WHEN TO CONSIDER X-LINKED ADRENOLEUKODYSTROPHY (ALD)

ALD primarily affects boys and men. There are three distinct clinical forms that may occur in isolation or in combination: Cerebral ALD (CALD), Addison's disease (primary adrenal insufficiency) and adrenomyeloneuropathy (AMN). In women, forms other than AMN are very rare

Clinical signs

Cerebral ALD (CALD) [1]

♂ Onset: from childhood to adulthood (as early as 2.5 years and at any age in adults)

Rapidly progressive inflammatory leukodystrophy

Initially normal development

Insidious neuro-behavioural changes

- **Decline in school performance, visuomotor and visuospatial difficulties Impaired attention, reasoning and behaviour (children, adolescents)**
- Depressive symptoms, cognitive decline, impulsivity, addiction (adults)

Rapid neurological deterioration (cognitive and motor):

- Reduced visual and hearing acuity, psychomotor regression (children)
- Tetraparesis, cerebellar syndrome, seizures, dysphagia, behavioural disturbances, dementia (children, adolescents, adults)

Progression to a bedridden state

Additional tests

Brain MRI (children/adults, CALD):
Confluent T2/FLAIR hyperintensities and T1 hypointensities with enhancement after gadolinium injection during the inflammatory phase
Most often begins in the corpus callosum (splenium extending to the parieto-occipital lobes, or genu to the frontal lobes).
More rarely, onset is in the pyramidal tracts, visual pathways or cerebellum

Adrenomyeloneuropathy (AMN)

♂ Onset: 20s–30s, ♀ often after age 40

Slowly progressive myeloneuropathy

Gait disturbances
(due to spastic paraparesis and proprioceptive ataxia)

Bladder sphincter dysfunction

Peripheral neuropathy with dysaesthesia

Additional tests

Spinal MRI (adults, myelopathy):
Possible hyperintensity of the corticospinal tracts low intensity on FLAIR sequences, no contrast uptake, progressive spinal cord atrophy

Addison's disease (primary adrenal insufficiency)

♂ Onset: from childhood to adulthood (often before age 40)

Often precedes neurological manifestations

Skin hyperpigmentation

Occasional episodes of acute adrenal insufficiency

+/- testicular involvement

Additional tests

Markedly reduced cortisol levels, elevated ACTH

Specialist assessment

X-linked adrenoleukodystrophy?

Prompt neurometabolic specialist opinion
CALD: THERAPEUTIC INTERVENTION ONLY POSSIBLE AT A VERY EARLY STAGE OF CEREBRAL INVOLVEMENT

Specialist assessment
in parallel with the investigation of other possible differential diagnoses[2]

Plasma very long-chain fatty acids (VLCFAs):
(elevated levels support the diagnosis[3])

Confirmatory genetic testing by a specialist centre (*ABCD1* gene)

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

https://brain-team.fr/les-membres/les-centres-de-reference/leucodystrophies/

Initial assessment, specialised care and implementation of specific treatments (where indicated), coordinated by an Expert Centre for paediatric or adult forms of leukodystrophy:
https://brain-team.fr/les-membres/les-centres-de-reference/leucodystrophies/

Refer to the national diagnostic and care protocol (PNDS): Haute Autorité de Santé [HAS, French National Authority for Health] - Adrenoleukodystrophy (has-sante.fr)

Genetic counselling and family screening at a specialist centre: Strongly recommended screening of female carriers and boys/men potentially affected by CALD and/or Addison's disease

Specialist medical opinion and reference laboratory

[1] Most severe form of ALD, which can result in a bedridden state within months and premature death. Cerebral ALD is categorised as childhood (C-CALD), adolescent (Ado-CALD) or adult onset (A-CALD)
[2] Other causes of adrenal insufficiency, leukodystrophy or leukoencephalopathy (inflammatory, neoplastic or infectious), other causes of spastic paraparesis
[3] VLCFA levels may be normal in women and may also be elevated in other pathological conditions (dyslipidaemia, other peroxisomal disorders)

BRAIN-TEAM Filière Nationale de Santé Maladies rares du système nerveux central

G2M Maladies rares Héréditaires du Métabolisme Filière nationale de santé