Childhood Hypertension in Autosomal-Dominant Hypertension With Brachydactyly

Okan Toka, Philipp G. Maass, Atakan Aydin, Hakan Toka, Norbert Hübner, Franz Rüschendorf, Maolian Gong, Friedrich C. Luft, Sylvia Bähring

Abstract—Affected individuals with autosomal-dominant hypertension with brachydactyly syndrome develop severe progressive hypertension and, if left untreated, develop stroke by age <50 years. In 1996 we described hypertension and brachydactyly and presented data on adults. We recently revisited this family and performed further studies, focusing particularly on the children in this family. We performed a genome-wide single-nucleotide polymorphism genotyping linkage analysis and confirmed our earlier linkage results. We accrued interesting ancillary data that we attribute to the rearrangements that we described earlier. We performed additional analysis focused on providing clinical criteria for the diagnosis in children and particularly to monitor the onset and to display the age-dependent development of hypertension and brachydactyly. We investigated 30 children; 12 were affected, whereas 18 were not. Brachydactyly with short stature presented as a maturing phenotype, becoming obvious during the prepubertal growth spurt. Stage 2 hypertension was already present in toddlers and increased with age. Thus, blood pressure measurement, rather than brachydactyly, was the most reliable phenotype for the very early diagnosis in children. Importantly, hypertension with brachydactyly occurs worldwide. Once the diagnosis is made, we recommend treatment of all individuals with stage 2 hypertension according to the current European and US guidelines on hypertension in children and adolescents. (Hypertension. 2010;56:988-994.)

Key Words: genetic hypertension • autosomal-dominant hypertension with brachydactyly • childhood hypertension • adolescent hypertension • prepubertal growth spurt

Bilginturan et al1 first described severe autosomal-dominant hypertension with brachydactyly (HBS) in a large kindred from northeastern Turkey in 1973. We re-investigated this family in 1994 and 2009 and have recruited 86 family members, spanning 4 generations with 31 currently affected individuals.2–8 Because of the severe consequences, we elected to treat all of the adult HBS patients since 1996. The decision to treat affected children has been more difficult. Thus, our objectives were to provide diagnostic and treatment criteria for HBS in childhood.

The discovery of molecular mechanisms causing genetic hypertension has brought great insight into the regulation of salt-sensitive forms of hypertension. However, none of these syndromes have been convincingly linked to the pathogenesis of essential hypertension, although rare independent mutations in renal salt handling genes can contribute to blood pressure variation in the general population.9–16 HBS is the first mendelian form of hypertension that resembles essential hypertension, because renin, aldosterone, and norepinephrine responses are normal, and no salt sensitivity is present.7 Other non-Turkish families that we have identified and the subjects reported here feature complex chromosomal rearrangements on the short arm of chromosome 12.17 An almost identical locus on chromosome 12p was mapped in Chinese families with essential hypertension.17 Furthermore, Harrap et al18 identified this locus as being associated with postural changes in systolic and diastolic blood pressures. Patients with HBS have severe hypertension that progresses remarkably with age. A randomized double-blind, placebo-controlled, crossover medication trial revealed no pharmacological phenotype regarding medication classes in affected individuals.5 Studies on the autonomic nervous system revealed decreased baroreflex sensitivity with significantly impaired blood pressure buffering.4,19 A central nervous system origin has been suggested for HBS, because baroreflex blood pressure buffering is disturbed, and neurovascular contact was demonstrated with MRI.20

In essence, all of the affected individuals with HBS develop severe hypertension and, if left untreated experience from stroke by age 40 to 50 years.5–7 Thus, HBS causes significant morbidity and mortality. An early diagnosis and effective antihypertensive treatment might already be indicated during childhood.
Methods
The Charité Internal Review Board approved the study (MDC1995: AA2/95/11, updated version Charité 2009: EA1/109/09), and written informed consent was obtained. In this investigation we studied 30 children aged 1 to 17 years; 12 were affected (verified by microsatellite genotyping and haplotypes), whereas 18 were not. All of the affected children with HBS were clinically asymptomatic. Only 1 severely affected adolescent reported occasional headache and tinnitus during exertion. However, under field working conditions, we did not perform expanded screening for secondary target-organ damage (eg, echocardiography and funduscopy).

