Spine

SPINE Volume 44, Number 1, pp E53–E59

LITERATURE REVIEW

''As Black as Ink''

A Case of Alkaptonuria-Associated Myelopathy and a Review of the Literature

Callum J. Donaldson, BSc,* Stuart L. Mitchell, MD,† Lee H. Riley III, MD,† and Khaled M. Kebaish, MD†

Study Design. Case report and literature review.

Objective. To characterize the rare presentation of myelopathy occurring secondary to alkaptonuria and to evaluate the available evidence regarding its treatment.

Summary of Background Data. Alkaptonuria is an autosomal recessive genetic condition with an estimated incidence of 1 in 250,000 to 1 in 1,000,000 people. Mutation of the enzyme homogentisate 1,2-dioxygenase leads to the production of high levels of homogentisic acid, with subsequent deposition in ligaments, cartilage, and menisci. Involvement of the spine is termed ''ochronotic spondyloarthropathy,'' of which myelopathy is an uncommon presentation.

Methods. We present the case of a 57-year-old man with alkaptonuria-associated myelopathy, who underwent surgical decompression. Ten additional cases were identified in the literature by a systematic search of PubMed and Google Scholar.

Results. In a patient presenting with myelopathy, alkaptonuria may be suspected because of medical history, family history, symptoms (including darkened urine, pigmented ear cartilage, and sclera), or radiographic changes, such as multilevel disc collapse, progressive wafer-like disc calcification, extensive osteophyte formation, and spinal deformity. The diagnosis can be confirmed by urine homogentisic acid testing. Of the 11 patients presented here or identified in the literature, 2 were treated nonoperatively, 8 were treated with decompressive spinal surgery, and treatment of the myelopathy was not discussed for 1 patient. In all cases in which outcomes were reported, substantial improvement in the patient's condition was seen.

Conclusion. Alkaptonuria is a rare cause of myelopathy, but one that clinicians should understand. Although no disease-modifying treatment currently exists for alkaptonuria, the use of symptomatic treatments and, particularly, surgical decompression is recommended to address myelopathy if it develops.

Key words: alkaptonuria, black bone disease, black urine disease, homogentisic acid, myelopathy, ochronosis, ochronotic spondyloarthropathy, spinal cord compression, surgical decompression, treatment.

Level of Evidence: 4

Spine 2019;44:E53–E59

Alkaptonuria is an autosomal recessive genetic disorder, with an estimated incidence of 1 in 250,000 to 1 in 1,000,000 people,[1] in which the enzyme homogentisate 1,2-dioxygenase is mutated.[2] A lack of functional homogentisate 1,2-dioxygenase prevents complete metabolism of phenylalanine to acetoacetate and instead, high levels of the intermediary homogentisic acid (HGA) are produced.[1] The HGA is then secreted in the urine. Oxidation of HGA produces a characteristic discoloration of the urine, first described in 1584 by Scribonius as being ''as black as ink.''[3,4] This is the origin of the common name of the condition, black urine disease. In the young patient, HGA undergoes efficient renal clearance, but as kidney function declines with age, it is retained in greater levels by the body.[5] HGA deposition in articular cartilage, ligaments, and menisci subsequently causes pigmentation and joint destruction (ochronosis).[1] Spinal involvement, termed ochronotic spondyloarthropathy, is common and often presents as chronic low back pain and stiffness.[5] Myelopathy is a rarer presentation, with just 10 reported cases in the literature, of which all were single case reports.[6–15] The aims of this article are to describe a patient with alkaptonuria who presented with thoracic cord compression and to review the relevant literature.

CASE REPORT

The patient was identified by the senior author and provided consent to be included in this study. Medical records and imaging studies were subsequently abstracted.

A 57-year-old man, with a known history of alkaptonuria, was referred by a local spine surgeon for a second opinion. In addition to alkaptonuria, he had been diagnosed with gout and osteoarthritis. The patient was experiencing

From the *Faculty of Life Sciences and Medicine, King's College London, London, UK; and †Department of Orthopedic Surgery, The Johns Hopkins University, Baltimore, MD.

