

Humoral and Cell-Mediated Immune Responses to Dog Dander and Hair in Asthmatic Children

TIMO VANTO, MARKKU VIANDER* and ANTTI KOIVIKKO

Dept. of Paediatrics and *Dept. of Medical Microbiology, University of Turku, Turku, Finland

Dog dander and hair (DDH) specific IgA and IgG antibodies from serum samples of 202 asthmatic children aged from 4 to 15 years were measured by enzyme-linked immunosorbent assay. The results were compared with clinical history, and with allergy tests (skin prick test, provocation test and RAST) using the same DDH extract. A blood sample for the *in vitro* lymphocyte stimulation test was obtained from 40 children, and a nasal secretion sample for analysis of the local DDH-specific IgA, IgG and IgE antibody levels was collected from 35 of them. In children of dog-keeping families, higher serum levels of DDH-specific antibodies, especially IgE antibodies, were observed if the dog had been in the home already during the first years of the child's life. The serum levels of DDH-specific antibodies, however, did not correlate with the degree of the present exposure to dogs. The serum levels of DDH-specific IgA and IgG antibodies did not correlate with each other, with the levels of specific or total IgE, or with the results of skin prick or provocation test. The serum levels of DDH-specific IgA were highest in children who were subjectively most sensitive to dogs. Nasal levels of DDH-specific IgE correlated positively with serum specific IgE levels. The correlation was weaker between nasal and serum titers of specific IgG, and not significant between nasal and serum IgA antibody levels. Specific IgE antibody levels were higher, while specific IgA and IgG antibody levels were lower, in nasal secretion from subjects with nasal symptoms on contact with dogs, when compared with subjects with other complaints (asthma, conjunctival or skin reactions). DDH-specific IgG levels correlated negatively with specific IgE level in the nasal secretion from subjects with a positive provocation test result, while the correlation was positive in subjects with a negative provocation test. The *in vitro* lymphocyte responses to DDH did not correlate with the results of allergy tests, or with the levels of DDH-specific antibodies in serum or in nasal secretion.

Key words: asthma; dog dander; nasal secretion.

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CLINICAL ASPECTS

Dog dander and hair specific IgA, IgG and IgE antibody levels in serum samples from 202 asthmatic children, and in nasal secretion from 35 of them, were compared with history of dog allergy and results of allergy tests.

The association of serum levels of dog dander and hair specific antibodies in relation to time of exposure to dogs in the home, gives support to the idea of a critical period in infancy, when the child is unusually susceptible to environmental allergens. However, the degree of the present exposure to dogs did not correlate with the specific antibody levels. Our results suggest that specific IgA and IgG act as blocking antibodies in nasal secretion, since low levels of these antibodies were associated with a history of nasal symptoms on contact with a dog, while higher levels were found in subjects without nasal complaints. The correlation between the serum and nasal levels of specific IgA and IgG antibodies was so poor that the serum levels cannot be used to predict the nasal concentrations. On the contrary, the serum levels of specific IgE antibodies correlated well with the nasal specific IgE, which lessens the need of laborious analysis of local IgE. Among these 202 asthmatic children, no cases who had a positive provocation test combined with a negative serum RAST had a history of dog allergy.

The immediate type of allergic reaction is usually mediated by allergen-specific IgE antibodies. Specific IgG antibodies, so-called short-time sensitizing IgG antibodies (17), have also been observed to provoke allergic reactions. On the other hand, specific IgG antibodies have been shown to act as blocking antibodies inhibiting the IgE-mediated allergic reactions (9, 21, 24, 28). The role of specific IgA antibodies in allergy is not fully explained. They have been suggested to act as blocking antibodies in nasal secretion (22, 23). The serum levels of specific IgA antibodies have also been found to correlate significantly with serum concentrations of specific IgE antibodies (14).

Most of the specific IgE and IgA antibodies are supposed to be produced locally, also some IgG antibodies (6, 7, 16). It is therefore logical to assume that the concentration of these antibodies, e.g. in the nasal secretion, has a better correlation with the clinical symptoms than the concentration in serum.

There is some evidence that the *in vitro* lymphocyte stimulation by pollen allergens correlates positively with IgE-mediated pollen allergy (2, 29). However, such a correlation has not been reported with perennial allergens, such as animal dander.

