Is Familial Hyperaldosteronism Underdiagnosed in Hypertensive Children?

Paolo Mulatero, Tracy Ann Williams, Silvia Monticone, Franco Veglio

Primary aldosteronism (PA) is the most frequent cause of secondary hypertension in adults, accounting for 5% to 15% of hypertensive patients, depending on the severity of blood pressure levels. Patients with PA undergo a higher rate of cardiovascular complications compared with essential hypertensives, and, thus, the screening of hypertensive subgroups of patients with higher prevalence of PA is recommended. Three genetic forms of PA have been described so far: familial hyperaldosteronism type I (FH-I), also known as glucocorticoid-remediable aldosteronism (GRA); familial hyperaldosteronism type II (FH-II); and familial hyperaldosteronism type III (FH-III; Table).

FH-I/GRA-affected patients display hypertension, elevated adrenocorticotrophic hormone–dependent aldosterone secretion, renin suppression, and high levels of the 180H-cortisol and 180xo-cortisol. FH-I/GRA is attributed to an unequal recombination between CYP11B1 (11β-hydroxylase) and CYP11B2 (aldosterone synthase), generating a chimeric CYP11B gene containing CYP11B sequences (including the promoter) at its 5′ end and CYP11B2 sequences at its 3′ end. Because CYP11B1 expression is regulated by adrenocorticotrophic hormone, the hybrid gene encodes a chimeric enzyme with aldosterone synthase activity and adrenocorticotropic hormone–dependent expression throughout the adrenal cortex. Most affected individuals develop severe hypertension in early life, but different degrees of severity and even normotension have also been described. FH-I/GRA is commonly made by long-PCR, and genetic testing for FH-I/GRA in adults is recommended for patients with onset of PA before 20 years of age and in those with a family history of PA or stroke at a young age (<40 years).

FH-II is a nonglucocorticoid-remediable form of PA, indistinguishable from sporadic PA. The molecular basis of FH-II is still unknown, although several analyses have shown a linkage with chromosomal region 7p22. Intriguingly, a linkage analysis performed in a large hypertensive population demonstrated aldosterone/plasma renin activity (PRA) ratio (ARR) to be in linkage with 7p21-22. However, the genetic background of this form seems to be heterogeneous, because not all of the families showed linkage with this chromosomal region. The diagnosis of FH-II requires PA to be confirmed in ≥2 family members and exclusion of FH-I/GRA and is suggested in hypertensive family members of PA patients.

FH-III is a new familial form of PA characterized by a particularly severe hyperaldosteronism that is resistant to aggressive pharmacotherapy and therefore requires bilateral adrenalectomy; the underlying genetic cause has been shown recently to be attributed to mutations in the gene encoding the potassium channel KCNJ5 (Kir 3.4, potassium inwardly rectifying channel, subfamily 1, member 5): the mutation occurs near the selectivity filter for potassium resulting in increased sodium conductance and cell depolarization, which, in adrenal glomerulosa cells, produces calcium entry and, thus, increased aldosterone production and cell proliferation. Intriguingly, somatic mutations in the same gene have also been shown in aldosterone-producing adenomas from PA patients with severe hypertension and hypokalemia.

FH-I/GRA is considered a very rare disease, accounting for <1% of PA patients; FH-II is considered more frequent, with a prevalence of ≈3%, whereas FH-III has only been shown so far in a single family. However, until now, the prevalence of familial hyperaldosteronism in hypertensive children was unknown.

Along with the epidemic increase in childhood obesity, the prevalence of pediatric hypertension is increasing in Western society, presently accounting for 3% to 5% of all children and 7% to 15% being prehypertensives. In children, secondary hypertension is more frequent in younger patients and in those with higher blood pressure levels. The most frequent secondary causes are kidney diseases, whereas endocrine causes account for ≈10% of all cases.

