Hyperkeratotic hand eczema compared to other subgroups of hand eczema – a retrospective study with a follow-up questionnaire

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Summary

Background. Only a few clinical trials on hand eczema have included further classification into subtypes, and there is a need for studies evaluating the present classifications.
Objectives. To examine differences in demographic factors, lifestyle factors and severity between subgroups of hand eczema patients, with a focus on hyperkeratotic hand eczema.
Methods. This was a retrospective study including hand eczema patients referred to the outpatient dermatological clinic, Bispebjerg Hospital, between January 2013 and July 2014. The study comprises information on subdiagnoses, treatment and foot eczema from patient files, as well as a follow-up questionnaire.
Results. A total of 120 patients were included, 10 of whom were diagnosed with hyperkeratotic hand eczema. A significantly higher proportion of the patients with hyperkeratotic hand eczema were male ($p = 0.002$) and received systemic or ultraviolet (UV) treatment ($p = 0.026$). The frequency of tobacco smoking was significantly higher in patients with hyperkeratotic hand eczema ($p = 0.016$), as well as in the other subgroups combined ($p = 0.049$), than in the background population.
Conclusions. Studies evaluating the subdiagnoses of hand eczema are needed, to further validate the classification system, and to provide more detailed information about demographic factors, severity and possible risk factors for different subgroups of hand eczema.

Key words: classification; hand eczema; hyperkeratotic; lifestyle factors; smoking.

Hand eczema is a common disease resulting in impaired quality of life (1), and, with the risk of sick leave and loss of job, it is a burden for both the individual patient and society (2–5). An improved understanding of which therapeutic actions to choose in specific cases is needed. Hand eczema comprises a broad spectrum of subdiagnoses, related to genetic or environmental factors (6, 7). Several studies on classification systems of hand eczema into subgroups have recently been published (8–10), primarily based on either aetiology or morphology. They all emphasize the importance of obtaining a subdiagnosis in clinical trials, as well as in the daily clinic. A better understanding of differences between subgroups could be a step towards achieving personalized treatment. However, clinical studies on hand eczema are few in number, and studies providing information on subdiagnoses even rarer (11, 12), so there is currently a need for validation of the present classifications, and further investigation of their applicability. Also, risk factors related to different subdiagnoses of hand eczema should be further explored, as these may differ between hand eczema subgroups (13), with the practical consequence that not all patients should receive the same guidance.

The aim of the present study was, in a population of hand eczema patients from a hospital outpatient clinic,

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to examine differences in demographic factors, lifestyle factors and severity between subgroups of hand eczema patients, focusing on hyperkeratotic hand eczema as compared with other subgroups. In addition, tobacco smoking is highlighted, and a comparison is made between the percentage of smokers in our patient groups and that in the background population.

Methods

All hand eczema patients referred to the outpatient clinic, department of dermatology, Bispebjerg Hospital, between 1 January 2013 and 1 July 2014 were eligible for the study. The study was retrospective and complemented by data from a follow-up questionnaire sent 1–2.5 years after the first visit to the outpatient clinic. The inclusion criterion applied was the ability to understand the Danish language sufficiently to read and answer the questionnaire. Patients aged <16 years were excluded. The study was approved by the Danish Data Protection Agency (ID number: BBH-2014-080) and by the Danish Health Authority.

Information on subdiagnoses, treatment and foot eczema was extracted from the patient files for those who gave permission for this. All patients underwent patch testing, and the subdiagnosis was registered in the patient file after testing. Subdiagnoses were based on medical history, exposure history, clinical examination, and results of the patch test, and corresponded to the classification suggested in the ESCD hand eczema guidelines (14): irritant contact dermatitis, allergic contact dermatitis, atopic hand eczema, contact urticaria, vesicular endogenous hand eczema, and hyperkeratotic endogenous hand eczema. If the diagnosis changed during the follow-up period in the outpatient clinic, the most recent diagnosis was used. Some patients were classified with multiple subdiagnoses or with an additional subdiagnosis. Treatment was registered as topical (comprising emollients, topical corticosteroids, tacrolimus, and tar) and systemic [comprising acitretin, alitretinoin, azathioprine, cyclosporine, methotrexate, prednisolone, and ultraviolet (UV) B and psoralen and UVA therapy]. Information on the presence of foot eczema was based on the doctor's clinical examination. The extraction of data from patient files was performed in September–October 2016.

