

Visual System Involvement in Cerebrotendinous Xanthomatosis: the role of Dentate Nucleus on eye movement control

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INTRODUCTION

Cerebrotendinous Xanthomatosis (CTX) is an autosomal-recessive lipid-storage disorder due to mutation of the CYP27A1 gene, characterized by systemic, neurological and psychiatric signs. Brain MRI signal changes of cerebellar dentate nuclei (DN) are considered peculiar findings. We aimed to describe specific afferent and efferent visual system changes in a CTX population. Eye movements results were interpreted according to the presence (CTXwD) or absence (CTXnD) of MRI DN abnormalities.

METHODS

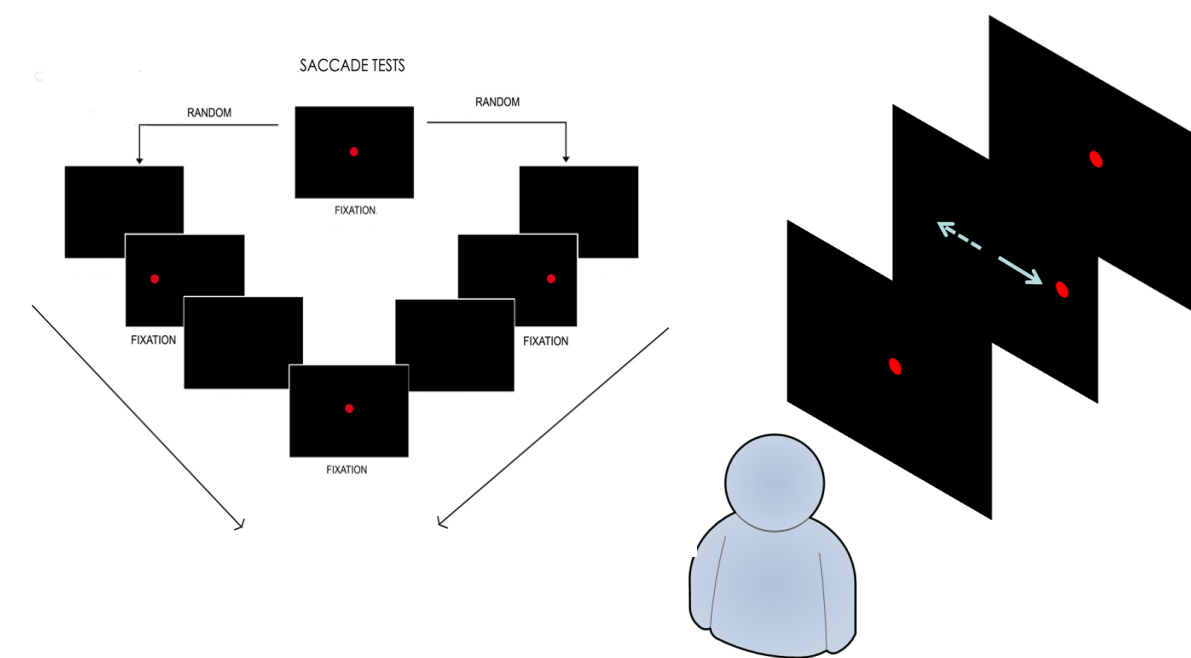
Subjects

Group	N. pts	Mean age	Age range	Sex
CTX	19	41±13.3	18-63	10F; 9M
CTXwD	13	46±11.6	27-63	6F; 7M
CTXnD	6	31±11.5	18-53	4F; 2M

