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Visual recovery in a patient with optic neuropathy secondary to copper deficiency

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ABSTRACT

Purpose: To highlight the utility of ganglion cell layer (GCL) analysis in early diagnosis of optic neuropathy secondary to copper deficiency and emphasize the importance of timely repletion for visual recovery.

Observations: A 67-year-old woman presented with four months of gradually decreasing vision bilaterally. Medical history was significant for Stage I duodenal and Stage III colon cancer treated with Whipple surgery and hemicolectomy. Her visual acuity at presentation was counting-fingers vision in both eyes (OU). No relative afferent pupillary defect was noted. Fundus exam revealed a questionable trace temporal optic disc pallor with symmetric cup-to-disk ratio of 0.4 OU. Intraocular pressures were within normal limits OU. On initial optical coherence tomography (OCT) analysis, retinal nerve fiber layer (RNFL) measurements were normal OU; however, GCL loss was noted in both eyes, left eye (OS) being worse than right eye (OD). On subsequent formal visual field testing, she had cecocentral scotoma and large nasal step in both eyes, again worse in OS. Laboratory investigations revealed a significantly depleted copper level at less than 500 μg per liter (normal limit of 810–1990), while levels of B1 (thiamine), B9 (folic acid), and B12 (cobalamin) levels were within normal limits. She was started on oral copper supplementation. At 2-year follow-up, her best corrected visual acuity improved to 20/25 OD and 20/40 OS while maintained on oral copper repletion.

Conclusions and importance: Optic neuropathy secondary to copper deficiency is a rare but treatable cause of vision loss. In early stages of disease, early GCL loss may precede changes in the RNFL thickness or even appearance of obvious disc pallor on fundus exam. Visual recovery post repletion may be favorable if detected in a timely fashion.

1. Introduction

Nutritional optic neuropathy describe a group of treatable, but often underdiagnosed causes of irreversible optic nerve atrophy and blindness.[1,2] These deficiencies predominantly present with deficits in central and color vision, as the papillo-macular bundle is particularly vulnerable to metabolic insults.[3] Among these micronutrients essential to visual function is copper, a trace element primarily absorbed in the proximal small bowel. Copper deficiency due to insufficient intake is remarkably rare and is most commonly due to malabsorption. Among those most at risk are gastric bypass patients, as studies show 10–20 % of patients are deficient in copper post-surgery.[4] Therefore it is essential to consider nutritional deficiencies when evaluating the visual complaints of patients with a history of gastric surgery, especially those with vision loss affecting both eyes. The varying degree of visual recovery seen in the literature makes early diagnosis particularly important to visual prognosis.[5–9]

To this end, we outline a patient case with optic neuropathy secondary to copper deficiency with significant visual recovery after repletion, highlighting the utility of ganglion cell layer (GCL) analysis with optical coherence tomography (OCT) imaging in early detection of disease.

2. Case report

A 67-year-old woman presented with four months of gradually decreasing vision bilaterally. Medical history was significant for Stage I duodenal and Stage III colon cancer diagnosed within the past year. She had undergone Whipple surgery and hemicolectomy, and post-op care was complicated by anemia, significant diarrhea, and poor oral intake, with family reporting gradual cognitive decline. She was evaluated by an ophthalmologist who noted presence of cataract in both eyes.

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However, her vision did not improve after the cataract removal.

Upon presentation to neuro-ophthalmology clinic, she exhibited profound central acuity loss, with counting-fingers vision in both eyes (OU). Color perception was markedly reduced OU (5/14 in the right eye (OD) and 4/14 in the left eye (OS) with Ishihara color plate test). No relative afferent pupillary defect was detected. Slit lamp exam was unremarkable, while fundus exam revealed only questionable trace temporal optic nerve disc pallor OU with symmetric cup-to-disk ratio of 0.4. Intraocular pressure was 10 and 11 mmHg in OD and OS, respectively. On initial OCT analysis, retinal nerve fiber layer (RNFL) measurements were normal OU (Fig. 1A); however, significant GCL loss was noted in both eyes (worse in OS) (Fig. 2A). On subsequent formal visual field testing, she had cecocentral scotoma and large nasal steps in both eyes, again worse in OS (Fig. 3A). The remainder of the neuro-ophthalmic exam was notable for gait imbalance and a positive Romberg sign, but no nystagmus was noted. A flat affect was also observed in the patient.

