Pediatric Nephrology (2020) 35:79–82
https://doi.org/10.1007/s00467-019-04329-0

CLINICAL QUIZ

A rare cause of hypertension in childhood: Answers

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Received: 23 July 2019 / Revised: 27 July 2019 / Accepted: 31 July 2019 / Published online: 20 September 2019

Keywords Low renin hypertension · Apparent mineralocorticoid excess · *HSD11B2* gene

Answers

1. What is the most likely diagnosis of our patients with hypokalemic metabolic alkalosis and low renin hypertension (LRH)?

The differential diagnosis of LRH with low aldosterone concentrations includes acquired causes and "classical genetic syndromes". Consanguinity and three cases from a family were suggestive of genetic causes, including apparent mineralocorticoid excess (AME), activating mutation of the mineralocorticoid receptor, Liddle syndrome, congenital adrenal hyperplasia due to 11β hydroxylase deficiency, 17α hydroxylase deficiency, Gordon syndrome, and glucocorticoid resistance [1]. In our patients, congenital adrenal hyperplasia and glucocorticoid resistance were excluded due to incompatible clinical and laboratory findings. Gordon syndrome, which presents with hyperkalemia, was excluded. Liddle syndrome is caused by constitutive expression and impaired degradation of epithelial sodium channel (ENaC). The autosomal dominant pattern and unresponsiveness to spironolactone are important features of Liddle syndrome and therefore, it was excluded in our patients. AME is the most likely diagnosis for our patients.

2. Which further investigations required for diagnosis?

In patients with AME, the urinary free cortisol (UFF)/urinary free cortisone (UFE) ratio is high, typically increased more than 10-fold, while in normal individuals, it is < 0.5 [2]. Although, the UFF/UFE ratio is a more appropriate diagnostic tool in AME, plasma cortisol (F)/cortisone (E) provides supporting diagnostic evidence. All three of our cases had significantly elevated UFF/UFE and plasma F/E ratios in addition to extremely low plasma cortisone levels. Even under treatment, cortisone levels still remained low and cortisol was high due to impaired metabolism. In fact, we have observed that both UFF/UFE and plasma F/E do not normalize under treatment in our patients. Thus, it is possible to diagnose AME by the measurement of UFF/UFE and/or plasma F/E in a patient who is already on treatment for hypertension.

AME was confirmed by sequencing, with a homozygous R374* (c.1120C>T, p. Arg374Ter) nonsense variant in the *HSD11B2* gene. Parents were heterozygous for the same mutation and were normotensive.

3. How should these patients be managed?

All three patients were treated with oral potassium and spironolactone, and significant response to treatment was observed. Spironolactone, a mineralocorticoid receptor (MR) antagonist that binds competitively and protects the receptor against excess activity, should be the drug of choice. Early diagnosis and initiation of treatment normalizes BP, corrects hypokalemia, improves growth, and prevents end-organ

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This refers to the article that can be found at https://doi.org/10.1007/s00467-019-04326-3.

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damage in AME [3]. Anthropometric and biochemical characteristics and end-organ damage status of the patients are demonstrated in Table 1. In our patients, hypokalemia and hypertension were controlled with oral potassium replacement and spironolactone.

Discussion

Secondary hypertension is more common in preadolescent children, especially in infants and young children. Therefore, it is recommended that children with hypertension should be evaluated for underlying causes of hypertension. Low renin hypertension is more commonly associated with a monogenic etiology in children.

AME, is a rare form of low renin hypertension, which is caused by biallelic mutations in the *HSD11β2* gene encoding the enzyme 11β-hydroxysteroid dehyrogenase type 2 (11βHSD2) [4]. 11βHSD2 prevents the MR from excessive stimulation by glucocorticoids [5]. Aldosterone is the physiologic agonist for MR; however, affinity of cortisol and aldosterone for the MR is similar due to sequence identity between the MR and glucocorticoid receptors [6]. MR overstimulation by glucocorticoids is avoided through the action of 11βHSD2, which inactivates cortisol, converting it to cortisone [5, 6]. Deficiency of 11βHSD2 causes overstimulation of MR which leads to sodium retention, hypokalemia, and hypertension [4].

Polyuria/polydipsia, failure to thrive, severe hypertension, hypokalemic alkalosis, and nephrocalcinosis are the characteristic features of AME. Untreated disease may progress to end-organ damage and mortality [7]. Since the first AME case was reported in the literature [8], a limited number of cases have been reported [9, 10]. The molecular cause of AME was first described in the 1990s [11].

Here we report clinical and biochemical characteristics of three children with AME from a consanguineous family. Two

Table 1 Clinical and laboratory features of patients with apparent mineralocorticoid excess (AME) at admission and at last visit

