

Achromatopsia: literature review and case study

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Abstract

Congenital achromatopsia is a rare macular dystrophy affecting one in 30,000 to 50,000 people. It is associated with five genetic markers, with mutations in the CNGA3 and CNGB3 genes responsible for over 90% of cases. The disease presents with colour vision defect, early onset of visual impairment, photophobia, pendular nystagmus, and an abnormal photopic electroretinogram (ERG). The disease has two forms: incomplete, which is milder due to residual cone function, and complete, which is severe due to the complete absence of cone function. The diagnosis of achromatopsia has been challenging due to the variability in clinical presentations and associated symptoms. The advent of spectral domain optical coherence tomography (SD-OCT) has revolutionized the evaluation and understanding of achromatopsia.

Achromatopsia is a rare macular dystrophy with variable presentation, presenting with a range of symptoms including reduced vision, photophobia, dyschromatopsia, and nystagmus. Diagnostic tests like SD-OCT, fundus autofluorescence, and electrophysiology aid in ruling out distinct aetiologies. Traditional diagnostic methods, such as diminished light-adapted flash photopic ERG and 30 Hz flicker, have been used to diagnose achromatopsia. Recent diagnostic modalities, like SD-OCT, have helped in evaluating achromatopsia, providing a better understanding of the disease. The use of SD-OCT has helped document a progressive degenerative process noted with increased age, with a flattened appearance of the cystic area on OCT. Animal genetic studies have further collaborated on the progressive

nature of the disease, with a CNGA3 genetic mutation contributing to the progressive form of the disease.

Achromatopsia is a rare macular dystrophy with variable presentation, presenting with vision reduction, photophobia, dyschromatopsia, and nystagmus [1,2]. Diagnosis traditionally involves a diminished light-adapted flash photopic ERG and 30 Hz flicker, which correlate with the functional loss of cone photoreceptors. Recent diagnostic modalities like SD-OCT have helped in evaluating achromatopsia, giving a better understanding of the disease. Congenital achromatopsia, also known as rod monochromatism, affects one in 30,000 to 50,000 people and is associated with five genetic markers. The disease presents with color vision defects, early visual impairment, photophobia, pendular nystagmus, and abnormal photopic electroretinograms. SD-OCT can help visualize characteristic morphological alterations linked to achromatopsia, aiding in diagnosis and potentially enhancing future therapeutic alternatives.

Introduction

Macular dystrophy is a condition that is linked with a malfunction or lack of cone photoreceptors. Congenital achromatopsia, which is also known as rod monochromatism, is such a condition. A uncommon form of macular degeneration affects about one in 30,000 and 50,000 people. As of right now, there are five genetic markers that are connected to this heterogeneous autosomal recessive cone dystrophy. The capacity of cone photoreceptors to respond to a light stimulus is impaired when there is a mutation in the gene that causes this malfunction [3]. The CNGA3, CNGB3, GNAT2, PDE6H, and PDE6C genes are among the known related gene mutations that are responsible for more than ninety percent of the instances with achromatopsia. It has been found that the most prevalent mutations are those that occur on the CNGA3 and CNGB3 genes.⁸ Due to the fact that the condition is caused by different genotypes, there is a great deal of variation in the clinical presentation of achromatopsia. The literature does not provide a lot of evidence to support the hypothesis that there is a correlation between a certain genotype and phenotypic expression.

Method

The traditional clinical presentation of achromatopsia involves a loss in colour vision, the beginning of visual impairment at an early age, photophobia, pendular nystagmus, and an aberrant electroretinogram (ERG) of the photopic region of the retina. There are two types of the condition, which may be distinguished from one another based on the frequency and severity of cone malfunction. The incomplete form is linked to a sort of visual impairment that is less severe since it is connected with residual cone function.

As a consequence of the total lack of any cone function, the full form is distinguished by a significant vision impairment that can range anywhere from 6/30 to 26/120.9,11

Despite the fact that there may be no indication of maculopathy already present, clinical ophthalmoscopic findings might range from a simple loss of foveal reflex to the more traditional confined maculopathy. There is a significant amount of variation in clinical presentations and related symptoms, which contributes to the difficulty of diagnosis.