In July 2015, all participants received a questionnaire including questions on current eczema and change in severity since the first visit, and questions on the current lifestyle factors, namely, tobacco smoking, physical activity, and being overweight/obese. To assess the severity of eczema at baseline, when the patient first attended the dermatological clinic, and the current severity, patients were asked to rate the severity for both baseline and for the last week on a scale from 0 to 10. The severity assessment was taken from the NOSQ 2002 question D12, and translated into Danish, with 0 meaning no eczema and 10 meaning extremely severe eczema (15). Tobacco smoking was divided into three categories: never smoker, former smoker, and current smoker. In the analysis, the smoking variable was dichotomized into current smoker at follow-up and non-smoker. Physical activity in leisure time, including transportation to and from work, was assessed in the following four categories: (i) almost physically passive or only light physical activity for < 2 h per week; (ii) light physical activity for 2–3 h per week; (iii) light physical activity for > 4 h per week or more strenuous physical activity for 2–4 h per week; or (iv) more strenuous physical activity for > 4 h per week, or regular hard training or competitions several times per week. The body mass index (BMI) was calculated from the height (in cm) and weight (in kg) reported by the patients, and being overweight was defined as a BMI of > 24.9 kg/m^2.

In the questionnaire, the patients were asked to give their permission for extraction of data from their patient files, according to Danish regulations, and data from files were used from patients who gave permission only. If the participants had not returned the questionnaire, up to two additional questionnaires were sent.

To compare the smoking status of the patients with that of the relevant background population, we used data on the prevalence of tobacco smoking for the population in the Capital Region of Denmark (16), which the catchment area for Bispebjerg Hospital is part of.

Differences regarding demographic factors, current lifestyle factors, and severity, both at baseline and follow-up, between patients with hyperkeratotic hand eczema and the other subgroups combined were investigated. In addition, tobacco smoking in the study population was compared with that in the relevant background population.

The Kruskal–Wallis test was applied to test for differences between non-responders, and included participants for continuous variables. The chi^2-test was applied for categorical variables. For statistical analyses of hyperkeratotic hand eczema versus other subgroups of hand eczema combined, binary logistic regression was used, with the results being given as odds ratios. In the multiple regression analysis, the factors adjusted for were sex and age. Two-sided p-values of < 0.05 were considered to be statistically significant. Calculations were performed with SPSS version 22 (SPSS, Chicago, IL, USA).

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Table 1. Non-responder analysis of sex and age (N = 225)

	Included responders (n = 120)	Non-responders (n = 105)	Total (n = 225)	*p*-Value*
Sex				0.71
Male, n (%)	44 (36.7)	41 (39.0)	85 (100)	
Female, n (%)	76 (63.3)	64 (61.0)	140 (100)	
Mean age in years (SD)	47.2 (15.6)	40.6 (13.5)	44.1 (15.0)	**0.002**

SD, standard deviation.
*Significant *p*-values are shown in bold.

Table 2. Demographic data stratified according to subdiagnoses (N = 120)

Main subdiagnosis	Total, n (%)	Male, n (%)	Female, n (%)	Age (years), mean (SD)
ACD	29 (24.2)	7 (24.1)	22 (75.9)	45.1 (12.4)
ICD	39 (32.5)	10 (25.6)	29 (74.4)	42.9 (15.7)
AHE	11 (9.2)	4 (36.4)	7 (63.6)	42.8 (11.9)
CU	1 (0.8)	1 (100.0)	0 (0.0)	51.0
Vesicular	6 (5.0)	3 (50.0)	3 (50.0)	48.0 (18.6)
Hyperkeratotic	19 (15.8)	14 (73.7)	5 (26.3)	59.7 (11.8)
Multiple subdiagnoses	7 (5.8)	1 (14.3)	6 (85.7)	47.0 (16.3)
Unclassified	2 (1.7)	1 (50.0)	1 (50.0)	67.5 (2.1)
No permission	6 (5.0)	3 (50.0)	3 (50.0)	45.0 (24.4)
Total	120 (100.0)	44 (36.7)	76 (63.3)	47.2 (15.6)
Additional subdiagnoses	7 (5.8)	3 (42.9)	4 (57.1)	41.3 (13.6)

