Aldosterone/Renin Ratio as a Diagnostic Tool in the Diagnosis of Primary Hypoaldosteronism in Newborn and Infants

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Introduction

Primary hypoaldosteronism is a rare inborn disorder with life-threatening symptoms in newborns and infants due to an aldosterone synthase defect. It is transmitted as an autosomal recessive trait. Mutations are located in the *CYP11B2* gene. Diagnosis is made based on clinical and laboratory findings. The interpretation is often difficult as plasma aldosterone concentration (PAC) can remain in the normal range and thus lead to misinterpretation and delayed initiation of life-saving therapy.

Objectives

This study aims to show that PAC/PRC (plasma renin concentration) ratio can be used as a reliable diagnostic tool for primary hypoaldosteronism in newborns and infants. Up to now this method is only validated to diagnose random conditions of disorders of the renin-angiotensin-aldosterone axis in adults.

Conclusion

1. **Normal plasma aldosterone concentration (PAC) level does not exclude primary hypoaldosteronism. Instead a PAC to PRC (plasma renin concentration) ratio <1 pmol/mU indicates an inappropriate low PAC for the stimulus and is suggestive for the diagnosis.**
2. **PAC/PRC ratio is a cost saving and reliable tool to diagnose primary hypoaldosteronism in newborns and infants.**

Patients and Methods

Therefore we collected data of nine patients who were initially diagnosed with primary hypoaldosteronism based on clinical and laboratory findings in the age from fifteen days to twelve months in the period from 2001 to 2013. The diagnosis was subsequently genetically confirmed in eight patients.

As patients were included, which were diagnosed in a period over 12 years in 3 different centres in Switzerland the analytic methods differed depending on time and place where they were performed. In order to enable a valid comparison of the values PACs and PRCs were correlated to reference methods based on correlation studies.

Results

In six patients (patient 1-6) the PAC/PRC ratio could be determined and showed continuously decreased values <1 pmol/mU (mean PAC/PRC: 0.0737 pmol/mU; range 0.0001-0.1968 pmol/mU) (Table 1).

In patient 7 PRC was only noted as a minimal value, as the material did not last for serial dilution analysis to determine the exact value. For this reason we could not calculate the exact PAC/PRC ratio in this case, therefore it was not considered.

In two patients (patient 8 and 9) renin was noted as plasma renin activity (PRA). The PAC/PRA ratios were also clearly decreased. Values lower than 28 (pmol/l)/(ng/ml x h) are correlated with hypoaldosteronism (Table 2).

Discussion

It was already shown in adults that a PAC/PRC ratio under 1 pmol/mU and a PAC/PRA <28 (pmol/l)/(ng/(ml x h)) helps to identify patients with primary hypoaldosteronism. Due to our results this seems to be a reliable tool in newborns and infants with aldosterone synthase deficiency as well, which can help to diagnose this life threatening disease faster and consequently initiate life-saving therapy earlier. And it is cost saving as molecular diagnostic becomes more dispensable.

Thus, we propose the introduction of the PAC/PRA ratio as a standard diagnostic tool for primary hypoaldosteronism.

▼ Table 1: Overview of patient 1-6 and patient 7 with laboratory values by date of diagnosis, PAC/PRC ratio and mutation

Pat.	Age at diagnosis	Sodium (mmol/l)	Potassium (mmol/l)	Corrected Plasma Aldosterone Concentration (PAC) in pmol/l	Corrected Plasma Renin Concentration (PRC) in mU/l	PAC/PRC Ratio (pmol/mU)	Mutation
Normal range		**134 - 144**	**3.5 – 5.0**	**27.7 - 4995**	**2.8 – 39.9**	**1 - 71**	**-**
Pat. 1	15 days	128	6.2	1´906	9´686	0.1968	homozygous mutation p.Thr185Ile in *CYP11B2* gene
Pat. 2	4 weeks	125	6.1	217	74´423	0.0029	homozygous mutation p.Thr185Ile in *CYP11B2* gene
Pat. 3	12 weeks	121	5.9	801	256´041	0.0031	homozygous mutation p.Thr185Ile in *CYP11B2* gene
Pat. 4	3 months	120	8.4	947	95´258	0.0099	homozygous mutation p.Thr185Ile in *CYP11B2* gene
Pat. 5	4 months	124	5.8	89	1´390´330	0.0001	heterozygoty for p.Thr185Ile and IVS8+1 G>A in *CYP11B2* gene
Pat. 6	2 weeks	117	6.2	470	3´634	0.1293	homozygous mutation p.Thr185Ile in *CYP11B2* gene
Pat. 7	6 months	122	5.4	838	>626	< 1.3387*	homozygous mutation p.Thr185Ile in *CYP11B2* gene

* In patient 7 PRC is given as a minimal value, therefore PAC/PRC is the highest assumable value

▼ Table 2: Overview of patient 8 and 9 with laboratory values by date of diagnosis, PAC/PRA ratio and mutation

Pat.	Age at diagnosis	Sodium (mmol/l)	Potassium (mmol/l)	Corrected Plasma Aldosterone Concentration (PAC) in pmol/l	Corrected Plasma Renin Activity (PRA) in ng/ml x h	PAC/PRA Ratio (pmol/l)/(ng/ml x h)	Mutation
Normal range		**134 - 144**	**3.5 – 5.0**	**27.7 - 4995**	**0.2 – 7.7**	**> 28**	**-**
Pat. 8	3 months	123	NA	138 - 230*	37	3.7297 – 6.2162	no mutation found in *CYP11B2* gene
Pat. 9	24 months	132	4.6	300	66	4.5455	homozygous mutation p.Thr185Ile in *CYP11B2* gene

* In patient 8 PAC is given as a range, therefore PAC/PRA is calculated as a range as well

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