



## AYURVEDIC MANAGEMENT OF ALKAPTONURIA – A CASE REPORT

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### ABSTRACT

Alkaptonuria is a rare, autosomal-recessive disorder of phenylalanine/ tyrosine metabolism due to congenital deficiency of the enzyme homogentisic acid oxidase characterized by triad of dark-colored urine, ochronosis and ochronotic arthropathy. The development of ochronotic arthropathy is the result of deposition of homogentisic acid (HGA) polymer within hyaline articular cartilage. Ochronosis primarily occurs in large joints of the body including spine thus producing loss of flexibility and ankylosis of the thoracic and lumbar segments. Here, a case of Alkaptonuria with ochronotic arthropathy affecting spine and knee is studied. It can be considered as *Sahaja vata vyadhi* (genetic disorder). Till now there is no pharmacological treatment which cures the disease. The Ayurvedic treatment was given to improve the quality of life of the patient and mainly to reduce the pain and stiffness of spine which affects day to day life. Internal medications for 3 months and IP Treatment for 11 days was given initially. In this condition continuous treatment is required so intermittent medication is prescribed for one year and better results were obtained. Here the drugs for metabolic correction, *Srota sodana* (clears blocks in metabolic pathways), diuretic drugs for increasing excretion of homogentisic acid and *Vatahara* drugs which prevents degeneration are given.

**Key Words:** Alkaptonuria, Ochronotic arthropathy, Homogentisic acid, *Sahaja vata vyadhi*

**INTRODUCTION:** Alkaptonuria also called black urine disease and black bone disease is one of the four disorders originally defined as inborn error of metabolism by Archibald Garrod in his Croonian lecture of 1902 [1]. It is a rare, autosomal-recessive disorder of phenylalanine/ tyrosine metabolism due to congenital deficiency of the enzyme homogentisic acid oxidase [2]. The HGD gene provides instruction for making enzyme homogentisic acid oxidase which helps breakdown of these aminoacids [3]. Mutations in HGD gene leads to accumulation of homogentisic acid, an intermediate metabolite of phenylalanine and tyrosine metabolism [2]. Homogentisic acid [HGA] pigment oxidizes to Benzoquinone acetate [BQA], which forms a melanin-like polymer that slowly turns urine black. Ochronosis occurs as the BQA accumu-

lates both intra and extra cellularly in connective tissue, which causes cartilage and skin to darken [4]. The ochronotic pigment has high affinity for the collagen fibres of articulation. So arthritis occurs in almost all patients with advancing age due to the buildup of this substance in the joints [5, 6]. The worldwide incidence of alkaptonuria is 1:250000. There are very few cases reported from India [7]. Darkening of urine is the only symptom suggestive of Alkaptonuria in the childhood. The patients usually remain asymptomatic until third or fourth decade [8]. The early involvement of intervertebral disc at thoracic and lumbar levels and large weight-bearing joints [hips, shoulder, knees] are very common [9]. Achilles tendon involvement is seen and its tearing is also common. The radiological picture is of severe osteoarthritis. The degenerative

changes in the lumbar spine occurs with narrowing of joint spaces and fusion of vertebral bodies, resulting in ultimate ankylosis and marked limitation of movements. The disease process most similar to ochranosis is ankylosing spondylitis. Ligaments, facets and the sacroiliac joints are characteristically involved in the ankylosing spondylitis whereas intervertebral discs are more involved in alkaptonuria. Lateral disc bulges may be seen and the discs are hard and brittle [9, 10]. The incidence in the two sexes are equal, but usually more severe in men [11].

