AETIOLOGICAL, CLINICAL AND HISTOPATHOLOGICAL STUDY OF BASAL CELL CARCINOMAS- AT RANGARAYA MEDICAL COLLEGE, KAKINADA

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ABSTRACT

BACKGROUND

Basal Cell Carcinomas (BCC) are the most common amongst the non-melanoma skin cancers. The existing literatures on BCC are scant in India. BCC are rare in dark skin, because of the inherent photoprotection of melanin and melanosomal dispersion. Risk factors include UV light exposure, ionising radiation, exposure to arsenic, mutations. Although, BCCs have excellent prognosis, if left untreated it causes significant disfigurement and invasion of surrounding tissues. The present study was aimed to evaluate the risk factors, clinical and histopathological spectrum of BCC in Eastern Andhra Pradesh. The objectives were to analyse clinical data with respect to age, sex, occupation, sunlight exposure, anatomical location, size of the lesion, morphological and histopathological subtypes.

MATERIALS AND METHODS

The present study was conducted in DVL Department, Rangaraya Medical College, Kakinada, Andhra Pradesh. A prospective analysis of 40 cases of BCC in a period of 3 years: January 2014 - December 2016 diagnosed and confirmed histopathologically.

RESULTS

Out of 40 cases, 65% were females. History of exposure to the sunlight was observed in all the cases. One case of 18-year-old female with xeroderma pigmentosum with BCC was seen. Sites noted were forehead (22.5%), ear, nose and infraorbital region (each 15%). Clinically, pigmentation was evident in 19 cases. Morphological types seen were ulcerative (55%), nodular (37.5%), swelling/cyst (5%) and morpheaform (2.5%). Histological types are nodular (57.5%), pigmented (25%), adenoid (7.5%), keratotic (2.5%) and with sebaceous differentiation (2.5%). Recurrent BCCs were seen in two cases.

CONCLUSION

This study highlights the role of sunlight and farming as aetiological risk factors of BCC and female preponderance. Forehead is the common site of presentation. Nodular and pigmented types (subtype of nodular variant) were common. Early detection of BCC lesions, particularly of small size (< 2 cm) helps in preventing further recurrences.

KEYWORDS

Basal Cell Carcinoma, UV Light Exposure, Histopathology.

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BACKGROUND

The incidence of basal cell carcinoma is increasing worldwide.[1] Basal cell carcinoma also known as basalioma is the most common cutaneous malignancy in white skinned people. In 1827, Arthur Jacob termed the skin tumour that we now call Basal Cell Carcinoma (BCC) ulcus rodens.[2] In 1900, Krompecher described BCC as a malignant, locally invasive and destructive cancer and named as carcinoma epithelial adenoides.[3]

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The non-melanoma skin cancers comprise of 1% - 2% of cutaneous neoplasm in Indians in contrast to one-third in whites.[4] Lesions occur both on sun protected and sun exposed sites. Approximately, 85% of BCCs occur on face, head (Scalp included) and neck, others appear on the trunk or extremities and rarely they may occur on hands.[5,6] Interestingly, the exact cellular origin of BCC is still unknown. Classically, they are thought to arise from epidermal basal cell layer, although current theory supports either a follicular or interfollicular stem cell origin.[7] Typically, basal cell carcinomas occur in the fourth decade of life and beyond,[8] although exceptions to this occur in particular in the scenario of specific genodermatoses or in patients with immunocompromised.[9] As there is increase in elderly population, the disease causes significant morbidity and become more problematic in future.

The existing literature on basal cell carcinomas in Indian skin is scant. Hence, we have taken up this study to know the

aetiological, clinical and histopathological spectrum of basal cell carcinomas in dark skinned individuals.

Aims and Objectives

The present study was aimed to know the aetiological factors and to evaluate the clinical and histopathological spectrum of basal cell carcinoma in Eastern Andhra Pradesh. The objectives were to analyse clinical data with respect to age, sex, occupation, exposure to sunlight, anatomical location (Topography), size of the lesion, morphological and histopathological subtypes.

MATERIALS AND METHODS

Patients of all ages attending DVL outpatient department with suspected lesions were screened for BCC after taking an informed written consent. Ethics Committee clearance was obtained. Patients with histopathologically confirmed BCC were enrolled in the study.

