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Research Article

Ten Year Retrospective Review of Bartter Syndrome at Sheikh Hospital 2008-2018

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ABSTRACT

Objective: Bartter syndrome is a type of autosomal-recessive genetic abnormality with a low prevalence. In this abnormality, due to the mutations in the cotransporters and channeling proteins that are responsible for the transfer of sodium, chloride and potassium electrolytes in the thick ascending loop of Henle, the body throws out a large amount of these electrolytes through the urine. Early birth (prematurity), polyhydramnios, alkalosis and hypokalemia are the most important side effects of Bartter syndrome. Accordingly, quick detection of this can improve the treatment.

Methods and Materials: The purpose of the current study is to investigate the symptoms of patients referred to Sheikh Hospital (Mashhad, Iran) over the past ten years due to Bartter's syndrome. Accordingly, by referring to patients' files, information about them is extracted from the historical documents and, statistically analyzed. Patients are also requested to complete a questionnaire, if necessary, through a telephone conversation.

Results: Our findings indicated that symptoms including fever, polyuria, polydipsia, nausea and seizure, fever, physical and mental retardation, and one death among 14 participants were reported. Also, the biochemical findings of this study showed that potassium ion (k+) concentration in the serum of neonates was significantly lower than normal (p = 0.0001), and the concentration of calcium ions (Ca2+) and urea composition was significantly higher than normal (p = 0.0001). Also, sonographic findings showed that nephrocalcinosis and microlithiasis were observed in the participants in this study. Potassium chloride, normal saline, Brufen and Aldactone were used for treatment.

Conclusion: It can be concluded that high concentrations of calcium and urea, low concentration of potassium ion, and complications such as fever and seizure along with polyhydramnios and nephrocalcinosis are the most important symptoms seen in patients with Bartter syndrome in the last 10 years.

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Introduction

In 1962, Bartter *et al*. identified a new syndrome characterized by hypokalemia and metabolic alkalosis with hyperaldosteronism and hyperplasia of the juxtaglomerular apparatus (JGA) [1]. Those patients were different from the typical patients with hyperaldosteronism because they were younger, had normal blood pressure, also had growth retardation. Bartter syndrome (BS) is currently recognized as a rare inherited renal tubular disorder that affects around 1 in 1,000,000 of the population. It is, caused by defective salt reabsorption in the thick ascending limb (TAL) of the loop of Henle, resulting in salt wasting, hypokalemia and metabolic alkalosis with relatively low levels of serum chloride [2]. Impairment in the sodium-potassium-chloride cotransporter (NKCC2) or the potassium channel (ROMK) affects the transport of sodium, potassium, and chloride in the thick ascending limb of the loop of Henle (TALH). This results in increased distal delivery of these ions, where only some sodium is reabsorbed, and potassium is secreted [3].

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BS is a heterogeneous disorder, both clinically and genetically, that can be classified into two clinical variants, antenatal BS (aBS) and classic BS (cBS), according to the onset age. Also, BS can be classified into at least five genetic subtypes according to the underlying mutant gene, all of which are expressed in the tubular epithelial cells of the thick ascending limb of the loop of Henle [2].

Types of Bartter syndrome:

i. Type I results from mutations in the sodium chloride/potassium chloride cotransporter gene (NKCC2).
ii. Type II results from mutations in the ROMK gene.
iii. Type III results from mutations in the chloride channel gene (CLC-Kb).
iv. Type IV results from the loss-of-function mutations in the gene encoding Barttin [4, 5].
v. Type V results from mutations in extracellular calcium ionsensing receptor and in the genes that encode the chloride channel subunits, ClC-Ka and ClC-Kb.

Bartter syndrome is usually seen in children and adolescents who also have stunted growth and complaints of polyuria, polydipsia, cramps, vomiting, dehydration, constipation, growth delays, and failure to thrive. A family history of nephrocalcinosis and detailed personal history ruling out the possibility of surreptitious vomiting and diuretic abuse should be practiced before making the diagnosis. Patients are usually emaciated with a prominent forehead, large eyes, strabismus, protruding ears, sensorineural deafness, and drooping mouth. Normal or low blood pressures are usually recorded. Long-standing cases may present with elevated blood pressures. Offspring with antenatal Bartter syndrome present with polyhydramnios secondary to intrauterine polyuria and are usually delivered prematurely. Fever, sensorineural deafness, profound polyuria, vomiting, and diarrhea leading to dehydration are common observations after birth [6]. Diagnosis is made by pertinent findings in the background and physical exam, potentiated with specific laboratory abnormalities. Bartter syndrome is associated with electrolyte and acidbase abnormalities, including hypokalemia and metabolic alkalosis in almost all cases [7].