ACD, allergic contact dermatitis; Additional subdiagnoses, patients with one or more subdiagnosis in addition to their main subdiagnosis; AHE, atopic hand eczema; CU, contact urticaria; Hyperkeratotic, hyperkeratotic endogenous hand eczema; ICD, irritant contact dermatitis; Multiple subdiagnoses, patients with more than one main subdiagnosis; No permission, patients who did not give permission for extraction of information from their patient files; Unclassified, patients who could not be classified; Vesicular, vesicular endogenous hand eczema.

Results

In all, 226 patients with hand eczema were eligible for the study. Of these, 121 patients answered the questionnaire, giving a response rate of 53.5%. Of the 121 respondents, 1 did not meet the inclusion criterion concerning age. The mean age was higher in responders than in non-responders, namely, 47.2 versus 40.6 years ($p = 0.002$) (Table 1). Six patients who answered the questionnaire did not give permission for extraction of information from their patient files, and for the analyses these patients were included in the other subgroups of hand eczema combined and compared with the group of patients diagnosed with hyperkeratotic hand eczema.

The demographic data for the included responders are presented in Table 2. Seven patients had multiple main subdiagnoses, and 7 other patients had, in addition to their main subdiagnosis, one or more additional subdiagnoses. Within the group of hyperkeratotic hand eczema patients, 1 patient was diagnosed with irritant contact dermatitis as an additional subdiagnosis.

Data on demographic factors stratified with respect to hyperkeratotic hand eczema and other subgroups of hand eczema combined are shown in Table 3. The percentage of males was significantly higher among patients with hyperkeratotic hand eczema than in the other subgroups combined (adjusted $p = 0.002$). No significant association was found between increasing age and hyperkeratotic hand eczema (adjusted $p = 0.160$). Data on severity and treatment are shown in Table 4. A significantly higher proportion of the patients with hyperkeratotic hand eczema than of the patients with other subgroups of hand eczema received systemic and/or UV treatment (adjusted $p = 0.026$). Involvement of the feet was found more often in the hyperkeratotic group in the univariate analysis, but this strong association was not significant after adjustment for age and sex, although a trend remained ($p < 0.001$ and adjusted $p = 0.086$, respectively) (Table 4). Data on lifestyle factors are shown in Table 5. There were no significant differences between the hyperkeratotic group and other subgroups combined regarding tobacco smoking, physical activity, or BMI.

To further evaluate the association with tobacco smoking, data from the background population were included. Figure 1 shows the percentages of smokers for different age groups in the background population in the Capital Region of Denmark (16), as compared with our patient population with hyperkeratotic hand eczema and other subgroups of hand eczema combined, respectively. The prevalence of smoking was significantly higher in

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Table 3. Demographic factors in patients with hyperkeratotic hand eczema and other hand eczema subgroups combined (N = 120)

				Crude		Adjusted	
	Total, n (%)	Other subgroups, n (%)	Hyperkeratotic eczema, n (%)	OR (95%CI)*	*p*-Value	OR (95%CI)†	*p*-Value
Sex					**0.001**		**0.002**
Females	76 (63.3)	71 (70.3)	5 (26.3)	1		1	
Males	44 (36.7)	30 (29.7)	14 (73.7)	6.63 (2.19–20.04)		6.94 (2.01–23.9)	
Age group (years)					0.16		0.16
16–24	7 (5.8)	7 (6.9)	0 (0.0)	-		-	
25–34	23 (19.2)	23 (22.8)	0 (0.0)	-		-	
35–44	23 (19.2)	20 (19.8)	3 (15.8)	0.18 (0.04–0.82)		0.15 (0.03–0.79)	
45–54	26 (21.7)	22 (21.8)	4 (21.1)	0.22 (0.06–0.89)		0.21 (0.05–0.95)	
55–64	21 (17.5)	18 (17.8)	3 (15.8)	0.20 (0.05–0.92)		0.15 (0.03–0.76)	
≥ 65	20 (16.7)	11 (10.9)	9 (47.4)	1		1	

CI, confidence interval; OR, odds ratio.
Significant *p*-values are shown in bold.
*Univariate analysis with the outcome OR for patients with hyperkeratotic hand eczema as compared to patients with non-hyperkeratotic hand eczema.
†Binary logistic regression analysis with the outcome OR of patients with hyperkeratotic hand eczema, adjusted for sex and age.

