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Case Report

Diagnostic Approach in Cystinuria: A Case Report

Selda Bülbül[1], Aliye Gülbahçe[1], Sevim Gonca Kocagözoğlu[2]

[1] Kırıkkale University School of Medicine, Department of Pediatric Metabolic Diseases and Nutrition, Kırıkkale, Turkey
[2] Kahramankazan Hamdi Eris Hospital, Ankara, Turkey

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Aliye Gülbahçe
Kırıkkale University School of Medicine, Department of Pediatric Metabolic Diseases and Nutrition, Kırıkkale, Turkey
ORCID: 0000-0003-1333-2648
aliyegulbahcedr@gmail.com

S. Bülbül 0000-0002-6457-149X
S.G. Kocagözoğlu 0000-0003-0894-4447

ABSTRACT

Cystinuria is an, inherited metabolic disorder progressing with recurrent kidney stones due to impaired reabsorption of dibasic amino acids and arises from mutations in the SLC3A1 and SLC7A9 on chromosome 2.
Cystine crystals were detected in the urinalysis of a 17-year-old male patient who was investigated for recurrent kidney stones. Because of demonstration of cystine excretion in the urinary amino acid analysis and having positive family history, we suspected Cystinuria Type B and initiated supportive therapy. However, based on the results of molecular analyses his diagnosis was changed as Cystinuria Type A.
In conclusion, our final diagnosis was changed according to the molecular analyses but our treatment approach did not change. Therefore we would like to emphasize that, prominent physical examination findings and supportive laboratory test results will be sufficient for the diagnosis of cystinuria.

INTRODUCTION

Cystinuria (OMIM 220100) is an inherited metabolic disorder (IMD) caused by a defect in the transport of cystine, lysine, arginine, and ornithine amino acids in the epithelial cells of the small intestine and renal tubular cells.[1] While the worldwide incidence of cystinuria was reported as 1/7000, two different studies from Turkey revealed higher incidences (1/1333 and 1/2065)[2,3] probably due to higher rates (17-22%) of consanguineous marriages in Turkey.[4]

Although reabsorption of cystine, lysine, ornithine, and arginine are all impaired, only cystine excreted in urine causes clinical findings because the other amino acids are soluble. As cystine could not be dissolved well in acidic pH, cystine stones form in the urinary system and cystinuria usually presents with recurrent urinary tract infections and kidney stones in the 2nd or 3rd decade of life. However, there are studies that report nephrolithiasis in infancy due to cystinuria.[5] If the disorder is not treated properly, it may lead to the formation of recurrent kidney stones and development of chronic renal failure in the future.[6] Early diagnosis and treatment prevent these complications. Treatment of cystinuria includes increasing the urinary cystine solubility through hydration, diet modification and urinary alkalinization. As dietary sodium intake increases the excretion of cystine through the urinary tract by an unknown mechanism, the use of sodium bicarbonate is restricted so potassium citrate is used for urinary alkalinization. In cases without any adequate response to this treatment, chelating agents such as D-penicillamine, mercapto propionyl glycine, and captopril are used to convert cystine into more soluble compounds.[7]

The diagnosis of cystinuria can be made easily with noninvasive methods that can be performed in

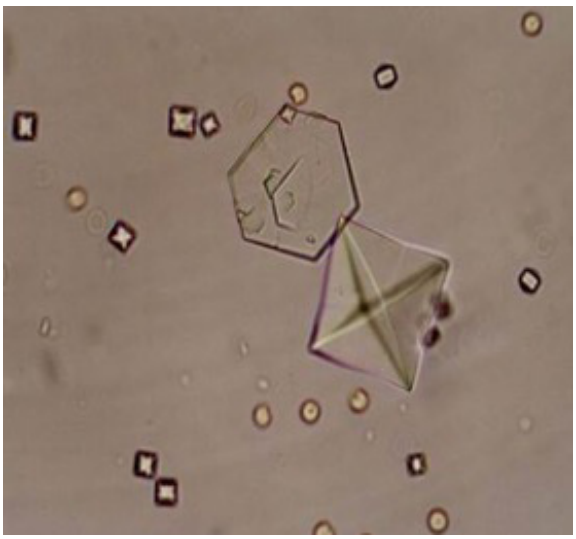

Figure 1. Cystine Crystals on Urine [14]

Figure 2. 1-2 drops of ammonia and 2 ml of 5% sodium cyanide solution added to 5 ml urine. After 5-10 minutes, 5 drops of freshly prepared sodium nitroprusside is added mixed. Changing the colour to red bud indicates the positive reaction.[9]

primary health care services. For definitive diagnosis, observation of cystine crystals on urine microscopy (Figure 1) and demonstration of an increase in cystine excretion in urinary amino acid analysis are considered to be adequate.[6] The observation of cyclamen color change on urine samples with the cyanide-nitroprusside test supports the diagnosis (Figure 2). Stone analysis can also be performed in nephrolithiasis cases. However, it is not necessary for the establishment of the diagnosis, and the treatment can be initiated as soon as possible.[8,9]