Tasks and eye movements recording

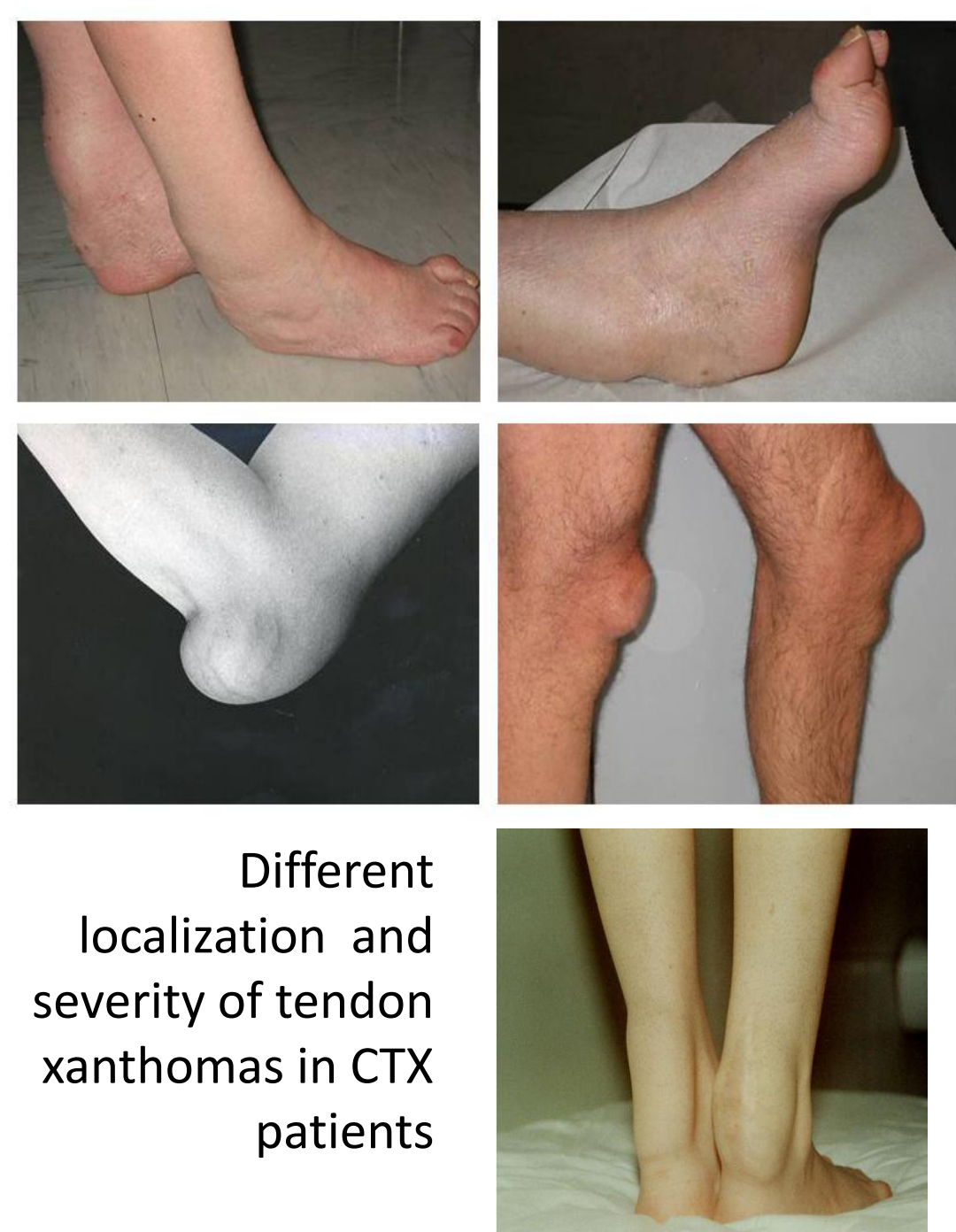
Data obtained using an infrared eye-tracker system (ASL 6000). A 9-point calibration performed. Visual stimulus presented on a 31x51 cm LCD screen. Sampling frequency: 240Hz. Data compared with 19 age-matched controls. Two tasks performed:

- Visually-guided horizontal ($\pm 10^\circ / 18^\circ$) and vertical (up/down 8°) saccade
- Antisaccade tasks at $\pm 10^\circ / 18^\circ$
- Fixation point: 1500-2500 ms