	Patient #1		Patient #2		Patient #3	
	At admission	At last visit	At admission	At last visit	At admission	At last visit
Age (years)	1.1	3.9	11.7	14.4	4.8	5.1
Gender	F		M		M	
Birth weight, g (SDS)	1660 (− 3.5)		1860 (− 0.9)		2100 (− 1.5)	
Weight, kg (SDS)	7.65 (− 2.0)	14.3 (− 0.8)	32.9 (− 3.1)	48.5 (− 1.0)	15.5 (− 1.3)	16.2 (1.1)
Height, cm (SDS)	72.0 (− 1.8)	95.3 (− 1.5)	134.8 (− 3.0)	155.0 (− 1.6)	105.8 (− 0.8)	107.7 (− 0.8)
Target height (SDS)	− 1.8		− 1.7		NA	
BMI (SDS)	− 2.2	0.2	− 2.2	− 0.2	− 1.4	− 1.2
BP, mmHg (95th p for age, gender, and height)/(SDS)	140/90 (101/58)	100/60 (1.1)	170/100 (112/77)	120/73 (1.3)	184/115 (108/67)	104/65 (1.3)
Creatinine, μmol/L (*N* 23.0–68.1)	20.3	19.4	39.8	75	27.4	31.8
Potassium, mmol/L (*N* 3.5–5.1)	1.8	3.6	2.9	3.2	2.3	3.6
Sodium, mmol/L (*N* 135–145)	143	143	145	144	146	140
Chloride, mmol/L (*N* 98–107)	100	99	97	100	102	101
Calcium, mmol/L (*N* 2.2–2.7)	2.7	2.7	2.5	2.6	2.4	2.5
Magnesium, mmol/L (*N* 0.62–0.95)	1.09	0.96	0.98	0.88	1.00	0.82
Blood pH (*N* 7.35–7.45)	7.52	7.44	7.43	7.42	7.47	7.41
Blood HCO_3, mmol/L (*N* 22.5–26.9)	34.5	24.7	33.3	25.7	25.2	27.4
Urine pH	7.0	7.5	7.0	7.5	7.0	7.0
Urine density	1002	1012	1005	1006	1002	1012
Urinary calcium/creatinine ratio	0.28	0.12	0.15	0.13	0.66	0.10
Renin, pmol/L (*N* 0.002–0.6)	< 0.002	< 0.002	< 0.002	0.001	< 0.002	< 0.002
Aldosterone, nmol/L (0.04–0.64)	0.024	0.08	< 0.0003	0.06	< 0.0003	0.07
UFF/UFE ratio (*N* < 0.5)	86	100	37	51	38	NA
Plasma cortisol/cortisone ratio (0.42–9.14)	NA	443.8	NA	515.4	NA	471.2
Nephrocalcinosis	+	+	+	+	+	+
Left ventricular hypertrophy	+	+	+	+	+	+
Hypertensive retinopathy	–	+	+	+	+	+

AME, apparent mineralocorticoid excess; *SDS*, standard deviation score; *BMI*, body mass index; *UFF/UFE*, urinary free cortisol/urinary free cortisone

of them had initially been diagnosed with Bartter syndrome and suffered from severe hypertension and end-organ damage. They were only reconsidered for diagnosis of AME following establishment of the AME diagnosis for P#1 based on careful blood pressure monitoring, assessment of renin-aldosterone axis, and urinary free cortisol/cortisone ratios.

In the classical form of AME, severe hypertension may be observed as early as the newborn period [7]. A 36-day-old male of Turkish origin was diagnosed with hypertension because of a focal neurological defect, ptosis. Although extremely elevated BP was detected at his first evaluation, the diagnosis of AME was delayed until he was three years old [7]. In our cases, although the typical laboratory results were observed in infancy, hypertension was detected at later ages. The importance of monitoring BP at any age is emphasized here.

Defects in renal salt transporters (Bartter or Gitelman syndrome) cause hypokalemic metabolic alkalosis, similar to patients with AME but with normal BP. Clinicians should carefully measure BP both initially and during follow-up in patients with hypokalemic metabolic alkalosis so as not to miss a diagnosis of AME, as in cases #2 and #3 here.

Nephrogenic diabetes insipidus may develop secondary to severe hypokalemia in AME [12]. All three patients in our study had prominent nephrocalcinosis at the time of diagnosis, possibly due to longstanding hypercalciuria and hypokalemia. Although it is reported that nephrocalcinosis may resolve under treatment [7], our patients still had nephrocalcinosis at the last evaluation. Compliance with treatment and duration of appropriate treatment may be important for resolution of nephrocalcinosis.

Mild hypermagnesemia was remarkable in our patients. To the best of our knowledge, this was not mentioned in the previous reports. Although the exact mechanism of slightly high magnesium levels in AME is unknown, it may be associated with increased reabsorption of magnesium due to altered transepithelial potential difference in the thick ascending limb (TAL) of Henle, which is the main location for paracellular magnesium reabsorption. Another possible mechanism may be altered expression of *Claudin-10*. Claudin-10 has been shown to be a key factor in cation transport in TAL [13] and loss-of-function mutations in *Claudin-10* are associated with hypermagnesemia [14].

Intrauterine growth retardation/low birth weight has been observed in all of the reported patients with AME, especially in severe phenotypes [3]. Diminished 11βHSD2 activity is also associated with decreased weight gain in early infancy. Placental 11βHSD2 deficiency may cause increased amounts of cortisol to cross the placenta and inhibit fetal growth [15]. Consistent with the above, our patients were born with low birth weight.

Approximately 100 cases of AME with 49 different mutations in the *HSD11β2* gene have been reported so far [16]. Most of these patients have homozygous mutations and relatively few are compound heterozygotes, meaning that *HSD11β2* mutations are found mostly in inbred populations. Genotype-phenotype correlation has been difficult to identify in AME [4]. A previously reported homozygous nonsense R374* (c.1120C>T, p.Arg374Ter) mutation was detected in our family [17].

Conclusion

AME should be considered in patients with low renin, low aldosterone hypertension. Twenty-four hour UFF/UFE and plasma cortisol/cortisone ratios are reliable diagnostic tests. Spironolactone is effective for the control of hypertension. Early diagnosis and accurate treatment of AME is important to prevent morbidity and mortality.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Patient confidentiality The patient's parents provided informed consent for publication of the submitted article and the results of the accompanying genetic analyses.

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