WHAT ARE YOU GOING TO DO ABOUT SUBCLINICAL EYE DISEASE?

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FINANCIAL DISCLOSURES

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- Konan Medical

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SUBCLINICAL DISEASE

Medical Definition
An illness that is staying below the surface of clinical detection
A disease that has no recognizable clinical findings
It is distinct from clinical disease, which has signs and symptoms that can be recognized during a clinical examination

Ophthalmologic Examination
- Patient history
- General medical observation
- Gross visual fields
- Basic sensorimotor examination
- External examination
- Adnexal examination
- Manifest refraction
- Slit lamp examination
- Biomicroscopy
- Ophthalmoscopy

Clinical Examination = Clinical Diagnosis
A clinical diagnosis is a determination based on the knowledge obtained from the patient’s medical history and from the results of the eye examination alone, without the benefit of diagnostic tests or procedures

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SUBCLINICAL DISEASE

A problem in which symptoms are mild or inapparent, and may not be diagnosed other than by more advanced testing measures
Subclinical does not mean that the problem is insignificant, or that there is no disease to detect. In fact, it reflects that conventional measures that have been used in the past may not detect changes early in the natural history of the condition
The presence of subclinical disease is a strong risk factor for disease progression compared to no detectable subclinical disease
Measurement of subclinical eye disease requires “non-traditional” thinking and modern technology

Physical Examination = Physical Diagnosis
A physical diagnosis is a determination supported by various diagnostic tests and procedures (e.g., OCT retinal imaging, fundus fluorescein angiography, etc)

SUBCLINICAL DIABETIC RETINOPATHY

Regarding the vascular form of the disease, subclinical diabetic retinopathy is the development of vascular abnormalities prior to the development of fundus-copically-evident diabetic retinopathy
In diabetes, a structure-function relationship exists between neurodegeneration and vision loss and in many patients, subclinical retinal neurodegeneration may be detected without visible retinal vasculopathy
Up to 36% of patients with no clinical diabetic retinopathy have OCTA-detected vascular abnormalities

RETINAL BLOOD MICROCIRCULATION

OCTA RETINAL IMAGING
NORMAL ANGIOGRAM

OCTA RETINAL IMAGING
SUBCLINICAL RETINOPATHY
From the optic disc, the major retinal arteries and veins and their successive divisions run in the superficial nerve fiber layer until the immediate precapillaries, which divide into two basic groups:

- Superficial capillaryplexus
- Deep capillaryplexus

Retinal Vascular Density Measurements:
- Looks at tissue perfusion, which is more tightly linked to tissue metabolism and physiologic function.
- Quantification software generates OCTA parameters that quantify the density of blood perfusion in different slabs of the retina.

### SUPERFICIAL RETINAL VASCULAR DENSITIES

#### Anatomic Region

<table>
<thead>
<tr>
<th>Vascular Complex Density Percentage</th>
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<tbody>
<tr>
<td>Superior hemi-macula</td>
</tr>
<tr>
<td>Inferior hemi-macula</td>
</tr>
<tr>
<td>Temporal parafovea macula</td>
</tr>
<tr>
<td>Nasal parafovea macula</td>
</tr>
<tr>
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<tr>
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</tbody>
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### OCTA RETINAL IMAGING

#### NORMAL PERFUSION

#### ABNORMAL PERFUSION

### STRUCTURAL ASSESSMENT

The advent of optical coherence tomography angiography (OCTA) has demonstrated the presence of vascular abnormalities in patients with diabetes that are not visible with ophthalmoscopic exam. This form of the disease is called subclinical diabetic retinopathy and retinal imaging studies have shown that it is characterized by the following clinical features:

- Alterations in capillary density
- Increased foveal avascular zone
- Abnormal branching angles
- Abnormal ratio of vessel length to diameter

### SUBCLINICAL DIABETIC RETINOPATHY

- 56-year-old white man with a 20-year history of diabetes
- Treatment: oral med – poor compliance on diet/exercise
- 20/20 best corrected visual acuity in each eye
- No complaints of decreased vision
- No apparent diabetic retinopathy

### OCTA RETINAL IMAGING

#### NORMAL PERFUSION

#### ABNORMAL PERFUSION
**SUBCLINICAL DIABETIC RETINOPATHY**

Diabetic retinopathy has always been defined as a complication of diabetes that starts with damage to the retinal blood microcirculation. The diabetes-induced vasculopathy is characterized by the following:
- Contraction and occlusion of the microvascular lumen
- Failure of the capillary network
- Increased vascular permeability
- Retinal perfusion alteration

**GANGLION CELL COMPLEX ANALYSIS**

- Diabetes-induced retinal neurodegeneration occurs in people with diabetes regardless of clinical markers of diabetic metabolic control.
- Clinically significant ganglion cell complex focal loss volume predates ophthalmoscopy-based detection of diabetic retinopathy in 22% of patients with diabetes.
- In some patients, this generalized neural gliopathy dysfunction can produce sensory abnormalities and a loss of visual function.
- Psychophysical measures of visual function such as contrast sensitivity, color vision, retinal sensitivities, and electroretinography can all be abnormal in patients with retinal diabetic neuropathy.

