CASE REPORTS

Hereditary Angioneurotic Edema: A Remarkable Family History

Charcot's Joint With Secondary Purulent Arthritis Treated With Intra-arterial Penicillin

Hereditary Angioneurotic Edema: A Remarkable Family History

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"I SHALL never forget a case in which my healing art would have proved unavailing and which would have terminated fatally had it not been for the advice of a worthy colleague. The disease was quite new to me in its manifestations and was amazing because of its sudden relapses. I will tell you briefly the whole story because it is to me the strangest of all my medical tales.

"A worthy gentleman, who, as a result of his sober way of living, had attained his 62nd year, awoke one morning with a remarkably puffy face. The lips and eyelids were unbelievably swollen, looking much as if he had been stung by a bee or a wasp. The swelling was lymphatic, without noticeable inflammation, and entirely without pain, burning, or itching. The pulse was natural and the body entirely healthy, though I should not forget to mention that he had suffered every winter from a kind of rheumatic cough from which he always recovered without medical aid.

"But this winter, instead of the usual cough, this strange malady appeared. I ordered the patient to bed and gave him draughts of elderberry tea with liquor anodinus and left the rest to nature. The swelling had completely disappeared by afternoon; it had left the face and descended to the scrotum. The patient felt the arrival there of the new swelling as a brief, sharp sting. Inside of fifteen minutes the whole scrotum was swollen larger than an ox bladder, like a monstrous hydrocele. But there was no burning, pain, or itching; nor were there chills, fever, or thirst. I saw no danger and deemed it a passing acrimony of the humors not yet ripened and ready for transpiration, so I stood fast by the elderberry tea which I had previously ordered and hoped for a healing sweat. I laid cotton soaked in juniper and burnt sugar on the edematous scrotum, and inside of five or six hours the malevolent trouble disappeared and flew to the tongue.

"The tongue could no longer find room in the throat. It swelled out through the lips and filled all who saw it with pity and fear. Now it was time to put other strings to our bow, to employ mightier means against this dangerous fellow. There was good reason to fear that the malicious vagabond might take a notion to invade the windpipe, the lungs, or the brain and cause deadly damage there. Cupping was tried, then blisters, sweats and emulsions of camphor; but the swelling remained stubborn, changing its place every day. Now it was the left, now the right ear, now both; now the eyelids, or the forehead, now the arm. A consultant suggested that the cause of the frequent relapses might be found in the digestive tract. Fortunately, this proved to be the case as the repeated use of tartar emetic alone was able to ban this remarkable and dangerous evil, which, with the continued use of the impotent elderberry tea, might perhaps have killed the patient in spite of his sound heart."

Franz Anton Mai, Professor at Heidelberg, published in 1777 a charming, widely-read book entitled, "Stolpertus, a Young Doctor at the Bedside," which contains this report of a case of angioneurotic edema.[16] The frontispiece woodcuts from the same work show the close association of the doctor of that time with the graveyard, a rare insight in a medical contemporary.

The disease may be defined as a transient edema which may involve the skin, mucous membranes, subcutaneous tissue and muscle; usually migratory, one swelling subsiding as another develops. It was well described by Quincke[20] in 1882 under the name of acute circumscribed edema and is often referred to as Quincke's disease or Quincke's edema. Among the other names for it in the early literature are "ephemeral congestive tumors of the skin," "ephemeral cutaneous nodosities," "giant hives," "wandering edema." Recognizing the neurotic element, Strübing[21] first called it "angioneurotic edema" in 1885. Osler,[18] in 1888, published an excellent description of the familial type. The typical swelling may involve a hand, or forearm and hand, or the face or some part of it, the lips and tongue, or the external genitalia, in fact, any part of the body surface. The swelling is usually of a brawny hardness, the border often being sharply demarcated from the adjacent normal tissue. Involvement of the hand makes flexion of the fingers impossible and the member useless. The swellings are deep and may involve skin, subcutaneous tissue and muscle; the skin is glossy and taut and subcutaneous bullae may be present. There is no inflammation.