Materials and Methods

I Ethical Considerations

This study was approved by the institutional review board of Mashhad University of Medical sciences. Informed consent was obtained from all patients or their parents.

II Inclusion Criteria

A total of 14 patients who were admitted to Sheikh Hospital with a diagnosis of Bartter syndrome from 2008 to 2018 have participated.

III Study Design

The information of all those 14 patients such as age, gender, clinical features and laboratory findings were abstracted from their files and evaluated.

IV Statistical Analyses

Data are expressed as mean ± SD. All analyses were performed using standard statistical software. The clinical backgrounds of the patients were compared using the Mann-Whitney, one-way ANOVA, one sample t-test and Student's *t*-tests, as appropriate. A *P*-value of <0.05 was considered statistically significant.

Table 1: Laboratory findings in patients.

	Number	Domain	Minimum	Maximum	Standard deviation		Variance
Urea	14	136.00	15.00	151.00	50.0714	36.24588	1313.76
Creatinine	14	6.4	0.30	6.7	1.1929	1.63258	2.66
Sodium	14	32.0	110.0	142.0	130.1429	8.36529	69.97
Potassium	14	2.5	2.2	4.7	3.2786	0.84323	0.71
Calcium	12	3.2	7.4	10.6	9.2917	1.06810	1.14
Phosphor	7	4.5	2.5	7	4.9714	1.40915	1.98
Urine SG	12	17.0	1003	1020	1006.3333	4.65800	2169
RBC in urine	5	17.0	3.0	20.0	7.8	7.08520	50.2
WBC in urine	3	16.0	2.0	18.0	9.3333	8.08290	65.3
Urine calcium	5	6.1	4.9	11.0	7.94	2.42549	5.88
Urine protein	1	0.00	28.0	28.0	28.0	0.0	0.0
Urine pH	12	3.0	5.0	8.0	6.41	1.16	1.35
Blood pH	14	0.47	7.2	7.67	7.5007	0.11317	0.013
pCO2	14	25.2	15.7	40.9	31.4143	7.72387	59.65
HCO3	14	21.7	15.3	37.0	25.7929	6.53140	42.65
Hb	13	6.3	8.1	14.4	10.6308	1.84001	3.38

Table 2: Clinical findings in patients.

Complication	Patients
Polyuria	2
Polydipsia	2
Growth retardation	9
Vomiting	10
Malnutrition	2
Weakness	5
Mental retardation	1
Nausea	4
Preterm labor	4
Polyhydramnios	2
Fever	9
Seizure	4
Nephrocalcinosis	2
Diarrhea	4
Death	1

Results

Our study aimed to review and evaluate ten-year information of patients with Bartter syndrome in Sheikh Hospital to diagnose this disease sooner and to help patients have a faster recovery. A total of 14 patients admitted to Sheikh Hospital with diagnosis of Bartter syndrome between 2008 and 2018 were included. The minimum age of participants was 36 weeks and the maximum age was 192 weeks. Also, 6 patients were male, and 8 patients were female. The minimum age of diagnosis was at week 2 and the maximum age was at week 132 of birth. The most important clinical features of patients were growth retardation, nausea, polyuria, fever and weakness (Table 2). Growth retardation was a common disorder in female patients (4 out of 6 newborns) while in male patients, weakness and nausea were more common.

I Polyuria and Polydipsia

Polyuria and polydipsia were found in just two patients as their chief complaint.

II Nausea and Vomiting

Nausea and vomiting were found in four patients, and analysis shows that there is no significant difference between the neonates' gender and this complication (P=0.594).

III Mental Retardation

Mental retardation is one of the most important symptoms in Bartter syndrome and it was found in one female newborn. There is no significant difference between the neonates' gender and this complication (P=0.175).

IV Malnutrition

Malnutrition was found in two female neonates.