Inclusion Criteria

Histopathologically confirmed cases of BCC were included in the study. Exclusion Criteria: Patients with clinically diagnosed as BCC, but not histopathologically confirmed were excluded from the study.

Detailed history with recording of various patient variables like age, gender, duration of symptoms, Fitzpatrick skin phototype, skin colour, average daily sun exposure (hours/day), occupation, residence place (rural or urban), exposure to chemicals including pesticides, radiation exposure history, treatment with psoralen UVA (PUVA) or narrow band UVB (NBUVB), smoking, alcohol intake, history of personal or family history of skin cancers, personal or family history of other cancers, history of genetic disorder like xeroderma pigmentosum, albinism and history of previous treatment.

Based on the clinical and histopathological findings, the results were analysed. Proportions were described as percentages.

Grading of the lesions were done based on the size into small (< 1 cm in diameter), medium (1 - 2 cm in diameter) and large (> 2 cm in diameter). Investigations included complete blood count with differentials, bleeding time, clotting time, renal function tests, liver function tests and viral markers. Additional investigations were done depending upon the clinical scenario. Diagnosis was confirmed by histopathological examination of biopsy specimen with documentation of histopathological variant.

To analyse the results, descriptive statistics such as mean, Standard Deviation (SD) and frequency tables were utilised. Fisher Exact test, Chi^2 test and P value were used for analysis and P value < 0.05 was considered as significant.

RESULTS

Demographic data of the present study includes a total of 40 histopathologically confirmed cases of BCC were enrolled in the study from 2014 to 2016. The number of cases diagnosed per year was 7, 14 and 19 patients in 2014, 2015 and 2016 respectively.

Among 40 patients, males were 14 (35%) and females were 26 (65%) with M: F being equal to 1:1.8. Age of the patients ranged from 18 to 75 years. The mean ± standard deviation of age of the patients was 56.95 ± 12.7 years. Although, the difference in mean age between males and females was not significant statistically (data analysis was done using unpaired t-test). It shows a clinical relevance as females tend to seek medical care earlier than males for cosmetically disfiguring lesions. Majority of patients were in the age group of less than 60 years 24 cases (60%), followed by > 60 years 16 cases (40%). The youngest age of presentation in case of females was 28 years, while in males the corresponding age was 50 years excluding the case of xeroderma pigmentosum of 18-year-old female. Correlation between age group and gender was not significant statistically (Fisher exact test, P value being 1), implying that these two variables are independent [see Table 1]. In the present study, mean duration of the disease was 2.16 years. All the patients had single lesion in head and neck region.

One female patient of age 18 years had features of xeroderma pigmentosum (who have more predilection for cutaneous malignancies) presented with basal cell carcinoma [see Fig. 2], squamous cell carcinoma, actinic keratoses and keratoacanthoma. There is history of consanguinity in parents and similar skin condition in younger sibling without any cutaneous malignancy.

There is no family history of systemic and cutaneous malignancies in our study. All the cases belonged to Fitzpatrick skin types IV and V. The size of lesions ranged from 0.5 cm to 5 cm in diameter. Majority of the lesions presented within 3 years are of size less than 2 cm. Majority of the lesions presented with more than 3 years of duration are of size more than 2 cm. The size of lesions was found to have a statistically significant association with duration of disease ($\chi 2 = 10.63$; P value = 0.004) [See Table 2]. Majority of cases had lesions confined to head and neck region.

The distribution of lesions in our study are involvement of forehead is seen in 9 cases (22.5%), around ear 6 cases (15%), nose 6 cases (15%), infraorbital 6 cases (15%), scalp 3 cases (7.5%), lower eyelid 3 cases (7.5%), cheeks 3 cases (7.5%), lower lip 3 cases (7.5%), eyebrow 1 case (2.5%) [See Table 3]. Forehead was the most common site of involvement in our study. The commonest morphological subtype of BCC was nodular/noduloulcerative growth (92.5%).

In our study, the most common histopathological variant was nodular subtype 23 cases (57.5%), other subtypes include pigmented BCC 10 cases (25%), adenoid BCC 3 cases (7.5%), superficial BCC 2 cases (5%), keratotic BCC 1 case (2.5%) and BCC with sebaceous differentiation 1 case (2.5%).

