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ASSOCIATION OF FUNCTIONAL VISION AND ORTHOPTIC TESTING WITH HIGH RESOLUTION OCT FINDINGS IN PATIENT WITH NEURODEGENERATIVE DISORDES

INTRODUCTION

Neuro-ophthalmology is a branch of ophthalmology which merges this discipline with neurology, focusing on the complex interaction between the eyes, brain and nerves. Neuro-ophthalmological disorders, such as degenerative and inflammatory diseases, are caused by etiopathogenetic mechanism affecting neurological structures including the eye, leading to a series of visual abnormalities such as the vision of scotomata, peripheral visual field defects or hemianopsia, loss of color vision, diplopia, eye movement disorders, exophthalmos and ptosis or anisocoria.

In order to better characterize visual abnormalities we can divide them in two groups: visual impairment and eye movement abnormalities. Visual impairment can be a manifestation of neurodegenerative diseases: inflammation and axonal degeneration contribute to neurological damage, leading to clinical disability. This is the result of the involvement of the optic nerve and its connections to the visual portions of the brain. Inflammation of the optic nerve usually leads to a decrease in contrast sensitivity: contrast sensitivity testing is more sensitive than just visual acuity examination to identify visual abnormalities. Moreover, the development of eye movement disorders is related to the fact that several regions of the brain control eye movements, and therefore a defect in these areas causes misalignment of the eyes and results in diplopia. [i] In case of acquired color disturbances the damage may occur along the entire line of sight. A known rule of thumb in relation to visual color abnormalities is the so-called "Köllner rule", whereby retinal diseases present yellow-blue perception disorders and optic nerve damage presents red-green perception abnormalities. [ii]

The embryological origin, anatomical structures and connections are shared between the retina and the optic nerve. Therefore, they represent a perfect study subject and a “window “on the neurological system that allows a direct visualisation of the nervous tissue and its circulation. Indeed this may represent a tool to evaluate early changes to reach an early diagnosis of relevant diseases such as multiple sclerosis (MS), neuromyelitis optica (NMO), Alzheimer’s disease and Parkinson’s disease. This could be really beneficial for prediction of a worse prognosis of these illnesses that have a strong impact on the quality of life of affected patients [iii] [iv]. Nevertheless, an early ophthalmological indicator and biomarker of these diseases is still lacking.

The study of the retina and the optic nerve is conducted with a neuro-ophthalmological assessment which includes a specific clinical and instrumental examination. It is possible to perform computerized visual field analysis, Optical Coherence Tomography (OCT) to quantify the nerve fibers layer thickness, and Optical Coherence Tomography Angiography (OCTA) to evaluate the vascular structures of the retina and optic nerve. [v]

Ophthalmological Imaging

Retinal imaging devices are primarily used for the diagnosis and for monitoring the response to treatment of retinal diseases, such as age-related or inherited maculopathies, and neurodegenerative disease such as glaucoma. A wide variety of conditions belonging to the neuro-ophthalmological and neurological field can be non-invasively investigated thanks to a detailed ophthalmological imaging and clinical assessment.
New high-resolution diagnostic tools such as enhanced-depth OCT, wide field retinography, OCT angiography (OCTA) and Adaptive Optics ophthalmoscopy (AOO) have been developed and recently introduced in ophthalmological clinical practice in the last 3 years. They have revolutionized the field of early diagnosis at a cellular level of retinal diseases and glaucoma [vi].
Combination of multiple retinal imaging may be a source of biomarkers for early diagnosis, characterization and prognosis of neuro-ophthalmological disorders.
These ophthalmological technologies may also provide more objective and precise measures for a quantitative assessment of biomarkers in order to reach an early diagnosis, characterization and prognosis of neuro-ophthalmological disorders, providing important insight into cerebrovascular neurodegenerative process in addition to what is currently possible with neuro-imaging.
Ophthalmological assessment using psychophysical examination and advanced eye technologies are very sensitive for the evaluation of clinical conditions and visual impairment of this group of patients. [vii]

Colour Vision and Contrast Sensitivity

Two different types of photoreceptors are present in the retina: cones and rods. The average human retina contains 92 million rods (77.9-107.3 million) and 4.6 million cones (4.08-5.29 million).
The concentration of the cones is highest within the fovea, while the rods concentration is around the 20 degrees from the fovea. The complex mechanism that leads to vision and in particular to perception of the colors begins at the retinal level and ends at the level of the primary visual cortex [viii].
The cones are assigned to the vision of light and colors and are divided into three different types depending on the photopigment located at the external segment[ix] .
Cones and rods translate the light that they absorb in electrical signal schemes that are transmitted through the synapses to the connective layer of bipolar cells. These put together the information received by the receptors and transmit it vertically to the layer next, ganglion cells, while horizontal cells and amacrine neurons distributed between the bipolar cells they transmit the information laterally [x]