In this issue of Hypertension, Aglony et al report a high prevalence of FH-I among hypertensive children in Chile. They studied a selected group of hypertensives aged 4 to 16 years, after exclusion of obesity, renal diseases, diabetes mellitus, hypercortisolism, and hypercalcemia. In this subgroup of patients they found an increased ARR in 3.9% and FH-I/GRA in 3.1% of children. The study of the relatives resulted in the identification of 13 other affected subjects (8 children and 5 adults). Of the 8 children with FH-I/GRA, 6 were hypertensives, 1 experienced an ischemic stroke at the age of 4 years, 1 was prehypertensive, and 1 was normotensive. Only 1 child was hypokalemic, in agreement with previous reports on the low prevalence of hypokalemia in FH-I/GRA patients. Of 8 displayed high aldosterone levels for age, and all displayed low PRA and high ARR. Normality levels of these hormones in children were derived.
from a recent evaluation of PRA and aldosterone levels in normotensive children performed by the same group of scientists. The exact prevalence of different types of secondary hypertension in children is usually difficult to obtain, given that the lack of population-based studies and clinical studies from referral centers might be biased toward a specific cause. The study by Aglony et al was also performed in a tertiary referral center for pediatric hypertension, and, therefore, the group of children under investigation might have been enriched by more severe forms of hypertension, resulting in an overestimation of the prevalence of FH-I/GRA. However, the results of this study are of significant importance; the authors performed a careful investigation aimed at the exclusion of other frequent causes of hypertension in children and measured the ARR in all of the other patients. Similar to adult hypertensives, ARR and low renin have shown to be the most sensitive parameters for suspecting PA, whereas hypokalemia and high aldosterone levels are much less useful. It should be noted that the performance of the test for FH-I/GRA in unselected hypertensive adults is not useful. However, a previous study in Chilean hypertensive patients showed a relatively high prevalence of FH-I/GRA also in adults (0.66% among hypertensive patients and 6.90% among PA patients). Therefore, it is possible that Chileans are a population with a particularly high prevalence of FH-I/GRA, and, thus, these important data on hypertensive children should be replicated in different ethnic groups; finally, it would be useful to determine the crossing-over point between the \textit{CYP11B1} and \textit{CYP11B2} genes to rule out the possibility of a founder effect in some cases.

Detection of familial forms of hyperaldosteronism is of paramount importance to prevent the detrimental effects of aldosterone on the cardiovascular system. Patients with FH-I/GRA display higher morbidity and mortality from cerebrovascular events (48% of affected families, 18% of subjects) at a young age (average age of first event: 32 years with an overall case fatality rate of 61%) and have been found to show early signs of target organ damage even before the development of high blood pressure levels. Therefore, given the higher aldosterone-mediated vascular damage and the relatively high prevalence in the pediatric hypertensive population of FH-I/GRA, this condition should always be excluded in hypertensive children, especially when obesity and kidney diseases are ruled out, like in the present study.

The most reliable biochemical evidence for FH-I/GRA is a marked, sustained suppression of plasma aldosterone throughout several days of dexamethasone. The test is considered positive if aldosterone is suppressed below 4 ng/dL after 4 days of dexamethasone (0.5 mg per 6 hours). However, this test may be difficult to perform in very young individuals and is not applicable as a screening test of families; furthermore, a high frequency of false-positive diagnoses has been demonstrated. Genetic testing overcomes these difficulties: the most widely used test is a long-PCR–based method that allows the amplification of the chimeric \textit{CYP11B1}/\textit{B2} gene. The selection of children who should undergo long-PCR testing for FH-I/GRA could be performed by measuring PRA, aldosterone, and potassium levels to hypertensive children of unknown etiology. In accordance with the data of Aglony et al, a long-PCR test should be performed in all patients with low PRA and normal/high aldosterone (and, thus, high ARR) and normal/low potassium levels.

The therapy is etiologically based on dexamethasone with or without adjunct of mineralocorticoid receptor antagonists.

