

# Review of Type III Non-Hereditary Angioedema Patients in Manitoba.

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## Short report

**Keywords:** Nonhereditary angioedema with normal C1 inhibitor, Nonhereditary angioedema with normal C1 level and function

**Posted Date:** September 16th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-76142/v1>

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# Abstract

**Introduction:** Non-hereditary angioedema with normal C1 esterase inhibitor level and function (NHAE-nC1INH) is a novel entity. The diagnosis of NHAE-nC1INH requires a high index of suspicion, given that there are no laboratory tests to confirm the diagnosis. There is limited evidence on the treatment efficacy for short- and long-term prophylaxis, and acute attacks. The aim of the study is to describe a cohort of NHAE-nC1INH in Manitoba, including an estimate of prevalence, as well as to analyze the response to plasma derived C1 esterase inhibitor (pdC1INH), and a bradykinin-2 receptor antagonist (Icatibant).

**Methods:** A retrospective chart review of patients diagnosed with normal C1 esterase level and function angioedema seen at the Clinical Immunology and Allergy Clinic at the Health Sciences Centre in Winnipeg, Manitoba, was done. Inclusion criteria included the following: (1) Reside within Manitoba (2) Aged 18 years and older (3) Angioedema without urticaria (4) Normal C1-INH antigenic level and function (5) No symptom resolution with antihistamines, epinephrine or corticosteroids. (6) No family history.

Five patients were included in the study who met the above inclusion criteria. The five patients charts were reviewed. Response to pdC1INH and Icatibant were defined as time to improvement of angioedema symptoms.

**Results:** Four out of five patients had an effective response to pdC1INH for prophylactic treatment and for on-demand treatment for angioedema episodes. pdC1INH was ineffective in 1 patient for prophylaxis and on-demand treatment; tranexamic acid was successful for prophylactic treatment in 1 patient who did not respond to pdC1INH for prophylaxis and for on-demand treatment. 3 of 5 patients have tried Icatibant. All three patients were not responsive to Icatibant.

**Conclusion:** This study suggests that pdC1INH may be an efficacious treatment option for NHAE-nC1INH patients. Larger studies are required to better elucidate the effectiveness of on-demand and prophylactic treatment for NHAE-nC1INH.

## Introduction

Recurrent angioedema is a serious, potentially life threatening condition characterized by swelling of the subcutaneous and submucosal tissue involving the skin, gastrointestinal tract, and the upper respiratory tract leading to airway compromise, asphyxiation and potentially death.<sup>1-7, 9,10</sup> Angioedema can be histamine, cytokine or bradykinin-mediated. Three types of hereditary bradykinin-mediated angioedema have been described. Types I and II are associated with low quantitative and qualitative of C1 esterase inhibitor (C1INH), respectively, as a result of a mutation in the C1-INH gene, SERPING 1. Type III hereditary angioedema, now known as HAE with normal C1INH (HAE-nC1INH), described by Binkley et al. in 2000, is associated with normal levels of C1 level and function. To date there are four types of HAE-nC1INH: mutation of the Factor XII gene, angiopoietin gene, plasminogen gene and of unknown origin.<sup>1,3-5,7-11</sup> Recently, a novel type of non-hereditary angioedema with normal C1 esterase inhibitor level and function (NHAE-nC1INH) has been described.

The diagnosis of NHAE-nC1INH requires a high level suspicion given there are no laboratory tests to confirm the diagnosis of NHAE-nC1INH.<sup>7</sup> The patient must not have a family history of angioedema, no urticaria and have no symptomatic response to antihistamines, steroids or epinephrine.<sup>1</sup>

There is limited evidence on the treatment efficacy for short- and long-term prophylaxis, and acute attacks.<sup>5</sup> For types I and II HAE, plasma derived C1INH (pdC1INH), has been approved in Canada for prophylaxis and treatment for acute angioedema attacks.<sup>4</sup> A bradykinin-2 receptor antagonist, Icatibant, has been approved in Canada and in other countries for symptomatic treatment for Type I and II HAE based on three Phase III trials.<sup>5,11</sup> However, it has not been approved for NHAE- or HAE-nC1INH.

The exact prevalence and incidence of NHAE-nC1INH is unknown. McKibbin et al. characterized six patients in Manitoba, Canada, with HAE-nC1INH, and analyzed each patient's response to C1INH, tranexamic acid and to a bradykinin-2 receptor antagonist.<sup>1</sup> The aim of this study is to analyze the prevalence of NHAE-nC1INH in Manitoba as well as to analyze the response to C1INH, tranexamic acid and to a bradykinin-2 receptor antagonist.