In addition to the surface swelling, internal organs and tissues may be involved. Swelling of the mucous membranes and of the subjacent tissues is common, particularly in the region of the mouth and larynx. Swellings of the lips and tongue make speaking and eating difficult. Involvement of the larynx may cause partial obstruction with stridor, cyanosis and labored breathing, or complete obstruction with death from asphyxiation. The edema may extend to the bronchial mucosa. However, there is some doubt about the classification of certain cases of transient localized areas of edema of the lungs with roentgenographic findings similar to those of tuberculosis. They are described as visceral manifestations of angioneurotic edema, but should probably be classed as examples of Löffler's syndrome, or as a manifestation of a disseminated visceral angiitis.

Severe cramp-like abdominal pain is a common symptom either accompanying surface swelling, or occurring in persons subject to the disease. The pain may be substernal or epigastric, suggesting swelling of the esophagus or stomach, or there may be generalized or localized abdominal pain, often accompanied by nausea and vomiting, or diarrhea, or both. The vomitus or stools may be grossly bloody and death has occurred in severe attacks.[17] Because the findings resemble so closely those of appendicitis,[22] biliary colic, or perforated peptic ulcer, with localized tenderness, muscle spasm, fever and leukocytosis, operations have been performed during an attack with various interesting findings.

A tense, swollen cecum and first portion of the ascending colon, with considerable retroperitoneal edema, was reported in one case.[22] No abnormality at all may be discovered except for large amounts of free peritoneal fluid.[8] Lundbaek[15] examined a patient gastroscopically during an attack of abdominal pain and found the entire mucous membrane of the stomach succulent in appearance. The folds were broad as if distended, the color deeper red than normal. There were no erosions and no exudate. Reexamination after the attack had subsided showed a normal mucosa. Attacks resembling ureteral colic with hematuria have occurred in this disease. Oliguria may be noted with attacks involving any portion of the body followed by polyuria as the attack subsides. One case of oliguria with angioneurotic edema occurring during pregnancy has been described, with relief obtained by giving theobromine and aminophyllin.[26] The baby born of this mother developed the typical swellings of the disease 56 hours postpartum. Swelling of the uterus and Fallopian tubes may occur.[4] Hydrarthrosis may be a manifestation of the disease.[21]

The nervous system is not immune to attack. A patient with signs of a brain tumor, including choked discs, vomiting and headache, was found at operation to have only edematous brain tissue.[1] He subsequently developed a typical attack of angioneurotic edema and the neurological signs cleared completely. An attack of transient hemiplegia with aphasia is described and certain migraines are believed to be angioneurotic.[1] A remarkable case of relapsing proptosis due to retrobulbar swelling has been reported. Recurring swellings of the eyelids accompanied by iritis with increased ocular tension and great pain occurred in a patient who also had attacks of Menière's disease.[13]

The disease is of two main types; the familial and the sporadic. Unfortunately, this distinction frequently is not made in the literature and some confusion results. The sporadic type, which may be acute or recurrent, is undoubtedly an allergic disease and occurs in persons and families with other allergic manifestations. There is no history in this form of the disease, however, of its occurrence in members of the family through generation after generation. It is common for an isolated attack to occur, or for the attacks to be limited to a period of weeks or months. Rarely they may extend over two or three years. In the familial disease, attacks recur irregularly throughout life. In sporadic cases, hives, a scarletiniform rash, or erythema multiforme may accompany the angioneurotic edema, and pruritus is often very distressing.

In differential diagnosis the following list of diseases with somewhat similar symptoms must be considered: Henoch's or Schönlein's purpura, Osler's erythema group of skin diseases with visceral manifestations, disseminated lupus erythematosus, periarteritis nodosa, Löffler's syndrome, Libman-Sachs disease, and possibly nephrosis.

