Thesis presented by

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Angio-neurotic oedema

and allied conditions.

Under the terms "acute local," "acute circumscripted" or "angio-neurotic" oedema a disease has been described, characterized by oedematous swellings in various parts of the body, which swellings are sudden in origin and last only a short time.

The occurrence of various transient phenomena of the nature of flushings, erythema, urticaria etc. in hysterical and dyspeptic patients, as well as in girls at menstural periods and women at the climacteric has long been recognised, and angio-neurotic oedema is closely allied to these affections.

I have chosen the above as a subject for this Thesis as I have had two or three cases of the disease under observation, and thought that they may
give support to certain theories regarding
the etiology of the disease.

The disease is evidently not very
uncommon as many writers have
collected cases.

It is first described as a definite
disease in 1882 by Aminoff who
called it "acute circumscribed oedema
of the skin."
Cases had been formerly described by
Watson and Laycock, (the latter of whom
described it as "fugitive oedema") but
Aminoff suggested the view that the
oedema depends on an altered
innervation of the part and quoting
evidently accepts this theory because
he gave the disease the name of
Angioneurotic oedema.
Cases had also been reported by
Milton in 1879 under the name of
"giant urticaria", and in 1882
Skelarton compiled all the cases up
to that time.
Since then reports have been made by
various observers as Jansen in 1883,
Graham and Stirling in 1885,
Falcone in 1886
Richt and Martos in 1887
Belen and Elliot in 1888, and
Randay Smith in 1894.

General description of the disease.
The disease is characterized by the occurrence of rather circumscribed
swellings coming on rapidly, usually
multiple and attacking preferably the
eyelids, lips, hands, feet, genitals and
thighs of patients.
As a rule there are no premonitory
symptoms. But general lassitude, headaches and impairment of appetite
may precede an attack.
Sensations—variously described as itching,
turning, prickling, &c.—are often
experienced before the swelling appears
in a part and then these give place
to a feeling of distension which is
accompanied in some instances by a
considerable amount of pain while in
others there is merely a sense of
stiffness when the swelling is at
its height.
Red spots and streaks occasionally take the place of these swellings but this is not often the case.
The swelling itself comes on very rapidly, reaching its maximum in about an hour or sometimes less.
When the oedema is at its height the parts are very swollen so much so that the eyes may be closed up, when the eyelids are affected, and movements of the fingers may be restricted or even impossible when it occurs in the hand.
The colour of the swelling may be reddish or a blue tinge; more often it is paler as a result of the pressure upon the smaller vessels, while often the colour varies during an attack being blue at one time or pale at another.
The temperature of the affected part is often raised at the commencement but later it is lowered and there again a variation may take place, the part being hot one minute and cold
The next.

In some cases it has been noticed that a kind of "tache cerebrale" could be obtained by stroking the skin with the finger even after the oedema had gone.

While, as a rule, the oedema occurs in the epidermoid structures already referred to, it is important to note that it may also involve mucous membranes, for example those of the trachea and pharynx, and it is in these situations that hyperaemia also occurs.

Again, while in its ordinary form the disease is connected with no danger as far as life is concerned it generally assumes a more serious aspect when these two parts are affected.

Fortunately, such cases are rare and while we find the mucous membranes involved in nearly every case, it is not common to meet with cases where breathing is difficult on account of the oedema in the larynx.

Still there are cases where the
membrane has led to the
scarification and later results one, and
Griffiths two cases where death occurred
from Bederna Glottidis.
Swallowing is also rarely interfered
with but Riehl reports a case in
which both swallowing & breathing were
affected.

In addition to these more local features,
we generally observe the occurrence
of nausea, vomiting, colicky pain
and constipation during an attack
and sometimes diarrhoea toward
its end.

These symptoms are more frequently
present than absent and may even
take the place of the swellings or
rather occur by themselves.
The vomiting may only be slight but
at times it is very profuse and
after the contents of the stomach
have been vomiting, bile colored
watery matter may be discharged.
The pains are as a rule in
proportion to the severity of an attack.
and are present in almost every case.

These symptoms belong to the alimentary system and are however not constant and many cases are seen where patients have no discomfort except that caused by the swellings. With the approach of the end of an attack all the symptoms disappear. Some weakness, lassitude and anorexia may persist for a little time after which the patient is quite comfortable again and keeps so till the next attack.

