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Case Report

Dent's disease: case series from a single center

Hilal Yaşar[1], Emre Leventoğlu[2], Bahar Büyükkaragöz[2], Kibriya Fidan[2], Sevcan A. Bakkaloğlu[2], Oğuz Söylemezoğlu[2]

[1]Faculty of Medicine, Gazi University, Ankara; [2]Department of Pediatric Nephrology, Gazi University, Ankara, Türkiye.

ABSTRACT

Background. Dent's disease (DD) is a rare X-linked recessive tubulopathy characterized by low molecular weight proteinuria, hypercalciuria, nephrocalcinosis/nephrolithiasis and chronic kidney disease. With this manuscript, we reported three patients diagnosed as DD in our department in the last 10 years and thereby described the genetics, pathophysiology, clinical presentation, course and management of the disease.

Cases. The first case was a male newborn who was consulted to our department after medullary nephrocalcinosis was detected. The second case was a 4-year-old boy who was treated with a diagnosis of urinary tract infection but was found to have proteinuria. Our last case was an 11-month-old male infant who was being followed up for recurrent urinary tract infection and who had millimetric crystalloids in the renal collecting system. Proteinuria and hypercalciuria were present in all cases. Variants were observed in the *CLCN5* gene for the first two cases (c.1852G>A and c.1557+1G>T, respectively) and *OCRL* gene (c.952C>T) for the last case. All patients were recommended oral hydration and a low-salt diet, and hydrochlorothiazide and enalapril were started. No deterioration in kidney function was observed in any patient.

Conclusion. DD is a disease that shows different phenotypes even among individuals with mutations in the same gene. Therefore, it should be considered in all patients with hypercalciuria, proteinuria, nephrolithiasis or nephrocalcinosis with/without proximal tubular dysfunction especially in the early childhood period. Classical treatments for hypercalciuria should be utilized, and a patient-based treatment plan should be drawn especially for proteinuria.

Key words: chronic kidney disease, hypercalciuria, nephrocalcinosis, nephrolithiasis, proteinuria.

Dent's disease (DD) is a rare X-linked recessive tubulopathy characterized by low molecular weight proteinuria (LMWP), hypercalciuria, nephrocalcinosis/nephrolithiasis and chronic kidney disease.[1] In some cases, microscopic/macroscopic hematuria, hypokalemia, hypophosphatemia and metabolic acidosis may accompany it.[2] The disease may also be accompanied by rickets or osteomalacia and growth retardation.[3] These features are usually detected in males up to 10 years of age. By the age of 50 years, about 80% of males develop kidney failure while females may have a milder phenotype due to X-chromosome inactivation.[4] Nephrolithiasis is rare, although hypercalciuria is seen in some females. Also, LMWP is of moderate severity and CKD rarely develops.[3] Mutations in the *CLCN5* gene are responsible for 60% of the disease and mutations in the *OCRL* gene for 15%, but no mutation has been identified in remaining patients so far.[5]

In this manuscript we report three patients diagnosed as DD in our department in the last 10 years and thereby describe the genetics, pathophysiology clinical presentation and course, laboratory evaluation and management of the disease.

✉ Emre Leventoğlu ▪ dremrelevent@gmail.com

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Case Presentations

Case 1

A male infant born to healthy parents after a full-term uneventful pregnancy with a birth weight of 3,750 grams was followed and treated in the neonatal intensive care unit due to central hypoventilation and was consulted to our department as nephrocalcinosis was detected on abdominal ultrasonography (US). There was no parental consanguinity or known history of kidney disease in family members.

On physical examination, his body weight was 3,690 grams (50-75th percentile) and height was 50 cm (50-75th percentile). Blood pressure was normal (90/60 mm Hg, <90th percentile) and he had no peripheral edema. He was receiving respiratory support due to central hypoventilation. Abdominal US revealed no pathology except nephrocalcinosis. Laboratory results showed normal serum creatinine, albumin, and electrolytes. Serum phosphorus was 6 mg/dL (normal range 4.3-9.3 mg/dL), 25-OH-vitamin D and parathyroid hormone (PTH) levels were also within normal ranges. Blood gases revealed a pH of 7.55 and a HCO_3 level of 30.4 mmol/L. Urine output was normal. There was no hematuria, and no evidence for hyperoxaluria or hypocitraturia. However, the patient had glucosuria, hypercalciuria, albuminuria and proteinuria. Spot urine albumin/creatinine ratio was 292 mg/g, protein/creatinine 3.2 mg/mg and calcium/creatinine 1.7 mg/mg. β2 microglobulin level in spot urine was high at 24.4 mg/L (normal range 0.04-0.22 mg/L). Tubular reabsorption of phosphate (TRP) was low at 74.2%, and fractional sodium excretion (FeNa) was slightly increased at 3.7%.

