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Research Article

Correlation between Serum Vit D3 Levels and Clinicoepidemiological Profile of Polymorphic Light Eruption Patients: An Interventional Study

Nikha Garg[1], Anu Chandra[2]*, MR Srivastava[3] and KS Dhillon[1]

[1]Department of Dermatology, Venereology and Leprosy, Era's Lucknow Medical College and Hospital, Era University, Dumka Medical College, Dumka, India

[2]Department of Biochemistry, Era's Lucknow Medical College and Hospital, Era University, Dumka Medical College, Dumka, India

[3]Department of Community Medicine, Era's Lucknow Medical College and Hospital, Era University, Dumka Medical College, Dumka, India

***Corresponding Author:** Anu Chandra, Professor, Department of Biochemistry, Era's Lucknow Medical College and Hospital, Era University, Dumka Medical College, Dumka, India.

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Abstract

Introduction: Polymorphic light eruption is the commonest photosensitive disorder, characterized by an intermittent eruption of non-scarring erythematous papules, vesicles or plaques that develop within hours of ultraviolet radiation exposure of patient skin. Together with the lesions, a terrible itch starts and increases with the spreading of the disease, sometimes aggravated by a sort of burning sensation. The exact pathogenesis of PLE is currently unknown but findings suggest that an abnormal immune response is responsible for the tissue damage in PLE. For prophylaxis besides conventional sunscreens phototherapy is effective in many cases, when administered over several weeks.

Material and Methods: The present study was carried out in the Department of Dermatology, Sexually Transmitted Diseases and Leprosy and the Department of Biochemistry of Era's Lucknow Medical College and Hospital, Lucknow, Uttar Pradesh. In this study 60 clinically diagnosed polymorphic light eruption patients and 30 age, sex and BMI matched controls were included. The design of the study was interventional study comprising two Interventional groups and a control group. The patients were divided into two groups randomly and treatment was constituted accordingly.

Observation and Results: The study evaluates clinic-investigative profile and serum vitamin D levels in patients with polymorphic Light Eruption. A total of 60 symptomatic patients who served as our experimental group and 30 normal healthy individuals, post hoc matched for age, sex and demographics were recruited and evaluated.

Estimation of serum 25-hydroxy-vitamin D3 levels in PLE patients and control group showed that the mean vitamin D3 level in PLE patients (15.98 ± 7.11 ng/mL) was significantly lower ($p < 0.001$) than the level seen in controls (30.97 ± 6.58 ng/mL). Majority of the PLE patients had insufficient (50%) or deficient (41.7%) Vitamin D3 levels while most of the individuals in the control group had optimal vitamin D3 status (70%) representing a significant gap ($p < 0.001$) amongst the two groups.

Conclusions: The results of this study clearly indicate that treatment with oral vitamin D3 supplement significantly diminished the appearance and severity of PLE symptoms in the study participants. A statistically significant reduction ($p < 0.001$) of PLE test scores by 33.3% was observed in patients receiving oral vitamin D3 supplementation for 3 weeks along with photoprotection in the form of topical sunscreen application (5.31 ± 1.73 vs. 3.54 ± 1.78).

Keywords: Polymorphic Light Eruption; Photosensitive; Ultraviolet Radiation Exposure; 25-hydroxy-vitamin D3; Photoprotection

Introduction

Polymorphic Light Eruption (PLE) also known as Polymorphous Light Eruption and Prurigo aestivalis is a common photodermatosis with a high prevalence of approximately 11 to 21% [1] and recurrence rate of 31.36% in the population [2]. The etiology is not known and is likely to be multifactorial. It has a polygenic mode of inheritance. The eruption of PMLE is induced by ultraviolet radiation (UVR) and perhaps rarely by visible radiation, either by sunlight or by artificial sources including sun beds. PLE appears to be an immunologically mediated response possibly a delayed hypersensitivity phenomenon to a photo antigen induced or up regulated in the skin after sun exposure [3]. Similar to Lupus Erythematosus (LE), an Ultra Violet (UV) inducible systemic autoimmune disease, PLE has a female preponderance with a mean onset in the second to third decade of life. PLE lesions are often itchy and typically appear on sun-exposed body sites in spring or early summer [4]. The quality of life in patients with PLE is often severely disturbed, as evidenced by high levels of anxiety and depression [5].