We performed a genome-wide linkage scan with the Affymetrix Genome-Wide Human SNP Array 6.0 according to the GeneChip Mapping Assay Manual (Affymetrix United Kingdom Ltd). This array contains >906 600 single-nucleotide polymorphisms (SNPs) and a similar amount of copy number probes. We selected highly informative meioses of 7 affected and 4 nonaffected family members. Genotyping was done with the Affymetrix Genotyping Console v2.1 using the Birdseed v1 algorithm. Data handling and quality control were managed by ALOHOMORA_M, a modified version of ALOHOMORA.21 We performed parametric linkage analysis with MERLIN using allele frequencies from whites and the deCODE genetic map according to the Affymetrix annotation file.22 We assumed a fully penetrant autosomal-dominant mode of inheritance with no phenocopy and a disease allele frequency of 0.0001 for the linkage analysis. We also analyzed copy number variations through the whole genome.

We measured height, body weight, and hand photographs and obtained representative roentgenograms. We used established Turkish percentiles for height and weight to compare affected versus unaffected individuals.23,24 To allow a more detailed screen of height percentile development between affected and nonaffected individuals throughout childhood and adolescence, we also used the far more expanded child growth percentiles provided by the World Health Organization.25 In the roentgenograms, we measured total bone length of each single metacarpal, basophalangeal, mesophalangeal, and telephalangeal bone in 6 affected (at 2, 5, 6, 12, 13, and 15 years of age) and 4 unaffected (at 1, 5, 9, and 13 years of age) individuals. The mean values of affected and unaffected bone lengths from 1 to 9 and 10 to 17 years of age were calculated for each bone and compared with mean values of age-matched reference values and illustrated as multiples of SD. Blood pressure and heart rate were measured by an oscillometric device (every 2 minutes), 10 minutes in sitting and 20 minutes supine (Dynapin). We used cuffs of appropriate size. The arithmetic mean value of systolic, diastolic, and mean arterial blood pressure measurements, in sitting and supine positions, was calculated to compare the blood pressure values of each individual. None of the subjects was being treated for hypertension at the time of measurement. Blood pressure values were then assessed by age-, sex-, and height-matched reference values (blood pressure percentiles) provided by the “Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.”27 Differences in blood pressures, heights, weights, and bone lengths between affected and nonaffected family members were determined by t test analysis. For blood pressure comparisons, we compared 1 affected with 18 unaffected subjects and for height 4 affected with 8 unaffected subjects in the age group 1 to 9 years and 9 affected versus 9 unaffected subjects in the age group 10 to 17 years. We relied on descriptive statistics and adjusted t tests for comparisons. Fiducial limits are mean ± SD.

Results
We first sought to verify our linkage data and, therefore, used the genome-wide SNP genotyping with the Affymetrix Genome-Wide Human SNP Array 6.0 to confirm the linkage to chromosome 12p. We sought to identify copy number variations within the linkage interval and elsewhere. The linkage analysis resulted in only 1 significant logarithmic odds ratio (LOD score) of 7.2 obtained with SNPs on the short arm of chromosome 12, as shown in Figure 1. The constructed haplotypes defined SNP rs10743190 as the distal flanking marker and SNP rs12366914 as the proximal flanking marker. Both showed recombination events within the pedigree (data not shown). Using the dense SNP array reduced the linkage interval to 280 kb at the distal border in comparison with the microsatellite study,5,6 and we observed unexpected dropdowns of the LOD score within the linkage region. The most remarkable dropdown reached a minimal LOD score of −2.2 and spanned >60 SNPs. This dropdown flanks the deleted region covered by BAC1848C8 of the complex genomic rearrangement. The analysis of copy number variations on the basis of the SNP array showed no causing copy number variation in the linkage interval. At the lower right of Figure 1 are intervals defining the common inversions among international families that we described earlier.2

We next focused on our primary clinical objective in this study, namely the children. The average age of affected individuals in the analyzed group was 9.8 years, versus 9.4 years in the unaffected group with similar age distribution. The sex distribution was 7:5 male:female in the affected group and 9:9 male:female in the unaffected group. Figure 2A illustrates the difference in birth weight between affected and nonaffected term infants. Affected children with HBS had a mean birth weight of 2600 g and were significantly lighter (P=0.016) than unaffected babies of the family (3 to 10 percentiles of Turkish birth weight percentile).23 The unaffected babies had a mean birth weight of 3205 g (25 to 50 percentiles of Turkish birth weight percentile).23

Figure 2B illustrates the mean height percentiles of affected versus nonaffected children divided in 2 age groups with consideration of prepubertal growth spurs. All of the affected children with HBS who underwent prepubertal growth spurt were below the fifth height percentile. However, younger affected children did vary between the second and 25th height percentiles. Thus, the difference between affected and nonaffected children in the younger group (1 to 9 years) was smaller (P=0.08). In the older-age group, with patients aged 10 to 17 years, affected children were significantly shorter than unaffected children (2.0 versus 30.2, mean percentile; P<0.01). The difference in height percentiles between the 2 affected groups (prepubertal group with age 1 to 9 years and older group with 10 to 17 years of age) was also significant (P<0.05). Figure 2C shows the results for affected and unaffected individuals divided in 2 different age groups (1 to 9 and 10 to 17 years of age). The results indicate a significant aggravation of the brachydactyly phenotype during puberty (P<0.001). As shown in Figure 2D, the difference between the mean blood pressure in affected versus nonaffected children was highly significant (P<0.001) throughout childhood and adolescence.

