• Review Article •

Ultraviolet association with vernal keratoconjunctivitis with perilimbal pigmentation

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Abstract

● Vernal keratoconjunctivitis (VKC) is a chronic bilateral ocular allergic disease affecting mainly children and adolescents. Perilimbal pigmentation (PLP) has been noted as a new sign of VKC in pigmented race of Asian and African origin. To analyze the etiology, clinical significance, and pathophysiology of PLP, and to explore the possible association between ultraviolet (UV) exposure and the presence of PLP in VKC. A PubMed search of articles between January 1983 and January 2024 on VKC with PLP was performed. PLP takes the appearance of spotty pigmentation in the interpalpebral conjunctiva. Activation and proliferation of the melanocytes in the limbus in the status of inflammation had been proposed as possible pathogenesis of PLP. However, the clinical significance of PLP in the process of VKC were still controversial. VKC with PLP were mostly seen in pigmented races in equatorial region with hot, dry climates and strong UV. The regionality of VKC patients with PLP and the interpalpebral distribution of pigmentation suggest possible association of PLP with UV. Elucidating this issue will help to prevent and treat this regional and racial specific VKC.

● **KEYWORDS:** vernal keratoconjunctivitis; perilimbal pigmentation; ultraviolet; itchiness; limbus
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INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral allergic disease of the external eye commonly seen in hot and dry climates. It is a recurrent and self-limiting disease with most of them be resolved during puberty[1]. Males have much higher incidence of VKC with male/female ratio ranging from 2:1 to 4:1[2]. Typically, patients with VKC present with itchiness, tearing, photophobia, foreign body sensation, hyperaemia, and mucous discharge. Severe VKC can be potentially sight-threatening and have a detrimental effect on the quality of life of patients[3]. Based on the part of the conjunctiva predominantly involved, VKC can be classified into three types: limbal VKC, palpebral VKC, and mixed VKC. Limbal VKC is characterized by the presence of gelatinous confluent limbal papillae that produce an opaque and thickened appearance. Horner-Tranta spots are characteristic feature of limbal VKC, mostly located in the superior limbus[4].

In addition to the established features of VKC, a new sign of perilimbal pigmentation (PLP) was reported in Indian patients with VKC[5-6]. PLP was first described in India in 2002 as fine, golden brown pigment dominantly located in the interpalpebral conjunctiva which can occur in all grades of VKC. It was found that PLP could be a useful sign in confirming the diagnosis of VKC in patients without characteristic features. However, it was not correlated with the intensity of symptoms[5]. Subsequent studies in VKC in India revealed that not all the VKC patients presented with PLP, which challenged the previous conclusion. PLP has also been found as a prevalent finding of VKC patients in Africa[7-11] and other Asia countries as Pakistan[12] and China[13]. In 2008, one study in HongKong, China came to the same conclusion that PLP might be a useful diagnostic sign for patients with subtle signs[13]. In Africa, PLP in VKC patients was recorded as a circumcorneal, pigmented limbal thickening, sometimes encroaching on to the cornea. It was noted that almost all the black VKC patients attending the clinics in Southern Africa belonged to limbal form VKC with PLP. Studies in Rwanda revealed that PLP was the most striking signs of VKC in black children and the severity of VKC was positively related to

the amount of pigmentation. The study in Pakistan found that inflammation might be the predominant cause of PLP in VKC and the duration of VKC was not correlated with the severity of PLP[12].

VKC with PLP was common in Africa, Indian and other Asian countries. However, this new sign of PLP in VKC hasn't been reported in China Mainland. In addition, the etiology, pathology and clinical significance of PLP in VKC remain controversial. We recently encountered several cases of VKC with PLP in Xizang Autonomous Region, which was significantly different from VKC in other region in China. We did a review of literature on VKC with PLP to have a more comprehensive understanding of this new sign of VKC.

MATERIALS AND METHODS

A PubMed search of articles between January 1983 and January 2024 on VKC with PLP was performed. Keywords included a combination of the following terms: "perilimbal pigmentation", "conjunctival pigmentation", "vernal keratoconjunctivitis", and "allergic conjunctivitis". The articles found were then reviewed for pertinence. There are 5 articles in Africa and 10 articles in Asia, including 8 articles in India, 1 in Pakistan and 1 in Hongkong, China. There are no articles of VKC with PLP in China Mainland, or Caucasion Nation.

