Clinical features and management of arterial hypertension in children with Williams–Beuren syndrome

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Abstract

Background. Hypertension is a common finding in children with Williams–Beuren syndrome (WBS).

Methods. The aim of this retrospective study was to review the clinical presentation of systemic hypertension in WBS children, its origin and management. We included 41 children with confirmed WBS who were referred to the paediatric nephrology or cardiology unit for hypertension.

Results. The mean age at diagnosis of hypertension was 4.7 years. Out of 41, 24 patients had systolic blood pressure (BP) between +10 and +30 mmHg above the 95th percentile (1.645 SD), and 20/41 patients had diastolic BP between the 95th percentile (1.645 SD) and >10 mmHg. Thirty-nine patients were asymptomatic. Arteriography, performed in 17/41 patients, revealed a renal artery stenosis (RAS) in 10 patients (58%). Echocardiography was performed in all patients and showed isthmic coarctation in four patients (9%). Calcium channel blockers were used in half of the patients (22/41) and seemed to control hypertension in most cases. Interventional treatment of RAS was performed in five patients (three angioplasty and two surgical bypass). It controlled hypertension in one patient but remained ineffective in the four others.

Conclusions. Medical treatment essentially calcium blockers improved hypertension in most cases. Interventional treatment of RAS has not been encouraging.

Keywords: arterial hypertension; renal artery stenosis; Williams–Beuren syndrome

Introduction

Williams–Beuren syndrome (WBS) (OMIM # 194050) is caused by a heterozygous microdeletion of the chromosome region 7q11.23, including among others the elastin gene. The main clinical features include a distinctive facial appearance with elfin facies, mental and statal deficiencies, cardiovascular abnormalities (commonly supravalvular aortic stenosis) and occasionally infantile hypercalcaemia [1]. WBS children are also at risk for systemic hypertension, with a frequency ranging from 5 to 70% in the literature (Table 1). A clear aetiology is found in only a minority of patients including renal artery stenosis (RAS) and/or diffuse aortic narrowing and/or aortic coarctation. The vascular lesions in WBS seem to be linked to reduced elastin synthesis and increased proliferation of vascular smooth muscle cells [2], but the exact pathways connecting the elastin deficiency to increased vascular cell proliferation are still unknown.

Pathological vascular lesions in WBS include increased intima–media thickness with thick irregular elastic fibres, swirling collagen and hypertrophied smooth muscle cells. However, the compliance of the large elastic arteries is not modified in these patients [8]. There are few data on the clinical characteristics and management of hypertension in these children. We report on a multicentric retrospective study including 41 WBS patients with systemic hypertension. Our aim was to study the clinical presentation and the aetioligic investigations of hypertension on the one hand and to evaluate the medical or endovascular management on the other hand.

Patients and methods

Clinical and biological data

A total of 19 paediatric nephrology units in France, Belgium and Canada were invited to participate in this retrospective study. A questionnaire for all children aged 20 years or less with a diagnosis of WBS associated with hypertension was filled. Thirteen centres (11 in France, 1 in Belgium and 1 in Canada) provided clinical information concerning 41 WBS patients referred for systemic hypertension between 1990 and 2008. Hypertension was defined for patients aged ≤17 years as average systolic BP (SBP) and/or diastolic BP (DBP) ≥ 95th percentile for gender, age and height on ≥3 occasions, based upon the 2004 National High Blood Pressure Education Program Working Group (NHBPEP) [3]. For patients aged >17 years at diagnosis, hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg [4]. BP was rarely reported of both arms which
would have eliminated the Coanda effect related to supravalvular aortic stenosis that may cause elevated BP only in the right arm [15]. The patient’s medical history was reviewed with emphasis on the occurrence of hypertension, including age, circumstances of diagnosis, BP measurements and symptoms related to hypertension. Left ventricular hypertrophy on initial echocardiography was noted. Other main features of WBS such as congenital heart defects and mental retardation were also noted. For each patient, serum creatinine values and total calcaemia from the diagnosis of WBS until the last follow-up were recorded. Hypercalcaemia was defined as a serum calcium > 2.75 mmol/l. Renal function assessed by estimated glomerular filtration rate (eGFR) according to the Schwartz formula was recorded, and renal insufficiency was defined as eGFR < 75 ml/min/1.73 m².

### Radiological findings

Data from kidney ultrasonography (US) performed when hypertension was diagnosed were recorded. Doppler US of renal artery, CT angiography and conventional renal arteriography were recorded when performed.