The swelling also gradually disappears and first usually in the parts first affected.

Paroxysmal haemoptoemia has been associated with this condition but it is very rare.

Periodical attacks of cardiac pain have also been met with.

In a case recorded by Quinnke and Hooker, the patient aged 22 had local oedema and colicky pains and in addition had cyanosis and
dyspnoea. The larynx had to be
scarified but there was no interference
with swallowing.
In a case of Goltz on the right hand
(a male aged 30) there was oedema of
the uvula and pharynx also swelling
of the arms and sternum.
Sander had swelling of his larynx
at intervals.
In Curtz's case there was dyspnoea
and sense of suffocation but these
passed off in a few hours.
Riehl's case had an acute attack
with difficulty in swallowing and
great breathlessness.
These cases are illustrative of the peculiar
laxity of the disease to limit
itself to one part or several
circumscribed areas.

These are therefore these two
characteristics of the disease:
(i) Local swellings,
(ii) Gastro-intestinal disorders.
and to these two it is necessary to
add a third namely that the
The tendency is also noticeable. Strübing and

the man had his grandmother (12 years) had

the mother old, attacks

in cases (a man) had

limited the disease

case was after his

brother father took it

but whose grandfather

a case of father and

causing the disease

This hereditary

noticed by Polo

Falcone

Dr. Quincke's case,

children one was

had, from three

of local bed

one of Strübing's

a son 12 to 14

while Falcone's case

of seven years had

been affected

Griffith's records

daughter 4/11.
a fatal result.

The disease usually begins at an early age and seems as common in the male as in the female. There is often a marked regularity in the attacks, which may recur at intervals of 7, 14 or 12 days. In Matos' case this was very well shown as the attacks came on daily at 11 or 12 a.m.

The following cases are illustrative of the various conditions described.

Case I.

Miss K., age 39. At one time a dressmaker but now housekeeper. Has suffered from periodical swellings of the hands and feet ever since she can remember. The swellings were noticed to be getting worse when she was about 21 years of age (the time she began dressmaking) and they have been recurring at fairly regular intervals ever since.
The hands and feet are the parts most commonly affected and when the swellings are about to appear the patient states that she experiences a burning or prickly sensation.

On examination of the hands at this time the whole hand is seen to be swollen and edematous. The swelling does not readily put on pressure and is sometimes painful when pressure is applied. The color of the part rarely being sometimes red or bluish and at other times pale and waxing looking. Generally the temperature of the part rarely, also being sometimes considerably raised while at other times the part is cold to the touch.

The same conditions are also noticed in the feet and after existing for a period these swellings disappear as rapidly as they appeared.

The patient has also noticed that at times the face has been the seat of swellings especially about the eyelids. This however is not so frequent as not to such a degree as in the hands or feet.
The swellings apparently occur also in
the planta and tarsus because at times
she not only complains of a slight difficulty
in swallowing but also of difficulty in
breathing and a hoarseness or loss of
tone.

This however has only occurred on one
or two occasions and it is worth noting
that, when it did occur, it was when the
hands and feet were worse than usual.

There is not a great deal, in the history of
this patient, with regard to digestive
troubles occurring before or during attacks
but she has had on certain occasions
pain, sickness and diarrhoea, more
especially during the winter of 1902-3
when she was in a bad state of general
health and during which time the
swellings were worse than she had ever
known them before.

Patient has never noticed that any
particular food has any effect on the
swellings except that if she had taken
anything which caused indigestion
(to which she is rather subject) the swellings
have a tendency to come on.
She also states that if anything upset or excites her in any way the swellings appear in the hands within a few minutes. As an example of this she says that any visitor coming to see her unexpectedly & finding her unprepared will bring on an attack.

The swellings may also appear if she is hurried in doing anything.

There has never been any Albumin in the urine.

**Family History**

Patient states that she has always been of a "nervous" or excitable temperament and that most of the members of her family were also "nervous."

There is no history of any actual nerve disease in the family.

She had five brothers and no sisters. Two of the brothers also have swellings of the hands at times, but not to any extent.

No further family history that is important can be obtained.

It is unnecessary to say much about the various systems of the body as most of them
are normal but it is necessary to add some notes regarding the alimentary and reproductive systems.