Pruritus, skin rashes, purpura, arthritis and the other systemic diseases just mentioned are not a part of the familial type of angioneurotic edema. Except for the hazard of death from edema of the glottis, it is a benign disease compatible with long life and good health. Attacks of abdominal pain with nausea and vomiting occur in both forms. A very striking difference between the two is that edema of the glottis is a common cause of death in the familial type, but probably does not occur in the sporadic form, although there may be discomfort and apprehension from swelling in that region. The importance of allergy in the sporadic form is indicated by the many reports of cures by desensitization or by elimination of the allergen. The allergens reported are numerous and curious. Foods and inhalants are common. Rowe[23] reports cures with careful elimination diets. Dorst[5] was successful in certain cases in desensitization with vaccines made from bacteria grown from the intestinal tract as well as from infected nasal sinuses and gallbladders. Drugs are common offenders, the coal tar drugs particularly.[3] Estrogenic substances,[24] chlorine in chlorinated drinking water,[14] and chicle[11] in chewing gum are reported as causes of angioneurotic edema. The disease has followed the use of diphtheria antitoxin and also quinine in the treatment of malaria. There are various precipitating factors in the individual attacks; mild physical trauma, like a bump on the head, may be followed by a swelling starting in the region of the trauma; a tight shoe, a fold in the clothing under the buttocks, are cited as precipitating causes. Exposure to cold or wind may precede attacks. Psychic causes are common; unusual emotion—pleasant or otherwise—undue nervous or physical fatigue, may be factors.

The hereditary factor in the familial type is very striking. Osler[18] in 1888 reported a family of 36 members with the disease occurring in several generations. In 1929 Dunlap and Lemon[7] tabulated 21 families from the literature and added one of their own. In the family here reported the disease extends through four generations. There are eight members, a grandfather, a son and daughter, one grandson

and three granddaughters, all of whom were affected. Two died of edema of the glottis.

Susceptibility to the disease is apparently a Mendelian dominant character without sex linkage (male and female are both affected) and there is usually no skipping of generations. Although the appearance and behavior of the swellings are so strikingly similar to those in the allergenic disease, there is great doubt that allergy is causative in the familial form. Certainly, search for allergens, elimination diets and immunization with vaccines have been futile in the familial type of the disease. Theories regarding the cause or causes of this disease and the pathological physiology of the swellings may be mentioned. Strübing, noting the fact that the disease occurred in high-strung, nervous individuals, thought that there was a disturbance of the nervous control of capillaries with a dilatation and exudation of fluid into the tissues.

Hives can be produced experimentally by injecting eserine, a cholinergic drug. However, direct stimulation of cholinergic nerves will not cause hives, refuting the theory that the psychosomatic influence alone causes anigoneurotic edema. Eserine applied locally causes the cells to liberate "H" substance, which initiates a wheal.[3]

Rowe[23] believes that all cases are allergic in nature. Other investigators, including Drysdale and Piness and Miller,[6] think that the hard, pale, non-itching swelling of the familial type is not due to allergy. Farquharson[9] believes both types have constitutional factors, by virtue of which an urticarial reaction is more easily elicited. He notes that both types occur in nervous, sensitive individuals and both are made worse by the patient's worrying about the condition. Farquharson relies on psychotherapy and stresses the fact that the allergen often cannot be found even in the sporadic cases.

Various blood studies have been carried out on patients during attacks. In some cases, counts of erythrocytes and leukocytes and hemoglobin and differentials may be found to be within normal limits. On the other hand, with abdominal pain especially, a high leukocytosis may occur with or without eosinophilia.[12] One wonders whether the attacks of abdominal pain with eosinophilia should not more properly be classified with the group of diseases included in visceral angiitis. The serum albumin-globulin ratio is said to be increased.[7] Black[2] treated patients with vitamin K on the theory that prothrombin formation might have something to do with the permeability of the capillary wall and that this mechanism might be affected by the administration of vitamin K. He found a good percentage of patients with prolonged prothrombin time and obtained relief of symptoms in many cases. Some patients with normal prothrombin time were also benefited.

