Renovascular hypertension in children and adolescents

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Renovascular hypertension in children and adolescents

- Etiology of pediatric hypertension
- Etiology of renovascular hypertension in children
  - fibromuscular dysplasia
  - syndromic RVH
- Pathophysiology of arterial hypertension in renal artery stenosis
- Treatment
- Perspectives & challenges
Etiology of arterial hypertension in children and adolescents – 2010+

Renal parenchymal diseases and renovascular hypertension is the main cause of secondary hypertension in children

<table>
<thead>
<tr>
<th>Condition</th>
<th>0-5</th>
<th>6-14</th>
<th>15-18</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal parenchymal diseases</td>
<td>74 (21.0)*</td>
<td>114 (32.5)</td>
<td>50 (14.2)</td>
<td>238 (67.7)</td>
</tr>
<tr>
<td>Renovascular</td>
<td>8 (2.3)</td>
<td>11 (3.1)</td>
<td>15 (4.3)</td>
<td>34 (9.7)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>7 (2)</td>
<td>11 (3.1)</td>
<td></td>
<td>18 (5.1)</td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
<td>3 (0.9)</td>
<td>4 (1.1)</td>
<td></td>
<td>7 (2)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>1 (0.3)</td>
<td>4 (1.1)</td>
<td>1 (0.3)</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Adrenocortical hyperfunction</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>4 (1.1)</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Turner's syndrome</td>
<td>1 (0.3)</td>
<td>3 (0.9)</td>
<td></td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Coarctation</td>
<td>5 (1.4)</td>
<td>3 (0.9)</td>
<td></td>
<td>8 (2.3)*</td>
</tr>
<tr>
<td>CNS disorders</td>
<td>7 (2)</td>
<td>4 (1.1)</td>
<td>2 (0.6)</td>
<td>13 (3.7)</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>6 (1.7)</td>
<td>3 (0.9)</td>
<td></td>
<td>9 (2.6)</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>2 (0.6)</td>
<td></td>
<td></td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (1.7)</td>
<td></td>
<td></td>
<td>6 (1.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>105 (29.9)</strong></td>
<td><strong>153 (43.6)</strong></td>
<td><strong>93 (26.5)</strong></td>
<td><strong>351 (100)</strong></td>
</tr>
</tbody>
</table>

*Excluding Coarctation

Causes of RVH in children

- Fibromuscular dysplasia
  - focal
  - multifocal
- Mid-aortic syndrome with RAS?
- Syndromic RVH
  - NF1
  - Williams syndrome
  - Alagille syndrome
  - other (TSC, moya-moya ?)
- Vasculitis
  - Takayasu’s disease
  - polyarteritis nodosa
  - Kawasaki disease
  - other vasculitides
- Extrinsic compression
  - tumors (neuroblasoma, Wilms tumor, paraganglioma, etc.)
- Other
  - trauma
  - post-surgical complications
  - radiation

RVH may not be isolated to renal artery/-ies

RVH may evolve and new stenoses may occur
Causes of RVH in children.
Fibromuscular dysplasia

Serial sections taken from multiple cuts, from the artery proximal to its entry into the renal hilum, showed very interesting findings. The wall of the artery itself was in general not altered, but the lumen was almost filled by a mass of tissue made up chiefly of smooth muscle outlined by an elastic lamella. Within this muscle plug were seen small vessels. There appeared to be a defect in the wall of the artery at one level characterized by thinning of the 3 layers and complete loss of elastic tissue.
## Fibromuscular dysplasia – from pathological to radiological classification

<table>
<thead>
<tr>
<th>Pathological classification (1971)</th>
<th>Radiological classification (2012- European Consensus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial fibrosis (75-80%)</td>
<td>Multifocal (string of beads)</td>
</tr>
<tr>
<td>Outer layer of media (10-15%)</td>
<td></td>
</tr>
<tr>
<td>Hypertrophy of media (1-2%)</td>
<td></td>
</tr>
<tr>
<td>Intimal dysplasia (&lt;10%)</td>
<td>Focal (&lt;1 cm); Tubular (&gt;1 cm)</td>
</tr>
<tr>
<td>Adventitial degeneration/dysplasia (&lt;1%)</td>
<td>Focal</td>
</tr>
</tbody>
</table>

### Radiological classification AHA (2014)

- Multifocal
- Focal:
  - unifocal
  - tubular
RVH is a disease not limited to renal arteries

