Bull. Tokyo Med. Dent. Univ., 19: 333–359, 1972.

NASOPHARYNGEAL STIMULATION AND ITS EFFECTS ON THE PLASMA 11-OHCS LEVELS

BY

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ABSTRACT

The nasopharynx is an interesting organ, however, investigations on the organ has been almost undeveloped, because this area is hidden and inconspicuous. Inflammation of the nasopharynx appears frequently in combination with allergic diseases and rheumatism. In this case, most become cured or better only by the treatment of nasopharyngitis itself.

The authors have tried to clear up the mechanism by measuring the plasma 11-OHCS levels using the method of De Moor et al. (1960).

The authors measured the plasma 11-OHCS levels before and immediately after the stimulation of the nasopharynx and calculated the increase rate between the two.

The rates of 32 of 35 simple nasopharyngitis patients (91%) were increased. Those of 9 of 12 allergic rhinitis cases (75%) were decreased or unchanged. Those of 5 of 6 steroid-treated patients (83%) were decreased or unchanged.

When the nasopharynx was not stimulated the plasma 11-OHCS levels were unchanged or decreased a little. The authors have proved that the increase rate is almost in proportion to the degree of the inflammation except in the allergic rhinitis cases and steroid-treated patients, being 30% or less in the mild cases, 20–50% in the moderate cases, and 40% or more in the severe cases. Generally speaking, as the inflammation subsides, the increase in the plasma 11-OHCS levels becomes mild.

Because of the fact that the nasopharyngeal stimulation raises the plasma 11-OHCS level, the authors concluded that treatment of nasopharyngitis is an effective therapy for allergic rhinitis and rheumatism. It is also effective for those who require steroid therapy.

INTRODUCTION

The nasopharynx usually means the part of the pharynx called the epipharynx, but actually this region is a part of the airway covered almost entirely by the ciliated epithel (Fig. 1). The inflammation of nasopharynx,

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Received for publication, August 7, 1972.

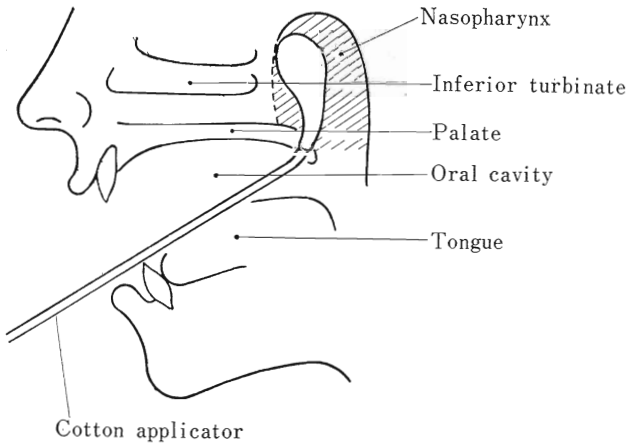

Fig. 1. Nasopharynx and method of stimulating.

nasopharyngitis, is customarily treated as rhinitis, sinusitis or pharyngitis, because the clinical features are apparently not obvious.

S. Horiguti[1-3] has grappled with "nasopharyngitis" for many years, observed the clinical signs in detail caused by nasopharyngitis, established the diagnosis by the method of smear examination stained by the Papanicolaou method[4,5], and furthermore paid attention to the relation between the disease and several systemic diseases[3,6].

In the case of nasal allergy, urticaria, pustulosis, stomatitis aphthosa and rheumatic diseases, most of the patients have "latent" nasopharyngitis. If they are treated for nasopharyngitis, most of them show cure or at least improvement of the original disease, while on the other hand these diseases are well known to frequently respond dramatically to adrenocortical steroid hormone or ACTH.

The authors consider that the stimulation or treatment of the nasopharynx may increase the level of the adrenocortical hormone in the plasma. As the mechanism of cure in nasopharynx treatment, the authors have tried to elucidate it from the point of the automic nerve system[7], plasma fibrinolytic system[8] and seroimmunology. In this paper the authors tried to show how the nasopharynx stimulation has an effect on the pituitary-adrenocortical system.

If the nasopharynx stimulation or treatment gives the same or nearly the same effect as ACTH or adrenocortical hormone, nasopharynx treatment is easy technically and economically and has no side effects, which is seen frequently with hormone. Therefore, this treatment should be worthy of wide attention.

Table 1. Classification of nasopharyngitis

Grade	Nasopharynx		Smear examination
	Touch-pain	Bleeding on touch	
Mild	+～++	−～+	Slight change
Moderate	++	+～++	Moderate change
Severe	++～+++	+++	Severe change

Material and Diagnosis

1. Material

The subjects used were 53 patients, 22 males and 31 females, ranging from 3 to 62 years of age, who visited the authors' outpatient clinic of otorhinolaryngology and were diagnosed as nasopharyngitis. Among these 12 had a complication of nasal allergy and 6 had been under a long-term steroid therapy. Among these, in 16 were observed in the plasma 11-OHCS level during the course of nasopharyngitis.

2. Diagnosis of nasopharyngitis

As the diagnosis of nasopharyngitis can not be made accurately by rhinoscope or by nasopharyngeal mirror alone, the authors adopted the method of examining the Papanicolaou-stained smear of the nasopharynx (Murakami[4], Ide[5] and Saito) and at the same time examining the touch-pain of the nasopharynx and bleeding (Ide and Saito). The authors classified nasopharyngitis into three groups as shown in Table 1.

Method

1. History of plasma 11-OHCS determination

Urinary 17-KS, 17-KGS, 17-OHCS and plasma 17-OHCS have been customarily used as the adrenocortical function tests but urinary steroid determination is too crude a test to observe the influence of nasopharynx stimulation and inadequate as a routine test in the outpatient clinic, since it requires collection of 24 hours urine for several days. While the plasma 17-OHCS determination requires 15 or 20 ml of blood and is unsuitable for the authors' test which requires drawing of blood two times per test.

In comparison with these methods, plasma 11-OHCS determination[12–17] has several merits, requires 2 ml of plasma per sample, is technically rather simple, requires about 2 hours to perform six samples, and the value obtained is more accurate than by the other methods. Plasma 11-OHCS is determined by the fluorimeter by measuring the specific fluorescence caused by the reaction between the principal plasma adrenocortical hormones

(hydrocortisone and corticosterone) and diluted sulphuric acid.

This method was proposed originally by Sweat (1954) to determine the plasma adrenocortical hormone using the silica gel column chromatography. This method has been used since then by several investigators (Peterson, 1957; Ely et al., 1958; McLaughlin et al., 1958; and Braunsberg et al., 1960). In 1958 Silber et al. found that silica gel chromatography could be omitted to determine the corticosterone in a rat plasma. In 1960 De Moor[14] used this fluorescent technique to measure the plasma 11-OHCS (11-hydroxycorticosteroids) in the human plasma. Next year they simplified this method[15,16]. Mattingly[17] published another method, but it was based on De Moor's method and is the same in principle.

An attempt to distinguish between hydrocortisone and corticosterone has been made by van der Vies (1958) and Stewart et al. (1958). For practical purposes this distinction appears to be unnecessary and the authors used De Moor's simplified method which is technically simple and seems more reliable.

2. (i) Condition of experiment

Blood was obtained by venepuncture between 10–12.00 a.m. Immediately after, stimulation of the nasopharynx was performed. The patients were ordered to sit quietly, and 15 minutes after the second venepuncture was performed. In the control, venepuncture was carried out two times at a 15-minute interval without stimulation. They were also ordered to sit quietly. In the control, No. 5 and 6 were measured at about 4.00 p.m. for comparison.

(ii) Reagents and solutions

1. Concentrated sulphuric acid
2. Methylene chloride
3. Ethyl alcohol
4. 0.1 N NaOH
5. Standard

A solution containing 10γ of hydrocortisone in 1 ml of alcohol and stored at 0°–4°C. It was prepared newly every 3 months. At the time of the measurement, 0.1 ml of the solution was dried, 2 ml of distilled water were added and used as the standard.

