

## Original Article

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# Characteristics of Danish children registered with and pharmacologically treated for hypertension

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**ABSTRACT**

**INTRODUCTION:** A previous study found that 0.04% of Danish children were registered with hypertension, among whom 54% were treated pharmacologically. Our study describes pharmacologically treated cases at the onset of antihypertensive therapy, noting whether the evaluation of target-organ damage could be improved.

**METHODS:** Our review of the medical records of children under 16 years living in Central and Eastern Denmark from April 2014 to May 2015 found that 119 children were registered with an International Classification of Diseases, tenth edition diagnosis of hypertension and treated with antihypertensive medicine.

**RESULTS:** The cohort consisted of 61% boys and 39% girls ( $p = 0.01$ ). The majority of patients (80%) had secondary hypertension. Renal aetiology was found in 52%. Echocardiography, retinal examination and examination for proteinuria were undertaken in 77%, 74% and 100%, respectively. Both echocardiography and retinal examination were undertaken in 61% of patients with renal aetiology. Among the remaining patients, 95% and 89% underwent these examinations, respectively ( $p < 0.001$  and  $p < 0.001$ ).

Abnormal echocardiography, abnormal retinal examination and proteinuria were found in 39%, 16% and 66%, respectively, of patients with renal aetiology and in 30%, 24% and 35% of the remaining patients ( $p = 0.3$ ,  $p = 0.4$  and  $p < 0.001$ ).

**CONCLUSIONS:** Examination for target-organ damage was performed less often in patients with hypertension of renal aetiology than in the remaining patients. Examination for target-organ damage is recommended in all hypertensive children to determine whether treatment is indicated to reduce long-term morbidity.

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**TRIAL REGISTRATION:** not relevant.

Hypertension affects approximately 25% of adults and is the leading risk factor for increased mortality due to cardiovascular disease in the adult population worldwide [1]. In an earlier population-based study including 553,784 Danish children < 16 years of age, only 222 (0.04%) were registered with hypertension and 119 (0.02%) were treated pharmacologically [2]. These very low figures may reflect that no systematic measuring of blood pressure is in place in children in Denmark. Previous clinical studies from the US have reported a 2-4%

prevalence of hypertension in children [3, 4] and established that 0.1-0.15% of children aged 3-18 years receive antihypertensive pharmacological treatment [5, 6]. Children with hypertension are likely to experience accelerated vascular ageing [1]. Both pharmacological and non-pharmacological treatment of hypertensive youths can reverse target-organ damage [1, 7, 8]. Therefore, early treatment is essential to reduce the lifetime burden of hypertension.

It is recommended to assess whether target-organ damage is present when hypertension is diagnosed in children [1, 9-11]. Antihypertensive pharmacological treatment is indicated in cases of target-organ damage, stage 2 hypertension (blood pressure > 99th percentile + 5 mmHg for age and sex), symptomatic hypertension, secondary hypertension and persistent hypertension despite non-pharmacological treatment [1, 9-11].

The aim of this study was to characterise the aetiology of pharmacologically treated paediatric hypertension; to evaluate whether pharmacologically treated hypertensive children had undergone examination for target-organ damage and, if so, to grade the organ damage according to stage of hypertension. We hypothesised that all pharmacologically treated hypertensive children had undergone examination for target-organ damage at the initiation of their antihypertensive medical treatment.



Echocardiogram performed by one of the study authors. The child's mother approved the use of the photograph in the article.

