J Ped Nephrol
Journal of Pediatric Nephrology

Case Report

Bartter Syndrome Type 4a in an Adolescent With Lower Extremity Pain: A Case Report

Reza Dalirani[1], Paniz Pourpashang[1*], Mahbubeh Mirzaee[1], Mahnaz Jamee[1]

1. Pediatric Nephrology Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Use your device to scan and read the article online

Citation Dalirani R, Pourpashang P, Mirzaee M, Jamee M.Bartter Syndrome Type 4a in an Adolescent With Lower Extremity Pain: ACase Report. Journal of Pediatric Nephrology. 2022; 10(4):190-193. https://doi.org/10.22037/jpn.v10i4.40097

https://doi.org/10.22037/jpn.v10i4.40097

Article info:
Received: 14 Aug 2022
Accepted: 25 Sep 2022
Publish: 01 Dec 2022

Corresponding Author:
Paniz Pourpashang
Address: Pediatric Nephrology Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail: punez_p@yahoo.com

ABSTRACT

Bartter syndrome is a rare genetic disease with 5 subtypes. In Bartter syndrome type 4, patients suffer from deafness and renal dysfunction since infancy. In this report, we introduced a 16-year-old girl with congenital deafness without any previous renal complaints referred to our center due to ankle pain.

Keywords: Bartter syndrome, Sensorineural deafness, Adolescent

Introduction

A defect in salt reabsorption in the thick ascending limb (TAL) of the loop of Henle causes Bartter syndrome (BS), a remarkably uncommon inherited renal tubular disease that impacts 1 in 1,000,000 people. The symptoms include hypokalemia, salt loss, and metabolic alkalosis with low serum chloride levels [1]. Decreased peripheral vascular resistance, hyperreninemic hyperaldosteronism, and hyporesponsiveness to antihypertensives are other symptoms. Because many patients with this disease fail to thrive, it is associated with increased prenatal and neonatal mortality [2].

Five different types of this disease exist. Type 4 BS is subdivided into type 4a and type 4b. Type 4a BS is caused by mutations in the BSND gene, which also affects barttin insertion in the plasma membrane of CLC-Kb and CLC-Ka channels in the Henle's loop and the inner ear, interfering with the transport of epithelial salt. Contrarily, type 4b is a digenic disorder caused by mutations in both the CLCNKA and CLCNKB genes. As a result, type 4b can cause severe salt wasting and deafness by impairing the operation of two chloride channels

Table 1. Laboratory data

Test	First Result	Second Result	Last Result
Blood urea nitrogen (mg/dL)	54	54	100
Serum creatinine (mg/dL)	2.2	5.2	4.7
Serum sodium (mEq/L)	136	136	129
Serum potassium (mEq/L)	2.5	3.5	3.9
Serum calcium (mg/dL)	8.8	-	9.3
Serum phosphorus (mg/dL)	4.4	-	7.8
Serum uric acid (mg/dL)	12.3	-	2.5
Serum magnesium (mg/dL)	1.6	-	-

[3]. Growth and mental retardation and sometimes premature progression of end-stage renal disease are common severe features in BS 4a and BS 4b patients. Some patients' glomerular filtration rate starts to decline at a young age [4, 5]. In this study, a 16-year-old girl was reported with lower extremity pain, and finally diagnosed with barter syndrome.

Case Report

A 16 years-old girl was referred to a pediatric rheumatology clinic with pain in her ankles and toes. She was the second child of a family with three children. Her parents were consanguineous. In the past medical history, she was born in 31 weeks with a birth weight of 1 kg. She had a history of deafness and used hearing aids from her early years. She had mild mental retardation and studied in special schools. No history of renal impairment existed in the patient or her family. However, she had a sister and two deaf cousins.

She had pain in her ankles and toes for a year before visiting a rheumatologist. The rheumatologist requested some laboratory studies and high creatinine and uric acid levels were observed in her evaluation. The girl was referred to a nephrology clinic for more evaluations. At the first visit, the weight was 47 kg and the height was 154 cm. X-ray radiography was taken of her ankles and toes. As shown in Figure 1, a lesion s observed in the proximal first toe and a lytic lesion with a sclerotic border in the proximal metatars and calcaneus. In the recent evaluation, she had metabolic alkalosis, hypokalemia, and elevated uric acid, and creatinine levels (Table 1).

In the renal sonography, renal echogenicity increased and corticomedullary differentiation decreased in both kidneys. A voiding cystourethrography (VCUG) was performed and was normal.

The patient's metabolic conditions were treated. Based on the presence of deafness in the patient and her family, mental retardation, and age of the patient, Bartter syndrome was suggested. Whole exome sequencing (WES) found a variant in the BSND gene (c.139G >A, P.G47R), confirming the diagnosis of Bartter syndrome type 4a (Table 2).

The patient's pain was resolved with metabolic treatments but her renal impairment progressed to chronic kidney disease (CKD) and she is now a candidate for renal transplantation.