Neuro-imaging of the brain and orbits did not show any acute abnormality or evidence of metastatic disease. Laboratory investigations at presentation revealed B1 (thiamine), B9 (folic acid), and B12 (cobalamin) levels within normal limits, albeit slightly at the lower end. Inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) were within normal limits. Notably, the patient's copper level was significantly low at less than 500 μg per liter (normal limit of 810–1990). Electromyography showed no clear evidence of large-fiber neuropathy nor myopathy except for left lumbosacral radiculopathy. At this point, the diagnosis for her gradual vision loss was thought to be copper deficiency induced optic neuropathy. Patient was started on oral copper supplement (copper gluconate formulation) at 4 mg twice a day for a month and then was maintained on 2 mg twice a day dosing onward. Supplementation was given only via oral route per patient's preference. At 6-month follow up, copper level was restored back to be within normal limit (Fig. 4). She was also empirically started on oral supplementations for Vitamin B1, B9, and B12 by her primary care physician given the concern for malabsorption. Her best corrected visual acuity gradually improved to 20/25 OD and 20/40 OS at the most recent visit, which was 2 years after her initial presentation.

3. Discussion

In this report, we present a case of a patient found to have bilateral symmetric optic neuropathy in the context of cognitive impairment, gait instability, and recent bowel surgery. The patient's presenting complaint and surgical history raised suspicion for potential nutritional deficiency. Deficiency in multiple nutrients such as group B vitamins (thiamine B1, folic acid B9, cobalamin B12) and copper have been associated with optic neuropathy. These nutrients play a critical role as antioxidants in controlling oxidative stress and in the mitochondrial electron transport that produces ATP.[10] Parvocellular retinal ganglion cells located in the papillo-macular bundle have a more limited mitochondrial reserve and are most susceptible to apoptosis under these

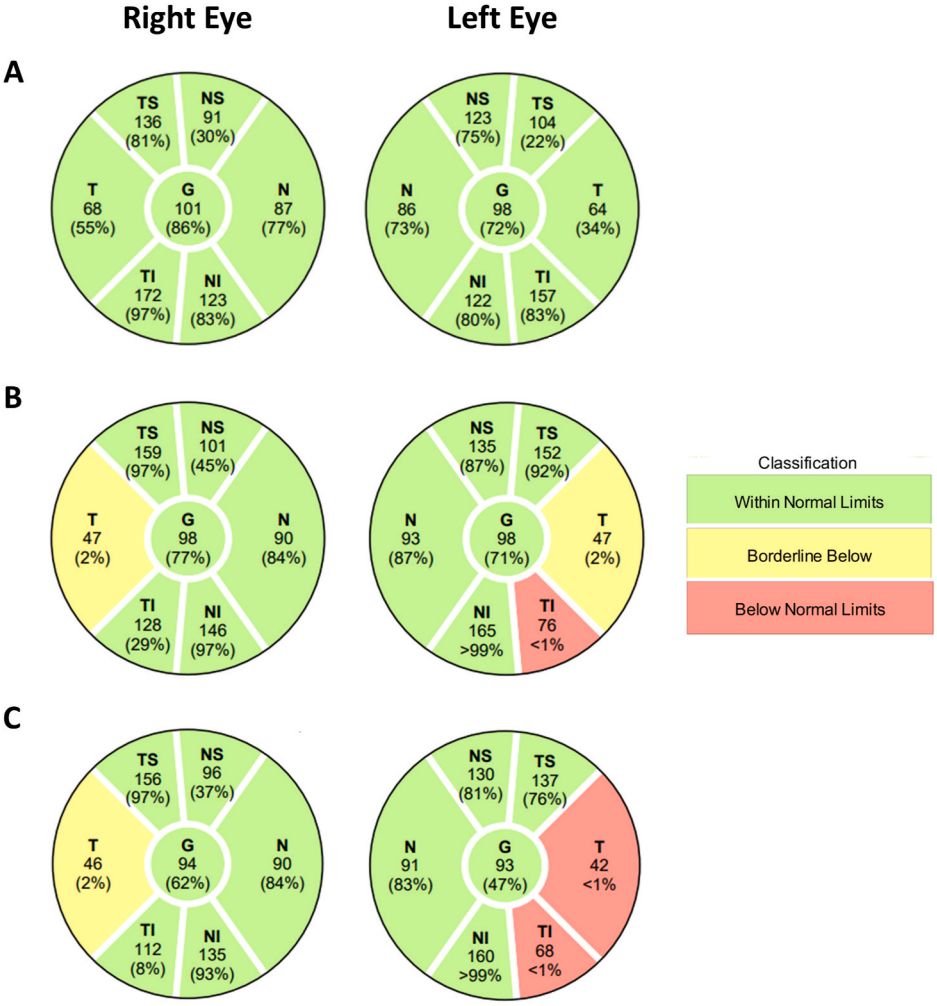

Fig. 1. OCT RNFL analysis for the patient at (A) baseline, (B) 1-year time-point, and (C) 2-year time-point. Her initial RNFL thickness was normal in both eyes at initial presentation. There was a gradual RNFL loss in the temporal sector (left eye more so than the right eye), suggesting of likely progressive papillo-macular thinning.

