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Case Report

Oculocutaneous Albinism – A Case Report with Recent Review

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ABSTRACT

Oculocutaneous albinism (OCA) is an autosomal recessive disorder which is characterized by reduced or complete lack of melanin pigment in the skin, hair and eyes. These disorders are classified as syndromic OCA and non-syndromic OCA. Non-syndromic OCA are divided into 8 subtypes from OCA1 to OCA8. The symptoms range from characteristic pale or white skin, hair, eye with poor visual acuity, photophobia and nystagmus. Due to clinical overlap between OCA subtypes, molecular diagnosis is necessary to establish the gene defect. This reduction or absence of melanin causes albinos to be highly susceptible for all types of solar damages such as pachydermia, actinic keratoses, solar lentigines, solar erythema and cutaneous malignancies such as squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and melanoma. As treatment of this condition still eluding us, these patients must be educated and counselled for the use of broad-spectrum sunscreens, avoidance of prolonged exposure to sunlight and during peak hours.

KEYWORDS: Oculocutaneous albinism, Autosomal recessive, Melanin, ABCDE criteria, Photosensitivity, Photophobia

INTRODUCTION

Albinism is a heterogenous group of disorders characterized by reduced or absent melanin pigmentation, usually involving ectoderm-derived tissues.[1,2] These mainly affect the ectoderm-derived tissues such as the skin, hair and eyes. Oculocutaneous albinism (OCA) are phenotypically similar genetic disorders, of seven types (non-syndromic) depending on the amount of melanin biosynthesis within the melanocytes.[2] These are autosomal recessive, with OCA1A which is the most severe form of OCA with complete lack of pigmentation, the other forms OCA1B, OCA2 to OCA7 are milder with characteristic decrease in skin pigmentation.[2,3] Recently, a new variant OCA8 has been discovered in France among a cohort of 230 unsolved albinism patients.[4,5] The identification of the responsible genes has made understanding the biochemical, molecular basis and pathogenesis of these disorders possible. Till date seven of these genes are identified which will help in accurate diagnosis, carrier detecting and prenatal diagnosis of these disorders.[1,3,6]

CASE REPORT

A 11-year-old boy, born of non-consanguineous marriage presented to dermatology outpatient department with complaints of light coloured skin, hair and eye with discomfort in daylight, diminished vision and involuntary rapid eye movements since birth. There was no history of recurrent infections. The patient's respondent was the mother, gave no history of developmental delays and history of being alert in school. There was no history of any skin lesions and trauma induced prolonged bleeding.

On general examination the patient was moderately built and nourished with normal vitals and growth was in-between 10th – 25th percentile for age. On skin examination, there was light coloured skin, hair and there were no lesions on the body. Systemic examination was under normal limits. With the symptoms and examination, the patient was diagnosed with oculocutaneous albinism. The patient was further referred to ophthalmology, pediatric and cardiology outpatient department for further examination and management.

The patient's respondent was counselled regarding the hereditary aspect of the condition and importance of usage of broad-spectrum sunscreens, sun avoidance during peak hours, usage of long-sleeved clothes and hats with sunglasses when going out in the sun. The patient's respondent was asked bring the patient to the dermatology outpatient department if any new skin lesions develop.