For prophylaxis besides conventional sunscreens [6], phototherapy is effective in many cases, when administered over several weeks for hardening in early spring before the first natural sun exposure takes place [7]. However, because prolonged treatment with UVB and/or phototherapy is potentially carcinogenic [8], the search for pathogenic mechanisms and new treatment options in PLE is ongoing.

Pathophysiology

Twin studies indicate a polygenic model may explain familial clustering. Sunburn reaction in patients affected by polymorphous light eruption is normal. UV-A is the usual part of the electromagnetic spectrum that provokes polymorphous light eruption (75% to 90%).

However, it can be triggered in some patients by UV-B or visible light. Exposure may be to sunlight or to an artificial or medical source of ultraviolet radiation [9]. The exact pathogenesis of PLE is currently unknown but findings suggest that an abnormal immune response is responsible for the tissue damage in PLE. Predominance of T total, T helper, and cells marked with Ia antigen were found [10]. There is resistance to UV- induced immune suppression and simultaneous immune reactions against sin photo-neoantigens [1,11]. According to recent studies, prevalence of thyroid disease is 14% in PLE cases and at least one autoimmune disease is diagnosed in 15% patients, indicating associations in the autoimmune aetiology [12]. Skin biopsy shows upper dermal edema, and a dense perivascular and periadnexal lymphocytic infiltrate without vasculitis. Plasmacytoid dendritic cells and T regulatory cells predominate [13]. Neutrophils may be seen in early lesions. Spongiosis, vesicle formation, and liquefaction degeneration may be seen dependent on the clinical signs. Direct immunofluorescence testing is negative.

In most patients with a polymorphic light eruption, blood tests will reveal normal results. However, positive antinuclear antibody and extractable nuclear antigen (anti-Ro/La) in low titer may be detected, even in the absence of other criteria to suggest a diagnosis of lupus erythematosus. When the history or clinical findings indicate, urinary and red cell porphyrin screening may be performed and are negative.

Narrowband UV light reduces systemic immune responsiveness via the induction of regulatory T cells. Radiant energy and 25-Hydroxy Vitamin D (25 (OH)D) levels may affect particular immune functions independently [14,15]. It has been proposed that vitamin D is an environmental factor that can modulate the immune system affecting the development of autoimmunity. Reduced serum 25-hydroxyvitamin-D3 (25 (OH) D) levels, which are used to classify vitamin D status, have been observed in several autoimmune diseases and are a suspected risk factor for the development of autoimmunity [16]. In an intra-individual half-body trial, investigators were able to demonstrate that topical administration of an immune-stimulatory 1,25 $(OH)_2$D3 analogue calcipotriol reduced PLE symptoms [14], which may work by reproducing or sensitizing for UV-induced suppression of cutaneous immunity.

The investigators have recently found that PLE patients had significantly reduced 1 a,25-dihydroxy-vitamin D3 (1,25 $(OH)_2$D3) serum levels (13 - 14 ng/ml) compared to the normal population (> 30 ng/ml) [16]. The levels of serum 25 (OH)D over which these effects are apparent should guide future interventions. In this randomized interventional study, the investigator attempted to study the effect of oral vitamin D3 supplementation on PLE symptoms.

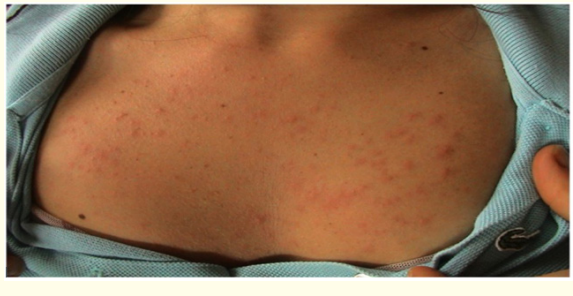

Figure a: Clinical picture of polymorphic light eruption in a young woman.

Materials and Methods

The present study was carried out in the Department of Dermatology, Sexually Transmitted Diseases and Leprosy and the Department of Biochemistry of Era's Lucknow Medical College and Hospital, Lucknow, Uttar Pradesh. In this study 60 clinically diagnosed polymorphic light eruption patients and 30 age, sex and BMI matched controls were included. The design of the study was interventional study comprising two Interventional groups and a control group.

