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Retinal Dystrophy New Early Signs Detection Towards Vision Improvement: A Case Presentation

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Abstract

Introduction: This is a case presentation of inherited retina dystrophy type *RPE65*. We enhanced signs for early diagnosis in order to prevent vision loss as this condition has treatment now-a-days.

Method opted: Phenotype and genotype investigation resulted in *RPE65* mutation, one sub-retinal injection was done in each eye.

Results: Vision is improved.

Discussion and conclusion: Early diagnosis is needed for LCA and retina dystrophies. This case presentation illustrated diagnosis is delayed due to the unknown early signs. Early signs are not detected by a specialist, even though for a mother is certain that vision is not normal for first month of life. There is treatment now and this may prevent loss of vision due to the degenerative nature of this condition, particularly as during first year of life treated patients manifest improved vision.

Keywords: Congenital; *RPE65* mutation; Macular atrophy; *RPE65* pathogenic variants

Case Report

A 2-month-old girl present with unusual wondering gaze. This characteristic wonder gaze is often presented during the day and more often during night. Her mother noticed she does not fix her vision and she is very happy with light, particularly during dusk. This child was taken to her paediatrician, neurologist, several ophthalmologists who said the child was within normal limits. Symptoms did not disappear, and few years passed. At the age of 5 years old this child was referred to us. We found other relevant features. She bumps very often into objects during first year of life. She developed fear of almost anything during dusk particularly.

During the examination, she presented with best corrected vision of central, fixes and remains steady OU. Pupils were sluggish. During fundus examination we found a very tiny mottling OU. Rest of ocular exam unremarkable. She does like to be near to her mother by 30 cm or less, she has no interaction with other children same age. Fundus pictures were taken with no relevant findings, no autofluorescence and ERG was not done. Other relevant medical history was negative.

We suspect inherited retina dystrophy Leber Congenital Amaurosis, we initiated phenotypal investigation of parents and request blood samples to complete with molecular test. We preformed PCR amplification of the coding sequence of *RPE65* and sequenced. We wanted to rule out *RPE65* as the possibility of treatment is now available. Platform used was WE sequenced ABI sequencer. We sequenced exons 4 and 5 of the *RPE65* gene in this proband and detected both the c.311G>T and the c.370C>T mutations in the heterozygous state. Analysis of the parental samples showed that the sequence change c.311G>T was inherited from one parent while the sequence alteration c.370C>T was inherited from the other parent. The results of this segregation analysis confirm the bi-parental inheritance of these two changes. Therefore, the molecular diagnosis in this

individual is consistent with the clinical diagnosis of *RPE65* related Leber Congenital Amaurosis.

At the age of 7 years old, she presented with severe and fast deterioration of vision to hand motions at 10 cm over 8 months' time, as natural history shows [1,2]. We proceed to AAV2-hRPE65v2 (voretigene neparvovec) (to deliver the human RPE65 cDNA) one subretinal injection [1,3-14]. After 1 month, she has improved her vision to 20/200 and about 100% functional.

Leber Congenital Amaurosis (LCA) occurs in 2 to 3 per 100,000 newborns reported in North America [11,15,16]. In Mexico, the National Institute of Statistics (INEGI), a Mexican statistics organization has not measured the incidence of this condition yet. Data in the only Mexican Inherited Retina Dystrophy registry shows there is apparently about 7 out of 100 registered patients with LCA diagnosis. We calculate there are probably 1200 cases in Mexico. LCA is one of the most common causes of blindness in children. Before 2017, LCA was among one of the retina degenerative diseases leading cause of irreversible blindness however now-a-days LCA type 2 has a cure [3,8,13,17-19].

