World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(CASE REPORT)

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Hereditary forms of apparent mineralocorticoid excess (AME): Report of a further case and literature review

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World Journal of Biology Pharmacy and Health Sciences, 2023, 15(01), 180–184

Publication history: Received on 17 May 2023; revised on 23 June 2023; accepted on 26 June 2023

Article DOI: https://doi.org/10.30574/wjbphs.2023.15.1.0284

Abstract

The syndrme of apparent mineralocorticoid excess (AME) is an extremly. rare autosomal recessive disorder. To date, more than 100 reported cases in the medical literature world-wide. It is caused by an impairment in the enzym 11-b-hydroxy steroid dehydrogenase (11-b-HSD) enzyme type 2, characterized by early onset hypertension, hypokalemia, metabolic alkalosis, low levels of seum renin and aldosterone. The majority of patients are usually have a low birth weight and failure to thrive (FTT). Nephrocalcinosis could be present. We describe an 11.5 year old girl, who presented in early infancy with poor growth, and not until a gene study done recently, which revealed a homozygous pathogenic variant in the HSD 11B2 gene c. 622 C >Tp. (Arg208 Cys). This is consistent with the diagnosis of AME This emphasizes the importance of genetic testing in the diagnosis of AME. A high index of suspicion required in managing such patients. Increased awarness among health care professionals is needed to avoid potential health hazards.

Keywords: Apparent Mineralocorticoid Excess (AME); 11-b-Hydroxy Steroid Dehydrogenase Enzyme 2; (11-b-HSD2); Hypokalemia; Alkalosis; Renin; Aldosterone; Failure to thrive (FTT); Genetic study

1. Introduction

Apparent mineralocorticoid excess (AME) syndrome is a fairly rare autosomal recessive disorder characterized by hypertension, and hypokalemia, associated with suppresed levels of serum renin and aldosterone. It is causef by the deficiency of 11-b-hydroxy steroid dehydrogenase type 2 enzyme. The syndrome first reported in the early seventies of the last century by New et al (1-3). Early report by Oberfield et al (4) suggested the role of cortisol in the pathogenesis. Later in 1988, Stewart et al (5) found the defiecency of 11 beta hydroxy steroid deydrogenase 2 activity (11 bHSD) of the kidney is the main pathological cause of AME with excessive cortisol action on mineralocorticoid receptor (MR). Wilson et al, in 1995 (6), identified the first HSD2b2 mutation in several siblings with typical characteristics of AME from a consanguineous Iranian family unraveling the genetic defects of AME. The majority of patients with Syndrome of apparent mineralocorticoid excess (AME) are congenital in nature,associated with wide spectrumm of gene mutations that manifest with variable presenations (7–13). On the other hand,acquired AME is so rare, and reported following the use of certain drugs (14-18). The syndrome of AME usually present in early Childhood with the typical features of hypertension, low birth weight, polyuria, polydipsia, and failure to thrive. The diagnosis can be achieved clinically, and biochemically. However this can be confirmed by molecular genetic studies (19-22).

