OLIVER McFARLANE SYNDROME AND CHOROIDAL NEOVASCULARISATION: A CASE REPORT.

Aruni Kumari Makuloluwa[1], Rutika Dodeja[1,2], Michalis Georgiou[4,5], Jose Gonzalez-Martin[2], Richard Hagan[3], Savita Madhusudhan[1], Michel Michaelides[4,5]

1. St. Paul's Eye Unit, Royal Liverpool University Hospital, Liverpool, United Kingdom.
2. Department of Ophthalmology, Alder Hey Children's Hospital, Liverpool, United Kingdom.
3. Department of Electrophysiology, Royal Liverpool University Hospital, Liverpool, United Kingdom.
4. Moorfields Eye Hospital, London, United Kingdom.
5. UCL Institute of Ophthalmology, University College London, London, United Kingdom.

Abstract

We report the first case of choroidal neovascularisation (CNV) secondary to Oliver McFarlane syndrome diagnosed in a ten-year-old white female who presented with reduced visual acuity and a macular haemorrhage in her right eye. CNV was confirmed on optical coherence tomography. She was initially treated with a single injection of intravitreal bevacizumab and 2 years later with an injection of intravitreal ranibizumab for a recurrence. Although macular scarring secondary to the CNV was observed, her vision has stabilised and she continues to be closely monitored.

Keywords

Oliver McFarlane syndrome; congenital trichomegaly; choroidal neovascularisation.

Introduction

There are 15 reported cases of Oliver McFarlane syndrome worldwide. To date, and to the best of our knowledge, no associations with macular choroidal neovascularisation (CNV) have previously been reported. In this paper, we present a patient with a diagnosis of Oliver McFarlane syndrome that was complicated by secondary CNV, which was treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections.

Literature Search

The authors searched PubMed on May 6, 2019, without date restriction for English-Language articles using the following terms singly and in combination: Oliver McFarlane syndrome, congenital trichomegaly, and choroidal neovascularisation.

Case report

A five-year-old white female was referred to the hospital eye department for a suspected left convergent squint. She was born of a non-consanguineous marriage by full term vaginal delivery, with a birth weight of 2980 grams. She was otherwise fit and well, with no significant past ophthalmic, medical, or family history. In addition, she did not have any history of ocular trauma.

Her best-corrected visual acuities were 6/9.5 in the right and 6/12 +2 in the left eye, with no significant refractive error. She had normal pupillary reactions and colour vision. Anterior segment examination was unremarkable. On dilated fundoscopy, there was bilateral diffuse pigmentary retinopathy with retinal pigment epithelial (RPE) changes at the maculae (Figures 1A and 1B). Optic discs were healthy with normal blood vessel calibre. The parents and siblings were examined and no retinal abnormalities were found.

At the age of nine, she started to notice symptoms of nyctalopia. At the age of ten, she experienced an acute reduction in visual acuity (VA) in the right eye to 6/12. Dilated fundoscopy and detailed retinal imaging revealed bilateral diffuse pigmentary retinopathy and chorioretinal atrophy, with a macular haemorrhage in the right eye (Figure 1C). She was also noted to have trichomegaly and have a short stature, which in association with the retinal phenotype raised the possibility of Oliver McFarlane syndrome (OMS). She had no signs of peripheral neuropathy. Optical coherence tomography (OCT) of the macula identified a CNV, with both intraretinal (IRF) and subretinal fluid (SRF) (Figure 1D). She was given a single intravitreal injection of bevacizumab which stabilised her macular lesion. Visual acuity stabilised at 6/18 in the right eye. She developed a right exotropia with manifest latent nystagmus and a small fibrotic macular scar.

Genetic testing was undertaken with whole exome sequencing, which identified two novel likely disease-causing compound heterozygous variants in the *PNPLA6* gene; c.3334G>A, p.(A1112T) and c.3547C>T, p.(R1183W). Test results from November 2015 confirm that parents were tested and that the bi-allelic missense mutations found in our patient were determined to be on 2 different copies of the PNPLA6 gene, that is, in *trans*, thereby confirming autosomal recessive inheritance, in keeping with a diagnosis of OMS.