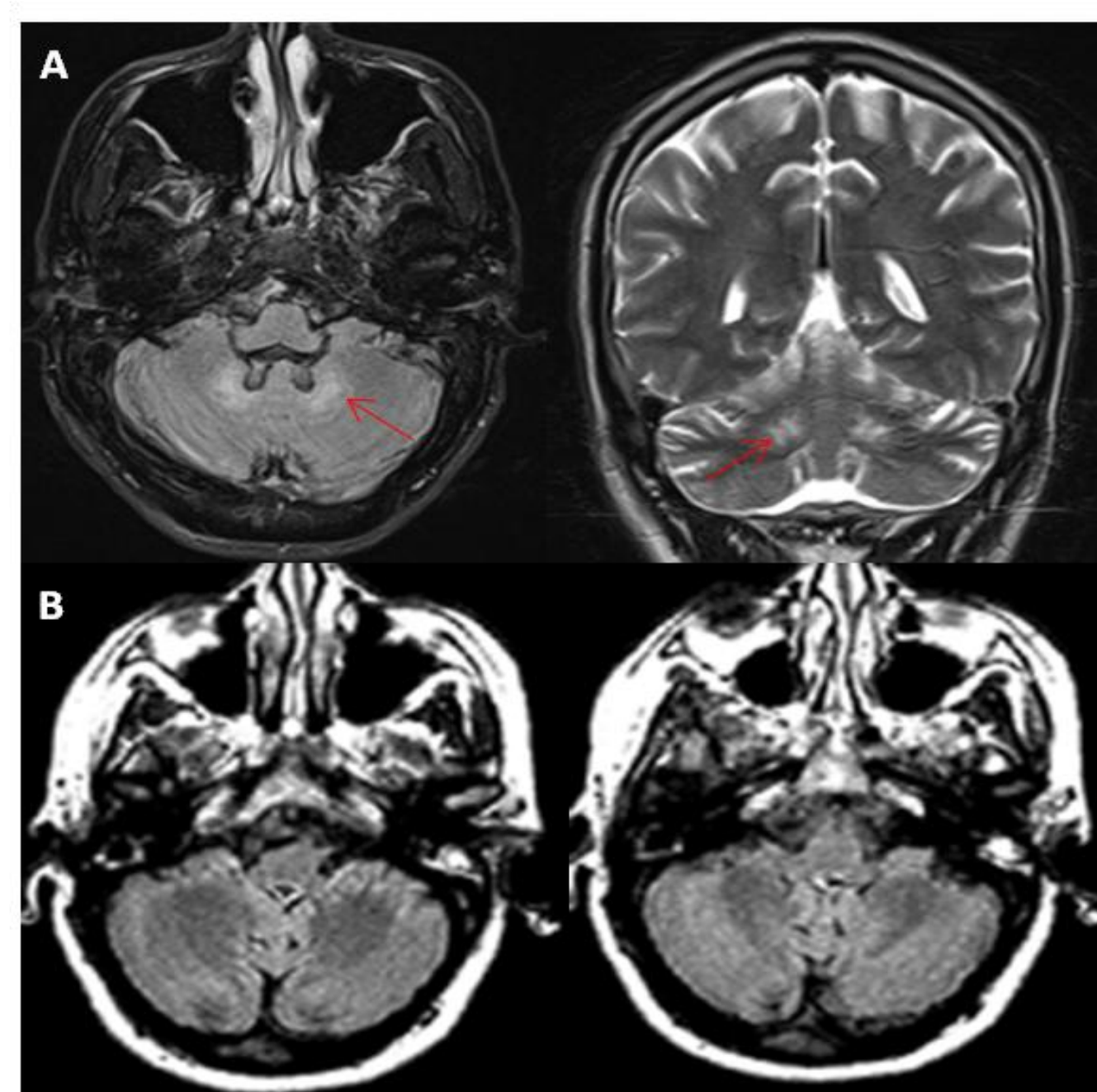


RESULTS

CLINICAL AND NEURO-OPHTHALMOLOGICAL FINDINGS



Different localization and severity of tendon xanthomas in CTX patients



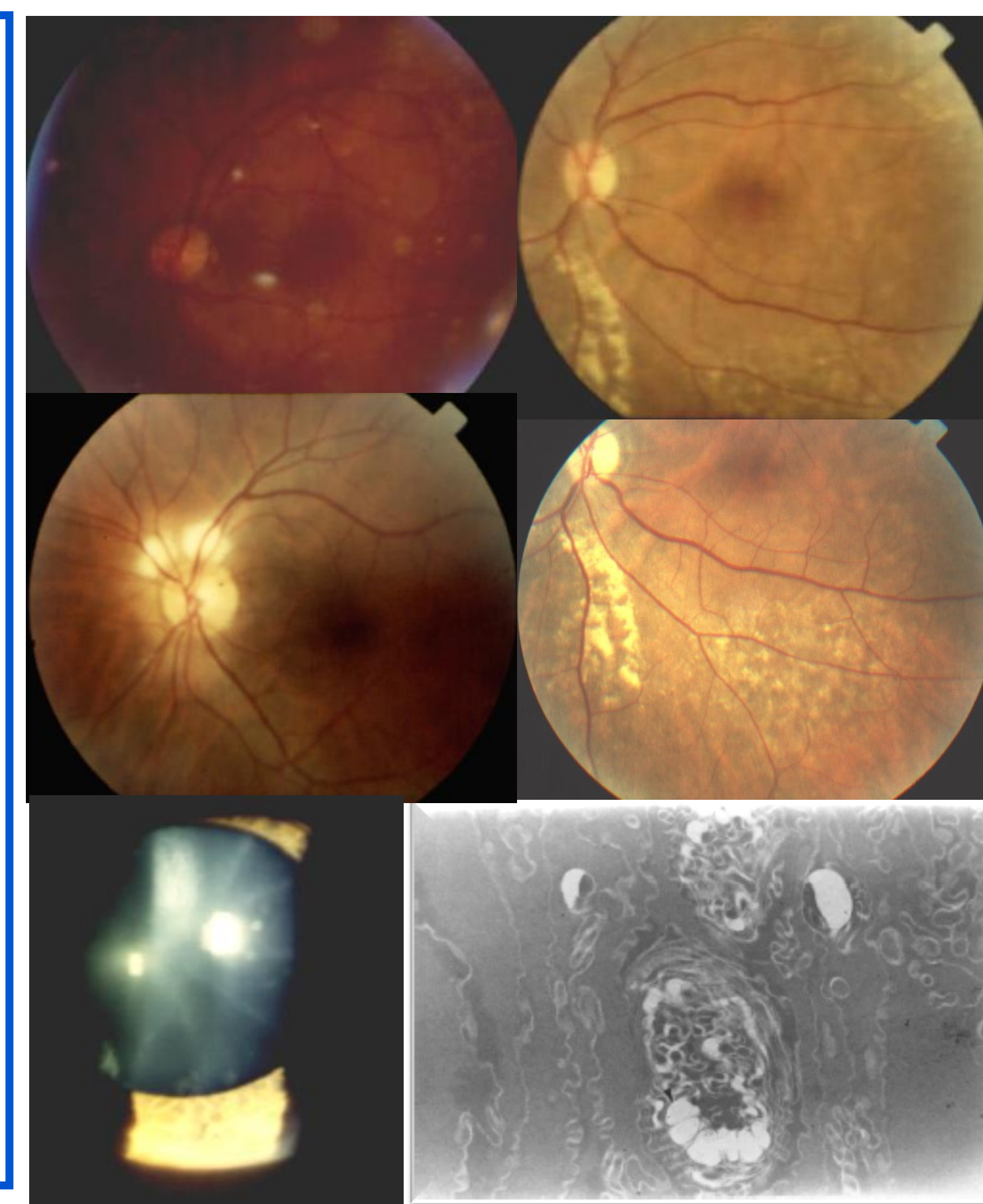
Brain MRI. (A) Brain MR of a CTX patient showing presence of bilateral DN hyperintensity (arrows) on axial FLAIR image (left) and coronal T2-weighted image (right). (B) Brain MR of a CTX patient showing absence of DN signal alteration on axial FLAIR images

Common neurological features:

- Cataracts, surgically treated in 15 pts
- Tendon xanthomas
- Cognitive and psychiatric disturbances
- Pyramidal spasticity
- Cerebellar symptoms