## METHODS

We evaluated a cohort of 119 children < 16 years of age living in central and eastern parts of Denmark registered

with an International Classification of Diseases, tenth edition (ICD-10) code of hypertension between April 2014 and May 2015 and pharmacologically treated for hypertension. At that time, 16 years was the upper age limit for patients at paediatric departments in Denmark. The cohort was extracted from a larger cohort created using the Danish National Patient Register and electronic data from ten paediatric departments in Central and Eastern Denmark [2]. We reviewed the medical records and noted whether patients had hypertension based on the information in the case reports and according to current guidelines. Hypertension was categorised as stage 1 (blood pressure at 95th-99th + 5 mmHg for age and sex) or stage 2 hypertension [9-11]. Based on associated diagnoses registered in the medical records, each patient was classified with primary or secondary hypertension [2, 9, 10]. Moreover, we extracted anthropometric data (age, sex, height, weight) and family history of hypertension if patients had symptomatic hypertension and data from any examination for target-organ damage. Data were collected at the time of diagnosis and when antihypertensive pharmacological treatment was initiated. If the interval between these two time-points was < 3 months, the first date was registered; otherwise, the interval was calculated in months.

Patients were classified as having renal aetiology in cases of reno-parenchymal disease, for example congenital renal anomalies [2].

Target-organ damage was assessed by gathering information on glomerular filtration rate, urine analysis for protein, results of echocardiography and retinal examination if these examinations had been performed at the initiation of antihypertensive pharmacological treatment.

Glomerular filtration rate was either determined by chrome ethylenediamine tetraacetic acid (EDTA)-clearance or estimated by the Chronic Kidney Disease in Children Cohort Study formula based on cystatin-C, creatinine and urea [12] or by the Schwartz formula [10]. Patients were classified according to chronic kidney disease stages with those younger than one year based on converting tables [13, 14]. Patients with a kidney transplant were classified with abnormal glomerular filtration rate.

Proteinuria was defined as > 0.1 g protein/m<sup>2</sup>/24-hour urine; but for children < 0.5 years, the limit was 0.2 g protein/m<sup>2</sup>/24-hour urine [15, 16]. If a 24-hour urine collection was not available, proteinuria was defined as a urine dipstick with at least 1+ for protein and at least 2+ in children < 0.5 years of age [15, 16].

Left ventricular hypertrophy was determined from standard echocardiographic measurements by M-mode, including measurements of end diastolic left ventricular and interventricular septal diameter and/or a left ventricular posterior wall thickness above two Z-scores on the Dubois formula [9].

Obesity was defined as an ISO Body Mass Index of at least 30 or an ICD-10 diagnosis of obesity [10].

If a certain group of patients contained < 5, the number was censored in accordance with The Danish Health Data Authority requirement that analysis of data should not make patients identifiable.

## **Ethics**

The study was conducted according to the Declaration of Helsinki and approved by the Danish Health Authority (3-3013-1172/1) as well as the Danish Data Protection Agency (2008-54-0472).

## **Statistics**

Results are presented as median and interquartile range in tables and range in text for continuous variables, and in absolute counts and percentages for categorical variables. Differences in proportions were analysed by binominal test and  $\chi^2$ -test. Differences in continuous variables were analysed by Mann-Whitney tests. p-values < 0.05 in two-sided tests were considered statistically significant. Statistical analyses were conducted in R Studio

and Open Source Epidemiologic Statistics for Public Health, updated in 2013.

Trial registration: not relevant.

## RESULTS

### Age, gender and stage of hypertension

The cohort consisted of 61% boys and 39% girls ( $p = 0.01$ ), **Table 1**.

**TABLE 1** Age, gender and stage of hypertension at treatment initiation in hypertensive children.

	Gender			p-value	Hypertension		
	girls	boys	total		stage 1	stage 2	p-value
Age, median (IQR), yrs	9.6 (3.7-13.7)	6.5 (1.4-10.7)	7.7 (1.7-11.7)	0.06	9.1 (2.6-13.2)	6.4 (1.6-10.6)	0.17
Age, n							
0-28 days	6	< 5 <sup>a</sup>	9	0.07	5	< 5 <sup>a</sup>	0.63
29 days-1 yr	< 5 <sup>a</sup>	19	22	0.002	9	13	0.47
2-6 yrs	8	16	24	0.55	9	15	0.25
7-11 yrs	13	22	35	0.83	16	19	0.76
12-15 yrs	16	13	29	0.04	18	11	0.08
Total	46	73	119	0.01	57	62	0.65

IQR = interquartile range.

a) The information is censored due to Danish regulations from the National Health Data Authority, stating no observations of patients may make the patients identifiable.

