

## VASCULAR REACTIONS IN HEREDITARY ANGIONEUROTIC EDEMA

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Hereditary angioneurotic edema is a rare condition with typical clinical symptoms and interesting biological abnormalities. One of the best descriptions and a review of the literature are given by Landerman (16). The disease is recognized by a family history of episodic edema of the skin, pharynx, larynx and/or intestines. Involvement of the gut often causes obstruction with vomiting and severe abdominal pain.

Landerman *et al.* reported in 1962 that patients with hereditary angioneurotic edema had a decreased amount of plasma inhibitor of kallikrein (17). The following year Donaldson and Evans (9) showed that they lack the normal plasma inhibitor of C'1 esterase. Kallikrein and C'1 esterase differ in their action and are probably two different substances (15). When injected intradermally in patients with hereditary angioneurotic edema both C'1 esterase and kallikrein produce an increased edematous reaction which does not occur in normal subjects (5, 17). We have found previously that kallikrein injected intradermally in patients with chronic urticaria causes a strongly increased edematous reaction although these patients have normal plasma concentrations of C'1 esterase inhibitor (13).

In the following the clinical picture of hereditary angioneurotic edema in a mother and her daughter will be described. In addition to the symptoms described earlier in this condition both patients often showed

edema of the urinary tract. While trying various treatments we found that certain drugs could provoke the symptoms. Their vascular reactions to kallikrein, bradykinin and histamine were also studied.

### Material and Methods

*Drugs used:* Histamine hydrochloride<sup>1</sup> 0.1 mg/ml, Bradykinin<sup>2</sup> 0.1 mg/ml, and Kallikrein.<sup>3</sup> The dry powder contained kallikrein 40 U, thiomersalsodium 0.02 mg and sodium chloride 3.44 mg and was dissolved in 1 ml of saline.

*Experimental procedure:* Intradermal injections of 0.1 ml of bradykinin, histamine and kallikrein were given on the volar side of the forearm. The area of the erythema and of the wheal with subsequent edematous infiltration was estimated by measuring the diameters and calculating that they were regular ellipses. All measurements were made by the authors at 20 minutes and 1, 2, 5 and 24 hours after the injections. When repeated cutaneous tests were done, care was taken to avoid skin areas used previously. Freshly prepared solutions of kallikrein were used throughout.

### Case Report

#### *Patient A. Female, 49 years*

The patient's grandmother and mother had recurrent attacks of edema in the skin and

<sup>1</sup> Vitrum AB, Stockholm, Sweden.

<sup>2</sup> BRS 640, synthetic bradykinin, kindly supplied by Sandoz, Stockholm.

<sup>3</sup> Padutin®, Bayer AG, Leverkusen, Germany.

larynx. Her mother died from laryngeal obstruction. Since the age of 2 years she has suffered from recurrent episodes of angioneurotic edema of the face and since the age of 14 years also of edema of other skin areas and of the pharynx and larynx. Since the age of 20 she had typical attacks of intestinal obstruction. On suspicion of appendicitis a normal appendix was removed during an attack. There had also been frequent attacks of edema around the urethra with inability to pass urine for 6–18 hours and causing severe pain. On the following days she often had symptoms of infection and frequent urination. Bacteria were found on some occasions. The attacks of swelling in the skin usually started as a numb sensation for 2 to 4 hours followed by circumscribed swelling reaching a peak within 12–16 hours and disappearing within 24–36 hours. There was no or only slight erythema and usually no pruritus. The patient had her attacks several days per month. The first time she was free from edema was during a first pregnancy in 1943. During two later pregnancies she had attacks of the same frequency as usual. It should be noted that her daughter born in 1943 had similar attacks of edema, whereas the children born when she had recurrent attacks during pregnancy are healthy. After the last pregnancy in 1950 she had anemia from loss of blood and was given blood transfusions. After the transfusions she was free from her attacks of swelling for 3–4 months. In 1959 hysterectomy was performed. Histological examination revealed a normal uterus with only a few small myomata. Because of blood loss during the operation repeated blood transfusions were given. Thereafter she was practically free from edema until 1964 when they recurred as before. Apart from the angioneurotic edema she had empyema, mastoiditis and osteitis as a child.

