Uncovering the cause of blindness in a retina unrevealed: Use of family & medical history to narrow the differential & guide electrophysiology & genetic testing.

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Abstract: A patient with no-light-perception presents with keratoglobus, retinal pigmentary abnormalities, and poor view of the retina. Family, medical, and case history guide testing and narrow the differential.

I. Case History

- Patient Demographics:
  - 67 year old white male
- Chief Complaint:
  - Right eye irritation, improved from previous visit (1 month prior)
- Ocular & Medical History:
  - Blindness caused by “undefined optic atrophy” in both eyes since approximately 37 years of age,
  - Bilateral keratoconus that eventually converted to keratoglobus in both eyes per chart notes
  - Arteriosclerotic cardiovascular disease, hyperlipidemia, atrial fibrillation, hypertension, GERD
- Systemic Review:
  - Denies ataxia, hearing loss, neuropathy, ichthyosis, hypogonadism, polydactyly, arrhythmia, anosmia, developmental or learning disabilities, or other known systemic abnormalities
  - Reports oculo-digital sign behavior as a child
  - Denies history of alcoholism, malnutrition, trauma, or toxin exposure (other than Agent Orange)
- Family History:
  - No family history of blindness or progressive vision loss
  - Primary and secondary relatives reviewed had no visual defects on history
  - Siblings were examined in past per history and had no symptomatic retinal or ocular findings
- Medications:
  - Prednisolone acetate qd OD, lacri-lube tid OD, celluvisc q2h OD & qid OS
  - Lisinopril, metoprolol, simvastatin

II. Pertinent Findings

- Clinical:
  - No light perception in both eyes
    - Patient does not remember initial presentation of visual field loss (central versus peripheral)
    - Patient does not remember if he had visual deficits as a young child that improved and then worsened
    - Patient does not remember if nyctalopia preceded general vision loss
- Physical:
Right eye: dense pannus across entire corneal surface, moderate stromal edema, diffuse 3-4+ superficial punctate keratitis
Left eye: pannus on superior and inferior peripheral corneal surface, stromal thinning along inferior third of cornea, mild diffuse superficial punctate keratitis
Corneas are negative for flecks or granulations
Very steep Munson’s sign noted in both corneas
Unable to visualize anterior chamber in right eye due to pannus
Unable to view fundus in left eye secondary to dense nuclear sclerosis

Laboratory Studies:
- Molecular genetic test results pending

Other Studies:
- Horizontal eye movement electrooculography reveals significantly reduced amplitude of both a and b wave measures
  - Proprioception was used for eye movements because patient is no-light-perception and cannot follow light targets
- Fundus autoreflourescence, optic nerve optical coherence tomography, or macular optic coherence tomography were impossible to perform because of dense pannus in right eye and dense nuclear sclerosis in left eye

III. Differential Diagnoses

Primary:
- Non-syndromic retinitis pigmentosa with confounding keratoglobus:
  - Photoreceptor and retinal pigment epithelium disorder with multiple inheritance patterns that typically involves nyctalopia, constriction of peripheral field of view, waxy optic nerve head pallor, vessel attenuation, and peripheral retinal pigment clumping (often “bone spicule” presentation)
  - Patient denies syndromic retinitis pigmentosa features or medical conditions
  - Total blindness not typical for fourth decade, but inheritance pattern and phenotypes are highly variable
  - Known associations with keratoconus and keratoglobus
- Leber’s hereditary optic neuropathy
  - Optic nerve dysfunction with mitochondrial inheritance pattern that usually involves rapid sequential central visual field loss, acute presentation of swollen optic nerve heads with peripapillary telangiectasias, and development of optic atrophy
  - No association with retinal pigmented epithelium changes
  - Condition more common in males and vision loss typically seen in third to fourth decade or later
  - No known association with keratoconus or keratoglobus
- Variant of Leber’s non-syndromic congenital amaurosis (RPE65-associated phenotype)
  - Oculo-digital sign, high hyperopia, pigmentary retinopathy, and profound vision loss in infancy or childhood are characteristic of most genetic polymorphisms of Leber’s congenital amaurosis
  - Phenotypes are highly variable despite typically devastating vision loss in infancy or early childhood
  - RPE65 defect can be associated with functional vision through the third to fourth decade and keratoglobus

Others:
• Kearns-Sayre syndrome
  ▪ Pigmentary retinopathy, progressive external ophthalmoplegia, ataxia, cardiac conduction problems, mitochondrial inheritance

• Drug toxicity
  ▪ Pigmentary retinopathy can develop from use of drugs, such as chloroquine and thioridazine

• Deafness-dystonia-optic neuronopathy (DDON)
  ▪ Progressive difficulty with hearing, movement, vision, and dementia

• Syndromic retinitis pigmentosa (all ruled out due to lack of systemic findings in this patient)
  ▪ Bardet-Biedl syndrome
  ▪ Neuropathy-associated retinitis pigmentosa
  ▪ Usher’s syndrome
  ▪ Refsum disease

• Bietti crystalline corneo-retinal dystrophy
  ▪ Pigmented retinopathy associated with crystalline flecks in the retina and cornea

IV. Diagnosis & Discussion
  • Patient presumed to have a variant of non-syndromic retinitis pigmentosa
    o Reported gradual onset of vision loss - matches with typical rate of progression of retinitis pigmentosa
    o Age of onset of retinitis pigmentosa varies, depending on inheritance pattern, and can occur in adulthood – matches patient’s claim that condition started around age 37
    o “Reticular degeneration 360” noted in both eyes in a previous provider note from patient’s initial visit at age 62 – reticular degeneration is not typically found at that age
    o “Moderate pigment spicules” observed nasal to left optic nerve head by attending doctor during past undilated fundus examination at age 65 – matches “bone spicule” pigmentation pattern frequently seen in retinitis pigmentosa
    o Pale nerves with small cupping previously noted in both eyes during first visit - retinitis pigmentosa often involves waxy optic disc pallor
    o Posterior subcapsular cataract observed in left eye at initial examination – this type of cataract is often seen in retinitis pigmentosa
    o Retinitis pigmentosa has an association with development of keratoconus and keratoglobus, while isolated bilateral keratoglobus is unusual
    o Although quite rare, development of bilateral no light perception vision from retinitis pigmentosa has been documented in literature

V. Treatment & Management
  • Research on epiretinal and subretinal microchip implants
  • Gene therapy research
  • Low vision services and vocational rehabilitation

VI. Conclusion
  • Retinitis pigmentosa and Leber’s congenital amaurosis are associated with highly variable phenotypes, inheritance patterns, and complex polymorphisms. In this case, genetic testing will be completed to determine if this patient has polymorphisms associated with non-syndromic
retinitis pigmentosa versus Leber’s non-syndromic congenital amaurosis (RPE65-associated phenotype)

- Challenges posed by this case included: lack of previous non-VA records, patient’s difficulty remembering details of visual field loss, patient presenting at VA eye clinic with no-light-perception in both eyes, and significant pannus in the right eye & cataract in the left eye preventing visualization and imaging of fundi

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