The patients were divided into two groups randomly and treatment was constituted accordingly.

Group	No. of subjects	Treatment
I	30 subjects	Standardized broad spectrum topical sunscreen applied in the dose of 2 mg/ cm^2 to all exposed areas.
I	30 subjects	Standardized broad spectrum topical sunscreen applied in the dose of 2 mg/ cm^2 to all exposed areas. Oral vitamin D3 supplementation as Cholecalciferol 60 KIU every 3rd day, i.e. twice weekly.

Table a

For this study 65 clinically diagnosed polymorphic light eruption patients were recruited who were older than 5 years, up to 70 years of age with no topical treatment with vitamin D derivatives for the past 3 month and no systemic treatment with vitamin D in the past 6 months, no presence of history of malignant skin tumours were recruited for the study. However, 60 patients completed the duration of the study. Fur patients were lost to follow-up, while one showed poor tolerance to oral vitamin D3 supplement. Informed consent was taken from all the patients.

Detailed history was elicit from each patient with special reference to mode of onset, progression of the disease, seasonal variations and the extent of the involvement and the past history of similar episodes and any autoimmune disorders.

General and cutaneous examinations were carried out in all cases with particular reference to distribution of skin lesions, type of skin lesion and any secondary changes.

Patients were scored in a blinded manner for pathological UV effects including area of PLE-affected skin by visual evaluation and skin infiltration by palpation. Pruritus was scored by the patients on a visual analogue scale.

A specific overall PLE test score was then calculated as followed [17]:

PLE Score = AA+ SI + 0.4P (Range: 0 - 12)

Where, AA- Affected Area:

0 = 0% of body surface area

1 = 1 - 24% of body surface area

2 = 25 - 49% of body surface area

3 = 50 - 74% of body surface area

4 = 75 - 100% of body surface area

SI- Skin Infiltration by palpation:

0 = None

1 = Slight

2 = Moderate

3 = Extensive

4 = Maximum.

P-Pruritus

Scored by the patient on a visual analogue scale ranging from 0-10 (None- maximum).

Patients were subjected to punch biopsy to assess histopathological changes and necessary investigations e.g. haemoglobin, total leucocyte count, differential leukocyte count, erythrocyte sedimentation rate.

PLE test score was ascertained for all patients, again after 3 weeks of initiation of therapy.

Photoprotection

Photoprotection was provided in the form of topical sunscreen lotion containing octinoxate, octisalate, homosalate and oxybenzone with SPF 30 and UVA as well as UVB filters. Patients were advised to apply the lotion to all exposed area of the body liberally, 20 to 30 minutes prior to sun exposure and repeat the application every 3 hours during the day time.

Vitamin D3 supplementation

Vitamin D3 Supplementation was one by administering milk soluble granules of cholecalciferol in a dose of 60 KIU once every

3rd day. Patients were advised to consume these by mixing in warm full fat milk at least 2hours before or after any meal.

Biochemical analysis

Estimation of serum hydroxyl Vitamin D3 was done by Direct Enzyme Linked Immunosorbent Assay before and after 3 weeks of therapy according to the group allocated. Baseline estimation of serum Hydroxy-Vitamin D3 was also done in controls.

The study was approved by Institutional Ethical committee of Era's Lucknow Medical College and Hospital, Era University.

Statistical analysis

The descriptive analyses and data summarization were done using means and standard deviations. Independent groups were compared by Student's t-test. Paired (pretherapy and post therapy) groups were compared by the paired t–test. Categorical groups were compared using the Chi-square (χ^2) test.

The confidence level of study was kept at 95%. Hence a two sided "p" value less than 0.05 ($p < 0.05$) was considered statistically significant for inter group differences.

Analysis were performed using SPSS software (PSAW Windows Version 18.0).

Results

The study evaluates clinico-investigative profile and serum vitamin D levels in patients with polymorphic Light Eruption. A total of 60 symptomatic patients who served as our experimental group and 30 normal healthy individuals, post hoc matched for age, sex and demographics were recruited and evaluated.

Based on characteristics of study participants, the subjects in both groups were demographically similar and comparable and thus may not influence the primary outcome measures of the study. I.e. The serum levels of vitamin D and effects of vitamin D supplementation (Table 1).