Drugs without certain effect were: Antihistamines, corticosteroids, pituitary implant, desferrioxamine<sup>4</sup> and two pharmacologic inhibitors of bradykinin.<sup>5, 6</sup> Drugs increasing the number and severity of the attacks were: Epsilonaminocaproic acid<sup>7</sup> (E-ACA), 3 g 6 times daily and the active isomer of aminomethyl-cyclohexane-carboxylic acid<sup>8</sup> (AMCA), 0.5 g 4 times daily for 2 weeks. Both epsilonaminocaproic and AMCA are used as inhibitors of fibrinolysis (1, 19). She also became worse after an inhibitor of decarboxylase, NSD-1055<sup>9</sup> 200 mg daily. These drugs were tried with the same results on two occasions and found to induce edema of both skin and gastrointestinal tract.—Pills containing codeine and sulphonamides also produced signs of gastrointestinal edema with vomiting. She developed ordinary acute urticaria from penicillin. The following drugs were found to be of benefit when edema had developed: Epinephrine, ephedrine and Calcium-Sandoz<sup>®</sup> and against abdominal pains spasmolytics. Since the patient became better after blood transfusions she was given fresh plasma 1000 ml daily for 2–3 days. They were given several times since 1966 and have kept her free from symptoms for 1–3 months.

The following laboratory data were recorded: C'1 serum esterase inhibitor 0.3 U/ml (normal value 15–20 U/ml). C'1 serum esterase activity 27–44 U/ml (ATEe technique, normal value 0), C'4 serum 50 U/ml (normal values 1600–32,000 U/ml). After plasma transfusion the C'1 serum esterase inhibitor increased to 11 U/ml and the C'1 serum esterase became normal (0 U/ml). After Trasylol<sup>10</sup> infusion the C'1 inhibitor and esterase activity in serum were unchanged. Other laboratory investigations gave normal results.

<sup>4</sup> Desferan<sup>®</sup>, CIBA, Basel, Switzerland.

<sup>5</sup> 21.401 Ba, CIBA, Basel, Switzerland.

<sup>6</sup> Anginin<sup>®</sup>, Banyu Pharm. Ltd., Tokyo, Japan.

<sup>7</sup> Episkapron<sup>®</sup>, AB Kabi, Stockholm, Sweden.

<sup>8</sup> AMCA, AB Kabi, Stockholm, Sweden.

<sup>9</sup> NSD-1055, Smith.

<sup>10</sup> Trasylol<sup>®</sup>, Bayer, Leverkusen, Germany.

Table 1. Reaction to intradermal injection of kallikrein

		Area of edematous infiltration in mm <sup>2</sup> ± SE of the man				
		20'	1h	2h	5h	24h
Patient A	48 yrs	510	1236	1413	7540	4710
Patient B	25 yrs	153	177	314	1650	3900
Controls	16-30 yrs	104 ± 11	119 ± 25	116 ± 25	316 ± 90	766 ± 158
Controls	>30 yrs	108 ± 16	126 ± 13	199 ± 21	342 ± 59	359 ± 89

*Patient B. Female, 25 years*

She was the daughter of patient A. Since the age of 13 she had edema of the skin and attacks of nausea and abdominal distension with cramping pains followed by vomiting. Appendectomy was performed after one of the first attacks. She also had attacks of edema in larynx, pharynx, urethra and vagina. The urethral edema causes troublesome distension of the bladder for 12-16 hours. By pressing on the abdomen she can squeeze out only a few drops of urine. The vaginal edema had no relation to sexual intercourse or menstrual periods. She usually had symptoms every month but less often than her mother. Swelling in the pharynx was provoked twice when she was operated for a mandibular cyst with complicating osteitis. The week before the edema she is often restless and considers herself aggressive. She was free from edema attacks during a first but not during a second pregnancy in 1967. Because of severe abdominal cramps at the time of delivery a cesarian section was performed. It was noted that the guts were swollen and distended. She lost blood and received several blood transfusions. Thereafter she had no edema for 4 months. The operation wound healed slowly and with suppuration. She also had a severe pneumonia during the same period.

