Maculopathy due to Cobalamin C (cb1C) Disease in an Amish Child

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ABSTRACT
A 5-year-old Amish boy diagnosed at birth as having a defect in intracellular cobalamin metabolism, cobalamin C disease (cb1C), presented to the pediatric ophthalmology service with severe visual impairment. Ophthalmoscopy showed bilateral bull’s eye macular lesions. Visual loss occurs from retinal degeneration in cb1C disease. This report highlights the importance of post-natal metabolic testing and ophthalmic evaluation in cb1C disease, especially in high-risk inbred populations.

INTRODUCTION
Cobalamin C disease (cb1C), also known as methylmalonic aciduria with hyperhomocysteinemia type cb1C, is an autosomal recessive defect of vitamin B12 metabolism due to a mutation in the MMACHC gene (OMIM 609831). This primary defect in vitamin B12 processing leads to inadequate production of adenosylcobalamin and methylcobalamin, which are cofactors for methylmalonyl-CoA mutase and methionine synthase, respectively, leading to both methylmalonic aciduria and hyperhomocysteinemia (Fig. 1). Clinical manifestations include vision loss from retinal degeneration, feeding difficulties, megaloblastic anemia, and neurologic and skin dysfunction.

We report the case of a 5-year-old Amish child from Ohio with cb1C disease who presented to the pediatric ophthalmology clinic with severe vision loss and nystagmus from associated retinal degeneration. To our knowledge, this is the first case of cb1C disease reported in the Amish community and the

Figure 1. Diagram illustrating metabolic steps involving cobalamin derivatives. Deficiency of methylcobalamin (MeCbl) causes a block in methionine synthase leading to accumulation of homocysteine. Deficiency of adenosylcobalamin (AdoCbl) causes a defect in methylmalonyl-CoA mutase, leading to accumulation of methylmalonic acid. Cobalamin is absorbed in the ileum and carried by one of several transcobalamins and other binding factors to the cell, where it is taken up into the lysosome. A variety of steps are involved in alteration of the redox state of the cobalt center of the cobalamin molecule and in the formation of the two active forms of the cofactor, MeCbl and AdoCbl. Complementation studies have demonstrated a variety of defects in this process, including those that affect the production of both MeCbl and AdoCbl, thus causing both methylmalonic aciduria and hyperhomocysteinemia. These include the complementation groups cb1 C, cb1 D, and cb1 F. Defects leading only to loss of MeCbl, cb1 E, and cb1 G are only associated with hyperhomocysteinemia. Defects involving only the synthesis of AdoCbl, cb1 A, and cb1 B are only associated with methylmalonic aciduria. The genetic defects for several of these complementation groups have been identified, including the MMACHC gene in cb1 C, but the specific functions of the proteins in cobalamin metabolism have yet to be elucidated. OH-cobalamin = hydroxycobalamin.
oldest patient with observed cb1C disease-related maculopathy. We highlight the importance of postnatal metabolic testing, especially in high-risk populations, and of ophthalmic evaluation in this rare and devastating disease.

CASE REPORT

A 5-year-old Amish boy with cb1C disease, diagnosed by newborn screening and treated since birth with vitamin supplements, presented to the pediatric ophthalmology service because his mother noticed that he “turns his head and looks out of the corner of his eyes.”

After being delivered at full term with a normal birth weight, the patient exhibited signs of lethargy and jaundice. Post-natal metabolic screening revealed methylmalonic aciduria with hyperhomocysteinemia that led to the diagnosis of cb1C disease, confirmed by fibroblast evaluation of propionic acid metabolism and complementation testing. Treatment with L-carnitine, intramuscular hydroxycobalamin, betaine, and protein restriction was started and maintained to date. Current medical problems included modest developmental delay and persistently elevated homocysteine blood concentrations, typically between 40 and 70 micromol/L despite therapy. Urinary methylmalonic acid excretion was generally low. The family history was positive for a cousin with strabismus.

Visual acuity was 20/50 in the right eye and 20/100 in the left eye. Examination revealed a fine torsional nystagmus and bilateral bull’s eye maculopathy with perifoveal rings of irregular areas of yellowish discoloration (Fig. 2). A diagnosis of macular disease secondary to cb1C disease was made. The rest of the ocular examination was within normal limits.

DISCUSSION

Methylmalonic aciduria with homocystinuria, or cb1C disease, has not previously been reported in the Amish population. Given the relative genetic isolation of this population, it is important to be aware that this condition exists within the Amish community so that it is screened for and appropriate treatment is promptly initiated when necessary. It is also recommended that patients with known cb1C disease receive early ophthalmic screening for maculopathy. The fundus images in this report illustrate the characteristic maculopathy associated with cb1C disease.

Cb1C disease is an autosomal recessive genetic defect in vitamin B12 metabolism that results in decreased synthesis of coenzymes adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl), ultimately leading to methylmalonic aciduria with hyperhomocysteinemia.1 Clinical manifestations include ophthalmic, neurologic, hematologic, dermatologic, and metabolic impairment.2 Unfortunately, early treatment with L-carnitine, vitamin B12, protein restriction, and betaine does not appear to prevent ophthalmic or neurologic dysfunction.3

The reduced vision and retinal changes in our patient are certainly in line with these observations;

Figure 2. Red-free retinal photographs demonstrating cobalamin C–related maculopathy. Right (A) and left (B) maculae show rings of irregular yellow discoloration in a bull’s eye pattern around the fovea.
the pathology occurred despite the institution of therapy early in life. Although treatment generally reduces methylmalonic acid blood concentrations and urinary excretion to near normal, it often inadequately controls hyperhomocystinuria and is associated with low concentrations of methionine. This has led to speculation that it is a deficiency in methionine, secondary to the reduced conversion of homocysteine by methylcobalamin, that leads to a general susceptibility to oxidative stress and subsequent damage to the retinal pigment epithelium. A study by Tsina et al. showed a positive correlation between methionine levels and rhodopsin phototransduction function, but there was no prevention of the progressive macular atrophy. Thus, it is implied that although reduced methionine may play a role in the disease process, it is not the sole cause.

Of the 250 cases of cb1C reported, 14 described ophthalmic disease including retinopathy, optic atrophy, strabismus, nystagmus, and “epileptiform eyelid flutering.” Cb1C disease retinopathy is characterized by progressive, parafoveal retinal pigment epithelium changes described as “mottled” or resembling “salt and pepper.” Histologically, there is photoreceptor loss in the central 3 mm of the macula, partial loss of the nerve fiber and ganglion cell layers, and partial optic atrophy. In addition, a “fine granular material” has been observed within cells throughout the orbit, including the retinal pigment epithelium and ganglion cells. Thus, it is possible that lysosomal and mucopolysaccharide storage dysfunction may contribute to the observed macular disease and associated loss of visual function.

Research regarding cb1C–related maculopathy is limited by the rarity of the condition. Further studies are needed to determine its molecular pathogenesis and the most appropriate management to prevent neurological and ocular dysfunction. In the meantime, post-natal screening, early treatment, and routine monitoring appear to be the most effective means of minimizing the mortality and morbidity of this disorder.

REFERENCES