Whole exome sequencing analysis revealed a hemizygous c.1852G>A (p.Val618Met) variant classified as likely benign in the *CLCN5* gene. In addition to promoting oral hydration, hydrochlorothiazide and an angiotensin converting enzyme inhibitor (ACEi), enalapril treatments were started due to hypercalciuria and proteinuria, respectively. The patient was then followed up every three months for 2.5 years. During this period, a significant decrease in proteinuria and calciuria was observed, medullary nephrocalcinosis persisted, and no deterioration in kidney functions was observed. However, as the patient had recurrent febrile urinary tract infections (UTIs), prophylactic dosage of nitrofurantoin was commenced. A dimercaptosuccinic acid (DMSA) scan performed at the age of 2 years due to recurrent UTI revealed no renal scar formation and relative cortical functions were normal.

Case 2

A 4-year-old boy was admitted to another center due to symptoms compatible with UTI. He was referred to our department for detection of proteinuria on different occasions after treatment. He had a personal medical history of frequent UTIs with normal DMSA scintigraphy.

He was born from non-relative parents at the 31st week of gestation with a birth weight of 2,020 grams (75-90th percentile). His uncle, the mother's brother, had nephrolithiasis with unknown etiology. On admission to our hospital, his body weight was 17 kg (25-50th percentile) and height was 104 cm (25-50th percentile). He was normotensive. The physical examination was unremarkable. The laboratory results revealed normal levels of serum creatinine, albumin and electrolytes. Serum phosphorus was 4.8 mg/dL (normal range 3.8-6.9 mg/dL), 25-OH-vitamin D and PTH were also normal. There was no evidence of polyuria/polydipsia. Urinalysis showed glucose and protein 1+ without hematuria. Urinary protein and calcium excretions were 18.4 mg/m^2/hour and 10 mg/kg/day, respectively. Urine albumin level was 220 mg per day (microalbuminuria as 30-300 mg/day). TRP and FeNa were in normal ranges at 93% and 0.5%, respectively. β2 microglobulin level in spot urine was high at 60.2 mg/L. Urinary US was normal, neither nephrolithiasis nor nephrocalcinosis was present.

A hemizygous c.1557+1G>T pathogenic variant was detected in the *CLCN5* gene by

targeted next generation sequencing. Aside from low sodium diet and a high daily water intake, hydrochlorothiazide (1 mg/kg/day) and enalapril (0.1 mg/kg/day) were started. The patient has been followed up in our hospital for 3 years with normal kidney functions. Urinary protein and calcium excretions decreased to 14.2 mg/m^2/hour and 1.6 mg/kg/day, respectively. No nephrolithiasis or nephrocalcinosis developed during this period.

Case 3

A 3,600 g male infant born at term to a healthy, non-related family was hospitalized for a UTI at postnatal 15th day with complaints of decreased feeding and malaise. He was subsequently followed up for recurrent UTI. At 11 months of age, he was referred to our department due to the presence of a few millimeters of crystalloids in the bilateral renal collecting systems on US.

At the time of admission, growth and development were appropriate for his age and physical examination was unremarkable. In laboratory analysis, serum creatinine, electrolytes, and albumin levels were in normal range. Serum phosphorus, 25-OH-vitamin D and PTH were also normal. There was no acidosis or alkalosis. Urinalysis showed pH 7, specific gravity 1010, no glucosuria, hematuria or pyuria. However, proteinuria and calciuria were present (32 mg/m^2/h and 11 mg/kg/day, respectively). Urine albumin level was 421 mg per day (macroalbuminuria >300 mg/day). Spot urine β2 microglobulin level was also markedly elevated (116 mg/L). The DMSA scintigraphy due to the history of UTI was normal.