<table>
<thead>
<tr>
<th>Cause</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uni-/bilateral focal FMD</td>
<td>36</td>
</tr>
<tr>
<td>Multifocal FMD of renal and infrarenal arteries</td>
<td>29</td>
</tr>
<tr>
<td>FMD + mid-aortic syndrome</td>
<td>15</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>14</td>
</tr>
<tr>
<td>Takayasu arteritis</td>
<td>3</td>
</tr>
<tr>
<td>Williams syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Alagile syndrome</td>
<td>1</td>
</tr>
<tr>
<td>FMD</td>
<td>71.5%</td>
</tr>
<tr>
<td>Syndromic RVH</td>
<td></td>
</tr>
<tr>
<td>- NF1</td>
<td>-24.3%</td>
</tr>
<tr>
<td>- Williams s.</td>
<td>- 2.5%</td>
</tr>
<tr>
<td>- velocardiofacial s.</td>
<td>- 1.3%</td>
</tr>
<tr>
<td>- Alagille s.</td>
<td>- 1.3%</td>
</tr>
<tr>
<td>Syndromic RVH</td>
<td>29.5%</td>
</tr>
<tr>
<td>Unilateral RAS</td>
<td>55.1%</td>
</tr>
<tr>
<td>Bilateral RAS</td>
<td>44.9%</td>
</tr>
<tr>
<td>Intrarenal disease</td>
<td>23%</td>
</tr>
<tr>
<td>RAS + mid-aortic syndrome</td>
<td>25.6%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>17.9%</td>
</tr>
</tbody>
</table>

N = 92
Renovascular hypertension - pathophysiology

3 (4) stages of RVH:

1 – elevation of BP caused by RAAS (unilateral renal artery stenosis) and/or RAAS and sodium retention (bilateral renal artery stenosis)

2 – maintenance of elevated BP with new threshold for natriuresis (bilateral RAS)

3 – kidney damage:

Ischemic kidney – ischemic nephropathy (decreased volume, tubular atrophy, tubulointerstitial fibrosis)

Kidney with patent renal artery and exposed to high BP – hypertensive nephropathy (arteriolar and glomelular injury)

4 – hypertensive crisis
RVH - pathophysiology

Ischemic kidney:
RAAS↑↑, autonomic NS↑↑
Na retention
Ischemic nephropathy

High-pressure kidney:
pressure natriuresis
Hypertensive nephropathy

Result:
high-renin hypertension, secondary hyperaldosteronism
relative hypovolemia/Na deficit
hypokalemia, metabolic alkalosis
RVH - pathophysiology

Bilateral RAS:
- Bilateral kidney ischemia
- RAAS↑↑, autonomic NS↑↑
- Na retention
- Secondary inhibition of renin generation

Result:
- Na retention, hypervolemia
- BP ↑ to excrete Na
- K – normal, low metabolic alkalosis
Renal consequences of RVH. Unilateral renal artery stenosis.

RVH in 12 months girl. Ischemic kidney. Tubular necrosis.

10 months old girl. Biopsy of kidney with patent renal artery and exposed to high BP (180-200/120 mmHg).
Hypertensive nephropathy:
- nephrothc proteinuria
- mesangial proliferation
- hypertrophy of arteriolar wall
Hypertensive nephropathy of right kidney (red line) with patent renal artery and exposed to high BP.

Before

After PTRA
RVH: pathophysiology

**Unilateral renal artery stenosis:**
- high renin activity/concentrations
- total peripheral resistance $\uparrow\uparrow\uparrow$
- relative hypovolemia
- stimulation of circulatory centers in CNS
- hypertensive injury of contralateral kidney

**Bilateral renal artery stenosis:**
- renin generation hampered by sodium retention
- hypervolemic hypertension with inadequate increase of total peripheral resistance
- ischemic injury of two kidneys
- stimulation of sympathetic centers in CNS
RVH in children and adolescents – clinical presentation

Clinical symptoms 40/87

BP screening 47/87
## RVH in children and adolescents – clinical presentation

### Table 1
**Presenting features in all children and according to the age at presentation: <5 years, 5–11 years and 12–17 years**