3. Material

Plasma is used. Blood is drawn by venepuncture using heparin as an anticoagulant. The blood is refrigerated immediately, the plasma is separated within 20 or 60 minutes and stored at 4°C. The determinations are carried out within 4 or 7 days.

4. Apparatus (Fig. 2)

Fig. 2.

Shimadzu Kotaki fluorimeter UM—S type
Filter: Primary filter 436 mμ
Secondary filter 530 mμ
Square: 5×1×1 cm cuvette of non-fluorimetric glass

5. Procedure

Two ml of the plasma are first extracted with 10 ml of methylene chloride by gently inverting the extraction tube with a glass stopper 30 times. After centrifugation for 7 minutes at 3000 r.p.m., about 9 ml of the methylene chloride extract are recovered using a pipette. The extract is washed two times with 1 ml of 0.1 N NaOH for 15 seconds. Five ml of the H_2SO_4/ethanol mixture (70:30) are added to the extract and mixed thoroughly for 15 seconds. The methylene chloride is then removed by aspiration. The light emitted secondarily is measured 15 minutes after mixing the methylene chloride extract with the H_2SO_4/ethanol mixture. Reagent blanks and standards are run through the same procedure.

The value is obtained as follows:

$$C=\frac{U-B}{S-B}\times\frac{100}{2}\ (\gamma/dl)$$

C=Concentration of the plasma
U=Value of fluorimetry of the plasma extract
B=Value of fluorimetry of the reagent blank
S=Value of fluorimetry of hydrocortisone standard

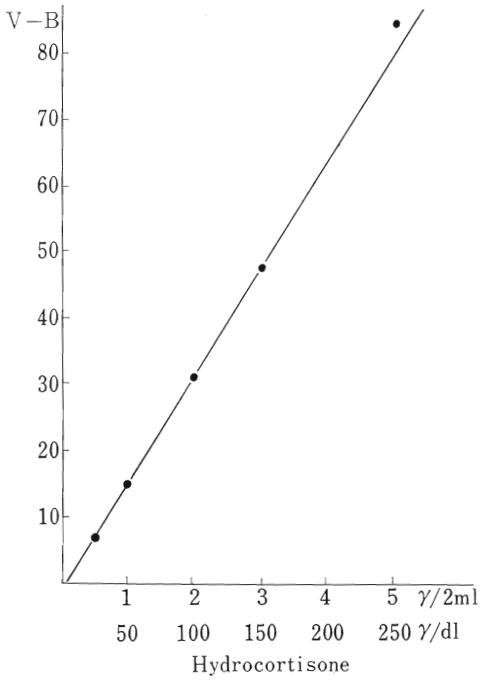

Fig. 3. Standard curve.

6. Washing of instruments

All glasswares were cleaned with chromic acid, followed by thorough washing with tap water and finally with distilled water, in order to avoid the non-specific fluorescence by the contamination of the instruments.

7. Stimulation of nasopharynx

In this experiment, the plasma 11-OHCS was measured just before and 15 minutes after the stimulation of the nasopharynx. As the method of stimulation, 1% $ZnCl_2$ solution was applied to the entire nasopharynx with a cotton applicator inserted through the nose and the mouth (Fig. 1).

The treatment of nasopharyngitis is quite the same as the method mentioned above, as the treatment of nasopharyngitis stimulates the nasopharynx at the same time.

RESULTS

1. Normal values

Normal values of plasma 11-OHCS have been reported as follows: by Silber 28.5±0.48/dl (9.00 a.m.); De Moor[14,15], 21±4.76 (9.00 a.m.) and 22.3 ±0.27; by Mattingly[17], 14.2 (6.5~26.3) (10.00 a.m.); by Wood[19], males

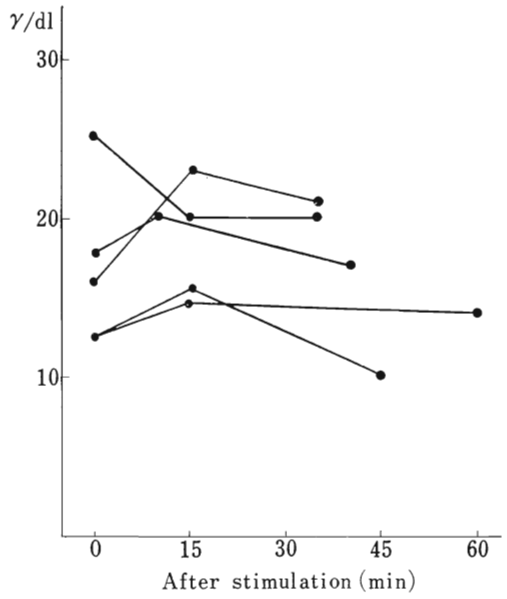

Fig. 4. Plasma 11-OHCS concentration after stimulation of nasopharynx.

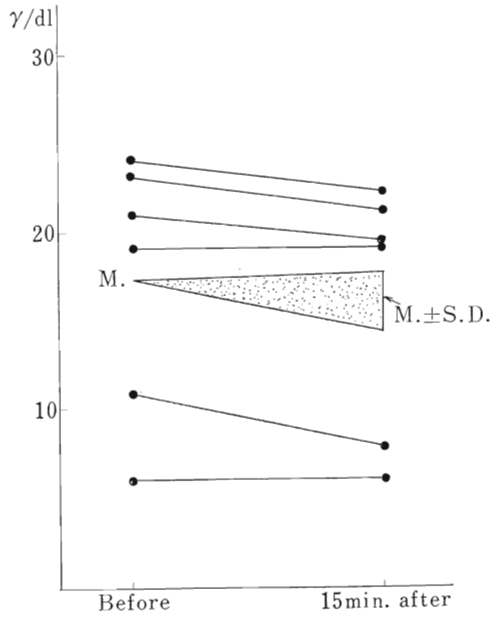

Fig. 5. Plasma 11-OHCS concentration without stimulation.

Table 2. Plasma 11-OHCS concentration (γ/dl) without stimulation

Case	Name	Age	Sex	Before	After	Differ.	Rate (%)
1	K.Y.	19	M	23.1	21.2	−1.9	− 8
2	Y.M.	23	M	24.1	22.2	−1.9	− 8
3	N.M.	20	F	19.2	19.2	0	0
4	T.O.	22	M	21.0	19.5	−1.5	− 7
5*	K.S.	24	F	10.9	7.8	−3.1	−28
6*	M.M.	50	M	6.1	6.1	0	0
Mean				17.4	16.0	−1.4	− 8 ± 9.4

* Measured between 3–4 p.m.

15.0±3.95, and females 14.5±4.00; by Nielsen[9], 21.4±5.6 (7.00 a.m.) and 13.0±3.3 (9.00 a.m.); by Kurata[13], 11.3±2.6 (9.00 a.m.); by Kunema[22], 13.4±2.7 (8.00 a.m.). The authors obtained the mean plasma 11-OHCS level of 16.9±3.2 μg per 100 ml in 10 healthy subjects.

2. Controls

For control, six persons who were normal otologically and endocrinologically were examined at 15-minute intervals two times a day between 10 and 12.00 a.m. without stimulating the nasopharynx. In this way, the authors could observe the direct influence of the stimulation of the nasopharynx for plasma 11-OHCS, which shows a daily rhythm[18,23] and daily change[14,15,22,23]. The second drawing of the blood was 15 minutes after stimulation, for, as Tanaka[6] reported, the influence of the stimulation of the nasopharynx almost reaches the maximum after 15 minutes. The authors obtained the same results as shown in Fig. 4.

The results of the control are shown in Fig. 5 and Table 2. The mean rate of increase is −8±9.4%. In other words, the plasma 11-OHCS in the morning never increases, hardly changing or decreasing a little without the nasopharynx being stimulated.