The cardiovascular lesions of ochranosis, include discoloration of the heart valves, endocardium and intima of the aorta. Increased incidence of generalized atherosclerosis and myocardial infarction is reported in such patients. Calcification of the heart valves may necessitate aortic valve replacement [12]. The discoloration tends to be most pronounced on sun-exposed sites, cartilage of the ears and nose, areas of high eccrine sweat gland density such as axillae, palms soles, and genitalia. The diagnosis is confirmed by the identification and quantification of homogentisic acid in urine using gas liquid chromatography [2]. In Ayurveda it can be considered as *Sahaja vata vyadhi*. Here *Beeja dusti* (defects of genes) causes *Sahaja dhatwagni mandhyam* (poor metabolic activity at the level of tissues) which results in improper formation of *Dhatu*s (tissue elements) and excessive accumulation of *Malas* (waste products). Thus causing vitiation of *Tridosha* predominantly affecting *Vata dosha*. Therefore proper *Shodhana* for excretion of accumulated *Malas* and *Vata samana* treatments along with *Agnideepana* (drugs which increases digestive fire) is done as treatment.

## CASE DESCRIPTION

A 38-year-old male (MRD-12205) came to the OPD of PNNM Ayurveda Medical College with complaints of chronic stiffness and pain of lower back, since last 3 to 4 years. Right knee joint pain since 4 months. He experienced difficulty to bend forward immediately after waking up after sleep and after rest. He also complained about discomfort of straightening the body after sitting few hours. Scoliosis and slight lordosis of lumbar spine conspicuous on standing diminished on lying down. He also has pain on the area above heels (on achilles tendon).

Patient had complaints of occasional low back ache and pain over achilles tendon on strenuous work even from his 20 years and he used to take some allopathic medicines occasionally when the pain increases.

His mother had noticed that his urine used to turn dark on standing in childhood, but ignored it. The symptoms of low back ache got aggravated only after his 30 years. Again since 3 months, complaints of low back ache along with right knee joint pain got aggravated. Then he consulted a senior orthopedician and he advised for X-ray lumbosacral spine and knee joint. From seeing his X-ray, he diagnosed the condition as Alkaptonuria and was sent for urine homogentisic acid testing for confirmation and found positive. Patient was told to take oral vitamin C 500 mg tab twice daily.

There were no systemic complaints. No bluish black discoloration noted in the skin anywhere in the body. The oral and genital mucosa was normal.

Personal history- Food- mixed diet, Appetite- normal, Bowel- normal, Micturition- 5-6 times during day time, Sleep- normal, Exercise- reduced recently due to pain, Allergy and Addiction- nil, Body weight-

82 kg. He is neither diabetic nor hypertensive.

*Ashtavidha Pareeksha- Nadi- 70 bpm/min, Mootra- turns black on standing, Malam- Normal bowel (madyama koshtam), Jihva- Slightly coated, Sabda-clear, Sparsham- Anushnaseeta, Drik-Prakruta, Akriti- Madhyamam.*

His parents were not consanguineous marriage and he was first in birth order. His sister also had similar complaints and found to have Alkaptonuria. His father died in his 55-year due to CVA. His parents don't have similar complaints. In his mother's family and father's family, no one had similar complaints. The case was diagnosed as *Sahaja vata vyadhi*. There is *Tridosha dusti* especially *vata dusti* and also excessive accumulation of *malas* due to improper formation of *dhatu*s. So *Agni deepana, Srotasodhana, mild purificatory therapies* for excretion of *malas* along with *vata samana chikitsa* is given.

