Retinal changes associated with multivitamin deficiency before and after supplementation

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Background: Nutritional visual defects are apparently uncommon nowadays in developed nations. Retinal change-related visual defects caused by hypovitaminoses may be underdiagnosed.

Aim of the study: To investigate the retinal structural and functional changes in a patient with multivitamin deficiency before and during vitamin supplementation.

Methods: A 51-year-old female had been on vegetarian diet as a child, and on restrictive vegan diet during the last 2 years, developing severe bilateral deterioration of visual function and polyneuropathy. Blood test revealed low levels of vitamin A, B6 and D. The patient underwent examinations with optical coherence tomography (OCT), computerized visual field examination (VF), electroretinography (ERG), visual evoked potentials (VEP) and neurography before and after vitamin supplementation.

Results: Visual acuity (VA) was 20/1000 and VF examination showed central scotoma in both eyes. Color vision was significantly affected. Full-field ERG showed normal rod and cone function, but a clearly reduced central peak was registered in multifocal ERG (mf-ERG), indicating impaired fovea function. VEP showed delayed latency and low amplitude of P100 in both eyes. Neurography showed sensory polyneuropathy. OCT showed significant thinning of macular ganglion cell plus inner plexiform layer (GCIPL) with rapid progression. Retinal nerve fiber layer (RNFL) was preserved and normal, which is in contrast to neuroinflammatory conditions. After 2.5 years of multivitamin supplementation, the visual functions were improved. GCIPL thickness was stable without further deterioration.

Conclusions: Multivitamin deficiency results in progressive thinning of GCIPL with severe visual deterioration. In contrast to neuroinflammation, RNFL is preserved and normal. Stabilized GCIPL during vitamin supplementation was associated with improved visual function. OCT provides a sensitive and objective measure for differential diagnosis, monitoring retinal change and response to therapy.

KEYWORDS
ganglion cell plus inner plexiform layer, optical coherence tomography, retinal nerve fiber layer, vitamin deficiency
1 | INTRODUCTION

Nutritional visual defects, especially due to deficiency in vitamins, are well known, but apparently uncommon nowadays in developed nations.\(^1\)\(^-\)\(^3\) Hypovitaminoses may be an imminent condition with increased bariatric surgery due to global epidemic of obesity,\(^4\) increased popularity of vegan or vegetarian diets and/or high alcohol consumption.\(^5\) Retinal change-related visual defects caused by hypovitaminoses may be underdiagnosed. The relationship between retinal structure changes and visual functions in hypovitaminoses as well as the course are not well defined.\(^6\) Optical coherence tomography (OCT) provides direct in-vivo, non-invasive, sensitive, and reliable measures of the retina.\(^6\) Examination with OCT does not need pupil dilation or direct eye contact. With help of OCT, macular pathology can be found and monitored both qualitatively and quantitatively at few micrometer level.

Here, we report a patient with multivitamin deficiency who developed ophthalmic symptoms and polyneuropathy. OCT measures including thickness of macular ganglion cell plus inner plexiform layer (GCIPL) and retinal nerve fiber layer (RNFL) were applied to monitor course of the disease before and after vitamin supplementation therapy. GCIPL and RNFL were obtained in parallel with ophthalmologic examinations including visual acuity (VA), color vision, visual field (VF), and visual evoked potentials (VEP).

2 | MATERIAL AND METHODS

A 51-year-old Caucasian woman was referred by the ophthalmologist to the neurology clinic due to a 6-month history of deteriorating vision and paresthesia in both legs. The patient smoked about 20 cigarettes per day for many years, had no high alcohol consumption. She reported that she was on vegetarian diet since she was 6-year-old, and had been on strict vegan diet during the last 2 years, and on vitamin supplementation with intramuscular injection of B12 1 mg every 3 months plus folic acid 1 mg daily since last 2 years. Visual impairment without pain occurred insidiously in both eyes over last 6 months. Recently, she reported central visual field defects in both eyes, with difficulties to read text or watch TV. She experienced fluctuating numbness in the both legs, especially inside the thighs for at least 1 year.