<table>
<thead>
<tr>
<th>Mode of presentation</th>
<th>All children 78 (%)</th>
<th>Age &lt; 5 years 26 (%)</th>
<th>Age 5–11 years 39 (%)</th>
<th>Age 12–17 years 13 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidental finding</td>
<td>36 (46%)</td>
<td>6 (23%)</td>
<td>23 (59%)</td>
<td>7 (54%)</td>
</tr>
<tr>
<td>Headache with vomiting, lethargy or excessive screaming</td>
<td>14 (17.9%)</td>
<td>3 (11.5%)</td>
<td>8 (20.5%)</td>
<td>3 (23.1%)</td>
</tr>
<tr>
<td>Cardiac features (palpitations, congestive heart failure or murmurs)</td>
<td>8 (10.3%)</td>
<td>4 (15.3%)</td>
<td>3 (7.7%)</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Neurological manifestations (seizure or ptosis and eye movement disorder)</td>
<td>7 (9%)</td>
<td>4 (15.3%)</td>
<td>2 (5.1%)</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Facial palsy</td>
<td>6 (7.7%)</td>
<td>5 (19.2%)</td>
<td>1 (2.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>3 (3.9%)</td>
<td>1 (3.8%)</td>
<td>1 (2.6%)</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Poor feeding and failure to thrive</td>
<td>2 (2.6%)</td>
<td>2 (7.7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hyponatraemic-hypertensive syndrome (HHS)</td>
<td>1 (1.3%)</td>
<td>1 (3.8%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>As part of investigations for neurofibromatosis type 1</td>
<td>1 (1.3%)</td>
<td>0 (0%)</td>
<td>1 (2.6%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

RVH in children and adolescents – clinical presentation

54% - asymptomatic, found at screening
but
16% presented as hypertensive crisis:
10/87 – severe hypertension with hypertensive retinopathy
3/87 – stroke

46% - asymptomatic, found at screening
but
21% presented as hypertensive crisis:
13/78 – severe hypertension with brain oedema
3/78 - stroke

Antoniewicz J et al. abstracts: Pediatr Nephrol 2002
J Hypertens 2007

RVH in children and adolescents – target organ damage

**ECG:**
- LVH: 58/64 (91%)
- LVH + rhythm disturbances: 1/64 (1%)
- LVH + myocardial ischemia: 5/64 (8%)

**ECHO:**
- LVH - 45/81 (56%)
- LVH: 40/60 (66.7%)
- Hypertensive retinopathy: 11/47 (23.4%)

LVH more often in symptomatic children (p<0.05)
## RVH in children and adolescents – target organ damage

<table>
<thead>
<tr>
<th>Retinal abnormalities</th>
<th>Renal function:</th>
</tr>
</thead>
<tbody>
<tr>
<td>68/87 (78%)</td>
<td>Kidney injury - 9/87 (10%)</td>
</tr>
<tr>
<td>I° - 41/68 (60%)</td>
<td>- proteinuria (incl. nephrotic proteinuria)</td>
</tr>
<tr>
<td>II° - 23/68 (34%)</td>
<td>- GFR↓</td>
</tr>
<tr>
<td>III° - 1/68 (2%)</td>
<td>19/78 (24%) – GFR &lt;90 ml/min/1.73m²</td>
</tr>
<tr>
<td>IV° - 3/68 (4%)</td>
<td></td>
</tr>
<tr>
<td>III°+IV° - 4/68 (6%)</td>
<td></td>
</tr>
</tbody>
</table>


**RVH in children and adolescents - diagnosis**

<table>
<thead>
<tr>
<th>Arterial hypertension, usually stage 2 or 3 (in adolescents ≥16 yrs old)</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory findings suggestive of RVH:</td>
<td>- Ultrasonography</td>
</tr>
<tr>
<td>- hypokalemia</td>
<td>- Doppler US</td>
</tr>
<tr>
<td>- metabolic alkalosis</td>
<td>- Scintigraphy</td>
</tr>
<tr>
<td>- secondary aldosteronism</td>
<td>- angioCT</td>
</tr>
<tr>
<td>- renin↑↑</td>
<td>- angioMRI</td>
</tr>
<tr>
<td>- ALDO↑↑</td>
<td>- Digital subtraction angiography – gold standard</td>
</tr>
</tbody>
</table>
RVH in children and adolescents – diagnosis
Ultrasonography: kidney length + Doppler

<table>
<thead>
<tr>
<th>test</th>
<th>sensitivity</th>
<th>specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Doppler</td>
<td>63%</td>
<td>96-100%</td>
</tr>
<tr>
<td>US Doppler + kidney length difference ≥1cm</td>
<td>73%</td>
<td>89%</td>
</tr>
</tbody>
</table>