#### Treatment outcomes

The results of the medical treatment or revascularization procedures were classified as follows: (1) resolved hypertension, when SBP and DBP became < 95th percentile (for gender, height and weight) without any medication, but after a treatment with one or more antihypertensive agents and/or after revascularization procedure; (2) controlled hypertension, when SBP and DBP become < 95th percentile with an ongoing antihypertensive treatment, whether they underwent a revascularization procedure or not (surgical reconstruction or angioplasty) and (3) unchanged hypertension, when hypertension persisted on antihypertensive agents or after a renal artery or aortic intervention. The results of the study were expressed as mean and the interquartile range.

### Results

#### Demographic data

Forty-one patients (24 males) were included in the study. The mean age at the time of the study was 10.66 years (range: 1–18 years). The diagnosis of WBS was confirmed in all patients by FISH analysis at a mean age of 2.53 years (range: 1 month–16 years). The other clinical features included cardiovascular abnormalities (39/41), with supravalvular aortic stenosis (n = 10), peripheral pulmonary stenosis (n = 10), aortic coarctation (n = 4) and both supravalvular aortic stenosis and peripheral pulmonary stenosis (n = 10), transposition of great vessels (n = 1), pulmonic valve stenosis (n = 1) and heart ventricular defect (n = 3). Developmental delay or mental retardation was present in 35/41 patients.

#### BP data

The average age at diagnosis of arterial hypertension was 4.72 years (range: 1 month–16 years). Thirty-nine out of 41 patients were asymptomatic. Hypertension was detected on routine BP measurement at follow-up visits. Two patients had headaches. Concerning systolic BP, 4/41 patients had values between 95th percentile (1.645 SD) and 10 mmHg above, 24/41 had values between +10 and +30 mmHg above the 95th percentile and 13/41 had values above 95th +30 mmHg. For diastolic BP, 20/41 patients had values between 95th percentile and 10 mmHg above, 16/41 had values between +10 and +30 mmHg above the 95th percentile, and 5/41 had values above 95th +30 mmHg (Task Force [3]). Left ventricular hypertrophy on initial echocardiography was found in 24/41 patients (58%).

#### Diagnostic studies

Renal ultrasonography (US) was normal in 33/41 patients. Abnormalities were detected in eight patients with a left multicystic kidney and an hypoplastic right kidney (n = 1), megacalycosis with bilateral ureterohydronephrosis (n = 1), left multicystic kidney (n = 1), bladder diverticula with a left multicystic kidney (n = 1), bilateral renal hypoplasia (n = 1), left renal agenesis (n = 1) and right renal hypoplasia (n = 1). One patient presented ultrasound findings consistent with nephrocalcinosis. Doppler examination of renal arteries was performed initially for 38/41 patients, it was normal in 21 patients and not conclusive because of child agitation in 8 patients.

Arteriography was performed in 17/41 patients. A RAS was found in 10 patients (58%). Stenosis was located in the main renal artery in five patients (bilateral in four cases and unilateral in one case), close to the ostium in two patients (bilateral in one patient and unilateral in the other) and located in the distal segments of the renal artery in three patients. Arteriography was normal in five patients and found
an aortic coarctation in the remaining two patients. All other vascular abnormalities detected were associated with RAS, they consisted in aortic coarctation with hypoplastic abdominal aorta (n = 1), hypoplastic abdominal aorta (n = 2), ostial stenosis of the celiac trunk (n = 1), stenosis of the superior mesenteric artery associated with stenosis of the celiac trunk (n = 1), and stenosis of the superior mesenteric artery (n = 1). CT angiography was performed in 14/41, and showed right RAS (n = 3), ostial stenosis of the right RA (n = 1) and bilateral RAS (n = 3). It was normal in five cases and showed an isolated aortic isthmic coarctation in one case, and hypoplastic abdominal aorta in three cases (concomitant to RAS in one case and to isthmic coarctation in one case and isolated in one case). When both arteriography and CT angiography were performed (three patients), results were concordant in one patient (bilateral RAS, patient 33), and discordant in two patients (RAS was found in CT angiography, while arteriography was considered to be normal, patients 25 and 41) (Supplementary Table 1). When both arteriography and Doppler US of the renal arteries were performed, the results were concordant in six patients (patients 4, 7, 12, 21, 33, 36) and discordant in three patients (patient 20, 25, 26) (Supplementary Table 1).

One patient had an acute ischaemic stroke without vascular lesions on MRI, and another one had five transient ischaemic attacks and two strokes with a supracilindric internal carotid artery stenosis on MRI. Two patients had a myocardial infarction with coronary artery lesions on computed tomography (left main coronary artery trunk and interventricular arteries).

