Abstract
Angioneurotic edema is a rare (1/100,000 births/inhabitants in France for the hereditary form) but potentially severe disease (risk of fatal laryngeal edema). It is a relapsing subcutaneous or submucosal edema caused by a deficiency in C1Inh (inhibitor of the C1 fraction of complement). From one individual to another, the episodes can be very different, but in a given individual, they often recur at the same site. The localization of the edemas varies widely: the limbs, the ENT (ear, nose, throat) region (life-threatening), digestive tract (the episode resembles a surgical emergency) etc... These edemas appear after trauma or stress, even minor; they do not respond to corticosteroids or antihistamines. Angioneurotic edema can be hereditary (autosomal dominant inheritance) or acquired (associated with a lymphoproliferative syndrome; presence of anti-C1Inh autoantibodies). All clinically suspicious cases should be subjected to the inddepth exploration of C1Inh (dosages of C3 and C4, weighted and functional dosage of C1Inh, immunoblot, search for anti-C1Inh antibodies). Hereditary forms are treated with Danazol and Tranexamic acid; concentrated C1Inh (blood-derived product) is used exclusively for very severe episodes. The treatment of acquired forms is not codified.

Keywords
angioneurotic edemas / angioedemas / C1Inh / danazol / C1Inh concentrate
**Name of the disease and synonyms**
Angioneurotic edema, angioedema

**Names of excluded diseases**
Allergic Qui ncke's edema, vasomotor edemas, histaminic edema.

**Definition**
It is a limited subcutaneous or submucosal edema, lasting at least 12 hours and relapsing more-or-less frequently. It is caused by a defective synthesis and/or functional impairment of C1Inh (inhibitor of the complement component C1 or, C1-esterase inhibitor). Angioneurotic edema (ANE) can be hereditary or acquired.

**History**
1882: First description by Dr. von Quincke
1917: Crowder and Crowder showed that hereditary ANE is transmitted by autosomal dominant inheritance
1963: Donaldson and Evans showed that it is linked to a quantitative or qualitative deficit in the C1Inh protein (inhibitor of the complement component C1 or, C1-esterase inhibitor)
1972: First published case of acquired ANE in the context of a lymphoproliferative syndrome
1976: Efficacy of danazol for ANE was shown in a double-blind study
1986: The gene encoding for C1Inh was identified on chromosome 11
1986: First case of acquired ANE caused by the presence of anti-C1Inh antibodies
1998: Bradykinin appears to be the main mediator of angioedema
2002: First animal model (mouse) of hereditary angioedema created by Prof. Davies.
2004: First therapeutic trials with kallikrein inhibitor and bradykinin receptor antagonist

**Diagnostic criteria**
The different ANE (hereditary types I and II, acquired types I and II, drug-induced) have the same symptoms but the biological characteristics and therapeutic management differ.
The diagnosis is often made late. Hereditary ANE is diagnosed on the average 7-12 years after the first attack. In such a case, the entire family, including asymptomatic members, should undergo screening. Acquired ANE may be the first sign of a severe pathology (neoplasms/malignancies, hemopathies).
Diagnosis of hereditary angioedema is based on precise diagnostic criteria that have been validated by the European study group on hereditary OAN (Table 1).

**Table 1: Diagnostic criteria of hereditary OAN**

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Biological criteria</th>
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<tbody>
<tr>
<td><strong>Major</strong></td>
<td></td>
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<tr>
<td>1-limited Subcutaneous angioedema, not associated with urticaria, lasting at least 12 hours and relapsing frequently</td>
<td>1-C1Inh concentration below 50% of the normal value; protein concentration is measured in two distinct samples taken from the same individual &gt;1 year old.</td>
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<tr>
<td>- Recurrent idiopathic abdominal pain lasting at least 6 hours</td>
<td>2- C1Inh functional activity below 50% of the normal value; protein activity is measured in two distinct samples taken from the same individual &gt;1 year old.</td>
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<tr>
<td>- Recurrent laryngeal edema</td>
<td>3- Detection of a C1Inh mutation altering the gene product synthesis and/or function.</td>
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<tr>
<td><strong>Minor</strong></td>
<td></td>
</tr>
<tr>
<td>Family history of recurrent edema and/or recurrent abdominal pain and/or recurrent laryngeal edema</td>
<td></td>
</tr>
</tbody>
</table>

ANE with weighted dosage and functional analysis of C1Inh, anti-C1Inh immunoblot and search for anti-C1Inh antibodies.

