Diagnosis of Cerebrotendinous Xanthomatosis: identifying a rare but treatable hereditary disease.

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BACKGROUND

- Cerebrotendinous Xanthomatosis (CTX) is an autosomal-recessive disorder of lipid storage caused by mutations in the CYP27A1 gene, encoding for a sterol 27-hydroxylase, leading to **increased deposition of cholesterol in multiple tissues**.
- Symptoms begin in **adolescence or young adult life**, but mean age at diagnosis is 35 years.
- **Clinical features: early non-neurological manifestations** (tendon xanthomas, juvenile cataracts and osteoporosis, cardiovascular involvement), and **adult-onset neurological dysfunctions** (spastic ataxia, dementia, psychiatric disorders, peripheral neuropathy).
- MRI neuroimaging: **cerebellar atrophy** and **hyperintensity of white matter and dentate nuclei**.
- Elevated levels of **serum cholestanol** might be detected.
- Early and long-term **treatment with chenodeoxycholic acid (CDCA) can halt neurological symptoms progression**.

CASE REPORT

- A 41-year-old man with vague diagnosis of "inherited neurodegenerative disease".
- **Clinical history:** JUVENILE CATARACTS (surgically treated), PROGRESSIVE MENTAL RETARDATION, early behavioural changes, several bone fractures, BILATERAL ACHILLES TENDONITIS, PROGRESSIVE GAIT ATAXIA.
- At the age of 36 years hospitalized in a nursing home due to relentless progression of psychiatric and cognitive impairment.
- **At admission**: MUTACISM, SPASTIC TETRAPLEGIA, BILATERAL PESCAVUS, HEAD DYSTONIA AND COMPLETE DYSPHAGIA.

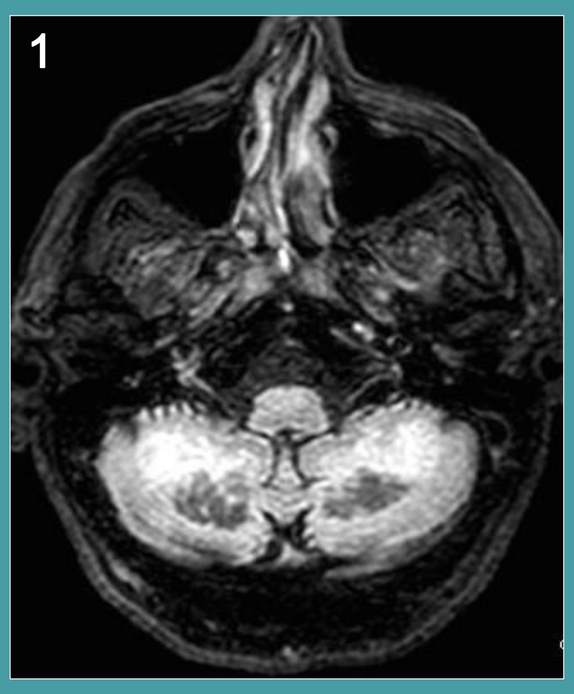
- **Family History (fig 4)**: *Consanguineous* parents (first cousins), with no relevant diseases. Six siblings: one stillborn male, three healthy middle-aged sisters.
- A sister who *dead* when she was 51 years old with **cataract, pescavus, gait disturbance and mental retardation**.
- A *55-years-old sister*, hospitalized in nursing home, with history of **cataract, pescavus, moderate mental retardation and spastic paraparesis. Still possible deambulation.**

- **Genetic Testings:**
- SPG4, SPG7 and Freidreich's Ataxia negative.
- CYP27A1 gene: homozygous splicing mutation c.1263+1A>G → diagnostic of **CEREBROTENDINOUS XANTOMATHOSIS (CTX)**.
- Genetic testing of other family members revealed the *same homozygous mutation in the hospitalized sister*, and a status of *asymptomatic carriers in two healthy sisters* (fig. 4).

Exams

- EMG: sensory-motor polineuropathy.
- EEG: no alterations.
- Electrocardiogram and echocardiography: normal.
- Abdomen US: gallbladder cholesterol polyps.

