Neuro-ophtalmological manifestations in neurometabolic diseases: The eye is a window to the brain

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INTRODUCTION

Neuro-metabolic diseases (NMDs) represent a heterogeneous group of hereditary pathologies, with phenotypic variability. Neuro-ophthalmological manifestations in NMDs are frequent, and can be seen at any stage of the disease.

Therefore, their characterization is paramount in the diagnostic approach.

AIM

Our aim was to caracterize neuro-ophthalmological manifestations in NMDs.

METHODS

Retrospective descriptive study, conducted over a 19-year period (January 2004-January 2023), at the Child and Adolescent Neurology Department of the National Institute of Neurology in Tunis.

Inclusion criteria	Exclusion criteria	Non-inclusion criteria
• Age **< 18 years** at the time of diagnosis • **Confirmed NMD Ophtalmological** involvement due to the underlying NMD • Clinical follow-up of at least six months	• Insufficient ophtalmological investigations to confirm the opthalmological involvement • Missing data • Patients lost to follow-up	• Age **≥18 years** at the time of diagnosis • Non-confirmed NMD • **Ocular myopathies** • **Underlying eye condition** unrelated to the NMD

RESULTS

- 63 patients (59 unrelated families) included
- NMDs due to **complex molecule** metabolism were the most represented group (table 1)
- The most frequent neuro-ophthalmological manifestation was **optic neuropathy** (figures 1,2)
- Significant associations were noted between NMD and ophtalmological manifestations (figure 3)
- The neurovisual **outcome** was unfavorable for all patients except for those with treatable diseases (Biotinidase deficiency, Homocystinuria)

Optic neuropathy:
-Optic disc pallor: 40 % (n=25)
-Optic atrophy: 24% (n=15)

Retinal involvement:
-Retinitis pigmentosa : 11% (n=7)
-Cherry red spot: 11% (n=7)
-Macular dystrophy: 6% (n=4)
-Other: 6% (n=4)

Oculomotor disorders:
-Strabismus: 20% (n=13)
-Oculomotor palsy: 8% (n=5)

Nystagmus:
38% (n=24)

Lens involvement:
-Ectopia lentis: 6% (n=4)

Corneal involvement:
-Corneal deposits: 6% (n=4)
-Kayser Fleisher ring: 6% (n=4)

Figure 1: Ophtalmological manifestations in our patients

Neurometabolic disease classification		Number	Percentage
Complex molecules (n=45)	Accumulation *CLN, GM2, LDK, LDM, MPS, OLS,*	**31**	**49%**
	Defective synthesis *INAD*	11	17%
	Cell processing and trafficking *CDG syndrome*	3	5%
Small molecules	Intoxication *HCY, PKAN, Wilson*	10	16%
Energy defects: Mitochondrial defects *Leigh syndrome, mitochondriopathies, Biotinidase deficiency*		8	13%

Table 1: Neurometabolic diseases in our cohort
CDG: congenital disorder of glycosylation; CLN : ceroide lipofuscinosis ; INAD: infantile neuroaxonal dystrophy; GM2: GM2 gangliosidosis ; HCY: homocystinuria; LDK: Krabbe's leucodystorphy ; LDM : metachromatic leukodystrophy ; OLS: oligosaccharidosis, MPS : mucopolysaccharidosis ; PKAN : panthotenate-kinase associated neurodegeneration

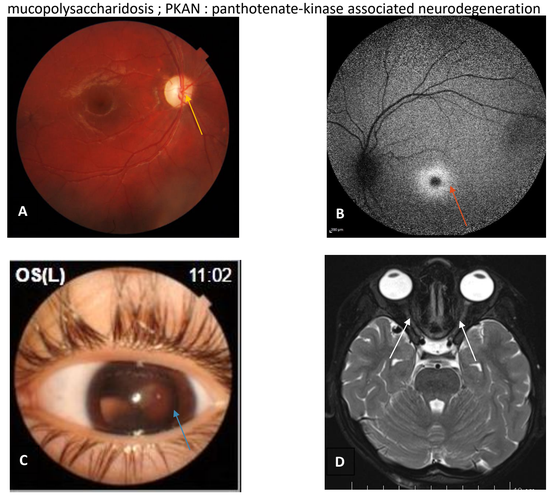

Figure 2 : Iconography of some ophtalmological manifestations in our patients
A: Fundoscopic examination showing optic disc pallor (yellow arrow)
B: Retinal photography showing a cherry red spot (red arrow)
C: Slit lamp photography showing ectopia lentis (blue arrow)
D: Axial T2 brain MRI showing bilateral extensive optic neuritis (white arrows)

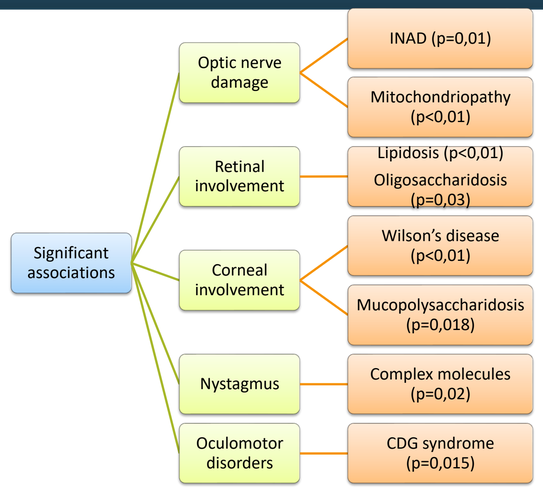

Figure 3: Associations between ophtalmological manifestations and NMD in our patients

DISCUSSION & CONCLUSIONS

Our study showcases the phenotypic heterogeneity of ophtalmological manifestations in NMD, in concordance with other studies (*Poll-The & al, 2011*). Specific manifestations such as retinal cherry red spot, ectopia lentis and Kayser Fleisher ring are key features in the aetiological orientation (*Rjappa & al, 2010; Whang HP & al, 2022)*. Neurovisual outcome depends on the NMD and precocity of management. The collaboration between neurologists and ophthalmologists is essential for the diagnostic approach and multidisciplinary management of NMDs. While treatable diseases should always be rulled-out first, genetic counselling remains crucial in all cases. This will reduce infantile morbidity and mortality and improve patients' overall quality of life.