Published in final edited form as:

Surv Ophthalmol. 2009 ; 54(3): 401–407. doi:10.1016/j.survophthal.2009.02.008.

Choroideremia: New Findings from Ocular Pathology and Review of Recent Literature

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Abstract

Histopathology of young individuals affected by choroideremia is rarely available to allow correlation with the clinical presentation. A 30-year-old male with choroideremia died in a motor vehicle accident and one eye was subjected to histopathological examination. Immunoblot analysis of protein derived from white blood cells of a living brother, also affected with choroideremia, confirmed the absence of Rab escort protein-1, the normal *CHM* gene product. Direct sequencing of the coding region and adjacent splice sites of the *CHM* gene was undertaken on genomic DNA from the living brother and revealed a transition mutation, C to T, in exon 6 (R253X) which resulted in a stop codon and was predicted to truncate the protein product. Histopathological examination of the eye of the deceased brother showed relative independent degeneration of choriocapillaris, retinal pigment epithelium and retina, similar to observations in the mouse model of choroideremia. In addition, mild T-lymphocytic infiltration was found within the choroid. The ophthalmic features and the pathology of choroideremia are discussed in light of new findings in the current case.

Keywords

choroideremia; histopathology; mutation analysis; retinal degeneration

Introduction

Choroideremia (CHM) is an X-linked degeneration of the choroid, retinal pigment epithelium (RPE) and retina caused by deletion or mutation of the *CHM* gene, encoding Rab escort protein-1 (REP1).⁴⁴ Virtually all mutations reported to date result in the absence of the normal protein product in affected males, as cited by Preising and Ayuso,³¹ and referring to a web site cataloguing reported mutations (see

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EDWARD COTLIER AND ROBERT WEINBER, EDITORS

Presented at the annual meeting of the Association for Research in Vision and Ophthalmology in Ft. Lauderdale, Florida, April 30 – May 4, 2006.

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<http://www.retina-international.org/sci-news/repmut.htm>). Carrier females exhibit signs of patchy chorioretinal degeneration which have been ascribed to random X-inactivation. In humans an autosomal gene, *CHML*, for choroideremia-like, has significant homology to *CHM* and encodes the protein, Rab escort protein-2. The tissue-specific expression of these genes could be required to maintain the normal balance of prenylation of Rab proteins during X-inactivation.⁷ This balance could be therefore maintained in vital organs, except the eye, when X-inactivation and a mutation in the *CHM* gene combine to result in expression levels of Rab escort protein-1 that fall below a critical level, resulting in the progressive signs observed in the fundus of female carriers.

Case Report

A 30-year-old male with CHM died in a motor vehicle accident. His eyes were recovered 15 hours post-mortem and donated to the Iowa Lions Eye Bank for research. He was first diagnosed with a retinopathy at age 7. At age 8, his electroretinogram had recordable waveforms but was not performed according to ISCEV standards (see <http://www.iscev.org/standards/index.html>). His last clinical examination, at age 18, noted that his uncorrected visual acuity was 20/15 (OD) and 20/20 (OS). Goldmann visual fields showed scotomas inferiorly with 160 degrees of horizontal field in either eye, exclusive of the blind spot. Remarkably, fundus photography suggested that the area of functional retina, as measured by the visual field, was not supported by a visible or intact retinal pigment epithelium (RPE) and choriocapillaris (Fig. 1 A and 1B).

A living brother was available to confirm the clinical diagnosis of CHM by immunoblot and molecular genetic analysis. Protein derived from white blood cells of the living brother was subjected to immunoblot analysis with an anti-REP1 monoclonal antibody, 2F1, according to a previously established protocol,²⁴ and showed the absence of REP1. Direct sequencing of the coding region and adjacent splice sites of the *CHM* gene was undertaken on genomic DNA from the living brother. A single base change, C to T, was found in exon 6 (R253X) which creates a stop codon. This mutation has been previously observed by our laboratory in testing other unrelated families with the diagnosis of CHM.²⁷

Histopathologic and Immunohistopathological Findings

Histopathological examination of the donated right eye was performed; the eye was fixed in 10% formalin, embedded in paraffin and cut through the pupillary-optic nerve plane horizontally. Sections were stained for hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), or deparaffinized for immunohistochemistry using avidin-biotin complex immunoperoxidase technique as described previously.^{5,39}