Age (years)	Male	Female	Total	(%)	Fisher Exact Test P Value
< 60	8	16	24	60	1^{NS}
> 60	6	10	16	40	
Total	**14**	**26**	**40**	**100**	

Table 1. Age - Sex Distribution

Duration	Small (<1 cm)	Medium (1- 2 cm)	Large (>2 cm)	Total	χ^2 (d.f.)	P value
0 - 3 years	5	13	10	28	10.63	0.004^{S}
> 3 years	0	1	11	12		
Total	**5**	**14**	**21**	**40**		

Table 2. Association between Duration of Disease and Size of Lesion

Site	No. of Cases	Percentage (%)
Cheek	3	7.5
Lower Eyelid	3	7.5
Eyebrow	1	2.5
Infraorbital	6	15
Nose	6	15
Forehead	9	22.5
Ear	6	15
Lower Lip	3	7.5
Scalp	3	7.5
Total	**40**	**100.0**

Table 3. Site Distribution

Morphology	No. of Cases	Percentages (%)
Nodular	15	37.5
Ulcerative	22	55
Morpheaform	1	2.5
Swelling/Cyst	2	5
Total	**40**	**100**

Table 4. Morphological types of BCC

Histopathology	No. of Cases	Percentage (%)
Nodular BCC	23	57.5
Pigmented BCC	10	25
Adenoid BCC	3	7.5
Superficial BCC	2	5
Keratotic BCC	1	2.5
BCC with Sebaceous Differentiation	1	2.5
Total	**40**	**100**