Acknowledgment date: May 21, 2018. Acceptance date: May 29, 2018.

The manuscript submitted does not contain information about medical device(s)/drug(s).

No funds were received in support of this work.

Relevant financial activities outside the submitted work: grants.

Address correspondence and reprint requests to Khaled M. Kebaish, MD, Department of Orthopedic Surgery, The Johns Hopkins University, 601 North Caroline St, Baltimore, MD 21287;
E-mail: editorialservices@jhmi.edu

DOI: 10.1097/BRS.0000000000002755

paresthesia in both lower extremities, starting just proximal to the knee and extending down to his feet. He reported difficulty with ambulation because of loss of sensation in his feet and problems with balance. He reported multiple previous falls, leading to the use of a walker. He reported no problems with the upper extremities; however, he did report bowel and bladder incontinence, beginning 5 months earlier. He had retired 6 months earlier because of his progressive, debilitating symptoms. He also reported a 30-year history of chronic low back pain, although this was not the reason for presentation.

His medical history was also notable for a motor vehicle accident 1 year earlier that resulted in a Hangman fracture and sternal fractures, which were treated nonoperatively, as well as a tibial/fibular fracture treated with intramedullary rodding. All of these injuries healed uneventfully. In addition, he had undergone elective total knee arthroplasty within the year before presentation.

Physical examination was notable for a profoundly myelopathic, slap-foot gait. He was unable to ambulate without using a walker because of stumbling and a sensation of imbalance. Power was slightly reduced (4/5 strength) in the right iliopsoas, tibialis anterior, and extensor hallucis longus muscles. Patellar and Achilles tendon reflexes were exaggerated bilaterally with sustained clonus. Babinski sign was positive. Otherwise, neurologic findings were normal.

Radiographs of the lumbar spine showed diffuse spondylosis, loss of disc height at numerous levels, and multiple osteophytes. Magnetic resonance imaging of the entire spine showed multilevel spinal stenosis with a particularly prominent, calcified disc herniation at T10–11 measuring 13 × 23 × 10 mm compressing the spinal cord (Figure 1A–C). The