Table 4. Eczema characteristics in patients with hyperkeratotic hand eczema and other hand eczema subgroups combined (N = 120)

				Crude		Adjusted	
	Total, n (%)	Other subgroups, n (%)	Hyperkeratotic eczema, n (%)	OR (95%CI)*	*p*-Value	OR (95%CI)†	*p*-Value
Information from questionnaire							
Severity							
Baseline (first visit), mean (SD)	6.6 (2.5)	6.4 (2.5)	7.5 (2.2)	1.23 (0.98–1.54)	0.081	1.18 (0.90–1.54)	0.22
Follow-up, mean (SD)	3.5 (2.8)	3.3 (2.7)	4.4 (3.2)	1.14 (0.96–1.35)	0.13	1.16 (0.95–1.41)	0.14
Clear of eczema for the last 6 months					0.60		0.28
No	110 (91.7)	92 (91.1)	18 (94.7)	1		1	
Yes	10 (8.3)	9 (8.9)	1 (5.3)	0.57 (0.07–4.76)		0.27 (0.03–2.86)	
Information from patient files							
Treatment (n = 114)					**0.001**		**0.026**
Topical treatment only	84 (73.7)	76 (80.0)	8 (42.1)	1		1	
Any systemic or UV treatment	30 (26.3)	19 (20.0)	11 (57.9)	5.50 (1.94–15.6)		4.32 (1.19–15.7)	
Eczema on feet (n = 114)					**< 0.001**		0.086
No	99 (86.8)	88 (92.6)	11 (57.9)	1		1	
Yes	15 (13.2)	7 (7.4)	8 (42.1)	9.14 (2.78–30.1)		3.35 (0.84–13.35)	

CI, confidence interval; OR, odds ratio; SD, standard deviation; UV, ultraviolet.
Significant *p*-values are shown in bold.
*Univariate analysis with the outcome OR for patients with hyperkeratotic hand eczema as compared to patients with non-hyperkeratotic hand eczema.
†Binary logistic regression analysis with the outcome OR of patients with hyperkeratotic hand eczema, adjusted for sex and age.

hyperkeratotic hand eczema patients ($p = 0.016$) and in the other subgroups combined ($p = 0.049$) than in the background population from the same area in Denmark.

Discussion

Hyperkeratotic endogenous hand eczema is defined as chronic eczema with hyperkeratosis in the palms, or pulpitis, in the absence of vesicles or pustules, and without documented exposure to contact irritants at the involved skin areas that are likely to cause irritant contact dermatitis (14). Differentiation between hyperkeratotic hand eczema and palmar psoriasis is difficult, and it could be debated whether hyperkeratotic hand eczema of the palms is an distinct disease entity or a variant of psoriasis (17). The factors causing hyperkeratotic hand eczema are still poorly understood (18).

In the present clinical study, exploring the differences between hand eczema subgroups with a focus on hyperkeratotic hand eczema, we found a higher percentage of males in the hyperkeratotic group. This is

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Table 5. Lifestyle factors in patients with hyperkeratotic hand eczema and other hand eczema subgroups combined

				Crude		Adjusted	
Information from questionnaire	Total, n (%)	Other subgroups, n (%)	Hyperkeratotic eczema, n (%)	OR (95%CI)*	*p*-Value	OR (95%CI)†	*p*-Value
Smoking (n = 118)					0.18		0.99
No	89 (75.4)	77 (77.8)	12 (63.2)	1		1	
Yes	29 (24.6)	22 (22.2)	7 (36.8)	2.04 (0.72–5.81)		1.00 (0.27–3.74)	
BMI groups (n = 118)					0.69		0.81
Normal and underweight	67 (56.8)	57 (57.6)	10 (52.6)	1		1	
Overweight and obese	51 (43.2)	42 (42.4)	9 (47.4)	1.22 (0.46–3.27)		0.87 (0.27–2.78)	
Physical activity (n = 114)					0.63		0.68
Almost physically passive	13 (11.4)	12 (12.2)	1 (6.3)	1		1	
Light activity for 2–3 h per week	27 (23.7)	22 (22.4)	5 (31.3)	2.73 (0.29–26.1)		2.72 (0.20–36.5)	
Light activity for > 4 h per week	60 (52.6)	53 (54.1)	7 (43.8)	1.59 (0.18–14.1)		2.46 (0.20–30.4)	
Strenuous activity for > 4 h per week	14 (12.3)	11 (11.2)	3 (18.8)	3.27 (0.30–36.3)		5.66 (0.33–97.6)	