3. Results

The level of the plasma 11-OHCS shows no change for 15 or 20 minutes when the nasopharynx is not stimulated. On the contrary the authors examined the plasma 11-OHCS change in 53 patients with nasopharyngitis just before the stimulation and 15 minutes after that.

The results are shown in Table 3 and Fig. 6. The increase rate was calculated and shown in Fig. 7. The rate of increase is from −75% to 220%. Thus the reaction of plasma 11-OHCS is varied, but the authors can find some regularity in them. Between nasopharyngitis without complications (the authors call this "nasopharyngitis simplex") and that with complications of nasal allergy and steroid-treated patients of long term the

Table 3. Results

Case	Name	Age	Sex	Nasopharynx		Plasma 11-OHCS (γ/dl)		
				Pain	Bleeding	Before	After	Change
1	T.H.	42	F	+	−	16.7	19.2	15%
2	H.H.	25	M	+	−	20.2	20.2	0
3	M.G.	20	F	++	−	19.0	28.5	50
4	Y.K.	29	F	+	−	34.6	23.1	−33
5	K.S.	27	F	+	−	25.8	22.8	−12
6	K.T.	28	M	++	±	14.2	20.2	41
7	S.W.	28	M	++	+	15.3	21.4	40
8	W.T.	33	F	++	+	11.5	18.3	59
9	Y.S.	19	M	++	+	13.0	20.4	57
10	T.O.	58	F	++	++	10.0	14.0	40
11	Y.H.	20	F	+	−	20.0	23.5	18
12	K.Y.	19	M	+	−	15.0	16.7	11
13	Y.S.	16	F	+	±	10.4	13.5	30
14	E.K.	20	F	++	+	13.0	18.0	39
15	Y.T.	58	F	++	++	6.1	19.5	220
16	I.S.	29	M	+	±	17.5	17.5	0
17	Y.T.	28	M	++	+	19.4	29.0	50
18	T.W.	20	F	++	+	30.8	28.9	− 6
19	N.K.	38	M	++	++	13.0	21.0	62
20	K.T.	32	M	+	−	24.0	12.0	−50
21	M.I.	26	M	±	−	19.7	19.7	0
22	H.A.	45	F	++	++	15.0	27.5	83
23	M.S.	46	F	+	+	18.0	22.0	22
24	T.Y.	51	M	+	−	18.3	22.1	21
25	K.O.	26	F	+	−	22.1	29.8	35
26	N.M.	62	F	++	+	23.4	30.0	28
27	M.S.	53	F	+	−	27.5	30.0	9
28	G.G.	18	M	+	−	32.5	27.5	−15
29	M.Y.	52	M	++	++	18.8	43.8	133
30	T.T.	42	M	++	−	25.5	40.0	57
31	H.H.	41	F	+	−	16.4	20.0	22
32	Y.N.	33	F	++	−	14.6	14.6	0
33	H.M.	41	M	++	−	33.3	12.5	−65
34	J.M.	33	F	++	++	7.1	10.8	52
35	A.K.	31	M	++	+	13.4	12.5	− 7
36	H.M.	12	F	++	++	20.0	5.0	−75
37	T.F.	49	F	+	±	11.0	11.0	0
38	Y.T.	58	F	++	++	15.0	22.5	50
39	M.N.	38	M	++	+	27.5	33.5	22
40	H.S.	16	F	+	−	20.7	10.3	−50
41	K.K.	40	F	+	−	32.5	37.5	15
42	K.A.	38	M	+	−	31.4	33.0	5
43	K.H.	56	M	+	+	33.3	29.7	−11
44	Y.N.	8	F	++	++	18.6	30.0	60
45	T.W.	20	F	++	−	21.9	26.0	19
46	K.O.	38	M	+	+	18.3	22.5	23
47	T.O.	40	F	+	+	18.3	18.3	0
48	M.M.	57	F	++	++	14.8	21.3	44
49	M.I.	26	M	±	−	19.7	19.7	0
50	M.Y.	52	F	++	++	22.2	38.8	75
51	H.N.	16	M	++	+	16.0	23.0	40
52	Y.K.	30	F	+	−	22.5	27.5	22
53	M.K.	32	F	++	++	16.7	22.9	37

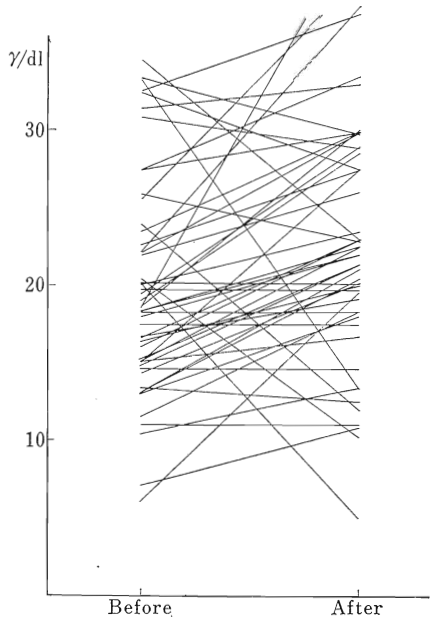

Fig. 6. Plasma 11-OHCS after stimulation of nasopharynx (53 cases).

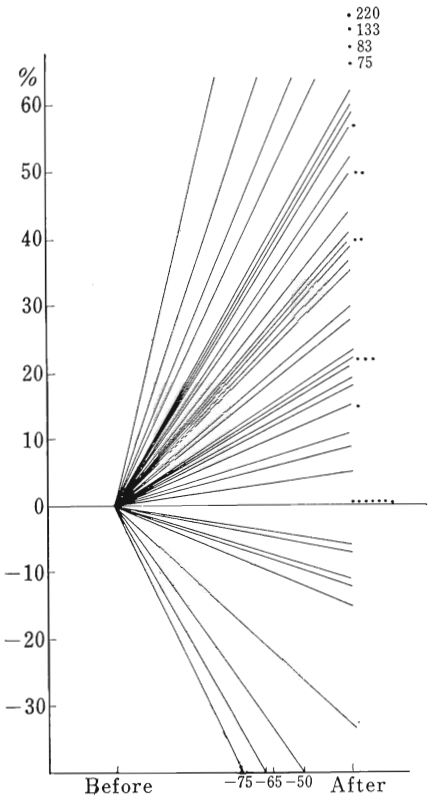

Fig. 7. Plasma 11-OHCS after stimulation of nasopharynx (53 cases).

reaction is apparently different.

In nasopharyngitis simplex the level of the plasma 11-OHCS is apt to increase after the stimulation and in nasal allergy and steroid-treated patients it is apt to decrease after the stimulation. In nasopharyngitis simplex, in 32 of 35 cases (91.4%) it increased and in 22 cases of these 32 cases (62.9%) it increased more than 30% (Fig. 8).

In nasal allergy, in 9 of 12 cases (75.0%) it decreased or remained unchanged and in 5 of 6 steroid-treated patients (83.3%) it decreased or remained unchanged (Fig. 9). The rate of increase after the nasopharynx stimulation and the frequency are shown in Fig. 10. Nasopharyngitis simplex inclines to the right and the nasal allergy and the steroid group incline to the left.

In nasopharyngitis simplex, the increase rate of plasma 11-OHCS is different according to the case. On this point, the authors examined the

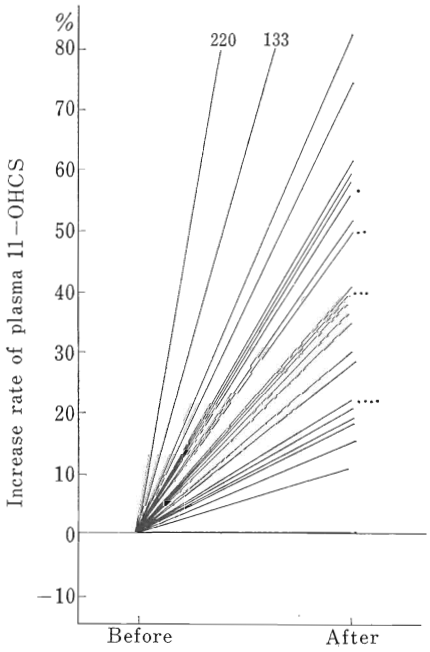

Fig. 8. Nasopharyngitis simplex (35 cases).

