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Letter to the Editor: New Observation

Bilateral Optic Neuropathies Due to Homozygous Lepore Hemoglobinopathy

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Compressive optic neuropathy is a rare complication of dysregulated hematopoiesis. Ineffective erythropoiesis can result in bone marrow expansion or in the growth of extramedullary hematopoietic masses. Here, we report a patient in whom bone marrow expansion occurred due to a rare hematological disorder.

This 50-year-old woman has a severe phenotype of non-transfusion-dependent β-thalassemia due to the very rare homozygous Lepore hemoglobinopathy. Due to the formation of multiple red cell antibodies, she was unable to maintain a chronic blood transfusion program and instead received multiple experimental treatments to control bone marrow expansion (arginine butyrate; sodium phenylbutyrate; 5-azacytidine). Nevertheless, in her twenties, she developed gradual symmetrical binocular visual loss due to optic neuropathies caused by compression by bone marrow expansion at the skull base and in the optic canals. This prompted radiation therapy and bifrontal craniotomy to decompress the optic nerves when she was 24 years old. The visual acuities, ophthalmoscopic optic disc appearances, optical coherence tomography (OCT), and degree of compression and hyperintense T2 signal on MRI scan have since remained stable.

There were also sequelae of suboptimally controlled severe thalassemia: facial bone expansion requiring surgical intervention, liver iron overload, multiple endocrinopathies (adrenal insufficiency, hypothyroidism, hypogonadism), osteoporosis, gout, pseudoxanthoma elasticum, and splenectomy.

Her brother also has homozygous Lepore hemoglobinopathy, was treated with butyrate medications, is transfusion free, and has no manifest extramedullary hematopoiesis.

Examination showed thalassemic facies (frontal bossing, hypertelorism, depressed nasal bridge, prominent maxillae). Visual acuities were 20/70- bilaterally. There was reduced colour vision, optic disc pallor, and nerve fibere layer visual field defects in both eyes.

Retinal nerve fibere layer thickness averages on OCT were 59 µm on the right and 56 µm on the left. Humphrey 24-2 automated perimetry showed right eye superior and inferior and left eye inferotemporal nerve fibere layer defects (Figure 1).

Thoracoabdominal imaging had shown asymptomatic paravertebral masses consistent with extramedullary hematopoiesis.

MRI scan showed diffuse calvarial thickening and expansion of the diploic spaces and generalized marrow hyperplasia involving the maxillary sinuses bilaterally, sphenoid wings, and clinoid processes. The hypertrophied bone caused crowding and diminished fat at the orbital apices and optic canals resulting in compression of the intracanalicular optic nerves bilaterally (Figure 2). T2-weighted images showed T2 signal changes in the intraorbital optic nerves (Figure 2).

Clinically, our patient had gradual symmetrical binocular visual loss due to bilateral symmetrical optic neuropathies.

Optic neuropathies may be caused by ischemic, inflammatory, infiltrative, infectious, toxic-metabolic, hereditary, traumatic, and compressive mechanisms. Vision loss may be abrupt, subacute, or slowly progressive. Patients present with vision loss and dyschromatopsia. The optic nerve may appear edematous, normal, or pale, depending on the cause and chronicity of the optic nerve injury. Perimetry and/or OCT can help localize the site of injury to one or both optic nerves. Structural neuroimaging with contrast MRI or CT scan of the orbits and brain and OCT may provide diagnostic information, including the fact of and the degree of compression of the optic nerves and, in the case of CT, the presence and type of bony abnormalities.[1]

Our patient's background, history, pattern, and clinical features did not support typical forms of ischemic, inflammatory, infectious, hereditary, or traumatic optic neuropathies.

None of her medical treatments have been associated with toxic optic neuropathies.[2]

Radiation was administered only after the optic neuropathies had become manifest, which makes radiation optic neuropathy highly unlikely.

There is no direct link between iron overload and the development of optic neuropathies. There is experimental evidence that oxidative damage by ferrous iron may contribute to some optic neuropathies (optic neuritis, non-arteritic ischemic optic neuropathy, traumatic optic neuropathy, glaucoma),[3] but our patient's optic neuropathies did not conform to these types of optic neuropathy.

