Review Article

Epidemiology and Management of acquired angioedema due to c1 inhibitor deficiency

Abstract:

AAE-C1-INH (acquired angioedema owing to C1-inhibitor (C1-INH) deficiency) is a dangerous illness that can lead to asphyxiation due to laryngeal edoema. It's linked to diseases like malignant B-cell lymphoma and others. Clinically, the angioedema symptoms that define AAE are indistinguishable from those seen in HAE patients who have a C1-INH deficit owing to mutations in one of the two alleles that code for this protein. AAE is caused by a deficit in (C1-INH), which can be caused by either consumption (type 1) or inactivation (type 2). An autoimmune illness or a malignant tumor can both cause enhanced catabolism. The sole clinical distinction between HAE and AAE is the age at which symptoms appea, AAE-C1-INH is usually diagnosed after 40 years of age. There is no licensed therapy for AAE-C1-INH at this time. AAE-C1-INH attacks are treated with HAE-C1-INH medicines such plasma-derived C1-INH concentrate (pdC1-INH) and the bradykinin B2 receptor antagonist, icatibant. These on-demand medications are thought to be most helpful when provided early in the attack. However, there is a scarcity of published data on the efficacy and safety of AAE-C1-INH therapies.

Comment [M1]: 1-Abstract must be revised and make it to the point.
2- Epidemiological and management touch must be included in Abstract.
3-Abstract must be title relevant

Comment [M2]: Key words should be included

Introduction:

Angioedema is characterized by one or more patches of well-demarcated, non-pitting edoema of deep subcutaneous tissues. The face, lips, tongue, and oropharynx are the most often affected areas, although it can also affect the genitals, distal extremities, and gastrointestinal mucosa. Because of the risk of life-threatening airway impairment, it is critical to diagnose angioedema as soon as possible. [1] AAE-C1-INH (acquired angioedema owing to C1-inhibitor (C1-INH) deficiency) is a dangerous illness that can lead to asphyxiation due to laryngeal edoema. It's linked to diseases like malignant B-cell lymphoma and others. [2]

Acquired angioedema due to C1-inhibitor (C1-INH) deficiency (AAE-C1-INH) or angioedema owing to acquired C1-INH deficiency (AAE-C1-INH) is characterised by acquired C1-INH deficiency, recurrent angioedema, and complement pathway hyperactivation. Due to edoema of the gastrointestinal mucosa, patients have recurring swellings or attacks of the skin (facial, limbs, and genitals) as well as severe stomach episodes, often with diarrhoea and vomiting. They may also have edoema of the upper respiratory tract, oral mucosa, and tongue, which can be life-threatening. Asphyxiation has been documented as a cause of death. Attacks frequently last 2 to 5 days and have no obvious cause. AAE-C1-INH has no epidemiological data, however its prevalence has been estimated to be between 1:100,000 and 1:500,000. [2-5]

Clinically, the angioedema symptoms that define AAE are indistinguishable from those seen in HAE patients who have a C1-INH deficit owing to mutations in one of the two alleles that code for this protein. Because angioedema is mediated by bradykinin episodically produced by improper activation of the contact-kinin system lacking its key physiologic regulator C1-INH in both types, this may be expected. Patients with AAE, like those with HAE, do not experience a significant urticaria flare. Patients with AAE, like those with HAE, do not experience a significant urticaria flare. Angioedema is characterised by disfiguring, non-pitting, non-pruritic edoema of the skin (face, limbs, genitals), severe abdominal pain due to edoema of the gastrointestinal mucosa leading to temporary bowel occlusion, life-threatening edoema of the upper respiratory tract, and edoema of the oral mucosa and tongue. [6]

