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Alkaptonuria - an atypical manifestation or management?

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Abstract

Alkaptonuria is a rare autosomal recessive disease, in which the metabolism of homogentisic acid is defective. Homogentisate 1, 2- dioxygenase deficiency results in homogentisic aciduria, ochronosis, and ochronotic arthritis, in which pigments precipitate in joints especially those under pressure like vertebrae. In this case of isolated alkaptonuria, we faced an atypical manifestation of alkaptonuria in a seven-year-old girl, which had not been previously detected by our colleagues.

Key Words: Alkaptonuria, Auditory problems, Neurological disorder.

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1- INTRODUCTION

Alkaptonuria (AKU) is a rare metabolic autosomal recessive disease with a frequency of 1 in 250,000-1000000**,** usually emerging at age 30. The highest incidence of AKU has been reported in Slovakia and Dominican Republic countries. AKU results from defective homogentisate-1, 2 dioxygenase (HGD), which is located at 3q2. Forty-three mutations in HGD have been detected (1). Manifestations of this disease include arthritis, ochronosis, and homogentisic aciduria. The main complication of the disease at young ages is darkened urine which has been reported in a 4-month-old infant and a 5-year-old boy (2, 3). In this article, we describe an eight-year-old girl with low hearing status since her childhood who was considered as a case of alkaptonuria after genetic counseling and laboratory investigations.

2- CASE PRESENTATION

An eight-year-old girl with auditory and developmental problems was admitted to Shams Shargh Medical center, Neyshabur city of Iran. Her parents were cousins. At her birth, her mother was hospitalized due to a problem with the fetal electrocardiogram, and the next day the baby was born by cesarean section and she had no particular problem. First signs including speech delay and then low hearing status had been observed when she was two and a half years old; and these problems made her parents consult with pediatricians. During the hearing tests, conductive hearing loss was diagnosed and a hearing aid was prescribed to the patient. Interestingly, no history of hearing problems had been reported in her family. Pediatricians only referred the patient to a speech therapist and neurologists, which was not effective. It seems that physicians neglected the urine color changing after child urination even though the parents mentioned it during the medical visit. Eventually, the parents referred to a geneticist due to the decision to get pregnant again. The known mutation related to alkaptonuria was reported in Whole-Genome Sequencing (WGS) (**Table 1**).

Table-1: Mutation detection by whole-genome re- sequencing of the patient′s blood sample

Genes	Refseq	Nucleic Acid Alteration	Amino Acid Alteration	Zygosity	Ch. Location	Mutation
HGD	NM_000187	c.175delA	p.S59fs rs397515517	Homozygous	Chr3	Pathogenic
MUT	NM_000255	c.A655T	p.N219Y rs121918256	Heterozygous	Chr6	Pathogenic

Afterwards, the patient underwent the necessary examinations again. Based on the obtained profile, the parents just complained about her speech problems and darkened urine. The child was normal in terms of developmental parameters and appearance (weight= 25kg, length= 130 cm, 25- 50th growth percentile). Examinations showed no problems with her eyes, joints or bones, and electrocardiogram tests were normal. There was no evidence of pigmentation on examination of the nails, teeth, and cheek mucosa. Laboratory tests of urinary organic acids were requested to evaluate the presence of homogenetic acid in urine. Serum amino acid chromatography was also demanded.

To treat and control the disease, the patient was referred to a nutritionist and dietary restriction of tyrosine and phenylalanine was prescribed. To prevent further complications at older ages, treatment with

a high dose of vitamin C (500- 1000 mg/day) and nitisinone (1 mg/ kg) was started. After starting treatment, her mother mentioned a decrease in urine color. In addition, the parents did not complain about problems such as chronic back pain or ochronosis. Subsequent issues of the disease were described to parents and they were advised to visit again.

2-1. Clinical Findings

DNA was extracted from a whole blood sample. Human whole-exome enrichment was performed using Agilent Sureselect V6 Target Enrichment Kit, followed by Next Generation Sequencing using Illumina Hiseq4000 platform to yield an average coverage depth of ~ 100X. All exons and flanking 10-bp were detected and analyzed. Detected variations included single point mutations and small Indels (insertion/deletion within 20bp).