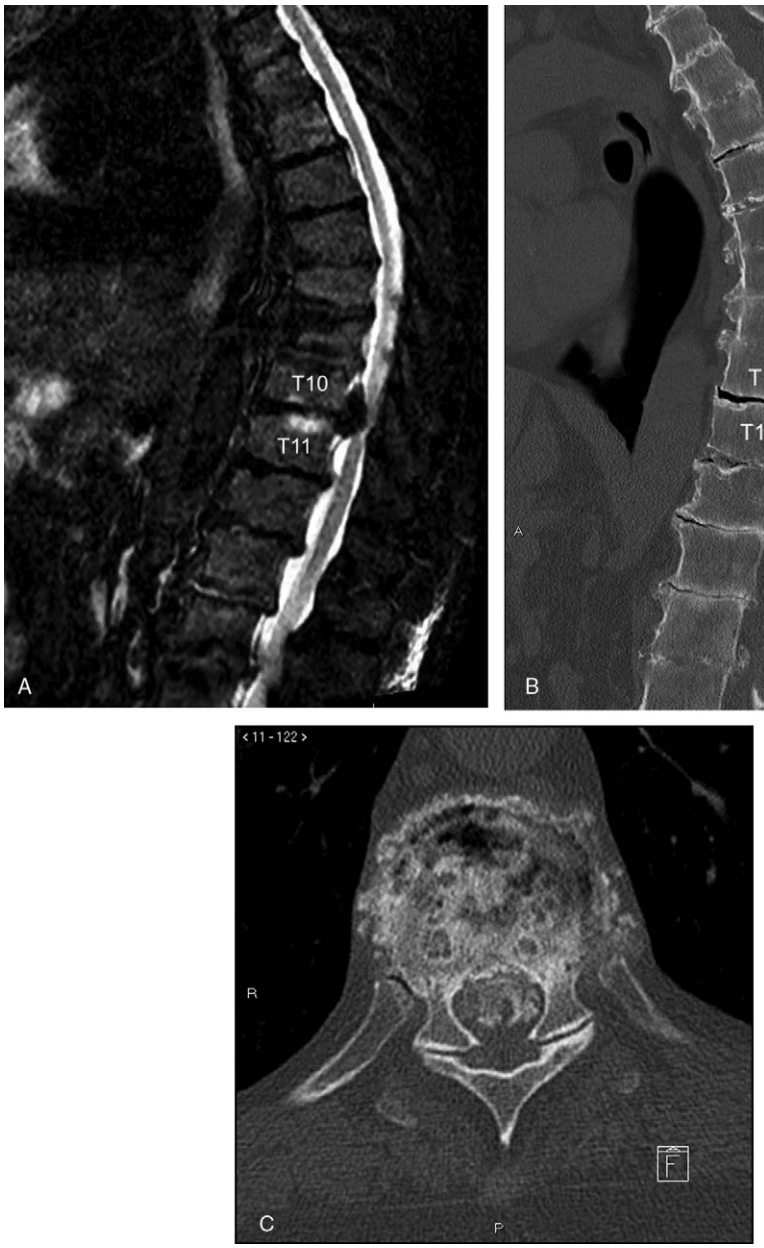

Figure 1. Sagittal short-tau inversion recovery magnetic resonance image (**A**) and sagittal (**B**) and axial (**C**) computed tomography scans showing a large, calcified disc herniation with cord compression with cord signal changes at T10-11, as well as characteristic findings of ochronotic spondyloarthropathy, including multilevel disc herniations and loss of disc height, diffuse spondylosis, and spinal deformity (excessive thoracic kyphosis).

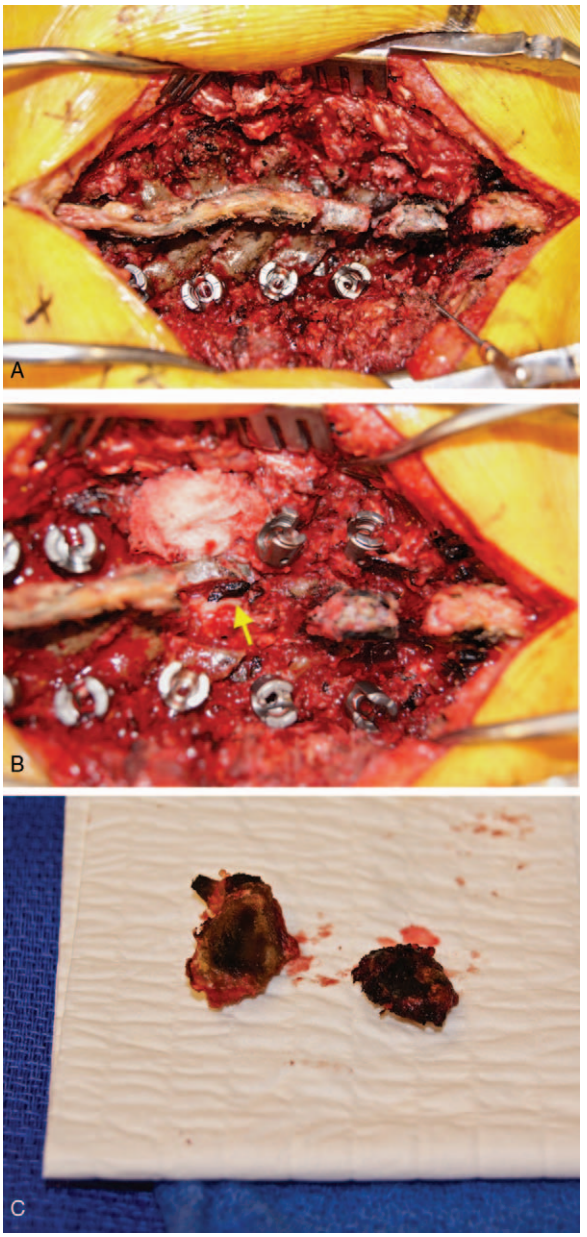

Figure 2. Intraoperative photographs showing characteristic ochronotic (dark) appearance of the interspinous ligament, bone, and cartilage (**A**), as well as calcified disc material being removed from beneath the thecal sac (**B**, *yellow arrow*), and a close-up view of resected facet joint cartilage (**C**).

patient's medical history coupled with his presentation allowed for a confident diagnosis of thoracic myelopathy related to alkaptonuric ochronotic spondyloarthritis.

