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Asymmetric Age-related Macular Degeneration

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KEYWORDS

Asymmetric, Age related macular degeneration, Dry AMD, Geographic atrophy

ABSTRACT:

Age-related macular degeneration (AMD) is a bilaterally symmetric disease influenced by genetic, environmental, and local factors. Genetic and environmental factors influence both eyes equally. However, unexpected asymmetry has been reported, with one eye affected more than the fellow eye. Asymmetry within the symmetry is a natural manifestation of AMD. The literature fails to identify the cause of asymmetric presentation in the same individual and warrants clinical research into local factors that influence the two eyes differently. By better understanding its pathophysiology, we can gain new insights into the development of asymmetry. Recent imaging techniques have helped identify early changes and explore the pathophysiology underlying AMD asymmetry. Genetics influences the early stage, but once the drusen area and volume increase, different local or environmental factors can produce synergistic effects, leading to a loss of symmetry between eyes.

1. Introduction

No biological system or structure has an identical right or left form or is unlikely to be perfectly symmetrical [1]. The human body, which appears to be right- and left-symmetrical, also manifests a degree of asymmetry [2,3]. Twin organs like the eye also exhibit asymmetry in parameters of the cornea, retina, etc [3]. Unsymmetrical clinical manifestations of various diseases have been reported in the eyes, including diabetic retinopathy, glaucoma, myopia, central serous chorioretinopathy (CSCR), etc. [3].

Age-related macular degeneration (AMD) is a progressive retinal neurodegenerative disease [2]. AMD is considered a bilaterally symmetrical disease [2,4]. The symmetry means two or more matching regions that are identical (or nearly identical) by either a mirror or rotational reflection [1]. Although asymmetry between ocular structures is considered abnormal, a significant asymmetry in retinal thickness among healthy individuals has been reported [1]. Studies have reported poor symmetry in the eyes with AMD [1,2,4,5]. One eye may have signs of AMD with a normal fellow eye [4]. (**Figure-1**) An interocular asymmetry was observed in patients with drusen, exudative (eAMD), and mixed disease [5]. Analysing color fundus photography (CFP) was also against bilateral equivalence [1]. Studies have reported bilateral similarity of geographic atrophy (GA) among 11% and eAMD among 22% of cases [2]. A degree of asymmetry was evident in the normative data used by SD-OCT software; however, most of these assumed symmetry [1]. A moderate agreement was observed between eyes diagnosed with any macular GA [2]. Studies have reported that approximately one-fourth of early and half of late unilateral AMD cases will progress to bilateral cases in the next five years [6]. Although, AMD has similar genetic and environmental factors that influence both eyes equally, an unexpected asymmetry has been reported [2]. In other words, genes remain the same, but environmental and local factors influence disease development and progression differently in each eye of an individual [7]. How do these environmental and local factors affect one eye more than the other remains unanswered and a provocative observation [2,3] ? The Majority of the AMD patients are among the early or intermediate (iAMD) stage (85%), and are asymptomatic [3]. Optical coherence tomography (OCT) and OCT angiography (OCT-A) can diagnose asymptomatic cases at an early stage and facilitate timely interventions [5]. Although a myriad of treatment options (several pharmacologic therapies) exist for wet AMD, no treatment guidelines are available

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for dry AMD [8]. The prevalence of dry AMD is only 0.44%; however, as the elderly population increases, the prevalence of AMD will also increase [8]. AMD causes loss of central vision and affects lifestyle [5]. Most of the available information is based on the asymmetric case management of neovascular AMD (wet AMD) in one eye and their fellow control eye [9]. However, questions remain regarding the pathophysiology of AMD, in which one eye is affected more than the other [1]. The literature fails to identify the reason for asymmetric presentation in the same individual [3]. Dry AMD has no available treatment guideline; therefore, early detection of early or iAMD remains a crucial step for preventing progression and for timely intervention before it reaches the irreversible stage [10,11,12]. We propose local changes with genetic susceptibility causing asymmetric AMD [13]. We plan this study to explore pathophysiology leading to the asymmetricity of disease with a focus on the early identification of non-exudative AMD. In this systematic review, a literature search was conducted across PubMed, Google Scholar, and Baidu Scholar using the following search terms: (Age-related macular disease OR AMD) AND (Asymmetric OR Symmetric OR Unilateral OR Bilateral) AND (Prevalence OR Diagnosis OR Treatment). Informed consent for the use of images has been obtained from participants in our medical college database.