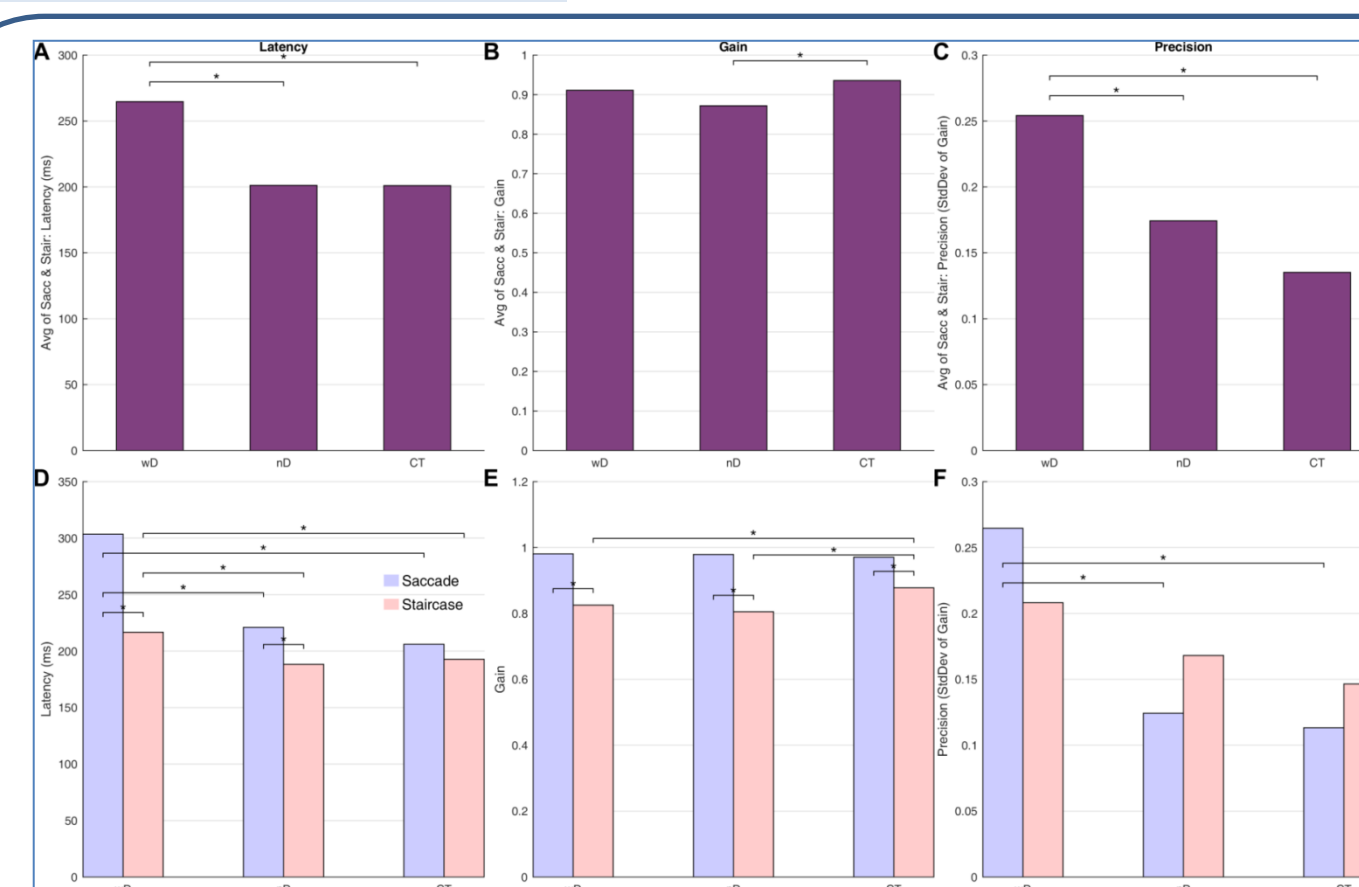