The effect of antihistamines and bradykinin inhibitor was uncertain. Further edema developed after AMCA, NSD-1055 and sulphonamides, like her mother. Best effect was observed after epinephrine or ephedrine and calcium against edema and of spasmolytics against abdominal cramps.

The following laboratory findings were

made: C'1 esterase inhibitor in serum 0 U/ml. C'1 esterase activity in serum 23 U/ml. They were unchanged after Trasylol infusion. Other laboratory investigations gave normal results.

*Controls:* Twenty-five apparently healthy men and women, mostly hospital personnel, aged 22-56 years, served as controls.

**Results**

The intradermal injection of kallikrein produced an edematous reaction which increased in size, to reach a maximum after 5-24 hours and then gradually disappeared (Table 1). It was tender to pressure and palpable as a tense, deep infiltration. Its area was about 5-20 times larger than that in normal subjects and if the volumes had been measurable the difference would have been even more striking. The overlying skin had a red-cyanotic hue.

The immediate reactions to histamine and bradykinin were normal and disappeared within one hour. After 4-6 hours the areas became slightly red and 12 hours after the injections an edematous and tender infiltration appeared. This was rather tense in the center and surrounded by a softer edema which was still visible 12-30 hours after injection.

**Discussion**

Our patients showed most of the typical clinical signs which might be observed in patients with hereditary angioneurotic edema. Edema of the urethra as found in our patients has been reported in a man who

also had massive edema of the perineum, scrotum and penis (4). In our patients the edema was usually localized around the urethra without vulvar involvement. The question of whether the bladder was also involved was not investigated. After the attacks they often had frequent painful micturition.

A favorable effect of the fibrinolytic inhibitor E-ACA has been reported in one patient with hereditary angioneurotic edema (19) and no effect in another (16). In our patients it provoked attacks of edema and worsened their conditions. Nausea and diarrhoea are common side effects of E-ACA and might have been a trigger factor for intestinal edema in our patients. We therefore tried AMCA which has been reported to have an even stronger antifibrinolytic activity without being toxic (1, 20). However, several trials with AMCA in both patients were unsuccessful and seemed to provoke more edema.

The mechanism behind this effect of E-ACA and AMCA is not known. On isolated guinea pig ileum Doleschel and Auerswald (7) found that lower doses of E-ACA and AMCA potentiated the effects of kinins whereas higher doses suppressed these effects. Back and Steger (3) found that *in vitro* both E-ACA and AMCA were less active inhibitors of kinin release activity than Trasylol. E-ACA does not inhibit the activation *in vitro* of C'1 or the esterolysis by C'1 esterase, whereas the former is blocked by Trasylol (8).

Histidinedecarboxylase inhibitor was tried since these patients sometimes show an increased excretion of histamine in the urine (2, 11). NSD-1055 inhibits histamine formation and decreases urinary histamine (18). However, it seemed to provoke edema and to worsen the condition of the patients. Nausea and vomiting has previously been described after NSD-1055 but with higher doses than those used by us (18). The attacks of vomiting a few hours after oral ingestion of sulphonamides might be due to an allergic reaction. Associated classical allergic diseases are reported to be rare in

hereditary angioneurotic edema (16). Since this reaction occurred in both patients it is also possible that the sulphonamides can trigger the formation of edema by some other mechanism. The fact that codeine (but not aspirin) can also precipitate the abdominal attacks might be due to its histamine releasing properties. A histamine release cannot be excluded as the trigger factor involved in all the drugs worsening their conditions. A histamine release could, like an injection of histamine, cause a leakage of plasma which might activate kallikrein.