ROUTINE HISTOLOGY

The details of the histology of this eye have been reported previously (I.M. MacDonald et al. Abstract No. 1034. Annual Meeting, Association for Research in Vision and Ophthalmology, Ft. Lauderdale, FL, 2006). Briefly, diffuse abnormalities of the retina, RPE and choriocapillaris were noted which varied from different areas and appeared to occur independent of each other. For example, retinal degeneration was observed above RPE and choriocapillaris with either preserved architecture or severe atrophy. Areas of relatively well-preserved retina were found abruptly adjacent to areas of severe degeneration (Fig 2A). In the lesion, the retina was thin, initially due to shortening of outer segments and loss of nuclei mostly from the outer nuclear layer (ONL). With depletion of the ONL, there was loss of lamination and further depletion of nuclei in the inner nuclear layer (INL). An interesting finding was the focally conspicuous presence of “ectopic” nuclei external to the external limiting membrane, apparently dropping into the subretinal space and, occasionally, appearing intermingled with RPE cells (Fig 2B,C).

The RPE was extensively absent, especially posteriorly, and thin with markedly decreased pigmentation anteriorly where it was better preserved. Scattered isolated zones of preserved RPE were also present. In places, the RPE appeared as a duplicated spindled layer (Fig 2C). An occasional rosette was seen (Fig 2D), formed by abnormal photoreceptors. In general, photoreceptor degeneration was less severe above the relatively preserved RPE, but advanced photoreceptor degeneration was occasionally seen in areas with preserved RPE. Similarly, loss of choriocapillaris vessels was usually seen beneath depigmented RPE and severely abnormal photoreceptors; however, occasionally preserved vessels were present in these areas. There was profound loss of most vasculature and melanocytes in the choroid.

IMMUNOHISTOPATHOLOGY

There was mild inflammatory cellular infiltration in the choroid beneath the abrupt transitions between retinal degeneration (atrophy) and relatively preserved retina. Inflammatory cells are also identified surrounding choroidal vessels. Most of the inflammatory cells were T-lymphocytes. Positive glial fibrillary acidic protein (GFAP) staining was observed throughout the retina, particularly at the transition between relatively normal and atrophic retina (Fig 3), indicating retinal gliosis.

Discussion

Despite accumulating knowledge of the genetics of CHM, the actual pathogenetic mechanism of the combined retinal, RPE and choroidal degeneration in cases is still ill-defined and has been speculated to be due to a deficiency in the prenylation of multiple Rab proteins.³⁷ Early clinical reports on the fundus of patients with CHM suggested that the loss of RPE in both males and females was either a primary event or a secondary result of changes occurring in the choroid.²⁵ Clues from the occasional pathological examination of the eyes of affected males and carrier females provide important information and add to our understanding of the natural history of the disorder.

Based on the examination of the eyes of two men with choroideremia aged 76 and 78, McCulloch suggested that atrophy of the choroid resulted in secondary loss of RPE and photoreceptors.²⁶ The men were part of a large kindred reported earlier by McCulloch and McCulloch.²⁵ Later, Rafuse and McCulloch reported the histopathological findings of one eye of a 61-year-old man affected by choroideremia, again part of the same kindred.³² At age 39, he had injured the eye; a glass shard had penetrated the eye, after which he recovered vision. A secondary cataract developed, all vision was lost and then the eye became “irritable” to the point that it was enucleated. Atrophy of the choroid and retina, with complete loss of the RPE and Bruch’s membrane was noted in the macula. Ghosh and McCulloch reported another two cases of CHM, ages 65 and 71.¹³ Inflammatory cells were not noted in either case within the choroid; however, the choroid at this late stage was very atrophic. The lack of outer segment phagocytosis by the RPE was documented; villous structures of the apices of the RPE did not contain outer segments. In a later paper, studying a 68-year-old carrier’s eye, no inflammatory cells were observed in the choroid and the choriocapillaris remained intact.¹⁴ Inflammatory cells were however seen in the choroid of a 91-year-old female CHM carrier.¹

Cameron and colleagues made the interesting observation of retinal glial migration through breaks in Bruch’s membrane in the eye of a 66-year-old man affected by CHM.³ Changes in the vascular endothelium of choroidal vessels and iris stromal vessels were also noted. Without the knowledge that biochemical pathways are impaired in choroideremia, the authors hypothesized that a slow “intracellular mechanism” led to atrophy of the vascular endothelial cells. Further, they hypothesized that the primary cause of CHM, as suggested by the condition itself, was a degeneration in the vasculature. Others, notably Flannery and colleagues, suggested that the primary defect was at the level of the RPE.¹² Finally, Syed and colleagues,

based on the study of an 88-year-old CHM carrier, hypothesized that the primary event was a degeneration of the rod photoreceptors.⁴⁰ Bonilha and colleagues observed cone degeneration with a relatively greater loss of blue cones in the eye of a 91-year-old CHM carrier.¹ Throughout these reports, the anatomic and functional integrity of the choriocapillaris, retinal pigment epithelium and photoreceptors appears to be at risk in the progression of choroideremia, while the bipolar cells and ganglion cells still remain present in the overlying neural retina.