The purpose of the present study was to measure the levels of dog dander-specific IgA and IgG antibodies in serum and nasal secretion from asthmatic children by enzyme-linked immunosorbent assay, and to investigate the association of these antibodies with dog allergy and with the *in vivo* lymphocyte stimulation by dog dander allergen extract. The correlation between the serum levels and nasal concentrations of the specific IgA, IgG and IgE was investigated.

MATERIAL AND METHODS

Patients

202 children (122 males and 80 females) from the Children's Asthma Register of the Paediatric Department of the University of Turku (12) were included in the study. The mean age of the children was 10.4 years (range 4–15

years). The severity of their asthma was variable; they had reported 20 ± 30 asthma days (mean $\pm$ SD) during the year preceding the investigation. None of the patients had previously been hyposensitized with dog or cat allergen extracts. Their clinical history was recorded by means of a detailed questionnaire, including questions about the past and present exposure to dogs, symptoms on contact with dogs and the present subjective sensitivity to dogs. A positive history of cat allergy was obtained in 46% of the subjects, a history of tree pollen allergy (birch, alder) in 39%, grass pollen allergy in 35%, and a history of fish hypersensitivity in 33% of the subjects.

A control group for the *in vitro* lymphocyte stimulation tests consisted of 19 clinically non-atopic children (15 males and 4 females), who were hospitalized for cardiological investigations. Their mean age was 10.9 years (range 3–15 years). A nasal secretion sample was obtained from five subjects in the control group.

Allergen extract

The allergen extract for the skin prick test was obtained from the Allergologisk Laboratorium A/S, Denmark (Soluprick-SQ[®], batch Hu 073). The same batch of this allergen as an aqueous extract was used for the provocation tests, for the specific IgA, IgG and IgE antibody determinations, and for the *in vitro* lymphocyte stimulation tests.

Skin prick tests

The prick tests were performed according to the method recommended by the Northern Society for Allergology (1), as described elsewhere (25).

Provocation tests

All patients were investigated by the bronchial and/or conjunctival provocation test as described elsewhere (25), and a nasal provocation test. A nasal secretion sample was collected from patients and the nasal provocation test was performed as an end-point titration by

spraying 0.05 ml of the allergen extract solution with a syringe against the inferior turbinate. The other nasal cavity was used as a control by spraying the control solution (the diluent) into it. If no reaction was observed within 15–20 min after application of the allergen or the control solution, the concentration of the allergen extract was increased in 10-fold steps until reactions occurred, or the highest concentration (1 mg/ml or approximately 1 HEP) was reached. The nasal test was considered positive, when at least two of the subjective symptoms (sneezing, itching, discharge, subjectively noted obstruction of the nose) and at least one of the objective changes (swelling, colour change, discharge) were noted in the nasal mucosa by rhinoscopy.

Blood samples

Blood samples for the lymphocyte cultures were obtained by venipuncture, and put immediately into sterile culture tubes containing 50 units of preservative-free heparin/1 ml of blood. The serum samples for antibody determinations were obtained by venipunctures and stored at -20°C until the determinations were carried out.

Nasal secretion samples

The nasal secretion samples were collected from 35 patients and five control subjects by a filter paper method according to Mygind (15) with few modifications. Two pieces of folded paper (35×10 mm) were placed in each nasal cavity. When the nose started dripping, or after 15 min, the paper was removed and placed in a plastic tube with 0.8 ml saline. The tube was kept frozen at -20°C before and after the sampling, until the determinations were done. Both the amount of saline and the sample were weighed to calculate the degree of dilution. Small samples (less than 0.1 g) were discarded. All samples were later processed and analysed simultaneously. The mucus and debris were removed by centrifugation through a filter net at 4000 rpm for 15–20 min. The analyses were then performed with the supernatant fluid.

IgE determinations

Total IgE levels in sera and nasal secretions were determined by Phadebas[®] IgE PRIST (Pharmacia Diagnostics AB, Uppsala, Sweden).

Specific IgE antibodies

The RAST analyses from sera and nasal secretion samples were done with dog dandruff (e5) discs using commercially available Phadebas[®] RAST materials. The serum samples were also analysed by paper RAST method with the same dog dander and hair allergen extract that was used in the allergy tests and in the determinations of specific IgA and IgG antibodies. The RAST analyses were performed as described elsewhere (26).