The Table shows the height percentile for affected and nonaffected family members based on both Turkish and World Health Organization reference values. Mean height percentiles were calculated with the expanded World Health Organization normal values to compare affected versus nonaffected family members in detail.24,25 The average height percentile in affected children versus nonaffected (age 1 to 17 years;
n = 30) was lower (4.5 versus 35.4 mean percentile; \( P < 0.001 \)) in the affected group. The Table provides a survey of body weight and body mass index of all of the analyzed children. There was no significant difference in the body mass index between affected (18.7) and unaffected children (17.6). Thus, obesity is not part of the HBS phenotype.

Figure S1 (please see the online Data Supplement at http://hyper.ahajournals.org) shows photographs of the right hands of affected and unaffected individuals at different ages. In the top panel, hands from two 4-year-old boys are shown. At this point in time, finger length and shape were not different. In the middle panel, hands from an 11-year-old affected boy and a 12-year-old unaffected girl are compared. Both had passed prepubertal growth spurts. The hand of the affected child is significantly shorter, involving all digits and all metacarpal bones. The shortening of the distal phalanxes is especially profound. The phenotype of brachydactyly in the affected children is clearly apparent at this age. In the bottom panel, the hands of 2 adolescents are compared. The brachydactyly in the affected individual is profound and involves all of the metacarpal and phalangeal bones. The shortening of digit V seems particularly pronounced. The panels show that brachydactyly occurs with progression during growth and can explicitly be diagnosed after prepubertal growth spurt.

We obtained age-matched radiographs of 3 other pairs of affected and unaffected children and adolescents. As illustrated in Figure S2, there was no significant difference between affected and unaffected children at the age of 1 to 2 years. The diagnosis of brachydactyly is not yet possible. At age 5 to 6 years, subtle differences can be seen that enable the diagnosis of brachydactyly. In the radiograph of the affected individual, a mild form of cone-shaped epiphyses at the middle phalanx of digits II and V and at the distal end of metacarpal bone V was observed. Furthermore, there was shortening of metacarpal bone V. However, the findings were subtle and required hand roentgenograms. In the radiographs in the bottom panel, hands from 2 adolescents are shown. The affected individual exhibits severe brachydactyly with generalized cone-shape epiphyses, typically described for brachydactyly type E. To quantify these age-dependent effects in the development of brachydactyly, we measured total bone lengths of each single metacarpal, basophalangeal, mesophalangeal, and telephalangeal bone of 6 affected and 4 unaffected individuals (19 measurements per hand).

The Table also shows systolic, mean, and diastolic blood pressure values of affected and unaffected children. The illustrated values are calculated arithmetic mean values of...
several measurements in sitting and supine positions. Also shown are the corresponding height-, age-, and sex-dependent blood pressure percentiles for systolic and diastolic measurements. Almost all of the affected children with HBS have systolic blood pressure values /H11022 99th percentile. Only in 1 affected child (11/AFF) was blood pressure between the 90th and 95th percentiles. Thus, according to the current guidelines of hypertension in children, all of the affected individuals with HBS, even the very young one at 3 years of age, can clearly be classified as hypertensive.27 The Table also shows that the systolic blood pressure percentiles of affected children are even higher than the diastolic percentile values, indicating the more profound systolic hypertension in HBS.

We also re-examined all of the affected and nonaffected adults in 2009 and reviewed their medications. In those compliant on the day of measurement (some deleted their tablets, purposely reasoning that we wanted to measure untreated blood pressure), blood pressure control was acceptable (data not shown). Only 1 affected person has died. That person had already experienced a severely disabling stroke before treatment (in 1994). No further strokes have occurred in any treated patients.