Unfortunately, very few pathological cases of young individuals with CHM have been studied and reported. Rodrigues and colleagues reported the eye pathology of a 19-year-old man with CHM who died in a diving accident.³⁴ “Rosette-like retinal structures” were identified with preservation of the RPE and underlying choriocapillaris. In the rosettes there were a few “pigment-filled macrophages.” These macrophages, examined with electron microscopy, had attached outer segment structures, phagosomes, occasional melanin granules and “curvilinear rod-like profiles.” The authors alluded to the possibility of a defect in outer segment phagocytosis.

Our current case is from a young man with diffuse severe degeneration of RPE, retinal outer segments and choroidal vasculature. Co-localization of focal T-lymphocytic infiltration and retinal gliosis suggest a reactive inflammatory response at the edge of the active disease. Recent literature has provided important evidence for inflammation in age-related macular degeneration (AMD). Localization of inflammatory elements such as complement factors, macrophages and microglia in AMD lesions support the hypothesis that local inflammation, activation of the complement cascade and possibly the systemic immune system, contribute to the pathogenesis of AMD.^{10,16,18,28,30,38,47} Genetic variants in immune-related molecules, notably complement factor H (CFH), CFB, C2, C3, are risk or protective factors for AMD.^{4,9,11,15,17,18,20,22,33,35} Associations of other inflammatory factors such as CX3CR1 or TRL4 and AMD have been documented.^{6,43,47} Since choroideremia presents with RPE and retinal degeneration, the finding of inflammatory cells at the active lesion might imply a local immune response, which has been documented in AMD.⁸ Indeed, many factors in the inflammatory and angiogenic cascade have been identified in the cellular (photoreceptors, RPE and choriocapillaries) and acellular (drusen) components of AMD eyes. Interestingly, we found the involvement of more T-lymphocytes than macrophages in choroideremia, in contrast to the involvement with more macrophage than lymphocyte in AMD. Further investigations are needed to understand inflammation, immune responses and the retinal degeneration in CHM.

Recently introduced retinal imaging modalities have been used to study CHM carriers and have provided new findings that allow some useful inferences to be made about the pathobiology of CHM. Twenty one CHM carriers, aged 6-61, were studied with scanning laser ophthalmoscopy and optical coherence tomography (OCT).²¹ The earliest disease states involved thickening of the retina with normal lamination. This stage was followed by photoreceptor loss, independent of, or associated with RPE changes, and then thinning of the retina in later life. Müller cell activation likely plays a central role in the retinal thickening and remodeling within the retina of the choroideremia carriers. In our case of an affected CHM male, the evident gliosis matches a pattern seen in other retinal disorders such as retinitis pigmentosa.²

The early clinical signs of progression in choroideremia were carefully defined by studying a young male affected by CHM at ages 4, 5 and 6. This patient had a complete deletion of the *CHM* gene inferred from molecular genetic testing.²⁹ In this case, progressively coalescent areas of nummular RPE and choriocapillaris atrophy in the mid-peripheral and peripapillary fundus were defined, sparing the central macula. The relative preservation of electrophysiological responses in face of the fundus changes suggested that the overlying

retinal neuroanatomy and function was less impaired than expected in face of the clinical findings at the level of the RPE and choriocapillaris, similar to the clinical observations in our case. This observation was further confirmed with OCT imaging of the retina showing RPE and choriocapillaris atrophy with overlying preservation of retinal thickness albeit with anomalous lamination. In contrast, the retinal lamination and thickness remained remarkably normal in areas in which the RPE was preserved. These observations suggest that RPE changes precede retinal degeneration.