Patients with cone alteration are unable to distinguish some colors: an anomaly in the perception of colors can be congenital or acquired. The causes of the acquired forms of the chromatic defects include pathologies affecting the macula and the optic nerve. There are numerous exceptions about the Kollner's rule, suggested in the introduction, such as glaucoma and optic atrophy, which affect the blue-yellow axis, and Stargardt disease, which involves primarily red-green axis.

Impaired colour vision and low contrast visual acuity (LCVA) may be a preclinical marker of neurodegeneration. Many studies demonstrated that these examinations are more sensitive for detecting visual abnormalities in patients affected by acute optic neuritis (ON) and Multiple Sclerosis (MS), so these examinations might be assessed for the early diagnosis. [xi]

Also, Parkinson's Disease (PD) patients may complain about alteration of colour discrimination and contrast sensitivity before the diagnosis, due to dopamine depletion into the retina. However, the pathophysiology of colour vision deficiency in PD is complex and multifactorial. [xii]

Several studies suggested that colour vision is a preclinical marker of neurodegeneration and that the LCVA reduction is associated with disease severity and cognitive impairment: this suggest that both symptoms may have prognostic or diagnostic value. [xiii]

Visual Field Test

Visual Field test, also called perimetry, is important in the diagnosis of neurodegenerative disease and helpful to localize the lesions that involving the visual pathways. It is a diagnostic examination that evaluates the amplitude of the visual space perceived by the eye.

Visual field test is used to diagnose and monitoring the disease and guide treatment in conditions like optic neuropathy (ON) and MS, pituitary adenomas, and other optic nerve injuries. It should be performed at the baseline and periodically, for the follow-up. Static perimetry testing has been shown to be adequate in neuro-ophthalmic practice and is now the gold standard for the follow-up examination. [xiv]

Pupillometry

The observation of a pupil abnormality requires a rigorous diagnostic approach. In case of anisocoria, it is necessary to study pupil diameter according to the illuminance. This sign of disease occurs when it is present an asymmetry of the pupil response to light, revealing a impairment of the function of the afferent system of one of the two eyes. In fact, when the light is placed in front of a healthy eye, both pupils symmetrically constrict themselves and then slowly re-expand; when the light is placed in front of the affected eye, the constriction is reduced or even absent while dilation is immediately evident. This process just described is called relative afferent pupillary defect (RAPD) and is one of the most important signs in neuro-ophthalmology. It provides objective evidence of optic nerve damage and is very important to recognise it as an early manifestation of visual loss. For this reasons, in optic neuritis, pupil response and reaction to light is routinely evaluated as one of the first sign of optic nerve inflammation. [xv]

Eye moviment abnormalities

Eye motility disorders often causes binocular diplopia. A first approach allows differentiating an infranuclear lesion (cranial nerves, neuromuscular junction or oculomotor muscle) from a supranuclear disorder, which affects conjugated movements. Eye movements, however, remain limited in the event of nuclear or subnuclear damage. In case of infranuclear lesion, it is important to determine if there is a dysfunction of a cranial nerve, neuromuscular junction or muscle oculomotor in itself. For this reason, the careful study of versions and ductions, of the coordination system (Hess Lancaster test) and the search for associated signs allow to orient the localization of the lesion. [xvi]

PURPOSE

Primary objective

The main purpose of this study will be to investigate the association between functional vision testing and OCT findings in patients with neurological diseases, including among all Multiple Sclerosis and Neuromyelitis Optica, for an early diagnosis and follow-up of these neurological disorders. Furthermore, we will correlate these parameters with neurological and neuro-radiological markers of disease progression.

Our ultimate goal will be to expand on the investigation between OCT and neurological findings, which is ongoing at the AOU Careggi. This project evaluate the role of multimodal imaging using new ophthalmological techniques as a source of potential biomarkers in the early diagnosis and follow up of some neurological disorders.

Secondary objective

Our secondary objectives will be to obtain long-term follow-up of eye movement disorders and variability of Visual Field over time in these patients.

The execution and interpretation of these tests is a domain shared between ophthalmologists and orthoptists.