The degree of the dilution in the nasal secretion samples was taken into account as described by Mygind (15). The specific IgE levels calculated for the original nasal samples were expressed as a percentage of counts per minute of the total added activity (cpm %).

Specific IgA and IgG antibodies

IgA and IgG antibodies to dog dander and hair were measured by the enzyme-linked immunosorbent assay (ELISA) as described elsewhere (27). The coefficient of variation ($100 \text{ SD} \times$) of this method has been previously shown to be 9.8% (28). The ELISA was performed in special microtiter plates, where each well was coated with 0.1 ml of dog dander and hair extract (0.1 g/l). After the coating, the plates were washed with PBS and then saturated by 2-h incubation with 0.1 ml of PBS containing 1% normal sheep serum (NSS-PBS). The patient sera were diluted in 1:50 in NSS-PBS and the nasal secretion samples in 1:10 in NSS-PBS. 75 μl of the dilutions were added onto the antigen-coated wells and incubated at 37°C for 2 h. After washing three times with 0.9% NaCl containing 0.05% Tween 20 (NaCl-Tw), 75 μl of 1:500 dilution (in NSS-PBS) of alkaline phosphatase conjugated swine antibodies against human IgG (Orion Diagnostica, Espoo, Finland) or 75 μl of 1:200 dilution of alkaline phosphatase conjugated

swine antibodies against human IgA (Orion Diagnostica) were added. After incubation overnight at room temperature the plates were washed three times with NaCl-Tw. The amount of alkaline phosphatase bound to the plates was quantified using *p*-nitrophenylphosphate (NPP, Sigma Chemical Co., St. Louis, Miss., USA) as a substrate in glycine, $MgCl_2$ buffer, pH 10 (Orion Diagnostica). The optical absorbance was measured at a wave length of 405 nm. A standard curve was prepared daily for each IgG assay using a highly positive reference serum as a standard; the same reference serum for IgG determinations was used throughout the study. The concentration of the DDH-specific IgG antibodies in the sample was expressed as a percentage of the antibody concentration in the reference serum (std %). For the serum samples, a proper highly positive reference serum was not found for the IgA determination. Therefore the specific antibody concentration were expressed as absorbance units. In the determination of nasal specific IgA, a proper positive standard serum was available, and the results were expressed as a percentage of the antibody titer in the reference serum. All determinations were made in duplicate.

In vitro lymphocyte stimulation test

Lymphocyte stimulation test by dog dander and hair extract and by PPD (Statens Serum-institut, Copenhagen, Denmark) was carried out in whole blood microcultures as described elsewhere (27, 29). Dog dander and hair extract was used in different dilutions (0.02, 0.2 and 2 g/l). The lymphocyte stimulation was calculated by measuring the uptake of ^{125}I -5-iodo-2'-deoxyuridine. The stimulation responses were expressed as net counts (cpms of the stimulated culture minus cpms of the control culture).

Statistical methods

The statistical significance of the differences between the two means was tested by using the Student's *t*-test after having applied the *F*-test.

The correlation coefficients were calculated with the aid of Pearson's formula for the product-moment correlation coefficient.

RESULTS

The keeping of a dog in the family during a child's infancy was associated with high serum levels of dog dander and hair (DDH) specific IgA and IgE antibodies in later childhood when compared with dog-keeping which had begun after the age of 1 year (Table 1). The trend was similar, even though not statistically significant, regarding the serum levels of DDH-specific IgG antibodies. It was interesting to note that the serum levels of specific IgA, IgG and IgE antibodies were lower in children who had first been exposed to dogs at home after the age of 1 year, than in those children who had never been exposed to dogs at home. The degree of the present exposure to dogs did not correlate with the serum levels of specific antibodies, but only when exposure had begun during the first year of life.

The subjective sensitivity to dogs, as could be presumed, correlated well with the serum levels of DDH-specific IgE antibodies (Table 2a). The serum level of specific IgA antibodies was highest in the group of most sensitive children. The serum levels of specific IgG antibodies did not correlate with the subjective sensitivity to dogs.

