Pediatric Bartter syndrome: The therapeutic challenge

Aamir Jalal Al Mosawi1,2*

1Advisor in Pediatrics and Pediatric Psychiatry, Children Teaching Hospital, Baghdad Medical City, Iraq
2Head, Iraq Headquarter of Copernicus Scientists International Panel, Baghdad, Iraq

Abstract

Background: There is no curative therapy for many of the rare genetic disorders such as Bartter syndrome. Many patients with such disorders will be treated to a large extent with symptomatic therapies, and many of them will continue to have some symptoms, and growth and mental retardation despite the traditional therapies generally known by the treating physician. Because of the rarity of such disorders, many specialist physicians may have limited experience with treatment of such disorders and treatment side effects may be sometimes encountered. It is hoped that advances arising from the accumulating research evidence can contribute to improving treatment of such conditions.

Materials and methods: A unique case of classical pediatric Bartter syndrome associated with low set ears and mental retardation that was treated unsatisfactorily was studied. The medical literatures were reviewed for the recent research evidence that may help in improving the therapeutic services for patients with Bartter syndrome.

Results: The occurrence the rare genetic disorder Bartter syndrome in Iraq has not been documented. A unique case of Bartter syndrome associated with low set ears and mental retardation in an Iraqi girl. The girl was treated before referral by some of the traditional therapies that improved her symptoms and condition, but she experienced some side effects of treatment and growth and mental retardation.

Conclusion: Literature review helped in recommending an evidence-based opinion suggesting the replacement of one drug with a safer one, and the addition of another evidence-based effective therapy.

Introduction

Bartter syndrome is a rare genetic disorder characterized by hypokalemia, hypochloremia, alkalosis, and normal or low blood pressure. There are three main clinical forms of Bartter syndrome, and a variant form including neonatal Bartter syndrome, classical pediatric Bartter syndrome, adult Bartter syndrome and a variant form (Gitelman syndrome) which is generally milder than neonatal and classic pediatric forms of Bartter syndrome [1–3].

Children with classic Bartter syndrome generally became symptomatic in the first two years of life, but they are usually diagnosed at school age or later. Children with classic Bartter syndrome also develop polyuria, polydipsia, and a tendency to dehydration, but they generally have normal urinary calcium excretion or mild hypercalcuria without significant tendency to develop kidney stones [1].

Other features of Bartter syndrome include [1]:

- Vomiting and growth retardation.
- Renal function is generally normal.
- Elevated plasma rennin and aldosterone.
- High urinary potassium and chloride despite low serum values.
- Hyperplasia of the juxtaglomerular apparatus on kidney biopsy.
- Excess production of prostaglandins by the kidneys is often found.

There is no curative therapy for many of the rare genetic disorders such as Bartter syndrome. Many patients with such disorders will be treated to a large extent with symptomatic therapies, and many of them will continue to have some symptoms, and growth and mental retardation despite the traditional therapies generally known by the treating physician. Because of the rarity of such disorders, many specialist physicians may have limited experience with treatment of...
such disorders and treatment side effects may be sometimes encountered. It is hoped that advances arising from the accumulating research evidence can contribute to improving treatment of such conditions [1,4,5].

**Materials and methods**

A unique case of classical pediatric Bartter syndrome associated with low set ears and mental retardation that was treated unsatisfactorily was studied. The medical literatures were reviewed for the recent research evidence that may help in improving the therapeutic services for patients with Bartter syndrome.

**Results**

The occurrence the rare genetic disorder Bartter syndrome in Iraq has not been documented. A unique case of Bartter syndrome associated with low set ears and mental retardation in an Iraqi girl. The girl was treated before referral by some of the traditional therapies that improved her symptoms and condition, but she experienced some side effects of treatment and growth and mental retardation. The girl was first seen at the pediatric psychiatry clinic at about the age of five years during June, 2018 as a known case of Bartter syndrome with poor speech development. She was also delayed in achieving motor mile stones. However, currently she can walk and run. The child had slow growth, episodes of vomiting, polydipsia, polyuria, and history of spasms. She has been treated with oral potassium supplementation (30mEq per day in divided doses) and indomethacin (12.5mg daily) which had to be stopped for some time before few months because of the development of serious gastric side effects with abdominal pain and vomiting.

Despite treatment, she had chronic hypokalemia as serum potassium was low in all the previously available performed tests (Table 1).

Although the girl had low set ears (Figure 1) and poor speech development, she was responding to her name, and had good eye contact. She responded when she asked to take the pen and try to copy a line, but she couldn’t hold the pen perfectly right nor could she copy the line.

This Iraqi girl had been treated traditionally by potassium supplement and indomethacin, but persistent correction of hypokalemia couldn’t be achieved.