**Incidence**
ANE is a rare disease, hereditary ANE has a worldwide prevalence of 1/100,000, i.e., 350 individuals in France and 10,000 to 50,000 in Europe.
For acquired ANE, only about 50 cases have been reported in the literature since 1972.

**Clinical description**
The clinical picture can vary widely from one patient to another, and even among members of the same family. ANE presents as follows:
1) Subcutaneous or submucosal, white, soft, non-pruritic edema that occurs episodically and lasts 3-5 days, often with an area of predilection

http://www.orpha.net/data/patho/uk-OAN.pdf
for each patient. These edemas do not respond to treatment with corticosteroids or antihistamines. The triggering events are: any trauma, even minor, stress, certain times of the female hormonal cycle.

2) Episodes of abdominal pain mimicking a surgical emergency (intense pain, contracture, occlusion...).

Morbidity, mortality
Edema affecting the ear, nose, throat (ENT) regions can be life threatening (25% mortality due to laryngeal edema not treated early enough).

Some patients (14-34%) undergo laparotomy for abdominal pain. Almost half the patients are hospitalized at least once for an ANE episode. Up to 144 days per year of disability (depending on the patient) are responsible for absenteeism and a depressive syndrome.

Management/treatments

Management
Patients with ANE should be referred as early as possible to clinical and biological specialists; they must assure that the pharmacy of the hospital closest to their residence has a supply of C1Inh concentrate (Baxter Laboratories). C1Inh should be available at home for patients at high risk for ANE.

It is essential that the patient be informed about the disease, its treatments and its consequences, and carries a card identifying the disease.

Treatment

1) Hereditary ANE
Chronic treatment for frequent and/or severe attacks (edema of the ENT region)
Danazol (increases C1Inh synthesis): 50-600 mg/day depending on the clinical response (after having controlled for the absence of contraindications or their elimination). The minimal dose required to achieve a satisfactory clinical effect should always be investigated. The treatment requires biannual hepatic function monitoring, biological follow-up is unnecessary Tranexamic acid: 3-8 g to be administered 3 or 4 times a day (when no contraindicated).

Treatment of moderate attacks
Danazol: 200 mg/8 h
Tranexamic acid: 1 to 2g every 4 hours

Treatment of severe life-threatening attacks
Hospitalization in an intensive care unit is necessary with administration of C1Inh concentrate, 25 U/kg. This treatment is effective within the first 30 min following injection, but is a blood-derived product. Switching to the administration of decreasing doses of Danazol is necessary (600 mg/day for 8 days, followed by 400 mg/day for 8 days, then 200 mg/days for 8 days, then discontinuation or continuation of the standard Danazol dose for those patients already under treatment).

Prophylactic treatment
Any surgical intervention (even without anesthesia), including dental work, must be scheduled. Hospitalization at least 24 h before the intervention, with Danazol administration 600 mg/day for the preceding 5-10 days. For emergency interventions, C1Inh concentrate (25 U/kg) should be given. Control for C1Inh level before any surgical intervention and then continuation of the treatment 3 days after using same dose are required.

2) Acquired ANE
- Type I: Tranexamic acid, Danazol, treatment of the associated disease is primordial and helpful in controlling angioedema.
- Type II: Tranexamic acid, Danazol, corticosteroids, cyclophosphamide, plasma exchanges, treatment of the associated disease (Danazol and C1Inh concentrate are not recommended).
- Drug-induced: definitive banning of the triggering molecule C1Inh can be effective but at higher doses than those used in the hereditary forms.

3) Contraindicated drugs
DextranS, ACE inhibitors, angiotensin II antagonist, cyproteron acetate (Di ane pill), Androcur.
Use of progestative pills is preferable to use of oestroprogestative pills.