The total number of cases is obtained by adding up all the cases in the literature included in the study. The average age of VKC patients was mean of all VKC patients in the literature. The age range of VKC onset, the ratio of male to female patients, and the incidence rate of PLP in all VKC patients were taken as the total range in all the literatures.

RESULTS

In Africa The earliest record of PLP in VKC was a study in South Africa in 1983. The authors first reported a striking different sign of VKC in black children. They show a totally different finding of circumcorneal, pigmented limbal thickening and sometimes encroaching on to the cornea[7]. Five clinical studies, including one study on the treatment of VKC with PLP and one review article were found in PubMed search (Table 1)[7-11]. The three original clinical studies collected 921 cases of VKC patients. In South Africa, average age of VKC patients was 7.5y, ranged from 2.5 to 18y[7]. In Sudan, North Africa, average of 720 VKC patients was 12y, ranged from 2 to 36y[8]. The male/female ratio of VKC patients was 3:1[7] and 2.3:1.3[8], respectively. Male predominance was also reported in the other study in Rwanda[9]. Symptoms of VKC included itchiness (main), tearing, photophobia and mucous discharge. In addition, children with VKC were 6 times more likely to develop corneal astigmatism >2 diopters[9]. The most noteworthy similarities of the above three studies were that PLP were found in all the VKC patients (100%) and the high percentage of limal VKC, ranged from 98.4% to 100%[7-9].

De Smedt *et al*'s[10] study on the treatment of VKC in central Africa revealed that ciclosporin can effectively reduce PLP score as well as other symptoms and signs for VKC patients. In a review on VKC in sub-Saharan Africa, 100% of the children with VKC had perilimbal conjunctival pigmentation in South Africa[11]. This was in accordance with the above two clinical studies in South[7], North[8] and Central Africa[9].

In Asia PLP was reported as a new clinical sign of VKC in India in 2002[5]. Since then, ten articles on VKC with PLP were be found (Table 2)[1,6,12-19]. Average age of VKC patients ranged from 7.5 to 26.2y for the 1491 cases included in the above ten articles. Most of the patients are predominantly male with percentage ranging from 71.43% to 86.49%. Limbal VKC percentage of all VKC varied greatly from different regions of India, 4% in Karnataka, southwest India[14]; 61.5% in Prayagraj, north India[17]; and 100% in Tamil Nadu, southeast India[14]. In India, itching, foreign body sensation, photophobia, excessive tearing and mucus discharge were the most common symptoms of VKC. The percentage of VKC with PLP of all the VKC patients ranged from 5.4% to 100%. In Rao *et al*'s[14] study in 2004, PLP was reported in all the VKC patients. It was described as multiple, discrete, dot-like pigment deposits that appeared like scattered pepper granules, with the color varying from brown to black. In Dubbaka *et al*'s[6] study, among the 152 VKC patients included, 53.29% of the patients were presented with PLP. The pigmentation were concentrated around the limbus and in the interpalpebral area of bulbar conjunctiva. And they were also described as multiple, scattered, black in color and mainly dot like in appearance.

VKC with PLP was mostly studied in India. In 2008, one study in Hongkong, China, reported that all the 19 VKC patients had PLP in at least one eye with bilateral involvement in 16 (84.2%) patients[13]. In 2012, another study in Pakistan reported that 94% of the VKC patients were presented with PLP, and there was no correlation between the duration of disease and severity of PLP[12].

DISCUSSION

Correlation of Region, Climate and Race with PLP in VKC

VKC is an allergic disease that is more prevalent in the regions with hot, humid climate, and higher load of airborne allergens. It is common in central Africa, India, and South America[14]. As an allergic disease, in most cases, allergen of VKC was unknown. In Rao and Padmanabhan's[5] letter to *Cornea*, VKC has environmental and racial predilections. Previous studies revealed that the incidence, subtype, demographic and clinical presentations of VKC have geographical variations. Up to now, VKC with PLP was mostly studied in India. After marking all the above regions that have reported VKCs with PLP on the map, it revealed that these regions were all located near the equator, along the coastline of Indian Ocean. The sun