## Methods

A chart review of patients diagnosed with non-hereditary normal C1 esterase level and function angioedema seen at the Clinical Immunology and Allergy Clinic at the Health Sciences Centre in Winnipeg, Manitoba, were reviewed. Inclusion criteria included the following: (1) Reside within Manitoba (2) Aged 18 years and older (3) Angioedema without urticaria (4) Normal C1-INH antigenic level and function (5) No symptom resolution with antihistamines, corticosteroids, or epinephrine (6) No family history. Five patients were included in the study who met the above inclusion criteria.

University of Manitoba's Research Ethics Board approval was obtained for this study.

The information abstracted in this study included, gender, age, site of angioedema, prophylactic medication, medication for treatment, and time to response of treatment. The time to response of treatment was defined as the number of hours from the time the treatment was given to resolution.

## Results

The study population included 5 patients, 3 females, and 2 males, with an age range of 30–56 years. 4 of 5 patients had an effective response to pdC1INH for prophylactic treatment and for on-demand treatment of angioedema episodes. pdC1INH was ineffective in 1 patient for prophylaxis and on-demand treatment; tranexamic acid was successful for prophylactic treatment in the 1 patient who did not respond to pdC1INH. 3 of 5 patients have tried Icatibant. All three patients did not respond to Icatibant.

Patient 1 is a 53-year-old female with previous episodes of angioedema involving her face, lips, tongue and abdomen, who was responsive to pdC1INH, and now is in remission since starting menopause. Previously, her symptoms completely resolved within 24 hours of receiving pdC1INH. Since being in

remission she now only receives pdC1INH as needed for infrequent episodes of angioedema. She has never tried Icatibant.

Patient 2 is a 38-year-old female, with hypothyroidism on levothyroxine, who develops recurrent episodes of facial and abdominal angioedema, lasting 3–5 days without treatment. Her angioedema episodes worsened post-partum with each of her three children. Despite prophylactic treatment of 1500U of pdC1INH intravenous three times a week, she continues to have recurrent episodes of angioedema two to three times per week. The symptoms resolve within 1–2 hours with pdC1INH for acute treatment. Has never had access to Icatibant.

Patient 3 is a 49-year-old female, with asthma, chronic rhinosinusitis with nasal polyps and GERD, with recurrent episodes of angioedema involving her tongue, throat, abdomen and vagina, not responsive to 1500U of pdC1INH intravenous three times a week, Tranexamic acid 500 mg BID and Montelukast 10 mg po daily. Despite the prophylactic treatment, she continues to have recurrent angioedema episodes three times per week. The symptoms resolve within 2 hours with pdC1INH for acute treatment for 75% of the episodes. Acute episodes of angioedema were not responsive to Icatibant.

Patient 4 is a 30-year-old male who has recurrent episodes of angioedema involving his lips and scrotum. He has had no further episodes since initiating pdC1INH 1500 intravenous three times per week. No response to Icatibant

Patient 5 is a 56-year-old male with recurrent swelling of face, lips, tongue and hands. pdC1INH as prophylaxis and as on-demand treatment was unsuccessful. He responded to Icatibant within 2 hours, although on 2 occasions, Icatibant had no effect, and the angioedema persisted for 24 hours. The number of episodes significantly reduced with tranexamic acid prescribed prophylactically. He had one mild episode following missing one dose of Tranexamic acid, since starting Tranexamic acid 12 months ago.

Patient	Age	Sex	Triggers	Site(s) of angioedema	Prophylaxis	Medications used for acute treatment
1	53 AC	F		Face, lips, tongue, abdomen	pdC1INH (1500U IV weekly)	C1INH (1500U IV prn)  In remission since menopause  No access to Icatibant
2	38 CC	F	Menstruation, URTI, lack of sleep	Face, abdomen	pdC1INH (1500U IV 3x/week)	pdC1INH (1500U IV prn)  No access to Icatibant  2-3 episodes per week
3	49 RM	F		Lips, tongue, throat, abdomen, vagina	pdC1INH (1500U IV 3x/week)  Tranexamic acid 500 mg po BID  Montelukast 10 mg po daily	pdC1INH (1500U IV prn)  No response to Icatibant  3 episodes per week
4	30 MD	M		Lips, scrotum	pdC1INH (1500U IV 3x/week)	pdC1INH (1500U IV)  No response to Icatibant
5	56 MM	M	No known triggers	Face, lips, tongue, hands	Tranexamic acid 500 mg po BID	No response to C1INH  No response to Icatibant