Table. Clinical and Biochemical Phenotypes of Familial Forms of Hyperaldosteronism

<table>
<thead>
<tr>
<th>Familial Hyperaldosteronism</th>
<th>Type I/GRA</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causal gene</strong></td>
<td>Hybrid \textit{CYP11B1/CYP11B2}</td>
<td>Unknown; linkage to 7p22 in some families but &gt;1 causal gene expected</td>
<td>\textit{KCNJ5}</td>
</tr>
<tr>
<td><strong>Transmission</strong></td>
<td>Autosomal dominant</td>
<td>Autosomal dominant</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Long-PCR</td>
<td>ARR-confirmatory test: confirmed PA in 2 members of the family</td>
<td>\textit{KCNJ5} sequencing</td>
</tr>
<tr>
<td><strong>Onset of hypertension</strong></td>
<td>Variable (mostly young)</td>
<td>Adulthood</td>
<td>Childhood</td>
</tr>
<tr>
<td><strong>Severity of hypertension</strong></td>
<td>Normal to resistant (more often severe to resistant)</td>
<td>Normal to resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td><strong>Aldosterone levels</strong></td>
<td>Normal to high (≤3 to 4 times normal)</td>
<td>Normal to high (≤3 to 4 times normal)</td>
<td>Very high (≤10 times normal)</td>
</tr>
<tr>
<td><strong>Hybrid steroids levels</strong></td>
<td>High (10 times normal)</td>
<td>Normal to mildly elevated (3 to 4 times normal)</td>
<td>Extremely high (50 to 100 times normal)</td>
</tr>
<tr>
<td><strong>Aldosterone response to dexamethasone</strong></td>
<td>Complete suppression</td>
<td>Partial/transient reduction</td>
<td>Paradoxical increase</td>
</tr>
<tr>
<td><strong>Adrenal pathology</strong></td>
<td>Ectopic hybrid enzyme expression</td>
<td>APA/BAH</td>
<td>Marked bilateral hyperplasia</td>
</tr>
<tr>
<td><strong>Groups of patients with higher detection</strong></td>
<td>PA patients with a family history of PA or stroke at young age or with onset at young age or children with low-renin hypertension</td>
<td>Hypertensive first-degree relatives of PA patients</td>
<td>FH-I/GRA negative children with severe hypertension, low renin, very high aldosterone and hypokalemia*</td>
</tr>
</tbody>
</table>

*Only 1 family was described so far: the possibility remains that other families with a milder phenotype and mutations in the same gene also exist; the prevalence of \textit{KCNJ5} somatic mutations in “sporadic” aldosterone-producing adenomas and the clinical use of its determination are still to be determined. PA indicates primary aldosteronism; APA, aldosterone-producing adenoma; BAH, bilateral adrenal hyperplasia; FH, familial hyperaldosteronism; GRA, glucocorticoid-remediable aldosteronism; \textit{KCNJ5}, Kir 3.4, potassium inwardly rectifying channel, subfamily 1, member 5; \textit{CYP11B1}, 11β-hydroxylase gene; \textit{CYP11B2}, aldosterone synthase gene.
Usually 0.50 to 0.75 mg/d of dexamethasone is necessary to suppress adrenocorticotropic hormone; however, it has been demonstrated that lower dosages are sufficient to obtain good blood pressure control, thus minimizing adverse effects. All of the FH-I/GRA patients identified in the study by Aglony et al. displayed good blood pressure response to glucocorticoid as expected: 10 of 13 patients had normalized blood pressure with cortisol or dexamethasone, and 3 of 13 required the addition of spironolactone.

The results of the studies of Fardella’s group, together with the demonstration of the genetic alterations responsible for FH-III and the relatively high prevalence of FH-II, which may be widely unrecognized in children, highlight the necessity for an increased awareness of these forms in hypertensive children. Future research should be addressed toward understanding the genetic causes of FH-II, the prevalence of mutations in KCNJ5 in “sporadic” PA, and the necessity of beginning pharmacological therapy in normotensive children with genetic alterations responsible for familial hyperaldosteronism.

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Disclosures
None.

References
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