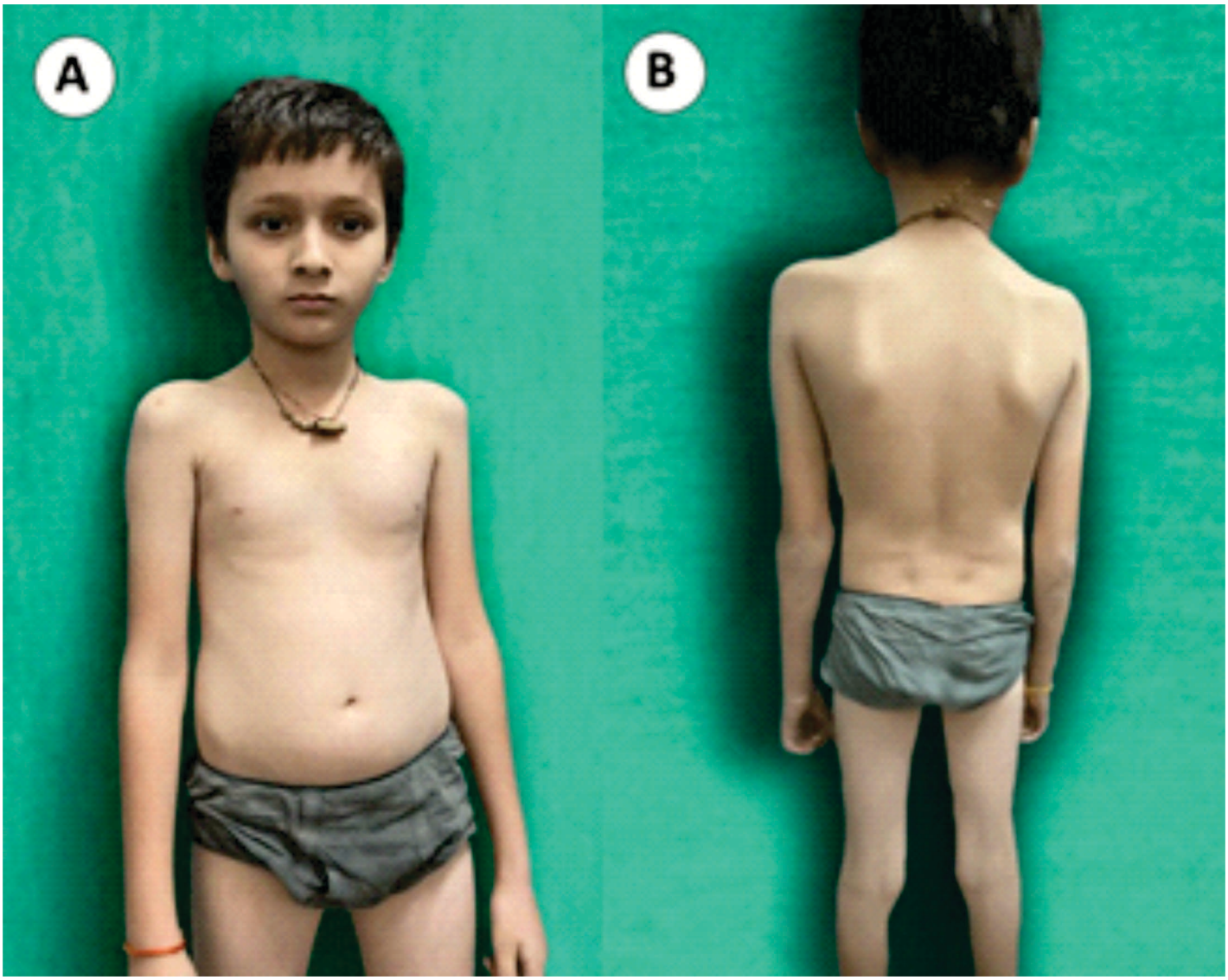

Figure 1: 11-year-old boy with oculocutaneous albinism showing pale skin.

Table 1. Prevalence of oculocutaneous albinism based on types.

Types of OCA	Prevalence	Countries seen in
OCA1	1:40,000	America and China (70%)
OCA2	1:39,000	America (1:36,000) [African Americans – 1:10,000] and Sub-Saharan Africa (1:3,900)
OCA3	1:8,500	Africa (primarily South Africa), Pakistan, Germany, India, and Japan
OCA4	1:1,00,000	Japan (24%), Germany, Turkey, India, Korea, China, Denmark, and Morocco
OCA5	Very rare	Pakistan
OCA6	Very rare	China and Eastern India
OCA7	Very rare	Consanguineous Faroese family
OCA8	Very rare	France (2 cases)

EPIDEMIOLOGY

The global burden of albinism is calculated to be at around 1:17,000 to 1:20,000 while the prevalence differs in different countries based on type of founder mutation. Form the global data we can infer that 1 in 70 people have the OCA gene.[3,7] The prevalence of individual forms of OCA included in Table 1.

ETIOLOGY

OCA is a group of autosomal recessive disorders which has fault in the melanin synthesis pathway consequence of which there is reduced formation of melanin.[8] A new report by Lee et al., discovered a new type of OCA2 mutation with an autosomal dominant inheritance pattern and attained normal pigmentation in their late twenties.[9] The melanocytes are about 5% to 10% in the epidermal basal layer and this number is not affected in these disorders. The capability of these cells to produce eumelanin is affected due to various gene mutations.[2] The summary of known types of OCA (non-syndromic) along with the genes associated are listed in Table 2.The summary of mechanism of dysregulation of melanin synthesis regarding to mutation is shown in figure 1.