As expected, the nasal concentration of DDH-specific IgE antibodies was highest in the children who were subjectively most sensitive to dogs (Table 2b). Contrary to the serum levels of specific IgA, the nasal DDH-specific IgA antibody concentrations were highest in the group of children who had no symptoms related to a contact with dogs. The levels of nasal DDH-specific IgG was lowest in the group of children who were subjectively most sensitive to dogs.

Nasal complaints were the most usual symptoms related to dog exposure in these asthmatic children. They were often combined with other symptoms (asthma, conjunctival or skin reactions). The serum levels of DDH-specific IgE antibodies were slightly, but not significantly,

Table 1

Association of the patient's age at the first exposure to a dog in the home with the dog dander and hair specific antibody levels in serum samples

	Previous or present dog-keeping in the home			<i>P</i>
	Patient's age when dog-keeping began		No dog- keeping	
	< 1 year	> 1 year		
Serum IgA-ab*	26.4 ± 9.7	20.2 ± 6.2	26.8 ± 15.4	< 0.05
Serum IgG-ab**	14.0 ± 15.1	11.1 ± 15.4	14.9 ± 19.1	NS
Serum IgE-ab***	8.32 ± 8.28	4.55 ± 6.30	4.88 ± 7.12	0.05
(<i>n</i>)	(30)	(39)	(129)	

* Mean ± SD, absorbance units.

** Mean ± SD, std %.

*** Mean ± SD, cpm %.

Table 2a

Serum levels of dog dander and hair specific antibodies and the sensitivity of occurring symptoms on contact with dogs

	Patient's subjective sensitivity to dogs				<i>P</i>
	-	+	++	+++	
Serum IgA-ab*	24.2 ± 10.7	22.3 ± 9.5	24.5 ± 12.0	36.2 ± 32.3	< 0.05
Serum IgG-ab*	13.8 ± 17.8	14.2 ± 20.0	14.2 ± 12.9	11.6 ± 19.4	NS
Serum IgE-ab*	3.49 ± 5.18	6.83 ± 7.86	7.95 ± 9.13	14.77 ± 7.87	< 0.001

* Mean ± SD, see Table 1.

- = No symptoms (including cases with doubtful history).

+ = Symptoms when stroking a dog.

++ = Symptoms when close to a dog.

+++ = Symptoms even more easily acquired.

higher in subjects with nasal symptoms, than in dog-allergic subjects without nasal symptoms (Table 3). This difference was more obvious, although not statistically significant, as regards nasal specific IgE. The nasal levels of specific IgA and IgG antibodies were lowest in the group of children with nasal symptoms associated with dog contact.

The serum DDH-specific IgE antibody titer correlated positively with the skin prick test results and with the serum total IgE ($r = 0.774$ and 0.481 , respectively; $n = 202$). The serum levels of specific IgA correlated almost significantly with the serum total IgE, ($r = 0.177$, $n = 202$), the specific IgG or IgE levels. The serum concentrations of specific IgG did not

correlate with specific IgA or IgE, either with the skin prick test results or with the total serum IgE.

The serum levels of specific IgE antibodies correlated positively with the nasal concentrations of specific IgE (Fig. 1). The correlation, however, was not statistically significant in the children with a negative provocation test result. The correlation between the nasal and serum levels of specific IgG antibodies was weaker ($r = 0.345$, $n = 34$, $P < 0.05$). No correlation was observed between the nasal and serum levels of specific IgA antibodies.

The correlation between the specific IgG and IgE antibodies in nasal secretion was positive in subjects with a negative provocation test, but

Table 2b

Nasal levels of dog dander and hair specific antibodies and the sensitivity of occurring symptoms on contact with dogs

	Control subjects	Patient's subjective sensitivity to dogs				
		-	+	++	+++	(+, ++, +++)
Nasal IgA-ab* (std %)	53.67 ± 16.98	30.18 ± 26.75	22.36 ± 13.18	21.29 ± 3.20	25.68 ± 14.31	23.20 ± 11.84 ^a
Nasal IgG-ab (std %)	3.448 ± 6.545	0.764 ± 0.536	0.495 ± 0.222	1.130 ± 0.900	0.142 ± 0.043	0.504 ± 0.503
Nasal IgE-ab (cpm %)	1.12 ± 0.19	4.73 ± 8.25	22.13 ± 26.88	32.27 ± 46.94	51.88 ± 31.69	33.33 ± 32.87 ^b
(n)	(5)	(19)	(8)	(3)	(5)	(16)

* Mean ± SD.