It is interesting to note that the patients were free from symptoms for several weeks after plasma or blood transfusions. On the days following transfusion a slight increase in serum inhibitor to C'1 esterase was found but this is not sufficient to explain why the patient is free from symptoms for several weeks (12). A logical therapy in these patients would be replacement of the normally occurring serum inhibitor of C'1 esterase. This inhibitor has, however, not been sufficiently purified.

Another therapeutic approach which we have tried is to inhibit the actions of kallikrein. The existence of such an inhibitor in serum was demonstrated as early as in 1928 by Frey and Kraut (10). Later Werle *et al.* (22) prepared a similar inhibitor, from ox lung, which was also found to inhibit plasmin and trypsin. It is commercially available<sup>11</sup> and has been tried in our patients (14). The effect was promising but unfortunately the treatment could not be continued since one patient suffered a severe allergic reaction.

Landerman *et al.* (17) found that intradermal injection of a purified human plasma kallikrein produced an inflammatory response which in controls had a peak at 30 minutes with an average wheal diameter of 12.7 mm. In one patient with hereditary angioneurotic edema they found a maximal response 14 hours after injection, with a diameter of 23.5 mm. These findings were confirmed by Burdon *et al.* (5) who also showed that C'1 esterase produced a similar reaction. In our patients the increased

<sup>11</sup> Commercial name: Trasylol®, Bayer, Laverkusen, Germany.

response to kallikrein as compared to controls was greater, probably due to the higher doses given. Besides the lack of inhibitor of C'1 esterase and of kallikrein it is also known that patients with hereditary angioneurotic edema may show either a decrease or an increase in histamine excretion during the attacks of edema (2, 11). The increased amounts of histamine in urine during attacks were noted at the same time as high levels of serum C'1 esterase (11). In what way these findings are connected is not known. Speculations have been made on the ability of C'1 esterase to provoke histamine release, possibly via formation of anaphylatoxin (6). C'1 esterase injected intradermally in guinea pig has been shown to produce a histamine release which can be prevented by antihistamine (21). However, when C'1 esterase is injected intradermally in healthy human subjects the permeability response is not blocked by antihistamines (15).

The change in reactivity to intradermal histamine and bradykinin in these patients has not been described previously. These delayed reactions have also been found in some patients with chronic urticaria (13). They are thought to be due to an activation of kallikrein produced by the initial leakage of plasma. After infusions of a kallikrein inhibitor these abnormal reactions disappeared, as did also the increased reaction to kallikrein which further strengthens the assumption that the kallikrein-kinin system is involved (14). These delayed reactions to histamine and bradykinin are interesting as they probably in a characteristic way reflect one of the mechanisms in the formation of edema in this disease.

#### SUMMARY

A mother and her daughter with hereditary angioneurotic edema are described. In addition to typical attacks of edema in the skin and gastrointestinal tract they also suffered attacks of urethral swelling with temporary urinary retention. The attacks were provoked by the fibrinolytic inhibitors E-ACA and AMCA, a histidine decarboxylase inhibitor, sulphonamides and codeine. The

best clinical effect was obtained with infusions of 3000 ml of plasma. A kallikrein plasmin/trypsin inhibitor also seemed to be of benefit. But when this treatment was repeated 6 weeks later one of the patients had a severe anaphylactic shock.

Intradermal injection of kallikrein produced a strong edematous reaction after 2-24 hours. Histamine and bradykinin injected intradermally showed normal initial reactions followed by a delayed edema after 4-24 hours. The hypothesis is advanced that the initial edema caused by histamine and bradykinin activates the formation of kallikrein which in these patients is enough to cause an edema since they lack the normally occurring kallikrein inhibitor.

#### Acknowledgement

We wish to thank Dr. Anna Britta Laurell, Lund, for determination of C'1 esterase inhibitor and Dr. Marcus Skogh for referring patient A.

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