WHEN TO CONSIDER ALKAPTONURIA (= HOMOGENTISATE 1,2-DIOXYGENASE [HGD] DEFICIENCY)

Clinical signs appear and progressively worsen from the second decade onwards, leading to progressive spondyloarthropathy and multi-organ involvement
Aspecific treatment is available

Clinical signs

MAIN PRESENTING SIGNS

Abnormal colour of the urine

+/- earwax and sweat

Main symptom in the paediatric age group

May be present early, from the first days of life

Urine turns dark/black a few minutes after being passed and coming into contact with atmospheric oxygen: black stains may be visible in infants' nappies

+/- hyperpigmentation of earwax and sweat (may stain clothing)

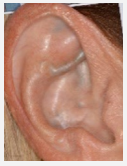
False proteinuria may be present[2]

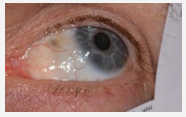
Abnormal pigmentation of connective tissue (= ochronosis)

Onset in young adults, preceding joint symptoms, with gradual worsening

Abnormal pigmentation:

- ochre/brown/black patches on the **conjunctiva and sclera**
- slate-blue patches on the **external ear** (especially the concha and antihelix), overlying the cartilage, +/- on the skin of the hands (overlying the subcutaneous tendons) or on the skin between the thumb and index finger
- black discolouration of bone and cartilage





Musculoskeletal involvement

Initially axial involvement around the age of 30, followed by progressive "peripheral ochronotic" arthropathy around the age of 40

Spinal pain (lumbar and thoracic, then cervical) and **spinal stiffness** initially, followed by:

Involvement of the large joints (mainly the knees and shoulders, but also the hips, elbows and wrists)

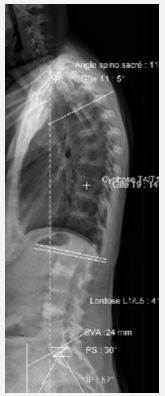
- **Chronic joint and spinal pain with both mechanical and inflammatory characteristics, ankylosis**
- Joint destruction

Possible **fractures** (vertebral and long bones)

Osteoporosis

Enthesopathy, tendon and muscle rupture

Black discolouration of cartilage and bone observed during possible surgical procedures



COMPLICATIONS

Genitourinary involvement

Renal and bladder stones[1]

Prostatic calculi

Rare report of mild renal impairment

Cardiac involvement

Valvular involvement, mainly aortic: calcifications progressing to stenosis, +/- valvular regurgitation

Possible arrhythmia

Other manifestations (rare)

Salivary and gallbladder stones

Pigmentary glaucoma

Additional tests

Spinal X-ray: characteristic **degeneration** and **dense calcification of the intervertebral discs**, particularly in the lumbar region, vertebral fusion, risk of spinal canal stenosis

Ligament ossification

Osteophytes

Specialist assessment

Alcaptonuria?

Specialist assessment
in parallel with the investigation of other possible differential diagnoses[3]

Measurement of urinary homogentisic acid → **Elevation: pathognomonic finding**

+/- subsequent Genetic testing (*HGD* gene)
by a specialist centre

Seek urgent specialist opinion from an Expert centre (Reference/Expert Centre for Rare Diseases): https://www.filiere-g2m.fr/annuaire/

Initial assessment, specialist management and disease-specific treatment (indications/initiation) coordinated by the Expert Centre

Genetic counselling, family screening in a specialist centre

For more information:
PNDS under preparation: French National Authority for Health - National diagnostic and care protocol (PNDS): (has-sante.fr)

Specialist medical opinion and reference laboratory

[1]Possible from childhood
[2]Interference of homogentisic acid with certain proteinuria assays. Normalisation under treatment.
[3]Main differential diagnoses: other causes of dark urine (e.g. porphyria), other causes of spondyloarthropathy, particularly ankylosing spondylitis

Maladies rares Héréditaires du Métabolisme
Filière nationale de santé