Table 1 VKC with PLP in Africa

Author & year	Country/region	No. of cases	Age (y)	Male/female	Seasonal	Clinical features	Symptoms	PLP	Inciting factors	Therapy	Journal
Dahan and Appel, 1983[7]	South Africa	80	2.5-18, Avg: 7.5	3:1	35% summer, 15% winter	Limbal: l00%	Itchiness (main), tearing, photophobia, mucous discharge	100% with PLP	Exposure to ultraviolet light; boys spend more time than girls	Steroids, sodium cromoglycate	*Br J Ophthalmol*
Zhang *et al*, 2005[8]	Sudan, North Africa	720	2-36, Avg:12	2.3:1.3	NA	Limbal: 100%	Itchiness, tearing, discharge photopia	100% with PLP	Hot, dry and intensive sunlight	Corticosteroids and adrenaline eyedrops	*International Eye Science*
De Smedt *et al*, 2012[9]	Rwanda, Central Africa	121	8-14	Male dominant	65.4% seasonal, 17.8% perinial	Limbal: 98.4%	Itchiness, stinging, tearing, photophobia, discharge, and corneal astigmatism	100% with PLP	Hot dry; severe VKC had more pigmentation; higher economic	NA	*Ophthalmology*
De Smedt *et al*, 2012[10]	Rwanda, Central Africa	366	NA	NA	NA	NA	Itchiness, tearing, discharge, photopia	PLP score 1.68-1.76	NA	Ciclosporin can reduce PLP score	*Br J Ophthalmol*
Nche *et al*, 2023[11]	Sub-Saharan Africa	2823	Avg: 6.3	Male dominant	43.9% worse hot dry, 13.6% worse rainy cold	Mixed: most	Itchiness (main) redness, tearing, photopia, discharge	100% with PLP in VKC in West Rand	NA	NA	*Curr Opin Allergy Clin Immunol*

VKC: Vernal keratocunjunctivitis; PLP: Perilimbal pigmentation; Avg: Average; NA: Not applicable.

Table 2 VKC with PLP in Asia

Author & year	Country/region	No. of cases	Age, y	Male/female	Seasonal	Clinical features	Symptoms	PLP	Inciting factors	Therapy	Journal
Khan *et al*, 2012[12]	Pakistan	50	3-15, Avg: 7.5	3:1	NA	Mixed: 30; tarsal: 14; limbal: 6	Itching	94% with PLP; fine, granular, discrete, dot like and multiple	No correlation between the duration of disease and severity of PLP	NA	*J Coll Physicians Surg Pak*
Luk *et al*, 2008[13]	Hongkong, China	19	≤18, Avg: 11.2	17:2	NA	NA	Itchiness (47.4%), mucous discharge (31.6%), hyperaemia (26.3%), tearing (26.3%)	100% with PLP; multiple, scattered, discrete, dot-like deposits	PLP not correlate with age, disease severity or the chronicity of disease	NA	*Eye (Lond)*
Rao *et al*, 2004[14]	Tamil Nadu, India	25	Avg: 7.5	21:4	NA	Limbal: 100%	Itching, FB sensation photophobia, burning, tearing and discharge	100% with PLP; spotty, light brown to dark black	Hot, dry, tropical; limbus rich in pigment	NA	*Cornea*
Sabbo *et al*, 2013[1]	Andhra Pradesh, Southeast, India	468	11-15, Avg: 12	6.4:1	36% perenial	Mixed (72%), tarsal (15.6%), limbal (12.6%)	Itching (88%), redness (86%), watering (65%)	52 cases (11%) with PLP	NA	NA	*Indian J Ophthalmol*
Jivangi *et al*, 2015[15]	Karnataka, Southwest, India	74	NA	2.7:1.13	79.72% seasonal	Mixed (61%), tarsal (35%), limbal (4%)	Itching (79.72%), watering (47.29%), discharge (40.54%), redness (66.21%)	4 cases (5.4%) with PLP	NA	NA	*Int J of Research in Med Sci*
Ashwini *et al*, 2015[16]	Bangalore, North India	450	Avg: 9.1	Male predominance	NA	Mixed (62%)	Itching (90%), redness (82%), mucoid discharge (60%), FB sensation (52%)	16% PLP	NA	NA	*Journal of Evolution of Medical and Dental Sci*
Sethi *et al*, 2017[17]	Jammu & Kashmir, North India	155	Avg: 10.31	4.96:1	100% seasonal	Mixed (42%), tarsal (37%), limbal (21%)	Itching (100%), redness (61.93%), watering (50.32%), photophobia (44.51%), discharge (41.93%)	13 cases (8.3%) with PLP	NA	NA	*Int J of Research in Med Sci*
Singh *et al*, 2022[18]	Prayagraj, North India	135	1.5-30	2.5:1	NA	Mixed :28.9%, tarsal: 10.4%, limbal :61.5%	Itching (97%), redness (54.7%), watering (45.9%), discharge (14.7%), photophobia (11.1%)	39 cases (28.9%) with PLP	NA	NA	*Rom J Ophthalmol*
Dubbaka *et al*, 2023[6]	Pune, Maharashtra, India	152	Avg: 11.4	79.61% male	26.31% perenial	Mixed: 48.68%, tarsal: 66.27%, limbal: 6.58%	Itching, discharge, redness, tearing	81 cases (53.29%) with PLP	PLP not correlate with age, sex and duration of VKC	NA	*Indian J Ophthalmol*
Nibandhe *et al*, 2024[19]	Hyderabad, middle India	32	6-52, Avg: 26.62	72% male	NA	NA	Nodular lesion (72%), redness 22 (69%), itching 15 (47%)	VKC with PEH, 26 cases (67%) with pigmentation	NA	NA	*Eye (Lond)*

