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Minireview

Ocular disease in the cobalamin C defect: A review of the literature and a suggested framework for clinical surveillance

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ABSTRACT

The association between combined methylmalonic acidemia and homocystinuria of cblC type (cobalamin C defect, cblC) and ocular disease is now well recognized, and is a significant component of morbidity and disability associated with the condition. In this review, through collation of historically reported cases of early- and late-onset cblC and previously unreported cases, we have attempted to characterize the epidemiology, clinical features, and pathomechanisms of individual ocular features of cblC. These data suggest that maculopathy and nystagmus with abnormal vision are extremely common and affect the majority of children with early-onset cblC, usually before school age; strabismus and optic atrophy are also seen at relatively high frequency. The timing of progression of macular disease may coincide with a critical period of postnatal foveal development. Maculopathy and retinal disease may be subclinical and show only partial correlation with the extent of visual deficits, and visual deterioration may be relentlessly progressive in spite of aggressive treatment of biochemical abnormalities. In later-onset forms of the disease, visual loss and ocular complications appear to be infrequent. Finally, we discuss investigational strategies in diagnosing and characterizing eye disease in individuals with cblC, explore possible therapeutic avenues that may attenuate progression and severity of eye disease, and propose a clinical surveillance guideline for monitoring progression of ocular disease in children and adults with cblC.

Contents

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1. Introduction

Combined methylmalonic acidemia (MMA) and homocystinuria of cblC type (also known as cobalamin C disease, cblC defect, or simply cblC) is an autosomal recessive disorder of vitamin B_{12} (cobalamin) metabolism with an incidence of approximately 1 in 100,000 newborns according to newborn screening (NBS) data from the state of New York [1]. Over 300 cblC patients have been reported globally to date. The protein product of *MMACHC* decyanates B_{12} in the cell cytosol [2]; in its absence, methylcobalamin and adenosylcobalamin, downstream derivatives of B_{12}, are deficient in the cytosol and mitochondria, respectively. These co-factor deficiencies cause potentially severe, combined, and partially treatable hyperhomocysteinemia and methylmalonic acidemia/aciduria, biochemical markers of cblC (as well as the rarer cblD, cblF, cblJ and cblX variants) that distinguish it from both severe isolated forms of MMA and from classical cystathionine β-synthase (CBS) deficiency homocystinuria. Low plasma methionine (MET) seen in cblC further distinguishes the disorder from other autosomal recessive disorders involving these two pathways and may be key to the pathogenesis of cblC.

Visual deterioration and blindness are frequent and serious complications of cblC and are a major determinant of quality of life [3]. Clinically apparent ocular disease appears to be significantly more common among individuals with *MMACHC* genotypes conferring early-onset disease phenotypes [4–6], defined as those with clinical onset before 12 months of age [7]. These patients are typically homozygous or compound heterozygous for frameshift or nonsense mutations, and typically have developmental delay as well as variable neurologic impairment [4,6,8–10]. Most patients with early-onset cblC have pigmentary retinopathy, macular disease [4,10,11], optic atrophy, or a combination of these entities, and may exhibit difficulties with vision associated with nystagmus from infancy onwards. Strabismus and refractive error also appear to be common. Eye disease may be mild, subclinical or absent in patients with late onset forms of cblC [8,12–14].

The aim of this review is to accurately characterize the spectrum of ocular disease observed in cblC. We hope to summarize and present historical reports of eye disease in cblC, and present available knowledge on the pathophysiology and natural history of ocular pathology associated with the condition. Finally, we have used available knowledge on this subject and our own clinical experience to create a framework of guidelines for clinical ocular surveillance in cblC.

2. Methods

We reviewed clinical and investigational data from case reports and case series published to date reporting clinical ocular disease in patients with cblC. Supplementary Tables 1 and 2 list and provide clinical details of patients with cblC for whom individual clinical details of ocular disease are available. PubMed search terms included “cblC”, “cobalamin C”, “ocular”, “ophthalmology”, “ophthalmologic”, “eye”, “retinopathy”, and “maculopathy”. We additionally included data from seven previously unreported patients with early-onset cblC managed at the University of Colorado or Mount Sinai School of Medicine. Some patients included were monitored longitudinally [4,6,10].

3. Results

We reviewed historical reports from 55 patients (24 male, 24 female, 7 sex not reported) with early-onset (defined as clinical onset before 12 months of age) and 38 patients (17 male, 21 female) with late-onset cblC disease that were reported with a reasonable level of clinical detail in the literature [4–6,8,10–12,14–47]. Patients with early-onset disease and those with disease presenting beyond 12 months of life (or otherwise presumed to represent later-onset disease) are listed in Supp. Table 1 and Supp. Table 2, respectively. We also included 7 early onset cblC patients (6 male, 1 female; patients numbered 56–62 in Supp. Table 1) who are previously unreported and are recently managed at our institutions. *MMACHC* genotypes were available in 66/100 patients; where genotype details were omitted, this was in most cases because patients were reported before 2006 when the *MMACHC* gene was identified as causative for cases of combined MMA and homocystinuria in the cblC complementation group [48]. The second causal mutation was not definitively identified in one patient (patient 38, Supp. Table 2). Of 131 *MMACHC* alleles reported in 66 patients, 42 (32%) were the common c.271dupA allele, associated with a frameshift and premature protein truncation. 11 of the patients with genotype data (17%) were homozygous for the c.271dupA allele, a genotype characterized by early-onset clinical phenotype and early childhood-onset maculopathy.

Clinical details of ocular features were sparse or unavailable in a large number of patients, as many patients were reported on the basis of other, non-ocular manifestations (hemolytic-uremic syndrome (HUS), pulmonary hypertension, and other complications) presenting at early ages, and did not systematically review the presence or extent of eye disease. Of 62 patients with early onset cblC, 37 (60%) had documented maculopathy at a median last follow-up age of 4 years; 44 (71%) had nystagmus. Optic atrophy and strabismus were both less common, affecting 16 (26%) and 14 (23%) early-onset patients, respectively. Among patients with macular atrophy or other maculopathies, poor visual acuity was often, but not uniformly present. Visual acuity in the early onset group was variable. Three patients (5%) in this group had normal vision [15,26], on the last follow-up of a median of seven years, 6 (10%) patients were mildly visually impaired (vision in best eye 20/30–20/40), 3 (5%) patients had moderately decreased visual acuities 20/50–20/80, 13 (21%) patients had moderate to severe visual impairment with acuities in the 20/100–20/800 range, and 9 (31%) patients were severely visually impaired or functionally blind. There was insufficient information on 28 patients (45%) to accurately determine their level of visual function. Of the three patients with ‘normal’ vision, two [26] were also documented to have nystagmus, which may indicate some level of subclinical visual impairment not noted due to age or method of testing.

Both abnormal photopic and scotopic ERG responses demonstrated a stronger correlation than fundus findings with a poor visual prognosis. Most patients with demonstrable optic atrophy also had decreased visual acuity. Results of ERG were reported in 29/62 early-onset cblC patients (47%), and were demonstrably abnormal in 18 patients (62% of those tested) in at least one eye out of those patients tested [4,10,11,16,27,29]. None of the 38 reported late-onset cblC patients had documented maculopathy or strabismus at a median follow-up of 19 years of age, although 3 patients in this category (5%) had optic disc pallor, and one patient had nystagmus.

4. Discussion

4.1. Epidemiology and clinical characteristics of ocular disease in cblC

4.1.1. Maculopathy, retinopathy and optic atrophy

Early-onset cblC is one of only a small number of disorders associated with infantile-onset progressive maculopathy. Initial signs of eye

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