The ocular phenotype of Peroxisome Biogenesis Disorders

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Introduction

- Peroxisome Biogenesis Disorders (PBD) are a group of autosomal recessive disorders with 14 known genes till date.
- Peroxisomes play an essential role in a variety of cellular catabolic and anabolic metabolic pathways.
- PBDs lead to Zellweger spectrum disorders (ZSDs) and rhizomelic chondrodysplasia punctate (RCDP).
- Defects in these genes result in different peroxisomal disorders with variable severity ranging from early lethality to subtle neurosensory aberrations.
- Core features of PBD include: developmental delay (DD), neurological abnormalities, liver & adrenocortical dysfunction, hearing & vision impairment.
- This study is the biggest series of patients with PBDs, that describes the systemic manifestations and detailed ocular phenotype.

Aim

Primary outcome

- To describe the pathognomonic ocular findings in patients with genetically confirmed PBD

Secondary outcome

- To describe the systemic manifestations, including central nervous system (CNS) involvement, face dysmorfism, liver dysfunction, sensory hearing loss (SNHL) and laboratory tests.

Methods

- Retrospective descriptive study of children who had PBD due to biallelic mutations in *PEX1*, *PEX6*, and *PEX26*.
- All patients had detailed ocular examination including visual acuity, anterior and posterior segment exams, cycloplegic refraction, retinal photography, full-field electroretinogram (ERG), and macular optical coherence tomography (OCT).
- Systemic manifestations, laboratory findings and genetic data were also collected from the patients' charts.

Results

- 9 children were included in the study (Age at presentation: 5 months to 9 years).
- Phenotypic severity varied between Zellweger disease (ZD; n = 4), Neonatal adrenoleukodystrophy (NALD)/ Infantile Refsum disease (IRD) (n=3) and Hiemler disease (n=2).
- All patients had SNHL, varying levels of DD and CNS involvement.
- Four each had mutations in *PEX1* and *PEX6,* respectively and one patient had mutations in *PEX26*.

Ocular Findings

- Anterior segment was unremarkable in 8 patients, and none had any lens involvement. One patient with PEX6 mutation and NALD/IRD phenotype, showed normal eye exam including good visual acuity, retinal appearance, OCT and ERG.
- Retinal examination showed interesting and unique features in 8 patients. These included rounded (nummular) pigment clumps distributed in the mid-peripheral retina (n = 6; Figure 1 & 4), or round deep retinal lesions with the same distribution (n = 2); further all 8 patients showed bilateral crowded optic nerves with overlying gliosis in at least 1 eye.
- Macular OCT showed disrupted outer retinal layers (outer and inner segments and outer nuclear layer), with (Figure 2) or without macular schisis in eight subjects.
- Patients without macular schisis showed foveal atrophy (Average: 120 µm thickness in 6 eyes), with relatively thick parafoveal region (Average thickness: 358 µm nasally and 299 µm temporally).
- ERG's showed severely reduced rod and cone function in 8 subjects (Figure 3).

Figure 1: RetCam photos of a 2-year-old female with NALD/IRD (biallelic PEX1 mutations) showing bilateral symmetric nummular pigment clumps.

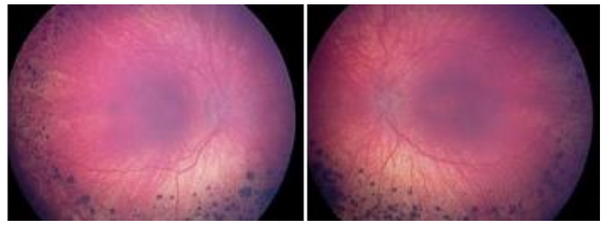


Figure 2: Foveal OCT from same patient showing bilateral macular schisis.

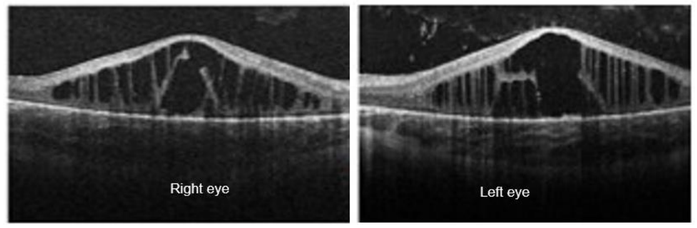


Figure 3: ERG of the same patient showing severely reduced cone and rod function.

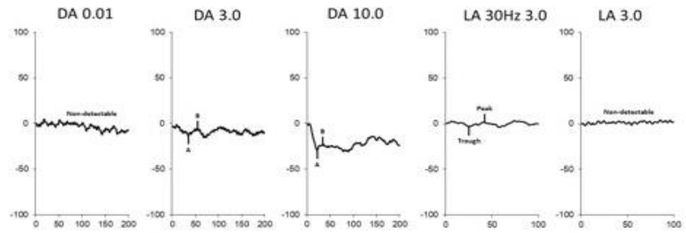
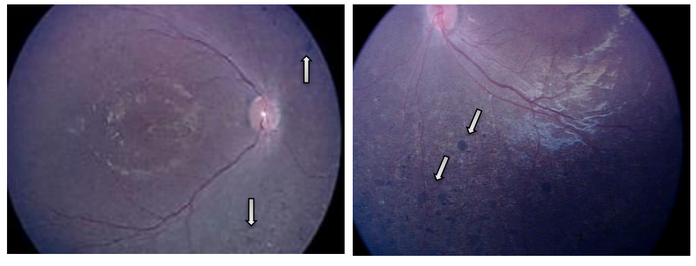


Figure 4: RetCam photos of a 5-year-old male with NALD/IRD (biallelic PEX6 mutation), showing bilateral hyperpigmented round lesions in the mid-periphery (arrows) with symmetric distribution. Notice the gliosis overlying the right optic disc



Conclusions

- PBDs can cause severe early onset retinal dystrophy.
- Retinal features described here are novel and pathognomonic.
- This can inform diagnosis as a subset of these children could first present to the Ophthalmologist with poor visual behavior.