It was believed that, without surgical intervention, the myelopathy would likely progress and could lead to paralysis. Surgical decompression was accomplished by T10–12 laminectomy with foraminotomies, as well as T11 partial corpectomy and T10–11 discectomy using a lateral extracavitary approach (Figure 2A–C). Stabilization was performed with posterior fusion and segmental instrumentation from T9 to L1. Multiple tissues, such as cartilage and ligaments, had a grossly black appearance (Figure 2), and formal pathologic interpretation was consistent with ochronosis.

Six months after surgery, the patient reported that his pain had resolved completely. He reported taking gabapentin for neuropathy in his feet, but this had improved substantially and no longer extended proximal to his feet. His bowel and bladder incontinence had resolved completely. He is able to ambulate again without assistance and has returned to his previous occupation from which he had retired.

Literature Review

Ochronotic spondyloarthropathy is a rare cause of myelopathy. To better characterize the presentation of this rare condition, we searched PubMed and Google Scholar to identify similar cases for comparison. Additional cases of myelopathy associated with ochronotic spondyloarthropathy were identified using the following search strategy: "(alkaptonuria OR alkaptonuric OR ochronosis OR ochronotic) AND (spine OR spinal OR cord compression OR myelopathy OR spondyloarthropathy OR spondyloarthritis OR spondylitis OR claudication)." Titles and abstracts were screened for relevance. We included articles only if (1) the patient(s) had a diagnosis of alkaptonuria/ochronosis (either known or diagnosed as a result of the presentation) and myelopathy, (2) the article was written in English, and (3) the full text was available for review. References in identified articles were also reviewed, and any additional relevant articles were included.

Ten cases (1 woman) were identified from 10 articles, for which the mean patient age was 58 years (range, 46–68). Cervical myelopathy was present most commonly (n = 5), followed by thoracic (n = 4) and lumbar (n = 3) myelopathies (Table 1).[6–15] One patient had myelopathy in the cervical and lumbar regions, and another patient had myelopathy in the thoracic and lumbar regions. Two other cases were identified in the literature review but were excluded because the full text was unavailable.[16,17]

DISCUSSION

We noted several cases in which alkaptonuria had been diagnosed before the presentation of myelopathy. Diagnosis of alkaptonuria can be made early in life following the observation of consistently darkened urine or after the third decade, when other features, including darkening of cartilage (*e.g.*, ears and nose) and sclera, early-onset arthritis, fractures, spinal degeneration, renal stones, hearing loss, and cardiac problems begin to develop.[18] In the setting of known alkaptonuria, myelopathy is an established yet rare presentation of ochronotic spondyloarthropathy. In contrast, alkaptonuria will rarely explain newly diagnosed myelopathy in a patient without a history of alkaptonuria, but clinicians should be aware of this possibility.

Prompt diagnosis of this rare condition requires not only an awareness of the previously mentioned clinical manifestations of the disease, but also knowledge of the characteristic radiographic findings.[6–12] These include multilevel disc collapse, progressive wafer-like disc calcification, extensive