Table 2. Summary of causative genes for oculocutaneous albinism.

Oculocutaneous albinism phenotype		Gene	Functions
OCA1	OCA1A	TYR	Loss of function of conversion of L-tyrosine to L-DOPA and L-DOPA to DOPAquinone leading to an inability to synthesize melanin
	OCA1B	TYR	
OCA2		OCA2 melanosome transmembrane protein P (P gene)	Encodes for chloride channel bound to melanosome membrane involved in controlling the intra-organelle pH
OCA3		TYRP1	defective stabilization and modulation of enzyme tyrosinase and loss of melanosome integrity
OCA4		SLC45A2 (MATP)	Normal function for transport of substances required for synthesis of melanin into melanosome is lost
OCA5		OCA5 (putative mutation in chromosome 4 (4q24), gene not yet found	Unknown
OCA6		SLC24A5	Same as OCA4
OCA7		C10orf11 (LRMDA)	Involved in the melanin differentiation pathway
OCA8		DCT	Encodes melagenetic enzyme - dopachrome tautomerase which converts DOPAchrome to DHICA-melanin and reduces cytotoxic effects of melanin intermediates

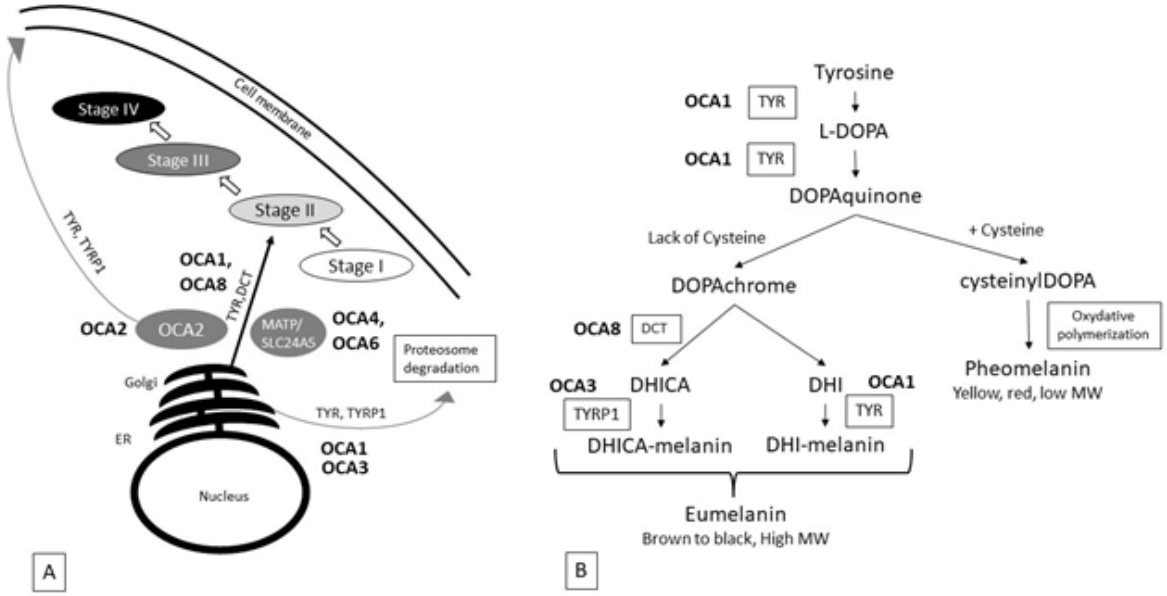

Figure 2: Tyrosinase (TYR) and Tyrosinase-related protein 1 (TYRP1) processing and the melanin biosynthetic pathway.

CLINICAL EFFECTS

Depending on the zygosity of the genes, some patients may or may not retain some residual activity. This leads to wide array of clinical and biochemical findings in the patients.[8] All types of OCA have almost similar findings such as congenital nystagmus, hypopigmentation of iris, reduced pigment in retina, foveal hypoplasia, reduced visual acuity and maybe colour blindness.[3]

The most common phenotypes of each variant, are given below:

- **OCA1**
  - Type A – There is complete lack of melanin in these patients leading to white skin and hair including the eyelashes and eyebrows. These patients do not tan.[2,3] Ocular findings include, blue grey iris which is almost transparent with red reflex, poor visual acuity, photophobia, nystagmus, foveal hypoplasia and misrouting of optic fibers at chiasma.[8,10] On iris transillumination show "pink irides" with spoke wheel appearance.[2] Keratin denaturation with aging might give hair a yellow colour.[11] They do not develop any pigmented lesions such as lentigines or pigment naevi. [3]
  - Type B–This condition was previously known as "yellow albinism" or "Amish albinism". [3,8] The newborn cases have white or very light-yellow hair which may darken to blonde or light brown as they age.[12] Tanning may be present in juveniles and adults. Temperature sensitive variants showed varied hair colour pattern depending on regional skin temperature making the hair in cooler regions to make pigment [13] Nystagmus can be visible at birth but usually not until 3 to 4 months of age. This will reduce and become less rapid with age.[2] Iris initially is blue grey may change to brownish tan or greenish hazel or even remain unchanged. Other ocular findings include, poor visual acuity and photophobia.[2,3,8]
- **OCA2**
  - **Classic OCA2:** The pigmentation of these patients varies from creamy white to tan in the skin and yellow, blonde, or light brown in the hair, eyebrows, and eyelashes. Iris colour varies from blue, hazel, brown, or gray and "pink irides" are absent.[2,3] Red reflex reduces as the patient ages and acquires pigment.[8] Nevi, freckles and lentigines can develop and are commonly seen in these patients.[2,3] When compared to OCA type 1 photophobia and nystagmus is often less severe in these patients.[11] There is slow and steady improvement in the visual acuity and vision which starts commonly after early childhood until the completion of second decade of life and commonly ranges from 20/60 to 20/100. [2,14]
  - **Brown OCA2:** The patients have almost normal skin, hair and eye pigmentation but have less pigmentation compared to family members.[2,15]
  - **Red OCA2:** The sequence modification in the melanocortin-1 receptor (MC1R) gene leads to the modification from the classic phenotype of OCA2. This is associated with melanocytes making yellow/red pheomelanin. The patients develop red hair and light skin which does not tan. Vision improves with age due to pigment accumulation in retinal pigment epithelium. [16]
- **OCA3:** This phenotype is classified as brown and rufous. This is most commonly seen in patients with type III-V skin colour.[15]
  - Rufous OCA3:This condition is described as "rufous or red OCA with brick-red bronze or mahogany skin and ginger or reddish hair".[16] These individuals have blue or brown irisesand may not have any detectable visual anomalies. [3,15,17]
  - Brown OCA3: Most prevalent in Black or Negroid population which results in tan or light-brown skin colour and light-brown hair with blue-grey irises. The iris can be transilluminated. These individuals can moderate tan. [15,17]
- **OCA4:** Similar to classic OCA2. [3]
- **OCA5:** White skin and golden hair with nystagmus, foveal hyperplasia, photophobia, and reduced vision are seen with these individuals. [2]
- **OCA6:**OCA6 has similar gene product function as OCA4 due to which the features are similar to classic OCA2
- **OCA7:** Previously called OCA5 but newer techniques has labelled it as a separate subset. The subjects have hypopigmented eyes, skin. Hair colour ranges from light blonde to dark brown. Common eye findings include congenital nystagmus, iris transillumination and translucency while foveal hypoplasia, reduced visual acuity, mild photophobia was seen in few reports.[18,19]
- **OCA8:**
  - Patient 1 – Moderate hypopigmentation of the skin and hair with congenital nystagmus, moderate foveal hypoplasia grade I, iris transillumination +, and retinal pigment layer hypopigmentation with reduced visual acuity (5/10, both eyes).
  - Patient 2 – Cream-coloredskin, light brown hair, nystagmus, photophobia, iris transillumination, retina hypopigmentation with reduced visual acuity (4/50 and 5/10). Fovea was not investigated in this patient.

DIAGNOSIS

The diagnosis of this condition is with the history and clinical features such as hypopigmentation of the skin, hair, and eyes with the other ocular findings. There is wide array of features seen in this condition which makes it almost impossible to clinically distinguish between the subtypes of OCA without molecular genetic testing such as denaturing high performance

liquid chromatography (DHPLC) or single stranded conformational polymorphism (SSCP), followed by DNA sequencing.[2,3,5,8]

MANAGEMENT

As there is no curative treatment for OCA, thus management lies on symptomatic treatment. [8]

1. Management of skin manifestation

The patient should be advised strict photoprotection to minimize the risk of cutaneous cancers.[8] The individuals should be educated regarding sedulous use of UV A and B topical sunscreens and clothing, such as long-sleeved shirts, long trousers with hats and sunglasses.[2,8]