**Discussion**

We focused on the children bearing the hypertensive phenotype. In the process of our re-evaluation, we also verified our linkage interval and confirmed the absence of other loci. Our studies allowed us to focus on imperative clinical issues. HBS is associated with high morbidity and mortality because of severe and progressive arterial hypertension in affected persons. Untreated affected adults usually develop fatal strokes between ages 40 and 50 years.5–7 Thus, an antihypertensive treatment that begins during childhood could be essential for the further course of these patients. However, the degree, progression, and severity of the phenotype in children with HBS are as yet not analyzed. Our major finding was that systolic blood pressure >99th percentile was a good phenotype to establish the diagnosis in our very young patients. Picking up the brachydactyly was not easy in young children, because this phenotype first becomes more manifest with

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**Figure 2.** A, Birth weights of affected (AFF; n=4) vs unaffected (NON; n=2) children. *Significance P<0.02. B, Height percentiles of AFF vs NON children separated in 2 age groups. B (left) shows children aged 1 to 9 years (n-AFF=4; n-NON=8); B (right) is children aged 10 to 17 years (n-AFF=9; n-NON=9). **Significance P<0.01. C, Mean radiographic bone length measurements for all 5 metacarpals, basophalanx, mesophalanx, and telephalanx of the right hand in a group of AFF (●) and NON (○) children. The differences in the mean value of AFF and NON groups from age-matched reference values for each bone length are illustrated as multiple deviations (STDV) from the reference value. D, Mean values calculated as arithmetic mean of repetitive sitting and supine measurements of age-dependent mean arterial blood pressure in AFF (black) and NON (white) children (P<0.001).
Type E brachydactyly typically includes shortening and thickening of both phalangeal and metacarpal bones. The shortening of metacarpal bones IV and V are particularly common. Epiphyseal growth disturbance leads to reduced bone growth, and the condition is associated with short stature.26,28 The growth rate during childhood has 2 peaks. The first peak occurs after birth and decreases within the first 3 years of life exponentially. Subsequently, children have an almost linear regression of growth rate until the prepubertal growth spurt begins.

Thus, we analyzed the progression of brachydactyly and hypertension in 2 age groups, namely before and after the prepubertal growth spurt.

We found that brachydactyly and the associated short stature present as a mature HBS phenotype that becomes gradually detectable during early puberty. The average age-and sex-matched height percentiles of affected children throughout childhood and adolescence (ages 1 to 17 years) were significantly lower in the affected group versus the unaffected group. After dividing the cohorts into 2 age groups that took prepubertal growth spurt into consideration, the difference was not significant in the younger group (age 1 to 9 years) but was still significant in the older group (age 10 to 17 years). We additionally compared pictures and analyzed radiographs of hands between affected and unaffected individuals. Our comprehensive hand bone analysis showed highly significant differences between these groups already at

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<td>14</td>
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<td>39.2</td>
<td>19.6</td>
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<td>67</td>
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<td>52.1</td>
<td>20.6</td>
<td>105</td>
<td>83</td>
<td>66</td>
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<td>Male</td>
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<td>22.2</td>
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<td>75</td>
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<td>75 to 50</td>
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Listed are age in years; sex classified as female and male; height in centimeters; weight in kilograms; body mass index (BMI) in kilograms per meter squared; systolic (Sys-RR), mean arterial pressure (Md-RR), and diastolic (Dia-RR) blood pressure in millimeters of mercury; systolic (Sys-Perc.) and diastolic (Dia-Perc.) blood pressure percentile normalized for age, sex, and height; weight percentile for Turkish children (T-WP); height percentile according to World Health Organization height standards in children (WHO-HP); and birth weight (BW) and the corresponding percentiles (BW-Perc.) for Turkish children.
age 4.3 years. However, the earliest time point at which we could detect subtle radiographic evidence in routine x-ray analysis was at 6 years. Our results show a significant aggravation of the brachydactyly phenotype during early puberty because of an impaired prepubertal growth spurt in children with HBS.

Body weight percentile and body mass index were not different between affected and unaffected children. Obesity is clearly not part of HBS phenotype in children. However, the birth weights did differ significantly. Affected individuals were low-birth-weight newborns. Blood pressure was an early phenotype during childhood, which allowed a clear separation between affected and unaffected individuals already during early infancy. The comparison of mean arterial blood pressure between affected and unaffected (age 1 to 17 years) was highly significant. In contrast to the brachydactyly phenotype, affected individuals were already hypertensive before the prepubertal growth spurt. The youngest affected child in the analyzed group was 3 years old, and according to the age, sex, and height, had normalized blood pressure reference values above the 99th percentile for both systolic and diastolic blood pressures. In only 1 of 18 unaffected individuals was the blood pressure above the 95th percentile. We would consider this 14-year-old girl as being hypertensive, although confirmatory measurements are necessary.