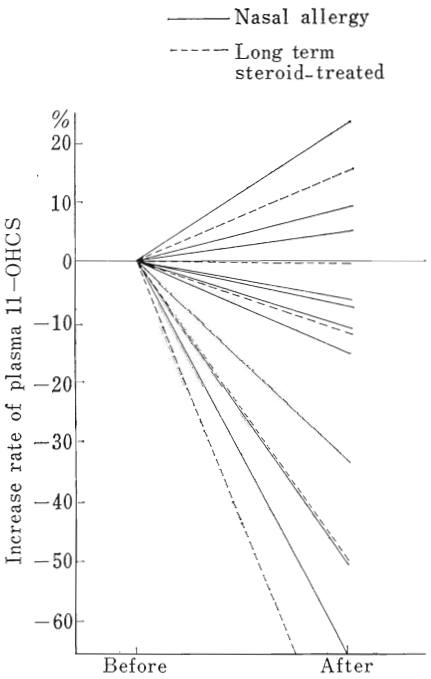

Fig. 9. Nasal allergy and long term steroid-treated cases (18 cases).

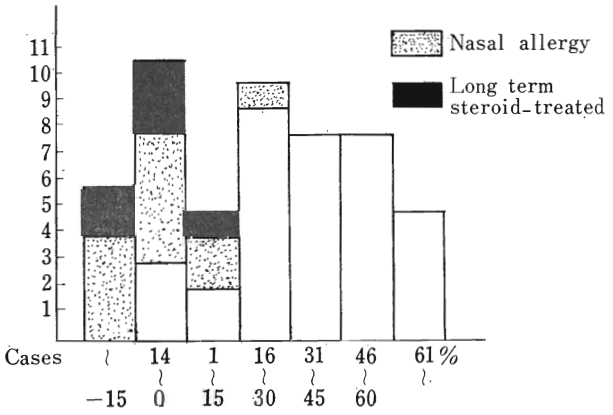

Fig. 10. Plasma 11-OHCS increase rate and frequency.

degree of inflammation of the nasopharynx of all patients and found a correlation between the degree of inflammation and the degree of the increase rate. The authors classified the grade of inflammation into three

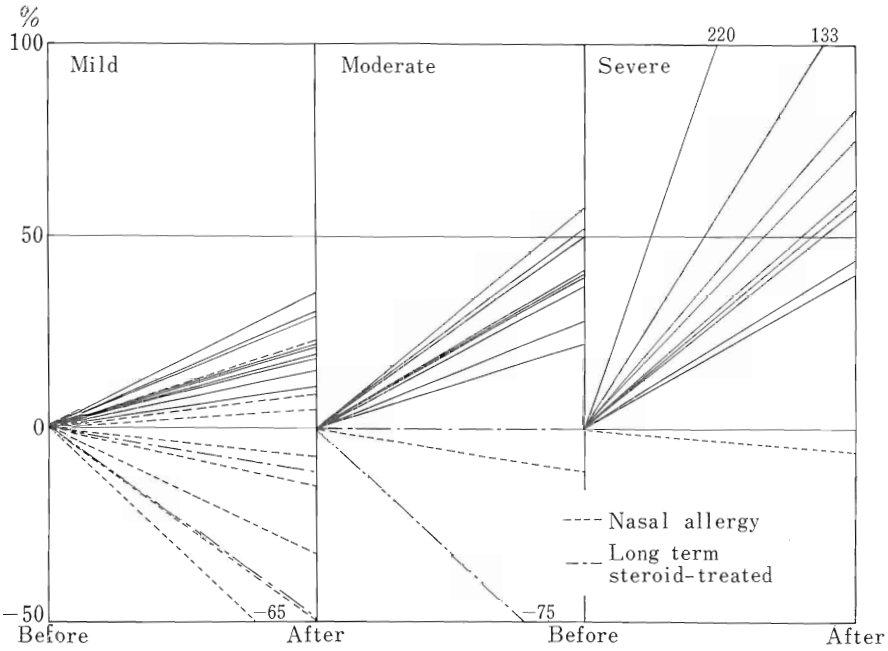

Fig. 11. Degree of inflammation of nasopharynx and increase rate of plasma 11-OHCS.

Table 4. Mild cases

Case	Name	Age	Sex	Before	After	Differ.	Rate (%)	Pain	Bleeding
1	T.H.	42	F	16.7	19.2	2.4	15	+	−
2	H.H.	25	M	20.2	20.2	0	0	+	−
3	Y.H.	20	F	20.0	23.5	3.5	18	+	−
4	K.Y.	19	M	15.0	16.7	1.7	11	+	−
5	Y.S.	16	F	10.4	13.5	3.1	30	+	±
6	M.S.	46	F	18.0	22.0	4.0	22	+	+
7	T.Y.	51	M	18.3	22.1	3.8	21	+	−
8	K.O.	26	F	22.1	29.8	7.7	35	+	−
9	H.H.	41	F	16.4	20.0	3.6	22	+	−
10	Y.N.	33	F	14.6	14.6	0	0	++	−
11	T.F.	49	F	11.0	11.0	0	0	+	±
12	T.W.	20	F	21.9	26.0	4.1	19	++	−
13	Y.K.	30	F	22.5	27.5	5.0	22	+	−
				17.5	20.5	3.0	17 ±10.7		

groups, mild, moderate and severe, as shown in Table 1.

The mean increase rates were: mild, 17±10.7% (n=13); moderate, 42±9.8% (n=12), and severe, 83±51.9% (n=10). In nasopharyngitis sim-

Table 5. Moderate cases

Case	Name	Age	Sex	Before	After	Differ.	Rate (%)	Pain	Bleeding
1	M.G.	20	F	19.0	28.5	9.5	50	++	−
2	K.T.	28	M	14.2	20.2	6.0	41	++	±
3	S.W.	28	M	15.3	21.4	6.1	40	++	+
4	E.K.	20	F	13.0	18.0	5.0	39	++	+
5	Y.T.	28	M	19.4	29.0	9.6	50	++	+
6	T.T.	42	M	25.5	40.0	14.5	57	++	−
7	N.M.	62	F	23.4	30.0	6.4	28	++	+
8	J.M.	33	F	7.1	10.8	3.7	52	++	++
9	Y.T.	58	F	15.0	22.5	7.5	50	++	++
10	M.N.	38	M	27.5	33.5	6.0	22	++	+
11	H.M.	16	M	16.0	23.0	7.0	40	++	+
12	M.K.	32	F	16.7	22.9	6.2	37	++	++
				17.7	25.0	7.3	42 ± 9.8		

Table 6. Severe cases

Case	Name	Age	Sex	Before	After	Differ.	Rate (%)	Pain	Bleeding
1	W.T.	33	F	11.5	18.3	6.8	59	++	+
2	Y.S.	19	M	13.0	20.4	7.4	57	++	+
3	T.O.	58	F	10.0	14.0	4.0	40	++	++
4	Y.T.	58	F	6.1	19.5	13.4	220	+++	+++
5	N.K.	38	M	13.0	21.0	8.0	62	++	++
6	H.A.	45	F	15.0	27.5	12.5	83	++	++
7	M.Y.	52	M	18.8	43.8	25.0	133	+++	+++
8	Y.N.	8	F	18.6	30.0	11.4	60	++	++
9	M.M.	57	F	14.8	21.3	6.5	44	++	++
10	M.Y.	52	F	22.2	38.8	16.6	75	++	++
				14.3	25.5	11.2	83 ±51.9		

plex the increase rate of plasma 11-OHCS after the stimulation seems to be in proportion to the degree of the inflammation.