Examination once or twice a year with dermatologist or with themselves according to melanoma ABCDE criteria.[2] These patients should be referred to dermatology OPD on time if any suspicious or changing lesions are found such as

i. New lesions on sub-exposed sites

ii. Painful, itching, bleeding, nonhealing, changing lesions, or

iii. ABCDE criteria - **A**symmetrical, irregularly **B**ordered, variably **C**oloured, **D**iameter greater than 6mm, **E**volving lesions.

iv. Changes to pink or red lesion, since majority of the melanoma in OCA are amelanotic melanoma.[2]

2. Management of ocular manifestation

In most cases nystagmus decreases as the subjects age. The subjects should learn to adjust head position to find the gaze position that gives lowest nystagmic amplitude which is called nystagmus null point. Optical correction will be required for reduced visual acuity depending on the subtype of OCA. Vision may not normalize even after optical correction due to foveal hypoplasia.

3. Management of inheritance

Genetic consultation and testing the unaffected partner if the condition is known in family of the other partner. Since OCA is an autosomal recessive condition, there is 100% chance of passing the gene to the offspring. This will help to know if the unaffected partner is a carrier or has wild-type genes and if there is chance for the offspring to inherit the condition.[2,3,8] The chance of inheriting the condition is depicted in figure2.

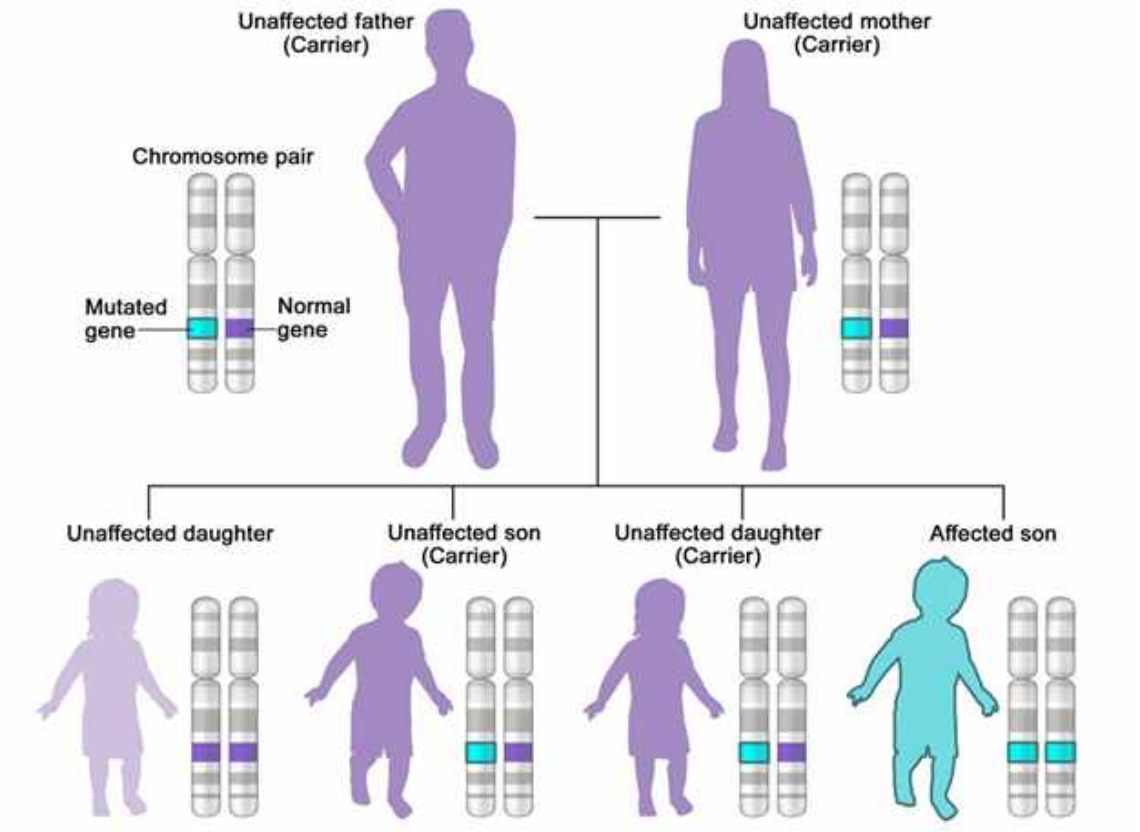

Figure 3: Carrier parents with possible offspring inheritance. The carrier parents have the capability to produce offspring with 25% chance of inheriting the condition, a 50% chance of producing a carrier offspring, and 25% of producing non-carrier offspring.