As before mentioned up to quite recently the patient had not had many troubles of the alimentary system such as are present in most cases. But since the beginning of last year (1903) she has been subject to attacks of diarrhoea which apparently come on without cause and passed off under treatment. Still more recently she has had the diarrhoea more frequently and in addition there has been pain & blood in the stools. At first the blood was small in amount but later it increased so that she was passing almost pure blood. This is her condition at the present time. The bleeding is ceasing under rest & treatment.

Reproductive System.

The patient states that she did not begin to menstruate until she was 21 years old and it was at this time that the swellings were noticed to be getting worse.
Since that time she has been very regular in her menstrual periods but has never had much discharge. The swellings in the hands and feet often come in just before a period.

Case II.

J. R. Male aged 4.

This child is an example of the class of case in which there is urticaria along with or preceding an attack of angio-neuritic oedema.

The mother states that the child has always been subject to attacks of "hives" which attacks are generally due to some article of diet. At times also she has noticed that the boy's feet and hands swell up and this generally occurs at the time of or immediately after an urticarial attack.

The child is a well-developed boy who has had no sickness except the urticaria. This urticaria is of the usual type and the swellings of hands and feet, although not so marked as in the other cases, leave no doubt as to the condition.
The feet especially are the part affected and they become swollen, pale and firm. Sometimes they may get red and irritable and then the condition gradually dies away along with the urticaria. Except for the distress of the itching, there is apparently not troubled by any symptoms at all, and the swellings do not seem to occur in other parts of the body.

As before mentioned, the urticaria is noticed to come on after certain articles of diet. Fish, for example produces it, also cocoa, chocolate and sweets of all kinds if many are eaten at one time. But in certain cases, it seems to occur apart from any special article of food.

The oedema does not occur every time he has an urticarial attack but fairly frequently and there is no regularity to be observed in the appearance of the oedema.

This patient has a brother (aged six) who also suffers from urticaria but not to the same extent. In this case
also, no oedematous swelling have been seen and there is no history of any other member of the family having either antecunea or oedema.

There has never been albumin in the urine ever examined.

Case III.

This case (the notes of which have been given me by the W.T. Clagq F.R.C.S(Ed)) is placed next as some points in connection with it resembled points in another case to be described more especially as regards treatment.

Female, aged 25, unmarried.

Had suffered for some years with periodical swelling of the left eyelids more especially the upper eyelid.

The swelling was oedematous and pale and disappeared in a short time.

There was no albumin in the urine and no structure of the lacrimal duct such as might be thought to cause such a swelling.

On examination there were never any
other swellings to be observed, and the patient had never noticed them in other parts.

The patient did not attach any importance to these swellings but consulted Dr. Clegg about the condition of her nose, which had given her trouble for some time. She complained of being “clipped up” in the left nostril and unable to breathe through it. The middle and inferior turbinated bones were found to be greatly enlarged. The mucous membrane over them congested.

The electric cautery was applied to the swollen mucous membrane in order to reduce the swelling and improve the nasal passage. This procedure was followed by a great improvement in her condition, and since that time she has had no return of the periodic swellings of the eyelids. It is well known that the removal of polypi and other operations on the nose (such as the one described above) have often a very marked effect on asthma, which is a nervous affection.
and now we have a similar operation apparently curing an oedematous swelling also of nervous origin. This circumstance will be mentioned again in treating of the pathology of the disease.

Case IV.

This case is one similar to Case III in so far as the patient had a swelling of the eyelid also hypertrophy of the nasal mucous membrane.

Male aged 35; married.

Complains that at times his left upper eyelid swells up apparently for no cause whatever and after a short time the swelling disappears.

The swelling is often so bad that the left eye is completely closed.

This patient has no gastric or intestinal symptoms in connection with the swelling and at no time has there been albumin in the urine.

The only thing he complains of (besides the eyelid) is the condition of the nostril and a strummatine this was found to be partially blocked by an
overgrowth of the middle turbinate bone.
This caused him a good deal of inconvenience and he was advised to
have the cautery applied to the tip that, besides curing the nasal condition
he might be freed from the oedema of the eyelid.
Unfortunately the patient did not return
and has been lost sight of, so that
it is impossible to complete the case
satisfactorily.
There is no doubt that these two cases
were angiomegaly, but the former one
was improved if not actually cured, by
the nasal irritation being removed.
There is therefore ground for believing that
had the other patient taken advantage
of the treatment, he might also have
had relief from the oedema.
Etiology.