TABLE 1. Summary of 11 Cases of Alkaptonuria-Associated Myelopathy

First Author	Year	Age (yr); Sex	Level of Compression	Presentation	Diagnosis of Alkaptonuria Made By	Treatment	Follow-up	Outcomes
Present case	2018	57; M	T10–11	Paresthesia, numbness, weakness, and hyperreflexia in BLE; impaired gait; bowel and bladder incontinence; LBP; Babinski sign (+)	Medical history (histologic confirmation)	T10-12 laminectomies with foraminotomies; T11 partial corpectomy; T10-11 discectomy; T9-L1 PSF	6 mo	Relief of paresthesia; complete resolution of bowel and bladder incontinence; independent ambulation; return to work
Bozkurt *et al*[9]	2017	47; M	Thoracic	Kyphosis; limited ROM; LBP; paresthesias, weakness in BLE; absent BLE reflexes; impaired gait; bladder dysfunction	Pigmentation of ear cartilage; dark urine; radiographic changes; histologic confirmation	PT; neuromuscular electrical stimulation therapy; pregabalin	4 wk	Pain and neurologic symptoms improved substantially; ambulates with crutch
Rahimizadeh *et al*[15]	2017	68; M	T11–12	LBP; weakness and spasticity in BLE; Babinski sign (+); urinary incontinence	Family history; pigmented ear cartilage and sclera; dark urine; urinary HGA testing	T11–12 laminectomy, discectomy, and interbody fusion; T9-L2 PSF	10 mo	"Quite satisfactory" neurologic examination; walks unassisted
Li *et al*[10]	2016	62; F	Cervical	Neck and back pain with stiffness; TL kyphosis resulting in reduced ROM; disturbance of gait; reliance on wheelchair; hand clumsiness	Pigmentation of ear, nose, and sclera; radiographic changes; dark urine; urinary HGA testing	C3 laminectomy, C4–7 laminotomies	1 yr	Improvement in JOA score from 7 to 11; patient satisfied; crutches required only to climb stairs
Rana *et al*[6]	2015	46; M	Cervical and lumbar	Arthritis in knees, hips, and vertebral column; tingling, pain, and numbness in feet bilaterally; weakness in BUE	Medical history	Bilateral shoulder replacement (no spinal treatment reported)	Not available	Increased ROM in the shoulder joints
Onda *et al*[8]	2012	55; M	T9-L1	Numbness and progressive weakness in BLE; hyperreflexia in patellar and Achilles tendons bilaterally; Babinski sign (+); cremasteric reflex (−); Beevor sign (+); mild bladder dysfunction	Medical history (histologic confirmation)	Selective posterior decompression at T9-L1 without fusion	20 mo	Full recovery of motor and sensory functions; walks unassisted

TABLE 1 (*Continued*)

First Author	Year	Age (yr); Sex	Level of Compression	Presentation	Diagnosis of Alkaptonuria Made By	Treatment	Follow-up	Outcomes
Reddy *et al*[11]	2012	50; M	L4–5	LBP; loss of lumbar lordosis; extensor hallucis longus weakness bilaterally; reduced sensation over L4 and L5 dermatomes; slow deep-tendon reflexes in BLE; claudication	Medical history (histologic confirmation)	L4–5 laminectomy	1 yr	Improvement in claudication distance from 10 to 500 m
Wilke and Steverding[14]	2009	61; M	C3–5	Not available	Diagnosed 7 years after presentation with myelopathy; dark urine, cardiac defects, pigmented sclera and cartilage, and histologic confirmation	C4 ventral corpectomy; C3-5 discectomies	7 yr	No mention of spine-related outcomes
Akeda *et al*[7]	2008	65; M	T8–9	Hip pain; progressive weakness in BLE; sensory loss distal to the inguinal region; hyperreflexia in patellar and Achilles tendons bilaterally; bladder incontinence	Medical history (histologic confirmation)	Bilateral laminectomy at T8–9 with fusion	10 mo	Normal strength in BLE; ambulates with crutches; recovery of most of sensory loss
Mavra *et al*[13]	1999	55; M	C3–7	LBP; pain in right hip and both knees; numbness, paresthesia, weakness, spasticity and absent tendon reflexes in all limbs; Babinski sign (+)	Pigmented ear cartilage; radiographic changes; dark urine; urinary HGA testing	PT; unspecified pain medication	Not available	Lost to follow-up
Kusakabe *et al*[12]	1995	67; M	C1–2	Numbness, hypoesthesia and hypalgesia in C6–8 dermatomes; gait disturbance; hyperreflexia in all limbs	Radiographic changes; urinary HGA testing	C1 laminectomy and posterior occipitoaxial arthrodesis	34 mo	Numbness in hands relieved; ability to walk improved