C1-INH-HAE (types 1 and 2) has a lower activity of C1-inhibitor owing to a mutation in the C1-inhibitor gene, whereas C1-INH-AAE has a deficit in C1-inhibitor due to autoimmune disorders. A considerable number of individuals with HAE who have a normal C1-inhibitor have elevated factor XIIa activity due to an FXII mutation (FXII-HAE). Treatment of C1 inhibitor-dependent angioedema relies on restoring regulation of BK formation by inhibiting CP proteases or inhibiting BK-mediated effects at the BKR2 on endothelial cells by restoring the balance between CP inhibitors and BK breakdown. [7]

Etiology:

hereditary angioedema (HAE) and acquired angioede AAE are uncommon. AAE is caused by a deficit in (C1-INH), which can be caused by either consumption (type 1) or inactivation (type 2). An autoimmune illness (e.g., systemic lupus erythematosus) or a malignant tumour can both cause enhanced catabolism (e.g., lymphoma). Angioedema can reoccur at any time and persist anywhere from two to five days. It might induce significant stomach discomfort owing to gastrointestinal mucosa edoema, in addition to the edoema of the locations listed above. Recurrence of AAE has been linked to a variety of diseases, including lymphoproliferative illnesses of various types. [1,8,9]

Comment [M3]: ?

The activation of the classical complement pathway and complement consumption, as well as the activation of the contact system, leads to the production of the vasoactive peptide bradykinin, increased vascular permeability, and angioedema, when C1-INH activity is reduced. Anti-C1-INH inactivating autoantibodies are usually linked with lymphoproliferative disorders ranging from monoclonal gammopathies of undetermined significance (MGUS) to non-lymphoma Hodgkin's (NHL) and/or AAE. The presence of actual B cell malignancy, non-malignant B cell proliferation, and pathogenic autoimmune responses shows that AAE patients are all impacted by altered B cell proliferation regulation, despite their clinical progression. [10]

B-cell lymphoproliferative diseases such as MGUS and non-Hodgkin lymphoma are both B-cell lymphoproliferative illnesses. Plasmocytoma, Waldenström's macroglobulinemia, and other lymphoproliferative diseases can all develop from MGUS. It's unclear how lymphoproliferative diseases cause C1-INH deficiency. C1-INH binding to the MGUS dysprotein or directly to lymphoma tissue may result in a low level of C1-INH. Anti-C1-INH autoantibodies play a less obvious function in C1-INH deficiency. MGUS might be the cause of AAE-C1-INH in the presence or lack of anti-C1-INH autoantibodies, and malignant lymphoma could be the cause of AAE-C1-INH in the presence or absence of dysproteins or anti-C1-INH autoantibodies. Some people with AAE-C1-INH have solely C1-INH neutralising autoantibodies and no additional symptoms. Whether lymphoproliferative diseases (MGUS and lymphoma) and anti-C1-INH autoantibodies have a same pathogenic pathway that leads to C1-INH deficiency is unknown at this time. [2]

Epidemiology:

Comment [M4]: Epidemiology must be in world, and local aspect and prevalence, surveillance study must be included.

Only around 1% to 2% of angioedema cases are classified as HAE or AAE, with HAE being 10 times more prevalent than AAE. While the prevalence of AAE is difficult to assess because to its rarity and possibility for misdiagnosis, some experts estimate it to be between 1:100,000 and 1:500,000. Trauma, medical procedures, emotional stress, menstruation, oral contraceptives, infections, and medicines are all potential causes, however flare-ups are unpredictable. Other important criteria include the fact that more than 90% of patients acquire AAE after the age of 40, and that those with AAE exacerbations have stomach pain less than 50% of the time, compared to those with HAE who have abdominal pain more than 80% of the time. [1]

The acquired deficit of C1 inhibitor (C1-INH), hyperactivation of the classical cascade of human complement, and recurring angioedema symptoms are the three major aspects of the acquired angioedema (AAE) condition, which was initially characterised by Caldwell in 1972. With little over 100 people recorded in the literature, it is considered a relatively unusual disorder. it's only estimated about its prevalence in the absence of epidemiological data. some Researchers detected one AAE for every ten individuals with the genetic type of C1-INH deficiency in their database of angioedema patients (hereditary angioedema, HAE). The population's minimal prevalence of HAE is 1.41/100,000, with an average estimated frequency of 1:10,000 to 1:50,000. As a result, a rough estimate of AAE prevalence might be anywhere between 1:100,000 and 1:500,000. Because the illness is commonly undiagnosed, experts suspect that true number is significantly greater. [6,11-14]