BMI, body mass index; CI, confidence interval; OR, odds ratio.
*Univariate analysis with the outcome OR for patients with hyperkeratotic hand eczema as compared to patients with non-hyperkeratotic hand eczema.
†Binary logistic regression analysis with the outcome OR of patients with hyperkeratotic hand eczema, adjusted for sex and age.

in agreement with two previous studies showing a male/female ratio of 1.25 (19, 20). One study suggested hard manual work as a possible risk factor for the development of hyperkeratotic hand eczema; in that study, one-third of the patients with hyperkeratotic hand eczema were engaged in hard manual work at the time of onset of symptoms (21). However, no current irritant exposure was identified in the present study. Regarding age, 47.4% of patients with hyperkeratotic hand eczema were aged > 65 years, whereas only 10.9% of patients in the other subgroups were aged ≥ 65 years. An association between increasing age and hyperkeratotic hand eczema has been previously reported by other authors (14, 18, 20); however, a statistically significant association was not found in the present study.

In a recent study investigating the factors associated with foot eczema in a cohort of hand eczema patients, combined hand and foot eczema was found in 29.8% of the total group, although more often (48.8%) in association with hyperkeratotic hand eczema (12). Two previous studies suggested that foot eczema is more common in males (12, 22), which may explain why the data in the present study lost significance after adjustments for sex and age. The association between hyperkeratotic hand eczema and systemic treatment found in the present study suggests lower efficiency of topical treatment regimens for hyperkeratotic hand eczema, resulting in a greater need for systemic treatment. This indicates a more chronic and severe course of hyperkeratotic hand eczema; however, no significant difference in self-assessed severity between hyperkeratotic hand eczema and other subgroups was found, although a trend for more severe eczema in the hyperkeratotic group was found at baseline in the univariate analysis. It has been suggested that combined hand and foot eczema is associated with more severe and long-lasting hand eczema (12). As a majority of the patients with hyperkeratotic hand eczema in our study had foot eczema, this might also have influenced the association with severity and treatment choices. Moreover, retinoids have been found to be more effective in the treatment of hyperkeratotic hand eczema (17), and this may also contribute to systemic treatment with, for example, alitretinoin being more often considered for patients with hyperkeratotic hand eczema than for those with other hand eczema subdiagnoses. Another reason could be that prevention has an important role in the treatment of subdiagnoses, such as irritant and allergic contact dermatitis, whereas, in other subgroups, such as hyperkeratotic eczema, prevention may be less efficient.

With respect to lifestyle factors, recent reports have indicated associations between hand eczema and tobacco smoking, physical activity, and high BMI (23–27), although there is no agreement on this (28, 29), which might be attributable to the variable subdiagnoses of hand eczema included in the studies. One study found smoking to be a particular risk factor for vesicular hand eczema (30). In the present study, no significant difference was found between hyperkeratotic hand eczema and other subgroups of hand eczema with respect to tobacco smoking. Our data support a previous finding of an association between tobacco smoking and the prevalence of hand eczema, the association being present for both

