Role of Endocrinological Factors in the Pathogenesis of Idiopathic Edema

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SHIMAMOTO, K., TANAKA, S., ANDO, T., NAKAO, T., NAKAHASHI, Y. and MIYAHARA, M. Role of Endocrinological Factors in the Pathogenesis of Idiopathic Edema. Tohoku J. exp. Med., 1980, 130 (1), 71-78 — In order to investigate the etiology of idiopathic edema, clinical findings and endocrinological abnormalities were analyzed in twenty-seven patients, and the following results were obtained. An easy occurrence of subcutaneous bleeding and positive Rumpel-Leede phenomenon were observed in the majority of the patients. ADH, plasma renin activity and plasma aldosterone concentration in the patients did not show abnormalities following water loading in the supine position when compared with normal controls. But the results obtained in the present study suggested that they might contribute to water and sodium retention in the upright position. In the patients, plasma prolactin levels were not decreased, but rather increased and urinary excretion of kallikrein and kinin was reduced significantly after water loading in the upright position. Thus, prolactin and urinary kallikrein-kinin system might also contribute to water and sodium retention in idiopathic edema, directly or indirectly through the augmentation of the action of ADH and of aldosterone. It was concluded that the increased vascular permeability and endocrinological polyfactors play a role, in a cooperative fashion, in the mechanism of this disease. —— idiopathic edema; ADH; aldosterone; urinary kallikrein-kinin system; prolactin

Idiopathic edema which occurs mostly in females is the pathological state in which the body fluid is retained without cardiac, renal, hepatic or allergic diseases, or hypoalbuminemia.

Regarding the endocrinological factors in the mechanism of this edema, many works on the renin-angiotensin-aldosterone system (Hill et al. 1960; Streeten and Speller 1966; Thorn 1968; Streten et al. 1973; Katz; 1977), antidiuretic hormone (ADH) (Streeten and Speller 1966; Debreceni and Csete 1970; Streten et al. 1973; Edwards and Bayliss 1976), sex steroid hormones (Kuchel et al. 1970; Edwards and Bayliss 1975), and the sympathetic nervous system (Kuchel et al. 1970; Kuchel et al. 1975, 1977) have been reported. However, the role of neurohumoral factors in the development of idiopathic edema has not been established up to the present time.

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Recently, it has been reported that prolactin has water-sodium retaining action (Horrobin et al. 1971; Buckman et al. 1976), and that the renal kallikrein-kinin system has water-diuretic and natriuretic action (Barraclough and Mills 1965; Marin-Grez et al. 1972; Mills et al. 1976).

In this study, the renin-angiotensin-aldosterone system, ADH, prolactin and kallikrein-kinin system were measured in patients with idiopathic edema in order to investigate the role of endocrinological factors in this disease.

**MATERIALS AND METHODS**

In twenty-seven patients with idiopathic edema (26 females and 1 male, age from 20 to 59 years), subjective and objective symptoms were examined. Plasma prolactin (Pr) levels in 11 normal females and 23 patients, blood kinin levels in 6 normal females and 5 patients, and plasma kininogen levels in 10 normal females and 7 patients were determined in the overnight dehydrated state. Urinary kinin excretion in 6 normal males and 6 patients, and urinary kallikrein excretion in 8 normal males and 9 patients were also determined from 24 hr urine samples.

Water loading in a supine position was performed in 8 normal females and 16 patients, and the water loading in an upright position was also done in 10 normal females and 14 patients.

Urine and blood samples were taken from the subjects who were in bed rest for 1 hr in an overnight dehydrated state. And after 20 ml per kg of water were administered orally for 30 min, blood and urine samples were taken until 120 min in a supine or upright position to determine the plasma osmolality, hematocrit value, plasma ADH levels, plasma renin activity (PRA), plasma aldosterone concentration (PAC), plasma Pr levels, blood kinin levels and plasma kininogen levels. In addition, water excretion rate, free water clearance, osmolar clearance, and urinary kallikrein activity were determined in the urine samples before and after the water loading.