Neurological examination revealed no focal deficiency. Ophthalmologic examination showed an extreme reduction in visual acuity (VA) reaching 20/1000 Snellen in both eyes. Color vision was significantly affected: Hardy, Rand, and Rittler pseudo-isochromatic plates test (HRR) resulted in 16 fails out of 24 in the right eye, and 14 fails out of 24 in the left eye (a score of more than 5 is considered abnormal). Intraocular pressure was normal in both eyes. Fundoscopy did not reveal any pathological signs (Figure 1A). Fundus fluorescence angiography showed normal retinal blood circulation (Figure 1B), as did angiography with indocyanine green for the choroidal circulation (not shown). A full-field electroretinogram (ERG) showed normal rod (Figure 1C) and cone function (Figure 1D), but multifocal ERG (mf-ERG) produced a clearly reduced central peak (Figure 1E), consistent with the low VA.

Optical coherence tomography (Figure 2A) showed normal thickness of RNFL (82 µm right, 87 left, within 95% normal limit), but significantly thinned GCIPL (59 µm right, 61 left, outside of 99% normal limit). The OCT parameters deteriorated at 3-month follow-up (56 µm right, 56 left). Humphrey perimetry showed bilateral central scotomas with a visual field index (VFI) of 82% in the right eye and 80% in the left (Figure 2B). VEP (Figure 2C) showed delayed latency: right 137 ms, left 127 ms (reference: <110 ms); and reduced amplitude: right 8.4 µV, left 7.0 µV (reference >10 µV). Neurography showed reduced sensory amplitude in bilateral ulnar (Figure 2D) and sural nerves (Figure 2E); amplitude of ulnar nerves: right = left 2.6 microvolts (µV) (reference >5 µV); sural nerves: right 1.6 µV, left 1.9 µV (reference >5 µV). Sensory conduction velocities were normal: above 45 m/s in ulnar nerves; above 40 m/s in sural nerves (not shown).

MRI of the brain and spinal cord were normal. Cerebrospinal fluid (CSF) were performed twice and showed no pleocytosis or oligoclonal IgG bands, negative for neurotrophic viruses and bacteria; but high level of neurofilament light chains, 14,400 and 7920 ng/L (reference <890), respectively, but normal levels of tau 342 ng/L (reference <400), phosphor-tau 40 ng/L (ref. <44 ng/L), and amyloid 868 ng/L (reference >550) in CSF. MOG and AQP4-antibodies were negative in both CSF and serum. In the serum, Vitamin A was 0.8 mmol/L (reference 1.0–3.3), vitamin B6 was 14 nmol/L (reference 20–122), and vitamin D was 21 nmol/L (reference >50). Vitamin B1, B12, and folic acid were normal.

The patient was treated with multivitamin supplementation plus B-complex injection, and oral vitamin A and D daily. The levels of vitamin A (1.1 mmol), B6 (23 nmol/L), and D (50 nmol/L) were normalized at 3–6 months follow-up. Her vision and paresthesia improved successively over 2.5 years’ period during the supplementation. She could now read text and watch TV, although with certain difficulties. VA was 20/50 Snellen in the right and 20/30 in the left. Color vision improved: 8 fails out of 24 in the right and 3 fails out of 24 in the left eye, according to HRR-test. GCIPL thickness remained stable (right 56 µm, left 54) and RNFL thickness was unchanged with normal
values at 3-year follow-up (Figure 3A). VF were improved with reduced central scotomas and improved VFI (Figure 3B). Improved latency and amplitude of P100 on VEP were also observed in both eyes (Figure 3C). Normalized values of neurography were registered in both arms and legs (Figure 3D). Three years follow-up showed stable clinical features and OCT parameters.

3 | DISCUSSION

Avoidable visual impairment is a major global issue: cataract and refractive errors are leading causes of blindness in developing countries, while age-related macular degeneration, diabetic retinopathy and glaucoma account for most cases of blindness in developed nations.\(^7\) Nutritional deficits are rare in developed countries but they represent a major cause of preventable blindness in developing countries. Vitamin A deficiency accounts for most cases of children blindness.\(^7\) Inflammatory diseases and ischemic accidents are common causes of visual impairment and constitute major differential diagnosis in neurology.\(^8\)

Here, we report a female patient with severe visual loss and progressive GCIPL thinning related to deficiency of vitamin A, B6, and D. The patient had been on a restrict vegan diet since last 2 years. Visual function measures including VA, VF, and color vision were severely affected. After multivitamin supplementation, visual function improvements were observed and GCIPL thinning was halted. After 2.5 years on vitamin supplementation, the patient showed remarkable improvement of the visual function, not only at subjective examinations as VA, VF and color vision improved, but also objective measurements of OCT and VEP. The thinned GCIPL remained unchanged without further thinning, and RNFL remained normal at 3-year follow-up.