No known pathogenic/likely pathogenic mutation associated with deafness was detected. Other findings are listed in **Table 1**.

Homozygous c.175delA (p. S59fs) mutation in HGD and Heterozygous c. A655T (p. N219Y) mutations in methylmalonyl CoA mutase (MUT) were detected. MUT encodes methylmalonyl-CoA enzyme, which is a component of propionate metabolism. Therefore, the patient is also a carrier for MUT deficiency.

2-2. Diagnostic Assessment

On the next visit by the medical geneticist after whole exome sequencing and double-checking of her past medical history and physical examination, we decided to do a urine exam. Quantitative evaluations of organic acids and acylglycines profile in her urine by GC- MS and LC- MS/ MS (Liquid Chromatography with tandem mass spectrometry), indicated 25.7 millimolar/millimoles per mole creatinine of homogentisic acid, (normal: <3); 19.2 mmol/mol crt of phenylpyruvic acid, (normal: <2.5); 25 mmol/mol crt of phenyllactic acid, (normal: <3); 71 mmol/mol crt of 4- hydroxyphenylpyruvic acid, (normal: <3); and 92.3 mmol/mol crt of 4- hydroxyphenyllactic acid, (normal: <4); which does not normally exist in the urine.

2-3. Therapeutic Intervention

There is no pharmacological effective treatment for this disorder, especially in childhood. Dietary elimination of phenylalanine and tyrosine reduces the excretion of HGA. A high dose of vitamin C (two 500 mg/day) can prevent the deposition of HGA in the joints and its attachment to the chondrocytes of the joints as well as the connective tissue, which might have reduced the consequences of alkaptonuria. Nitisinone, which inhibits tyrosine decomposition and 4-hydroxyphenylpyruvate hydroxylase activity, can prevent HGA production and its precipitation in the tissues; and ultimately prevents ochronosis (4). For our patient, treatment with a high dose of vitamin C (500- 1000 mg/day) and nitisinone (1 mg/ kg) was started after final laboratory diagnosis.

2-4. Outcome and follow-up

After starting treatment, her mother mentioned a decrease in urine darkness. In addition, the parents did not complain about problems such as chronic back pain or ochronosis. Subsequent issues of the disease were described to the parents and they were advised to visit again.

3- DISCUSSION

Alkaptonuria is a rare genetic disorder, which occurs as the result of defective Homo-Gentisic Acid (HGA) oxidase. The enzyme is necessary to convert HGA to maleylacetoacetate during the metabolism of phenylalanine and tyrosine. Defects of HGA oxidase lead to the oxidation of HGA to benzoquinone. In

alkaptonuria, HGA is accumulated in tissues, for 2,000 times more than normal. When urine is exposed to air and oxygen, HGA turns almost black which is the most common symptom at younger ages. During the course of the disease at older ages, pigments precipitate in eyes, ears, teeth, nails, skin, joints and bones. This process is named ochronosis (5). The most common symptoms at older ages are spondyloarthropathies, which lead to disability in the fourth decade of life. Large joints such as the knee, hip, spine, tibiofemoral, glenohumeral, and acetabulofemoral are usually affected and small joints are rarely involved. Unlike Osteoarthritis, sacroiliac joints are not affected in this disease, but radiological examinations are similar to osteoarthritis. The spinal discs become involved due to the deposition of pigment in that area. Similar to ankylosing spondylitis, dorso-lumbar spine region is more infected than lumbosacral spine. Intervertebral disc calcification and narrowing of the spinal canal are obvious symptoms, but clinically it is similar to rheumatoid arthritis. AKU cases with chronic musculoskeletal symptoms need more attention. In patients who do not respond to anti-inflammatory drugs and in severe degenerative cases, joint replacement is required (6). Complications about mitral and aortic valves are common, and the patients manifest narrowing of the outlet of the valves and thickening of the valves. Coronary artery disease, as well as ischemia and myocardial infarction are the main reasons leading to death over the age of 40 (7). Moreover, these patients also complain about problems with the ENT system, (Ear, Nose, and Throats), which appear as discoloration of the eardrums, pharyngeal ducts, and nasal septum. Discoloration of the ear cerumen usually appears before the age of 30, even in childhood, and is one of the first symptoms of the disease. Therefore, annual examinations of the auditory system in these patients are necessary to prevent their hearing loss in the future (8). Other common complications in these patients include leukemia, which has been reported in the form of kidney and prostate stones in people over 65 years of age (9).The reported cases of AKU in childhood are rare due to its being asymptomatic. The main complication at young ages is darkened urine, which has been reported in 4-month-old infants and 5-year-old boys (2, 3). Diagnosis and identification of these patients is done by measuring HGA and benzoquinone acetic acid by Gas Chromatography/Mass Spectrometry (GC-MS) method. This method is used to evaluate the treatment process. Biochemical laboratory measured the HGA urine excretion in these patients which is about 4 to 8 grams; however, its plasma levels are small. Discoloration of urine occurs due to polymerization and oxidation of HGA. Alkaline conditions increase this process, but the reaction ceases in acidic condition. This can be considered as one of the reasons for the disease diagnosing delay (10).