VKC: Vernal keratocunjunctivitis; PLP: Perilimbal pigmentation; PEH: Pseudoepitheliomatous hyperplasia; Avg: Average; NA: Not applicable; FB: Foreign body.

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shines directly on the equator twice throughout one year. The equatorial region belongs to the tropics, with hot weather and high sunshine intensity all over the year. This subtype of VKC with PLP seemed to have geographical variations.

Rao *et al*[14] postulated that the hot, dry and tropical weather might be the inducing factors of VKC with PLP. Hot and humid climate has also been reported to be associated with VKC in previous studies. In addition, VKC in tropical countries have shown less associations with personal and family history and are usually presented with a perennial form of the disease[18].

VKC with PLP has only been reported in people in pigmented races in Asia and Africa. It hasn't been reported in light-skinned races. In the study of VKC in Rwanda, PLP has been described as the most striking signs of limbal VKC in black children[9]. Van Vuuren[20] also concluded that darker skin may increase the presence of PLP in patients with VKC. In addition, De Smedt *et al*[3] reported that Congolese children with VKC were 4.8 times more likely to develop PLP. The reason for the racial variation of PLP in VKC might be that in pigmented races, the limbus is richer in melanocytes which could be activated and proliferated in VKC.

PLP in Normal People and Conjunctival Pigmentation in Anthropoid Primates in the Equator Region So far, the pathophysiology of PLP in VKC patients was not clear. One theory by Rao and Padmanabhan[5] was that the limbus might be in a state of disordered proliferation state in VKC patients. The limbus contained a rich concentration of melanocytes, especially in pigmented races[1]. Melanocytes might be proliferated into visible pigments and migrated along with the antigen-carrying Langerhans cells. Dubbaka *et al*[6] had also proposed that PLP in VKC is the result of increase in melanocytic activity in response to inflammation of the surrounding connective tissue. So in early studies on VKCs with PLP, the occurrence of PLP has been reported as a new and specific sign of VKC[5,14]. It was suggested that PLP may be useful in the diagnosis of VKC patients with early disease, quiescent disease, or in other conditions that may present with nonspecific symptoms of VKC[14]. However, one study in Pakistan challenged the above perspective. PLP could be seen in controls without VKC. The extent of PLP in controls was less than that in VKC patients[12]. In South Africa, Van Vuuren[20] also found that 6.4% of controls without VKC presented with PLP. One study on ocular colourization of anthropoid primates revealed that primates living closer to the equator had more pigmented conjunctiva. And conjunctival pigmentation might play photoprotective functions in anthropoid primates[21]. Maybe PLP in people near the equator are related to strong ultraviolet (UV) radiation, and the resultant PLP can reflect strong UV radiation to protect the eye.