It is known that vitamin A deficiency causes nyctalopia.\(^8\) Profound cone dysfunction and photoreceptor abnormalities have been observed in animal models.\(^8\) Co-existence of multivitamin deficiency, in particular B vitamin deficiency including B6, may accelerate retinal dysfunction due to vascular endothelial impairment.\(^3\) Vitamin D receptor is expressed throughout the human body including eye tissues and may be involved in the regulation of cell proliferation, differentiation, or apoptosis.\(^9\) This patient had a clearly reduced central peak on mf-ERG indicating impaired fovea function, which was consistent with the low VA and central scotoma. The fovea, responsible for the sharp vision, is characterized by a depression in the retinal surface with densely packed cone photoreceptors and bipolar cells, and presents the highest metabolism, and it thus is most susceptible to injuries. No anatomical alteration of this area was noted on OCT, instead, remarkable thinning of GCIPL with rapid progression was observed in the patient. This process of thinning was halt after several months on vitamin supplementation. RNFL remained normal without significant changes during 3-year follow-up. Improved VA, VF, and color visions paralleled improved P100 values on VEP and no further thinning of GCIPL on OCT.

Vitamin deficiency also affects ganglion cells, as demonstrated in tobacco-alcohol neuropathy. The pathogenesis is mitochondrial dysfunction due to deficiency in B-complex vitamins, in particular cyanocobalamin B12, thiamine B1, riboflavin B2, niacin B3, and pyridoxine B6.\(^2\)\(^3\)

Ganglion cell plus inner plexiform layer thinning has been described in many ocular and neuro-ophthalmologic diseases including glaucoma\(^10\) and ethambutol-induced toxic optic neuropathy.\(^11\) Retinal neurodegeneration with retinal GCIPL thinning has been described also in diabetic retinopathy\(^12\) and in neuro-inflammatory conditions such as multiple sclerosis (MS) and other demyelination like neuromyelitis optica spectrum diseases (NMO).\(^6\) Most of these diseases usually cause RNFL thinning as well. GCIPL loss appears to precede RNFL loss in the case of glaucoma,\(^10\) anterior ischemic optic neuropathy,\(^3\) and optic neuritis (ON).\(^13\) GCIP loss without RNFL thinning provides an important evidence speaking against ON, MS, and NMO. Progressive RNFL and GCIP loss have been observed in both ON and non-ON eyes of patients with MS.\(^14\) Significant reduction of both RNFL and GCIP was correlated with subsequent functional visual deficits after acute autoimmune ON.\(^15\)

Our findings suggest that co-existing deficiency of vitamin A, B6, and D results in severe visual dysfunction including VA, VF, and color vision. The condition causes not only photoreceptor layer change with cone dysfunction, but also progressive GCIPL thinning with preserved RNFL. Long-term vitamin supplementation is important to reverse the visual defects and maintain retinal structure stable without further deterioration. The process can be monitored not only with visual functional tests, but also with anatomical assessments, where OCT has been shown to be of great value for both differential diagnosis and prognosis.
FIGURE 3 (A–E) OCT measures, visual field (VF) tested with Humphrey perimetry and visual evoked potentials (VEP) during vitamin supplementation. The thickness of the macular ganglion cell and inner plexiform layer (GCIPL) remained stable without further deterioration in both eyes (A). VF test showed normalized left VF and reduced central scotoma in the right VF (B). VEP showed improved latency and increased amplitude of P100 (C). Neurography showed normalized sensory amplitude in bilateral ulnar (D) and sural nerves (E).

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CONFLICT OF INTEREST
The authors declare no conflicts of interests of research, authorship and/or publication.

ETHICAL APPROVAL
Study number 2013/1411-31.

DATA AVAILABILITY STATEMENT
I confirm that my article contains a Data Availability Statement even if no data is available (list of sample statements) unless my article type does not require one (e.g., Editorials, Corrections, Book Reviews, etc.). Yumin Huang-Link.

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