American Journal of Ophthalmology Case Reports 36 (2024) 102173

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Macular telangiectasia type 2 in a patient with Down syndrome: A possible association

Safa Halouani *, Alexandra Miere, Hoang Mai Le, Nabil Herda, Alina Cirneanu, Eric H. Souied

Department of Ophthalmology, Centre Hospitalier Intercommunal de Créteil, Créteil, France

ARTICLE INFO

Keywords:
Down syndrome
Macular telangiectasia
Mactel 2
Multimodal imaging

ABSTRACT

Purpose: Down syndrome (DS) is one of the most prevalent genetic diseases associated with a variety of ophthalmic disorders, including reported retinal abnormalities. Macular telangiectasia type 2 (MacTel 2) is a late-onset neurodegenerative retinal disease with a substantial genetic component. We hereby describe a case of a female with DS who presented with MacTel 2, and we discuss the possible pathways associating both entities.
Observation: We report the case of a 49-year-old female with a medical history of DS and hydroxychloroquine (HCQ) intake. She was referred for HCQ retinal toxicity screening. The multimodal imaging revealed a temporal perifoveal gray area with crystal deposits on multicolor fundoscopy with parafoveal outer retinal atrophy and ellipsoid zone loss with inner retinal cavitations in both eyes on the optical Coherence Tomography (OCT) B scan. The corresponding swept-source OCT angiography confirmed the presence of bilateral macular telangiectasia.
Conclusion and importance: Metabolic pathways including serine/glycine and sphingolipids are incriminated in both entities' pathogenesis suggesting a possible association, hence, the importance of raising awareness of this association. More cases are likely to be found since DS patients currently have a nearly normal lifespan. Additional retinal examination of DS adults is then necessary to look for signs of MacTel 2.

1. Introduction

Down syndrome (DS) is one of the most prevalent genetic diseases in the world, with a reported incidence of approximately 1 in 1000 to 1 in 1100 live births worldwide.[1] Patients with DS have experienced significant increases in life expectancy over the past few decades, owing to reduced institutionalization and improved access to medical care, such as surgical intervention for congenital heart defects.[2,3] DS has been associated with a variety of ophthalmic disorders, including strabismus, keratoconus, cataracts, and optic nerve abnormalities. Reported retinal abnormalities include a high incidence of foveal hypoplasia, with abnormalities of the inner retinal layers especially prevalent.[4,5]

Idiopathic juxtafoveal retinal telangiectasis type 2 or Macular telangiectasia type 2 (MacTel 2) is a bilateral neurodegenerative retinal disease affecting between 0.004 and 0.1 % of the population.[6,7] It is characterized by alterations of the macular capillary network and neurosensory atrophy beginning temporal to the fovea. Symptoms typically start in the 5th and 6th decade of life[8,9] and lead to progressive loss of central vision.[6,7] Several factors suggest that MacTel has a substantial genetic component. The disease occurs bilaterally and is heritable based on studies of monozygotic twins, siblings, and families.[10]

We hereby describe a case of a 49-year-old female with DS presenting with MacTel 2, and we discuss the possible pathways associating both entities.

2. Case report

2.1. Patient information

We report the case of a 49-year-old female with a medical history of DS, cerebral meningioma surgery, and immune thrombocytopenic purpura under corticosteroids, rituximab, and hydroxychloroquine (HCQ). She was referred to our department for HCQ retinal toxicity screening.

2.2. Clinical findings

On the ophthalmological examination, her best corrected visual acuity (BCVA) was 20/32 in the right eye (RE) and 20/25 in the left eye (LE). She was pseudo-phakic in both eyes. The multimodal imaging

* Corresponding author. Centre Hospitalier Intercommunal de Créteil 40 avenue de Verdun, 94000, Créteil, France.
E-mail address: safaa.halouani@gmail.com (S. Halouani).

https://doi.org/10.1016/j.ajoc.2024.102173
Received 11 December 2023; Received in revised form 31 August 2024; Accepted 12 September 2024
Available online 14 September 2024

revealed a temporal perifoveal graying area with crystal deposits on multicolor fundoscopy with slightly increased reflectance and autofluorescence on the blue light and autofluorescence images respectively, in both eyes. The B scan passing through these areas in spectral-domain optical coherence tomography (SD-OCT) was consistent with parafoveal outer retinal atrophy and ellipsoid zone loss in both eyes (figure). The presence of early hyperfluorescent followed by diffuse leakage in the late frames of fluorescein angiography confirmed the vascular origin of these lesions. The corresponding swept-source OCT angiography (SS-OCTA) allowed enhanced visualization of the abnormal retinal capillaries with superficial capillary vessels dragging and a small blunted right angle venule temporal to the fovea in the RE and a discreetly distorted foveal avascular zone in superficial capillary plexuses and capillary ectasia in the deep capillary plexuses in the LE.