Adult studies:
Sensitivity: 60-100%; Specificity: 70-100%

Conclusion:
- Sensitivity and specificity of US-doppler in diagnosis of RVH is lower in children than in adults
- Doppler US has low power in detection of segmental, small branches or accessory RA stenoses
- nevertheless, it is the first screening test in diagnostic scheme of RVH
RVH in children and adolescents – diagnosis
Renal scintigraphy

- Renal scintigraphy with captopril:
  - False negative 7/47 (15%)
  - True positive 40/47 (85%)

  [Antoniewicz J et al. 2002/2007]

- Renal scintigraphy:
  - Sensitivity: 47.5%
  - Specificity: 73.3%

  [Tullus K Pediatric nephrology CME, GOSH 2010]

AAP 2017:
„nuclear renography is less useful in children and should generally be avoided“
RVH in children and adolescents – diagnosis
AngioCT, angio MRI

<table>
<thead>
<tr>
<th>test</th>
<th>sensitivity</th>
<th>specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>angioCT</td>
<td>88%</td>
<td>81%</td>
</tr>
<tr>
<td>angioMRI</td>
<td>82%</td>
<td>62%</td>
</tr>
<tr>
<td>angioCT+angioMRI</td>
<td>100%</td>
<td>75-86%</td>
</tr>
</tbody>
</table>

Trautmann A et al. Pediatr Nephrol 2017

US-Doppler + scintigraphy

angioCT

Digital Subtraction Angiography
Confirmed hypertension
Blood pressure >95th centile

Blood pressure 90–95th centile
Continue to monitor

Blood pressure <90th centile
Discharge

Undertake primary investigation for hypertension focusing on secondary causes (coarctation, renal, and endocrine, including renal doppler ultrasound)

No cause for hypertension recorded and no signs suggesting renovascular hypertension (panel 2)

Blood pressure well controlled on 1–2 drugs
At present, no further investigation

Blood pressure not well controlled on ≥2 drugs

Pre-captopril and post-captopril scintigraphy and/or CT and/or magnetic resonance angiography (depending on local availability and preferences)

Findings suggestive of renovascular hypertension OR strong clinical suspicion of renovascular hypertension

Digital subtraction angiography and renal vein renin sampling

Signs suggesting renovascular hypertension

Tullus K et al. Lancet 2008
Abnormal. Suggested RVH

AngioCT aortic and renal arteries.

DSA with PTRA

Surgical revascularization

Follow-up: ABPM, US-Doppler, ev. renal scintigraphy

Normal

Treatment according to phenotype

No effect. Resistant hypertension

Cure/improvement/repeated PTRA

HT 2\textsuperscript{o} and/or 1\textsuperscript{o} <10yrs and/or intermediate phenotype suggesting RVH
RVH in children and adolescents – treatment. Pharmacotherapy

<table>
<thead>
<tr>
<th>UNILATERAL RENAL ARTERY STENOSIS</th>
<th>BILATERAL RENAL ARTERY STENOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAAS blockade</td>
<td>Diuretics + MR antagonists</td>
</tr>
<tr>
<td>- beta-adrenolytics (preferable vasodilating beta-adrenolytics)</td>
<td>Beta-adrenolytics (preferable vasodilating beta-adrenolytics)</td>
</tr>
<tr>
<td>- MR antagonists</td>
<td>Vasodilators</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
</tr>
<tr>
<td>- calcium channel blockers</td>
<td>- calcium channel blockers</td>
</tr>
<tr>
<td>- alpha-adrenolytics</td>
<td>- alpha-adrenolytics</td>
</tr>
<tr>
<td>CNS inhibitors</td>
<td>CNS inhibitors</td>
</tr>
<tr>
<td>ACEi/ARBs</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacotherapy

Normal BP – 4/87 (5%)
Improvement – 28/87 (32%)
Ineffective – 55/87 (63%)

Median number of antihypertensive drugs – 3 (1-8)

Normal BP (<90pc) – 2/37 (5.7%)
Improvement (90-95pc) - 8/37 (21.6%)
Ineffective (>95pc) – 27/37 (72.9%)

Median number of drugs – 2.7 (1-6)

Kari JA et al. 2015


Conclusion:
pharmacotherapy does not cure and is only a bridge to invasive procedures

Stadermann MB et al. NDT 2009
RVH in children and adolescents. Causal treatment. Revascularization. PTRA.

