.

According to previous studies, NF1 is recognized as a predisposing condition for HTN due to an increased prevalence of RAS [19], which is reported to occur in 1–2 % of NF1 patients [20]. Another cause of HTN associated with NF1 is pheochromocytoma. Although it is found at an increased rate in NF1 patients (up to 2 % of this population) [20, 21], this tumor is seven-fold less frequent than RAS in NF1 pediatric patients with HTN [25] and occurs at an older age [22]. Even though HTN in NF1 is associated with those two rare diseases, it could not, however, explain the high prevalence of increased BP in NF1 found in our study, suggesting that the great majority of HTN in NF1 is a common primary feature of the disease itself rather than a product of a specific rare complication.

A number of studies evaluated the rate of HTN among individuals with NF1. Ambulatory blood pressure monitoring (ABPM) for 24 h diagnosed HTN in 16–18.5 % of patients evaluated at ages 5–25 years [18, 17, 27]. Another report in which imaging studies were used to investigate vasculopathy in NF1 children found a 6 % prevalence of HTN in 181 children aged 0–18 years, however, 40 % of the children with HTN had a known vascular cause [26].

While there is a clear association between HTN and obesity in the general pediatric population [4, 12, 28], we did not find any association in children with NF1. Rather, the BMIs of all of the children in our cohort who were diagnosed as having HTN were within the normal range.

Moreover, the fact that HTN is much frequent in children with NF1 compared to the general pediatric population, while the frequency of pre-HTN is the same, emphasizes as well the uniqueness of increased BP among children with NF1. These difference characterizations could support the possibility that HTN in NF1 has a different etiology than HTN in the general pediatric population, possibly related to vasculopathy attributed to NF1.

Interestingly, the results of this study detected an increased rate of reported developmental delay among NF1 patients with elevated BP compared with those with normal BP values. Given the small number of children with at least two abnormal BP measurements, and the fact that the data on developmental delay were retrieved from reports in patient records, further evaluation of the effect of HTN on neurological findings in NF1 is recommended.

Given these results, pediatric NF1 patients should be closely monitored by regular BP measurements. Early detection of abnormal BP values should signal the need to evaluate secondary causes (mostly RAS and, much less probably, pheochromocytoma) in order to target intervention and treatment [29]. It is recognized that 12–14 % of individuals with pre-HTN in this population will become HTN within 2 years [30]. While the natural history of pre-HTN in NF1 patients is not yet known, given the adverse effects of HTN, it is advisable to closely monitor NF1 patients with pre-HTN. It may be beneficial to utilize ABPM in cases of suspected HTN, given its advantages in the detection of sustained or masked HTN.

There are some limitations associated with this study. First, the examined BP measurements had been obtained with an oscillometric BP device. Such devices are less accurate than auscultatory mercury sphygmomanometers in children [31]. However, due to its simplicity of use and the scarcity of auscultatory sphygmomanometers, the oscillometric devices have gained widespread popularity. Also, some studies have shown that BP values obtained with the oscillometric method closely resemble those determined with the conventional auscultatory method [32–34]. Second, given the retrospective nature of this study, we were unable to assess the contribution of additional useful diagnostic tests, such as ABPM and Doppler. Third, given the relative rarity of NF1, the study is limited by a small cohort size, in addition to a lack of a control pediatric population in the same clinical setting.

In conclusion, our data suggest that increased BP is common among the pediatric population with NF1, probably as part of the essential disease characterization. Moreover, it is possible that renal abnormalities are more frequent among children with NF1. A meticulous evaluation of BP including ABPM when possible should be performed in this high-risk population for targeting timely and appropriate initiation of therapy. In addition, renal US screening with Doppler examinations of renal vessels and the suprarenal aorta may be justified for all individuals with NF1.

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Ethical approval The study was approved by the institutional ethical committee, and parental consent was not required for this retrospective anonymous chart review.

Conflict of interest The authors declare that they have no conflicts of interest.

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