**DIABETIC RETINOPATHY ASSESSMENT**

**Thomas Classification System**

A proposed new classification system for diabetic retinopathy
- The goal of including subclinical diabetic retinopathy is to represent all stages and manifestations of diabetic retinopathy.
- The Diabetic Macular Edema Scale is replaced with a Diabetic Maculopathy subdivision to more accurately reflect what OCT retinal imaging is showing us about the pathophysiology of diabetes-induced macular disease.
- Remember, clinically significant macular edema can be present at any stage of diabetic retinopathy.

**FUNCTIONAL VISION ASSESSMENT**

Subclinical diabetic retinopathy is also a neurodegenerative disorder of the retina that is characterized by a loss/derangement of the following neural elements:
- Ganglion cell bodies
- Retinal nerve fiber layer
- Photoreceptors

This neuropathic form of subclinical diabetic retinopathy is known as retinal diabetic neuropathy (RDN) and can be quantified either structurally or functionally.

**MEDICAL DECISION-MAKING**

The clinical diagnosis of “no apparent diabetic retinopathy” is changed to a physical diagnosis of subclinical diabetic retinopathy.

Prescribe a treatment program that is designed to delay the development of diabetic retinopathy with tighter metabolic control:
- Diet
- Exercise
- Medicine
- Nutritional supplementation
- Patient education

**The relative afferent pupillary defect (RAPD) is an important clinical sign of asymmetric retinal ganglion cell and axonal damage.**
- In patients with glaucoma, an asymmetry of 27% or more in retinal nerve fiber layer thickness will likely produce a RAPD.
- During a clinical examination, the detection of a RAPD is a human observation-based assessment.
- If detected, a RAPD is quantified by performing the swing flashlight test and equalizing the pupil response with 0.3-log unit neutral density filters.
SUBCLINICAL PUPIL DEFECTS

- 62-year-old black man presents for a routine eye exam
- Good health – physically fit – no medications
- 20/20 uncorrected visual acuity in each eye
- Intraocular pressures are 11 mm Hg in each eye

PUPILLARY LIGHT REACTIVITY

Afferent Neural Pathway
Ganglion cells connect to the pretectal nucleus of the upper midbrain, bypassing the lateral geniculate nucleus

Efferent Neural Pathway
Axons from the Edinger-Westphal nucleus run to both the right and left oculomotor nerves to innervate the constrictor muscle of the iris

TESTING PUPILLARY REACTIVITY

Normal pupils have equal response to light stimulus

Testing pupillary reactivity involves comparing the velocity and amplitude of the pupillary response

During a clinical examination, the procedure is usually accomplished by performing the “swinging flashlight test” on the patient with a penlight or transilluminator

Abnormal findings include an asymmetry in the pupillary light reflex, a condition known as relative afferent pupillary defect (RAPD)

Neutral density filters in 0.3 logarithmic unit steps aid in the detection and quantification of RAPD

Goal of pupil light reflex testing is to determine if there is a defect in either neural light reflex pathway

NON-INVASIVE, NON-CONTACT AUTOMATED PUPILOMETRY ENHANCES THE ABILITY TO DETECT A RAPD

The RAPDx Score has been shown to have a strong correlation with the difference in mean deviation between each eye of patients with glaucoma

RAPDx Scores > 0.30 may be abnormal

The RAPDx Score has been shown to have a strong correlation with the difference in mean deviation between each eye of patients with glaucoma

FUNCTIONAL VISION ASSESSMENT

Relative Afferent Pupillary Defect

Ischemic Optic Neuropathies

Glaucma

Optic Neuritis

Ischemic Retinal Diseases

Optic Nerve Compression

Orbital Disease

Midbrain Lesions

STRUCUTRAL ASSESSMENT

- Glaucomatous optic atrophy on OCT retinal imaging is characterized by a thinning of the retinal nerve fiber layer and the ganglion cell complex
- Macular ganglion cell complex parameters include Focal Loss Volume (FLV), global loss volume (GLV), mean, superior and inferior thickness
- Highest diagnostic accuracy for early glaucomatous optic atrophy is GLV parameter

Because glaucomatous damage to the retinal nerve fiber layer has a predilection for the inferotemporal and superotemporal regions of the optic disc, focal defects in these areas are strongly suggestive of glaucoma.

**FUNCTIONAL VISION ASSESSMENT**

- Color contrast thresholds are depressed in some patients with glaucoma
- Electrotetroenography measures the photopic negative response (PhNR) to evaluate the function of the innermost retinal layers and the ganglion cells; abnormal test results can be a diagnostic marker for glaucoma
- Visual evoked potential testing evaluates the integrity of the afferent visual sensory system

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Glaucoma produces a widespread, non-descript loss of retinal sensitivity. The diffuse loss of retinal sensitivity should be considered highly diagnostic of glaucoma when it is asymmetric and correlates with asymmetric changes in intraocular pressure, optic disc appearance, or pupil reactivity.

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**MEDICAL DECISION-MAKING**

The clinical diagnosis of relative afferent pupillary defect is changed to a physical diagnosis of partial optic nerve atrophy.

Prescribe a treatment program that is designed to monitor the patient for optic neuropathy disease progression:

- More intense eye exam surveillance schedule
- More intense OCT and OCTA structural assessments
- More intense functional vision assessments

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**CONCLUSION**

- The measurement of subclinical disease provides an approach for identifying individuals who may be candidates for more active intervention to delay or prevent the development of clinical disease
- For patients with established risk factors for clinical disease, manage this increased risk by increasing your index-of-suspicion for subclinical disease and deploying advanced diagnostic technologies to assist in early detection

“Risk Management Through Early Detection”