Case Report

Achromatopsia: The First Case Report in Thailand

Ngamkae Ruangvaravate MD*, Patthanee Samsen MD*,
Atiporn Thuangtong MD*, Nacha Chanvarapha MSc*

**Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Achromatopsia, also known as rod mon-ochromacy, is a congenital and nonprogressive ocular disorder characterized by an absence of functional cone photoreceptors in the retina. Affected subjects usually present in infancy with photophobia, nystagmus, low visual acuity and inability to discriminate colors. Fundus examination is normal, but electroretinography demonstrates absent photopic (cone) responses and normal scotopic (rod) responses. Achromatopsia is rare in the general population and inherited as an autosomal recessive trait. The authors report the first case of achromatopsia in Thailand with complete electrophysiological findings and long-term follow-up (8 years).

***Keywords**: Achromatopsia, Rod monochromacy, Photophobia, Nystagmus*

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Achromatopsia or rod monochromacy is a severe retinal disorder characterized clinically by impairment of visual acuity in daylight, photophobia, nystagmus and total color blindness[1]. This is an autosomal recessive hereditary disorder manifested by absence or malfunction of the retinal cones, the specialized sensory cells responsible for normal trichromatic color vision. Electrophysiological test is the diagnostic tool for this disorder. Electroretinographic recordings (ERGs) in patients demonstrate that rod photoreceptor function is normal, whereas cone photoreceptor function is extinguished. Achromatopsia is rare in the general population (1: 20,000 – 1: 50,000)[2] and, to the best of the authors' knowledge, this is the first case report in Thailand, with long-term follow-up (of 8 years).

Case Report

A 5-year-old boy came to Siriraj Hospital in June, 2002 due to poor vision in both eyes. He has had a history of nystagmus, photophobia and poor vision since he was an infant. His mother took him to see many ophthalmologists, hyperopic refractive error was diagnosed but his vision slightly improved with glasses. He was the first child with one younger brother in the family. His brother was healthy and had normal vision. No one in the family had symptoms the same as him. He was a well baby and had a history of normal labor. He was referred to Siriraj Hospital for further investigation. The authors first saw him in June 2002, his visual acuity was finger counting both eyes (without glasses) and 20/400 both eyes (with hyperopic glasses). He had nystagmus and photophobia, slit lamp examination and fundoscopy were normal both eyes. His refraction was +5.50D -0.50axis 165° in the right eye and+5.75D -0.75axis 10° in the left eye. A color vision test revealed total color blindness in both eyes.

When the authors shone the penlight to his eyes, he had photophobia. Then, the authors turned off the room light, he could widely open his eyes and saw better (Fig. 1). Electrophysiologic tests were performed by using electrodiagnostic instruments (Neuropto os 5, Medelec Limited, England) with skin electrodes (Ag/AgCl). ERGs demonstrated non-

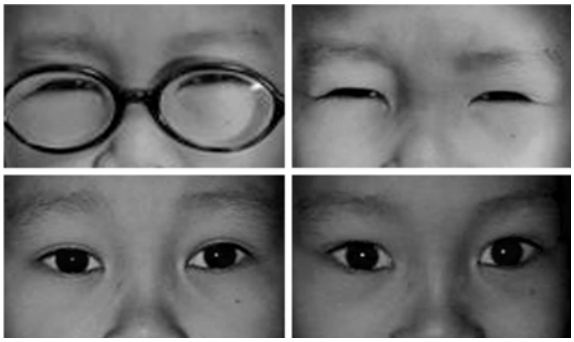

Fig. 1 The patient was 5 years old. He had photophobia when we shone the penlight to his eyes (top left and top right). He could widely open his eyes when we remove penlight (bottom left) and turn off the room light (bottom right)

Correspondence to:
Ruangvaravate N, Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
Phone: 0-2419-8033-4, Fax: 0-2411-1906
E-mail: sinrv@mahidol.ac.th

recordable in photopic and flicker, but normal response in scotopic. Flash visual evoked potential (VEP) was normal both eyes. These findings showed that he had absence of cone function with normal rod response, and then achromatopsia was diagnosed in this patient. The authors advised him to use tinted lenses (sunglasses) for his hyperopic correction to avoid bright light. His mother was reassured that her son would not be blind from achromotopsia. This was a stationary disorder: nystagmus would decrease as he got older. Genetic counseling was given to his mother as well. After using tinted lenses, his quality of life improved, he learned better at school and had a normal life with other people. The authors recommended him to be followed-up every six months and electrophysiological tests were performed every year.