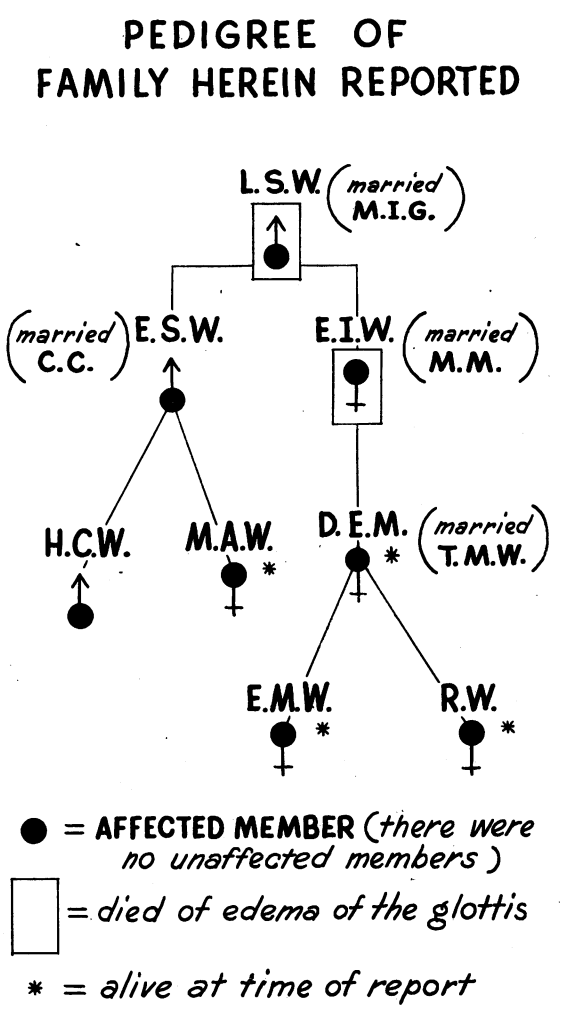
Endocrine dysfunction has been considered a cause of angioneurotic edema. Certainly in the family here reported there are no stigmata of such disorders, and medication with thyroid, parathyroid and ovarian extracts has been of no value.

CASE REPORT

The family here reported is remarkable in that every member was affected. L. S. W. was the first one known to have had the disease, although his mother was thought to have had it. He had two children, E. S. W. and E. I. W., both of whom were affected. L. S. W. died in his twenties from a swelling following a tooth extraction. His son, E. S. W., suffered swellings only occasionally and they became less frequent as he grew older. E. S. W.'s niece remembers one swelling of her uncle's hand caused by the pressure of his thumb over the nozzle of a hose. He died at 47 from another cause. E. S. W. had two children, H. C. W. and M. A. W., both of whom were afflicted. The boy was known to have had one swelling which was thought to have started from the pressure of his watch on his cheek when it slipped down from under his pillow at night. As far as is known, he did not have serious trouble with the swellings. His sister is still alive, quite an old lady, thin and delicate in health. She remembers her first attack—in the throat at the age of 17. She had frequent attacks in her hands and feet during her girlhood. Later, she had only one or two attacks for a period of 13 years, although still later she suffered again from very frequent swellings. She feels that food causes swellings and is also convinced that the swellings are more apt to occur when she is weak and nervous. E. I. W., the daughter of L. S. W., suffered the usual swellings of the extremities and

TABLE 1.—*Tabulation of Cases of Angioneurotic Edema of the Familial Type Collected from the Literature by Dunlap and Lemon in 1929*

	Generations	Members	Members Affected	Deaths	
Osler	6	42	24	2	
Crowder and Crowder	5	64	28	15	
Ricochon	4	....	9	3	
Schlesinger[25]	4	15	5	....	
Ensor	5	80	33	12	
Dinkelacher	2	4	3	....	3rd member reported by Valentin
Strübing	2	4	3	....	Father, son, daughter
Falcone	3	....	2	....	Grandfather and child
Krieger	2	....	2	....	Mother and son
Fritz	3	9	8	5	Deaths from edema of glottis
Roy	2	....	2	....	Mother and daughter
Yarian	2	15	10	2	One death from edema of glottis
Griffith	2	....	2	2	Father and patient died from edema of glottis
Harbitz	3	....	6	....	
Morris	2	....	3	1	Death from edema of glottis
Halsted	3	....	7	....	
Halsted	2	....	4	....	
Halsted	2	....	3	....	
Smith	2	....	2	....	Mother and daughter
Mendel	4	12	9	6	Deaths from edema of the glottis
d'Appert and Delile	3	....	5	....	
Dunlap and Lemon	4	23	11	6	Two died of edema of glottis



