



PROJECT Artificial Intelligence in the management of Dominant Optic Atrophy

Supervisor: _____ Dott. Piero Barboni _____

Title: _____ Medicina molecolare _____

Curriculum: _____ Medicina clinica e sperimentale _____

Link to the personal page of the University or relevant hospital site website: _____

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Dominant Optic Atrophy (DOA) is the most common inherited optic neuropathy in the worldwide general population (3 cases per 100,000 individuals). Approximately 70% of affected individuals have a pathogenetic mutation in the OPA-1 gene (3q28-q29), although other mutations have also been associated with this condition (ACO2, AFG3L2, WFS-1) (1,2). Specifically, the nuclear gene OPA-1 encodes for a multifunctional mitochondrial protein, closely linked to mitochondrial activity: it is crucial in mitochondrial inner membrane fusion, contributing to mitochondrial cristae morphology, in maintaining mitochondrial DNA integrity, and regulates the efficiency of the respiratory chain and calcium ion exchange. (2,3). Pathogenetic mutations of DOA can therefore have a multitude of effects: they can alter proper mitochondrial structure, leading to mitochondrial network fragmentation and promoting mitophagy activation, decrease oxidative phosphorylation efficiency, and facilitate progressive accumulation of mitochondrial DNA mutations, particularly favoring the appearance of multiple deletions in post-mitotic tissues. All cells are carriers of the mutation in DOA, but only specific tissues such as retinal ganglion cells are damaged, compromising visual functionality with optic nerve atrophy. The most plausible hypothesis is that smaller-sized retinal ganglion cells, which shaped the parvocellular component, have very long axons lacking myelin coating in their intra-retinal portion with particularly high metabolic demands. This results in asymmetric distribution of mitochondria along the axonal pathway, with mitochondria tightly "packaged" in the portion preceding the lamina cribrosa. The preferential involvement of the papillomacular bundle reflects the vulnerability of these neurons, especially due to the unfavorable ratio between axonal surface



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and volume, which does not allow accommodating the required number of mitochondria efficiently. DOA manifests with symmetric and bilateral visual loss associated with dyschromatopsia and centrocecal scotoma (4,5). Onset age may vary, but it commonly manifests in youth or early adulthood. Visual symptoms may progress slowly over time, leading to marked visual loss in advanced stages of the disease. However, structural changes may not directly correlate with visual symptoms, generating a function-structure mismatch. In this regard, optical coherence tomography (OCT) provides essential data in the management of inherited optic neuropathies and their differential diagnoses (6,7). The ganglion cell layer thickness (sum of the inner plexiform layer and ganglion cell layer, GC-IPL) is severely reduced with progression throughout the macular area. Additionally, retinal nerve fiber layer (RNFL) thickness is equally reduced in sectors connected to the papillomacular bundle, namely temporal and inferior quadrants. A particular issue posed by modern OCT machines is the so-called "floor effect," i.e., the difficulty of the instrument to differentiate retinal ganglion cell thickness values near the resolution limit. Consequently, the machine does not differentiate changes beyond a certain critical value. To overcome this limit, our group has recently studied, in a large cohort of DOA patients, the correlation between the numerical thickness data of ganglion cells (positioning the ETDRS grid at the macular level to discriminate between different sectors) and the functional parameters of visual acuity (8). A direct proportionality between mean thickness of cells and visual acuity was clearly evident. Furthermore, sectorial analysis revealed that the inner superior and outer superior thickness correlated more strongly with visual function. This confirms two important hypotheses: the early and preferential involvement of the inter-papillomacular bundle (inner sectors) and in the second phase of progression and deepening of damage in the outer sectors with further worsening of visual acuity. The next step involves integrating OCT structural parameters with other functional parameters (e.g., computerized perimetry) and reworking the diagnostic pathway through machine-learning protocols.

Rationale and hypothesis

Dominant optic atrophy is a heterogeneous condition with childhood onset, often presenting with severe visual involvement and consequently significant impact on both familial and social aspects. A precise phenotypic characterization of the disease is important in anticipation of new interventional therapies, such as gene therapy, which should be performed early and in patients at higher risk of visual progression.

Objectives and specific aims

- Integration of functional parameters (visual acuity, visual field test, color vision, electrofunctional exams) with OCT anatomical parameters (RNFL, ganglion cells) to stage patients and provide useful data to clinicians for differentiating approaches based on severity.



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- Application of machine learning algorithms allowing rapid and intuitive aggregation of patient data and structuring of a new classification paradigm that considers severity and progression parameters.
- Correlation with the type of mutations in the OPA1 gene, distinguishing between mutations predicted to cause haploinsufficiency and missense mutations that are often predicted to act through a dominant negative mechanism.

Expected outcomes

- Improvement of the diagnostic and classification approach for DOA.
- Integration of different parameters into a clinical severity score.
- Identification of specific biomarkers for therapeutic trials.

Skills that the student should acquire (max. 600 characters including spaces):

1. Conduct an investigative study in Clinical and Experimental Medicine.
2. Perform statistical analysis and write a high-profile scientific paper.
3. Utilize tools of ophthalmological clinical practice.
4. Understand and develop relevant procedures in ophthalmological clinical practice

References (max. 15)

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5. Carelli, V., Ross-Cisneros, F. N. & Sadun, A. A. Optic nerve degeneration and mitochondrial dysfunction: Genetic and acquired optic neuropathies. *Neurochem. Int.* (2002) doi:10.1016/S0197-0186(01)00129-2.
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