He came to Siriraj Hospital regularly as scheduled from 2002 to 2010 (8 years follow-up). His visual acuity was stable at finger counting without correction and 20/400 with glasses both eyes. Color vision test remained total color blindness. Slit lamp examination and fundoscopy were still normal both eyes. Electrophysiological tests (ERG and VEP) were performed every year. The authors have changed the equipment for electophysiological tests from the old one (Neuropto os 5, Medelec Limited, England) to the new one (Nicolet Viking select master software V7.1, Nicolet Biomedical Inc, USA) since 2005. The results of ERG (Fig. 2) and VEP were stable. In 2007, a blood test was done for mutation analysis of CNGB3, CNGA3 and GNAT 2 genes in achromatopsia patient. Mutation screening in 18 exons of CNGA3 gene, 7 exons of CNGB3 gene and 8 exons of GNAT2 gene was performed using single standard confirmation polymorphism (SSCP) followed by direct DNA sequencing. Clinical sensitivity (detection rate) of the CNGB3, CNGA3 and GNAT2 genes mutation using SSCP is between 75-80%[3,4]. The result showed that no mutations were identified in this patient. This may be that he had a novel mutation gene which was not previously detected. The final eye examination on October 21, 2010 demonstrated that vision with corrected glasses was 20/400, 20/400, and with illuminated pocket magnifier was 20/50, 20/50. Anterior segment and fundoscopy were normal. His refraction changed to +1.00 D – 1.75 axis 180° right eye, +1.75 -2.00 axis 14° left eye. ERG (Fig. 2) and VEP recordings were stable when compared to the previous examinations. Currently, he is thirteen years old and healthy with normal growth and development. He still has had photophobia (Fig. 3), but nystagmus decreased. Complete eye examination with electophysiological tests has been recommended to follow-up every year.

Discussion

The photoreceptor dystrophies are an important cause of childhood blindness and represent a broad spectrum of disorders. Daylight and color vision depends on the presence and functional integrity of three types of retinal photoreceptors: the cone pigments sensitive to long (red), middle (green), and short (blue) wavelengths, which are characterized by the expression of specific visual pigments (cone

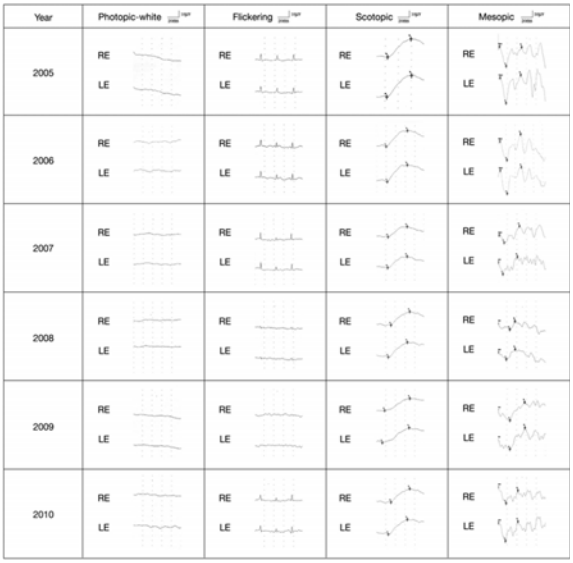

Fig. 2 ERGs from years 2005-2010 showed non-recordable in photopic and flicker, but normal response in scotopic and mild decrease of b wave in mesopic

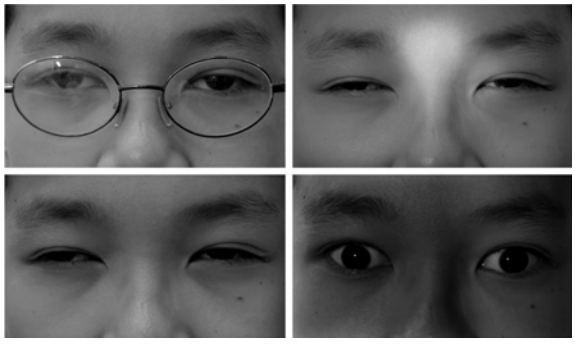

Fig. 3 The patient was thirteen year old. He had less hyperopic glasses (top left). He still had photphobia when we shone the penlight to his eyes (top right) . He could widely open his eyes when the penlight was removed (bottom left) and the room light was turned off light (bottom right)

opsins). Color discrimination relies on the differential excitation of the cone pigments by light stimuli of specific wavelengths and the appropriate generation of the post receptor signals[2]. Functional loss or alterations of cone photoreceptors as caused by mutations, deletions, or structural rearrangement of one of the opsin genes may result in selective color vision abnormalities, such as the common forms of X-linked red-green color blindness (protan and deutan) or the less common autosomal dominant trait blue-yellow (tritan) deficiency[5]. Another form of color blindness involves the degeneration, dysfunctions, or absence of two or more types of cone photoreceptors, as in patients with cone dystrophies or achromatopsia. Cone dystrophy is the progressive degeneration of cone photoreceptors which causes progressive central visual loss with total color blindness. Whereas, achromatopsia denotes a group of congenital and stationary retinal disorders with absent or limited cone photoreceptor but normal rod function[6].