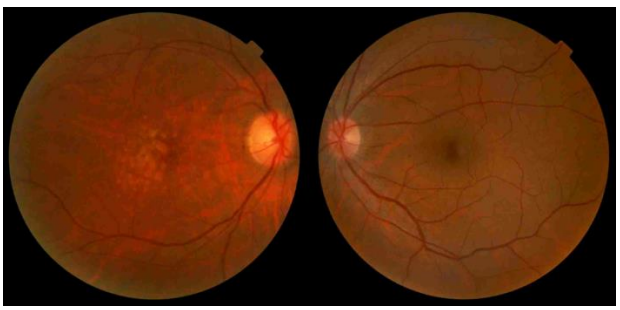

Figure 1- Asymmetric Early AMD (Early AMD OD and Normal OS)

2. Pathogenesis of Asymmetry

AMD is assumed to be a bilaterally symmetric genetic disease with both environmental and local influences [2,3,4]. The genetic and environmental factors similarly expose both the eyes [2]. However, we observed a pattern of asymmetry in the clinical presentation, as one eye was affected more severely than the other [1,3]. This warrant clinical research into local factors fora better understanding of disease asymmetry [11,12]. Macula receives its blood supply from the retina and the choroid [3]. The blood supply of the eye comes through the common carotid, but the right and left originate from the brachiocephalic trunk in neck and aorta in thorax, respectively [3]. Interocular asymmetry attribute to hemodynamic differences leading to asymmetric blood flow [14]. OCT has reported some degree of asymmetry in retina and choroid among healthy fellow eyes [14]. Asymmetry in choroid thickness and choroid vascular index has also been reported among fellow eyes in normal adults [14]. Further analysing the different quadrants of the macula, it was found that the asymmetry was more in the nasal part of the macula between the eyes of healthy individuals [3]. Fovea receives its nourishment from choriocapillaris (CC) and CC flow deficit has been reported with age increase [15]. The ambiguous mechanism of pathogenesis is further complicated by multifactorial etiology [16]. The genetics factors play a significant role in disease onset; however, the roles of environmental influences and local factors become more significant, causing asymmetry [2]. Evidence suggest choroidal perfusion is an important local factor in AMD pathogenesis [13]. Studies have reported flow deficit in the CC and unsymmetrical dilatation of the vortex vein among fellow eyes of unilateral AMD cases, which show no signs of AMD [17]. These asymmetry of local hemodynamic parameters within the CC may cause relative hypoxia, which may progress to early AMD changes [17,18]. These CC dropout areas serve as stimuli for large choroid vessels to move and occupy the CC area to fulfil the requirement of hypoxia [19,20]. Studies have reported a decrease in flow perfusion in the CC area in AMD cases compared with that in normal [21]. OCTA reports CC density reduction and/or loss that appears as a dark zone in early AMD [16]. With disease progression, this loss of CC is replaced by large vessels of the choroid in the advanced stages [16,17]. In iAMD, choroidal CC density reduction is seen below and near the drusen area, accompanied by a reduction in retinal vessel density in both the superficial and deep regions [17]. Another study reported a decrease in CC flow as an early change and high risk of AMD development [14,16]. Although age also affects CC flow deficit, its severity is higher in AMD fellow eyes [14]. CC dysregulation is also related to early and iAMD stages [16]. Among patients with

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asymmetrical AMD, Plasma long-acting vasoconstrictor peptide (Endothelin-1) values, abnormal Short Posterior Ciliary Artery blood flow rates, and an increased Resistance Index have been reported [22]. Endothelin-1 binding sites have been identified in retinal vessels, choroidal vessels, and the retinal pigment epithelium (RPE) [22]. This asymmetry change between eyes further complicates by the age-related changes in Bruch's membrane (BrM) thickness or composition, hindering the transport of nutrients and fluid required for photoreceptors (PR) [16]. Early AMD cases were diagnosed based on the size of drusen [2]. The drusen area and volume have been shown to correlate with complement factor H, a reported risk factor in patients with AMD [2]. The complement checks and defends local intraocular homeostasis [12]. Complement factor H levels were found to increase with the increase of severity of AMD [7,21]. Complement factor C3 plays a very important role in three biochemical pathways of the innate immunity system (classical, alternative, and lectin), and it further activates C5 to form a membrane attack complex (MAC) and inflammasome [12]. Among the complement proteins, C5a can pass through BrM, leading to inflammation [12]. As AMD progresses, it manifests asymmetry with an increase in Drusen size, number, and pigmentary changes [20]. Large drusen height is correlated with predictive OCT biomarkers for GA [17].