Plasma ADH levels (Shimamoto et al. 1976), PRA (Haber's method—Haber et al. 1969—CIS kit), PAC (Dainabot kit) and plasma Pr levels (Daiichi kit) were determined by radioimmunoassay methods.

Plasma kininogen and blood kinin levels (Tanaka et al. 1978), urinary kinin levels (Shimamoto et al. 1978) and urinary kallikrein activity (Nakao et al. 1978) were determined by radioimmunoassay methods which were established in our laboratory.

Plasma osmolality was determined by freezing point determination (Osmette Precision Osmometer, Precision Systems, Framingham, Mass.).

Statistical analysis was performed with Student's t-test for paired and unpaired data.

**RESULTS**

In most patients with idiopathic edema, edema was observed in the face and/or the hands in the morning, and in the legs in the evening.

Edema was not related to the menstrual cycle, which was irregular in 29 per cent of the patients. An increase of the body weight from the morning to the evening was more than 1.2 kg in all patients, and this increase was significantly larger than that in the normal females in whom it was less than 1.0 kg. Personality with nervous character was observed in 70 per cent and systolic blood pressure under 100 mmHg in 22 per cent of the patients. An easy occurrence of subcutaneous bleeding was found in 74 per cent and Rumpel-Leede phenomenon was positive in 71 per cent. In the glucose tolerance test by 50 g O-GTT, 27 per cent of the
patients showed diabetic and 20 per cent borderline pattern.

Water excretion rate after water loading in supine and upright position was 102.6±6.9% (mean±s.e.m.) and 91.1±5.7%, respectively, in the control group, and 94.1±6.2% and 55.5±5.7%, respectively, in the patient group. In upright position, the excretion rate in the latter group was significantly lower, while in the former group no significant difference was observed between the two positions. An increase of free water clearance following water loading in the supine position was 5.7±0.6 ml/min and there was no significant difference when compared with upright position (4.5±0.4 ml/min) in normal females. On the other hand, in the patient group, it was 5.4±0.6 ml/min and 3.3±0.5 ml/min in supine and upright position, respectively, and the latter was significantly lower than the former. An increase of osmolar clearance following water loading was 1.6±0.5 ml/min and 1.2±0.2 ml/min in supine and upright position, respectively, in normal females, and there was no significant difference between the two positions, but was 1.3±0.3 ml/min and 0.4±0.3 ml/min, respectively, in the patient group, and this difference was significant.

Hematocrit values reduced significantly following supine water loading in both the normal and patient group, but there was no difference in the per cent change of blood volume calculated by the change of hematocrit value between the normal (104.6±0.6%) and the patient group (104.0±0.6%). In upright position,

Fig. 1. A: Plasma ADH levels following water loading in supine (upper panel) and upright (lower panel) position in the normal control (○—○) and the patients with idiopathic edema (●—●). *Significantly different from control values. †Significantly different from the corresponding value in the normal persons.

B: Ratio of the changes of plasma ADH levels to the changes of plasma osmolality (ΔADH/ΔOsm) at the time when ADH showed the minimal level after water loading.
Fig. 2. Plasma renin activity and plasma aldosterone concentration following water loading in supine (upper panel) and upright (lower panel) position in the normal control (○—○) and the patients (●—●). *Significantly different from control values. † Significantly different from the corresponding value in the normal persons.

Fig. 3. A: Plasma prolactin levels following water loading in supine (upper panel) and upright (lower panel) position in the normal control (○—○) and the patients (●—●). * Significantly different from control values.

B: Percent changes of plasma prolactin levels at 90 min after water loading to the basal levels.
hematocrit value increased significantly in both groups, and the per cent change of blood volume was significantly lower in the patient group (92.0±0.8%) than in the normal control (95.2±1.0%). Plasma osmolality decreased insignificantly in supine but significantly in upright position following water loading in both groups.

The decrease of plasma ADH levels following water loading in both groups are shown in Fig. 1 (A). In the supine position, there was no significant difference between the two groups, while in the upright position they were significantly higher in the patient group at 30 min after water loading. The ratios of the changes in plasma ADH levels to the changes in plasma osmolality (ΔADH/ΔOsm), at the time when plasma ADH showed the minimal level following water loading, are plotted in Fig. 1 (B). This ratio was significantly lower in the patient group in upright position.