had seven or eight attacks in her throat. Once it was thought to have been caused by leaning her forehead against her hymn book in church. The inhalation of steam from boiling vinegar was believed to bring relief. She died at the age of 27, when her daughter, D. M. W., was three months old. She was standing by the stove and fell dead. Autopsy showed death from asphyxiation due to swelling of the larynx.

D. M. W., living in 1947, aged 73, was the source of information regarding her family. Her first attack, she was told, was when she was 3 or 4. She suffered attacks of acute abdominal pain during childhood which were called bilious attacks. The first swelling she remembers occurred when she was 17. It was in her hand or arm and came during a period of illness in the family, when she was anxious and depressed. She had attacks of stomach trouble at this time and frequent swellings of hands and face. She was treated with stomach lavage and iron. Her first prolonged period of migratory swellings occurred during her first pregnancy and lasted ten days. She suffered many swellings in her throat, some of them producing difficulty of breathing and cyanosis. On two occasions, obstruction to breathing was complete and tracheotomy became necessary.

This woman, as can readily be imagined, was constantly haunted by fear of her disease. She suffered from malnutrition at one time, due entirely to a fear of causing a swelling by some food. She was almost entirely free of attacks during the two years her husband was away from home during the first World War, and had a comparatively long period of freedom following a severe attack of measles in adult life. The attacks, except when they involved the digestive tract and throat, were not painful but were usually accompanied by malaise of sufficient degree to cause her to take to her bed.

Her daughters, E. M. W., aged 43, and R. W., aged 42, have the disease in forms similar to their mother's except that they suffer less malaise. Both have had attacks of seyere abdominal pain, however, requiring morphine for relief. E. M. W. was operated upon for appendicitis during one attack which resembled that disease closely. There were a leukocytosis of 22,000 with 90 per cent polymorphonuclears, exquisite tenderness at McBurney's point and rebound tenderness. At operation, a normal appendix was found but the peritoneal cavity was full of a pinkish fluid which coagulated instantly on cooling. The patient recovered uneventfully and was absolutely free from swellings for two years after the operation.

R. W.'s story is in most respects similar to her sister's—swellings of extremities and face, and abdominal colic. She had one attack of edema of the glottis necessitating tracheotomy. These sisters, the last of the line, are unmarried.

Attempts at therapy have been numerous and futile. D. E. W. was skin tested, and although she gave positive reactions to certain foods, dust and pollens, elimination diets and immunization to other allergens were of no benefit. Vaccines made from her intestinal flora were tried. The following were used unsuccessfully in treatment of this patient:

Adrenalin	Ephedrine
Pituitrin	Thyroid
Bromides	Vitamin B 1 and B 6
Chloral	Ultraviolet rays
Atropine	Soda
Pilocarpine	Autogenous vaccine from intestinal flora
Histamine	
Benadryl	Parathormone
Ovarian extract	Gynergen
Aspirin	Activin
Morphine	Torantil
Calcium lactate	Pyribenzamine

Those that were suggested but not tried were insulin, bee venom, autogenous blood, horse serum, Vitamin K, and x-ray.

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Charcot's Joint With Secondary Purulent Arthritis Treated With Intra-arterial Penicillin

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SECONDARILY infected tertiary syphilitic lesions are frequently equally resistant to anti-syphilitic measures with either the heavy metals or antibiotics and present a difficult therapeutic problem. A standard treatment by arsenicals or bismuth is ineffectual because of the superimposed bacterial infection, and although penicillin may be effective against the particular infecting bacteria and also treponemacidal, it may fail when administered intramuscularly or intravenously because of the poor permeation into the involved region. Local factors of impaired vascularity and fibro-osseous barriers prevent penicillin from gaining entrance into the involved area when the drug is administered by the intramuscular or intravenous methods; but, fortunately, by the intra-arterial route it is possible to overcome these barriers and thus achieve the desired therapeutic result. The following case report illustrates that after the failure of intramuscular penicillin therapy of a secondarily infected syphilitic lesion a prompt desirable result attended treatment with smaller dosages of penicillin given by the intra-arterial route.