Table 5. Histopathological Variants

Clinical Types

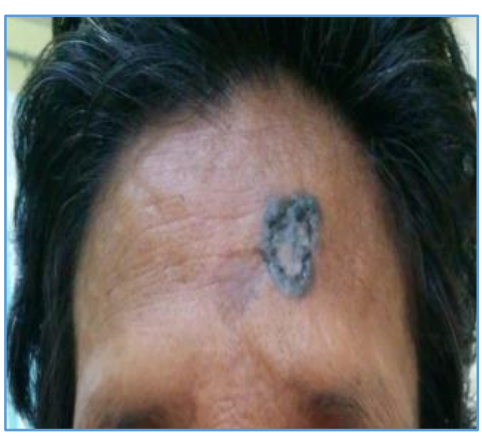

Figure 1. Nodular BCC

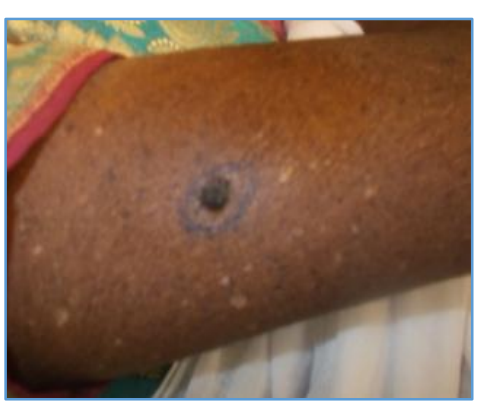

Figure 2. Nodular BCC in Xeroderma Pigmentosum

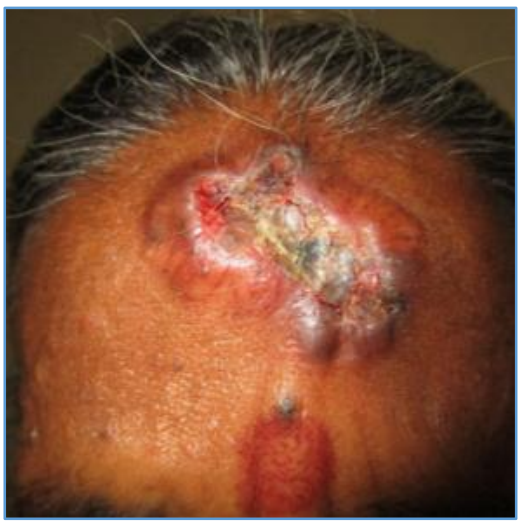

Figure 3. Noduloulcerative

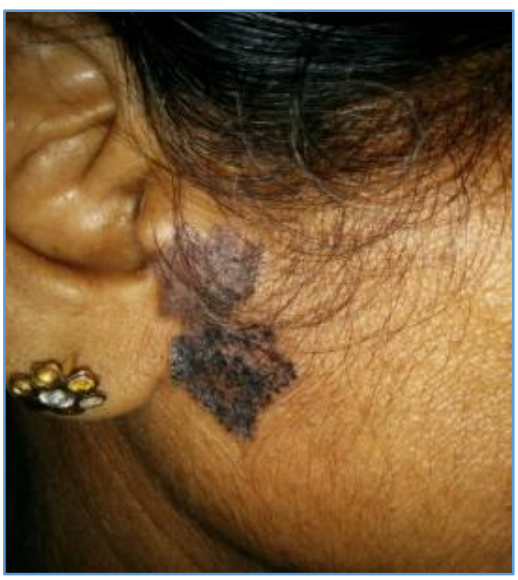

Figure 4. Superficial BCC

Histopathological Types

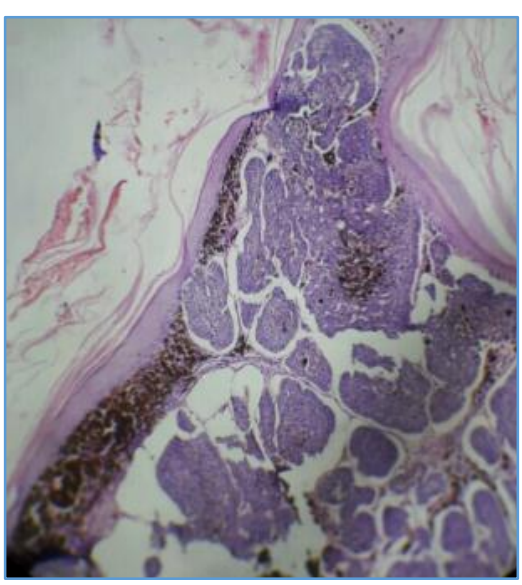

Figure 5a. H & E Stain (Low Power) showing Multiple Nodules of Tumour Lobules with Pigmentation

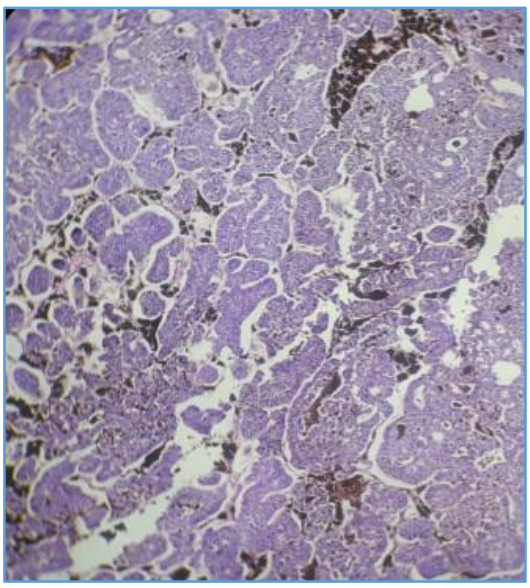

Figure 5b. H & E Stain on High Power showing Multiple Tumour Nodules of varying Sizes

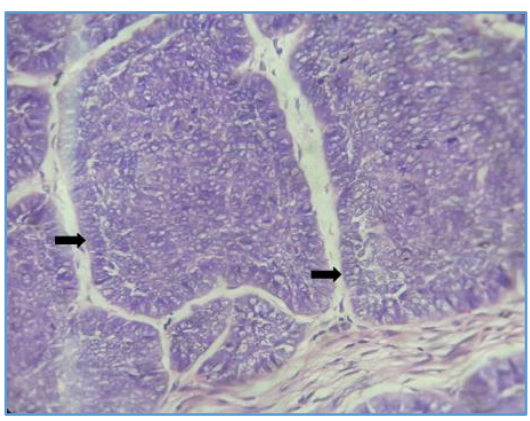

Figure 5c

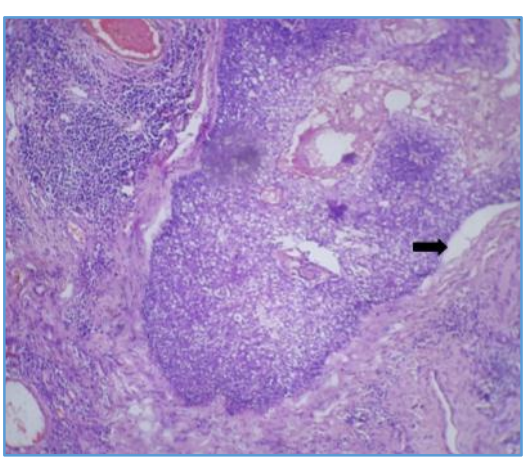

Figure 5c & d. Showing Nests of Basaloid Cells with Peripheral Palisading accompanied by Slit-Like Retraction

