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CASE REPORT

Detection of alkaptonuria in a 1-week-old infant

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SUMMARY

Alkaptonuria is a rare disorder that results from an inherited deficiency of aromatic amino acid metabolism. Only 21% of the children under the age of 1 year having the disease are identified in clinics. We report a case of a 1-week-old child of a first-degree consanguineous couple with a symptom of frequent nappy staining. Analysis of urine showed a homogentisic acid concentration exceeding 200 mg/dL. The physical examination revealed that the child was healthy. The parents' watchfulness and the close attention paid to the child were the keys to the early detection of this rare disease. After identifying the disease, adequate follow-up of the patient is important to reduce further complications. Anti-inflammatory therapy and increasing the muscle strength by exercises such as swimming would be useful to restrict joint pains and immobilisation. A low protein diet also could be recommended; that fact is yet to be proven by clinical trials.

BACKGROUND

Alkaptonuria (AKU) occupies a unique position in the history of medical genetics because it was the first human condition known to transmit in a typical Mendelian recessive manner. AKU results from an inherited deficiency of aromatic amino acid metabolism. The enzyme, homogentisate 1,2-dioxygenase (HGD), which is normally found in the liver and kidney, is deficient in patients with AKU. Therefore, this condition is characterised by accumulation of homogentisic acid (HGA) in the body and its excretion via urine.[1]

The clinical interest in AKU is related to its association with ochronosis.[2] During this process, an oxidative product of HGA, also known as 'alkaptone', accumulates slowly in the connective and cartilaginous tissue throughout the body, and leads to a blue-black pigmentation.[2] Ochronosis does not occur in body tissues until they are exposed to HGA for a long period of time. In many cases, the disease remains masked until adulthood.

Only 21% of the children under the age of 1 year having the disease are identified in clinics.[3] So far, the earliest identification of the disease has been in a 4-month-old girl.[4] We report a case of a 1-week-old child presenting with frequent nappy staining to a general practitioner in the North Central Province of Sri Lanka.

CASE PRESENTATION

A 1-week-old baby boy, whose parents were from a first-degree consanguineous marriage, was noted by his parents to have frequent darkening of his nappy when left at room temperature and on application of soaps (alkaline) during washing. He has healthy siblings with no AKU or other genetically related medical conditions such as haemolytic anaemia. The baby appeared normal and physical examination revealed a healthy boy with no abnormal pigmentation of the sclera, conjunctiva, cornea or ear cartilage.

The baby's urine appeared normal during voiding but later turned black when left at room temperature. Laboratory investigations were normal and no skeleton anomalies were detected. The patient is on regular follow-up at the outpatient clinic of Teaching Hospital, Anuradhapura, Sri Lanka. For family screening, urine samples were obtained from siblings, parents and grandparents from the maternal and paternal sides of the child; other blood relations (siblings of the mother and father) were also screened; all were found to be healthy with no evidence of AKU.

INVESTIGATIONS

Urine examination of the child by ferric chloride test and ammoniacal silver nitrate test were positive. The urine samples were analysed obtaining absorption spectra in the visible range to observe the presence of HGA.[5] In the quantitative analysis of HGA in the child's urine, the gas chromatography-mass spectrometric data showed a HGA concentration exceeding 200 mg/dL level, which confirmed the diagnosis. (Normally HGA is not present in urine.)

TREATMENT

Many therapeutic approaches have been predicted such as high-dose vitamin C, nitisinone and dietary restriction of phenylalanine and tyrosine.

FOLLOW-UP

The patient's parents were advised to bring the baby to monthly clinics at the Outpatient Department of the Teaching Hospital, Anuradhapura, to observe any complications of the disease. At 9-month follow-up, the baby has not shown complications. Reports indicate that low protein intake in childhood may prevent complications later in life. The patient's parents were also instructed to restrict his protein intake, but leaving sufficient amounts for muscle maintenance and growth. Nitisinone is still not generally prescribed in Sri Lanka.