Numerous observers who have noticed this fugitive edema have implied their opinion of its origin in such terms as "nervous," "hemorrhagic," and "angio-neurotic." There is convincing evidence that there is a distinct neurotic taint in many patients suffering from the disease and consequently among predisposing causes should be placed hysteria, neurasthenia, and other emotional states.

As before mentioned, heredity plays an important part in the etiology and some observers have been able to trace nervous diseases to parents or grandparents, though not always the same nervous disease from which the patient himself suffers.

The exciting causes of the disease are very varied. It has been noticed that, in the female, the menstrual period has an influence on the condition and that attacks may occur either just before or just after the period.

The onset of puberty and also the
Characteristic have been put down as exciting causes but they are not so common as many of the others to be mentioned. Alcohol is certainly one of the exciting causes of the attacks and this fact has been proved by Max Joseph whose three cases were all alcoholics. It was noticed that when alcohol was abstained from, the attacks did not come on but when alcohol was allowed the swellings reappeared.

Stastic irritation is another exciting cause of the attacks and this fact lends weight to the idea that this disease and urticaria are closely related.

The eating of fish, apples etc. or the smoking of a cigar have been known to act as causes of an attack and indigestion is a common symptom in persons with the disease.

In other cases, fatigue, colds, physical exercise, and exhaustive nervous strain (as seen in masturbators) are given as causes.
Pathology.

The influence of the nervous system on the production and situation of oedema is very important. It is known that the vasomotor system is affected by various emotional states and the indications of this, as seen in blushing, pallor, etc., are generally regarded as those of normal conditions.

But the influence which the vasomotor system has over vessels generally is greatly increased, when we look at cases in which there is a change in the mental condition, as for instance when hysteria is present.

It is of interest in this connection when we remember that the great majority of cases of angioneurotic oedema occur in persons who are either of neurotic tendency or belong to a neurotic family. We see the evidence of this in hysterical girls with a pale skin which does not bleed on pricking it and also in women at the menopause who suffer from flushings and sweats.
but of these facts the question arises whether, in a nervous person, the dilatation of vessels can go so far that, instead of a mere hyperaemia, an oedema is produced.

It has been shown that many skin conditions, such as palor, congestion, urticaria and even localized oedema are very common in hysterical subjects and, moreover, occur in these individuals without any other obvious cause.

For example, there is recorded the case of a surgeon who could produce an attack of urticaria at will by fixing his mind on the subject.

Crocker mentions the case of a woman who developed urticaria whenever strangers appeared and Case I of this series rather resembles Crocker's case inasmuch as the patient developed oedema when strangers or visitors came to see her unexpectedly.

Saville records the case of a boy in whom urticaria appeared wherever he was worried by his school lessons and also if he were placed in such a position.
that he felt sevems.

He also records the case of a woman who developed localized oedema just before or just after her menstrual period; when she also suffered from the nervous disorder usual at those times.

This case had no other disturbance and therefore no evidence of any change in the blood or blood vessels; but on the other hand he mentions a similar case in a boy who also had had purpura so that in this case there was probably some change in the blood to partly account for it.

Sydenham noted that oedema of one ankle may occur in hysteria. This oedema differed from dyspnoe in that it only appeared on one side of the body, did not pit on pressure, and was greatest in the morning.

There are also many cases recorded where oedema has been seen along with nervous conditions other than hysteria. Gowers records a case of trigeminal neuralgia with zones of distension of the same side during the paroxysm and
another case in which there was an
oedema of the whole scalp.
Brachial neuralgia and injury to nerves
have resulted in oedema and dump
paroxysms of neuralgia, arterial dilatation
has been demonstrated by the sphygmograph.
In hypotonic paralysis also it has been
noticed that oedema occurs in the
affected limb; the oedema passing off
with the return of movement.
And the example of deafness due to nervous
influence is seen in the effusion
into joints in tabetic arthropathy and
This is interesting in this connection
because in one of Quincke's cases of
angiosclerotic oedema there were effusions
into various joints.
Oedema has also been seen in myelitis
and it is also fairly familiar in
alcoholic neuritis while, in hemiplegia
who develop deafness (renal or cardiac)
the oedema is more marked on the
paralysed side.

The above are all clinical evidences of
a relation between the nervous system
and oedema but there is also certain experimental evidence.

By the experiments of Betram and Colletum, (which are practically the same) a relation between oedema and the nervous system is shown.