- = No symptoms (including 3 subjects with a doubtful history).

+ = Symptoms when stroking a dog.

++ = Symptoms when close to a dog.

+++ = Symptoms even more easily acquired.

^a $P = 0.002$, when compared with the control subjects.^b $P = 0.005$, when compared with the control subjects and non-dog-hypersensitive asthmatics.

Table 3

Levels of dog dander and hair specific antibodies, and the type of symptoms when in contact with dogs

	Rhinitis	Other symptoms	No symptoms
	Alone or combined with other symptoms	Asthma, conjunctival or skin reaction	Including cases with doubtful symptoms
Nasal IgA-ab* (std %)	22.3 ± 8.4	28.2 ± 14.9	30.2 ± 26.8
Nasal IgG-ab* (std %)	0.557 ± 0.686	0.853 ± 0.984	0.764 ± 0.536
Nasal IgE-ab* (cpm %)	44.2 ± 36.4***	29.2 ± 28.1**	4.73 ± 8.25
(n)	(8)	(6)	(19)
Serum IgE-ab (cpm %)	18.9 ± 14.8**	14.9 ± 11.4***	5.7 ± 8.4
(n)	(60)	(29)	(111)

* Mean ± SD.

** $P < 0.01$, when compared with subjects without symptoms.*** $P < 0.001$, when compared with subjects without symptoms.

negative in subjects with a positive provocation test (Fig. 2). The difference between the correlations was statistically significant ($P < 0.01$). Of the children with a positive bronchial and/or

conjunctival provocation test, 19 were later investigated by nasal provocation test. Three out of the 19 children had a negative result in the nasal test. Even though all of these three chil-

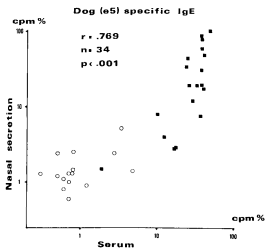


Fig. 1. Correlation between the nasal and serum levels of dog dander specific IgE antibodies measured by RAST using dog dander (e5) discs.

■ = positive provocation test result.
○ = negative provocation test result.

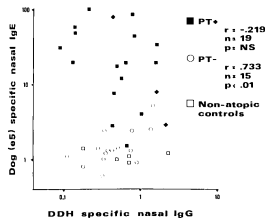


Fig. 2. Correlation between dog dander specific IgE and IgG antibodies in nasal secretion. IgE antibodies were measured by RAST using dog dander (e5) discs, whereas IgG antibodies were measured by ELISA using the same dog dander and hair (DDH) extract, which was used in the skin and provocation tests.

■ = positive provocation test results.
◆ = positive bronchial and/or conjunctival provocation test with a negative nasal provocation test.
○ = negative provocation test result.
□ = non-atopic control subjects.

dren had a high serum level of specific IgE (RAST class 3–4), two of the children had a relatively low (Fig. 2) level of specific IgE in

nasal secretion combined with a high level of nasal specific IgG. The nasal specific IgA levels correlated slightly positively, but without statistical significance, with the nasal specific IgG and IgE antibody levels. There was a significant positive correlation ($r = 0.507$, $P < 0.01$) between the serum and nasal total IgE concentrations.

The *in vitro* lymphocyte stimulation by the optimal concentration (2 mg/ml) of dog dander and hair was slightly, but not significantly higher in asthmatic children with a positive provocation test (633 ± 1826 net cpm; $\times \pm SD$), as compared with other asthmatic children (377 ± 441) or with the control subjects (335 ± 324). Significant responses (> 1000 net cpm) to DDH were, however, observed in only two out of 24 subjects, with positive provocation tests, in one out of 16 asthmatic subjects with a negative provocation test, and in none of the 19 control subjects. The lymphocyte responses to DDH did not correlate with the allergy tests (skin prick tests, provocation test, serum or nasal IgE to DDH), or with the levels of IgA and IgG antibodies to DDH in serum or in nasal secretion.