At the initiation of antihypertensive pharmacological treatment, more girls than boys were > 12 years of age, 16/46 (35%) versus 13/73 (18%), ( $p = 0.04$ ).

Most of the children with stage 2 hypertension, 56/62 (90%), received antihypertensive medicine within three months of their diagnosis, compared with 36/57 (63%) of those with stage 1 hypertension, ( $p = 0.001$ ).

### Aetiology

Secondary hypertension affected 95/119 (80%) patients; of these, 62/119 (52%) presented renal aetiology, **Table 2**.

Patients with primary hypertension tended to be older, median 11.1 years (range: 0-15.7 years), at the initiation of their pharmacological treatment than patients with secondary hypertension, median 6.7 years (range: 0-15.6 years), ( $p = 0.07$ ).

**TABLE 2** The aetiology of hypertension in children receiving antihypertensive medication.

	Age at initiation of pharmacological treatment, median (IQR), yrs	Gender			p-value
		girls, n	boys, n	total, n	
<i>Primary hypertension</i>	11.1 (2.7-13.3)	9	15	24	0.90
Essential	12.5 (2.9-12.9)	< 5 <sup>f</sup>	7	9	0.30
Prematurity	6.0 (0.4-10.8)	5	< 5 <sup>f</sup>	8	0.20
Obesity	14.8 (11.1-14.8)	< 5 <sup>f</sup>	5	7	0.60
<i>Secondary hypertension<sup>g</sup></i>	6.7 (1.7-11.7)	37	58	95	0.90
Renal aetiology: <sup>a-d</sup>	7.4 (2.4-10.3)	25	37	62	0.70
Congenital renal anomalies <sup>a</sup>	6.5 (1.6-9.2)	< 5 <sup>f</sup>	18	21	0.01
Acquired kidney disease <sup>b</sup>	9.2 4-12.1)	12	12	24	0.20
Polycystic renal disease <sup>c</sup>	0.1 (0-9.1)	5	< 5 <sup>f</sup>	7	0.07
Syndromes or conditions with kidney affection, and unspecified impaired kidney function <sup>d</sup>	5.5 (4.1-8.6)	5	5	10	0.40
Non-renal aetiology <sup>e</sup>	5.8 (1.4-13.2)	12	21	33	0.75
Total	7.7 (1.7-11.7)	46	73	119	0.01

IQR = interquartile range.

a) Including patients with posterior urethral valves, renal hypoplasia, renal agenesis, dilated vesicourethral reflux, hydronephrosis, renal dysplasia, unspecified

cystic renal disease, horseshoe kidney, duplex system.

b) Including 17 unspecified glomerulonephritis, Henoch-Schönlein purpura, haemolytic uremic syndrome, Wegener's granulomatosis, interstitial nephritis, pyelonephritis sequelae.

c) Including autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease.

d) Including Alport syndrome, Bardet-Beidel syndrome, kidney affection due to mitochondrial disease and unspecified impaired kidney function.

e) Including 13 congenital reno- and cardio-vascular anomalies (< 5 with coarctatio aortae), 12 pharmacologically induced hypertension, miscellaneous, endocrinological disease.

f) The information is censored due to Danish regulations from the the National Health Data Authority.

g) In total, 10 patients with secondary hypertension also had obesity.

## Assessment of target-organ damage

All patients underwent renal and urine examinations, whereas only 92/119 (77%) underwent echocardiography and 89/119 (75%) underwent retinal examination, **Table 3**.

**TABLE 3** Results of examination for target-organ damage in hypertensive children at start of treatment, classified in accordance with aetiology of hypertension. The values are n (%).