### Systemic Examination and Investigations

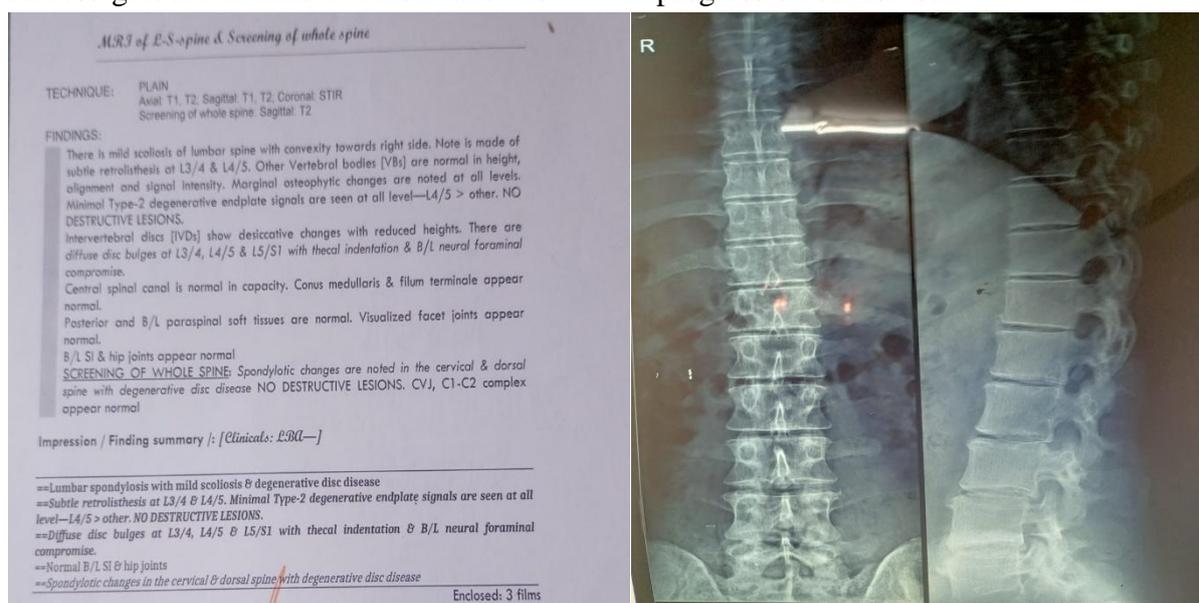
Examination of spine revealed scoliosis and slight lordosis of lumbar spine, tenderness grade 2 in whole lumbar and tho-

racic region, no edema, all movements possible but painful. Full flexion takes time due to stiffness. SLR - negative Examination of knee joint (right) – no deformity, slight oedema present, tenderness grade 2, no temperature rise, All movements possible but complete flexion was very painful. Squat test- positive.

Examination of ankle joint - tenderness on achilles tendon, all movements were possible but slightly painful.

His ECG, echocardiogram, USG abdomen, Complete blood count and serum biochemistry were normal. Homogenthesic acid in urine is found positive.

Radiological examination of spine showed loss of lumbar lordosis, reduction in all disc spaces, marginal osteophytes, superior and inferior end plate changes of all dorsolumbar vertebra and dense calcification of intervertebral discs at multiple level. Examination of knee joint revealed slight narrowing of joint space, osteophyte formations on sides of patella. The MRI report (figure1) and the Xray which is taken on 2014 (figure 2) and 2019 (figure 3) are attached here to see the pathological progression of disease.





### INTERVENTIONS

#### OP TREATMENT FOR 3 MONTHS PHASE 1 [1-7-2019 to 1-10-2019] Table-1

<i>Drakshadi kashayam</i>	60ml in the morning before food[6am]
<i>Punarnavadi kashayam</i>	60 ml in the evening before food[6pm]
<i>Chandraprabha gulika</i>	0-0-1 with <i>Punarnavadi kashaya</i>
<i>Ardhivilwam kashayam</i>	1 litre as drinking water
<i>Dhanwantaram mezhupakam</i>	1 tsp at bed time, hot water <i>Anupanam</i>
<i>Dhanwantaram tailam</i>	daily applied on whole body and fomented (30 minutes)
<i>Nimbamritadierandam</i>	25ml for purgation with luke warm water once in a month

Regimen- Patient is told to follow vegetarian diet, avoid cold, spicy, bakery and hotel food. Told to reduce weight gradually as he was overweight and to do exercise daily so that all joints get movement,

#### IP Treatment for 11 Days Phase 2 [1-10-2019 to 12-10-2019]

- *Abhyangam* and *Bhashpaswedam* with *Dhanwantaramtailam* and *Sahacharaditailam* for 7 days
- *Patrapotaliswedam* with same oil (ingredients – leaves of *eranda*, *arka*, *nirgundi*, tamarind, moringa, lemon) for next 3 days
- *Matravasti* with *Dhanwantharam tailam*-70ml done on last 3 days

- *Panchatiktaka ksheeravasti* on 11/10/2019

- *Murivenna taila pichu* bandage was given to both foot and on knee joint on all 11 days.