In nasal allergy the rate was −13±7.6% and in the steroid group it was −17±31.8%. In both of these the plasma 11-OHCS did not increase so much even in the case with a complication of severe nasopharyngitis. No correlation was observed in these cases between the inflammation and the increase rate of plasma 11-OHCS. Fig. 11 shows the relation between the increase rate of plasma 11-OHCS and the degree of inflammation in all of the 53 patients.

4. Specificity of the stimulation of the nasopharynx

Table 7.

(a) Nasal allergy

Case	Name	Age	Sex	Before	After	Differ.	Rate (%)	Pain	Bleeding
1	Y.K.	29	F	34.6	23.1	−11.5	−33	+	−
2	I.S.	29	M	17.5	17.5	0	0	+	±
3	T.W.	20	F	30.8	28.9	− 1.9	− 6	++	+
4	K.T.	32	M	24.0	12.0	−12.0	−50	+	−
5	M.I.	26	M	19.7	19.7	0	0	±	−
6	M.S.	53	F	27.5	30.0	2.5	9	+	−
7	G.G.	18	M	32.5	27.5	− 5.0	−15	+	−
8	H.M.	41	M	33.3	12.5	−20.8	−65	++	−
9	A.K.	31	M	13.4	12.5	− 0.9	− 7	++	+
10	K.A.	38	M	31.4	33.0	1.6	5	+	−
11	K.H.	56	M	33.3	29.7	− 3.6	−11	+	+
12	K.O.	38	M	18.3	22.5	4.2	23	+	+
				22.8	18.9	− 3.9	−13 ± 7.6		

(b) Long term steroid-treated

Case	Name	Age	Sex	Before	After	Differ.	Rate (%)	Pain	Bleeding
1	K.S.	27	F	25.8	22.8	− 3.0	−12	+	−
2	M.I.	26	M	19.7	19.7	0	0	+	−
3	H.M.	12	F	20.0	5.0	−15.0	−75	++	++
4	H.S.	16	F	20.7	10.3	−10.4	−50	+	−
5	K.K.	40	F	32.5	37.5	5.0	15	+	−
6	T.O.	40	F	18.3	18.3	0	0	+	+
				22.8	18.9	− 3.9	−17 ±31.8		

Is the increase of plasma 11-OHCS level caused by the stress of touch-pain or some specific factor of the nasopharynx besides the stress of pain? The authors carried out the following experiments to study this. The first was to study the painful effect of gauze changing at the beginning part of the post-operative period of chronic otitis media and the second after tonsillectomy, both under local and general anaesthesia (Table 8).

During the painful stage after the operation on the ear the increase rate of plasma 11-OHCS (from before the operation to 5 minutes after changing the gauze) was 5±33.8% (n=4), the maximum rate being only 34%. The most painful cases were chosen for the study. In contrast with this the stimulation of the nasopharynx with inflammation increased the plasma 11-OHCS to more than 40% in 18 of 35 cases (51.4%), the increase rate at the time of gauze changing being definitely small.

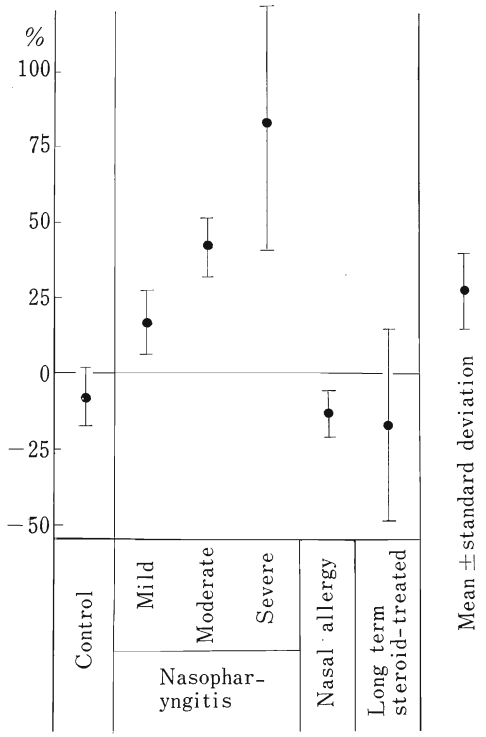

Fig. 12. Increase rate of plasma 11-OHCS in nasopharyngitis and others.

With tonsillectomy under local anaesthesia the alteration in the plasma 11-OHCS (from 10 minutes before operation to 10 minutes after operation) was 6.3±14.1% (N=3). This was unexpectedly low as compared with that by the stimulation of the nasopharynx. By tonsillectomy under general anaesthesia the alteration (from 5 minutes before operation to immediately after operation) was 34.7±25.0% (n=7). This means that under general anaesthesia when one is definitely free of pain, plasma 11-OHCS increases after the operation due to the stress caused by the operation.

Since the tonsil and nasopharynx are closely related physiologically, anatomically and pathogenetically, the authors consider that the factor which increases the plasma 11-OHCS during the operation without pain perhaps plays an important role in the increase of plasma 11-OHCS after the stimulation of the nasopharynx. In connection with this, the reaction in the case of nasal allergy is very interesting. In spite of the presence of severe nasopharyngitis, in 9 of 12 cases of nasal allegy the stimulation of the nasopharynx acts "negatively" on plasma 11-OHCS. Accordingly, in

Table 8. Results of control study

Case	Age	Sex	Plasma 11-OHCS (γ/dl)			Rate (%)	Treatment or operation
			Control	After	Differ.		
1	19	M	12.1	14.7	2.6	21	Gauze changing after radical operation of ear
2	25	M	26.0	13.0	−13.0	−50	,,
3	20	M	15.2	17.6	2.4	16	,,
4	20	F	6.5	8.7	2.2	34	,,
5	37	M	25.0	30.0	5.0	20	Tonsillectomy under local anaesthesia
6	20	F	32.3	28.2	− 4.1	−13	,,
7	32	M	26.5	29.8	3.3	12	,,
8	30	F	28.1	34.8	6.7	24	Tonsillectomy under general anaesthesia
9	26	M	23.9	38.1	14.2	54	,,
10	5	F	21.4	30.4	9.0	42	,,
11	20	M	21.4	23.7	2.3	10	,,
12	6	F	23.6	36.7	13.1	24	,,
13	16	F	17.7	32.3	15.6	83	,,
14	8	F	25.8	27.2	1.4	6	,,

Table 9. Change of increase rate of plasma 11-OHCS and the course of nasopharyngitis

Case	Name	Age	Sex	Increase rate		Course of nasopharyngitis	Duration	
				Before	After			
1	Y.K.	29	F	−33	−13	Mo→Mi	2 m	NA
2	T.Y.	51	M	0	17	Mi→C	1 m	
3	S.W.	28	M	40	33	Mo→Mi	2 m	
4	Y.T.	58	F	220	50	S →Mo	1 m	
5	T.T.	42	M	57	0	Mo→C	3 m	
6	Y.K.	29	F	−13	22	Mi→C	5 m	NA
7	H.A.	45	F	83	50	S →Mo	1 m	
8	M.Y.	52	M	133	75	S →Mo	1 m	
9	H.M.	13	F	−75	41	S →Mi	2.5m	St
10	Y.N.	8	F	60	23	S →Mi	1 m	
11	Y.N.	8	F	23	− 5	Mi→C	1.5m	
12	Y.I.	27	F	33	0	Mi→C	1 m	
13	Y.K.	29	F	63	22	S →C	1.5m	
14	S.S.	20	M	59	0	S →C	5 m	
15	Y.S.	16	F	30	25	Mi→C	2 m	
16	M.S.	53	F	9	27	Mi→C	5 m	NA
17	T.W.	20	F	− 6	19	Mo→Mi	2 m	NA

Mi: Mild, Mo: Moderate, S: Severe, C: Cured,
NA: Nasal allergy, St: Long term steroid-treated