	Total (N = 119 (100%))	Glomerular filtration rate <sup>a</sup>		Proteinuria <sup>b</sup>		Echocardiogram			Retinal examination		
		normal (n = 68 (57%))	abnormal (n = 51 (43%))	normal (n = 58 (49%))	abnormal (n = 61 (51%))	normal (n = 61 (51%))	abnormal (n = 31 (26%))	not available (n = 27 (%))	normal (n = 71 (60%))	abnormal (n = 18 (15%))	not available (n = 30 (25%))
Primary hypertension	24 (20)	21 (88)	< 5 <sup>c</sup>	13 (54)	11 (46)	15 (63)	8 (33)	< 5 <sup>c</sup>	15 (63)	7 (29)	< 5 <sup>c</sup>
<i>Secondary hypertension</i>											
Renal aetiology <sup>d</sup>	62 (52)	18 (29)	44 (71)	21 (34)	41 (66)	23 (37)	15 (24)	24 (39)	32 (52)	6 (10)	24 (39)
Non-renal aetiology <sup>e</sup>	33 (28)	29 (88)	< 5 <sup>c</sup>	24 (73)	9 (27)	23 (70)	8 (24)	< 5 <sup>c</sup>	24 (73)	5 (15)	< 5 <sup>c</sup>
Subtotal	95 (80)	47 (50)	48 (50)	45 (47)	50 (53)	46 (48)	23 (24)	26 (27)	56 (59)	11 (12)	28 (29)

CKD = chronic kidney disease.

a) Including 24 children < 1 yr, by converting tables [14] these patients were placed as normal in 17 cases or the corresponding CKD stages 2-5 in 7 cases.

b) Based on a 24-h urine analysis in 63 patients and a urine dipstick in 56 cases.

c) The information is censored due to Danish regulations from the National Health Data Authority.

d) See Table 2 notes a-d.

e) See Table 2 note e.

Patients with renal aetiology of hypertension more often had chronic kidney disease (44/62; 69%) than the remaining patients (7/57, 13%;  $p < 0.001$ ); the same applied to patients with renal aetiology of proteinuria (41/62, 66% vs. 20/57, 35%;  $p < 0.001$ ).

Patients who were pharmacologically treated for primary hypertension underwent echocardiography, (23/24, 96%) and retinal examination (22/24, 92%) more often than those treated for secondary hypertension (69/95, 73% and 67/95, 71%), respectively ( $p < 0.01$  and  $p < 0.05$ ), **Table 3**.

For patients with renal aetiology, both echocardiography and retinal examination were performed in 38/62 (61%) of cases, whereas the remaining patients underwent echocardiography in 54/57 (95%) of cases ( $p < 0.001$ ) and

51/57 (89%) of cases ( $p < 0.001$ ), Table 3.

Abnormal echocardiography including left ventricular hypertrophy was found in 15/38 (39%) of the patients with renal aetiology and in 16/54 (30%) of the remaining patients ( $p = 0.3$ ). Abnormal retinal examination was found in 6/38 (16%) of the patients with renal aetiology and in 12/51 (24%) of the remaining patients ( $p = 0.4$ ), Table 3.

Patients with stage 2 hypertension more frequently underwent retinal examination (55/62, 89%) than patients with stage 1 hypertension (34/57, 60%;  $p < 0.001$ ).

## Symptoms

Symptomatic hypertension was registered in 45/119 (38%) of patients, most often headache which affected 29/119 (24%) of the patients. About half of these patients (16/29, 55%) had headaches  $> 3$  times a week.

## Obesity and family history

Obesity was reported in 17/119 (14%) of patients, and more often in those with primary (7/24, 29%) than with secondary hypertension (10/95, 11%;  $p = 0.02$ ). Based on family history, at least one parent had diagnosed hypertension in 17/119 (14%) of patients; of these, 8/24 (33%) had primary hypertension and 9/95 (9%) had secondary hypertension, ( $p < 0.005$ ).