Basic characteristics	Cases (n = 60) (%)	Controls (n = 30) (%)	t/x² value	P value
Age (yrs)				
Mean ± SD	29.75 ± 14.25	31.60 ± 13.84	0.59	0.559
Sex				
Female	39 (65.0)	15 (50.0)	1.88	0.171
Male	21 (35.0)	15 (50.0)		
Height (cm)				
Mean ± SD	159.38 ± 19.77	163.20 ± 7.53	1.02	0.311
Weight (kg)				
Mean ± SD	56.60 ± 15.68	57.30 ± 11.34	0.22	0.828
Occcupation				
Farmer	3 (5.0)	0 (0.0)	8.28	0.141
House wife	15 (25.0)	11 (36.7)		
Labour	5 (8.3)	6 (20.0)		
Shop keeper	8 (13.3)	2 (6.7)		
Student	23 (38.3)	6(20.0)		
Teacher	6(10.0)	5 (16.7)		
Duration of daily sun exposure				
0 - 2 hrs	33 (55.0)	10 (33.3)	3.93	0.140
3 - 6 hrs	19 (31.7)	13 (43.3)		
> 6 hrs	8 (13.3)	7 (23.3)		
Flitzpatrick skin type				
1	0	0	5.44	0.066
2	0	0		
3	8 (13.3)	5 (16.7)		
4	50 (83.3)	20 (66.7)		
5	2 (3.3)	5 (16.7)		
6	0	0		

Table 1: Basic characteristics of two groups.

61.75% patients observed an acute onset of disease whereas Duration of illness at the time of presentation was 0 - 6 months in majority of patients (45%), with 26.7% patients reporting an illness for 7-12 months and 28.3% for more than a year 33% patients had prior history of seasonal recurrence (Table 2).

History of present illness	PLE cases (n = 60) (%)
Onset of disease	
Acute	37 (61.7)
Insidious	23 (38.3)
Duration of disease	
0 - 6 month	27 (45.0)
7 - 12 month	16 (26.7)
> 12 month	17 (28.3)
Seasonal recurrence	
No	40 (66.7)
Yes	20 (33.3)

Table 2: History of present illness among PLE cases.

A majority of patients had no addictions (75%) while 8.3% were addicted to tobacco, which was not significantly different from controls (Table 3).

Addictions	PLE cases (n = 60) (%)	Controls (n = 30) (%)	t/χ^2 value	p value
No	45 (75.0)	21 (70.0)	6.57	0.363
Alcohol	2 (3.3)	0 (0.0)		
Smoking	4 (6.7)	5 (16.7)		
Smoking + Alcohol	1 (1.7)	1 (3.3)		
Smoking + Alcohol +Tobacco chewing	2 (3.3)	0 (0.0)		
Smoking + Tobacco chewing	1 (1.7)	2 (6.7)		
Tobacco chewing	5 (8.3)	1 (3.3)		

Table 3: Frequency of addictions in PLE cases.

The vitamin D status of controls and Interventional group is presented in table 4. Comparing the vitamin D status, χ^2 test revealed significantly 8.3% cases with sufficient vitamin D levels, as compared to controls (70.0% Vs 8.3%, $X^2 = 39.08$, $P < 0.001$).

Vitamin D status	Controls (n = 30)	Cases (n = 60)	X^2 value	P value
Deficient	1 (3.3)	25 (41.7)	39.08	<0.001
Insufficient	8 (26.7)	30 (50.0)		
Sufficient	21 (70.0)	5 (8.3)		

Table 4: Vitamin D status of two groups.

To see the effect of Vitamin D3 supplementation on serum Vitamin D levels in PLE cases, the PLE cases were randomized equally in two groups and treated either with sunscreen or sunscreen plus Vitamin D3. The pre- therapy and 3 weeks post-initiation of therapy serum Vitamin D levels of two groups are summarized in table 5.

Groups	Pre treatment (n = 30)	Post treatment (n = 30)	Paired t Value	P value
Sunscreen	16.67 ± 7.82	16.62 ± 7.78	0.25	0.808
Sunscreen + Vitamin D3	15.29 ± 6.40	28.77 ± 5.09	21.63	<0.001
Student' t value P value	0.75 0.458	7.15 <0.001	-	-

Table 5: Pre and post serum Vitamin D levels (Mean ± SD) of two treated groups.