3 ) Children
About 50-75% of children will the first attack before 15 years old.
Children can have very serious abdominal attack 50% of girl will have more attack after puberty
Treatment as adult for indications Tranexamic acid: 20-30mg/kg/day for chronic treatment and 10mg/kg every 6 hours for attack treatment
Danazol: 100-400 mg per week
Prophylactic treatment: danazol 10mg/kg per day 10 days before the intervention

4 ) Women
Contraception: progestative pill and intra uterin device are well tolerated; oestroprogestative pill worsened OAN in almost all cases
Menses worsened OAN for 40%
Menopause improve OAN for 31%
Pregnancies worsened OAN for 35.7% and improved it for 27%. There are only 7.8% of attacks during or just after deliveries. Natural
deliveries must be done if possible and peridural anesthesia is possible. Tranexamic acid can be proposed during pregnancies after the first term. Danazol must be avoided. C1Inh concentrate must be present in the delivery room; it must be administrated in case of caesarean or in case of attack during delivery. There no more gynaecological events (abortion, cancer,...) than in general population. Fertility is the same

Etiology
Classification
1) Hereditary ANE
Is transmitted by autosomal dominant inheritance; thus all affected individuals are heterozygotes. It appears particularly in adolescents and young adults (20-40 years old) and can have two forms:
type I, which concerns 85% of the cases, is caused by the defective synthesis of C1Inh (low levels of C1Inh);
type II, affects 15% of the cases and is the consequence of a functional abnormality of C1Inh (normal concentration of C1Inh but a low level of functional activity).

2) Acquired ANE
Develops especially in individuals over 50 years and can be induced in three situations:
type I results from the excessive intake of C1Inh secondary, which results into the hyperactivation of the classical complement pathway mediated for example by immune circulating complexes (in lymphoproliferative syndrome, autoimmune disease...);
type II is the consequence of the neutralization of C1Inh by antibodies;

3) Oestrogen dependant angioedema
Angioedema appeared with oestrogen treatment (contraceptive pill, substitutive hormonal treatment) or during pregnancies. We can find a low C1Inh functional level.

4) Angioedema appeared with ACE inhibitors
(with an incidence of 1-3/1,000 users per year) and with angiotensin antagonist receptors.

Pathophysiology
C1Inh (the only known inhibitor of C1), controls the classical complement pathway, the contact phase of coagulation and the fibrinolytic cascade. It inhibits factor XII by 90%, and kallikrein and plasmin by 42%. In the case of a C1Inh deficit, any endothelial trauma will overactivate the contact phase of coagulation and the classical complement pathway, and will lead to the release of large quantities of bradykinin and kinin-like substances which will trigger edema.

Method of biological diagnosis
The weighted dosage of C1Inh must be measured in serum (collected in a dry tube). Three techniques are available: radial immunodiffusion, electroimmunodiffusion and nephelometry. C1Inh function is analyzed by measuring the inhibitory activity of plasma C1Inh (collected on citrate or EDTA) against C1s with the kinetic test devised by the Immunology Laboratory of Grenoble. Other determinations can be performed with other substrates; commercially are sold available kits (e.g.,The binding site, Quidel, etc.). The C1Inh protein is analyzed by vertical electrophoresis throught a sodium dodecyl sulfate-polyacrylamide gel (SDS-PAGE), followed by C1Inh immunoblotting. In this way, the native (that is to say functional) forms of C1Inh can be distinguished by their higher molecular mass, 105 kDa, from those that have been truncated (non-functional), 95 kDa, or those complexed with C1s. The search for anti-C1Inh antibodies is done by enzyme-linked immunosorbent assay (ELISA). The result is positive or negative; the antibody level is not measured, as it has no clinical value. Indeed, it has been shown that the level is not correlated with the severity of the disease.

Prenatal diagnosis/genetic counseling
For hereditary ANE, genetic studies are in progress. There are many mutations, with the discovery of almost one different mutation per family (more than 300 mutations). For a child born to an affected parent, it is not necessary to undertake prenatal genetic testing. Nor is it necessary to measure C1Inh in cord blood because the concentration does not reach its maximum before the 6th month of life. To determine if a child is affected, C1Inh should be dosed after the 6th month.

Unresolved questions
Genetic studies are advancing and will probably help improve our understanding of the wide variety of clinical pictures. Therapeutic management is not optimal; available treatments have major side effects. New therapies are needed; bradykinin-receptor antagonists and kallikrein inhibitors may be of benefit in treating ANE. Acquired ANE are poorly known; no therapeutic protocol has been well defined.

References
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http://www.orpha.net/data/patho/uk-OAN.pdf