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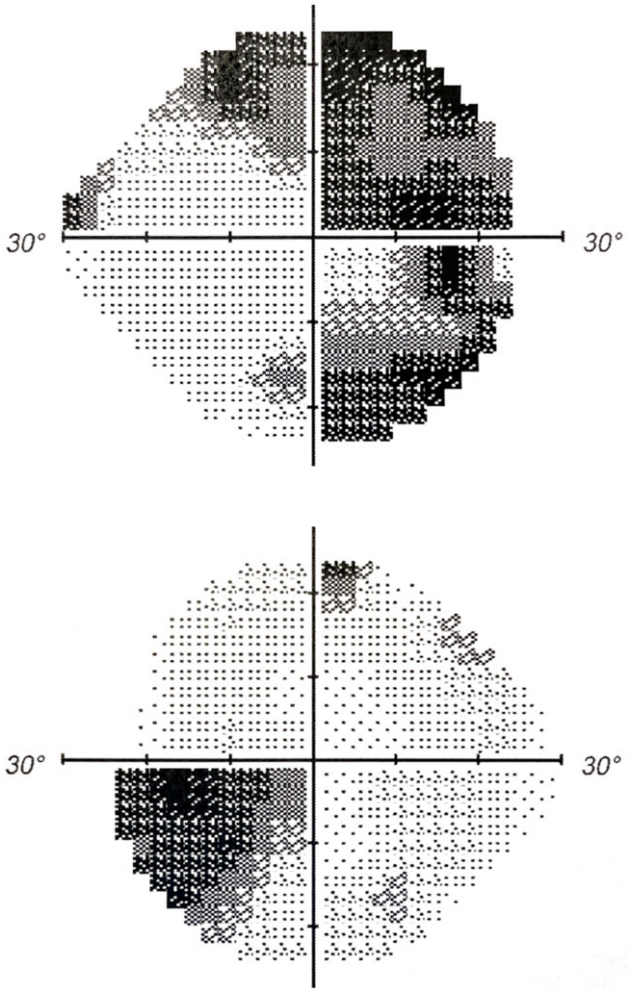

Figure 1: Humphrey 24-2 automated perimetry showing right eye superior and inferior and left eye inferotemporal nerve fibere layer defects.

The history, setting, and imaging pointed to a compressive mechanism of optic neuropathy.

Ineffective hematopoiesis, bone marrow expansion, and extramedullary hematopoiesis can be triggered by hematological disorders such as thalassemia and myeloproliferative neoplasms. Neurological complications may rarely arise as a result of thalassemia.[4] Four cases of optic neuropathy due to thalassemia have been reported,[5–8] but to our knowledge, none due to the very rare homozygous form of Lepore hemoglobinopathy.

Homozygous Lepore hemoglobinopathy behaves phenotypically like the severe end of the thalassemia spectrum, from severe thalassemia intermedia to thalassemia major.

The optic neuropathies and visual loss in our patient were due to compression by the expansion of bone marrow of the clivus, anterior clinoid processes, and sphenoid bones and by narrowed optic canals due to expansion of sphenoid bone marrow.

Radiation or decompressive surgery may be indicated in such patients with progressive visual loss. Our patient stabilized clinically and radiologically after these treatments. Regenerative medicine may one day offer effective treatment for such hemoglobinopathies.

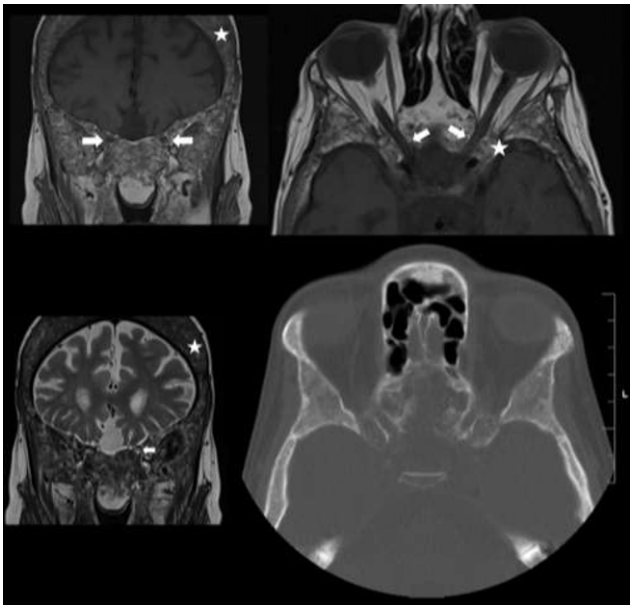

Figure 2: Upper two images: MRI T1-weighted coronal and axial images of the orbits showing diffuse calvarial thickening and expansion of the diploic spaces (star) and generalized marrow hyperplasia involving the maxillary sinuses, sphenoid wings, and clinoid processes. The hypertrophied bone causes crowding and diminished fat at the orbital apices and optic canals resulting in compression of the intracanalicular optic nerves (arrows). Lower left image: MRI T2-weighted coronal images of the orbits with fat suppression showing subtle bright T2 signal changes in the optic nerves, greater on the left. Lower right image: CT axial image of the skull base showing medullary expansion of the bony structures.

Hematological causes of intracranial benign bone and soft tissue lesions should be considered in cases of progressive visual loss due to optic neuropathy.

Conflict of Interest. All authors have no conflicts of interest to declare.

Statement of Authorship. Conception and design (FT; AS), data collection (FT; AA; RW; AS), manuscript preparation (FT; AA; RW; AS), critical appraisal (FT; RW; AS), review of the manuscript (FT; RW; AS).

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