Genetic analysis by targeted next generation sequencing revealed a c.952C>T (p.Arg318Cys) hemizygous likely pathogenic variant in the *OCRL* gene. Hydrochlorothiazide was started at 1 mg/kg per day due to persistence of hypercalciuria despite dietary recommendations and adequate hydration. Also, enalapril was started due to a mild increase in proteinuria at the age of 2 years. Urinary calcium excretion decreased to 4.6 mg/kg/day when the dose of hydrochlorothiazide was increased to 2 mg/kg/day. However, proteinuria increased to 96 mg/m^2/h despite enalapril, and it decreased to 60 mg/m^2/h after addition of angiotensin receptor blocker (ARB) as losartan (0.7 mg/kg/day) to the treatment.

During 8 years of follow-up, no significant deterioration was observed in kidney function tests. Kidney dimensions and parenchymal echogenicity were normal on the last urinary US. In the right kidney, there were several crystalloids, the largest of which was 3 mm in diameter in the lower pole. In addition, ophthalmic examination was normal. There were no behavioral problems, nor intellectual deficits. His serum creatine kinase level was slightly high (252.3 U/L, normal range 0-190 U/L), however there was no finding compatible with myopathy.

A summary of clinical information regarding the cases is shown in Table I.

Written informed consent was obtained from parents for the use of clinical and laboratory data for publication.

Discussion

In this study, we report three pediatric patients with DD who were being followed up in a tertiary pediatric nephrology center. Although variations were found in two different genes, the phenotypic features of all patients were quite different. Despite the presence of proteinuria and hypercalciuria in all patients, their levels varied. Two of the cases had either nephrolithiasis or nephrocalcinosis on urinary US, but remarkably, one patient had no ultrasonographic findings. In this manuscript, we tried to draw attention to this rare disease and its different clinical manifestations. Furthermore, although the variant detected in Case-1 was previously classified as "likely benign", the clinical features of this patient were consistent with DD and no major variant was detected in the whole exome sequencing that could explain the clinical condition. We

Table I. Summary of clinical information of the cases.

Patients	Sex	Variants	At admission					Drugs	Follow-up durations (years)	At last control			
			Age	GFR (mL/min/1.73m^2)	Urinary protein excretion	Urinary calcium excretion	Nephrolithiasis / Nephrocalcinosis			GFR (mL/min/1.73m^2)	Urinary protein excretion	Urinary calcium excretion	Nephrolithiasis / Nephrocalcinosis
Case-1	Male	c.1852G>A in *CLCN5*	22-days-old	85.3	3.2a	1.7a	- / +	Hydrochlorothiazide/ Enalapril	2.5	127.3	1.8a	1.1a	- / +
Case-2	Male	c.1557+1G>T in *CLCN5*	4-years-old	127.6	18.4b	10.0c	- / -	Hydrochlorothiazide/ Enalapril	3.0	129.7	14.2b	1.6c	- / -
Case-3	Male	c.952C>T in *OCRL*	11-months-old	121.7	32.0 b	11.0 c	+ / -	Hydrochlorothiazide/ Enalapril/Losartan	8.0	114.3	60.0b	4.6c	+ / -

GFR, glomerular filtration rate.
[a]Spot urine sample; mg/mg creatinine, [b]24-hour urine sample; mg/m^2/h, [c]24-hour urine sample; mg/kg/d

believe that this manuscript may pave the way for functional studies to clearly assess the pathogenicity of this variant.

Dent's disease is a rare genetic disorder characterized by proximal tubular dysfunction, described by Dent and Friedman in 1964 as hypercalciuric rickets.[6] It has a highly heterogeneous phenotype. Some cases are diagnosed with asymptomatic proteinuria, while others have nephrocalcinosis/nephrolithiasis and chronic kidney disease. Although the symptoms begin in childhood, asymptomatic patients may be diagnosed in adulthood.[7] Although US had not been performed on the parents of our patients, they had no history of hematuria/nephrolithiasis/urinary tract infection and no symptoms compatible with nephrolithiasis/nephrocalcinosis. However, considering that asymptomatic patients may also be present, we believe family members of every patient with DD, especially the parents of our patients, should be screened for nephrolithiasis/nephrocalcinosis by US.