To verify the diagnosis, supplementary testing, such as photopic electroencephalograms, has been utilised for a considerable amount of time. Functional assessment was corroborated by a significant drop in response to the 30 Hz flicker, which was attributed to a malfunction of the cones. On the other hand, structural evaluation of the illness was restricted to histology studies that revealed the lack of foveal cone photoreceptors or their distortion[4].

Discussion

The assessment and comprehension of achromatopsia have been completely transformed as a result of the introduction of spectral domain optical coherence tomography (SD-OCT), which has the capacity to clearly identify the inner segment/outer segment (IS/OS) junction. There is a structural correlation between the defective cones and the lack of the subfoveal insulin-secretion system junction. The typical hyporeflective 'punched out' subfoveal zone on optical coherence tomography (OCT) can lead to the diagnosis of

achromatopsia even when only modest ophthalmological symptoms are present [5,6]. This zone correlates to the absence of the IS/OS junction. Recent discussions in the academic literature have brought up these findings, which have not been without their share of dispute.

During the course of a case study, a Hispanic guy who was 24 years old appeared with complaints of photophobia and reduced vision that had been present for a long time. He denied that he had ever had nyctalopia or a limitation in his vision field. His medical background was not very noteworthy. Since an early age, the patient has been diagnosed with a vision impairment of uncertain aetiology, according to their previous ocular history. His family history indicated that his maternal aunt had maculopathy, which was likewise linked with diminished visual acuity and had a congenital origin. However, there was no recognised diagnosis for the ailment because it was not diagnosed until much later.

According to the modified Early Treatment Diabetic Retinopathy Study (mETDRS), the visual acuity of both the right and left eye was equal to 6/36. The manifest refraction of the right eye was $-3.75-2.50 \times 045$, and the left eye was $-6.25-1.50 \times 135$. Additionally, there was no afferent pupil defect in either eye, and the pupils were circular and receptive to light in equal measure [6]. There were so many people on the confrontation fields that it was impossible to count them all. In every single look, the extraocular muscles of both eyes were completely free. While the contralateral eye was occluded, the right and left eyes exhibited a little horizontal nystagmus in primary gaze. This was seen in both right and left eyes. A significant colour vision impairment was discovered through the use of the Hardy Rand and Ritter 4th Edition Pseudoisochromatic plates for colour vision testing. As a consequence, the individual was unable to enjoy any colour vision with either eye. Additional colour vision testing with both saturated and desaturated Farnsworth D-15 found that there was no colour discrimination at all, and there was also no colour defect pattern connected with it.

Examination with a slitlamp revealed nothing unusual. Using Goldmann tonometry, the intraocular pressures were

measured to be 12 mmHg on both R and L. During the dilated fundus examination, both eyes were found to have pink optic nerves that were different from one another and had cup-to-disc ratios of 0.3/0.3. Both eyes had an artery to vein ratio of two thirds, which indicated that the retinal vasculature seemed to be normal. Clarity was observed in the vitreous of both eyes. It was observed that the macula of both eyes had a little disturbance in the retinal pigment level. In both cases, the peripheral retinae were not notable [7].

The results of the SD-OCT showed that both eyes had blunt foveal contours that were symmetrical and linked with macular thinning. According to Figure 2, there were sub-foveal hyporeflective flattened 'punched out' zones in both eyes. These zones were connected with a missing IS/OS connection. Both the light-adapted whole field ERG and the 30 Hz flicker experiments showed that there was no response to the photopic stimulus, and the amplitudes of the 30 Hz flicker experiment were almost undetectable. It was determined that the patient had total achromatopsia according to the findings of the clinical examination and the auxiliary tests.

Counselling was provided to the patient on the diagnosis. However, several low vision aids were demonstrated to the patient, and the patient had a positive response to several devices, such as a Specwell 8D monocular telescope to assist in distance identification and an Optelec Compact + for near work. After the patient reported that he felt satisfied with his ability to function in his day-to-day activities, he was shown several low vision aids. A reading device, specifically an Apple iPad and an Amazon Kindle, was also presented to the patient. An Apple iPhone was already in the possession of the patient, and they were already aware with the different tools and programmes that are available to assist patients who have limited vision. Several different lens filters were demonstrated to the patient in order to alleviate the photophobia that he was experiencing. Because the patient believed that he did not require any devices at this time, no lenses or devices were issued to him [8] with the exception of an updated correction for his spectacles). The progression of the patient is being monitored on a yearly basis through this process.