Achromatopsia or rod monochromatism is true color blindness or congenital absence of cones which is inherited as an autosomal recessive trait. Fully affected patients have absence of cone function and see the world in the shades of gray[7]. This disorder presents at birth with nystagmus[8], poor central vision and an aversion to bright lights. As the individual gets older, varying degrees of color vison a abnormalities occur, ranging from a complete loss to some degree of abnormal color perception. It is this difference in color capability that has led to classify rod monochromatism into complete and incomplete varieties[7, 9].

Patients with complete achromatopsia usually present with nystagmus within the first month after birth with severe photophobia under daylight conditions. Visual acuity is usually less than 20/200 and there is a complete disability to discriminate colors. Nystagmus and photphobia may improve with time. The clinical course varies slightly from case to case. Most patients have hyperopic refractive error and glasses can improve vision somewhat but will not restore normal levels of vision[8]. Eye examination reveals normal anterior segment and fundoscopy. Color vision test shows complete color blindness. The diagnosis may be missed as congenital nystagmus unless an ERG is performed. While fundus examination is normal, electroretinography shows absent cone (light adapted or photopic) responses and normal rod (scotopic) respones. These ERG findings are diagnostic and characteristic for this disorder[7]. Dark adaptometry shows no cone plateau, and no cone-rod break occurs in the dark-adaptation curve. Pathologic studies of eyes of patients with complete achromatopsia show normal rods and a marked reduction in extrafoveal cones to 5 to 10% of normal. Foveal cones are normal in number but abnormal morphologically[7].

To date, three achromatopsia genes, CNGA3, CNGB3 and GNAT2 have been identified. The first locus for achromatopsia CNGA3 (ACHM2) has been identified on chromosome 2q11[3,6] and the second locus CNGB3 (ACHM3) has been localized on chromosome 8q21[2,4]. CNGA3 and CNGB3 code for the alpha and beta subunits of the cGMP gated channel in cone cells, respectively. Germline CNGA3 mutations have been detected in approximately 25% of achromatopsia kindreds and CNGB3 are thought to account for more cases[6]. The latest locus for achromatopsia (ACHM4) was identified as a germline mutation in the alpha subunit of cone transducin (GNAT2) on chromosome 1p13[10]. Further studies are required to find out novel loci and determine if there are any phenotypic (clinical, electrodiagnostic) differences between CNGA3, CNGB3, GNAT2 and novel loci mutations associated achromatopsia.

Achromatopsia is a very rare condition in the general population. Genetic analysis in the future may identify other novel mutation genes for this disorder. This case is the first report in Thailand with long-term follow-up for confirmation that he has had a stationary disorder. The authors followed these clinical symptoms and signs with electrophysiological tests for 8 years and these findings have been stable. After reassuring the patient and his parents that this is not a progressive disorder, they have a better psychological mind and quality of life. He has been advised to use tinted lenses in daylight to avoid photophobia, therefore, he can learn in school with other normal children. No other member in his family the same symptoms as him. Consanguineous marriage was not found in this family. Genetic study for mutation analysis of CNGA3, CNGB 3 and GNAT 2 genes in achromatopsia was done and the results were negative. This may be that he has a novel mutation gene which has not been described previously. Genetic counseling was given to his family that this is an autosomal recessive hereditary disorder which is characterized by absence or malfunction of the retinal cones, however, this is a stationary disorder.

Conclusion

The authors presented a rare case of congenital photoreceptor disorder. According to electronic searching, this is the first case report in

Thailand with ERG recordings and long-term follow-up. Because of its rarity, it is usually missed from the differential diagnosis list of congenital nystagmus in childhood. The diagnosis is established by clinical recognition and typical electrophysiological findings. Molecular genetic study will assist in finding a specific mutation of genes in this disorder.

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Potential conflicts of interest

None.

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Achromatopsia: รายงานผู้ป่วยรายแรกในประเทศไทย

งามแข เรืองวรเวทย์, ภัทนี สามเสน, อติพร ตวงทอง, ณัชชา จันทร์วราภา

Achromatopsia หรือเรียกอีกชื่อหนึ่งว่า rod monochromacy เป็นโรคที่เป็นมาแต่กำเนิด และอาการจะคงที่ไม่เพิ่มขึ้น โดยมีการเสียการทำงานของ cone cell ที่จอตา ผู้ป่วยมักเริ่มปรากฏอาการให้เห็นตั้งแต่วัยทารก โดยจะมีอาการกลัวแสง ตาสั่น ระดับสายตาเลือนราง และมองไม่เห็นสีต่างๆ ตรวจจอตาจะปกติ แต่การตรวจคลื่นไฟฟ้าของจอตา จะไม่พบการทำงานของcone cell ส่วนการทำงานของ rod cell จะปกติ ภาวะนี้พบได้น้อยมาก และมักถ่ายทอดทางพันธุกรรมแบบ autosomal recessive ผู้นิพนธ์ได้รายงานผู้ป่วยโรคนี้ เป็นรายแรกในประเทศไทย พร้อมผลการตรวจคลื่นไฟฟ้าที่จอตา โดยติดตามอาการและผลการตรวจ เป็นระยะเวลานาน 8 ปี