After IP treatment most of the internal medicines are stopped. Told to continue *Panajalam* and take *Tikthakam ghritam*-1tsp at bedtime. He is advised to do external application of *Dhanwantaram tailam* with fomentation and hot water bath once in a week for next months.

It is told to restart the same internal medicine, when urine gets dark on checking. So in a year, 3-4 course of medicine is taken for a duration of 1 month.

#### CRITERIA FOR ASSESSMENT PAIN VISUAL ANALOGUE SCALE



**TENDERNESS (Table-2)**

TENDERNESS	GRADE
No tenderness	0
Tenderness to palpation with grimace	1
Tenderness with grimace or flinch on palpation	2
Tenderness with withdrawal(jump sign)	3
Jump sign with non-noxious stimuli	4

**STIFFNESS (Table-3)**

STIFFNESS	GRADE
No Stiffness	0
Mild Stiffness	1
Moderate Stiffness	2
Severe difficulty due to Stiffness	3
Severe difficulty more than 10 minutes	4

**CREPITUS (Table-4)**

CREPITUS	GRADE
No crepitus palpable or audible	0
Crepitus palpable but not audible	1
Soft audible and palpable crepitus	2
A louder grating or snapping sound	3

**OBSERVATION AND RESULT (Table-5)**

Complaints	Before treatment	AFTER PHASE1	AFTER PHASE 2	AFTER PHASE 3 (after 1 year)
Knee joint [right]	Pain on walking Pain-2 Tenderness-2 Crepitus -3 Slight Warmth And Soft tissue oedema was present No stiffness, Rom- full flexion highly painful, Squat test + ve	No pain on walking ,pain on stepping stairs persists, Pain-1, Tenderness-0, Crepitus-2 No oedema and temperature rise, Slight pain on full flexion	No pain on walking and stepping stairs, Pain-0, Tenderness-0, Crepitus-1 Full flexion possible without pain.	Knee joint pain didn't occur after the treatment. Priorly he was not able to sit in <i>sukhasana</i> , but now possible. Crepitus grade 1 present. Complete squat is not yet possible
Achilles tendon pain	Pain-2 Tenderness-2 ROM -all movements possible but slightly painful	Pain-0 Tenderness-0 All movements possible without pain	Pain-0 Tenderness-0 All movements possible without pain	The pain on achilles tendon didn't occur for last 1 year
Low back	Scoliosis and postural change present.	Pain-2 Tenderness-1	Pain-0 Tenderness-0	Pronounced scoliotic pos-

	Pain-3 Tenderness-2 Stiffness-3 Rom-flexion was almost normal ie.60° but stiffness was more that he take time to get in to full flexion. Extension and lateral flexion was normal	Stiffness-2 Range of movements- flexion became more easy that stiffness got reduced	Stiffness got much reduced to 1 and movements became free compared to before.	tural change got reduced, Though stiffness grade 1 persists, initial stiffness on change of posture got much reduced
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**DISCUSSION:** No complete cure is possible for this disease at present. Supportive therapy like NSAIDs and physiotherapy is used for pain management. Dietary restriction of some food such as milk, meat, poultry, egg, cheese and nuts containing phenylalanine and tyrosine can be advised. This has limited role in reducing the excretion of homogentisic acid, but can prevent further progression of arthropathy. The complete restriction of these foods is not advised as it can lead to deficiency diseases. Vitamin C (ascorbic acid), given in the dose of 500 mg twice daily, act as antioxidant and inhibits the polymerization of homogentisic acid. This can reduce the tissue damage. But its efficacy has not been proven [2].

