

Unusual Presentation of Hypertension in Children-Liddle's Syndrome

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Abstract

The incidence of high blood pressure in children is not so common it is close to 1-5%, most cases are secondary, and the most common cause of secondary high blood pressure in children is a kidney problem. It is very important to discover the cause of high blood pressure, to treat it before the development of complications.

We present an isolated case of Liddle's syndrome in a 10 years old girl, a 10 year old girl had been admitted with complaints about polydipsia and polyuria that started before 1 month., ECG was performed to rule out a cardiac problem, on evaluation she was found to have hypokalemia and metabolic alkalosis, bilateral nephrocalcinosis was diagnosed by renal ultrasound.

At first, treatment with potassium was started and the girl was treated as she had Barter syndrome but no improvement in blood pressure was seen.

Later on, the level of renin was low, Liddle syndrome and adrenal hyperplasia was considered in the differential diagnosis, and a total investigation was taken of hydroxyprogesterone and aldosterone, Liddle syndrome was suspected when we received low levels of renin, a normal level of aldosterone and 17-hydroxyprogesterone. In light of this, amiloride treatment was started, and there was an improvement in blood pressure and in the level of potassium in the blood.

Keywords: Hypokalemia; Hypertension; Liddle's syndrome; Renin; Aldosterone

Abbreviations: ENaC: Epithelial Sodium Channel; IUGR: Intrauterine Growth Restriction; ECG: Electrocardiography; β ENaC: Beta Subunit of Epithelial Sodium Channel

Introduction

Liddle syndrome is one of the causes of secondary pediatric hypertension. It is also known as Pseudoaldosteronism which is characterized by hyperaldosteronism (hypokalemia, high blood pressure, and metabolic alkalosis), [1] but there is no increase in the level of aldosterone in the blood.

Liddle's syndrome is a rare autosomal dominant condition characterized by an ENaC mutation. However, sporadic cases of Liddle's syndrome have been stated in the literature [2-4].

Genetic studies have revealed that mutations affecting the cytosolic tail of the β subunit of the Epithelial Sodium Channel (ENaC) could lead to this disorder [3,4]. Leading to a primary increase in sodium reabsorption from the collecting tubule and secretion of potassium in the majority of the cases. Patients mostly are young, although there are cases that are detected in adulthood.

Liddle is a familial syndrome presented by severe hypertension, hypokalemia (in most cases) and metabolic alkalosis mimicking

hyperaldosteronism [4]. However, these patients have low renin and aldosterone levels, and there is conservation of sodium and excretion of potassium in the absence of mineralocorticoids excess [1].

The treatment of Liddle's syndrome differs from other forms of essential or secondary hypertension, treatment with drugs that work on aldosterones such as Spironolactone and Eplerenone is ineffective [5,6]. Treatments with sodium channels Blockers in the kidneys such as Amiloride and Triamterene is also associated with control of blood pressure and potassium in the blood, and are considered to be effective in this syndrome [7,8].

Liddle syndrome is characterized by severe, early-onset hypertension (high blood pressure). Although the condition may not be associated with any signs and symptoms initially, untreated hypertension can eventually lead to heart disease and stroke. Affected people may also have hypokalemia (low blood potassium) and metabolic alkalosis. Symptoms of hypokalemia can include weakness, fatigue, muscle pain (myalgia), constipation or heart palpitations.

IUGR, delayed growth, lack of urine concentration in the kidneys that it is secondary to chronic hypokalemia [9,10] and in rare cases secondary to hypercalciuria and nephrocalcinosis, which is unclear.

It is important to note the importance of genetic counseling and to screen other children's in the same family because it is a hereditary disease. In addition it is necessary to monitor renal function, heart, and growth, usually appropriate treatment and follow-up reduce the long-term complications.

Case Study

A 10 years old girl had been admitted with complaints about polydipsia and Polyuria that started before one month. Besides she had muscle weakness, abdominal distension, vomiting, and drowsiness.

In her history, Oligohydramnios she was born with low birth weight 2 kg, delayed motor development, But without a family history of increased blood pressure in childhood.

In her Physical examination, the child was drowsy, with a dysmorphic face, and increased blood pressure in all four limbs around 150/90 mmhg, the rest of the physical examination with no significant findings. Her height and weight were in the third percentile.

A laboratory was sent including electrolytes and complete blood count, and ECG and thyroid function was performed to rule out acute cardiac and thyroid causes.

The results showed hypokalemia and metabolic alkalosis, and bilateral nephrocalcinosis was diagnosed by renal ultrasound.

At first, treatment with potassium was started, and the girl was treated as she had Barter syndrome, but no improvement in blood pressure was seen, later on, the level of renin was low, so in the differential diagnosis was Liddle syndrome and adrenal hyperplasia, so a complete investigation was taken of hydroxyprogesterone and aldosterone (Table 1 and Table 2).

