Seizures with Alkaptonuria in Adults- The Untold

Nithish Mukunthan M.¹, Santhosh V.², Balaji T.³, Suresh J.⁴, Rajaram Manoharan T.⁵

¹Department of Anaesthesia and Critical Care, Preethi Super Speciality Hospitals, Madurai, Tamilnadu, India.

²Department of Anaesthesia and Critical Care, Preethi Super Speciality Hospitals, Madurai, Tamilnadu, India.

³Department of Anaesthesia and Critical Care, Preethi Super Speciality Hospitals, Madurai, Tamilnadu, India.

⁴Department of Anaesthesia and Critical Care, Preethi Super Speciality Hospitals, Madurai, Tamilnadu, India.

⁵Department of Anaesthesia and Critical Care, Preethi Super Speciality Hospitals, Madurai, Tamilnadu, India.

INTRODUCTION

Alkaptonuria, is a rare metabolic autosomal recessive disorder, which affects 1:1,000,000 people. It is also called endogenous ochronosis. Though it is mainly seen in children, in adults it usually presents after the age of 30.¹ It arises from decreased activity of liver homogentisate 1,2-dioxygenase which leads to accumulation of homogentisic acid (HGA) and production of a melanin-like polymer which is deposited mainly in cartilaginous tissue, mucous, skin, bone surface, internal cardiac structures, as well as excreted in urine.² The main presentation of alkaptonuria is valvular calcifications and osteoarthritis of spine, along with dark pigmentation of skin, cartilage, sclera and other connective tissues. It is diagnosed by a combination of clinical history, histopathological examination, and estimating the levels of homogentisic acid in urine.³

PRESENTATION OF CASE

Figure 1.
Scleral Discolouration in Alkaptonuria

This is a rare case report of 40 years old male who presented with a complication of seizure with alkaptonuria. Consent form was obtained from the patient for the publication. The patient was a known hypertensive not on any medications presented to us with history of single episode of seizure on day of admission, manifested as unconsciousness episode with up rolling of eye balls. This seizure episode was preceded by 3 days history of high grade, intermittent fever with no other contributory history. In the ER patient was drowsy, arousable and haemodynamically stable. On clinical examination the patient had yellowish pigmentations in both eyes. On initial investigations the patient's Serum sodium was 115 meq/L, Serum potassium was 2.5 meq/L while rest of the investigations were within normal limits. Patient was initially worked up for hyponatremia and was diagnosed to be the cause of seizures. Patient was slowly corrected with 3% normal saline infusion and put on anti-epileptic drugs. Serum osmolality was 237 mosm/Kg with urine sodium 29 meq/L and urine osmolality 163 mosm/Kg. Neurologist opinion was obtained and EEG done was normal, CT brain done was suggestive of diffuse cerebral oedema secondary to hyponatremia.

Corresponding Author:

*Dr. Nithish Mukunthan M.,
Department of Anaesthesia & Critical Care,
Preethi Super Speciality Hospitals,
Melur Main Road, Uthangudi,
Madurai-625020, Tamilnadu, India.
E-mail: nithishchat@gmail.com*

DOI: 10.14260/jemds/2020/285

*Financial or Other Competing Interests:
None.*

How to Cite This Article:

*Mukunthan NM, Santhosh V, Balaji T, et al.
Seizures with alkaptonuria in adults- the
untold. J. Evolution Med. Dent. Sci.
2020;9(15):1313-1315, DOI:
10.14260/jemds/2020/285*

*Submission 04-02-2020,
Peer Review 16-03-2020,
Acceptance 22-03-2020,
Published 13-04-2020.*

Figure 2.
*Darkening of Urine on
Long Standing/ Exposure
to Atmosphere*

Patient was catheterized on first day of admission to monitor urine output. It was observed that on long standing the collected urine became dark in colour. Urine Homogentisic acid was sent which resulted positive. Patient was diagnosed with alkaptonuria. Patient was subsequently worked up for alkaptonuria. CT spine was done was suggestive of extensive premature degeneration with intra discal calcifications and vacuum phenomenon seen at most of thoraco lumbar vertebrae suggestive of ochronosis. Rest of the investigations done pertaining to alkaptonuria like ECHO, MRI brain were all normal. The patient did not show any signs of bone or cartilage involvement other than the radio graphic findings so was put on vitamin C supplementations and anti-epileptic drugs and discharged.

DISCUSSION

Sir Archibald Garrod in 1901 from London was the first one to describe about AKU as an inborn error of metabolism. AKU is an autosomal recessive genetic disorder. There is inborn error of metabolism of phenylalanine and tyrosine which manifests as inability to metabolize HGA.⁴ The HGA is part of phenylalanine and metabolic pathway. The deficiency of homogentisic acid oxidase enzyme leads to its accumulation, which polymerizes to a melanin like pigment having a high affinity for connective tissues like cartilage giving it an ochre colour, hence the name ochronosis.³

It is mainly diagnosed in children by identifying darkening of urine after long standing period in rest or in contact with environment or in babies by identifying blackened spots in diapers. But in adults, after fourth decade of life, it mainly manifests as osteoarthritis, manifesting as changes in eyes, wars, skin, CVS, renal and musculoskeletal system.⁵ Ocular manifestations are seen as brown scleral pigmentation. Dilated conjunctival vessels can be present and they supply the pigmented areas on the conjunctiva.⁶

The usual diagnosis is through clinical history and noting the changes in urine colouration when exposed to environment or air. Confirmation is by estimating the amount of HGA levels in urine.⁷

In our case it was a rare presentation of alkaptonuria with seizures. There has been instances were a case report of alkaptonuria manifesting as seizures has been reported in a 8 year old boy with EEG picking up classical epileptic activity.

However they could not establish a causal between both and concluded it to be a co-existing independent event.⁸

In addition to seizures the other significant finding in our case was the hyponatremia. There are case reports of alkaptonuria associated with renal tubular acidosis.⁹ Renal dysfunction is uncommon and late complication of alkaptonuria, that manifests as decreased renal excretion and increased parenchymal concentration of HGA.^{10,11} Renal biopsy will show chronic tubulointerstitial disorder with ochronotic coarse granular pigment deposition, along with occasional glomerular sclerosis and connective tissue destruction.^{12,13}

Though we don't have evidences to prove renal tubular acidosis in our patient as he was not willing for renal biopsy, so with the presence of hypokalemia and hyponatremia we hypothesize that the patient would have had distal renal tubular acidosis as renal tubular secretion is important for the elimination of HGA, which if impaired leads to both distal RTA and alkaptonuria.

Medical therapy reduces the rate of deposition of pigment. Reduction of phenylalanine and tyrosine reduces HGA excretion. Vitamin C, in a dose of 1 g/day, is recommended for older children and adults. Ascorbic acid being an antioxidant helps in slowing the process of conversion of homogentisate which is deposited as polymerized material in cartilaginous tissues.^{14,15} Use of nitisinone, 4-hydroxyphenylpyruvate dioxygenase enzyme inhibitor, which inhibits formation of HGA and accumulates the upstream precursor tyrosine has been reported but its use is limited.¹⁶ In our case as the patient was asymptomatic in all other aspects and improved clinically we discharged the patient with Vitamin C tablet supplementations and anti-epileptic drugs.

CONCLUSIONS

Though it is still unclear, and not enough reports and evidences are available to establish a causal relationship between alkaptonuria and seizures, we hypothesize based on all the previously available case reports that alkaptonuria has, induced hyponatremia, secondary to distal RTA which in turn has caused seizures in our patient.

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