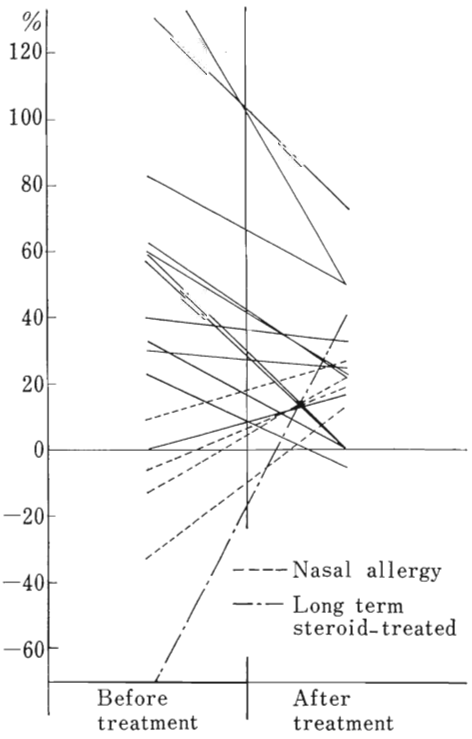

Fig. 13. Change of increase rate of plasma 11-OHCS through the course of nasopharyngitis.

nasal allergy, even in the case of severe nasopharyngitis with a strong touch-pain, in most cases the plasma 11-OHCS rarely increases. From the facts mentioned above, the stimulation of the nasopharynx seems to have a specific influence, other than the pain stimulus, on the plasma 11-OHCS.

5. Change of increase rate of plasma 11-OHCS during the course of nasopharyngitis

In contrast to the increase rate of 11-OHCS at the time of the first visit to the authors' clinic, it was measured in 16 of 53 patients two or more times during the course of nasopharyngitis (Table 9 and Fig. 13). In 6 of 11 patients with nasopharyngitis simplex, the plasma 11-OHCS increase rate decreased from high to low, with a corresponding improvement of nasopharyngitis. In 5 patients there was no decrease in the increase rate. These patients were all mild cases of nasopharyngitis and the increase rate did not seem to reflect the minute change in the inflammation.

In nasal allergy, the 11-OHCS was observed to increase to the normal level from "negative". In four of 5 cases it was at first less than 0%. It

was observed that "negative" became "positive" as the nasopharyngitis improved. This, the authors think, suggests that treatment of nasopharyngitis influences greatly the nasal allergy.

The plasma 11-OHCS increase rate after the stimulation of the nasopharynx after healing is shown in Fig. 13. In ten of 16 cases (62.5%) it is concentrated between 0 and 25%. It is considered that plasma 11-OHCS secretion became normal as the nasopharyngitis became cured or improved. One case of long-treated steroid patient also became "positive" from "negative".

6. Cases

A few typical cases are shown.

Case 1. Y.N. age 8, female (Fig. 14)

Chief complaint: Attack of dizziness.

Diagnosis: Orthostatic dystonia (O.D.) and subacute nasopharyngitis.

History of disease: Five years ago she felt dizzy in the morning and could not stand up. She laid in bed for three days and then was taken to a hospital where she was diagnosed as hypotension. Electroencephalogram, electrocardiogram and blood examination were performed but no abnormal

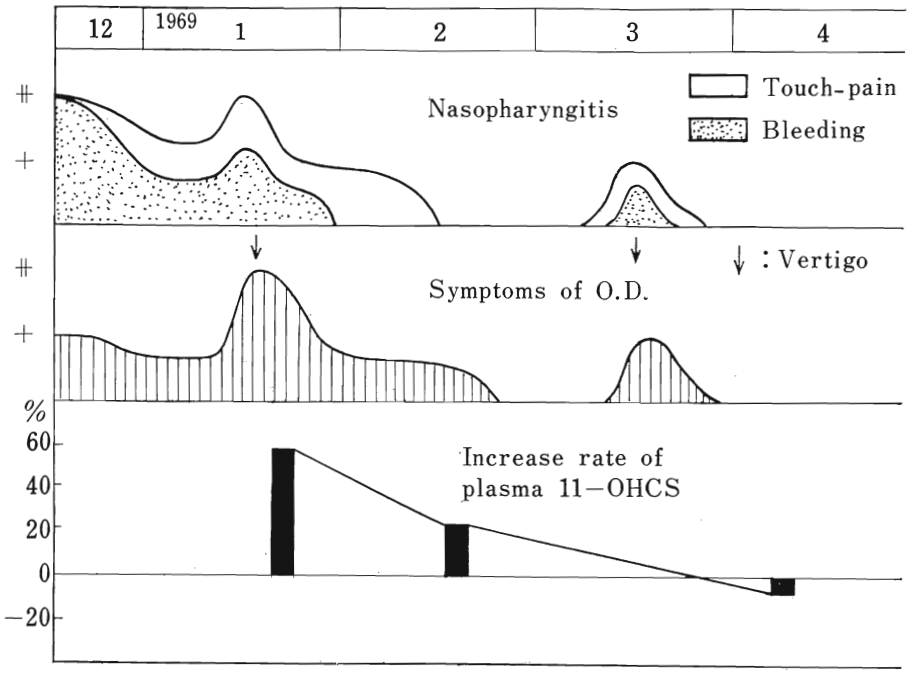

Fig. 14. Nasopharyngitis simplex (Case 1). Y.N. age 8, female: Orthostatic dysregulation (O.D.).

findings were found.

She did not feel abnormal thereafter, but there were attacks of dizziness once in three months. Since two years ago the attack of dizziness appeared once in two months. She came to the authors' clinic at the end of December in 1968. Hearing and vestibular function tests revealed normal findings. The findings of the nasopharynx revealed very marked touch-pain in the nasopharynx, and bleeding and smear examination revealed many desquamated epithelial cells, many white blood cells and red blood cells. She was diagnosed as subacute nasopharyngitis.

Course: Only the nasopharyngeal treatment with 1% $ZnCl_2$ was carried out on her consecutive days. Ten days after the beginning of treatment, the first attack of dizziness appeared. The attack subsided after three days by staying in bed quietly. Immediately after this attack the plasma 11-OHCS was measured. The pre-stimulation value was 18.6 γ/dl and the value of 15 minutes after the stimulation was 30.0 γ/dl (increase rate 60%). Aggravation of the nasopharynx was observed clinically and by smear examination. After the first attack of dizziness treatment of the nasopharynx was continued everyday.

The second examination was made 30 days after the first attack. The value before the stimulation was 16.0 γ/dl and 19.7 γ/dl (23%) after the stimulation. This may mean that her nasopharyngitis became better. In the middle of March, the second attack of dizziness occurred. The duration of this attack was three days but her condition was better than that of the first attack. She could stand up and walk on the second and third day. Soon after this attack, her facial complexion improved and she hardly caught cold.

At the beginning of April, touch-pain in the nasopharynx almost disappeared without bleeding. The third test showed a pre-stimulation value of 27.4 γ/dl and a post-stimulation value of 25.9 γ/dl (−5%). In this case, 3 measurements were carried out through the course of her disease. There seemed to be a correlation between the degree of nasopharyngitis and that of the increase rate of plasma 11-OHCS. It seemed that in this case the increase rate of plasma 11-OHCS became 0% or nearly 0% after the disappearance of nasopharyngitis.

Case 2. Y.K. age 29, female (Fig. 15)

Chief complaints: Water-like nasal discharge, sneezing and diarrhea.

Diagnosis: Nasal allergy, allergic diarrhea, subacute nasopharyngitis.