## DISCUSSION

In this retrospective cohort study, secondary hypertension was identified in 80% of children  $< 16$  years of age who had been registered with hypertension and treated pharmacologically. Renal aetiology was found in 52% of these patients, which is in line with previously reported figures [1, 9-11]. All present patients underwent renal and urine examinations. Both echocardiography and retinal examination were performed in 61% of patients with renal aetiology and less frequently than in the remaining patients. Consequently, our hypothesis that all the present patients had undergone examination for target-organ damage at the initiation of their antihypertensive medical treatment was not confirmed. A worrying incidence of cardiovascular subclinical organ damage in children following kidney transplantation has been reported with up to 41% of patients suffering from uncontrolled or untreated hypertension [17]. Such patients may suffer cardiovascular organ damage due to other causes, but patients with renal diseases have a high risk of future complications due to cardiovascular disease [18]. Hence, it is of concern that 39% of the present hypertensive children with renal aetiology did not undergo evaluation for target-organ damage before their antihypertensive pharmacological treatment was initiated. We speculate that for some children with chronic kidney disease, the focus may have been on hypertension without awareness of the need to assess any target-organ damage. Based on the high risk of cardiovascular disease in renal patients, we find early detection of target-organ damage important in such patients.

Paediatric patients with hypertension rarely present with overt symptoms of cardiovascular disease. Assessment of left ventricular hypertrophy remains a cornerstone when diagnosing target-organ damage in paediatric hypertension [9]. We found that 39% of the examined children with hypertension of renal aetiology had abnormal echocardiography, as had the remaining patients in our analysis, which is comparable with another study [9]. It might be of concern that, as not all patients were examined for target-organ damage, some hypertensive children might miss treatment that could reverse target-organ damage [1, 7]. Blood pressure can be controlled effectively in hypertensive children by pharmacological treatment [8, 19]. Clinical data are lacking, but antihypertensive drugs that effectively reduce blood pressure lead to regression of left ventricular hypertrophy, reduction of intima-media thickness and microalbuminuria in childhood [1, 7, 8].

In our cohort, 66% of patients with acquired renal aetiology had proteinuria at initiation of antihypertensive

pharmacological treatment, which is consistent with other studies [9]. In children with chronic kidney disease, strict blood pressure control may lead to less progressive kidney disease [1].

A total of 20% of the present patients had retinal changes at the initiation of pharmacological treatment. This percentage is higher than the 9% found in a previous study that excluded hypertensive patients with diabetes and renal disease [20]. Based on European guidelines, routine application of funduscopy should be restricted to assessing the presence of hypertensive encephalopathy or malignant hypertension [11]; this, however, is not the case for American and Danish guidelines [9, 10].

Headache was the most prevalent symptom at diagnosis in children treated pharmacologically for hypertension; this highlights the importance of blood pressure measurement in children with headache.

### Strengths and limitations

The analyses were possible owing to the strong Danish tradition for health registers and the high quality of these registers [2]. Moreover, it is a strength that all medical records were available for review and that antihypertensive medications were prescribed in accordance with national and international guidelines [1, 9-11].

The limitations of the study were its retrospective design and the fact that diagnosis, treatment and examinations were carried out by different physicians, although paediatricians in Denmark in general follow national guidelines [10]. Moreover, it is a limitation that, in Denmark, children are not screened systematically for hypertension. Those who were diagnosed and treated might therefore represent a special group with a high risk of hypertension [2]. We included patients who were registered with an ICD-10 diagnosis of hypertension. However, some children with hypertension and other diagnoses, e.g. cancer, may remain unregistered for hypertension as the diagnosis of hypertension was of lesser importance and therefore not recorded. Consequently, some hypertensive patients might not have been identified in our study.

### CONCLUSIONS

Secondary hypertension was identified in 80% of children < 16 years of age who were registered with hypertension and treated pharmacologically. The majority (52%) had hypertension of renal aetiology. Only 61% of these patients underwent a full evaluation for target-organ damage prior to initiation of antihypertensive pharmacological treatment. We recommend that all hypertensive children undergo a full examination for target-organ damage as this may potentially reduce their long-term morbidity.

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