Comparing the mean serum Vitamin D levels within the groups (i.e. between periods), paired t test revealed significant increase (improvement) in serum Vitamin D levels of Sunscreen + Vitamin D3 group at post-therapy evaluation as compared to pre-therapy (15.29 ± 6.40 vs. 28.77 ± 5.09, $t = 21.63$; $p < 0.001$) while in sunscreen group it not differ significantly between the two periods (16.67 ± 7.82 vs. 16.62 ± 7.78, $t = 0.25$; $p = 0.803$) i.e. vitamin D levels were found to be statistically the same (Table 5).

Further, comparing the mean serum Vitamin D levels between the groups, Student's t test revealed similar levels between the two interventional groups at pre-treatment assessment (16.67 ± 7.82 vs. 15.29 ± 6.40, $t = 0.75$; $p = 0.458$) indicating comparable serum Vitamin D levels. However, at post – treatment assessment , the mean serum Vitamin D levels of sunscreen + Vitamin D3 group were found significantly different and higher (47.1%) as compared to Sunscreen group (16.62 ± 7.78 vs. 28.77 ± 5.09, $t = 7.15$; $p < 0.001$) (Table 5).

Further, evaluating the pre- and post-treatment serum Vitamin D status (deficient/insufficient/sufficient) of the two Interventional groups (Table 6), X^2 test revealed similar status between the groups at pre-treatment evaluation (X^2 = 0.24; p = 0.887) while significantly different at post- treatment assessment (X^2 = 18.49; p < 0.001). Further, no change in status form pre- to post- therapy was observed in Sunscreen group (X^2 = 0.23; p = 0.890) while in Sunscreen + Vitamin D3 group the patients improved significantly (6.7% vs. 36.7%, X^2 19.70; p < 0.001).

The effect of Vitamin D3 supplementation on PLE scores was also observed and is summarized table. Comparing the mean PLE scores within the groups (i.e. between periods), paired t test revealed significant increase (9.9%) in PLE scores of Sunscreen group (4.79 ± 4.63 vs. 5.27 ± 1.35, t = 2.92, p = 0.007) while significant decrease (33.3%) in Sunscreen plus Vitamin D3 group (1.73 vs. 3.54 ± 1.78, t = 6.16, p < 0.001) (Table 7).

Further, comparing the mean PLE scores between the groups, Student's t test revealed similar score between the two groups pre-treatment (4.79 ± 1.63 vs. 5.31 ± 1.73, t = 1.18; p = 0.242) indicating PLE scores comparable. However, post-treatment, the mean PLE score of Sunscreen + Vitamin D3 group was found significantly different and 43.2% improvement as compared to Sunscreen group (5.27 ± 1.35 vs. 3.54 ± 1.78, t = 4.23; p< 0.001) (Table 7).

Periods	Serum Vitamin D Status	Sunscreen (n = 30) (%)	Sunscreen + Vit D3 (n = 30) (%)	X^2 Value	P Value
Pre treatment	Deficient	12 (40.0)	13 (43.3)	0.24	0.887
	Insufficient	15 (50.0)	15 (50.0)		
	Sufficient	3 (10.0)	2 (6.7)		
Post treatment	Deficient	12 (40.0)	0 (0.0)	18.49	<0.001
	Insufficient	16 (53.3)	19 (63.3)		
	Sufficient	2 (6.7)	11 (36.7)		
Pre Vs. post	χ^2 value	0.23	19.70	-	-
	p value	0.890	<0.001		

Table 6: Pre and post serum Vitamin D status of two treated group.

Groups	Pre treatment (n = 30)	Post treatment (n = 30)	Paired t Value	P value
Sucscreen	4.79 ± 1.63	5.27 ± 1.35	2.92	0.007
Sunscreen + Vit D3	5.31 ± 1.73	3.54 ± 1.78	6.16	<0.001
P value	0.242	<0.001	-	-

Table 7: Pre and post PLE scores (Mean ± SD) of two treated groups.

The two treated PLE groups were also followed for 3 months for any recurrence and findings are summarized in table 8. The X^2 test revealed significantly different and lower (60.0%0 recurrence in Sunscreen + Vitamin D3 group as compared to Sunscreen group (83.3% vs. 23.3% X^2 = 21.70; p < 0.001).