Two years later, VA in the right eye reduced to 6/75 and that of the left eye was maintained at 6/9. Clinical examination revealed a right macular haemorrhage and a resolved left parafoveal haemorrhage. OCT identified a reactivation of the CNV, with new IRF and SRF in the right eye (no active CNV in the left eye); and she was treated with a single intravitreal injection of ranibizumab which resulted in resolution of disease activity.

One year since the last anti-VEGF injection, VAs remain stable at 6/60 and 6/9 in the right and left eyes, respectively. There has been increasingly marked chorioretinal degeneration with clumps of pigment in the posterior pole and mid-peripheral retina (Figures 1E and 1F). Macular OCT scans (Figures 1G and 1H) show sub-foveal fibrosis with minimal chronic IRF in the right eye, and loss of outer retinal structure in both eyes. There is no evidence of fibrosis or fluid in the left eye.

The electrodiagnostic testing (EDT) was repeated at the age of thirteen (Figure 2), which showed marked attenuation of rod and cone function on full-field ERGs, with greater rod than cone dysfunction. Multi-focal electroretinogram (mfERG) showed reduced responses most obvious in ring 2, although both the central hexagon and ring 3 responses were reduced, in the right eye and reduced responses outside the central hexagon with central sparing in the left eye. The electro-oculogram was flat with a light peak to dark trough ratio of one, suggesting severe dysfunction of the RPE. Overall, there was marked deterioration compared to EDT undertaken six years previously, when the cone responses were normal, mixed rod and cone responses were borderline normal, and rod pathway responses were marginally reduced for amplitude and latency.

She was considered as severely sight impaired at the age of fourteen due to marked constriction of her peripheral visual fields. She was initially monitored every 3 months and then every 6 months on a *pro re nata* treatment protocol. She remains under direct monitoring by the endocrinology services due to failure to attain menarche at the age of 15 years.

Discussion

Oliver McFarlane syndrome (OMS), was first described in 1965 in a patient with long eyelashes, pigmentary degeneration of the retina, and both growth and developmental delay.[1] Since then, 15 cases have been published in the literature and we present the 16th case (Table 1).

Sequence variants in the *PNPLA6* gene have been shown to be the genetic cause of OMS.[2] It is inherited in an autosomal recessive manner and carriers are asymptomatic with no discernible phenotype.[2] Using whole exome sequencing, Hufnagel *et al*. showed compound heterozygous variants in *PNPLA6* in six patients with OMS.[2] *PNPLA6* encodes the enzyme, neuropathy target esterase (NTE) that catalyses de-esterification of membrane phosphatidylcholine into fatty acids and glycerophosphocholine, therefore it is integral in maintaining membrane integrity.[3] Dysfunction of this gene has also been implicated in other conditions, namely, Boucher- Neuhäuser syndrome, Gordon Holmes syndrome, Laurence Moon syndrome and Spastic paraplegia type 39.[3]

PNPLA6 has been found to be widely expressed in adult and human embryonic tissues including the neural retina, RPE, choroid, anterior and posterior pituitary, cerebellum and ventricular zones.[2] It is also found in the epidermis, lens, extraocular muscles, nasal epithelium, trigeminal ganglion and diencephalon.[2] Therefore, *PNPLA6* sequence variants have been shown to give rise to an array of phenotypes that include chorioretinal dystrophy, anterior hypopituitarism, cerebellar dysfunction, upper and lower motor neuron dysfunction and hair anomalies.[3] Thyroid and growth hormone deficiencies may lead to impairment of intellect and growth.[2] Interestingly, to date, our patient has not been found to have abnormal peripheral neurology.

Chorioretinal atrophy is typically noted in the first five years of life.[2] This may relate to abnormalities of multiple membrane phospholipid functions: outer segment disc membrane formation in photoreceptors, lipid second messengers in visual transduction, degeneration of optic nerve axons and vitamin A analogue processing or melanosome trafficking in RPE.[2] The case presented by Patsi *et al*. had retinal detachment requiring surgery on a background of high myopia.[3] Retinal detachment has otherwise not been reported with *PNPLA6* related disorders, thus, it may relate to the high myopia or be part of the spectrum of the phenotypes observed in these disorders.