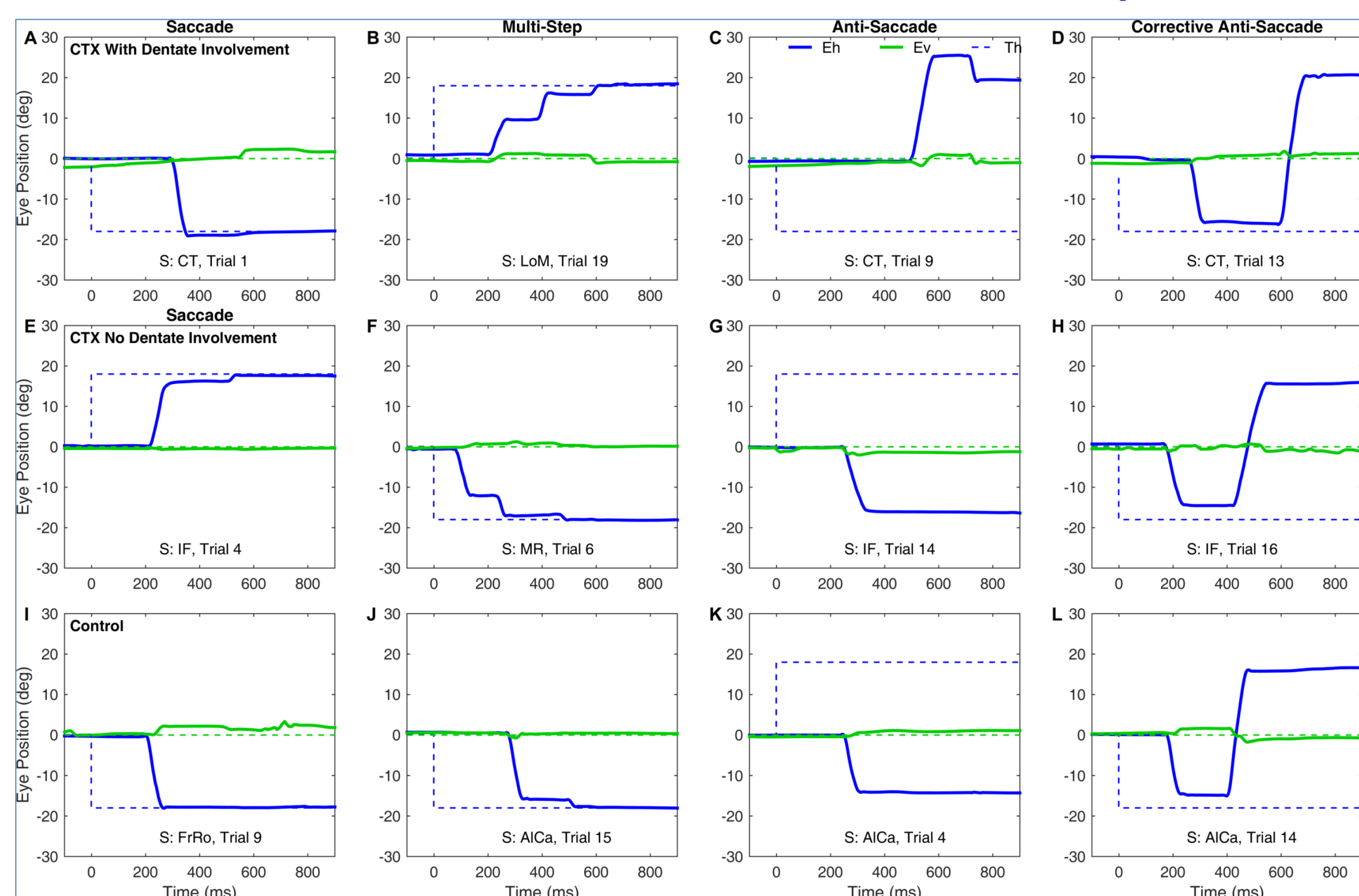
Eye abnormalities