Recurrence	Sunscreen	Sunscreen + Vitamin D3 (n = 30) (%)	X^2 value	p-value
No	5 (16.7)	23 (76.7)	21.70	<0.001
Yes	25 (83.3)	7 (23.3)		

Table 8: Distribution of recurrence of two treated groups.

Discussion

Polymorphic light eruption is an idiopathic disorder characterized by a delayed, abnormal response to electromagnetic radiation, usually sunlight, with a varied morphology of papules, plaques and vesicles on exposed areas of the skin. Although the aetiology and pathogenesis of PLE are currently unknown, recent studies suggest that it is an auto-immune-like skin disease that may involve resistance to UV-induced immune suppression, resulting in unwanted immune reactions against UV radiation-induced photo-neoantigens [18,19].

Clinical and investigative profile of subjects

Age incidence

In our study, the maximum incidence was noted in the age group of 21 to 30 years and the minimum was in the age group more than 50 years. According to Morison, the age of onset varies between 20 - 40 years [20]. This corresponds to the age group of working population who may have more sun exposure as a consequence of their profession in contrast to very young and very old individuals.

Sex incidence

Females were predominantly afflicted with PLE in our study as compared to males with a female to male ration of 1.86:1. This is in accordance with the observations made by Tutrone WD., *et al*. [21], Morrison [20] and Berg [22], who reported a higher incidence in females as compared to males ranging from 2:1 to 3:1.

Occupation and family history

The maximum incidence was observed in students, comprising 23%, 15% in house wives and 8% in shopkeepers. In our study, 11.7% patients had positive family history. Ros., *et al*. [23] as well as Jansen [24] reported a familial tendency to the disease ranging from 3 to 56%.

History, symptoms and associated disease

The onset of lesions was acute in 61.7% of the cases. In 45% of the patients, the duration of disability was between 0-6 months and in 28.3% of the cases it was more than a year. Itching was present in 45% of the patients and coincidently burning sensation was also observed in 31.7% of the patients 33.3% patients reported recurrence in the same season in previous years. Melasma was found in 18.3% of the cases and 6.7% of the patients had freckles associated with PLE.

Norris., *et al*. [25] recorded transient, non-scarring, pruritic papules and vesicles, typically developing hours or days after sun exposure and resolving over several days without sequelae. Similar observations were made by van de Pas., *et al* [26].

Clinical types

Popular type occurred in 61.7% of the patients, plaque type in 31.7% and eczematous type in 6.7% of the patients. The commonest form was the popular type, followed by plaque type.

According to Dummer., *et al*. popular and popular-vesicular eruptions were the most common [27]. According to Kontos., *et al*. [28] and Dermatologic Disease Database [29], the popular type was commonest; but 66.7% of the cases had multiple lesions i.e. polymorphic lesions, with distribution of lesions being maximum on sun-exposed areas namely neck and forearm (45%), in accordance with the observations of Berg [22], Frian-Bell [30] as well as Jansen [31].

Vitamin D status

Estimation of serum 25-hydroxy-vitamin D3 levels in PLE patients and control group showed that the mean vitamin D3 level in PLE patients (15.98 ± 7.11 ng/mL) was significantly lower ($p < 0.001$) than the level seen in controls (30.97 ± 6.58 ng/mL).

Majority of the PLE patients had insufficient (50%) or deficient (41.7%) Vitamin D3 levels while most of the individuals in the control group had optimal vitamin D3 status (70%) representing a significant gap ($p < 0.001$) amongst the two groups.

This is consistent with findings of Gruber-Wackernagel., *et al.* [13] who observed that PLE patients had low levels of 25 (OH)D throughout the year compared to that of the control subjects.

In early spring, the mean vitamin D3 level was 14.9 ± 3.0 ng/mL in the PLE patients and significantly lower than that observed in the matched control population (34.4 ± 12.5 ng/mL).

Conclusion

The results of this study clearly indicate that treatment with oral vitamin D3 supplement significantly diminished the appearance and severity of PLE symptoms in the study participants. A statistically significant reduction ($p < 0.001$) of PLE test scores by 33.3% was observed in patients receiving oral vitamin D3 supplementation for 3 weeks along with photoprotection in the form of topical sunscreen application.

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