The most common mutation, the *CLCN5* mutation, causes DD type 1 (DD1), while the rarer *OCRL* mutation causes DD type 2 (DD2). Although *CLCN5* and *OCRL* mutations cause the same disease, they are generally not sufficient to explain phenotypic differences in patients. There is a growing number of patients carrying *CLCN5* or *OCRL* mutations but with incomplete phenotypic features. This phenotypic diversity can lead to unnecessary kidney biopsies, undiagnosed or misdiagnosed DD and, unfortunately, inappropriate treatment.[8] For example, in cases where DD is not considered, patients undergoing kidney biopsy for nephrotic range proteinuria may have focal segmental glomerulosclerosis (FSGS), which may lead to immunosuppressive therapy such as corticosteroids and calcineurin inhibitors.[9] Therefore, even if nephrotic level proteinuria is present, DD should be considered in the differential diagnosis if a patient has accompanying hypercalciuria, nephrolithiasis/nephrocalcinosis. Some patients with DD2 are likely to have mild extrarenal features such as

muscle weakness, ocular abnormalities and mild intellectual disability.[4] In addition, hidradenitis suppurativa can be seen very rarely in DD2.[10] In these patients, it may be more easily recognized that there is an underlying diagnosis such as DD other than primary FSGS.

The *CLCN5* gene is involved in the production of the electrogenic chloride channel Cl-/H+ antiporter ClC-5 protein. The ClC-5 protein has important roles in the acidification in the endosomes of proximal tubule cells. In the absence of functional CLC-5, the endocytosis is inhibited. Therefore, the reabsorption of LMWPs is disrupted by being located at the brushy edge of the plasma membrane in proximal tubule cells (Fig. 1).[4,11] Furthermore, the endocytosis defect in proximal tubule cells leads to increased PTH concentration in urine and thus to increased 1,25-$(OH)_2$-vitamin D3 levels. Consequently, intestinal absorption of calcium increases and hypercalciuria and nephrocalcinosis/nephrolithiasis may develop.[12] In some in vivo models, despite the same mutation in the *CLCN5* gene, LMWP and hyperphosphaturia have developed in all models, while hypercalciuria and nephrolithiasis have not been observed in some.[13,14]

The *OCRL* gene encodes a member of the inositol polyphosphate-5-phosphatase enzyme family. It is expressed in the trans-Golgi network in glomeruli and all tubule segments and acts as a second messenger in vesicular transport.[15] It has also been shown that *OCRL* mutation disrupts early endosome functions due to defects in F-actin filaments.[16] Furthermore, *OCRL* regulates TRPV6 trafficking in the intestinal epithelium. In the case of *OCRL* mutation, TRPV6 cannot be inhibited, which increases intestinal absorption of Ca^{2+} leading to hypercalciuria (Fig. 2).[16] Both DD2 or Lowe syndrome (which is an X-linked multisystemic disorder characterized by the triad of congenital cataracts, cognitive and behavioral impairment and a renal proximal tubulopathy) can develop due to *OCRL* mutation. However, it seems impossible to determine a genotype-phenotype correlation for this gene, as mutation in the same gene can cause both diseases.[7] However,

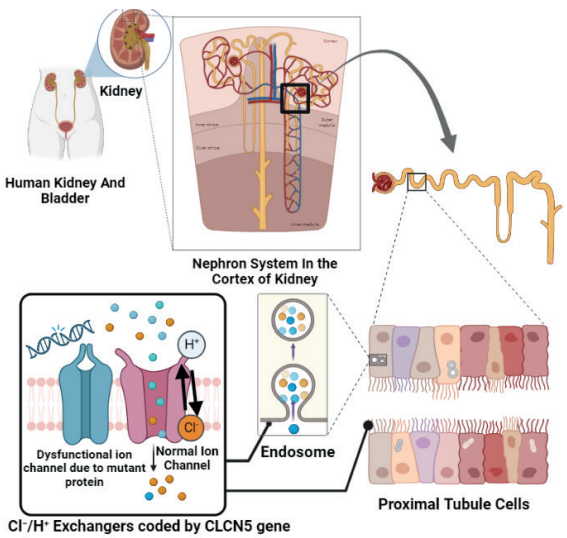

Fig. 1. Functions of the CLC-5 protein encoded by the *CLCN5* gene.