DISCUSSION

Basal cell carcinoma is the most common cutaneous malignancy in white people.[10] Previous studies have shown that most of the basal cell carcinomas occur in fair skinned individuals. There is rise in incidence of basal cell carcinoma worldwide, accordingly in India similar trends were observed though dark skinned individuals have more protection and fewer propensities to develop basal cell carcinomas. As per the basal cell carcinoma statistics, there is equal sex distribution in some studies, men outnumbered women in some studies. But in our study, female preponderance is observed. BCCs are more common in the elderly age group. In recent years, the incidence rate has increased significantly in younger patients and in females according to De Vries et al[11] and Sobjanek et al.[12] Most common age group in our study is less than 60 years (60%) followed by > 60 years (40%). This closely resembles the findings in a study in North India.[13] The time of first UVR exposure is very significant and patients with high UVR exposure at < age 20 have a higher likelihood of developing BCC later in life (Walther et al[14]).

Increased frequency among rural population when compared to urban population was seen as most of the cases gave history of outdoor activities. Bauer et al[15] reported that those persons working in fields like farmers are at greater risk of developing BCC due to early and long-term exposure to sunlight. Indeed, outdoor workers are 43% more likely to develop BCC. Farming was the main occupation in all 14 male patients (100%), while both farming and housekeeping was the major occupation among 22 female patients (86.4%). However, the females were intermittently exposed to high intensity sunlight due to work in open kitchens, household activities and fields during sowing and harvesting seasons. None of these patients had been taking photoprotective measures such as use of sunscreens and protective clothing. Role of pesticides and arsenic may be doubtful.

Zhang et al[16] reported that UV rays induce specific nucleotide changes in PTCH gene as well as the tumour suppressor gene TP53 are implicated in the development of early onset of BCC. Most of the cases belonged to the age group 40 to 60 years and more than 60 years due to the cumulative UV-induced DNA damage. Basal cell carcinomas are seen almost exclusively on hair bearing skin, especially on the face. UV rays in particular UVB is the most important aetiopathogenic factor, as 80% of tumours are distributed in head and neck region.[17] Intermittent periods of intense sun exposure instead of cumulative exposure increase the risk of BCC. Other factors include ionising radiation, arsenic exposure, inherited syndromes and immunosuppression particularly post organ transplantation.[18]

The commonest site in our study is head and neck region. All the cases belonged to this group, which is on par with Malhotra et al study.[19] BCC occurring at certain body sites or that BCC of a particular histological subtype may define certain clinical behaviour and may even have a different aetiology.[20] BCCs of the head and neck were more frequent in women (85.2%) than in men (81%), independent of their histological subtype. According to these authors nodular BCCs could result from chronic sun exposure, whereas superficial BCCs could be due to intense and intermittent sun exposure. This hypothesis was mainly based on the respective anatomical distribution of both types, superficial BCCs showing a distribution similar to that of superficial spreading melanomas.[21,22]

Morphological Variants

Out of 40 cases, morphological types seen are ulcerative 22 cases (55%), nodular 15 cases (37.5%) [see Fig. 1], swelling/cyst 2 cases (5%) and morpheaform 1 case (2.5%) [See Table 4]. A significant proportion of cases were clinically

pigmented and histopathologically confirmed. Similar results were found in Ceyan C et al[23] study made in Izmir, Turkey of 10 years' duration, in which nodular and ulcerative variants 69.8% are dominant. In our study, most common presentation is ulcerative [see Fig. 3] in 22 cases (55%), which is on par with Saraswathy Sreeram et al study from Karnataka (Indian study).[24]

Topography

Previous studies have shown that nose was the commonest site. In our study, forehead (22.5%) was the most common site of involvement followed by nose (15%), around ear (15%), infraorbital (15%), scalp (7.5%), lower eyelid (7.5%), cheeks (7.5%), lower lip (7.5%) and eyebrow (2.5%). As per our cultural norms there is no usage of head covering for females, hence forehead may be the most common site in our study. Involvement of scalp is seen in 7.5% of cases. Tumours of the scalp were more common in male farmers and thus hair acts as a protective factor in women according to Szewczyk M et al.[25] Interestingly, in our study scalp involvement is seen in one female patient.