METHODS

Patients affected by neurodegenerative and demyelinating disorders referring from neurological specialists to our Eye Department (AOU Careggi, Florence) will be evaluated using vision colour test, contrast sensitivity test, pupillometry and visual field. The ophthalmologist will perform multimodal imaging with new ophthalmological techniques (OCT, OCTA) to determine their role in the early diagnosis and to correlate the visual performance with the ganglion cells, retinal nerve fiber layer and vascular state.
Written informed consent will be obtained from all subjects. Baseline best corrected visual acuity (BCVA) will be measured for all patients using ETDRS charts then converted into a logarithm of the minimum angle of resolution (LogMAR) for statistical evaluation. Slit-lamp biomicroscopy of the anterior segment and fundoscopic examination by indirect ophthalmoscopy will be carried-out in all patients by the ophthalmologist.

All patients will undergo:

1. **Colour Vision Test**
   - Ishihara test is the most used clinical test to identify red-green defects. The examination was designed to screen for protan and deuteran defects. It consists of a control table followed by 16 tables that the subject have to identify. Patient with color deficiency will be able to identify only a few plates.
   - The Farnsworth-Munsell 100-hue test is the most sensitive for the confirmed defects of color vision and for those acquired. It consists of 85 hoods of different shades in four grids. The results are recorded on a circular graph. Each form of dyscromatopsia is characterized by the absence of a meridian on the graph.

- Hardy Rand and Rittler Pseudoisochromatic Plates (HRR) test is as good as Ishihara test, like reported by Cole et al., for the detection of red-green defect but unlike Ishihara test, HRR have plates for detecting the tritan defects (blu-yellow). [xvii]

2. **Contrast Sensitivity**
   The Pelli-Robson chart consists in eight lines of letters, each letter subtending 3 degrees at a viewing distance of 1 meter. In every row the letter decreases in contrast by a factor of l/□2. The contrast level of the last letter read gives the subject's LCVA score. [xviii]

3. **Visual field test:**
   Static perimetry testing (Humphrey Automated Field) using the 30.2 Swedish Interactive Thresholding Algorithm (SITA) Standard program with an appropriate lens correction if needed. To perform the exam we examine each eye alternatively. The patient fixes a central target and press a button every time a luminous stimulus into the couple is seen.

4. **Pupillometry** is a non-invasive examination that determine the diameter of the pupil in different light conditions. For the examination the patient observes a target with variable brightness, according to the environmental condition that you want to simulate. Pupillometry determines the pupil dynamism measured by varying the examination brightness from daylight to scotopic condition.

5. **Eye movements evaluation:**

- STEREOPSIS EVALUATION: the sense of depth or three-dimensional vision, which can be partially or totally absent in case of collaboration deficit of the two eyes, will be examine by Lang I and II tests.
- EYE MOTILITY EXAMINATION and COVET TEST investigate the possible presence of hyper and / or hypofunctions affecting the extraocular muscles, abnormalities of coordinated movement of the two eyes (in particular convergence and divergence defects.
- DIPLOPIA STUDY TEST evaluates the possible presence of double vision and its relative nature (horizontal, vertical and oblique). We perform the red filter test to investigate this abnormality.
- SCREEN OF HESS LANCASTER AND GRACIS: it will be carried out to established the presence of strabismus or diplopia, to quantify the extent of the deviation and especially the state of the muscles affected by the problem.

SAMPLE SIZE

We estimate to recruit the following new and existing patients, given clinical practice volumes at the Departments of Neurology and Ophthalmology of the AOU Careggi:
- Multiple Sclerosis: 20 new and 50 existing patients
- Neuromyelitis Optica: 10 new and 10 existing patients

Recruitment will take place in the first year and follow-up visits will be carried out every 6 months for the 3-year duration of the project.

Since the Candidate role will be the collection of test results and their interpretation, which are consistent with the professional profile of an orthoptist, all statistical analyses will be part of the broader ongoing research project which is investigating the relationships between neurological and ophthalmological testing in these patients.

CONCLUSION

Our project aims to perform and analyse several specific neuro-ophthalmologic tests to investigate various pathological frameworks that may be useful for early diagnosis and follow-up of patients suffering from relatively common neurodegenerative diseases. This study also aims to correlate the tests previously described with instrumental examinations such as OCT and OCT angiography, in order to evaluate their possible use to characterize the various pathologies at different stages of disease. Careful orthoptic evaluation with non-invasive tests can be useful to better study these patients, to monitor progression and treatment response, even when we are faced with subclinical eye and vision involvements.

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