V Weakness

Weakness also found in two male and three female neonates, and there is no significant difference between the neonates' gender and this complication (P=0.657).

VI Preterm Labor

Preterm labor was found in one male and three female neonates, and there is no significant difference between the neonates' gender and this complication (P=0.604).

VII Polyhydramnios

Polyhydramnios is an important sign in Bartter syndrome and was found in two neonates. There is no significant difference between the neonates' gender and this complication. As polyhydramnios is an obvious manifestation of Bartter syndrome it reminds the necessity of gestational ultrasonography.

VIII Fever

Four male and five female neonates showed fever during the disease, but there was no significant difference between the neonates' gender and this complication (P=0.657).

IX Seizure

Seizure almost found in association with fever in one male and three female neonates.

X Nephrocalcinosis

Nephrocalcinosis was reported in only two female neonates. There was no significant difference between the neonates' gender and nephrocalcinosis (P=0.308).

XI Hearing Loss

Hearing loss was found in two infants.

XII Diarrhea

One male and three female neonates showed diarrhea as their chief complaint.

XIII Mortality

All patients were treated, and one female neonate died due to the complications.

XIV Drugs

Drugs used for 13 survived patients included potassium chloride, normal saline, Aldactone and ibuprofen.

XV Genetic Evaluation

A genetic evaluation was performed on a few patients and two Bartter syndrome cases were confirmed, and one Pseudo Bartter syndrome (congenital diarrhea with chloride excretion) was reported.

XVI Sonography Findings

Sonography findings showed no abnormality in the kidneys of five patients, while the rest had nephrocalcinosis and nephrolithiasis as one of the complications. Due to the 65% prevalence of these complications the necessity for ultrasound examination of these patients is indicated.

XVII Biochemical Laboratory Findings

Biochemical factors measured in our study include urea, creatinine, sodium, potassium, calcium, phosphor, and fasting blood sugar, RBC and WBC in urine, urine calcium, urine protein, urine pH, blood pH, pCO2, HCO3, and hemoglobin (Table 1).

XVIII Potassium

Potassium normal range in children is 3.5-5.5 mEq/l, while the potassium range in Bartter syndrome patients in our study is 2-4.5 mEq/l. This finding shows that the potassium level in participants is significantly less than the normal population (P=0.0001).

XIX Urea

The normal range of urea in children is 5.4-24.3 mmol/l. Our study demonstrates that urea is significantly higher than normal in participants (15-151 mmol/l), and blood urea nitrogen has a significant increase in neonates with Bartter syndrome (P=0.0001).

XX Sodium

Our findings showed that serum sodium levels in participants have no significant difference with that of the normal population. The normal sodium level in neonates is 135-145 mEq/l and in our participants, it is 110-142 mEq/l.

XXI Blood pH

One of the most important findings in Bartter syndrome is metabolic alkalosis. In this study, the bicarbonate serum levels in participants ranged from 17 to 37 mEq/l while the normal range in children is 17-28 mEq/l. Although the bicarbonate range in patients was higher than normal, it is not statistically significant.

XXII Family History

Given the genetic status of Bartter syndrome as an autosomal recessive disease, the history of 4 out of 14 patients revealed a positive family history of the disease.

Discussion

Bartter syndrome is an autosomal recessive genetic disorder. Impairment in the sodium-potassium-chloride cotransporter (NKCC2) or the potassium channel (ROMK) affects the transport of sodium, potassium, and chloride in the thick ascending limb of the loop of Henle (TALH). Bartter syndrome affects neonates and causes preterm labor in infants with this disorder. The most prevalent complications include polyuria, polydipsia, polyhydramnios, metabolic alkalosis and fever.

In a study conducted by Simon. B D *et al*., they demonstrate Bartter's syndrome, featuring hypercalciuria, hypokalemia, metabolic alkalosis and early presentation with severe volume depletion. They also discussed the link between the Bartter's syndrome and the renal Na–K–2Cl co transporter gene NKCC2 and identified frame-shift or non–conservative missense mutations for this gene that co–segregate with the disease [8]. Similar to our study, the potassium level in all participants was significantly lower than the normal range.