As a result of advances in DNA technology, the demonstration of affected genes in the diagnosis of hereditary diseases is one of the leading diagnostic methods used in advanced centers. Sequencing of many genes has shown that each disorder has millions of genetic variants. SLC3A1 or SLC7A9 are the responsible mutations in cystinuria. At least 104 (SLC3A1) and 152 (SLC7A9) different mutations associated with these subtypes have been reported.[5] Some of these variants cause symptomatic disease, some increase the risk of disease occurrence, while others have no clinical effect. Besides, false-negative results can be obtained. However, negative mutation analysis results do not exclude preliminary diagnosis in the presence of obvious physical examination findings and supportive laboratory test results. While it is difficult to assess the exact effects of these mutations, it is still necessary to provide specific treatment options for patients.[1] Therefore, we aimed to discuss whether it is necessary to perform molecular analysis to make the diagnosis of cystinuria.

CASE

A 17-year-old male patient was consulted for investigating the etiology of recurrent urolithiasis. He had no known chronic disease. The constant abdominal pain was started at the age of 10 years, and kidney stones were detected with basic laboratory analyses. Percutaneous nephrolithotomy had been performed twice, but recurrent stone formation continued. Stone analysis revealed a cystine stone. Upon this result, the patient was referred to our clinic.

There was a second-degree consanguineous marriage between his parents. His father and a cousin had also a history of recurrent kidney stones. We couldn't perform their urine amino acids analysis because they were living in different provinces

Physical examination and first step laboratory tests revealed no pathological findings. Stone formation was not observed in direct abdominal radiographs, but more than one echogenicity (calculi?) were

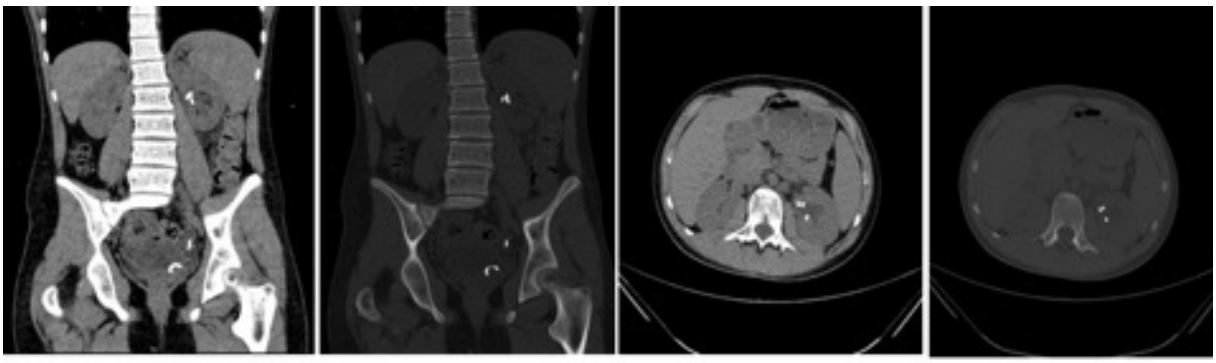

Figure 3. Post-operative cotrol CT images

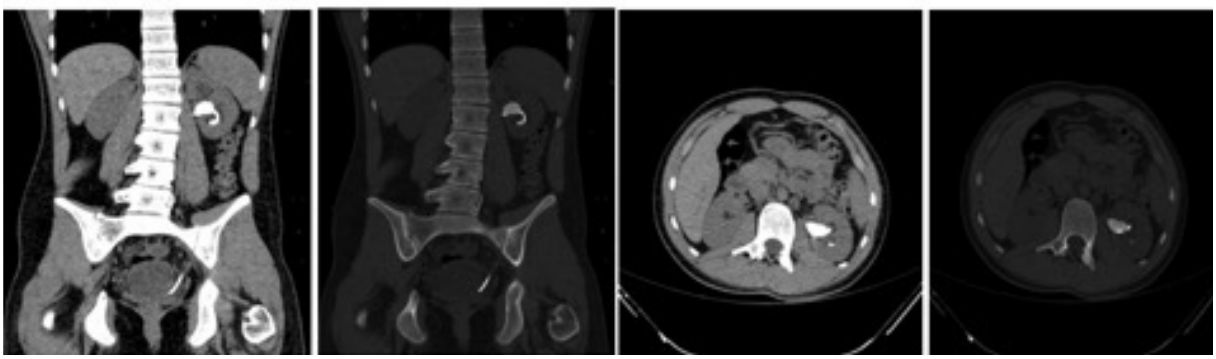

Figure 4. Control CT images after kidney stone recurrence

shown in kidneys by renal ultrasonography. Computed tomography images were also compatible with nephrolithiasis (Figure 3, 4). Upon detection of cystine crystals in microscopic analysis of patient's urine, we planned to perform amino acid analysis in plasma and urine. The cyanide-nitroprusside test was (+++) positive. Analysis of urinary amino acids revealed increased cystine excretion [1675 µmol/gr creatinine (Normal 0-200 µmol/gr creatine)]. With these results, cystinuria was thought and alkalinization of urine with potassium citrate treatment was initiated.