**Treatment**

**Medical treatment.** Twenty-two patients were given a single antihypertensive agent, 11 two agents, 1 three agents, 3 four agents. Twenty-two patients received calcium channel blockers (22/41). Angiotensin-converting enzyme (ACE) inhibitors were used in 14/41 and beta-blockers in 12/41 patients. Other agents [alpha and beta-blockers (labetalol) and angiotensin-2 receptor blockers] were used less frequently (Supplementary Table 1). In patients who were exclusively under medical treatment (27/41), hypertension was cured in 1 patient, controlled in 24 patients and remained unchanged in 2 patients. In patients who did not receive any medical treatment (4/41), BP normalized with a salt-restricted diet.

**Interventional treatment**

Four different interventional treatments were performed: (1) A 2-year-old patient with bilateral RAS and hypertension resistant to four concomitant antihypertensive agents underwent an aorto-renal bypass using the hypogastric artery, with an initial improvement allowing a reduction of antihypertensive therapy. Two months later, he underwent an angioplasty for left side renal artery bypass stenosis with transitory improvement, but a single antihypertensive agent was introduced within the following 2 months. (2) A spleno-left renal-artery anastomosis for bilateral RAS and hypertension under bitherapy was performed on a 13-year-old patient, but hypertension remained severe after surgery, and 5 years after the procedure the patient was under cal-cium channel inhibitors associated with a beta-blocker with a partial improvement. (3) A percutaneous transluminal renal angioplasty (PTRA) was performed in three children aged 2, 6 and 11, respectively, with bilateral stenosis of the main renal artery and uncontrolled hypertension under multidrug therapy. The technique used for PTRA was balloon dilatation alone. It was unsuccessful in the three children. Nonetheless, after the angioplasty, one of them had an aorto-renal bypass that controlled the hypertension. (4) A surgery of aortic coarctation was performed in four patients. Hypertension was cured in two of them and controlled in the two others.

**Discussion**

This study was not designed to evaluate the prevalence of hypertension in WBS since we have only considered patients with high BP. The prevalence of hypertension is highly variable in the literature ranging from 5 to 70% in the different series (see references in Table 1). However, hypertension was asymptomatic in all patients except two in this cohort, suggesting that hypertension is probably underestimated in this syndrome. Since the initial report of Daniels et al. [5] describing the causal relationship between vascular abnormalities and hypertension, arterial lesions in WBS have received much attention. The lesions include localized or diffuse narrowing of elastic arteries and may be progressive [6]. Intravascular ultrasound shows severe arterial wall thickening with secondary lumen narrowing in WBS [7] and the pathology shows elastic disorganization, hypertrophied smooth muscle cells and collagen bundles. However, in many patients, vascular lesions are not found and hypertension remains unexplained. Various hypotheses such as a decreased compliance of the large arteries in WBS have been put forward but the compliance of the carotid arteries is not significantly modified in these patients [8]. Wessel et al. [9] found that the mean heart rate in WBS is high in both daytime and nighttime in normo and hypertensive patients with WBS, suggesting that a high sympathetic activity might play a role in hypertension. Broder et al. found [17] that hypertension is significantly more common in WBS subjects with a history of infantile hypercalcaemia, but no direct relationship between hypercalcaemia and hypertension was found until now.

In our study, arteriography was performed in 17 patients (41%). RAS and/or aorta narrowing was found in 10 patients (58%). In the literature [11,12], the incidence of renal artery narrowing in WBS is variable ranging from 44 to 61% when arteriography is performed. We recommend to perform at least an echocardiography and a Doppler renal US in the initial evaluation of a child with WBS and hypertension; CT angiography should be discussed when hypertension is severe and resistant to medical therapy, and/or the results of non-invasive tests are inconclusive. MRI angiography is an evolving procedure that now competes with CT angiography, and can visualize main and co-dominant renal arteries. It is a non-radiating procedure with good diagnostic performance especially in adult patients. However, its use in paediatrics is still limited in this indication with many technical problems, such as respiratory artefacts. It may in
the future become a good procedure for detecting renovascular hypertension in WBS children with hypertension.

In our cohort, two patients had ischaemic stroke and two others a myocardial infarction. This prompts for better control of arterial hypertension in WBS children, in order to reduce the already important vascular risk.