**Bartter syndrome treatment research progress**

Bartter syndrome was originally treated by the physicians who first reported the condition, initially with potassium chloride supplements, and later they performed partial adrenalectomy. Symptoms were relieved for several months without potassium supplements after partial adrenalectomy, but serum potassium remained low (3.3–2.8mEq/L). Fifteen months after partial adrenalectomy, significant hypokalemia (Serum potassium: 2 mEq/L) and tetany returned [1,6,7].

George T Bryan and colleagues reported that spironolactone with low-sodium diet increased serum potassium to normal level in Bartter syndrome. They also reported that infusion of albumin was associated with a rapid increase in serum potassium and a reduction in aldosterone secretion rate [8].

The use of indomethacin has been reported by many authors including Verberckmoes, et al., Zancan and colleagues, Littlewood and colleagues, Proesmans and colleagues, Dequiedt, et al., Kornerup and colleagues, Konomi, et al., Valles, et al., Floret, et al., Favre, et al., and Storm and colleagues [1,3,9–17].

The work of Kornerup and colleagues suggested that long-term treatment with indomethacin may be ineffective in maintaining normal potassium balance in Bartter syndrome [9]. Konomi, et al., reported the occurrence of pseudotumor cerebri in Bartter syndrome during indomethacin therapy [14].

The use of other inhibitors of prostaglandin synthetase in treatment of Bartter syndrome including ibuprofen [18,19], aspirin [20], naproxen [21], ketoprofen were also reported [22,23].

Gill JR, et al., reported that treatment with ibuprofen which is an inhibitor of prostaglandin synthetase having

| Date        | Serum Potassium mEq/L | Serum chloride mEq/L | Blood PH | Serum bicarb mEq/L | Serum sodium mEq/L | PCO2 | Serum Creatinine mg/dL | Blood urea mg/dL | Serum calcium |
|-------------|-----------------------|----------------------|----------|--------------------|--------------------|------|------------------------|-----------------|--------------|
| Jan, 22, 2017 | 2.3                  | 88                   |          | 7.39               |                    |      |                        |                 |              |
| Jan, 31, 2017 | 2.3                  | 96                   | 7.428    | 24.7               | 135                | 36.9 | 0.36                  |                 |              |
| May, 8, 2017  | 2.9                  | 92                   | 7.49     | 27.8               | 139                | 36.7 | 0.34                  | 24 mg           | 10.1         |
| Jul, 6, 2017  | 2.2                  | 96                   | 7.49     | 27.8               | 139                | 36.7 | 0.34                  |                 |              |
| Sept, 28, 2018| 2.2                  | 95                   |          | 7.49               |                    |      |                        |                 |              |

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different structure from indomethacin was associated with metabolic effects which were qualitatively similar to those of indomethacin [18].

Norby, et al., treated a young patient with Bartter syndrome was for three months with 100 mg/kg/day of aspirin to inhibit prostaglandin synthesis. Treatment was associated with disappearance of clinical symptoms and elevation of serum-potassium from 2.9 to 3.5mmol/l. Norby, et al., thought that overproduction of prostaglandins has a central role in the pathogenesis of Bartter syndrome [20].

Littlewood and colleagues reported a nine-month old boy with Bartter syndrome who had poor weight and height gain. They treated him initially with oral potassium supplements and later with spironolactone which restored plasma potassium to normal. However, the patient experienced little or no effect on his growth. At the age of thirty-three months, indomethacin therapy was started, and was associated with dramatic results. Symptoms disappeared, and his height and weight accelerated to reach the normal range. Because of the toxicity of indomethacin, Littlewood and colleagues replaced it after twelve months by another prostaglandin synthetase inhibitor, ketoprofen. The use of ketoprofen was associated with a satisfactory result. Littlewood and colleagues thought that treatment with prostaglandin synthetase inhibitors is the best available treatment for Bartter syndrome [22].

Larizza, et al., reported the occurrence of pseudotumor cerebri during ketoprofen treatment in Bartter syndrome [23].

Simatupang, et al., studied the effect of anti-kaliuretic agents (spironolactone, amiloride) and antiprostaglandin agents (indomethacin, ibuprofen) on plasma rennin activity and potassium metabolism in a patient with familial Bartter syndrome. They reported the followings [24].

- The reduction in renal potassium clearance in response to antikaliuretic treatment was transient, whereas marked potassium retention occurred with indomethacin therapy.
- Plasma rennin activity consistently increased after kaliuretics, while a marked reduction occurred in response to antiprostaglandin agents.

Cunningham, et al., reported the treatment of two patients with Bartter syndrome with propranolol, spironolactone, and potassium supplements initially. The addition of ibuprofen made potassium supplements no longer required. In both patients, plasma rennin activity was reduced, plasma volumes increased, and a “catch-up” in linear growth resulted. The report of Cunningham, et al., emphasized the value of the prostaglandin synthetase inhibitor, ibuprofen in the therapy of Bartter syndrome [25].