**PTRA - RESULTS**
- 14/78 (17.9%) – cure after first PTRA
- 31/78 (39.7%) – improvement after first PTRA
- 18/78 (23%) – no improvement despite good hemodynamic result
- 7/78 (9%) - no improvement of BP control, no hemodynamic improvement after PTR
- MAS – improvement but not cure
- NF1
  - 6/19 (31.6%) – normotension
  - 10/19 (52.6%) – improvement
  - 3/19 (15.85) – no improvement

**PTRA – NUMBER OF PROCEDURES**
- 14/78 – 2 procedures
- 5/78 – 3 procedures
- 3/78 >3 procedures

N = 70

PTA ineffective 11 (16%)  Improvement 36 (51%)  Cure 23 (33%)

Surgery 35 (50%) 4 (6%) 31 (44%)

Primary surgery N=37

Unilateral procedure  n=33

Cured  n=15

Improved  n=12

Unchanged  n=3

Bilateral procedures  n=4

Secondary surgery  n=7

Cured  n=2

Improved  n=2

Unchanged  n=1

Tertiary surgery n=2

Unilateral  n=1

Bilateral  n=1


Stadermann MB et al. NDT 2009

PTA + surgery or surgery alone may lead to cure in 47-50% of pts and significant improvement in 37-44% of pts
RVH in children and adolescents. Effects of treatment

EFFECTS IN RELATION TO RAS LOCALISATION

<table>
<thead>
<tr>
<th>Localisation</th>
<th>Cure</th>
<th>Improvement</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral RAS</td>
<td>24/38 (63%)</td>
<td>14/38 (37%)</td>
<td></td>
</tr>
<tr>
<td>Bilateral RAS</td>
<td>6/18 (33.3%)</td>
<td>8/18 (44.4%)</td>
<td>4/18 (22.2%)</td>
</tr>
<tr>
<td>Mid-aortic syndrome</td>
<td>4/13 (30.6%)</td>
<td>7/13 (54%)</td>
<td>2/13 (15.4%)</td>
</tr>
<tr>
<td>Distal RAS</td>
<td>6/13 (46.2%)</td>
<td>7/13 (53.8%)</td>
<td></td>
</tr>
</tbody>
</table>

NUMBER OF ANTIHYPERTENSIVE DRUGS (MEDIAN AND RANGE)

- Unilateral RAS: 24/38 (63%) vs 14/38 (37%) (Antoniewicz J et al. 2002/2007)
- Bilateral RAS: 6/18 (33.3%) vs 8/18 (44.4%) vs 4/18 (22.2%) (Stadermann MB et al. NDT 2009)

Left ventricular hypertrophy

- 45/81 (56%) vs 18/81 (22%) (Antoniewicz J et al. Pediatr Nephrol (abstracts) 2002)
RVH in children and adolescents.

Conclusions

RVH is the leading cause of secondary hypertension in children.

Pharmacotherapy does not cure but may lower BP.

PTA and/or surgery may cure in 50% of cases.

However, RVH is not only disease of renal arteries.
RVH in children and adolescents is not limited to renal arteries.

<table>
<thead>
<tr>
<th>FIBROMUSCULAR DYSPLASIA</th>
<th>SYNDROMIC RVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 61% is limited to renal arteries</td>
<td>NF1 – new stenoses may develop</td>
</tr>
<tr>
<td>In 24% two arterial sites are involved (renal + visceral or renal + extra-/intracranial arteries)</td>
<td>Cases of progressive course of FMD and moya-moya disease</td>
</tr>
<tr>
<td>In 16% more than three or more arterial beds are involved (renal + visceral + extra/intracerebral)</td>
<td><strong>FMD or mid-aortic syndrome</strong></td>
</tr>
<tr>
<td>Moya-moya disease is a form of FMD</td>
<td>• Generalized or segmental pathology of arterial wall</td>
</tr>
</tbody>
</table>

**ARCADIA-POL Registry**

Need to standardize diagnostic procedures and treatment

What about stents?

Genetics

FMD – local or generalized pathology of arterial wall?

Do relatives of FMD pts have increased CV risk?

Long-term follow-up

**Registries:**

- US Registry for FMD
- ARCADIA (France, Belgium)
- ARCADIA-PROFILE
- ARCADIA-POL