Diagnosed:

AAE-C1-INH is usually diagnosed after 40 years of age. In contrast to the kinds of hereditary angioedema (HAE) that are caused by or related with particular mutations in the genes coding for C1-INH, factor XII, plasminogen, or angiopoietin, AAE-C1-INH has no genetic connection or family history of angioedema. AAE-C1-INH patients exhibit low plasma levels of C1-INH (functional and antigenic) and C4, which are generally less than half of what they should be. The majority of AAE-C1-INH patients have lower C1q levels than HAE-C1-INH patients. Anti-C1-INH autoantibodies and the lack of C1-INH genetic alterations can help doctors diagnose AAE-C1-INH. [2]

The sole clinical distinction between HAE and AAE is the age at which symptoms appear, which occurs in more than 90% of HAE patients in their second decade of life and after the fourth decade for those with AAE. Looking at varied rates of recurrence at certain areas reveals some further slight variances. Angioedema of the gastrointestinal mucosa generating abdominal discomfort is reported by over 80% of HAE patients, although only about half of our AAE patients and about a third of those from Bouillet et al reported similar symptoms. Nonetheless, in the literature, AAE has been associated with stomach symptoms. In HAE patients, cutaneous angioedema is usually limited to the limbs. Even though this area is also present in individuals with AAE, angioedema occurs more commonly in the face than in the limbs, and the tongue and uvula are frequently involved. [6,15-18]

In a research by Bork K, et al, it was discovered that 1 patient with AAE-C1-INH for every 9.3 patients with HAE-C1-INH had the condition. In additional investigations, incidence rates of 1:8.8, 6%, and 10% were found. Bork K's clinical picture of AAE-C1-INH patients varies from that of a large group of HAE-C1-INH patients. In comparison to HAE-C1-INH patients, AAE-C1-INH patients have a larger number of face swellings (29.6% compared 1.6%), a lower number of extremities swellings (25.7 percent versus 45.1 percent), and a higher number of tongue swellings (1.8 percent versus 0.3 percent). The difference in swelling patterns between AAE-C1-INH and HAE-C1-INH demonstrates that a low level of functional C1-INH activity does not influence the swelling pattern on its own. In addition, the number of patients with previous erythema marginatum in AAE-C1-INH patients (4.5%) is lower than in HAE-C1-INH patients (5.5%). (30 to 60 percent). [2,19-22]

Treatment:

There is no licensed therapy for AAE-C1-INH at this time. AAE-C1-INH attacks are treated with HAE-C1-INH medicines such plasma-derived C1-INH concentrate (pdC1-INH) and the bradykinin B2 receptor antagonist, icatibant. These on-demand medications are thought to be most helpful when provided early in the attack. However, there is a scarcity of published data on the efficacy and safety of AAE-C1-INH therapies, and none of it has been fully investigated. [2]

The goal of treatment for a patient with AAE should be to prevent angioedema-related deaths first, and secondly to prevent angioedema-related disabilities. The cause of angioedema-related deaths is laryngeal edoema. The similar strategy has been employed for AAE based on the success of plasma-derived C1-INH replacement treatment in reversing laryngeal edoema in individuals with HAE. This medication works in the majority of AAE patients, but not all, and by experience, some AAE patients grow less susceptible to plasma-derived C1-INH over time or require higher dosages. There is no known therapeutic alternative to plasma-derived C1-INH for life-threatening angioedema attacks in patients with AAE since no other medication for angioedema attacks has been extensively utilised in people with AAE. Invasive operations have just been performed on non-responsive patients in order to maintain upper airway patency during an emergency. [6]

in a research A few AAE-C1-INH patients have been reported to require therapy with large doses of pdC1-INH or to have been entirely or partially resistant to this treatment. Autoantibodies to C1-INH concentrate were found in several of these individuals. These findings reveal that the great majority (93.8%) of attacks in patients with anti-C1-INH autoantibodies react favourably to pdC1-INH, and that the response rate was comparable to those without anti-C1-INH autoantibodies (99.4 percent of attacks). As a result, patients who have anti-C1-INH antibodies can react to pdC1-INH. [2]