History: She had been troubled with attacks of sneezing and water-like hyperrhinorrhea in the mornings and evenings and when entering an air-conditioned room. She had a tendency to have loose bowels when eating

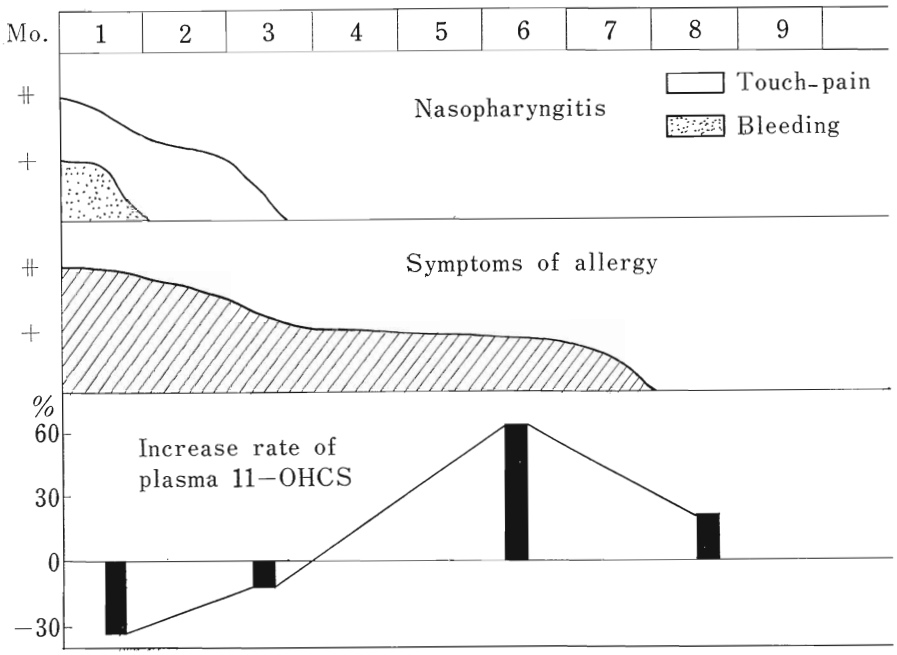

Fig. 15. Case of nasal allergy (Case 2). Y. K. age 29, female: Nasal allergy.

oranges, "soba", milk or chocolate. She had often felt dizzy when standing up and easily had car sickness. She visited the authors' clinic in March, 1967. Intradermal skin tests (house dust, several pollens, etc.) were negative. Nasopharynx findings were touch-pain (++) and bleeding (+). Smear examination showed desquamated epithelial cells, moderate deformation of the cells, many white blood cells, lymphocytes and red blood cells.

Course: Treatment of the nasopharynx with 1% $ZnCl_2$ was performed without combining any other therapy. At the time of the first visit the plasma 11-OHCS levels before the stimulation were 34.6 γ/dl and 23.1 γ/dl 15 minutes after stimulation and the increase rate was −33%. After therapy every other day for 3 months, her rhinorrhea and sneezing became better. Two months after when she got better, the second test for plasma 11-OHCS was performed, showing a pre-stimulation value of 37.5, a post-stimulation value of 32.5 and an increase rate of −13%.

Four or 6 months after, she became free of giddiness and car sickness. Then the third test was performed which revealed a pre-stimulation value of 12.0, post-stimulation value of 19.9 and an increase rate of 63%. The reaction of her plasma 11-OHCS had been negative for 6 months and this time it became positive, observing a "positive conversion phenomenon".

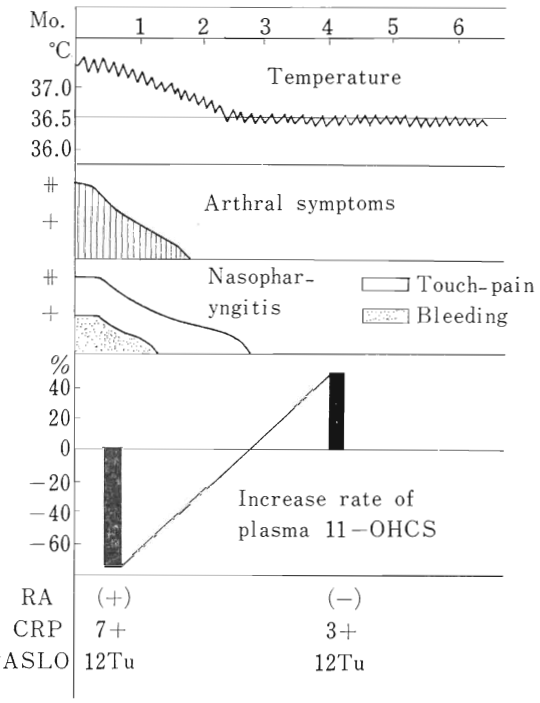

Fig. 16. Long term steroid-treated (Case 3). H. M. age 12, female: Rheumatoid arthritis.

On the 8th month her nasopharyngitis almost disappeared clinically and cytologically. The fourth test was performed and showed a pre-stimulation value of 22.5, post-stimulation value of 27.5 and an increase rate of 22%. About this time her diarrhea became better and the nasal allergy had almost disappeared. This was a typical case of nasal allergy which was cured only by the treatment of the nasopharynx every other day for almost 8 months and later two times a week.

During the course, the increase rate of plasma 11-OHCS changed from "negative" to "positive" after 6 months of treatment. Two months after that it was confirmed that the increase rate was "positive", but at present no adequate explanation can be made about the difference in the increase rate (63%→22%).

Case 3. Y.M. age 12, female (Fig. 16)

Chief complaints: Slight fever and arthralgia.

Diagnosis: Rheumatic arthritis and subacute nasopharyngitis.

History: Since from about the age of 5 years, she occasionally had a high fever of ca. 40°C. and became thin gradually. Two years ago she had a

pain and swelling in both ankle joints and knee joints. She visited a pediatrics clinic and was diagnosed as juvenile rheumatic arthritis. She was prescribed adrenocortical steroid for a long time, but her symptoms of arthritis and fever did not necessarily become well. She visited the authors' clinic with a moon-face, the side effect of steroids. She had tenderness in both ankles and knee joints and swelling was observed.

X-ray examination of the joints showed a picture of Steinbrocker grade II.

Fever, 37.5°C.; blood sedimentation rate, 15 mm/1 hour; serum R.A. (+); C.R.P., 7 (+); ASLO, 12 Todd units; plasma 11-OHCS, 20 γ/dl and 5 γ/dl after stimulation; and increase rate, −75%.

Course: Only the treatment of nasopharyngitis was done without combination of any other therapy including steroid hormone. Bleeding after treatment disappeared after less than one month by treatment every other day.

One and a half months afterwards the arthralgia almost vanished. After two months, the touch-pain in the nasopharynx disappeared. At almost the same time slight fever, which had continued obstinately, decreased to 36.5°C. from 37.5°C. when the serological examination revealed and ASLO 12 Todd units. The plasma 11-OHCS (##) R.A. (−), C.R.P. level showed a pre-stimulation value of 13.2, post-stimulation value of 18.6 and an increase rate of 41%.

After three months of treatment of nasopharyngitis with 1% $ZnCl_2$ solution, her moon-face, which was present when she visited the authors' clinic the first time due to the long use of steroids, disappeared and signs of arthritis vanished strikingly. In the course of 3 months, the plasma 11-OHCS increase rate, which had been "negative" originally, became "positive" by the stimulation of the nasopharynx. This "positive conversion phenomenon" seems to imply that the "negative", which is caused by the long use of steroid, tends to become "positive", which seems to be the normal reaction during stress, by activating the adreno-cortical function by the treatment of the nasopharynx.

Discussion

It has been already clarified by many senior staff members of the authors' department that most cases of nasal allergy and rheumatism are complicated by severe nasopharyngitis and these become cured or better only by the nasopharyngeal treatment by applying a 1% $ZnCl_2$ solution, as the nasopharyngitis heals. As for the mechanism, it might be considered

that the nasopharyngeal stimulation or treatment should show some influence on the secretion of adrenocortical hormone. The authors speculated that the stimulation of the nasopharynx might have an influence on the adrenocortical system or have the same effect as ACTH, and the authors examined the relation between the stimulation of the nasopharynx and the change in the plasma adrenocortical hormone levels.