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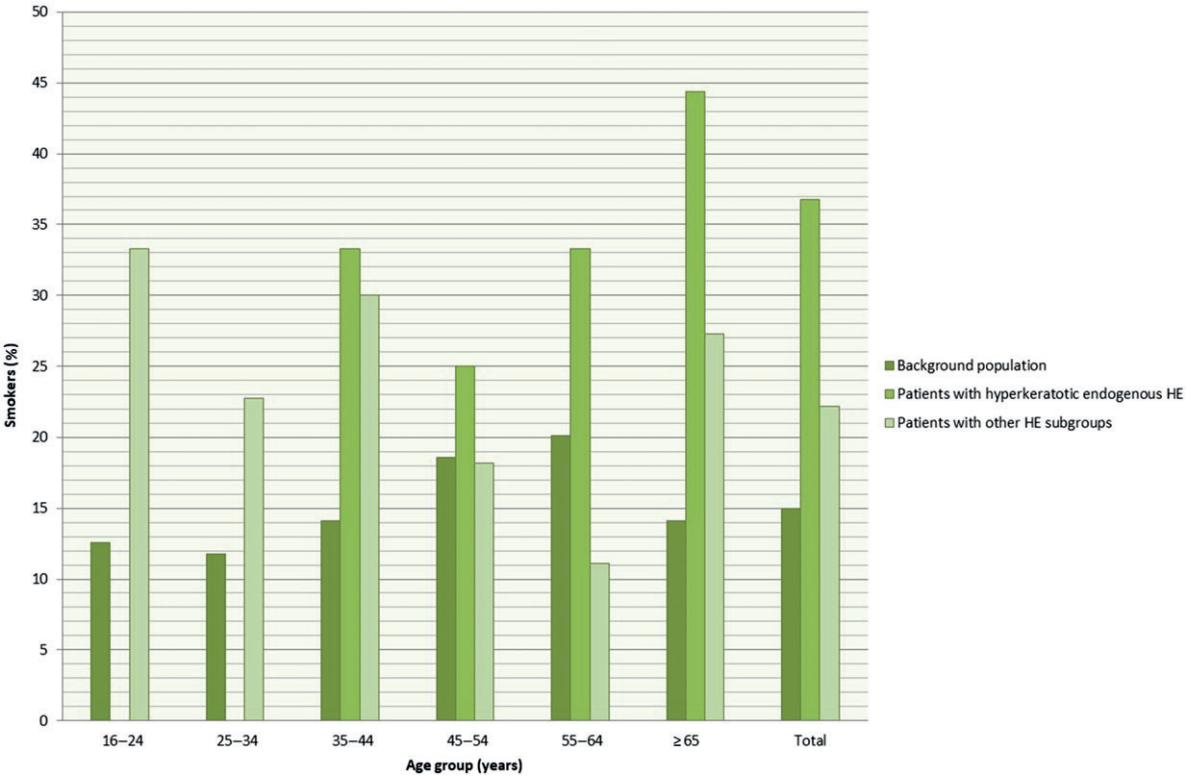


Fig. 1. Percentage of daily smokers stratified into different age groups for background population, hyperkeratotic hand eczema (HE) patients, and other hand eczema subgroups combined.

the hyperkeratotic group and the other subgroups of hand eczema, when the percentage of smokers in our patient population is compared with that in the relevant background population. Regarding physical inactivity and BMI, we found no association with hyperkeratotic hand eczema. Obesity is known to be related to psoriasis (31), and hyperkeratotic hand eczema is considered by some to be a variant of psoriasis, involving only the hands and feet (17). The finding of no association in the present study between obesity and hyperkeratotic hand eczema supports the finding of hyperkeratotic hand eczema being a separate entity, independent of psoriasis (21).

Given the small sample size and limited response rate, the present study is exploratory and the first step towards a hypothesis-generating study. A strength of this study is that it is clinical-based, whereas most studies on this subject are population-based, and the patients were diagnosed according to the recently published classification system for hand eczema (14). A drawback of this study is that the information on the subgroups of hand eczema was obtained from 1 year earlier than the information collected in the follow-up questionnaire. One other limitation concerns the data collection for the severity of hand eczema, whereby patients were asked to retrospectively rate the severity both at baseline and during the week before they received the questionnaire. These self-reported hand eczema severity rates could be inaccurate.

Conclusions

In the present study, hyperkeratotic hand eczema was found to be associated with male sex and more use of systemic or UV treatment, and with a tendency for a higher prevalence of foot eczema. Studies evaluating the different subgroups of hand eczema are needed to further validate the classification, and to provide more detailed information about demographic factors, eczema severity and possible risk factors for the different subgroups.

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