Short- and long-term prophylaxis uses attenuated androgens (17-alkylated androgens), such as danazol and stanozol. Attenuated androgens have been proven to lower the frequency and severity of attacks in randomised, double-blind, placebo-controlled crossover trials. Prospective open-label studies back up this reduction in frequency and severity. Furthermore, reduced androgens resulted in a full remission in a considerable number of patients. Virilization, weight gain, voice deepening, altered lipid metabolism, hypertension, increased liver enzymes, and, in rare cases, liver neoplasms are the most prevalent adverse effects of androgen therapy. [7]

Shortening attacks with plasma-derived C1-INH on-demand therapy, avoiding attacks with long-term prophylaxis with antifibrinolytics or androgens, or treating the accompanying illness can all help to reduce impairment linked to angioedema

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recurrences. When the linked disease has a clear signal to be treated, the latter is the preferred option. AAE resolution varies depending on the severity of the underlying illness, ranging from symptomatic improvement to complete biochemical and clinical recovery. Treatment of the underlying condition for the sole purpose of controlling angioedema symptoms necessitates a thorough risk/benefit analysis. Because the accompanying condition is almost invariably lymphoproliferative, deciding whether to put a patient on chemotherapy or immunosuppression is not always easy. In both HAE and AAE, long-term therapy to avoid angioedema symptoms is commonly employed. While androgen derivatives are highly efficient as preventative medicines in HAE, they may not be as effective in AAE. The reason behind this is a little ambiguous. it's known that attenuated androgens can raise C1-INH levels in the blood. Even while therapeutic androgen dosages in HAE do not necessitate a detectable rise in C1-INH in plasma, it is plausible that these medicines are dependent on C1-INH formation and that their efficacy is reduced when C1-INH catabolism is quick. Antifibrinolytic medicines, on the other hand, the second class of pharmaceuticals used for symptom prevention in HAE, appear to be more effective in AAE than in HAE. [6,23-26]

Ecallantide (Dx88) is a recombinant protein produced in Pichia pastoris that inhibits KK selectively. Ecallantide reduced the time it took for symptoms to improve from 240 minutes in the placebo group to 165 minutes in the treatment group. Ecallantide may certainly lessen the length of an attack, according to an open-label follow-up research, however 5% of the patients reported hypersensitive responses. Icatibant inhibits BK-induced vasodilation in vivo as a selective BKR2 antagonist. BKR1 does not interact with Icatibant. Icatibant has been demonstrated to be successful in the treatment of acute attacks in two randomised, double-blind controlled studies. Icatibant reduced the median time to alleviation of symptoms from 4.6 hours in the placebo group to 2.5 hours in the treatment group in the For Angioedema Subcutaneous Treatment (FAST) 1 trial. [7,27-30]

Conclusion:

AAE-C1-INH (acquired angioedema owing to C1-inhibitor (C1-INH) deficiency) is a dangerous illness that can lead to asphyxiation due to laryngeal edema. Although

the disease in uncommon there's no enough published data about the disease prevalence and numbers is believed that is much higher than reported. Distinguishing of the acquired and hereditary angioedema relies on age of onset, acquired is commonly reported after age of 40. As of treatment although there's no standard licensed treatment for the disease medical teams relies on HAE-C1-INH medicines such plasma-derived C1-INH concentrate (pdC1-INH) and the bradykinin B2 receptor antagonist, and icatibant. We hope for more studies on efficacy and safety of these drugs as well as the developing of new drugs.

References:

Comment [M7]: References must be increase please

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