As for the methods to examine the secretion of adrenocortical hormone, measurement of the urinary 17-KS, 17-OHCS, 17-KGS and plasma 17-OHCS and 11-OHCS have been used[11]. Urinary steroid determination requires collection of 24-hour urine, and it is inadequate to observe the minute changes before and after stimulation. Plasma 17-OHCS determination requires 15–20 ml of blood and the procedure is complicated and requires much time. Plasma 11-OHCS determination is almost the only method to examine the influence of nasopharyngeal stimulation.

The plasma adrenocortical hormone concentration changes easily and there is a diurnal rhythm[18,23] and daily difference[14,15,22,23]. The authors confirmed that the plasma 11-OHCS concentration does not change in 15 minutes if the nasopharyngeal stimulation is not done. When the nasopharynx was stimulated with a 1% $ZnCl_2$ solution in patients with nasopharyngitis, in 37 of 53 cases (70%) the plasma 11-OHCS concentration increased during the interval of 15 minutes. In 32 of the 35 cases (91%) with nasopharyngitis simplex which had no complications the concentrations increased from 220% to 20%. In other words, by the stimulation of the nasopharynx 11-OHCS is secreted into the blood. The secretion of plasma 11-OHCS seems to depend upon the degree of the inflammation (Fig. 11).

The plasma 11-OHCS increase rate tends to near a certain range in the course of nasopharyngitis. In contrast to nasopharyngitis simplex, in nasal allergy and the steroid-treated group the plasma 11-OHCS rather decreased after the stimulation. How does the stimulation of the nasopharynx influence the level of plasma 11-OHCS? Sever inflammation increases the level of plasma 11-OHCS and a strong pain is felt, when the nasopharynx is touched. But the great increase in the plasma 11-OHCS is not necessarily brought by only the pain in the nasopharynx. For instance, in nasal allergy the plasma 11-OHCS concentration does not increase even if the touch-pain is great. When changing the gauze in the case of the radical operation of otitis media, which seems to show a severe pain, the plasma 11-OHCS concentration increases far less than when stimulating the nasopharynx. In tonsillectomy under general anaesthesia, when pain is not felt at all, the post-operative value is clearly higher than the pre-opera-

tive value[26]. This increase is caused not by the pain but by the surgical invasion or the so-called "stress".

Tonsil and nasopharynx are closely related anatomically, physiologically and pathogrenetically. Therefore, "the factor increasing the plasma 11-OHCS without pain" seems to be very important also in the case of the stimulation of the nasopharynx. In consideration of the facts mentioned above, the chief factor which increases the plasma 11-OHCS by the stimulation of the nasopharynx is not necessarily the stress caused by pain but by the specific sensitivity of the nasopharynx.

As for the adrenocortical function in nasal allergy, Sekiya (1965) reported a mean plasma 11-OHCS value of 11.5 γ/dl in 15 cases of nasal allergy and stated it was rather low compared with the normal. On the other hand, Robson[24] determined the plasma 11-OHCS in 34 patients with asthma and obtained a rather high value (16.4±6.20) compared to the normal subjects (13.0±4.41).

In allergy, the plasma 11-OHCS concentration was quite abnormal when it was determined just before and after the stimulation of the nasopharynx. As shown in Fig. 9, the post-stimulation value did not increase in nasal allergy, even when severe nasopharyngitis was present. The same phenomenon was observed in long-term steroid-treated patients. These cases, however, were observed to show a normal pattern in accordance with the recovery of the original disease by the treatment of nasopharyngitis. It other words, as Vaccarezza[9], Robson[24] and Sundberg[25] reported, in the case of allergy, adrenocortical dysfunction becomes clearer when a stimulation, for example ACTH test,, nasopharyngeal stimulation, etc. is given. Robson reported that the plasma 11-OHCS was rather lower in 34 patients with asthma, than in the normal subjects but after the injection of ACTH the reaction was apparently lower than in the normal. Sundberg had 24 patients with allergy take a Finnish sauna bath and obtained an unreactive value of urinary 17-OHCS which was lower than in the normal persons who showed reactions after bathing.

The authors' examination showed that in 12 cases with nasal allergy 9 cases (75%) showed a lower plasma 11-OHCS concentration after the stimulation of the nasopharynx than before stimulation (negative). This seems to reflect the adrenocortical dysfunction, which agrees with the interpretation of Robson and Sundberg et al. A phenomenon was discovered that cases which had been "negative" at first changed to "positive" gradually as the nasopharyngitis improved. This was observed both in the nasal allergy and in the steroid-treated group, and the authors called this the "positive conversion phenomenon".

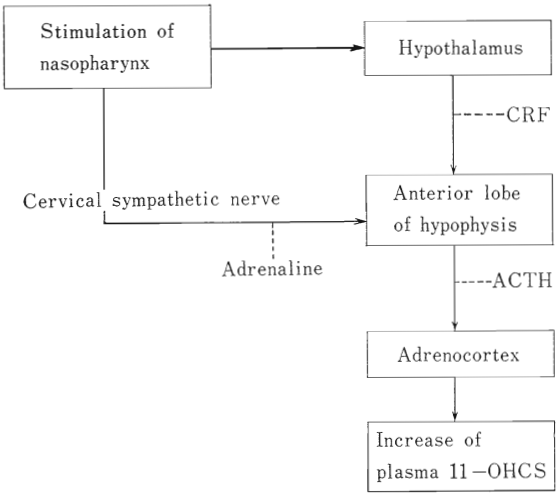

Fig. 17. Mechanism of secretion of plasma 11-OHCS after nasopharyngeal stimulation.

As for the mechanism of the increase of plasma 11-OHCS by stimulation of the nasopharynx, the authors infer from knowledge which is known and believed widely that by the stimulation of the nasopharynx the hypothalamus is stimulated directly, and the CRF (corticotrophin-releasing factor) is secreted, and this enters the hypophyseal portal system at the median eminence. Then ACTH is secreted into the blood when the CRF reaches the anterior lobe of the pituitary. By the increase of the ACTH adrenocortical hormone in the blood, it is known that there is an increase in the plasma 11-OHCS. Fig. 17 shows the schema of what was mentioned above. As the effect of nasopharyngeal treatment, Harada[7] found improvement in the autonomic nerve disturbances, Tanaka[8] and Ichikawa reported on the normalization of the plasma fibrinolytic system, and Takayama discovered the immunological improvement. In order ot understand the fact that nasal allergy, rheumatism and other diseases frequently become cured by the treatment of the nasopharynx, it seems that this endocrinological effect cannot be overlooked.

Conclusion

For the nasal allergy, allergic cutaneous diseases, rheumatism and other diseases, the treatment of the nasopharynx proposed by S. Horiguti is frequently strikingly effective. To clear up a part of the mechanism, the authors tried to elucidate from the point of adrenocortical function using

the method of fluorimetric determination of plasma 11-OHCS which had been developed primarily by De Moor et al. Tests were performed just before and 15 minutes after the stimulation of the nasopharynx and the increase rate was calculated. The following is the summary of the findings:

1. In nasopharyngitis simplex (without complications such as nasal allergy, other rhino-pharyngeal diseases, and steroid-treated cases) 32 of 35 cases (91%) showed an increase after the stimulation.
2. Nasopharyngitis was classified into three groups. The increase rate was observed to agree with the degree of the inflammation of the nasopharynx. Mild cases, 0–30%; moderate cases, 20–50%; and severe cases, 40% or more.
3. In nasal allergy and the steroid-treated cases, the increase rate was negative.
4. The stimulation of the nasopharynx seems to be specific from the results of several studies.
5. With the disappearance of the inflammation, in nasopharyngitis simplex the plasma 11-OHCS increase rate decreased to 0~20% and in the nasal allergy and steroid-treated group it increased to 0~20%.
6. The stimulation or treatment of the nasopharynx was observed to have the effect of stimulating or activating the pituitary-adrenocortical system. Accordingly, the authors think that the treatment of the nasopharynx is an effective therapy where adrenocortical steroid hormone is indicated, such as in allergic diseases and rheumatism.

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