2.3. Diagnostic assessment and follow-up

Based on the typical fundings in multimodal imaging, the age of the patient, and the bilaterality of the lesions we concluded that the patient had bilateral MacTel 2. Due to the existing maculopathy, we decided to stop HCQ intake after agreement with the referring physician and a close follow-up for early detection of neovascular complications.

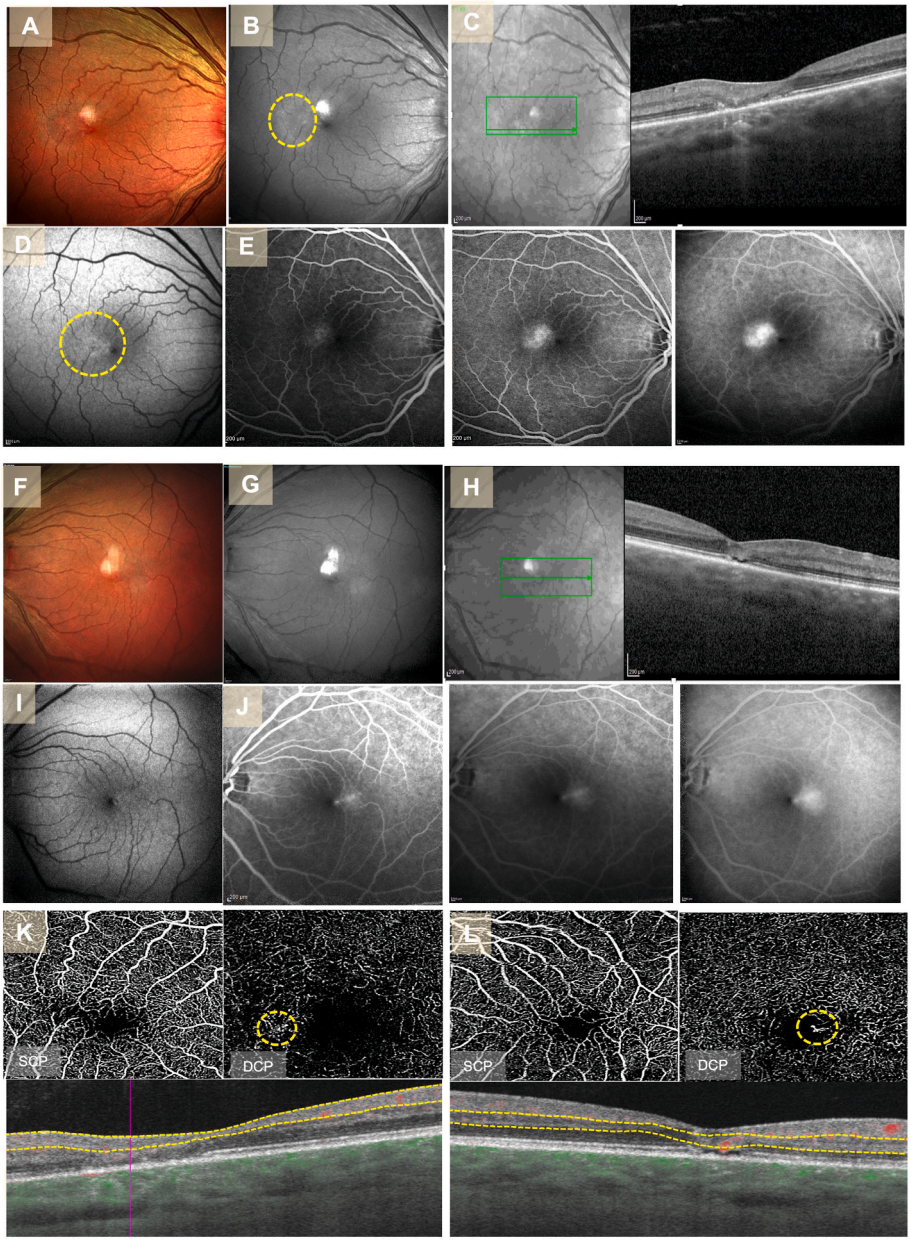

Fig. 1. Multimodal imaging of both eyes of a forty-nine-years old adult with Down syndrome presenting with bilateral macular telangiectasia type 2. Multicolor fundoscopy images of the right (**A**) and left (**F**) eyes showing temporal perifoveal graying area. These areas are hyper auto-fluorescent (**D, I**) and with slightly increased reflectance (**B, G**) in the blue light images. The presence of early hyper fluorescence followed by diffuse leakage in the late frames of fluorescein angiography (**E, J**) confirmed the vascular origin of these lesions. The macular Spectral-domain optical coherence tomography revealed outer retinal atrophy in the right eye (**C**) and ellipsoid zone loss in the left eye (**H**). Swept-source OCT angiography with the corresponding B scan (**K, L**), allowed enhanced visualization of the abnormal retinal capillaries with superficial capillary vessels dragging as well as a small blunted right angle venule temporal to the fovea in the right eye (**K**) and a distorted foveal avascular zone in superficial capillary plexuses (SCP) and capillary ectasia in the deep capillary plexuses (DCP) as seen in the left eye (L). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3. Discussion