There is little information focusing on medical treatment of hypertension in WBS children and there is no recommendation for drug selection in these patients. Some authors recommend beta-blockers [9] taking into account the fact that sympathetic overactivity may contribute to the occurrence of hypertension. Calcium channel blockers have also been frequently used in many retrospective series [13,14]. In the present series, 22/41 patients were under one antihypertensive treatment, essentially a calcium channel blocker (10/22) or ACE inhibitors (6/22). Under exclusive medical therapy (27/41), hypertension was cured in 1 patient, controlled in 24 patients and remained unchanged in 2 patients. Thus, from our experience, calcium channel blockers and/or ACE inhibitors are often successful in controlling BP. There is little information regarding the interventional treatment on RAS in WBS (Table 2). In our series, two patients underwent surgical treatment for severe hypertension due to bilateral RAS. The first had an aortorenal bypass that controlled hypertension and the second had a spleno-left-renal-artery anastomosis that had no effect on hypertension. PTRA was ineffective in the three children. We cannot conclude about the real efficacy of renal artery revascularization with surgical reconstruction and/or PTRA in these children, as the experience is still limited. Thus far, only four children have been reported in the literature (Table 2), with only one successfully dilated RAS reported. Renal artery revascularization with surgical reconstruction and/or PTRA seems globally not very encouraging.

Conclusion

Arterial hypertension in children with WBS is a common finding and all patients with WBS should undergo regular BP measurements. Aetiological investigation searching for a renovascular aetiology should be performed in all cases, including, at least initially, a Doppler renal US and echocardiography. CT angiography should be discussed when hypertension is severe and resistant to medical therapy or when pathological findings are noted on renal US. Renal arteriography remains the gold standard for the diagnosis of RAS; however, it should be performed only if PTRA is considered. Medical treatment seems to be efficient in most cases, essentially calcium channel blockers and/or ACE inhibitors. The results of interventional treatment of RAS in WBS remain poor.

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Conflict of interest statement. None declared.


Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

References


Table 2. Outcome of the revascularization procedure for children with Williams–Beuren syndrome and renovascular hypertension: review of the literature

<table>
<thead>
<tr>
<th>Sex/age</th>
<th>Type of lesion</th>
<th>Type of treatment</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/5</td>
<td>Bilateral RAS</td>
<td>Angioplasty</td>
<td>Unsuccessful</td>
<td>Courtel et al. [21]</td>
</tr>
<tr>
<td>M/6</td>
<td>Bilateral RAS</td>
<td>Angioplasty</td>
<td>Unsuccessful</td>
<td>Present study</td>
</tr>
<tr>
<td>M/11</td>
<td>Left RAS</td>
<td>Angioplasty</td>
<td>Successful</td>
<td>Rose et al. [22]</td>
</tr>
<tr>
<td>M/14</td>
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<td>Surgery</td>
<td>Unsuccessful</td>
<td>Sugayama et al. [19]</td>
</tr>
<tr>
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<td>Surgery</td>
<td>Unsuccessful</td>
<td>Present study</td>
</tr>
<tr>
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<td>Unsuccessful</td>
<td>Present study</td>
</tr>
<tr>
<td>F/11</td>
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The endogenous modulators of Ca$^{2+}$–Mg$^{2+}$-dependent ATPase in children with chronic kidney disease (CKD)

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Abstract

Background. Calcium homeostasis is disturbed in many ways in the course of chronic kidney disease (CKD). The concentration of free cytoplasmic calcium in erythrocytes is increased. Maintenance of a high concentration gradient (between the cytoplasmic and extracellular space) is possible only due to a finely tuned cooperation between many regulating systems in the cytoplasmic membranes and cell organelles. The aim of our study was to evaluate the activity of Ca$^{2+}$–Mg$^{2+}$-dependent ATPase (PMCA), calmodulin and calpain–calpastatin (CANP–CAST) system in erythrocytes of CKD children treated conservatively in the stages II–IV.

Methods. A total of 36 patients with CKD were enrolled in the study. Group A contained patients with CKD stage II; group B with CKD stage III; and group C with CKD stage IV. The control group D consisted of 30 healthy subjects. In the serum, we determined the following: intact parathormon, total calcium, creatinine; in the red blood cells: free cytosolic calcium concentration ([Ca$^{2+}$]), activity of Ca$^{2+}$–Mg$^{2+}$-transporting ATPase (PMCA), calmodulin and calpain–calpastatin (CANP–CAST) system in erythrocytes of CKD children treated conservatively in the stages II–IV.

Results. In all groups, Ca$^{2+}$ concentrations were significantly higher, whereas PMCA and bPMCA activity were lower than in the controls. CANP concentrations in group A were elevated compared to the controls, whereas in groups B and C they were significantly lower. In group C, the mean CAST activity reached the highest values. CALM concentrations were decreased versus controls in all groups of patients.

Conclusions. The intracellular Ca$^{2+}$ homeostasis is disturbed in children with CKD and aggravates the deterioration of renal function as well. The reasons for the progressing increase of erythrocyte calcium concentration are...