- **Brain MRI**: brainstem and cerebellar atrophy, lesions in dentate nuclei, cerebral and cerebellar white matter. Hyperintensity of whole cortico-spinal tracts **(Fig 1,2,3).**



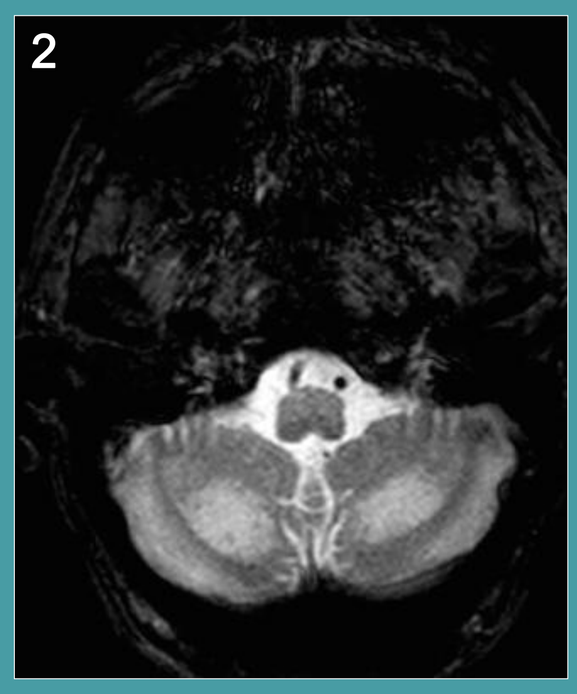
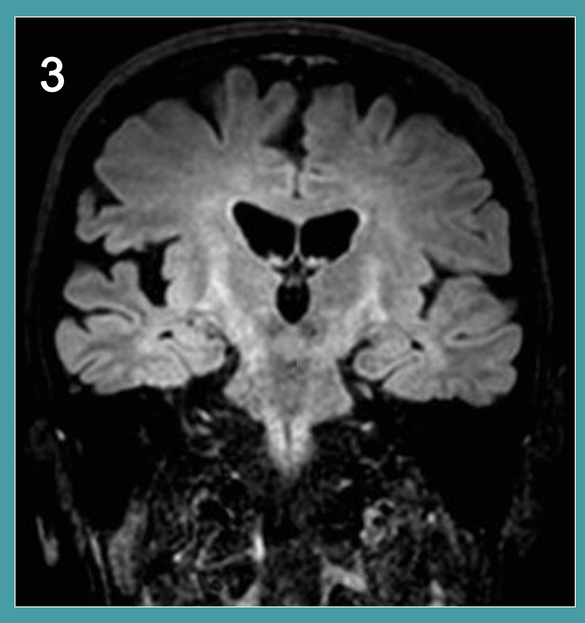


Fig 1-2. Flair and Gradient-echo images: cerebellar atrophy and hyperintensity of cerebellar white matter and dentate nuclei.

Fig 3. Flair image: Diffuse brain atrophy and bilateral hyper-intensity of cortico-spinal tract.



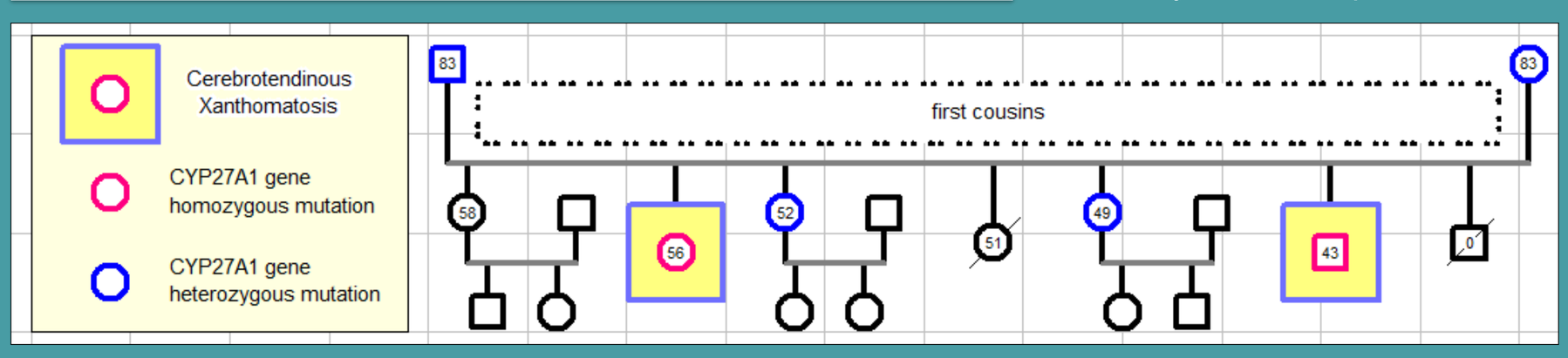


Fig 4. Family pedigree: affected subjects (homozygous mutation, *red*) and two asymptomatic sisters (heterozygous mutation, *blue*).

DISCUSSION and CONCLUSIONS

- Clinical heterogeneity of CTX → frequent diagnostic delay of several years.
- Report of two siblings, with different clinical course of CTX, who remained undiagnosed till a significant disability.
- Since CDCA treatment may halt progression, the diagnosis of CTX should be suspected in all cases characterized by combinations of **EARLY CATARACT, MENTAL RETARDATION and SPASTIC ATAXIA, PARTICULARLY ON A BACKGROUND OF TENDON XANTHOMAS.**