4- PATIENT PERSPECTIVE

We propose taking a precise medical history and physical examination including neurological assessments, which might have reduced the consequences of alkaptonuria like speech impairment, hearing loss, and developmental problems. Undoubtedly, the utilization of appropriate prenatal screening procedures is much more effective and inexpensive than late treatments. In addition, performing accurate neonatal examinations helps accurately detect homozygous metabolic deficiencies.

5- ETHICAL CONSIDERATIONS

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/relative of the patient.

6- CONFLICTS OF INTEREST

None.

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8- REFERENCES

1. Srsen S., Müller CR, Fregin A, Srsnova K. Alkaptonuria in Slovakia: thirty-two years of research on phenotype and genotype. Molecular genetics and metabolism, 2002. 75(4): p. 353-359.

2. Datta AK, Mandal S, Dasgupta A, Ghosh TK. Alkaptonuria diagnosed in a 4-month-old baby girl: a case report. Cases journal, 2008. 1(1): p. 1-4.

3. Al Mefraji, S., Alkaptonuria in a 5-year-old boy in Iraq. EMHJ-Eastern Mediterranean Health Journal, 14 (3), 745-746, 2008, 2008.

4. Introne WJ, Perry MB, Troendle J, Tsilou E, Kayser MA, Suwannarat P, O'Brien KE, Bryant J, Sachdev V, Reynolds JC, Moylan E, Bernardini I, Gahl WA. A 3-year randomized therapeutic trial of nitisinone in alkaptonuria. Molecular genetics and metabolism, 2011. 103(4): p. 307-314.

5. FJ, C.S. Ochronosis: a case report with multisystemic affectation, including pericardium. In Anales de medicina interna (Madrid, Spain: 1984). 2002.

6. Perry MB, Suwannarat P, Furst GP, Gahl WA, Gerber LH. Musculoskeletal findings and disability in alkaptonuria. The Journal of Rheumatology, 2006. 33(11): p. 2280-2285.

7. Hannoush H, Introne WJ, Chen MY, Lee SJ, O'Brien K, Suwannarat P, Kayser MA, Gahl WA, Sachdev V. Aortic stenosis and vascular calcifications in alkaptonuria. Molecular genetics and metabolism, 2012. 105(2): p. 198-202.

8. Al-Shagahin, HM, Mwafi N, Khasawneh M, Al Zubi K, Alsbou. Ear, nose, and throat manifestations of alkaptonuria patients from Jordan. Indian Journal of Otology, 2019. 25(3): p. 109.

9. Wolff F, Biaou I, Koopmansch C, Bossche MV, Pozdzik A, Roumeguère T, Cotton F. Renal and prostate stones composition in alkaptonuria: a case report. Clinical nephrology, 2015. 84(6): p. 339-342.

10. Al-Sarayreh SA, Al-Tarawneh IN, Al-Sbou MS, Albatayneh EM, Al-Shuneigat JM, Al-saraireh YM. Measurements of Homogentisic Acid levels in Alkaptonuria Patients Using an Optimized and Validated Gas Chromatography Method. 2014: Hashemite University.