In the context of inherited chorioretinal diseases, chronic inflammation promoting an angiogenic drive, disruption and degeneration of the RPE and dysfunction of choroidal circulation, may all play a role in inciting secondary CNV.[4-5] CNV has been described in many inherited retinal diseases, including retinitis pigmentosa, Stargardt disease, fundus flavimaculatus, Sorsby fundus dystrophy, Bietti crystalline dystrophy, Best disease, and autosomal recessive bestrophinopathy, which have been successfully treated with either intravitreal bevacizumab or ranibizumab – often with a single injection[6-15] or photodynamic therapy.[16-18] Prager *et al.* also presented a case of CNV secondary to Sorsby fundus dystrophy, which was successfully treated with three systemic injections of bevacizumab (5mg/kg) at two-weekly intervals, with no serious ocular or systemic side effects.[19] In the majority of these cases, the CNV resolved with a degree of scarring. Autosomal recessive bestrophinopathy, has also been successfully managed with surgical removal of the CNV.[20]

The literature to date describes various treatment protocols, which makes it difficult to propose a protocol for frequency of treatment. Batioglua *et al*. showed no recurrence at 3

years and maintenance of VA following three four-weekly intravitreal injections of ranibizumab for CNV associated with Best disease.[11] Similarly, Chhablani *et al*. described a case of CNV associated with Best disease that was treated with two four-weekly injections of bevacizumab, that showed resolution of CNV and no evidence of recurrence at 9 months.[12] Mohla *et al*. treated a patient with CNV secondary to Sorsby fundus dystrophy with two four-weekly injections of bevacizumab. They showed that the lesions resolved and remained stable with no recurrence five months after the last injection.[15] Tsokolas *et al*. presented a case of two siblings who were treated initially on a *pro re nata* basis and then switched to a treat and extend protocol. They showed that the latter is a more effective protocol in reducing the recurrence of CNV secondary to Sorsby fundus dystrophy.[21]

Conclusion

In this manuscript, we have presented the first case of OMS complicated by recurrent CNV, which was successfully treated with intravitreal anti-VEGF agents at both the initial episode and reactivation. However, vision was poor following the second injection due to macular scarring.

Conflict of interests

None.

Funding

MM is supported by a grant from the National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital National Health Service Foundation Trust and UCL Institute of Ophthalmology.

References

1. Haritoglou C, Rudolph G, Kalpadakis P, Boergen KP. Congenital trichomegaly (Oliver-McFarlane syndrome): a case report with 9 years' follow up. Br J Ophthalmol. 2003;87(1):119-20.

2. Hufnagel RB, Arno G, Hein ND, Hersheson J, Prasad, Anderson Y6, Krueger LA, Gregory LC, Stoetzel C, Jaworek TJ, et al. Neuropathy target esterase impairments cause Oliver-McFarlane and Laurence-Moon syndromes. J Med Genet. 2015;52(2):85-94.
3. Patsi O, De Beaufort C, Kerschen P, Cardillo S, Soehn A, Rautenberg M, Diederich NJ. A new PNPLA6 mutation presenting as Oliver McFarlane syndrome. J Neurol Sci. 2018;392:1-2.
4. Marano F, Deutman AF, Leys A, Aandekerk AL. Hereditary retinal dystrophies and choroidal neovascularization. Graefes Arch Clin Exp Ophthalmol. 2000;238(9):760-4.
5. Cakir M1, Cekiç O, Yilmaz OF. Intravitreal bevacizumab and triamcinolone treatment for choroidal neovascularization in Best disease. J AAPOS. 2009;13(1):94-6.
6. Battaglia Parodi M1, De Benedetto U, Knutsson KA, Scotti F, Librando A, Bandello F, Iacono P. Juxtafoveal choroidal neovascularization associated with retinitis pigmentosa treated with intravitreal bevacizumab. J Ocul Pharmacol Ther. 2012;28(2):202-4.
7. Battaglia Parodi M, Munk MR, Iacono P, Bandello F. Ranibizumab for subfoveal choroidal neovascularisation associated with Stargardt disease. Br J Ophthalmol. 2015;99(9):1268-70.
8. Tejerina AN, García-Pous M, Pozos EP, Esteban MC, Boronat JM. Ranibizumab for choroidal neovascularization in fundus flavimaculatus. Retin Cases Brief Rep. 2008;2(3):250-2.
9. Gemenetzi MK, Luff AJ, Lotery AJ. Successful treatment of choroidal neovascularization secondary to sorsby fundus dystrophy with intravitreal bevacizumab. Retin Cases Brief Rep. 2011;5(2):132-5.
10. Nachiappan K, Krishnan T, Madhavan J. Ranibizumab for choroidal neovascular membrane in a rare case of Bietti's crystalline dystrophy: a case report. Indian J Ophthalmol. 2012;60(3):207-9.
11. Batioglua F, Ozmerta E, Surena E, Demirel S. Intravitreal Ranibizumab for the Treatment of Choroidal Neovascularization in Best's Vitelliform Macular Dystrophy. J Med Cases. 2012;3(4):250-3.
12. Chhablani J1, Jalali S. Intravitreal bevacizumab for choroidal neovascularization secondary to Best vitelliform macular dystrophy in a 6-year-old child. Eur J Ophthalmol. 2012 Jul-Aug;22(4):677-9.
13. Madhusudhan S, Hussain A, Sahni JN. Value of anti-VEGF treatment in choroidal neovascularisation associated with autosomal recessive bestrophinopathy. Digit J Ophthalmol. 2013;19(4):59–63.
14. Khan KN1, Mahroo OA, Islam F, Webster AR, Moore AT, Michaelides M. Functional and anatomical outcomes of choroidal neovascularization complicating best1-related retinopathy. Retina. 2017;37(7):1360-1370.
15. Mohla A, Khan K, Kasilian M, Michaelides M. OCT angiography in the management of choroidal neovascular membrane secondary to Sorsby fundus dystrophy. BMJ Case Rep. 2016;2016. pii: bcr2016216453.
16. Cheng JY1, Adrian KH. Photodynamic therapy for choroidal neovascularization in stargardt disease and retinitis pigmentosa. Retin Cases Brief Rep. 2009;3(4):388-90.
17. Souied EH, Pawlak D, Algan M, Sayag D, Coscas G, Soubrane G. Photodynamic therapy for choroidal neovascularization on late-onset fundus flavimaculatus. Am J Ophthalmol. 2005;140(2):312-4.
18. Frennesson CI, Wadelius C, Nilsson SE. Best vitelliform macular dystrophy in a Swedish family: genetic analysis and a seven-year follow-up of photodynamic