BLE indicates bilateral lower extremities; BUE, bilateral upper extremities; F, female; HGA, homogentisic acid; JOA, Japanese Orthopaedic Association; LBP, low back pain; M, male; PSF, posterior spinal fusion; PT, physical therapy; ROM, range of motion; TL, thoracolumbar.

osteophyte formation (resulting in so-called "pseudo-blocked" vertebrae), and spinal deformity, but a lack of ligamentous calcification.[7,19] The latter is particularly helpful in making the distinction from ankylosing spondylitis or diffuse idiopathic skeletal hyperostosis.[19] If alkaptonuria is suspected, then urinary HGA testing can be used to confirm the diagnosis.[20]

Although the diagnosis of alkaptonuria with ochronotic spondyloarthropathy is an important one to make for many reasons, no effective disease-modifying treatment is available. Phornphutkul *et al*[1] showed that although nitisinone, an inhibitor of the HGA-producing enzyme 4-hydroxyphenylpyruvate dioxygenase, can significantly decrease HGA levels, it also causes concerning elevations in plasma tyrosine concentration. Furthermore, administration of high-dose vitamin C, in an attempt to block the oxidative process leading to HGA polymer formation, has repeatedly been shown to be ineffective.[1,21] Dietary restriction of the amino acids phenylalanine and tyrosine, in addition to being impractical, also seems to have minimal effect on HGA production in adults.[22] Therefore, the treatment of patients with alkaptonuria-associated myelopathy should rely solely on management of the myelopathic symptoms.

Of the 11 patients presented here or identified in the literature, 2 were treated nonoperatively, 8 were treated with spinal surgery, and 1 patient's treatment was not discussed. One patient was treated nonoperatively with physical therapy, neuromuscular stimulation, and pregabalin.[9] After 4 weeks of treatment, pain and neurologic symptoms had decreased substantially and ambulation had improved so the patient could walk with the aid of a crutch. The other patient treated nonoperatively, with physical therapy and unspecified pain medication, was lost to follow-up.[13] Eight patients underwent surgical decompression of the spinal cord. In seven of these patients, including the patient presented here, substantial improvement in the patient's condition was reported, with one patient experiencing complete neurologic recovery and return to unassisted ambulation.[7,8,10–12,15] Spine-related outcomes were not discussed for the other patient treated with surgery.[14] For the remaining patient, treatment of the myelopathy was not discussed.[6] The longest period of follow-up was 7 years. Thus, based on these pooled and mostly short-term outcomes, the use of symptomatic treatment and, particularly, surgical decompression is recommended for patients with alkaptonuria presenting with myelopathy. However, because ochronotic spondyloarthropathy is progressive and currently incurable, progression or recurrence of the myelopathy is possible and long-term outcomes may be less favorable.

CONCLUSION

Alkaptonuria can cause ochronotic spondyloarthropathy and, in rare cases, myelopathy. Conversely, alkaptonuria is even more rarely the cause of myelopathy in a patient without a known diagnosis of alkaptonuria. In the patient presenting with spinal cord compression of unknown cause, the characteristic pattern of symptoms and radiographic findings, coupled with urinary HGA testing, may make the diagnosis of ochronotic spondyloarthropathy. Treatment of alkaptonuria-associated myelopathy is largely surgical but can substantially improve quality of life for such patients over the short term.

➢ Key Points

- ❑ Alkaptonuria is an autosomal recessive genetic disorder in which high levels of HGA are produced and deposited in cartilage, ligaments, and menisci.
- ❑ Involvement of the spine can present as myelopathy in rare cases.
- ❑ In a patient presenting with myelopathy but without a history of alkaptonuria, the diagnosis of alkaptonuria may be made on the basis of characteristic symptoms, radiographic findings, and urine testing.
- ❑ No disease-modifying treatment exists for alkaptonuria, but symptomatic treatment of myelopathy, particularly surgical decompression, can substantially increase patients' quality of life.