- Cataracts
- Secondary opacities
- Fuctuating yellowish vitreous flakes
- Ophthalmoscopic anomalies:
 - Bilateral OD pallor
 - Retinal vessel sclerosis
 - Small hard exudates with pigmentary changes
 - Cholesterol-like deposits along the vascular arcades
 - Myelinated nerve fibers
- FAG: Persistent hypofluorescence of the optic disk



EYE MOVEMENTS ANALYSIS

Pro-saccades and antisaccades examples

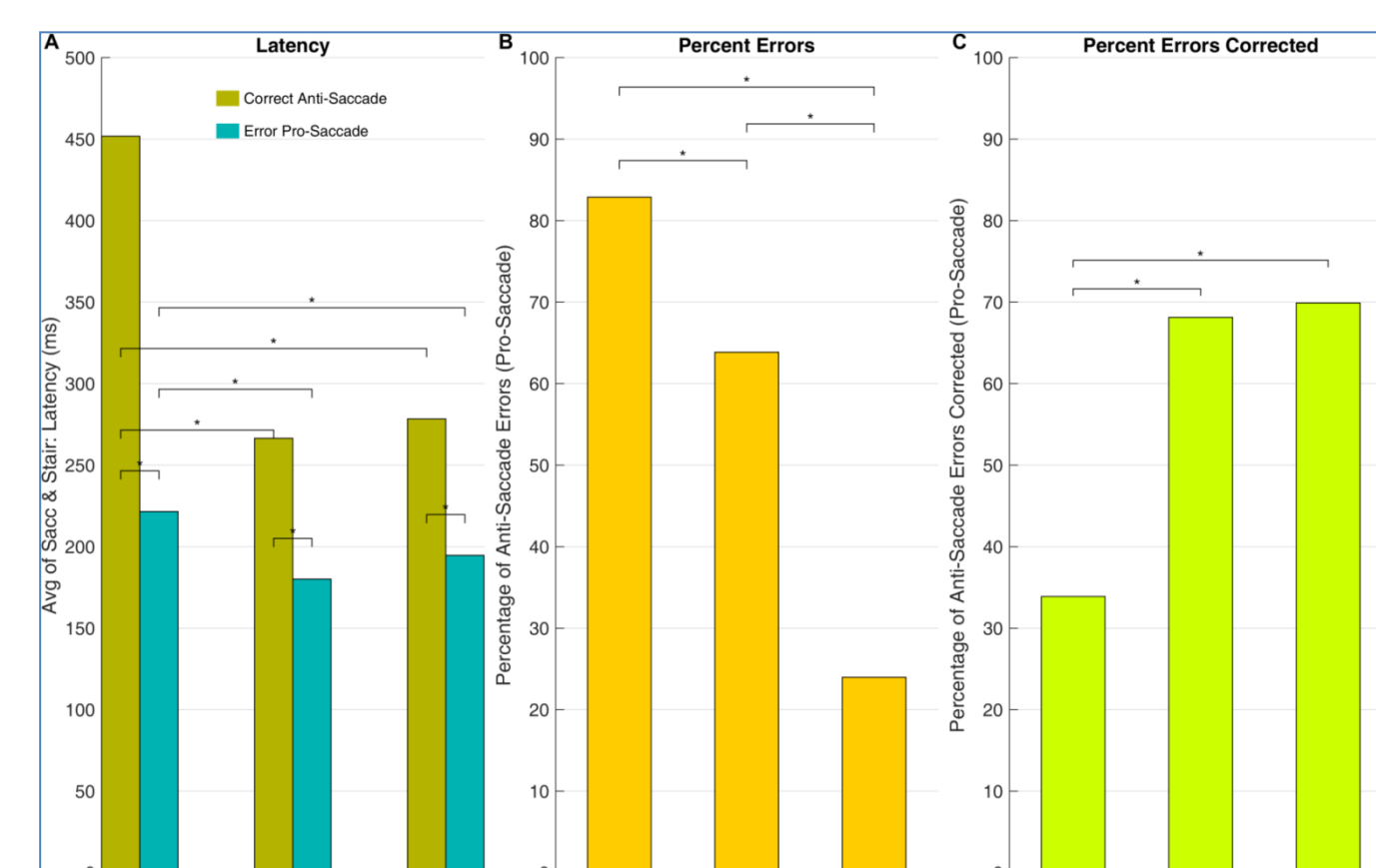


Prosaccade analysis

(A-C) Mean values of single-step and multistep saccades pooled together. (D-F) Blue bars: mean values of the single-step saccades; pink bars: mean values of the multistep saccades.

Antisaccade analysis

- (A) Mean latencies of correct antisaccades (olive) and erroneous prosaccades (teal)
- (B) Percentage of antisaccade errors
- (C) Percentage of corrections after erroneous prosaccades



CONCLUSIONS

Afferent system

The peculiar widespread abnormalities express an impairment of cholesterol metabolism in CTX, with higher levels of cholestanol.

Efferent system

- All CTX : well-spaced saccadic dynamics.
- All CTX: release of premature reflexive saccades.
- CTXwD: longer latencies, imprecise saccades and more frequent errors not followed by corrections.. .

All CTX

- Sparing of medial cerebellar structures
- Reduced inhibition from frontal areas on subcortical structures

DN damage

- Longer motor planning
- Lower precision

CONCLUSION

- Two cerebellar pathways for saccade amplitude:
 - Medial (vermis and fastigium) for accuracy
 - Lateral (DN and hemispheres) for precision