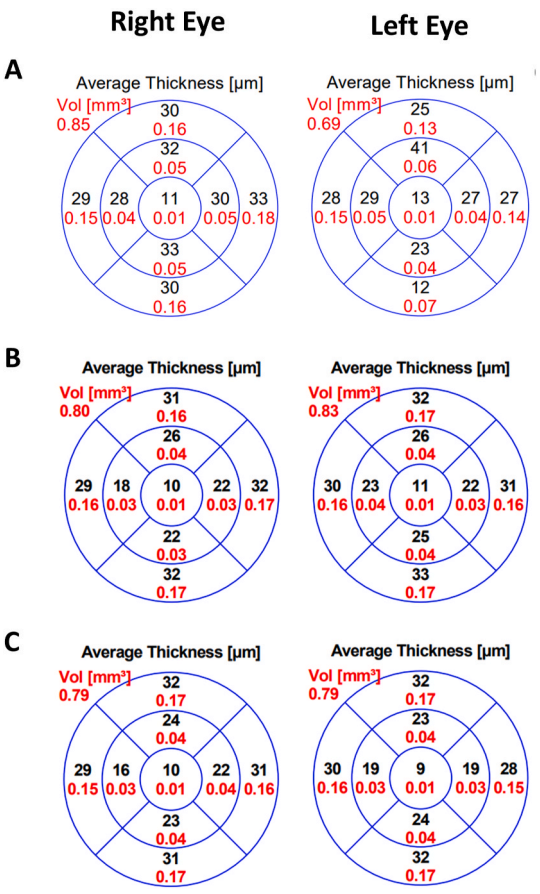

Fig. 2. OCT GCL analysis for the patient at (A) baseline, (B) 1-year time-point, and (C) 2-year time-point. Even though her RNFL thicknesses in both eyes were within normal limit at initial presentation, there was thinning of her GCL volumes in both eyes then. We also observed a mild gradual thinning of the GCL volumes in both eyes over the 2-year timespan.

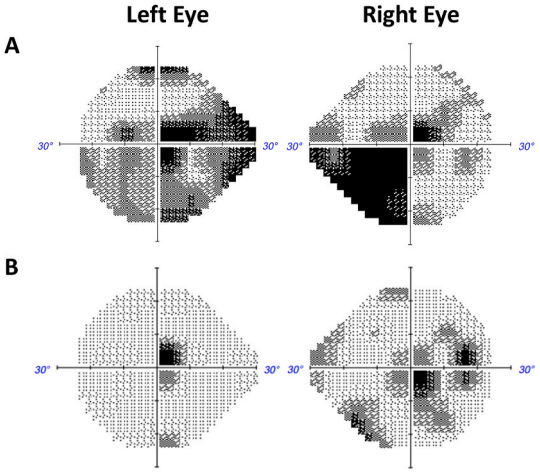

Fig. 3. Visual field results at (A) 1-year time-point and (B) 2-year time-point. No reliable visual field testing was obtained at the initial visit due to patient's severely limited vision. When we were able to obtain reliable visual field testing at 1-year follow-up appointment, there was still significant cecocentral scotomas and nasal field loss in both eyes, right eye being worse than left eye. Fortunately, after copper repletion with 4 mg twice daily for a month and then maintenance dosing of 2 mg twice daily, there was improvement of her visual fields with reduced cecocentral scotomas and nasal field loss in both eyes at 2-year time-point.

circumstance.[10] Temporal pallor as seen in this patient is consistent with damage to these cells, resulting in reduced color vision and cecocentral scotomas. However, at early stage of the disease, such trace amount of temporal pallor is difficult to visualize; hence this case highlights the diagnostic utility of OCT in aiding the diagnosis. Copper deficiency can also cause myelopathy, peripheral neuropathy, and cognitive impairment; therefore, the constellation of these symptoms should increase the suspicion of this nutritional deficiency.[7] As such, magnetic resonance imaging of the spine and/or electromyography can also be considered to investigate other potential associated abnormalities due to copper deficiency. Once copper deficiency is confirmed, appropriate replacement can prevent further deterioration and in rare cases improve visual outcome.[5,6]