From the Surgical Service of Owen H. Wangensteen, M.D., University of Minnesota Hospital.

CASE REPORT

The patient, a man 64 years of age, had had swelling and purulent drainage from his left foot over a ten-year period (1935-1945) and had been incapacitated because of it many times. Since May, 1945, there had been an exacerbation of symptoms and he was finally admitted to a hospital in mid-August, 1945, and given a six-day course of 20,000 units of penicillin intramuscularly every three hours (160,000 units daily). This had no effect on the swelling or purulent drainage and both conditions continued to increase in severity. On referral of the patient to the University of Minnesota Hospital on 27 September, 1945, physical examination revealed a small, thin, fairly well developed man with a temperature of 102° F. and a pulse rate of 100 per minute. There were erythema and edema of the medial distal one-half of the left foot and two indurated purulent draining sinuses on the plantar surface of the first metatarsal of the foot. A moderate edema of the left leg extended up to the knee and an enlarged tender left inguinal node was palpated in the groin. The blood pressure was 165 mm. of mercury systolic and 68 mm. diastolic, but the heart was otherwise normal, as were the lungs.

Neurological examination of the patient revealed that the pupils reacted sluggishly to light but normally to accommodation. Anisocoria was present, with the right pupil larger than the left. Knee jerks and ankle jerks were diminished and posterior spinal column disease was further evidenced by a positive Rhomberg test, decreased muscle, tendon, joint, and testicular pain, and decreased sense of vibration and position in the lower extremities. Superficial sensation was intact. As to mental status the patient was of normal intelligence with no gross abnormalities. Venereal history was denied but a clinical diagnosis of tabes dorsalis with Charcot's joint of the foot was confirmed by a neuropsychiatric consultant. Laboratory studies revealed a hemoglobin of 10.4 gm. and a leukocyte count of 13,850 per cubic millimeter with a differential count of 84% neutrophiles and 16% lymphocytes. The blood sedimentation rate was 120 mm. in 60 minutes (Westergen). Blood chemistry determinations, including fasting blood sugar, were within normal limits. Upon urinalysis a trace of albumin and an occasional cast were found. A culture of the purulent exudate from the foot revealed coagulase-positive staphylococcus aureus to be present. Results of initial serological tests for syphilis were: Kline, doubtful; Hinton, doubtful; Kahn, negative. Subsequently, reactions to the Kolmer test were negative, to the Kline test 2+, and to the Eagle test 3+. The spinal fluid cell count was normal (2 cells per cubic millimeter) but the protein was elevated to 304 milligrams per 100 cc. A first zone colloidal gold curve was present but results of spinal serology were negative. A roentgenogram of the foot (Figure 1) showed a destruction of the first metatarsophalangeal joint with considerable fragmentation and new bone formation in the soft tissues characteristic of Charcot's joint with probable secondary purulent arthritis present.

Intra-arterial injections of 50,000 units of penicillin were given into the femoral artery twice daily over a five-day period until a total of nine injections had been given. The penicillin was diluted in 10 cc. of normal saline and given into the femoral artery in a perpendicular plane using a 10 cc. syringe and a 20-gauge two and one-half inch needle. A blood pressure cuff was placed on the left thigh and inflated to 80 mm. of mercury prior to the intra-arterial injection and maintained at that pressure for ten minutes following each injection. Foot soaks of potassium permanganate solution (1:9000 concentration) were used twice daily as a therapeutic adjunct. The cellulitis cleared entirely in 48 hours and drainage ceased in 72 hours. Following intra-arterial penicillin therapy a sterile dressing was applied to the foot and the skin had entirely grown over the sinus tracts