The treatment of Bartter syndrome with angiotensin converting enzyme inhibitor has been reported by several authors including Aurell and Rudin, Hené, et al., Aurell and Rudin, Hené, et al., Morales, et al., Volpi, et al., Scherling, et al., [26–33].

Hené, et al., treated seven patients with Bartter syndrome for three months by enalapril. Treatment was associated with elevation of Serum potassium from 2.4±0.5 to 3.9±0.6mmol/L, elevation of serum magnesium and lowering of serum bicarbonate, stimulation of rennin and reduction of aldosterone. Lowering of blood pressure. Clinically important short–lasting hypotension associated with oliguria was recorded twice. Blood pressure returned to pre–treatment levels within 72hours despite continuation of converting–enzyme inhibition. Renal function recovered, though a moderate fall in function persisted. No other side effects were recorded by Hené, et al., Hené, et al., thought that converting–enzyme inhibition can improve the potassium metabolism of patients with Bartter syndrome without improving the abnormal renal sodium handling [29].

Van de Stolpe, et al., studied total body potassium in three patients with Bartter syndrome before, after three months and after 1 year of treatment with enalapril. In two patients, total body potassium was reduced before treatment, whereas total body potassium was within the normal range in the third measurement. During treatment serum potassium and total body potassium increased in each patient, and the symptoms of fatigue and tetany disappeared. Van de Stolpe, et al., thought that enalapril can be associated in the treatment of Bartter syndrome as it improves serum potassium, total body potassium and symptoms [30].

Volpi, et al., reported the long–term treatment of three sisters with Bartter syndrome with captopril therapy [31].

Scherling, et al., from Denmark reported the treatment of a thirteen years old girl with Bartter syndrome who had [33].

- Lassitude and polyuria.
- Hypokalemia.
- Elevated plasma rennin and urinary prostaglandin excretion.
- Normal plasma aldosterone level and normal urinary aldosterone excretion.
- Normal blood pressure.

The initial treatment of the patient with oral potassium was not satisfactory.

Treatment with acetylsalicylic acid was associated with some effect, and an allergic reaction led withdrawal of treatment. Treatment with the angiotensin converting enzyme inhibitor captopril and oral potassium was associated with clinical and biochemical improvement.

**Discussion**

Bartter syndrome was probably first described by Pacita Pronove, Ross C MacCardle and Frederic Crosby Bartter in 1960. They reported a five–year old boy with hypokalemia, alkalosis, primary aldosteronism, normal blood pressure, unique renal lesion which is hyperplasia of the juxtaglomerular apparatus.
In 1962, Frederic Crosby Bartter, Pacita Pronove, John R Jill Jr, and Ross C MacCardle published a paper emphasizing that the condition which was described earlier by three of them in 1960 was a new syndrome. Frederic Crosby Bartter and his team also described a second black male patient. Frederic Crosby Bartter and his team considered the two patients they described as having a new syndrome [1,6,7]. Bartter syndrome was classically and originally associated with hyperplasia of the juxtaglomerular apparatus of the kidneys. However, several patients with Bartter syndrome have been reported without evidence of hyperplasia of the juxtaglomerular apparatus [1,9,34].

The Iraqi girl being reported had mental retardation and low set ears. Simopoulos reviewed the literature and found that the majority of patients with Bartter syndrome showed some degree of mental retardation. However, low set ears has not been reported with this syndrome [35].

The paper of Kornerup and colleagues suggested that long-term treatment with indomethacin may be ineffective in maintaining normal potassium balance in Bartter syndrome [9]. Konomi, et al., reported the occurrence of pseudotumor cerebri in Bartter syndrome during indomethacin therapy [15].

Gill JR, et al., reported that treatment with ibuprofen which is an inhibitor of prostaglandin synthetase having different structure from indomethacin was associated with metabolic effects which were qualitatively similar to those of indomethacin [18].

Cunningham, et al., emphasized the value of the prostaglandin synthetase inhibitor, ibuprofen in the therapy of Bartter syndrome.

Therefore, the available evidence suggests replacing indomethacin with ibuprofen.

I am reluctant to recommend adding anti-kaliuretic agents (spiromolactone or amiloride) to the treatment of the girl because Simatupang, et al., studied the effect of anti-kaliuretic agents (spiromolactone, amiloride), and antiprostaglandin agents (indomethacin, ibuprofen) on plasma rennin activity and potassium metabolism in a patient with familial Bartter syndrome, and reported that the reduction in renal potassium clearance in response to antikaliuretic treatment was transient, whereas marked potassium retention occurred with indomethacin therapy [24].

Plasma rennin activity consistently increased after kaliuretics, while a marked reduction occurred in response to anti-prostaglandin agents. There is also convincing evidence that the addition of enalapril could be of value in improving treatment in this Iraqi patient [30].

Conclusion

Literature review helped in recommending an evidence-based opinion suggesting the replacement of one drug with a safer one, and the addition of another evidence-based effective therapy.
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