Recurrent Angio-oedema – Three Cases of C1 Inhibitor Deficiency


Abstract
C1 Inhibitor deficiency is a rare disorder, characterised by recurrent angio-oedema of skin, upper respiratory and gastrointestinal tracts. It can be a mimicker of acute abdomen or anaphylaxis to drug or food and lead on to unnecessary overtreatment. Three case reports of such patients with history of recurrent abdominal pain and angio-oedema due to C1 Inhibitor deficiency is reported here.

Introduction
C1 inhibitor (C1-INH) is a plasma protease inhibitor that regulates several pro-inflammatory pathways. In disorders where C1 inhibitor is deficient or defective, there are recurrent episodes of angio-oedema, without urticaria or pruritus, which most often affects the skin or mucosal tissues of the gastrointestinal and upper respiratory tract. Laryngeal involvement may cause fatal asphyxiuation.

The disorders of C1 inhibitor may be divided into two broad categories: Hereditary angio-oedema (HAE) and Acquired C1 inhibitor disorders. C1-INH regulates three inter-related pathways, the coagulation, fibrinolytic, and kinin-generating pathways. The function of C1-INH in the kinin generating pathway most directly relates to the pathogenesis of HAE. The defective function of C1INH leads to excess of bradykinin, a potent vasodilatory peptide, underlies the pathogenesis of angio-oedema in HAE, although the precise biochemical events responsible for an attack have not been fully identified.¹

Case Report
Case 1
The patient was an 18 year old girl, who presented with sudden onset oedema of face and lips, which was suggestive of angio-oedema. It was not associated with itching or urticaria. There was no history of any drug or food intake that precipitated the event. She did not give history of drug allergy. No history of wheeze, dyspnoea or cough was associated with the event. She had abdominal pain from the second day of admission which was poorly localised and colicky type of pain. It was not associated with vomiting and was not precipitated by food intake. She had several episodes of similar abdominal pain in the past five years, one or two in a month, which were self limiting in about two or three days. She had two similar attacks of angio-oedema three years back. All these episodes resolved over a period of two to five days time. There is no history of similar illness in her family.

She had severe angio-oedema of her face, but there was no stridor and no laryngeal oedema on laryngoscopy. Her vital signs were stable and examinations of all other systems were within normal limits. She was treated with adrenaline and steroids from outside but there was no decrease in the oedema. She had a normal haemogram and ESR was 38 mm/hr. Her urine routine examination, renal and liver function tests were
all within normal limits. With this clinical picture of recurrent attacks of abdominal pain and angio-oedema, the possibility of a C1 inhibitor deficiency was suspected. The serum C4 levels, which may be used as a screening test in suspected cases\(^2\) was low: 2.2 mg/dl (normal >14 mg/dl). So even without a family history, there was a strong clinical suspicion of C1 inhibitor deficiency and serum C1INH functional assay showed a very low value, < 10 % (normal > 67 %) confirming the diagnosis. In the absence of family history for the disease, the possibility is that of an acquired C1 inhibitor deficiency. In the acquired form there is excessive consumption of C1INH either due to immune complexes formed between anti-idiotypic antibody and monoclonal IgG produced by B cell lymphomas, monoclonal gammopathies or to an autoantibody directed to C1INH in an autoimmune disease.\(^4\) This patient did not have any lymphadenopathy or organomegaly to suspect lymphoma. USG abdomen also did not show hepatosplenomegaly or lymphadenopathy. Bone marrow examination showed normal myeloid and erythroid maturation without any abnormal cells. Tests for serum ANA and AntiDsDNA were negative and other clinical features were absent to satisfy the criteria for diagnosis of an autoimmune disease like SLE. Serum electrophoresis did not show an M band. The evidence for an underlying cause could not be found out. But, angio-oedema may develop before or after symptoms of systemic disease and the clinical onset of the conditions may be separated by years. She was initially treated with supportive measures and her angio-oedema and abdominal pain resolved in 5 days. Since she is having recurrent attacks of abdominal pain or angio-oedema every month, she was started on long term prophylaxis against these attacks. Tranexamic acid and Danazol are available for long term prophylaxis.\(^2\) Tranexamic acid is the recommendation as the initial drug and if it is not effective, it is substituted by Danazol. This patient was started on tranexamic acid 1 gram three times daily and is being followed up regularly to look for appearance of any underlying disease as the cause. She had improvement in symptoms for the last 6 months, with only 3 episodes of mild abdominal pain and did not develop angio-oedema.

**Case 2**

This patient was a 17 year old girl. She presented with a history of recent hospitalisation with severe abdominal pain and generalised nonpruritic face and limb swelling. She was having hypotension on presentation and was treated as a case of anaphylaxis, with adrenaline and steroids. She had many episodes of abdominal pain and history suggestive of angio-oedema in the past. Each time she was treated as anaphylaxis to food or drug and got relieved in few days time. Her elder sister had died of similar complaints and dyspnoea at a younger age. Her vital signs were stable and examinations of all other systems were within normal limits. She also had a normal haemogram and ESR, renal and liver function tests. With a positive family history and history of recurrent episodes of abdominal pain and angio-oedema the possibility of hereditary angioneurotic oedema was suspected. Her serum C4 level was 6 mg/dl (normal >14 mg/dl) and serum C1INH antigenic levels were 4.7 mg/dL (normal > 200 mg/dL) confirming the diagnosis. She had symptoms suggestive of a severe attack, in which treatment with C1 esterase inhibitor replacement protein (C1INHCRP) is recommended. Since it was not available, she was treated with fresh frozen plasma, tranexamic acid and symptomatic measures till the symptoms resolved. She is having recurrent attacks of abdominal pain or angio-oedema almost every month. Hence this patient was started on tranexamic acid 1 gram three times daily for long term prophylaxis and was followed up regularly. She had good improvement in symptoms for the last one year, with only few episodes of mild abdominal pain and did not develop angio-oedema.