A literature review completed on March 31, 2024 utilizing PubMed and Google Scholar using the key words copper optic neuropathy, nutritional optic neuropathy, and copper deficiency neuropathy revealed 5 previous reports of the ophthalmologic exam findings of a patient with optic neuropathy secondary to copper deficiency.[5–9] All presenting patients had a history of gastric surgery in some form, as is the case in our patient who underwent a Whipple procedure and hemicolectomy. Our patient experienced the onset of visual symptoms one year after surgery, which is the earliest onset of symptoms amongst these cases. Previous reports cite time of onset of symptoms as soon as three years[5,6] and ranging up to 22 years.[8] The rapid onset of symptoms in our patient may be in part due to the previously described two-hit hypothesis suggested by Spinnazi et al.,[11] whereby the combination of inadequate intake and malabsorption or excessive excretion lead to the onset of symptoms in those with gastric surgery. Therefore, new gradual visual decline in patients with history of gastric resection surgery should warrant prompt nutritional work-up.

Our patient exhibited significant visual recovery post copper repletion, with best corrected vision improving from counting-fingers vision OU to 20/25 OD and 20/40 OS. This degree of improvement has been seen only twice in previous cases, with improvements from 20/400 OU to 20/25 OU[6], and from 20/200 OD and 20/70 OS to 20/20 OD and 20/25 OS.[5] Other previous reports describe modest to no improvement.[8,9] Such variabilities in visual prognosis despite repletion may reside in the timing of diagnosis and subsequent repletion, as patients such as ours who showed visual improvement post treatment had gastric surgery and presumed onset of cooper deficiency less than three years before onset of symptoms and presentation.[5,6] This pattern emphasizes the importance of early identification and treatment in improved prognosis for this condition, a trend supported by data from other forms of nutritional optic neuropathy.[12]

Important diagnostic utility of OCT is also well demonstrated in our case. Though the RNFL thickness was full in our initial evaluation, there was disproportional loss of GCL, raising the concern for optic neuropathy with the pathology originating at the ganglion cells (Figs. 1 and 2). The importance of OCT analysis in patients with toxic and nutritional optic neuropathy has previously been proposed,[13,14] with small scale studies describing decreased GCL thickness in these patients.[15] The OCT results of patients with optic neuropathy secondary to copper deficient have been mixed, with RNFL analysis showing either decreased thickness[5,8,9] or full thickness.[6] GCL (or ganglion cell complex in other OCT imaging modalities) analysis has only been described on one occasion,[6] where it was found to be thin. Our patient presenting with normal RNFL thickness but reduced GCL thickness is similar to the patient reported by Rapoport et al.,[6] which may imply that GCL changes are seen earlier than RNFL changes on OCT in patient with copper deficiency induced optic neuropathy. This is supported by the fact that both patients had gastric surgery three years ago or less as compared to longer timelines in patients with RNFL changes.[8,9] Evidence from other diseases of the optic nerve such as glaucoma has revealed that GCL analysis may be more more sensitive than RNFL in early stages of disease, with similar performance in moderate stages.[16,17]