The *CLCN5* gene is involved in the production of the electrogenic chloride channel Cl-/H+ antiporter ClC-5 protein. The ClC-5 protein has an important role in the acidification of the endosomes of proximal tubule cells. In the absence of functional CLC-5, endocytosis is inhibited. Created in BioRender. https://BioRender.com/z35o223

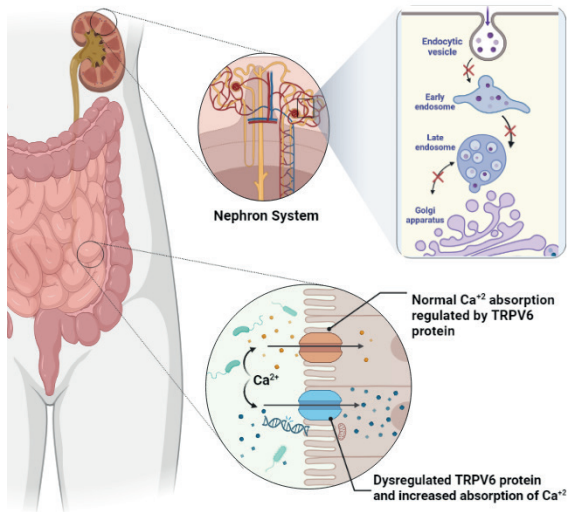

Fig. 2. Functions of *OCRL* gene products.

The *OCRL* gene encodes a member of the inositol polyphosphate-5-phosphatase enzyme family. It is expressed in the trans-Golgi network in glomeruli and all tubule segments and acts as a second messenger in vesicular transport. Also, *OCRL* regulates TRPV6 trafficking in the intestinal epithelium. Created in BioRender. https://BioRender.com/u24d663

a review by Gianesello et al. reported that the *OCRL* mutation site and mutation type largely determine the DD2 phenotype. In our study, we cannot comment on the genotype-phenotype relationship due to the limited number of cases. Considering the rarity of the disease, it is thought that a multicenter evaluation with large case series would be appropriate.[17]

Two of our patients had a variant in the *CLCN5* gene, and one had a variant in *OCRL* gene. The c.1852G>A variant in *CLCN5* in Case-1 was previously classified as likely benign.[18] However, despite whole exome sequencing, no other variant was found that could explain LMWP, hypercalciuria and nephrocalcinosis in our patient. Also, in silico analyses, the Combined Annotation Dependent Depletion (CAAD) score was 25.9, Rare Exome Variant Ensemble Learner (REVEL) score was 0.941, phylogenetic P-values (phyloP) were 7.44 and Polymorphism Phenotyping (PolyPhen) score was 0.996.[19] The CADD score is a score that assesses the likelihood of a variant being associated with genetic harm. A value of 15 and above is considered noteworthy for pathogenicity. A score of 25.9 in our patient indicates that the variant is likely to cause loss of function. REVEL is a score that estimates the pathogenicity of rare variants. It ranges from 0 to 1. A high score of 0.941 indicates that the variant is probably harmful. PhyloP is the evolutionary conservation score. A high score of 7.44 indicates that this region is highly evolutionarily conserved and that changes here are likely to be harmful. PolyPhen is a tool that predicts the effect of an amino acid change on protein function. It produces a score between 0 and 1. A high score of 0.996 indicates that the variant is likely deleterious.[20] However, it should be noted that while the detected variant is likely to have a high deleterious effect, in silico assays may not always fully reflect reality as they only provide a prediction of pathogenicity. Therefore, we think that it is very important to identify individuals with the same variant and to re-evaluate the pathogenicity of this variant which was previously classified as likely benign. In particular, functional analyses are needed to definitively classify the detected variant as disease causing/pathologic. The c.1557+1G>T variant in the *CLCN5* gene, which was found in Case-2, was previously described by Tosetto et al.[21] In a patient with DD, a G to T transversion was detected in intron 8 of *CLCN5*, resulting in a splice site mutation and the formation of an mRNA transcript lacking part of exon 8, which was confirmed by real time-polymerase chain reaction (RT-PCR) analysis. The variant was classified as pathogenic as a result of evaluation with tools that predict the pathogenicity of a variant.[21] However, since the phenotypic characteristics of the patient are not detailed in that manuscript, a comparison with our patient cannot be made. The c.952C>T variant in the *OCRL* gene found in Case-3 is a mutation that has been previously detected in patients with DD. In a multicenter study presented by Sekine et al.[22] the same variant was demonstrated in three patients. The age of the patients was between 9.5-15.3 years. It was reported that one patient did not have cataract or intellectual-behavioral impairments, however no evaluation of the other patients was mentioned.[22] In our patient, no extrarenal findings were observed during the 8-year follow-up period, as previously mentioned.