We hereby discuss a case of an atypical presentation of a bilateral MacTel 2 patient with DS. Our case is consistent with two previously reported cases,[11,12] one of them postmortem, as being younger than the mean age of MacTel 2 patients.[8,9]

Through our observation, we try to discuss a possible association between MacTel 2 and DS. Although incompletely known, the causative disease mechanisms imply both genetic and metabolic dysregulation in both conditions.

If the genetic background of DS is solidly undeniable, MacTel 2 is also defined as a late-onset degenerative retinal disease with a complex genetic architecture. Although rare causative mutations have been identified through whole-exome sequencing and pedigree analyses, they only account for less than 5 % of cases.[13] To better support the genetic-metabolic correlation, recent genome-wide association studies (GWAS) have, indeed, highlighted significant associations at three independent loci, two of which are implicated in the glycine/serine metabolic pathway.[13] Consistently, metabolomic surveys of patient populations have linked MacTel to changes in metabolites related to the cysteine/methionine cycle.[10] Serine biosynthesis is also a critical part of Muller cells' defense against oxidative stress.[10] Dysregulation of this pathway can potentially cause macular pathology.[10,14] To support this metabolic pathway's implication in retinal cells, researchers have explored MacTel 2 pathogenesis pathways through a cellular model like induced pluripotent stem cells differentiated into retinal pigmented epithelial cells (iRPE) from MacTel 2 donors. These models have replicated the low serine levels observed in patients with MacTel, shedding light on potential mechanisms underlying the disease.[15] Some studies even link serine and glycine metabolism deficiencies to sphingolipids dysregulation, not only in MacTel patients[10] but also in patients presenting with neural and retinal degeneration.[16,17] A low level of serine is concomitant with an increase in a neurotoxic, atypical lipid species, 1-deoxysphingolipids (1-dSLs).[10] Furthermore, a subtype of sphingolipids, i.e. ceramides, have a broad role in degenerative retinal diseases and in a retinitis pigmentosa model for instance, blocking ceramide biosynthesis prevented photoreceptor cell death of retinitis pigmentosa.[18] Interestingly, ceramides are increased in MacTel patients as they act as pro-apoptotic signaling molecules.[10]

In DS patients, previous literature has already thoroughly studied the metabolic and epigenetic factors. However, while there is substantial evidence supporting the involvement of serine/glycine metabolism in MacTel 2, no direct evidence currently links this metabolic pathway to DS. Moreover, abnormalities in ceramide levels have been reported in DS pregnancies, implicating sphingolipid metabolism in the condition.[19] Ceramides alter metabolites in DS fetuses and serve as biochemical markers of DS.[19,20] Nevertheless, current evidence does not explicitly establish a common ceramide pathway alteration in both DS and MacTel 2.

Thus, further research is needed in order to shed light on the possible susceptibility of DS patients to develop MacTel 2.

Our case report is one of the few documented instances of MacTel 2 in a patient with DS. The coexistence of these two conditions, which are rarely reported together, provides a unique opportunity to explore potential overlapping pathways in their pathogenesis. While the involvement of serine/glycine metabolism and sphingolipid metabolism in MacTel 2 is well-established, this was not proven of DS. Although this report hypothesizes on the possibility of a similar metabolic dysregulation in DS, that could predispose these patients to retinal diseases like MacTel 2, further research into the metabolic and genetic links between these conditions is needed. Moreover, given the increasing life expectancy of DS patients, it is crucial to consider comprehensive retinal screenings to detect signs of MacTel 2 early and manage it appropriately.

4. Conclusions

In summary, this case report aims to increase awareness of this possible association especially since more cases are likely to be found with DS patients currently having a nearly normal lifespan. Additional retinal examination of DS adults is necessary to further investigate signs of MacTel. Further studies, especially metabolomics, and genetic analysis, are required to understand why this association occurs.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

CRediT authorship contribution statement

Safa Halouani: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Alexandra Miere:** Writing – review & editing, Validation. **Hoang Mai Le:** Methodology. **Nabil Herda:** Investigation. **Alina Cirneanu:** Data curation. **Eric H. Souied:** Writing – review & editing, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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