DISCUSSION

There is some evidence of a critical period in early life, when the infant is unusually susceptible to various environmental allergens, e.g. food (11, 19) or pollen and animal dander (20). In our study, the exposure of the infant to a dog in the home was found to be reflected in later childhood as higher levels of dog dander specific antibodies, especially IgE antibodies. This phenomenon may be associated with a transient depression of T cell function in the first 6 months of life (11). The children who had a dog in their later childhood, had lower amounts of dog dander specific antibodies, including IgE antibodies, in the serum, when compared with other asthmatic children. This may be due to natural selection: those asthmatic children who had a low tendency of IgE response against dog allergens, could be exposed to a dog without a worsening of their allergic symptoms. It was interesting to note that the degree of the present exposure to dogs

did not correlate with the levels of dog dander specific antibodies.

In our study, a significant positive correlation was observed between the specific IgE antibody titers in serum and nasal secretion. The good agreement between the serum RAST and the provocation test (26) and the nasal specific IgE indicates that the measuring of the local specific IgE in cases of negative serum RAST (10) is of minor clinical importance, as concluded by Deuschl & Johansson (8). However, a few cases were found with high serum levels and low nasal levels of specific IgE; two of these subjects had a negative result in the nasal provocation test, but a positive result in either bronchial or conjunctival test.

There was a peculiar discrepancy between the levels of specific IgA antibodies in serum and nasal secretion: the serum levels were highest in the group of children most sensitive to dogs, while the nasal levels were highest in the children who observed no symptoms related to a contact with dogs. Additionally, the levels of specific IgA antibodies in serum did not correlate with nasal levels. It could be that the specific IgA antibodies in the nasal secretion have some blocking activity, while the specific IgA antibody titer in serum merely reflects a higher general responsiveness to this antigen.

Our results suggest that the specific IgG antibodies in nasal secretion may have a blocking action, because the most sensitive children had the lowest nasal level of specific IgG. The possible blocking effect of nasal specific IgA and IgG antibodies is also in accordance with our observation that the nasal levels of specific IgA and IgG were lower in subjects with nasal symptoms, when compared with those who had other complaints. The negative correlation between the nasal levels of specific IgG and IgE antibodies can be explained by the suppression of specific IgE formation by specific IgG antibodies, as concluded by Michael & Bernstein (13). Because of the small number of subjects investigated the conclusions drawn from our results regarding the specific nasal antibodies should be treated with caution.

It should be stressed that we have measured the total amount of specific antibodies directed

against numerous different antigens in dog dander and hair (3). It is possible that more relevant results would have been obtained by measuring antibodies against purified allergens (5), even though our experiences with purified dog serum albumin do not support this idea (27). Our results gave no evidence of the positive correlation of the specific IgG antibody levels with hypersensitivity; however, the measuring of the different IgG subclasses, especially IgG₄ (4), might have given more relevant information.

The lack of correlation between the *in vitro* lymphocyte responses and the IgE-mediated dog allergy is discrepant with studies concerning pollen allergy (2, 29). One may, however, speculate that perennial exposure to an allergen like dog dander may cause suppression of lymphocyte responses rather than activation. This idea is supported by the observations of Prahl et al. (18), who showed that the lymphocytes from patients with allergic asthma due to cow epithelium antigens showed a statistically significant decreased responsiveness to an extract from cow dander, compared to that seen with lymphocytes from asthmatic patients without allergy to cow, or lymphocytes from normal controls. On the other hand, we measured the *in vitro* lymphocyte responses from peripheral blood, which may give a mirror image of lymphocyte activities in the peripheral lymphoid tissues. It must also be admitted that the use of purified dog dander antigens might have given results with a better correlation with the IgE-mediated allergy. However, our studies with dog serum albumin showed that only one albumin-sensitive subject had a significant *in vitro* lymphocyte stimulation response to dog serum albumin (27).

Our study gives evidence of the blocking action of local specific IgA and IgG antibodies, while the levels of these antibodies in the peripheral blood did not correlate with the sensitivity of the respiratory tract. Similarly, no correlation was observed between the antigen-specific proliferative responses of peripheral blood lymphocytes and nasal allergy. Therefore it seems reasonable that one should study the local immune responses rather than their re-

flections in the peripheral blood when investigating the regulation of immune responses to allergens in atopic subjects.

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Address:

Dr. *Timo Vanto*

Dept. of Paediatrics

University of Turku

SF-20520 Turku 52

Finland

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