Current hypotheses based on the study of animal models have posited that the process of retinal degeneration in choroideremia is independent of a primary cell type or retinal layer. In a comprehensive study of mouse models of choroideremia, Tolmachova and colleagues demonstrated the effect of mutation in the *rep1* gene on development.⁴² At postnatal day 7, heterozygous-null females showed patchy depigmentation of the RPE. By P17, the ONL was reduced in thickness by 20% and a delay in the development of photoreceptors could be inferred. A retinal degeneration was observed at one month of age with progressive loss of the ONL such that by 8 months, there were some areas of severe retinal degeneration with no photoreceptors, and 1-2 rows of nuclei in the ONL. Ultrastructure of eyes from 9-month-old animals showed areas of RPE depigmentation, variable shortening and disruption of the outer segments and areas of severe photoreceptor loss with nuclei of the ONL adjacent to the RPE. Further elegant experiments creating separate tissue-specific knockouts of the *rep1* gene in photoreceptors and in RPE did not result in corresponding loss of RPE and photoreceptors, respectively, suggesting that the degeneration of these layers occurs independently. Our observations from pathological examination of the 30-year-old man with CHM tend to support this concept.

A defect in phagocytosis in CHM has been supported by ultrastructural observations in the naturally occurring zebrafish model of choroideremia.²³ This animal model has homozygous nonsense mutations in the *rep1* gene that result in a progressive photoreceptor degeneration. This model does not exactly replicate the human condition, as the zebrafish does not have a second gene akin to *CHML* which compensates for the lack of *rep1*. There are however helpful insights that derive from this research. The RPE from mutant animals show anomalies in the maturation, size and density of melanosomes, likely reflecting the lack of *rep1* and its role in the prenylation of Rab proteins involved in the trafficking of melanin into the melanosomes. As well, the RPE of mutants had undigested outer segments within it suggesting a defect in the maturation of phagosomes and perhaps interactions with lysosomes. The functional deficit of outer segment phagocytosis appeared to be rescued in mosaic animals when normal RPE was experimentally juxtaposed with mutant photoreceptors. In contrast, normal photoreceptors in contact with mutant RPE showed a degenerative phenotype.

van den Hurk and colleagues were unsuccessful in creating a male mouse model of choroideremia.⁴⁵ First, a construct with disruption of exon 8 of *rep1* was introduced into male embryonic stem cells and then chimeras were bred to derive female carriers; however, the carriers did not produce either male or female offspring reflecting a requirement for *rep1* in placental or extra-embryonic tissues. The eyes of chimeric males showed patchy areas of photoreceptor degeneration with normal RPE. As well, the carrier female mice showed a reduction in the ONL from loss of photoreceptors and again a normal RPE.

In our case, the findings of T-lymphocytic infiltration and gliosis, and their contribution to the pathology of CHM are intriguing. Although gliosis is likely a secondary event resulting from the loss or atrophy of photoreceptor and neuronal cells, inflammation could play a role, at least partially, in the initial event of neurodegenerative disease. Chronic inflammation is now considered to be central to the pathogenesis of not only multiple sclerosis, cardiovascular disease, diabetes, and cancer, but also neurodegenerative diseases such as Alzheimer and

Parkinson disease. Recent investigation in an AMD model of deficient mice has raised the hypothesis that subretinal microglia accumulation, resulting from a migratory defect associated with CX3CR1, plays a key role in drusen formation, choroidal neovascularization, and retinal degeneration - the main features of AMD.⁶ Further research studies are required to understand the effect of lack of REP1 on phagocytosis of outer segments by the RPE, as well as the role of inflammatory components in choroideremia.

Method of Literature Search

We consulted PubMed for articles related to choroideremia up to July 20, 2008 and searched with the headings: choroideremia, choroideremia and animal models. A hand search of literature prior to 1950 was performed to identify ocular pathology reports of choroideremia. The reference of Bonilha and colleagues was added in proof.

Acknowledgements

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article. Support for this research was provided by the Intramural Research Program of the National Eye Institute, NIH. The authors are indebted to Dr. Gerald A. Fishman who referred the living brother of this patient for genotyping. The authors also wish to thank Dr. Francis Garrity, Polk County Health Department, Des Moines, Iowa and the Iowa Lions Eye Bank for providing the eye for examination and Dr. James Folk of the University of Iowa, who kindly provided the fundus photographs.

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Fig. 1. Fundus photographs of OD (A) and OS (B) of an 18-year-old CHM-affected man showing symmetrical profound chorioretinal atrophy with preservation of central macula.

Fig. 2. Histopathology of the eye of a 30-year-old CHM-affected man showing A: abrupt transition area from relatively well-preserved structure (arrow) to severe degeneration; B: ectopic nuclei (arrows); C: apparent areas of RPE duplication (arrow); D: occasional rosette formation (arrow).

Fig. 3. Immunohistochemistry of glial fibrillary acidic protein staining in the transition area from relatively normal retina to atrophic retina, and mild T-lymphocyte infiltration of the choroid (arrows).