Distribution of Pigmentation and Limbal Lesions In VKC patients, PLP usually presented as a spotty pigmentation of the bulbar conjunctiva. The fine, golden brown pigment is mostly present in the perilimbal bulbar conjunctiva and gradually decreases in density towards the fornix[14]. The occurrence of PLP has been reported as a new and specific sign of VKC[5,14]. In Africa, the most noteworthy characteristic was that PLP was associated with high percentage of limbal VKC, ranged from 98.4% to 100% respectively[7-9]. In India, the percentage of VKC with PLP of all the VKC patients ranged from 5.4% to 100%. The percentage of PLP occurrence among all VKC patients varied. However, it was found that PLP was associated with the limbal form VKC. Various forms of VKC have geographical variations. Palpebral forms are said to be more prevalent in Europe and the USA, whereas the mixed and limbal forms are more commonly seen in Asia and Africa[22]. In another words, PLP occurred specifically in VKC that have limbal lesions. Pigmentation was concentrated around the limbus and in the interpalpebral area of bulbar conjunctiva[12]. The distribution of PLP and the limbal lesions were in accordance with the area exposed to sunlight. In the earliest reports on VKC with PLP, the authors proposed that exposure to strong UV light might be the cause of limbal form VKC[7,9]. The finding that the pigment were found only in the exposed conjunctiva with limbal lesions of VKC supported the hypothesis that UV exposure was the main cause of the disease.

Similarities Between VKC with PLP and Actinic Conjunctivitis Literature review on conjunctival pigmentation and UV revealed another inadequately described disease called actinic conjunctivitis. It is an ocular photosensitivity reaction to UV found mainly in children of the highlands of Ecuador[23]. VKC with PLP and actinic conjunctivitis are similar in the following four aspects. First, they both belong to ocular surface allergic diseases that mainly affect children or adolescents in regions with strong UV radiation. Early stage actinic conjunctivitis was frequently misdiagnosed as VKC as it also had an allergic component[23]. In addition, children affected by actinic conjunctivitis also complained of itching. Histopathological analysis showed solar elastosis, vascular congestion and lymphoplasmacytic infiltrate in specimens obtained from patients with stage 3 actinic conjunctivitis[23]. Second, they both manifested as proliferative changes around the limbus. Stage 2 and stage 3 actinic conjunctivitis manifested as various degrees of markedly thick and pigmented lesions around the limbus in the interpalpebral region (Figures 1-2)[19,23]. Severe VKC with limbal stem cell deficiency presented with limbal mass lesions too (Figure 2)[19]. Third, stage 2 and 3 actinic conjunctivitis are accompanied by pigmentary changes in the interpalpebral area as VKC

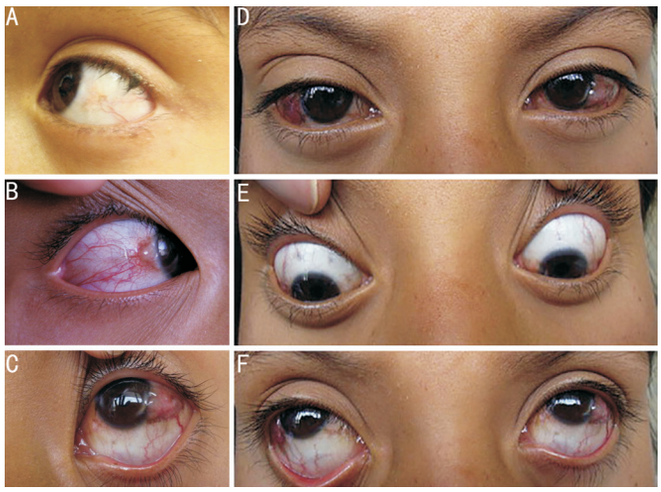

Figure 1 Reproduced by the kind permission from Engel *et al*[23] The three stages of actinic conjunctivitis: stage 1 (A), stage 2 (B), stage 3 (C). In stage 2, the limbal lesion becomes thicker with pigmentary changes and feeder vessels. In stage 3, the limbal lesion is markedly thick and pigmented. Typical ocular changes of advanced (stage 3) case of actinic conjunctivitis (D). Same patient looking downward (E) and upward (F) shows that lesions in actinic conjunctivitis majorly involve the exposed bulbar conjunctiva.