The diverse appearance of achromatopsia, which is an uncommon form of macular dystrophy, is one of the factors that adds to the difficulty of diagnosis. The condition known as achromatopsia can manifest itself with a wide variety of symptoms, such as a loss in vision of varied degrees, photophobia, dyschromatopsia, and the presence or absence of nystagmus. A long-standing history of visual impairment, together with accompanying photophobia, was shown by our patient. Additionally, the clinical appearance might range from a loss of foveal reflex to a maculopathy that is later in its progression. The macular disturbance that our patient exhibited was fairly mild and bilaterally symmetrical. The fact that the structural alterations in individuals with achromatopsia frequently do not coincide with the functional changes [9,11,14] is another factor that contributes to the difficulty of the diagnostic process. Stargardt's disease, hypoplastic fovea associated with ocular albinism, inverse retinitis pigmentosa, and Best's disease are some of the differential diagnoses that can be made for early-onset maculopathies that are associated with visual impairment. Vitreomacular traction, early age-related macular degeneration, drug-related maculopathies (plaque or tamoxifen macular toxicity), lamellar hole, idiopathic macular hole, and solar maculopathies are some of the conditions that can be included in the differential diagnosis of acquired maculopathies in adult patients who have visual impairment. These additional disorders are distinct from achromatopsia in a variety of aspects, including the start of symptoms, clinical presentation, and results on optical coherence examination (OCT). The use of diagnostic procedures, including as fundus autofluorescence, electrophysiology, and SD-OCT, help in the process of eliminating different aetiologies [9,10]. This is in addition to the rigorous and extensive eye examination that is performed. A comprehensive case history can be helpful in eliminating a number of potential causes, such as medication toxicity. If a patient has Stargardt's disease, fundus autofluorescence can be used to confirm the distinctive general rise in autofluorescence that is associated with the condition. The diagnosis of inverse retinitis pigmentosa, on the other hand, is validated by electrophysiological testing

that reveals a dampened scotopic electroretinogram (ERG). These maculopathies, which include vitreomacular traction, lamellar hole, and solar maculopathies, may be easily verified with the use of SD-OCT. This is due to the fact that each of these maculopathies has its own unique SD-OCT results. In contrast to the morphological results that are linked with congenital achromatopsia, these findings are different.

A reduced light-adapted flash photopic ERG and a 30 Hz flicker have traditionally been utilised in the diagnostic process for achromatopsia since its inception. With the functional loss of the cone photoreceptors, there is a correlation between the diminished flash photopic ERG and the 30 Hz flicker activity. A flash photopic electroencephalogram (ERG) of our patient revealed that there were no A, B, or C waves present, and there was a flicker response of 30 Hz that was almost impossible to detect [10,11].

The examination of achromatopsia has been assisted by more contemporary diagnostic methods, such as the SD-OCT, which has resulted in a better knowledge of the condition. It would appear that the SD-OCT is able to distinguish the structural alterations that are linked with the loss of cone photoreceptors subfoveally. Patients diagnosed with achromatopsia have subfoveal disruption of some kind at the level of the interocular space (IS) and the outer layer of the retina (OS), and in more advanced cases, retinal pigment epithelium atrophy.

SD-OCT pictures were analysed by Thiadens and colleagues⁹ in forty individuals who were diagnosed with achromatopsia. In the research, the standard OCT result was described. This finding featured a subfoveal hyporeflective 'punched out' zone that was coupled with an intact hyper-reflective external limiting membrane and the underlying retinal pigment epithelium. It has been found that the lack of the IS/OS junction is correlated with the hyporeflective zone. In addition to the thinning of the outer nuclear retinal layer, other findings associated with achromatopsia include a change in the foveal contour, a reduction in the foveal depth, and overall thinning of the retina [12]. The variability in SD-OCT findings may contribute to the overall distinct fundoscopic presentations that are associated with achromatopsia.

Thomas and his colleagues made a significant contribution to the expansion of our knowledge of the disease by establishing a connection between the pathophysiology of the disorder and a specific SD-OCT appearance [12]. The foveal contour changes that were observed within the SD-OCT were thought to be correlated with the classic 'punched out' zone that was also observed on the SD-OCT. This was attributed to structural change that occurred as a result of progressive age-related dysfunction of the cone photoreceptors [12]. Furthermore, they believed that the progressive cone degeneration that was observed in patients with achromatopsia could be attributed to the loss of phagocytotic activity at the level of the retinal pigment epithelium. With the passage of time, this appears to grow increasingly apparent [12].