The description of this disease was first made by Leber in 1989 [20-23], as:

1. Sluggish or near-absent pupillary reactions reflecting the severe retinal dysfunction.

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- 2. Nystagmus that is pendular or roving and present in all positions of gaze. However, this sign is late, once vision is lost.
- 3. High hyperopia (> 5 diopters), which is thought to result from impaired emmetropization (the ability of the eye to accommodate to visual stimuli) as a consequence of early-onset visual impairment.
- 4. Photophobia. However, this symptom is not present very often.
- 5. Keratoconus, a non-inflammatory, self-limiting axial ectasia of the central cornea.
- 6. Blindness or severe visual impairment presenting in infancy, frequently before age six months. Individuals with LCA usually do not achieve visual acuity better than 20/400 [17].
- 7. Extinguished or severely reduced scotopic and photopic electroretinogram (ERG).
- 8. The oculo-digital sign, characterized by poking, rubbing, and/ or pressing of the eyes [23,24]. The oculo-digital sign has been claimed to be virtually pathognomonic for LCA; however, it can also be seen in other syndromic forms of severe vision impairment.
- 9. Family history typically consistent with autosomal recessive inheritance [15,18,21,25].

Diagnosis is not made soon enough to make an early diagnosis and follow up. Diagnosis should be made withing first 6 months of life since treatment could prevent loss of vision. Very early signs of LCA-*RPE65* type are not known among physicians, as in this case.

Diagnosis usually takes 3-4 years even though parents notice some abnormalities of the child vision since the first month of life. Signs not previously described are:

A) Presence of starring at sun.

B) Unusual behaviour-related eye movement at dusk, child likes light (with marked change in behavior),

C) Mom feels her child is insecure, particularly at dusk.

Retinal findings

No retinal lesion is diagnostic of LCA or specific for certain genetic subtypes. Although fundus abnormalities are frequently present later in life, infants with LCA typically show either a normal fundus appearance or only subtle retinal pigment epithelial (RPE) granularity, retinal vessel attenuation and, uncommonly, various stages of macular atrophy.

The diagnosis of LCA in this case was established by clinical findings, parents' allegations and observation about abnormalities as well as pupillary response.

Pathogenic variants in at least 17 genes are known to cause LCA: GUCY2D (LCA1), *RPE65* (LCA2), SPATA7 (LCA3), AIPL1 (LCA4), LCA5 (LCA5), RPGRIP1 (LCA6), CRX (LCA7), CRB1 (LCA8), NMNAT1 (LCA9), CEP290 (LCA10), IMPDH1 (LCA11), RD3 (LCA12), RDH12 (LCA13), LRAT (LCA14), TULP1 (LCA15), KCNJ13 (LCA16), and IQCB1 [26,27]. Together, pathogenic variants in these genes are estimated to account for more than half of all LCA diagnoses.

Of note, the three more specific retinal phenotypes that can be observed are [15,26,28-33].

- 1. Preserved para-arteriolar retinal pigment epithelium (PPRPE) in individuals with CRB1 pathogenic variants.
- 2. "Translucent RPE," white dots, and a peculiar star-shaped maculopathy in individuals with *RPE65* pathogenic variants
- 3. A progressive macular atrophic lesion presenting in infancy or later in some individuals. Because of its sharply defined borders, this lesion has been at times called a "macular coloboma." While it has been reported to occur with pathogenic variants in AIPL1 and CRB1, the correlation of this LCA phenotype is most prominent with pathogenic variants in NMNAT1 [30-33].

However, this case illustrates that none of the features previous described was present in this child. Findings described with "Translucent RPE," white dots, and a peculiar star-shaped maculopathy in individuals with *RPE65* pathogenic variants, were not present at the very beginning in this patient, or otherwise fundus is within normal limits.

Discussion and Conclusion

Early diagnosis is needed for LCA and retina dystrophies. This case presentation illustrated diagnosis is delayed due to the unknown early signs. Early signs are not detected by a specialist, even though for a mother is certain that vision is not normal for first month of life.

Early diagnosis is needed for two reasons: 1) Vision develops during first decade of life. 2) There is treatment now and this may prevent loss of vision due to the degenerative nature of this condition, particularly as during first year of life treated patients manifest improved vision [33].

Awareness of early signs as in this case presentation:

- A) Presence of starring at sun,
- B) Unusual behaviour-related eye movement at dusk,
- C) Child likes light (with marked change in behaviour) should be taken into account.

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