In another study, N Takahashi *et al*. showed that Bartter syndrome can cause polyuria and polydipsia in all humans and animals' samples. They demonstrated that disease complications become more severe as a result of a mutation in renal the Na–K–2Cl cotransporter gene [9]. Similarly, two participants in our study were diagnosed with polyuria and polydipsia. According to these findings, gene therapy can be a suitable treatment for these patients.

In another research by Seik UV *et al*., the case of a woman with recurrent hydramnios in three pregnancies, whose only surviving infant was later found to have Bartter's syndrome, was described. The finding of maternal hydramnios in the present case and 12 other reported cases of Bartter's syndrome suggests that increased fetal voiding is the most likely causative factor in the development of increased amniotic fluid volume. They also indicate that early-onset hydramnios might signify Bartter's syndrome in the offspring in families with an index case [9]. In line with our study, polyhydramnios was found in two participants.

The study conducted by Hannsjörg W. Seyberth *et al*., turned out that a congenital hypokalemic tubular disorder is described with many features resembling Bartter syndrome. Additional features include prenatal onset with polyhydramnios and premature labor, failure to thrive, episodes of fever, vomiting, diarrhea, and renal electrolyte and water wastage, hypercalciuria, nephrocalcinosis, and osteopenia [10]. Similar to our study, the potassium level in all participants was significantly lower than the normal range, in addition, nephrocalcinosis was found in two patients diagnosed with Bartter syndrome.

Conclusion

Based on our findings, resulting from the history and information taken from the patients diagnosed with Bartter syndrome in Sheikh Hospital in the last 10 years, the most important clinical features of Bartter syndrome consist of growth retardation, hypokalemia, increased blood urea nitrogen, and nephrocalcinosis and kidney microlithiasis according to laboratory findings and sonography. In addition, some patients have complications such as preterm labor, seizure, nausea and vomiting, diarrhea and polyhydramnios. Considering these findings, we can

diagnose the disease faster and improve the process of patients' treatment.

REFERENCES

1. Bartter FC, Pronove P, Gill Jr JR, MacCardle RC (1962) Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis: a new syndrome. *Am J Med* 33: 811-828. [Crossref]
2. Lee BH, Cho HY, Lee H, Han KH, Kang HG et al. (2011) Genetic basis of Bartter syndrome in Korea. *Nephrol Dial Transplant* 27: 1516-1521. [Crossref]
3. Simon DB, Bindra RS, Mansfield TA, Nelson Williams C, Mendonca E et al. (1997) Mutations in the chloride channel gene, CLCNKB, cause Bartter's syndrome type III. *Nat Genet* 17: 171-178. [Crossref]
4. Janssen AG, Scholl U, Domeyer C, Nothmann D, Leinenweber A et al. (2009) Disease-causing dysfunctions of barttin in Bartter syndrome type IV. *J Am Soc Nephrol* 20: 145-153. [Crossref]
5. Kitanaka S, Sato U, Maruyama K, Igarashi T (2006) A compound heterozygous mutation in the BSND gene detected in Bartter syndrome type IV. *Pediatr Nephrol* 21: 190-193. [Crossref]
6. Bokhari SRA, Zulfiqar H Mansur A (2017) Bartter Syndrome. StatPearls [Internet]: *StatPearls Publishing*. [Crossref]
7. Thabet M, Sharaki OA, Fathy HM, Ayoub AZ (2017) Clinical and laboratory study of infants and children with Bartter syndrome attending Alexandria University Children's Hospital (10 years experience). *Alexandria J Pediatrics* 30: 1.
8. Simon DB, Karet FE, Hamdan JM, Di Pietro A, Sanjad SA et al. (1996) Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na–K–2CI cotransporter NKCC2. *Nat Genet* 13: 183-188. [Crossref]
9. Takahashi N, Chernavvsky DR, Gomez RA, Igarashi P, Gitelman HJ et al. (2000) Uncompensated polyuria in a mouse model of Bartter's syndrome. *Proc Natl Acad Sci U S A* 97: 5434-5439. [Crossref]
10. Seyberth HW, Rascher W, Schweer H, Kühl PG, Mehls O et al. (1985) Congenital hypokalemia with hypercalciuria in preterm infants: a hyperprostaglandinuric tubular syndrome different from Bartter syndrome. *J Pediatr* 107: 694-701. [Crossref]