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Original article

Multimodal imaging and genetic characteristics of autosomal recessive bestrophinopathy

Imagerie multimodale et caractéristiques génétiques de la bestrophinopathie autosomique récessive

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Summary

Purpose

To report the ocular manifestations, multimodal imaging characteristics and genetic testing results of six patients with autosomal recessive bestrophinopathy (ARB).

Methods

This was an observational case series including 12 eyes of 6 patients who were diagnosed with ARB. All patients underwent a complete ophthalmic examination including refraction, slit-lamp biomicroscopy, dilated fundus examination, fundus autofluorescence, optical coherence tomography and electrooculography. *BEST1* gene sequencing was also performed for all patients.

Results

The mean age was 22.8 years and the male–female ratio was 0.50. All ARB patients had a hyperopic refractive error. A spectrum of fundus abnormalities, including multifocal yellowish subretinal deposits in the posterior pole, subfoveal accumulation of vitelliform material and cystoid macular edema, was observed. Fundus autofluorescence imaging demonstrated marked hyperautofluorescence corresponding to the yellowish subretinal deposits. Optical coherence tomography revealed serous retinal detachment, intraretinal cysts, brush border appearance caused by elongation of the outer segments of photoreceptors, and hyperreflective dome-shaped deposits at the level of the retinal pigment epithelium. Fundus fluorescein angiography showed hyperfluorescence with staining of the yellowish subretinal deposits. Electrooculography showed reduced Arden ratio in all patients. In addition, biallelic pathogenic variants in the *BEST1* gene were detected in all patients.

Conclusion

ARB is a rare autosomal recessive inherited retinal disorder with biallelic pathogenic variants in the *BEST1* gene and may present with a wide range of ocular abnormalities that may not be easily

diagnosed. Multimodal retinal imaging in conjunction with EOG is helpful to establish the correct diagnosis.

Résumé

Objectif

Rapporter les manifestations oculaires, les caractéristiques d'imagerie multimodale ainsi que les résultats des tests génétiques de six patients atteints de bestrophinopathie autosomique récessive (ARA).

Méthodes

Une série de cas d'observation comprenant 12 yeux de 6 patients diagnostiqués comme ARA. Tous les patients ont subi un examen ophtalmique complet comprenant réfraction, biomicroscopie à la lampe à fente, examen du fond d'œil dilaté, autofluorescence du fond d'œil, tomographie par cohérence optique et électro-oculographie. Le séquençage du gène *BEST1* a également été effectué pour tous les patients.

Résultats

L'âge moyen était de 23,8 ans et le ratio hommes–femmes était de 0,50. Tous les patients ARA avaient une erreur de réfraction hypermétrope. Un spectre d'anomalies du fond d'œil, y compris des dépôts sous-rétiniens jaunâtres multifocaux dans le pôle postérieur, une accumulation sous-fovéale de matériel vitelliforme et un œdème maculaire cystoïde, ont été observés. L'imagerie par autofluorescence du fond d'œil a démontré une hyperautofluorescence marquée correspondant aux dépôts sous-rétiniens jaunâtres. La tomographie par cohérence optique a révélé un décollement séreux de la rétine, des kystes intrarétiniens, un aspect de bordure en brosse provoqué par l'allongement des segments externes des photorécepteurs et des dépôts hyperréfléchissants en forme de dôme au niveau de l'épithélium pigmentaire rétinien. L'angiographie fluorescente du fond d'œil a montré une hyperfluorescence avec coloration des dépôts jaunâtres sous-rétiniens. L'électro-oculographie a montré une réduction du rapport d'Arden chez tous les patients. De plus, des variants

pathogènes biallélicques du gène *BEST1* ont été détectés chez tous les patients.

Conclusion

L'ARB est une maladie rétinienne héréditaire autosomique récessive rare avec des variantes pathogènes biallélicques du gène *BEST1* et peut se présenter avec un large éventail d'anomalies oculaires qui peuvent ne pas être facilement diagnostiquées. L'imagerie rétinienne multimodale associée à l'EOG est utile pour établir un diagnostic correct.

Introduction

Bestrophinopathies are a spectrum of inherited retinal dystrophies which are caused by the pathogenic variation in the Bestrophin-1, the protein product of the *BEST1* gene (OMIM 607854, formerly known as *VMD2* gene) found on the long arm of chromosome 11 (*11q12*), that is a 585-amino acid pentameric Ca^{+2} activated Cl^{-} channel localized to the basolateral membrane of retinal pigment epithelium (RPE) [1], [2]. This multifunctional gene product plays important roles in different intra- and extra-cellular ionic mechanisms in addition to adjustment of normal ocular development [2], [3], [4]. Pathogenic variants in the *BEST1* gene lead to a variety of ocular phenotypes including Best vitelliform macular dystrophy (BVMD) (OMIM 153700); adult-onset vitelliform macular degeneration (AVMD) (OMIM 608161); autosomal dominant vitreoretinochoroidopathy (ADVIRC) (OMIM 193220); microcornea, rod-cone dystrophy, cataract, and posterior staphyloma syndrome (MRCS) (OMIM 193220); atypical retinitis pigmentosa (OMIM 613194) and autosomal recessive bestrophinopathy (ARB) (OMIM 611809) [1], [2].
ARB is caused by biallelic pathogenic variants in the *BEST1* gene and has been first described in 2008 with findings consisting of central visual loss due to subretinal fluid or macular edema, characteristic retinopathy with the punctate flecks and vitelliform material deposition, an absent or severely reduced electrooculogram (EOG), abnormal or subnormal electroretinogram (ERG), and hyperopia with in some cases of shallow anterior chamber [5], [6], [7].

In this article, six cases with ARB are presented along with their clinical findings, multimodal retinal imaging characteristics and genetic analysis.

Section snippets

Methods

The study was undertaken in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. The study protocol was approved by the Ethics Committee. All patients were white Caucasians, except case 6 who was a Syrian refugee.

Comprehensive ocular history and ophthalmic examinations, including the best-corrected visual acuity (BCVA) tests, using the Snellen chart (20 feet); intraocular pressure measurements using Goldmann

Results

Six patients from 5 families were included in the study. Case 2 was older sister of case 1. The demographic and clinical characteristics of all participants are summarized in Table 1. At the time of presentation, patients were 10–39 years old (mean: 22.8). Four of the patients were female and the remaining 2 were male (Female-to-male ratio: 2).

All patients had hyperopic refractive errors in which maximum hyperopic refraction was OD: +5.00 +0.50 × 80 diopters and OS: +5.50 +0.75 × 95 diopters in case

Discussion

In this study, we presented six cases of ARB, all were confirmed by genetic analysis. Patients with ARB were characterized by a variety of retinal findings including macular edema, serous retinal detachment, intraretinal cystic cavities and multifocal subretinal vitelliform deposits in addition to presence of subretinal deposits' brightly autofluorescence in FAF and decreased Arden ratio in EOG.

Furthermore, all patients had hyperopic refractive errors, 2 of them had shallow anterior chambers

Disclosure of interest

The authors declare that they have no competing interest.