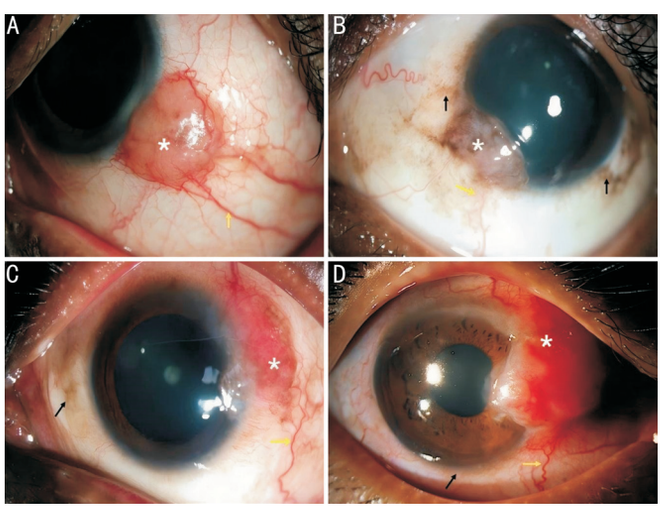

Figure 2 Reproduced by the kind permission from Nibandhe *et al*[19] Ocular surface lesions associated with VKC can present as an elevated nodular lesion (A), hyperpigmented lesion (B), diffuse flat lesion (C), or with an extensive involvement encroaching onto the cornea (D). It generally has associated intralesional pigmentation (Asterisk) with adjacent feeder vessels (yellow arrow). The lesions were concentrated in the interpalpebral area of bulbar conjunctiva.

with PLP. Most of the limbal mass lesions in VKC patients were accompanied by feeder vessels (64%) and intralesional pigmentation (67%; Figure 2)[19]. Fourth, the limbal lesions in both VKC and actinic conjunctivitis were concentrated in the interpalpebral area of bulbar conjunctiva. In patients with VKC, the upper and lower bulbar conjunctiva were clear (Figure 2B, 2C) or mildly reactive hyperemia (Figure 2A)[19]. The most striking aspect of actinic conjunctivitis was that changes of the nonexposed bulbar conjunctiva and the palpebral conjunctiva were minal[24]. The above similarities between VKC with PLP and actinic conjunctivitis strongly implied that VKC with PLP might be also associated with excessive exposure to UV as actinic conjunctivitis.

VKC with PLP and Tropical Endemic Limboconjunctivitis

Tropical endemic limboconjunctivitis (TELC) is another chronic allergic conjunctivitis characterized by severe pruritus, brownish pigmentation of the conjunctiva, papillae on the upper palpebral conjunctiva, severe limbitis with Trantat's spots. It mainly affects young children[25]. Except for papillae on the upper palpebral conjunctiva, the above manifestations are similar to VKC with PLP. Literature on TELC are mainly in French and presented without figures[25-28]. So we cannot visually compare these two diseases. TELC has been firstly reported in Benin, a western African country in 1993. Recently, TELC has been reported in Cameroon[26] and Burkina Faso in Western Africa. TELC is frequently associated with the with-the-rule astigmatism[27] and increased risk of lacrimal hyposecretion[27]. A recent article in Douala equals TELC to tropical endemic VKC[28]. Along with the manifestation similarity between TELC and VKC with PLP, we speculate that they might be the same disease. VKC with PLP were mainly reported in India, Pakistan and some African countries. TELC were predominantly reported in western Africa. Literature on VKC with PLP were in English, while literature on TELC were in French. TELC and VKC with PLP might be the same disease prevalent in different regions. Due to language and cultural differences, the name of the diseases have not been unified. Literature review revealed that the etiology of TELC might be dust, dryness or UV rays[25], which partially supports our view that UV radiation may be the main cause of VKC with PLP.

In conclusion, VKC with PLP were mostly seen in pigmented races in equatorial region with hot, dry and strong UV climate. Clinical significance and pathology of PLP in VKC needs further study to verify. The regionality of VKC with PLP and the distribution of pigmentation suggest possible association of strong UV and this special type of VKC. Elucidating this issue will help to prevent and treat VKC patients with PLP.

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