For genetic counseling and family screening we planned to send blood samples for molecular analysis. Primarily, the SLC7A9 gene mutations were evaluated considering autosomal dominant inherited cystinuria (Type B). As the test was negative, Cystinuria Type A was evaluated thereafter. The presence of c.647C> T homozygous mutation in SLC3A1 gene was demonstrated. Although consanguineous marriage indicates cystinuria Type A as the preliminary diagnosis, due to limitation in financial sources we could not send samples of all family members at the same time, priority was given to the children of the family. Genetic counseling was given and family screening was planned, however as some relatives lived abroad they were advised to apply to the nearest metabolic clinic.

For treatment the patient received medications only for urine alkalinization. During the follow-ups, his complaints were resolved, and at the sixth-month visit we observed a significant decrease in urinary excretion of cystine (225 µmol/gr creatinine).

DISCUSSION

Cystinuria is an inherited amino acid transport defect which was first described by Garrod in 1908.[5] The diagnosis is based on showing the excretion of dibasic amino acids in the urine. The observation of hexagonal cystine crystals in urine microscopy is also pathognomonic. While the amount of urinary excretion of cystine in healthy individuals is 50-60 mg/dl/1.73 m^2, this may increase up to 400 mg/dl/1.73 m^2 in cystinuria patients.[10] The maximum cut-off

value is accepted as 150 micromole/mmol creatinine. There would be no change in plasma levels of cystine and other dibasic amino acids. In our case, the amount of urinary cystine excretion was 1675 mg/dl/1.73 m^2 and plasma amino acid concentrations were within normal limits.[11]

Depending on the different mutations, the degree of transport defect of these amino acids varies. Disease is divided into two main clinical subtypes according to these mutations and inheritance type. Cystinuria Type A (Type 1 Cystinuria) is autosomal recessively inherited disease and occurs as a result of a mutation in SLC3A1 gene on the 2nd chromosome, Cystinuria Type B shows an autosomal dominant inheritance and is caused by a mutation in the SLC7A9 gene on the 19th chromosome. In very rare cases, there are two different mutant alleles on the same gene and this rare subtype of cystinuria is defined as Type AB. At the first assessment, we thought that our patient may have Type B cystinuria due to the detection of a high concentration of cystine in the urine and a family history of kidney stones. But molecular analyses revealed no pathological mutation at this gene site. We sent a second sample to detect presumed Type A cystinuria, to be sure of the diagnosis on a molecular basis and a homozygous mutation was found in SLC3A1 gene. In many studies, it has been reported that there is no genotype-phenotype correlation in patients with cystinuria, and also no mutation is shown in 5% of patients.[12,13] Therefore, detection of increased urinary cystine excretion still remains the main tool in assessing the prognosis and deciding on appropriate treatment.

In our case, the existence of consanguinity between parents, a positive family history (father and cousin), positive cyanide nitroprusside test result, increased urinary excretion of cystine, result of the stone analyses and demonstration of stones by imaging techniques have strengthened the diagnosis. As stated above, no mutation might be shown in genetic analysis in some patients. For this reason, physicians should not exclude diagnosis of any inherited disorder in clinical practice based on negative molecular test results.

Cystinuria is the most common cause of kidney stones encountered during childhood.[5] Apart from cystinuria, other metabolic disorders such as hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria may also cause urolithiasis.[10] Performing molecular analysis in cystinuria cases may also be beneficial in differential diagnosis from other causes of kidney stones. However, it should be kept in mind that, first-line metabolic tests should be the primary step for differential diagnosis.

Diagnosis of cystinuria can be made with a proper anamnesis, an accurate physical examination, and using primary laboratory tests. Genetic tests are not mandatory during diagnostic process. While a positive mutation analysis supports the diagnosis, a negative result does not exclude.

Molecular analysis are expensive methods and are not still available in many clinical centers. The use of this expensive method in the diagnostic process does not provide a significant benefit in the treatment, prognosis or predicting complications of the disease. Therefore examining the cystine crystals in urine and conducting cyanide- nitroprusside test would be enough for accurate diagnosis. Both of these tests could be applied easily and treatment could be initiated without further delay. Subtyping of the disease by molecular analyses in centers with technical capacity would contribute to the scientific literature. Therefore, maintaining a persistent attitude in the presence of clinical suspicion will be useful in the diagnosis of single-gene diseases and in the discovery of new mutations.

CONCLUSION

In recent years, the use of molecular diagnostic methods has increased, especially in inherited metabolic diseases. Due to many diseases caused by unknown genetic mutations or unknown mutations in the relevant gene regions, false-negative results can be obtained by these methods. In the presence of obvious physical findings and supportive laboratory test results as in the presented case, genetic analysis are not needed or negative molecular test results can not exclude the current diagnosis.

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