As these asymmetries persist, they further damage the retina due to the malfunctioning of mitochondria in retinal pigment epithelium (RPE) cells [23]. This mitochondrial dysfunction has been reported to cause oxidative stress (reactive oxygen species), mt-DNA damage, protein aggregation, and inflammation in eyes with asymmetric RPE BrM complex and choroidal vasculature abnormalities [23]. These inflammatory microenvironment activates the monomer C-reactive protein (CRP) (found in drusen), further disrupting the barrier function of endothelial cells [21]. The vicious cycle of multiple inflammatory factors continues to cause further asymmetry, and phenotypic changes, secondary to RPE and PR degeneration [17]. The thinned PR layer eventually headway to a thicker RPE + BrM complex, leading to AMD [17]. Low internal reflectivity of drusen and RPE with overlying EZ damage are high-risk factors for advanced AMD [17]. The incidence of AMD in people exposed to sunlight (excess blue causes RPE damage and excessive white causes PR damage) for a longer period of time was significantly higher [12]. Therefore, it can be concluded that genetics influences the early stage, but once the drusen area and volume increase, different local or environmental factors produce synergistic effects leading to loss of symmetry between eyes [2]. The availability of advanced multimodal imaging guides us to identify and locate subtle changes in the retina and choroid at earlier stages for timely intervention and helps avoid irreversible vision loss [14]. Eventually, it has been reported that if the patient lives long and both eyes achieve the end stage, AMD is again reported to become symmetrical [2]. Therefore, we can conclude that asymmetry is present in the progression phase, but symmetry is achieved at the end-stage of the disease [1].

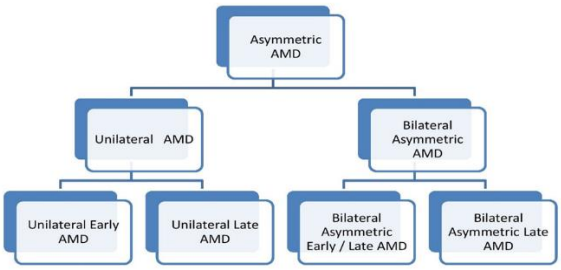

Figure 2- Classification of Asymmetric AMD

3. Definition

Asymmetric AMD can be categorized as either unilateral or bilateral asymmetric AMD. (**Figure-2**) Unilateral AMD is define as early or late AMD present in only one eye (other eye normal/age changes). It can be further divided into unilateral early AMD and unilateral late AMD. Unilateral early AMD is define as early/intermediate AMD present in only one eye (other eye normal/age changes). Unilateral late AMD is a late AMD (GA /eAMD /mixed) present in only one eye (other eye normal/age changes). Bilateral asymmetric AMD is define as AMD present in both eyes, but at different stages. It can be of two types. Bilateral asymmetrical early/ late AMD (one eye early/intermediate and another eye late AMD (**Figure-3**) and another type is bilateral asymmetrical late AMD (one eye GA other wet eAMD). The majority of studies are based on bilateral asymmetric AMD, in which one eye has an advanced stage (GA /eAMD /mixed), and a fellow eye was used to study the progression of AMD.

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Progression is the conversion from unilateral to bilateral AMD or from bilateral asymmetric to bilateral symmetric AMD [6].

4. Future Trends

Understanding the pathogenesis of AMD could pave the way for the development of novel therapeutic approaches [16,24]. Various serum biomarkers, such as C-reactive protein (CRP) and proinflammatory cytokines, such as IL-8, cholesterol, and interferon can be used for early AMD diagnosis, monitoring, progression, and treatment response [24]. Therefore, further research on the early phases of AMD and asymmetry is warranted [16]. AI technology has emerged to assist ophthalmologists in determining and formulating the best monitoring and management strategy for AMD [12].

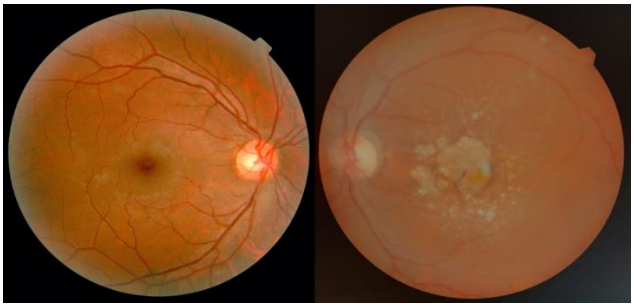

Figure 3- Bilateral Asymmetric early / late AMD (Early AMD OD & eAMD OS)

5. Conclusion

Asymmetry within the symmetry is a natural manifestation of AMD. By better understanding the pathophysiology of factors that may differ between the eyes of the same individual, we can gain new insights into the development of future targeted therapies. The number of AMD cases is expected to increase along with an increase in the elderly population.

6. Financial support and sponsorship

Nil.

7. Conflicts of interest

There are no conflicts of interest.

8. Legend

Figure-1 Unilateral Asymmetric Early AMD

Figure-2 Types of Asymmetric AMD

Figure-3 Bilateral Asymmetric Early/Late AMD

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