The main goal of DD treatment is to preserve kidney function by reducing hypercalciuria and related complications. Low sodium diet, adequate hydration and thiazide diuretics are classically used for hypercalciuria. In case of hypokalemia, metabolic acidosis and hypophosphatemia, supportive treatments are implemented.[23] In all of our patients, adequate oral fluid intake, low sodium diet and hydrochlorothiazide diuretics were used.

Since Dent's disease is mainly a nonglomerular disease and patients have tubular proteinuria, the rationale for the use of ACEi/ARB therapy is unclear.[23] In a review, some patients treated with ACEi/ARBs had a reduction in proteinuria, some had no effect, and some had a reduction in glomerular filtration rate (GFR).[24] In another

study, it was reported that pre-existing tubular proteinuria may be accompanied by glomerular proteinuria during the follow-up period and enalapril use may be necessary. However, in that article, it was pointed out that GFR may decrease with enalapril.[25] Specifically in the *CLCN5* mutation, FSGS can be seen on kidney biopsy. This supports the hypothesis that *CLCN5* is involved in protein trafficking in podocytes also, and its mutation may cause glomerular proteinuria due to disrupting normal cell physiology and filtration barrier.[26] In a study evaluating the phenotypic spectrum of Dent's Disease and ACEi/ARB response to proteinuria, it was shown that albuminuria could be controlled with ACEi and/or ARB treatment in half of the children. However, genotypes, glomerular lesions, age at treatment initiation and duration of treatment could not explain the difference in antialbuminuric response.[27] All of our patients were prescribed ACEi and/or ARB due to proteinuria and a decrease in proteinuria was shown in each, most significant decline in Case-1. We think that more studies are needed in this field to explain why Case-1 benefited more from antiproteinuric treatment. Fortunately, no patient had a decrease in GFR. In addition, since no biopsy was performed in any of our patients, no definite information about renal histopathology can be given. However, when urine protein analysis was performed in our patients, the significantly higher proportion of tubular proteins in the urine may suggest that glomerular damage was not severe.

In DD, GFR decreases by 1.0 to 1.6 mL/1.73 m^2/min per year.[1] Approximately 30% to 80% of male patients with DD develop kidney failure between the ages of 30 and 50 years. The age at which kidney failure develops can be as late as the 7^{th} decade. Even within the same family, there are individuals with different ages of onset of kidney failure.[23] The follow-up period in our patients ranged from 2.5 to 8 years. Since all of our patients were in the pediatric age group, we did not observe any patient with kidney failure development. Fortunately, none of our patients had a decrease in GFR.

It is noteworthy that all three patients in our study had a history of recurrent UTIs. The relationship between nephrolithiasis and UTIs is complex. To date, it has been generally emphasized that certain bacteria pose a risk for kidney stone formation.[28] However, a study by Cetin et al. evaluated risk factors for UTI in children with nephrolithiasis and found that recurrent UTI was significantly more common in patients with risk factors for stone formation, especially in patients with hypercalciuria.[29] The presence of marked hypercalciuria in all our patients may have been the reason for the development of recurrent UTI.

In conclusion, DD is a disease that shows different phenotypes even among individuals with the same mutation. It has the potential of leading to impaired kidney function in the absence of appropriate follow-up and treatment. Therefore, DD should be considered in all patients with hypercalciuria, proteinuria, nephrolithiasis or nephrocalcinosis with/without proximal tubular dysfunction especially in early childhood. Classical treatments for hypercalciuria should be utilized, and a patient-based treatment plan should be drawn especially for proteinuria. Since there is a genetic basis, genetic counseling should not be ignored.

Ethical approval

Informed consent was obtained from the parents of each patient included in the study for the use of patient data for scientific and academic purposes, provided that the identity information of the patients remained confidential.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: HY, EL, BB; data collection: HY, EL, BB, KF, SAB and OS; analysis and interpretation of results: HY, EL, BB; draft manuscript preparation: HY, EL, BB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declares that there is no conflict of interest.

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