Table 2. Whole exome sequencing result

Gene & Transcript	Variation	Chromosomal Location	Associated Disease	OMIM	Zygosity	CADD Score	dbSNP	ACMG	Inheritance
BSND NM-057176-3	Exon1 c.139G > A P.G47R	Chr1-55464998 G > A	Bartter syndrome type 4a	602522 602522	HOM	23.3	Rs74315289	VUS	AR

Abbreviations: OMIN: Online Mendelian inheritance in man; CADD: Combined annotation dependent depletion; ACMG: American college of medical genetics; VUS: Variant of uncertain significance; AR: Autosomal recessive.

J Ped Nephrol
Journal of Pediatric Nephrology

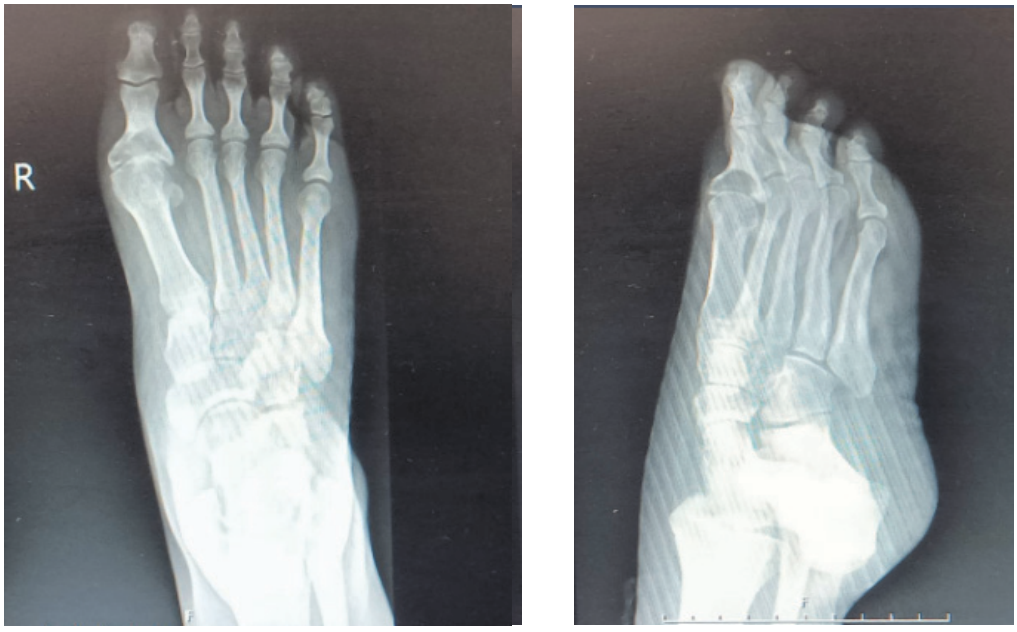

Figure 1. X-ray radiography from ankles

A lesion was observed in the proximal of the first finger and a lytic lesion with a sclerotic border was observed in the proximal metatars and calcaneus.

Discussion

BS is an autosomal recessive inherited renal tubular disease caused by mutations in genes encoding ion transporters or channels. Bartter et al reported this disease [6]. A report in 2008 mentioned that the incidence of BS is about 1100000 [7].

The mechanism of pathogenicity of BS is gene mutation. BS is divided into five types, type I BS occurs due to mutations in the sodium-potassium-chloride co-transporter (SLC12A1), type II BS due to mutations in the renal outer medullary potassium channel (KCNJ1), type III BS due to mutations in ClC-Kb (CLCNKB), type IVa BS due to mutations in barttin (BSND), and type IVb BS due to mutations in ClC-Ka and ClC-Kb (CLCNKA and CLCNKB) [8, 9]. In our patient, the WES demonstrated that she had a BSND mutation and she was diagnosed with type 4a BS.

All types of BS (except BS type 3) start in the neonatal period and in babies with preterm birth (gestational age between 29 to 33 weeks). Also, massive polyuria exists, which causes dehydration and weight loss. BS type 4 makes sensorineural hearing loss [10]. Unfortunately, some cases face a considerable diagnostic delay predisposing them to irreversible complications. Our patient did not have renal complaints such as polyuria but she suffered from hearing loss. The presence of familial hearing loss accompanying with patient's hearing loss and mental retardation was one of the causes for conducting gene sequencing.

In the BS, hypokalemia is a common complication following vomiting [9]. In our case, no history of vomiting existed and hypokalemia did not correlated with vomiting. Hypokalemia seems to be unrelated to vomiting in patients with BS and hypokalemia should have other reasons.

The ClC-K channels are located in the basolateral membrane of the epithelium of nephrons and require a barttin subunit to work properly. Barttin deficiency causes BS type 4a with loss of NaCl from the kidney [2]. ClC-Ka is expressed in the thin limb of the Henle loop [11]. ClC-Ka and barttin are also expressed in the ear [12]. Therefore, the reason why patients with BS type 4a struggle with deafness may be explained by the dysfunction in these proteins in the ear.

Genetic testing can be beneficial to patients and their families to confirm the clinical diagnoses, manage overlapping diseases, genetic counseling, and screen deafness in BS type 4 [13].