The changes in PRA and PAC following water loading in the supine and upright position in both groups are shown in Fig. 2. PRA in upright position increased in both groups, and this increase was greater in the patient group. Similarly, the increase of PAC in upright position in the patient group was greater than in the control group.

Plasma Pr levels in the overnight dehydrated state were significantly higher in the patient (28.8±2.4 ng/ml) than in the normal group (18.3±1.1 ng/ml). The change of Pr levels following water loading in the supine and upright position was shown in Fig. 3 (A). In the supine position, they decreased significantly in both groups. In the upright position, they decreased significantly in the normal control, while rather increased in the patient group. Per cent change at 90 min after the water loading was shown in Fig. 3 (B). This change was significantly high in the patients as compared with the control in the upright position.

Blood kinin levels in the overnight dehydrated state were 455±142 and 300±
69 pg/ml and plasma kininogen levels were 2.8±0.2 and 2.6±0.3 μg/ml in the control and the patient group, respectively. There were no significant differences in either blood kinin or plasma kininogen level between the two groups.

Urinary kallikrein and kinin excretion were significantly lower in the patient group as shown in Fig. 4. The changes in urinary kallikrein activities following water loading are shown in Fig. 5. In the supine position, they did not change significantly in either group, but the activity was significantly lower both before and after water loading in the patient group. And in the upright position, it was also lower in the patient and was elevated significantly after water loading in the normal control, but not in the patient group.

![Fig. 5. The changes of the urinary kallikrein activity following water loading in supine (left panel) and upright (right panel) position in the normal control and the patients.

- ■, normal control; □, idiopathic edema. * p<0.05, † p<0.01.](image)

**DISCUSSION**

In the present study, it was demonstrated that idiopathic edema was characterized by water retention after water loading in an upright position, and that this retention was due to a reduced augmentation of both free water clearance and osmolar clearance following water loading.

It is worthy of note that subcutaneous bleeding and positive Rumpel-Leede phenomenon, which indicate increased vascular permeability, were found in more than 70% of the patients. This increased permeability might account for the larger reduction of plasma volume in the upright position, resulting in less decrease of ADH and greater increase of PAC, and the higher plasma ADH levels, and PAC might further retain water and sodium mediated through the decrease of free water and osmolar clearance, respectively. Thus, ADH and aldosterone may have some role in the genesis of edema secondarily through increased vascular permeability.

However, since it is well known that neither aldosterone nor ADH administration does induce edema by the so-called escape phenomenon, and that edema is not observed in primary aldosteronism or SIADH, it should be considered that aldosterone or ADH by itself would not cause edema in this disease.
Pathogenesis of Idiopathic Edema

Recently, it has been reported that prolactin has water-sodium retaining action (Horrobin et al. 1971; Buckman et al. 1976) and that the renal kallikrein-kinin system has a water diuretic and natruriuretic action (Barraclough and Mills 1965; Marin-Grez et al. 1972; Mills et al. 1976). In the present investigation, it was demonstrated that plasma prolactin levels were significantly higher and urinary kallikrein and kinin excretion were significantly lower in the patient group. Therefore, an increase of plasma prolactin, and the suppressed renal kallikrein-kinin system may have some role in the etiology of idiopathic edema. Moreover, it has been reported that prolactin restores the aldosterone and ADH actions in the escape state (Burstyn et al. 1972; Horrobin et al. 1973), and the renal kallikrein-kinin system may be related to the escape phenomenon (Carretero and Scicli 1976). Higher plasma ADH levels and aldosterone concentration in the upright position, therefore, may contribute to the development of edema, possibly through hyperprolactinemia and suppression of the renal kallikrein-kinin system.

In conclusion, all the results presented herein may support the idea that the increased vascular permeability and the endocrinological polyfactors are related, in a cooperative fashion, to the etiology of idiopathic edema.

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References