DISCUSSION

Urine of individuals with AKU appears normal at the time of voiding, but turns dark when left at

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room temperature. The colour change is due to the oxidation of HGA followed by polymerisation. In acidic urine, the darkening is not seen, but when it becomes alkaline it turns dark.[2] Therefore, the condition often remains masked until adulthood. Delay of identification of the disease can cause arthritis or ochronosis. Repeated dark nappy staining observed in childhood gives a valuable clue for AKU.

AKU shows an autosomal recessive inheritance, which results from a defect in the gene code of HGD. This enzyme is involved in the cleavage aromatic ring of HGA, converting it into maleylacetoacetic acid, and finally into fumaric and acetoacetic acid.

HGA is a reducing substance that produces positive results with Benedict reagent, strong alkali and ferric chloride. Screening tests for the presence of HGA in urine, such as ferric chloride test and ammoniac silver nitrate test, are used to establish the diagnosis. The detection of elevated HGA levels in the urine is measured by gas chromatography-mass spectrometry or colorimetric acid analysis, which confirms the diagnosis.

Ochronosis refers to deposition of oxidative products of HGA pigment in the dermis of the skin, which appears blue-black in colour, and is usually evident in the sclera and cartilage of the ears after the third decade of life. The pigmentation of sclera is prominent between the cornea and the outer and inner canthi. The prominent systemic manifestation of AKU is arthritis, which also often begins in the third decade of life. Degeneration of disk spaces with subsequent calcification leads to kyphosis and loss of height. However, in this case, none of the clinical symptoms were observed, because the disease was detected in a very early stage of life; the child was only 1 month old at the time of compiling this report.

Nitisinone is approved by the US Food and Drug Administration for the treatment of tyrosinemia type I, which is currently under investigation as a treatment option for AKU. This compound inhibits 4-hydroxyphenylpyruvic dioxygenase, the enzyme that produces HGA. It has been observed that nitisinone dramatically reduces urine HGA levels in patients with AKU.[6] Long-term clinical trials are planned to determine the benefit of nitisinone in preventing joint deterioration and pain caused by accumulation of oxidative metabolites of HGA.

In our case, the parents' watchfulness and the close attention paid to the child was the key for detection of this rare metabolic disorder at 1 week of age. The identification of the disease at an early age is beneficial in delaying the potential complications with the help of adequate parent counselling and follow-up. An improvement in community awareness about consanguineous marriages would be helpful to reduce future incidence of AKU and other genetically transmitted diseases.

Learning points

- Parent's awareness about the child is a key point for early detection of alkaptonuria.
- After early diagnosis, precautions could be taken to delay the possible complications of the disease.
- Consanguineous marriage is the reason for this case of alkaptonuria. Therefore, community awareness needs to be improved about genetically transmitted diseases especially among rural communities.

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REFERENCES

1 Nafees M, Muazzam M. Alkaptonuria: an inborn error of amino acid metabolism. *Annals* 2008;14:68–71.
2 La Du BN. Alkaptoneuria and ochronotic arthritis. *Mol Biol Med* 1991;8:31–8.
3 Mistry JB, Bukhari M, Taylor AM. Alkaptonuria. *Rare Dis* 2013;1:e27475.
4 Datta AK, Mandal S, Dasgupta A, *et al*. Alkaptonuria diagnosed in a 4-month-old baby girl: a case report. *Cases J* 2008;1:308.
5 Tokuhara Y, Shukuya K, Tanaka M, *et al*. Detection of novel visible-light region absorbance peaks in the urine after alkalization in patients with alkaptonuria. *PLoS ONE* 2014;9:e86606.
6 Intron WJ, O'Brien KJ, Ghal WA. Nistionine use in hereditary tyrosinemia and alkaptonuria. In: Thoene JG, ed. *Small molecule therapy for genetic disease*. New York: Cambridge University Press, 2010:114–30.