These observers were able to cause oedema in the tongue of a frog when they cut the spinal nerve and irritated the peripherial end by currents of gradually increasing strength.

Rasmus, who experimented in this subject, found that, in ligaturing the chief vein in the hind of a dog, oedema was not produced but that, if the sciatic nerve of the same limb were cut, then oedema appeared.

This experiment has been recently done by Horsley and Borrie with a like result.

Sergius destroyed the spinal cords of frogs and then found that they become oedematous under certain conditions.

It has been proved also by Jagenstot and Santesson that the passage of living fluids through membranes
Such as vessel walls, is due to more than mere changes in pressure within the fluid.

From the foregoing facts and experiments it can be assumed that oedema, in certain cases, may be caused by the influence of nerves on the walls of blood vessels whereby these structures become more permeable.

If this be so, then a course of events takes place as follows.

First there is a local paralysis of the vas-constrictors or a reflex stimulation of the vas-dilator nerves.

This causes a dilatation of vessels in the subcutaneous tissue and a partial stasis of the blood stream.

Then, as there is increased permeability of the vessel walls, an exudate is produced which may be so slight as to be almost unnoticeable or may be so diffused as not to cause any lifting of the epidermis.

If the epidermis be raised then the oedema is more localised or an urticaria results.
Many observers have noted the close relationship of angioneurotic oedema to urticaria and cases have been described where they occur together. This is well seen in Case II.

It has been suggested that the two diseases are really the same and that the wheal in urticaria is due to contraction of the muscles of the skin, while, in angioneurotic oedema, no wheal is formed owing to a want of tone in these muscles.

As the majority of the cases occur in nervous and hysterical patients, there would naturally be a tendency to loss of tone in the muscles and therefore the theory is quite feasible.

It has lately been suggested that these oedemas (and also probably renal and cardiac oedema) are due to toxins, acting, in the case of angioneurotic oedema, locally on the skin and in the other oedemas acting more generally.

As has been already shown there are
Persons who seem to have an irritability of the nerve mechanism of the vessels and in these people very slight causes set up either an urticaria or a neutritic oedema.

This is supposed to be due to the toxin causing a contraction of the veins and a subsequent exudation but it has not yet been shown whether it also causes an inflammatory alteration in the walls of vessels so facilitating the exudation.

In considering this toxin theory of the disease it is interesting to remember that erythemas and oedemas are often produced by drugs as Arsenic, Belladonna and Moccasin Iodide.

Death from oedema of the lungs has been attributed to Moccasin Iodide in two cases.

The toxins received in the bites of insects also very frequently cause an oedema.

A consideration of the cases of which I have given details does not give much support
The toxic theory, but rather favors the purely nervous theory of the disease. Case III certainly seems to have been purely nervous as on the removal of the cause of a nervous condition the edema did not reappear. Case IV was probably another case of the same character, but it is unfortunate that the patient did not have the same procedure carried out.

Cases I and II might be thought to have as a cause a toxic origin to the gastric and intestinal troubles which are present. It is a question however whether these troubles are not due to an exudation taking place from the mucous membranes of the affected organs. This is supported by the fact that the patient mentioned in Case I has lately suffered from hemorrhage from the bowel. She has had at the same time attacks of the edema in her hands and feet and the bleeding from the bowel may be simply the same process going on there. The only difference
seeing that the exudation is haemorrhagic in the latter position.
Some cases of this disease do lend themselves to the toxic theory but
the cases which I have mentioned certainly seem to show that there are
many cases which are purely nervous in character.

Diagnosis.

This as a rule is
an easy matter. In cases affecting
the feet, nasal and cardiac
edema may have to be eliminated
and the decision is made after
an examination of the urine.
As a rule, no albuminuria occurs
in these fugitive edemas but
occasionally a transient albuminuria
is met with which is easily
distinguished.

Prognosis.
The prognosis in these cases
is good as the disease is not dangerous
to life unless the swellings have a tendency to occur in the larynx.
In such a case there is risk of sudden death due to oedema glutitidae.

Bibliography

Graham. Canadian Practitioner. 1883
Gowers. Diseases of the nervous System. 1886
Crocker. Diseases of the Skin. 1888

Clouston. "neuroses of Development." 1891

Reports of Johns Hopkins University.

Jamican. "Edinburgh Medical Journal." 1883