treatment of a young boy with choroidal neovascularization. Acta Ophthalmol. 2014;92(3):238-42.
19. Prager F, Michels S, Geitzenauer W, Schmidt-Erfurth U. Choroidal neovascularization secondary to Sorsby fundus dystrophy treated with systemic bevacizumab (Avastin). Acta Ophthalmol Scand. 2007;85(8):904-6.
20. Moreira CA Jr, Moreira-Neto CA, Junqueira Nobrega M, Cunha de Souza E. Ten-Year Follow-Up after Bilateral Submacular Neovascular Membrane Removal in a Case of Autosomal Recessive Bestrophinopathy. Case Rep Ophthalmol. 2017;8(1):265-270.
21. Tsokolas G, Almuhtaseb H, Lotery A. Evaluation of Pro-re-Nata (PRN) and Treat and Extend Bevacizumab treatment protocols in Sorsby Fundus Dystrophy. Eur J Ophthalmol. 2020 Jan;30(1):26-33. Epub 2018 Nov 13.
22. Haimi M, Gershoni-Baruch R. Autosomal recessive Oliver-McFarlane syndrome: retinitis pigmentosa, short stature (GH deficiency), trichomegaly, and hair anomalies or CPD syndrome (chorioretinopathy-pituitary dysfunction). Am J Med Genet A. 2005;138A(3):268-71.
23. Sonmez S1, Forsyth RJ, Matthews DS, Clarke M, Splitt M. Oliver-McFarlane syndrome (chorioretinopathy-pituitary dysfunction) with prominent early pituitary dysfunction: differentiation from choroideremia-hypopituitarism. Clin Dysmorphol. 2008;17(4):265-7.
24. Pedroso JL, Rivero RL, de Miranda VA, Avelino MA, Dutra LA, Ribeiro RS, Nunes KF, Manzano GM, Barsottini OG. Neuroimaging features in congenital trichomegaly: the Oliver-McFarlane syndrome. J Neuroimaging. 2014;24(4):418-20.
25. Sheng X, Zhang S, Peter Boergen K, Li H, Liu Y. Oliver-McFarlane syndrome in a chinese boy: retinitis pigmentosa, trichomegaly, hair anomalies and mental retardation. Ophthalmic Genet. 2015 Mar;36(1):70-4.