Histological Variants

Histological diagnosis and classification of BCCs are essential in planning the patient management. The risk behaviour of BCC whether low risk or high risk depends on different morphological types and also play role in prognostic significance. Other factors of importance include size of the lesion and the status of excised surgical margins.[26] From histological point of view, BCCs can be divided into two groups as differentiated and undifferentiated.[27] BCCs showing no differentiation are called solid BCCs. They can be subdivided into (Circumscribed and infiltrative). Those with differentiation towards hair structures are keratotic, towards sebaceous differentiation and towards tubular glands are adenoid basal cell carcinomas. In our study basal cell carcinomas demonstrate a variety of types of differentiation, out of which nodular is the commonest 23 cases (57.5%) followed by pigmented BCC in 10 cases (25%), adenoid BCC in 3 cases (7.5%) and superficial in 2 cases (5%) [See Fig. 4], keratotic and sebaceous differentiation 1 case each (2.5%) [See Table 5]. Studies done till present time have not found any correlation between facial regions exposed to UV light and histopathology aspect of basal cell carcinoma.[28]

The nodular variant of BCC is characterised by discrete small or large nests of basaloid cells in either the papillary or reticular dermis accompanied by slit-like retraction from a stroma[29] [See Figure 5a, b, c, d]. Pigmented BCC is a rare variant, in which melanin is produced by melanocytes that colonise the tumour and is present in melanophages located in the surrounding stroma.[30] Superficial BCC is characterised by a proliferation of atypical basaloid cells that form an axis parallel to the epidermal surface and slit-like retraction of the palisaded basal cells from the subjacent stroma. The keratotic BCC variant shows large nests of basaloid tumour cells that are rounded and show central keratinisation and degeneration. It represents a variant of nodular BCC. The BCC with sebaceous differentiation is differentiated from sebaceous adenoma by having a germinative cell component, which occupies greater than 50% of the transverse diameter of tumour lobules that typically manifest a rounded morphology with areas of slit-like retraction accompanied by mitosis and apoptotic debris.[29] Adenoid BCC shows arrangement of cells in the intertwining strands and radially around islands of connective tissue, resulting in a tumour with a lace-like pattern.[31]

Recurrence

About 40% of patients who have had a basal cell carcinoma will develop another lesion within 5 years.[32,33] In our study there are 2 cases of recurrent BCC till date; one on the scalp after 6 months of excision and grafting and another on preauricular region after 1 year of excision in two years followup. Patients are still under followup for 5 years. The risk of recurrence of BCC was significantly greater in farmers.[25] Depending on the site of lesion, size of tumour and treatment modality up to 10% tumours recur making the treatment of recurrent lesion a common problem.[34] The recurrence rates may also differ based upon the anatomic site, particularly as regards to lesions of the nose and ears where higher recurrence rates may reflect peculiarities of the anatomy or a natural hesitancy on the part of clinicians to perform mutilating surgical procedures in these locations.[35,36,37]

CONCLUSION

This study highlights the female preponderance and exposure to the UV light increases the risk of BCC as evident by the involvement of rural and agricultural population. The commonest site of involvement is forehead in our study. Clinically, pigmentation was evident in majority of the cases. Nodular and pigmented (variant of nodular) are the commonest histopathological variants. Early detection of BCCs helps the clinicians as size of the lesions are smaller (< 2 cm) and hence the removal of the tumour is more amenable and it further prevents recurrence. Increasing trends in the BCCs were noted in the past few years in Indian skin suggests the need to introduce screening programme by trained healthcare professionals by doing annual skin examination.

Limitations

We have not seen any cases in children and immunocompromised individuals. The sample size of the study is small and immunohistochemistry could not be done due to poor resource settings; hence, we recommend further studies to elucidate the problem in future.

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