The Liddle syndrome was suspected when we received low levels of rennin, normal levels of 17-OHP, and aldosterone. In light of this, amiloride treatment was started, and there was an improvement in blood pressure and the level of potassium in the blood (Table 3 and Table 4).

Table 1: Laboratory investigations.

| Lab | Serum Electrolytes | Urinary Electrolytes |
|---------------------|--------------------|----------------------|
| BUN mg/dl | 15 | - |
| Creatinine mg/dl | 0.6 | 10 |
| Mg mmol/L | 2.4 | - |
| Na mmol/L | 135 | 25 |
| K mmol/L | 2.2 | 16 |
| Chloride mmol/l | 96 | 55 |
| Bicarbonat mmol/lit | 29 | - |
| Osmolarity | 285 | 130 |

Table 2: Laboratory investigations.

| | |
|-------------|--------------------------|
| Renin | 0.06<(normal;3-40)nng/DL |
| 17-OHP | 0.5 (0.03-0.9)nng/DL |
| Aldosterone | 6 (1-15)PG/DL |

Discussion

Once the common causes of hypertension have been ruled out, hypertension will be associated with unknown cause. In these cases, there is a chance of a dominant or recessive hereditary disease that can be the cause of high blood pressure [3].

Liddle's Syndrome is a rare disease with autosomal dominant inheritance, manifested in mutations in the sodium channels in the kidneys, which causes over-activation of the sodium channels, its caused by changes (mutations) in the SCNN1B or SCNN1G gene [11,12]. Each of these genes provides instructions for making mutations in β ENaC or γ ENaC subunits of a protein complex called the epithelial sodium channel (ENaC).

These channels are found on the surface of certain cells (epithelial cells) throughout the body, including the collecting tubule in the kidneys. The ENaC channel transports sodium into cells. Mutation in this channel can leads to increased Na^+ transport by two different mechanisms. First, this mutation increases ENaC expression at the plasma membrane. The genetic defects either mutate tyrosine or a proline-rich sequence, the PY motif, or delete the intracytoplasmic C-terminus of β or γ ENaC. The PY motif works as a binding site for the Nedd4 family of ubiquitin-protein ligases Nedd4-2 targets and degrades the channel and decreases ENaC expression to the surface. Thus, Liddle's syndrome mutations increase ENaC surface expression by disrupting its interaction with Nedd4-2 [10,13,14].

Second, this mutation increases the proteolytically cleaved (active) fraction of ENaC at the plasma membrane leading to more Na^+ transport [14]. A combination of hypokalemia, elevated blood pressure and metabolic alkalosis are the usual presentations in patients with Liddle's syndrome. These findings mimic other disorders caused by mineralocorticoids excess. The final diagnosis of this disease is by genetic examination of a mutant in ENaC [2] but in our case, the diagnosis was based on the exclusion of other causes in addition to a good response to appropriate treatment.

Treatment for Liddle syndrome consists of following a low sodium diet and taking potassium-sparing diuretics, which reduce blood pressure and correct hypokalemia and metabolic alkalosis. Conventional anti-hypertensive therapies are not effective for this condition [15]. The ENaC antagonist's amiloride and triamterene directly block the ENaC and correct both hypokalemia and the hypertension, [8]. Spironolactone is ineffective in treating Liddle's syndrome because Liddle's syndrome is not mediated by aldosterone.

Conclusion

A 10 years old female presented muscle weakness, severe hypertension, hypokalemia and metabolic alkalosis was found [16]. Further study had supported the autosomal dominant inherited disease Liddle's syndrome. That it is a rare syndrome in children's manifested in mutations in the sodium channels in the kidneys.

Table 3: Blood pressure trend.

| Blood pressure trend | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Follow-up |
|-----------------------------|--------|--------|--------|--------|--------|-----------|
| Systolic/ Diastolic mmHg | 145/89 | 140/80 | 135/70 | 131/69 | 122/65 | 112/60 |

Table 4: Potassium level trend.

| Potassium level trend | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Follow-up |
|-----------------------|-------|-------|-------|-------|-------|-----------|
| | 2.2 | 2.2 | 2.4 | 2.95 | 3 | 3.4 |

Amiloride treatment was started, and there was an improvement in blood pressure and the level of potassium in the blood. Once the common causes of hypertension have been ruled out, hypertension will be associated with unknown cause. In these cases, there is a chance of a dominant or recessive hereditary disease that can be the cause of high blood pressure.

There are cases in which this syndrome is not diagnosed and not treated accordingly, causing multiple complications such as stroke, heart, and kidney problems and even death, so it is important to diagnose this disease and treat accordingly to avoid long-term complications.

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