In BS type 4, the risk of CKD and end-stage renal disease (ESRD) exist [10]. Our patient had a progressive condition of CKD ESRD. She is currently a candidate

for renal transplantation. Little evidence is reported about renal transplants in patients with BS. In a report by Lee et al. a patient presented with classic BS at the age of 3 months and proteinuria at the age of 7 years. A renal biopsy was performed when he was 11 years old and it revealed a focal segmental glomerulosclerosis (FSGS) perihilar variant. Kidney transplantation was performed at the age of 16 years. The post-transplantation course was uneventful for more than 3 years with the complete disappearance of BS without the presence of FSGS [14].

Conclusion

Bartter syndrome type 4a is rare and can manifest in older children as described in this report. The familial history of deafness and renal involvement are crucial keys to suspect this disease. The main diagnostic method is gene sequencing. It is essential that physicians must be aware of the course and progression of the disease because it can progress from mild renal dysfunction to chronic renal disease or end-stage renal disease in a short period.

Ethical Considerations

Compliance with ethical guidelines

No ethical considerations were considered in this research

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors equally contributed to the preparation of this article.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Lee BH, Cho HY, Lee H, Han KH, Kang HG, Ha IS, et al. Genetic basis of Bartter syndrome in Korea. Nephrol Dial Transplant. 2012; 27(4):1516-21. [DOI:10.1093/ndt/gfr475] [PMID]

[2] da Silva Cunha T, Heilberg IP. Bartter syndrome: Causes, diagnosis, and treatment.Int J Nephrol Renovasc Dis. 2018; 11:291. [DOI:10.2147/IJNRD.S155397] [PMID] [PMCID]

[3] Vergine G, Fabbri E, Pedini A, Tedeschi S, Borsa N. Bartter syndrome type 1 presenting as nephrogenic diabetes insipidus. Case Rep Pediatr. 2018; 2018. [DOI:10.1155/2018/9175271] [PMID] [PMCID]

[4] Heilberg IP, Tótoli C, Calado JT. Adult presentation of Bartter syndrome type IV with erythrocytosis. Einstein. 2015; 13(4):604-6. [DOI:10.1590/S1679-45082015RC3013] [PMID] [PMCID]

[5] Nomura N, Kamiya K, Ikeda K, Yui N, Chiga M, Sohara E, et al. Treatment with 17-allylamino-17-demethoxygeldanamycin ameliorated symptoms of Bartter syndrome type IV caused by mutated Bsnd in mice. Biochem Biophys Res Commun. 2013; 441(3):544-9. [DOI:10.1016/j.bbrc.2013.10.129] [PMID]

[6] Bartter FC, Pronove P, Gill Jr JR, MacCardle RC. Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis: A new syndrome. Am J Med. 1962; 33(6):811-28. [DOI:10.1016/0002-9343(62)90214-0] [PMID]

[7] Ji W, Foo JN, O'Roak BJ, Zhao H, Larson MG, Simon DB, et al. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nat Genet. 2008; 40(5):592-9. [DOI:10.1038/ng.118] [PMID] [PMCID]

[8] Cruz AJ, Castro A. Gitelman or bartter type 3 syndrome? A case of distal convoluted tubulopathy caused by CLCNKB gene mutation. BMJ Case Rep. 2013; 2013:bcr2012007929. [DOI:10.1136/bcr-2012-007929] [PMID] [PMCID]

[9] Nozu K, Yamamura T, Horinouchi T, Nagano C, Sakakibara N, Ishikura K, et al. Inherited salt-losing tubulopathy: An old condition but a new category of tubulopathy. Pediatr Int. 2020; 62(4):428-37. [DOI:10.1111/ped.14089] [PMID]

[10] Konrad M, Nijenhuis T, Ariceta G, Bertholet-Thomas A, Calo LA, Capasso G, et al. Diagnosis and management of Bartter syndrome: Consensus and recommendations from the ERKNet working group for tubular disorders. ERKNet Working Group for Tubular Disorders. 2021; 1-17. [Link]

[11] Hennings JC, Andrini O, Picard N, Paulais M, Huebner AK, Cayuqueo IKL, et al. The ClC-K2 chloride channel is critical for salt handling in the distal nephron. J Am SocNephrol. 2017; 28(1):209-17. [DOI:10.1681/ASN.2016010085] [PMID] [PMCID]

[12] Jentsch TJ, Pusch M. CLC chloride channels and transporters: Structure, function, physiology, and disease. Physiol-Rev. 2018; 98(3):1493-590. [DOI:10.1152/physrev.00047.2017] [PMID]

[13] Konrad M, Nijenhuis T, Ariceta G, Bertholet-Thomas A, Calo LA, Capasso G, et al. Diagnosis and management of Bartter syndrome: Executive summary of the consensus and recommendations from the European rare kidney disease reference network working group for tubular disorders. Kidney Int. 2021; 99(2):324-35. [DOI:10.1016/j.kint.2020.10.035] [PMID]

[14] Lee SE, Han KH, Jung YH, Lee HK, Kang HG, Moon KC, et al. Renal transplantation in a patient with Bartter syndrome and glomerulosclerosis. Korean J Pediatr. 2011; 54(1):36. [DOI:10.3345/kjp.2011.54.1.36] [PMID] [PMCID]