Previously we studied 17 affected individuals in a randomized, double-blind crossover trial including all first-line antihypertensive drugs. We show that significant reduction of blood pressure was possible in single-drug therapy with \( \beta \)-blocker, \( \alpha \)-blocker, calcium channel blocker, and converting enzyme inhibitor compared with placebo. Three adolescent children (age 13 to 15 years) were included in that trial. Their blood pressure reduction was effective, and all of the medication classes were tolerated without any adverse effects. The blood pressure reduction in currently treated adults who mostly require a combination therapy with \( \beta \)-blocker and converting enzyme inhibitor or angiotensin II receptor antagonist is 11 to 38 mm Hg (mean arterial blood pressure, data not shown). Only 1 affected adult died since we started treatment of affected adults 13 years ago, and this individual had already had a severe stroke before our treatment. Currently, the oldest affected patient of the family is 60 years old and is sufficiently treated for hypertension (blood pressure of 131/78 mm Hg) with a combination therapy of an angiotensin II receptor antagonist and a \( \beta \)-blocker. No untreated individual in this Turkish family has ever lived beyond age 50 years. Thus, treatment of hypertension in HBS is possible and most likely decreases morbidity and mortality substantially. Therefore, we suggest that therapy should begin during childhood before developing severe target-organ damage.

In adults, hypertension is a lifelong commitment. In children, no data are available on long-term effects of untreated hypertension. Data on adverse effects of antihypertensive drug treatment on growth and development are incomplete. Therefore, defined criteria for initiating such a pharmacological therapy should be given before a drug is prescribed. Fortunately, the numbers of available and labeled antihypertensive drugs and drugs that have been studied systematically in children have increased substantially in the last 10 years.

The "Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" defines the indications for antihypertensive drug therapy in children for symptomatic hypertension, secondary hypertension, hypertension with target-organ damage, and persistent hypertension despite nonpharmacologic treatment and comorbidity in terms of diabetes mellitus (types 1 and 2). The report does not restrict pharmacological treatment to a specific age boundary. The recommended drugs in this report for treatment of childhood hypertension are provided for ages 1 to 17 years. The recommendations for the aimed blood pressure reduction for children with uncomplicated primary hypertension and no hypertensive target-organ damage are to reduce blood pressure under the 95th percentile for sex, age, and height, whereas for children with chronic renal disease, diabetes mellitus, or hypertensive target-organ damage, the goal blood pressure is recommended to be under the 90th percentile for sex, age, and height. These recommendations are similar to recommended treatment of hypertension in adults. Only 1 affected individual of the investigated cohort reported occasional headache and ear buzzing during exertion. Neither headache nor ear buzzing is a reliable internal reporter of hypertension. All of the other affected individuals were asymptomatic. Under field conditions, we did not perform expanded screening for secondary target-organ damage in our pediatric cohort.

Perspectives
HBS is rare but occurs worldwide. Diagnosis in childhood is important; however, routine genotyping is not yet practicable. The brachydactyly phenotype can be diagnosed roentgenographically, but this overt phenotype is masked until the prepubertal growth spurt begins. Blood pressure is regularly elevated, even in infants. When considering HBS, the blood pressure phenotype should guide the diagnosis. Once the diagnosis is made, treatment recommendations should be based on current guidelines for antihypertensive treatment in childhood and adolescence. Therapy should be started already during early infancy if blood pressure is reliably above the 95th percentile, if patients are symptomatic or have microalbuminuria, left ventricular hypertrophy, or fundoscopic changes. We concur with international guidelines and begin treatment in all children with stage 2 hypertension.
Disclosures

None.

References


Childhood Hypertension in Autosomal-Dominant Hypertension With Brachydactyly
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CHILDHOOD HYPERTENSION IN AUTOSOMAL-DOMINANT HYPERTENSION WITH BRACHYDACTYLY
ONLINE SUPPLEMENT

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Franz Rüschendorf \textsuperscript{2}, Maolian Gong\textsuperscript{2}, Friedrich C. Luft\textsuperscript{2}, and
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\textbf{Short title:} Genetic childhood hypertension

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Supplement Figure S1. Hand photographs of affected (AFF, left panel) and unaffected (NON, right panel) at different ages. Upper shows two 4 year-old boys, middle shows an 11 year-old and a 12 year-old girl. Lower shows two 16 year-old boys. All photographs included a cm scale.
Supplement Figure S2. Hand radiographs of affected (AFF, left) and unaffected (NON, right) at different ages. Upper shows a 1 and a 2 year-old boy. Middle shows a 5 and a 6 year-old boy. Lower shows two 13 year-old boys.