**Case 3**

This patient is a 30 year old lady. She presented with history of swelling of the lips which she noticed for last 2 years. From her childhood, she had history of recurrent colicky abdominal pain of mild to severe intensity. She had consulted many doctors and had undergone several investigations including imaging and endoscopy studies. Her brother, 33 year old, who had a similar history, died one year back due to sudden onset facial swelling and dyspnea. Her vital signs were stable and examinations of all other systems were within normal limits. Routine investigations done were within normal limits. Serum C4 level was 1.9 mg/dl (normal > 14 mg/dl). A C1INH antigenic level was estimated and was found to be 2.8 mg/dL (normal > 200 mg/dL). With the typical clinical history and family history of similar illness, the diagnosis was a hereditary angioneurotic oedema due to C1INH deficiency. She had a mild attack and was treated with tranexamic acid and symptomatic measures and she improved over 3 days. As this patient also had recurrent attacks of abdominal pain, she was started on tranexamic acid 1 gram three times daily and followed up monthly. She had improvement in symptoms for the last 2 years, with only few episodes of mild abdominal pain and one attack of angio-oedema of lips which were treated supportively.

**Discussion**

C1 inhibitor deficiency (C1-INH) is a rare disorder
that can be due to genetic or acquired causes. The prevalence of hereditary angio-oedema (HAE) is estimated at 1 individual per 50,000\(^2\) in which there are mutations in the C1 inhibitor gene are present. It may be divided into two types; Type I HAE (85 per cent of affected families) is characterised by low levels and reduced functional tests of C1 inhibitor (C1-INH).\(^3\) Type II HAE is characterised by reduced functional tests of C1-INH in the presence of normal or elevated C1-INH protein levels, which is due to a dysfunctional inhibitor.\(^3\) Hereditary angio-oedema usually presents in children and adolescents and is not associated with other underlying diseases. Acquired C1 inhibitor disorders involve antibodies which bind to the C1 inhibitor and thereby block function or lead to premature clearance. The suspicion of this disease should be there in cases where there is recurrent angio-oedema without urticaria, unexplained recurrent episodes of self-limited colicky abdominal pain, family history of angio-oedema, unexplained laryngeal oedema (even a single episode) and low C4 levels especially in the setting of angio-oedema.\(^2\) Levels of C4, C1 inhibitor or C1 inhibitor functional assay are recommended as initial tests in these patients.\(^2\) Acquired C1 inhibitor deficiency may be associated with underlying systemic disorders. In the review of a total of 128 cases of acquired C1 inhibitor deficiency,\(^4\) lymphatic malignancies were identified in 35 per cent, monoclonal gammopathy of uncertain significance (MGUS) in 32 per cent, other malignancies in 6 per cent, and autoimmune disease in 8 per cent. No underlying disease was found in 15 per cent. The first case had no family history of similar disease and had onset of the symptoms in the adolescence. So the possibility is that of an acquired C1 inhibitor deficiency, but there was no evidence to suggest an underlying cause. But, angio-oedema may develop before or after symptoms of systemic disease, and the clinical onset of the conditions may be separated by years. So she should be followed up for development of an underlying autoimmune disease or malignancy. The second and third patients have hereditary C1INH deficiency with a positive family history and recurrent symptoms from childhood. Mild acute attacks are treated with symptomatic measures and hydration. For moderate to severe acute attacks, treatment with C1 esterase inhibitor replacement protein (C1INH-RP) is recommended. It is costly and is not freely available. Therefore, plasma, in the form of FFP, has been used in the treatment of acute laryngeal and severe abdominal attacks, as it contains C1 inhibitor. Antifibrinolytics like tranexamic acid and epsilon amino caproic acid can be used in the acute treatment of severe attacks, as a second-line therapy. Their mechanism of action is not known.\(^2\)

Prevention of further attacks can be established through general measures like avoidance of triggers like trauma to the face, recognition and prompt treatment of oral and dental infections, drugs like ACE inhibitors, oestrogen containing drugs and tamoxifen. Short term prophylaxis is recommended for patients if intubation, dental work, oral surgery, or general surgery is planned. Danazol 10 mg/kg/day is the recommendation for short term prophylaxis. Long-term prophylaxis is given to decrease the overall number of attacks. It should be considered for patients with more than one severe event per month or who are disabled for more than five days per month or who have experienced a laryngeal attack. Tranexamic acid is preferred drug at a dose of 3 g/day in 3 divided doses. If it is ineffective, Danazol or C1INH-RP is considered.\(^2\)

References