Understanding the fact that Alkaptonuria is a rare genetic disorder and not curable, the treatment plan was designed to improve the quality of life of the patient and mainly to reduce the pain and stiffness of spine which hamper day to day life. There is no established methodology in Ayurveda to treat this *Sahaja vata vyadhi*. The medicines used in this condition were *Drakshadi kashayam* which alleviates *pitta*, is used for correcting errors in *Dhatuparinama* (proper formation of basic tissues) and regulate proper *Sarakittavibhajana* (proper separation of bodily waste and essence). Thus it helps in metabolic correction and prevents the vital

organs from accumulation. *Punarnavadi kashayam* imparts *srotosodhana* (cleansing of channels), augments excretion of metabolic waste from the body. It also helps in reducing the excess acidity formed in the body due to irregular metabolism. *Chandraprabha gulika* is told to alleviate *Tridosha* vitiation, *Sarvaroga pranasana* (cures all diseases), *Balyam* (strengthening), *Vrishyam* (aphrodisiac), *rasayana* (rejuvenative) and act as alkaliser [13]. *Ardhivilwam kashaya panajalam* helps in easy excretion of homogentisic acid through urine. *Dhanwantaram tailam* is indicated in *Deerkharoga kshapita vapusham* [chronic debilitated diseases], so it is used as *samana* here [14]. Mild *Sodhana* with *Nimbamritadi erandam* was done monthly to eliminate the accumulating *Malas* along with oral medication.

After 3 months of internal medicine, application of *Sneha* (external application of oil), *Sweda* (fomentation) and *Sodhana* (purificatory procedure) was aimed to relieve *Vatavikaras* especially *Stambha* (rigidity), *Graha* and *Ruja* (pain). Even though we can't expect much change, improvement we got after the IP treatment on stiffness of low back is sustained even after 1 year. As there is no inflammation, direct *Abhyanga* was given. By external *Sneha* and *Sweda*, flexibility got much improved. *Ksheeravasti* is done with *Panchatiktaka ksheera kashayam*,

*Tiktakam ghritam* and *Dhanwantaram mezhupakam*. Here there is loss of *kharatwa* (roughness) of *Asthidhatu*. *Tikta rasa* (bitter taste) have *Kharatwaguna*, so *tikta* is found to have effective in *Asthidhatukshaya*. According to *vagbhata*, in *Asthidhatukshaya* the *Ksheeravasthi* medicated with *tikta rasa* should be used [15]. *Asthi* is the seat of *Vata* and *Vasti* is prime treatment for *Vata*. Thus *Vasti* helps to eliminate the morbid *Doshas* from the *Srotas* especially *Asthivahasrotas*. After 3 months internal medication and IP treatment, urine colour became normal even after 24 hours when kept open. Knee joint pain completely resolved. Flexion of lumbo sacral spine became easy and initial stiffness on change of posture got reduced and the score got reduced from 3 to 1.

The patient is advised to take 3-4 courses of internal medicines in a year. Internal medication ensures proper excretion of homogentisic acid, thus accumulation in joints are prevented up to some limits. In the other time, told to continue *Tiktaka ghrita* at bedtime and to continue *Panajalam*. He is told to do mild *Virechanam* (purgation) once in a month and to do external application of *Dhanwantaram tailam* on spinal area once in a week. It is found that the improvement got after the IP treatment persists even after 1 year.

Patient is recommended IP treatment when the stiffness and pain aggravates, or otherwise once annually. Thus mobility and wellness is maintained. And told to do active surveillance for cardiac, renal and prostate complications in every 2 years.

Some practitioners use *Kalyana kshara* in the initial stage to reduce excess acidity in the body and also for getting fast results. In this case it is not used as the accumulation of homogentisic acid is less. Even

without using *kshara*, good result was obtained.

## CONCLUSION

Alkaptonuria is very rare inherited disorder, which occurs when body can't produce enough of enzyme homogentisic acid oxidase. This can cause accumulation of homogentisic acid in body. In this condition no effective allopathic treatment is available. Even though condition is not curable, we have many drugs which can decrease the progression of disease without much side effects. Our treatment aims at augmenting excretion of homogentisic acid and correction of metabolism and decreasing the degeneration of joints. Treatment is to be done repeatedly in regular intervals for better results. Also long term effect of the ayurvedic medications in the management of such diseases should be studied.

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