In the past, achromatopsia was considered to be stable and non-progressive. However, the use of SD-OCT has assisted in the documentation of a progressive degenerative process that is observed with increasing age [9,10]. Genead and colleagues investigated SD-OCT findings in individuals with achromatopsia who were of varying ages [13]. According to what they observed, the traditional SD-OCT finding does not appear to be present among younger individuals. Their study revealed that only seventeen per cent of patients under the age of nine presented with the classic SD-OCT findings, while all patients over the age of 40 displayed the classic OCT finding associated with the hyporeflective subfoveal 'punched out' zone of the missing IS/OS junction.[14] The use of the SD-OCT further documents a change in the classic finding, whereby a flattened appearance of the 'punched out' cystic area on OCT is noted with an increase in age[9,13]. The flattening or disappearance of the cystic hyporeflective space correlates to overlying retinal layers merging with the retinal pigment epithelium [9]. Although our patient was only 24 years of age, the SD-OCT revealed a more flattened cystic-like space associated with a missing subfoveal IS/OS junction. This conclusion is consistent with the findings of earlier investigations and the hypothesis that the illness exhibits a progressive character. The findings of the progressive SD-OCT and the link between those findings and the age of the patient have been the subject of significant debate. After

evaluating forty individuals who had achromatopsia [13]. Sundaram and colleagues discovered that there was no association between the age of the individual and the SD-OCT results that were related with it [11]. The authors did not deny the progressive character of the ailment; rather, they hypothesised that the absence of an IS/OS zone was not connected to the phenotypic expression of the patient or to the patient's age. There is a possibility that future longitudinal research will give more demonstrable data in relation to this dispute. Despite the fact that there are no studies conducted on humans, genetic research conducted on animals has further contributed to the observation that the disease is progressive. The CNGA3 genetic mutation was found to be a contributor to the progressive form of the disease, according to a study that examined the retinas of knockout mice, which are mice that do not have cone-specific channels [15]. Histological examination of the retina of these young mice revealed that only 10 to 20 percent of their cones were functional, whereas the retina of the older mice had complete degeneration of all of their cones[14].

When it comes to macular dystrophy, achromatopsia is an uncommon condition that can appear in a variety of ways, which adds to the difficulty of diagnosis. A variety of symptoms, including a decrease in vision, photophobia, dyschromatopsia, and the presence or absence of nystagmus, may be present in patients with this condition. It is possible for the clinical appearance to range from a loss of foveal reflex to more severe maculopathy, with mild bilateral symmetrical macular disruption appearing in some cases. There is frequently no correlation between structural abnormalities and functional changes, which makes diagnosis even more challenging. Stargardt's disease, hypoplastic fovea associated with ocular albinism, inverse retinitis pigmentosa, and Best's disease are some of the differential diagnoses that can be made for early-onset maculopathies that are associated with visual impairment. Vitreomacular traction, early age-related macular degeneration, drug-related maculopathies (plaquenil or tamoxifen macular toxicity), lamellar hole, idiopathic macular hole, and solar maculopathies are some of the conditions that can be included in the differential diagnosis

of acquired maculopathies in adult patients who have visual impairment.

A reduced light-adapted flash photopic ERG and 30 Hz flicker are generally taken into consideration when making a diagnosis of achromatopsia. These two characteristics are associated with the functional loss of cone photoreceptors. On the other hand, more contemporary diagnostic techniques such as SD-OCT have allowed for the evaluation of achromatopsia, which has resulted in a better knowledge of the condition. In the subfoveal region, the SD-OCT appears to be able to distinguish structural alterations that are related with the loss of cone photoreceptors. Patients diagnosed with achromatopsia have subfoveal disruption of some kind at the level of the interocular space (IS) and the outer layer of the retina (OS), and in more advanced cases, retinal pigment epithelium atrophy.