References

1. Phornphutkul C, Introne WJ, Perry MB, et al. Natural history of alkaptonuria. *N Engl J Med* 2002;347:2111–21.
2. Fernandez-Canon JM, Granadino B, Beltran-Valero de Bernabe D, et al. The molecular basis of alkaptonuria. *Nat Genet* 1996;14:19–24.
3. Garrod AE. The incidence of alkaptonuria: a study in chemical individuality. 1902. *Mol Med* 1996;2:274–82.
4. Mannoni A, Selvi E, Lorenzini S, et al. Alkaptonuria, ochronosis, and ochronotic arthropathy. *Semin Arthritis Rheum* 2004;33:239–48.
5. Hamdi N, Cooke TD, Hassan B. Ochronotic arthropathy: case report and review of the literature. *Int Orthop* 1999;23:122–5.
6. Rana AQ, Saeed U, Abdullah I. Alkaptonuria, more than just a mere disease. *J Neurosci Rural Pract* 2015;6:257–60.
7. Akeda K, Kasai Y, Kawakita E, et al. Thoracic myelopathy with alkaptonuria. *Spine (Phila Pa 1976)* 2008;33:E62–5.
8. Onda A, Kikuchi S, Yabuki S, et al. A case of thoracic myelopathy secondary to alkaptonuric spondylosis. *J Orthop Sci* 2012;17:495–9.
9. Bozkurt S, Aktekin L, Ugurlu FG, et al. An unusual cause of myelopathy: ochronotic spondyloarthropathy with positive HLA B27. *Am J Phys Med Rehabil* 2017;96:e206–9.
10. Li N, Tian W, Yuan Q, et al. Cervical spondylotic myelopathy due to the ochronotic arthropathy of the cervical spine. *J Korean Neurosurg Soc* 2016;59:65–8.
11. Reddy R, Vijayasaradhi M, Biswal D. Focal ligamentum flavum hypertrophy with ochronotic deposits: an unusual cause for neurogenic claudication in alkaptonuria. *Asian Spine J* 2012;6:148–51.
12. Kusakabe N, Tsuzuki N, Sonada M. Compression of the cervical cord due to alcaptonuric arthropathy of the atlanto-axial joint. A case report. *J Bone Joint Surg Am* 1995;77:274–7.
13. Mavra M, Chadha G, Henein MM, et al. Alcaptonuria with myelopathy and neuropathy. *Med Principles Pract* 1999;8:73–6.
14. Wilke A, Steverding D. Ochronosis as an unusual cause of valvular defect: a case report. *J Med Case Rep* 2009;3:9302.

15. Rahimizadeh A, Soufiani H, Hassani V, et al. Symptomatic pseudarthrosis in ochronotic spine: case report. *J Neurosurg Spine* 2017;26:220–8.
16. Sharma RR, Ravi R, Bhama BA, et al. Cervico-medullary compression secondary to ochronotic arthritis affecting cranio-vertebral joints syndesmo-dental ochronotic arthritis. *J Postgrad Med* 1988;34:253–7.
17. Srinivasan V, Natarajan N, Subramanian G. A case of alkaptonuric ochronosis producing spinal cord compression. *J Assoc Physicians India* 1971;19:49–51.
18. Ranganath LR, Jarvis JC, Gallagher JA. Recent advances in management of alkaptonuria (invited review; best practice article). *J Clin Pathol* 2013;66:367–73.
19. Laskar FH, Sargison KD. Ochronotic arthropathy. A review with four case reports. *J Bone Joint Surg Br* 1970;52:653–66.
20. Introne WJ, Gahl WA. Alkaptonuria. In: Adam MP, Ardinger HH, Pagon RA, editors. et al. *GeneReviews*. Seattle, WA: University of Washington; 2003.
21. Wolff JA, Barshop B, Nyhan WL, et al. Effects of ascorbic acid in alkaptonuria: alterations in benzoquinone acetic acid and an ontogenic effect in infancy. *Pediatr Res* 1989;26:140–4.
22. De Haas V, Carbasius Weber EC, De Klerk JB, et al. The success of dietary protein restriction in alkaptonuria patients is age-dependent. *J Inherit Metab Dis* 1998;21:791–8.