Despite our best effort in supplementation, there was still mild

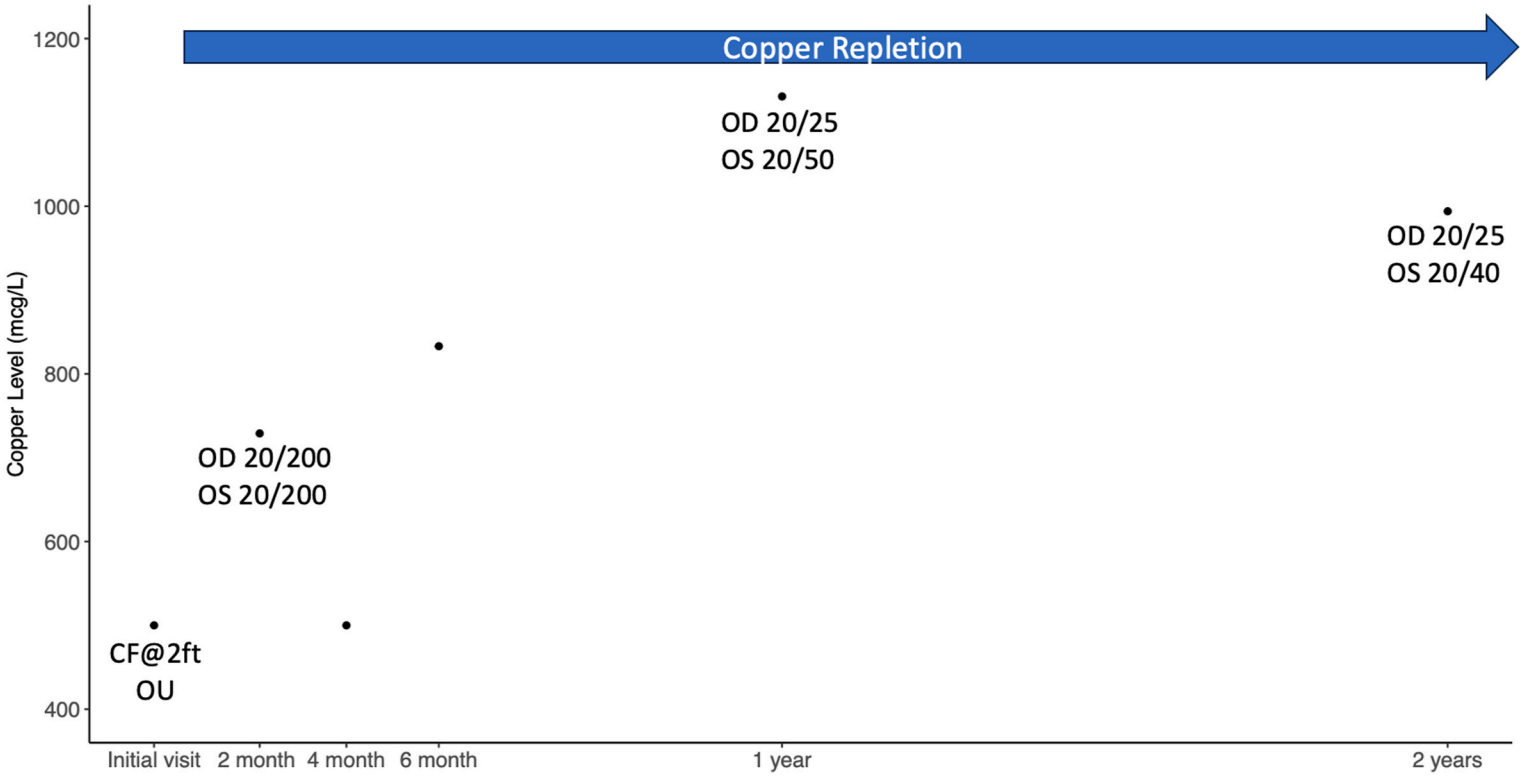

Fig. 4. Comparison of patient's serum copper levels over time with her corresponding central visual acuity changes. As described, she first presented with counting-fingers vision in both eyes. There was corresponding improvement in patient's vision with copper replacement therapy (4 mg twice daily for a month and then maintenance dosing of 2 mg twice daily). Copper levels are reported in mcg/L. Copper level is assigned as 500 mcg/L if undetectable (<500 mcg/L). Of note, there were no corresponding acuities at 4-month and 6-month time-points as patient was not evaluated physically then and only copper levels were checked. CF: counting finger vision. Ft: feet.

progressive thinning of RNFL and GCL thicknesses over the course of monitoring (Figs. 1 and 2). We believe that this could be due to multiple reasons. First. it is possible that there was likely already ongoing ganglion cell death due to copper deficiency at the time of diagnosis, which was unlikely to reverse despite supplementation. Such loss was therefore observed as reduction in subsequent OCT scans. Second, external supplementation could not consistently replete patient's copper loss due to her poor intake and malabsorption. Thus, we still observed mild thinning of the RNFL and GCL thicknesses, though likely much less severe than if the copper deficiency was untreated. Fortunately, the supplementation was still effective in restoring her visual functions in the long-term (Fig. 4).

4. Conclusions

Optic neuropathy secondary to nutritional deficiency, such as copper in our patient case, should be considered on the differential diagnosis in patients presenting with progressive visual decline in both eyes who have history of gastrointestinal surgery, malabsorption, and/or poor intake. OCT analysis can provide key diagnostic clue when there is a disproportional loss of macular GCL with relatively preserved RNFL measurement. As illustrated in our case, prognosis for visual recovery is favorable if the nutritional deficiency is detected and treated early.

CRediT authorship contribution statement

Arman Mosenia: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Soman Khan:** Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Moe H. Aung:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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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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