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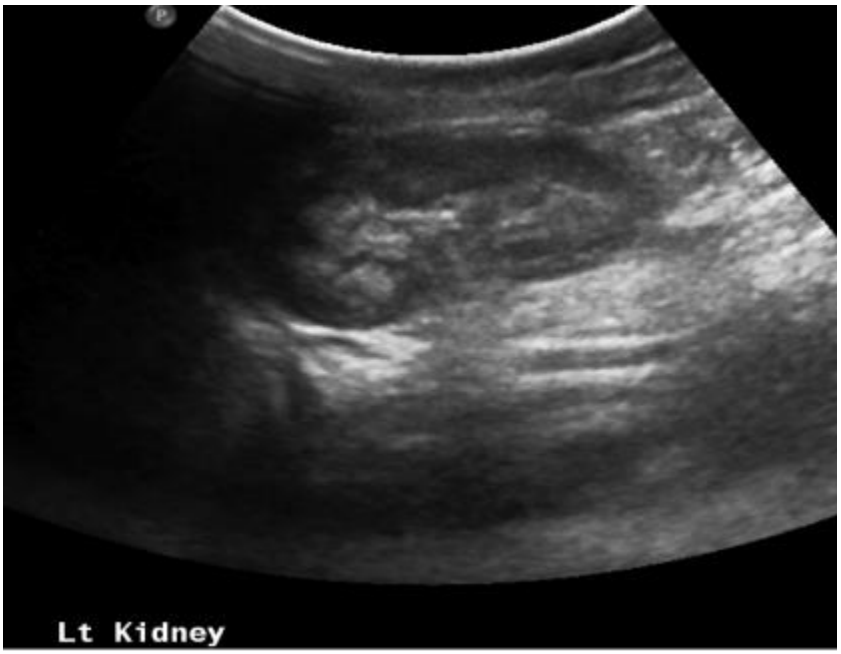
In this article, we report an 11.5 year old girl diagnosed with the syndrome of apparent mineralocorticoid excess (AME) at a later age, through gene testing. This emphsizes the importance of having a high index of suspicion in managing such patients. Increased awarness among the health care professionals is required to optimize the care.

2. Case Report

The patient is an 11.5 year old girl, who was seen and initially evaluated for failure to thrive (FTT), persistent hypokalemia and metablic alkalosis at the age of three years and nine months of age She was the product of 35 weeks of gestation, who was delivered by an emergency caeerian section due to oligohydramnios. The birth weight was severel retarded at 1200 grams. There were no history of drug intake, nor neonatal hypoglycaemia or jaundice. The neuro development was appropriate. No history of hospitalization, nor recurrent infections. The parents were consaguneous and healthy with three other normal siblings. No similar disorder,or renal disease in the family. Physical examination revealed a small sized child, with no hyper pigmentation or dysmorphic feature. Height of 91.8cm, and weight of 8.9 kg, (both below the third percentile). Blood Pressure of 110/70mmHg, persistently high, between 90 and 95th percentiles. The rest of physical examination was unremarkable. Laboratory investigatios revealed normal coplete blood count (CBC), Bone, liver and thyroid function tests were normal. Adenotropic hormone (ACTH), and cortisol were normal while aldosterone and renin low. Serum aldosterone level of 1 ng/dl (N;1.76-23), and serum renin of 1.58. uIU/ml (N;2.8-39.9 supine and 4.4-46.1 upright). Renal function showed normal BUN and Creatinine, however, she was severely hypokalemic, seum potassium 2.9 mmol/L, (N ;3.5-5.3) with metabolic alkalosis, chloride of 99 mmol/L (N;98-106) and CO2 of 32 mmol/L, (N;23-30) The renal sonography. Sweat chloride test and celiac screen were normal.

Recently, a Whole Exome Sequence(WES) study was performed Which showed a homozygous pathogenic varient in the HSD11 B 2 gene c. 622C >Tp. (Arg208Cys), that suggest the diagnosis of apparent mineralocorticoid excess syndrome. Meanwhile,low sodium diet was initiateted, with oral potassium supplementation added. Amiloride 5 mg was given twice daily recently started. A trial of growth hormone therapy was tried with no clinical improvement. The patient continued to have poor growth. Hypokalemia, and alkalosis persisted during the follow up period. Currently, serum electrolyte showed the following; Hypercalciuria was evident. The Calcium to Creatinine ratio was high 0.5 (N;0.21), Serum Calcium (repeatedly) was normal, ranging from 2.3-2 55mmol/ L (N;2.2-2.6). Repeated renal sonography (fig 1) showed mild nephrocalcinosis. Serum electrolytes showed a remarkable improvement, serum Sodium of 142mmol/L (N;135-145), Potassium 3.79mmol/(N; 3.5-5.2). Co2 was 25.9mmol/l (N;23-30), Chloride of 104mmol/L (N;98–106).Liver, and Bone profiles, glucose, and Mg were normal.