4. Direct therapeutic modalities

Clinical trial is ongoing on the basis that nitisinone triggers tyrosine accumulation in blood and mouse models which could improve pigmentation in OCA patients. The use of aminoglycosides should yet to be substantiated. The use of adeno-associated viruses (AAV) vectors for gene therapy is potential area for future researches.[2]

DIFFERENTIAL DIAGNOSIS

- Syndromes such as Hermansky-Pudlak syndrome (HPS), Chediak-Higashi syndrome (CHS), Griscellisyndrome, Waardenburg syndrome type II (WS2), Prader Willi syndrome, Vici syndrome, Tietz albinism-deafness syndrome and Angelman disease.[2,3]
- Ocular albinism[2]
- Optic nerve atrophy and hypoplasia[2]
- Infantile nystagmus syndrome[2]
- Aniridia shows foveal hypoplasia, nystagmus, amblyopia, and cataracts[2]
- Alanad Island eye disease (Forsius-Eriksson Syndrome) shows fundal hypopigmentation, foveal hypoplasia, myopia, nystagmus, astigmatism, night blindness [2,20]
- Cross-McKusick-Breen syndrome shows hypopigmentation of the skin, gray hair, microphthalmia, corneal opacification, nystagmus. Mental retardation, athetosis, ataxia, joint contractures, and spastic tetraplegia may be seen[2,21]
- Achromatopsia due to dysfunctional cone cells in retina with partial or complete loss of colour vision associated with photophobia, nystagmus, reduced vision.[2,22]

COMPLICATIONS

- Reduced visual acuity can cause disabilities for the subject. These people have a problem to procure a job due to poor vision and social discrimination. [7]
- Increased solar dermatoses such as pachydermia, actinic keratoses, solar lentigines, solar erythema.[23]
- Basal and squamous cell carcinoma (BCC, SCC) is commonly reported in these individuals. SCC can develop very early such as adolescents and is reported to be more than 75%.[2,24] Risk of malignancy can be as greater as 1000 times than the general population.[25] Incidence for cutaneous cancer increases as the subject age and males are affected more than the females.[26] 24% of malignancies are BCC and rest 1% are malignant melanoma. These lesions are commonly seen on the head and neck region (mostly on the sun exposed areas) while even some lesions can also be seen in non-sun exposed areas so the physician must be careful in assessing these patients.[2,24-26] Amelanotic melanoma can also be presented in albinos which can make the diagnosis difficult for the dermatologist. [27]

ALBINISMIN INDIA

There is lack of proper studies regarding the extent of prevalence of albinism and its social impact on the individuals. As per Rights of Persons with Disabilities (RPWDs) Act (2016),government of India has announced impaired vision due to albinism as a disability and included it in the list. [28] Jan Vikas Samiti a nonprofit non-government organization (NGO) conducted a white paper research and analysis on albinism in five states in India consistingof 76 subjects[26] and concluded that,

- Age and sex ratio: Mean age of the subjects was 25.59 years and had a 1.04:1 male to female ratio.
- Education: More than 80% of the subjects were literates.
- Family income: 92% had less than one lakh per annum.
- Employment status: Students (31.6%) and housewives (9.2%), unemployed(21.6%), daily wage labourer (18.4%) and part time employed (10.5%).
- Awareness: 22.4% only knew the reason as albinism while 26.3% knew it as a skin disease and rest weren't aware of the disease.
- Skin: Photosensitivity was seen in 83% of subjects while only 13.2% only reported to using sun protection. 12% reported to have some form of skin lesion such as lentigines, solar erythema, ephelides.
- Vision: 88% of subjects reported having issues with vision.
- 50% of the subjects reported that they have never visited a doctor for regular check-up.[29]

CONCLUSION

For a normal individual melanin gives natural photoprotection while it is missing in the albinos, making them susceptible for all kinds of solar damage. In developing countries like India, public health schemes are targeted towards the basic needs of the people and factors such as illiteracy, lack of knowledge of this condition led to this being under reported and mismanaged. Early diagnosis and regular examination of patients is of utmost importance as it could help in proper management and may help in reducing the unwanted complications. Goal of management is proper education and counselling as this can improve their quality of life andfurther could help them leada normal life in the society.

CONFLICTS OF INTEREST: None

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