The pathophysiology of the condition has been linked to a specific SD-OCT presentation, with foveal contour alterations found within the SD-OCT connected with the IS/OS typical 'punched out' zone. This has been the case since the ailment became apparent. It is possible that the decrease of phagocytotic activity at the level of retinal pigment epithelium is responsible for the progressive cone degeneration that is seen in individuals who have achromatopsia[15].

The findings of SD-OCT have contributed to the documentation of a gradual degenerative process that is observed with increasing age. On the other hand, there has been debate over the findings of the progressive SD-OCT and the connections between those findings and the age of the patient. In addition, animal genetic studies have been conducted in order to better investigate the progressive aspect of the disease. For example, a research conducted on the retinas of knockout mice revealed that a genetic mutation known as CNGA3 was responsible for the progressive form of the disease [13,14].

This unusual form of macular dystrophy is characterised by the malfunction or lack of cone photoreceptors. Congenital achromatopsia, which is also known as rod monochromatism, is another name for this condition. In addition to being linked

to five genetic markers, it affects between one in 30,000 and 50,000 persons nationwide. Mutations in genes are responsible for more than ninety percent of instances, with the genes CNGA3, CNGB3, GNAT2, PDE6H, and PDE6C being the most prevalent candidates. A number of symptoms, including colour vision deficits, early visual impairment, photophobia, pendular nystagmus, and aberrant photopic electroretinograms, are commonly associated with this condition. Incomplete forms of the illness are characterised by a less severe visual impairment, whereas complete forms of the disease are characterised by a more progressive visual impairment. The results of a clinical ophthalmoscopic examination might range from a lack of foveal reflex to confined maculopathy. Due to the fact that dysfunctional cones are correlated with the lack of the subfoveal IS/OS junction, the introduction of spectral domain optical coherence tomography (SD-OCT) has brought about a revolution in the evaluation and comprehension of achromatopsia. These findings have been investigated in the research literature, and they have been met with some degree of debate.

In the course of a case study, it was observed that a Hispanic guy, aged 24, who had been experiencing photophobia and impaired vision for a considerable amount of time appeared without any previous history of nyctalopia or visual field limitation. His family history indicated that his maternal aunt had maculopathy, which likewise had a congenital origin and was linked with diminished visual acuity. His medical history was ordinary, but his family history presented a concern. On the modified Early Treatment Diabetic Retinopathy Study (mETDRS), the patient's visual acuity was measured at 6/36, and a little horizontal nystagmus was seen in primary gaze [15]. Through the use of colour vision tests, it was discovered that the individual had a significant colour vision deficiency, which led to the inability to enjoy any colour vision with either eye. During the dilated fundus examination, the optic nerves were found to be pink and distinct, and the vasculature of the retina looked to be normal. The results of the SD- OCT showed that there were bilateral symmetrical blunt foveal contours, linked with macular thinning, sub-foveal hypo reflective flattened 'punched out' zones, and a missing IS/

OS junction. The diagnosis of total achromatopsia was made after the light-adapted whole field ERG and the 30 Hz flicker showed that there was no response to the photopic stimulation of the patient. The patient was counselled on the diagnosis and shown different low vision devices, such as a Specwell 8D monocular telescope for identifying distances and an Optelec Compact + for working in close proximity to objects. In an effort to alleviate his photophobia, he was presented with a variety of lens filters; however, no equipment or lenses were provided to him. The progression of the patient is being monitored on a yearly basis through this process [14,15].

Conclusion

It is important to note that this particular case is a typical example of congenital achromatopsia, which highlights the diagnostic relevance and benefits of an SD-OCT.

Due to the fact that achromatopsia can manifest in a variety of ways, the diagnosis of the condition can be difficult. Visualising the typical morphological changes that are associated with achromatopsia may be accomplished through the use of SD-OCT, which can thus be of assistance in the diagnosing process. Having a better understanding of achromatopsia might potentially lead to improvements in the therapy options available in the future. It is possible that the use of SD-OCT might be of critical importance in the timely detection of achromatopsia during its first phases, as well as in the identification of people who can possibly benefit from upcoming treatment options. In addition, the changes in structure that are seen on spectral domain optical coherence tomography (SD-OCT) can be employed to monitor the progression of the illness being studied.

The subjective and objective parameters of SD-OCT can be utilised, in a manner analogous to that of other retinal illnesses, in order to evaluate the efficacy of proposed treatment strategies for persons who have achromatopsia.

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