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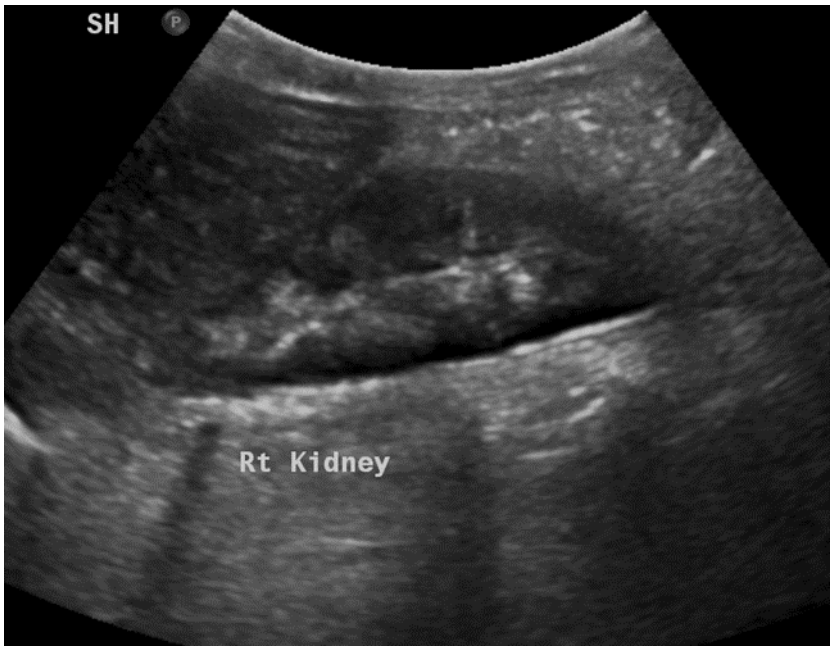

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Figure 1 Longitudinal ultrasound views of left kidney (a) and right kidney (b) demonstrate faint hyperechoic rim around the medullary pyramids consistent with grade 1 medullary nephrocacinosis

3. Discussion

Diagnosing a patient with the syndrome of apporent mineralocorticoid excess (AME) can be difficult and often challenging. It is an extremly rare autosomal recessive disorder reported in more than one hundred patients world wide. The disorder can be either congenital in nature, or rarely acquired secondary to drugs. A high index of suspicion always required and a detailed comprehensive history is essential (19,23,24) AME remains an. important differential diagnosis for patients who present with low birth weight, failure to thrive, hypokalemia and alkalosis associated with hypertension.The diagnesis of AME can be confirmed by further biochemical and hormonal studies (25-29). Typically, in the inhereted form, the symtoms appear in early childhood with low birth weight and failure to thrive However. Ifnot discovered early other symtoms or signs could be developed. Gene testing is the main stay in the disgnosis, howeve, this is not available to every professional. Whole exome sequencing has emerged as a cost effective test to detect pathogenic mutations, and to be particularly suitable in patients with clinical features suggestive of apparent. mineralocorticocoid excess syndrome. (8-12, 30-33) The treatment of AME is challenging and aims to prevent end-organ (central nervous system,renal,cardiac and retina) damage. Low Sodium diet couppled with oral Potassium supplement is the first step in management. The blocked of mineralcotticoid receptor by spironolactone is proved to be effective in controlling blood pressure. However, amiloride is better in the long term. (19, 34-36) Renal transplant is found curative in almost all clinical cases.(37,38). On the other hand, patients with AME acquired by ingesting certain substances, such as, liquorice and antifungal medications that block 11-b-hydroxysteroid dehydrogenase type two. Cessation of those agents will reverse the condition (39,40).

4. Conclusion

Apparent mineralocorticoid excess (AME remains an important differential diagnosis in the management of hypokalemic alkalosis. A high index of suspicion should be present and a detailed history available for accurate management.

Compliance with ethical standards

Acknowledgments

The authors would like to thank Mr Ibrahim N. A Al -Jurayyn (Medical Student) for his kind help and assistance in preparing this manuscript.

Disclosure of conflict of interest

The authers have no conflicts of intersf to declare.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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