Patient	Duration of episode without treatment	Duration of episode with pdC1INH	Duration of episode with Icatibant
1	72 hours	24 hours	N/A
2	72–120 hours	1–2 hours	N/A
3	96 hours	2 hours for 75% of the episodes	No response
4	24 hours	No response	No response
5	24 hours	No response	No response

## Discussion

There are few studies on NHAE-nC1INH. However, in HAE-nC1INH, the clinical manifestations are highly variable. The overall prevalence of NHAE-nC1INH remains unknown. According to this study, the prevalence of NHAE-nC1INH in Manitoba is approximately 5 per million people, with a population of 1.3 million people.<sup>1</sup> HAE-nC1INH tends to present during adulthood, whereas Type I and II HAE usually is present during childhood. HAE-nC1INH predominantly affects women, which is consistent with this study of 3/5 of the study population being women.<sup>4,7,9,10</sup> Individuals with HAE-nC1INH have more facial and oropharyngeal angioedema and less frequent gastrointestinal involvement, compared to Type I and II HAE.<sup>4,7,10</sup> All patients are at risk for life-threatening laryngeal angioedema. The angioedema lasts 2–5 days without treatment.<sup>7,9,10</sup> The episodes are exacerbated with physical trauma, stress, sleep deprivation, illness, menstruation, pregnancy oral contraceptives, hormone replacement therapy, and/or angiotensin-converting enzyme inhibitors.<sup>4,7,9,10</sup>

Most current treatment options for HAE-nC1INH are aimed to reduce the production and/or biologic effects of bradykinin, which is the main culprit causing the angioedema episodes. To date, there are no randomized, controlled studies of on-demand and prophylactic treatment in patients with HAE-nC1INH or NHAE-nC1INH.<sup>5</sup> Numerous randomized, controlled studies have shown success with the on-demand and prophylactic treatments used for Type I and II HAE. Plasma-derived C1INH seems to be effective used both as an on-demand and prophylactic treatment, even though patients with nC1INH have no deficiency or dysfunction of C1INH. A study completed in 2016 by Bork and colleagues concluded a mean duration of an episode acutely treated with pdC1INH was 26.6 hours compared to 64.2 hours without treatment.<sup>12</sup> This study concluded a mean duration of an episode acutely treated with pdC1INH was 15 to 15.2 hours compared to 57.6 to 67.2 hours without treatment. Icatibant, a bradykinin-2 receptor antagonist, has also shown to be an effective on-demand treatment. Boccon-Gibod and Bouillet concluded, symptom improvement within a median of 40 minutes with Icatibant.<sup>11</sup> In this study, no patients responded successfully to Icatibant. However, some studies have reported individuals having no response or delayed responses to Icatibant. Inactivated plasma kallikrein (eg Ecallantide) and fresh frozen plasma have been

shown to be effective in 1 patient in HAE-nC1INH not responding to pdC1INH or Icatibant. Several studies have shown effective response to tranexamic acid, an antifibrinolytic, in patients with HAE-nC1INH.<sup>4</sup>

In this study 4 of 5 had an effective response to pdC1INH for on-demand treatment, and 3 out of 5 had reduction in the number of episodes with pdC1INH. One of the patients who responded to pdC1INH on-demand treatment did not have reduction in the number of episodes with pdC1INH prophylaxis. In addition, one patient had reduction in the number of weekly episodes with pdC1INH prophylaxis, however, still had frequent episodes. No severe or serious adverse effects were reported. One patient responded successfully to tranexamic acid as a prophylactic treatment, and was nonresponsive to C1INH for prophylactic and on-demand treatment, and nonresponsive to Icatibant. Unfortunately public and private insurance in Manitoba will not cover the cost of Icatibant in these individuals; hence few have had the opportunity to try it.

In the McKibbin et al study, all six patients with HAE-nC1INH successfully responded to Icatibant; compared to this study where no patients with NHAE-nC1INH responded to Icatibant for acute treatment. This could be largely due to the small sample size; only 3 of the 5 patients had the opportunity to use Icatibant. Thus larger, double blind placebo controlled studies are required to further analyze the effectiveness of Icatibant in both, NHAE-nC1INH and HAE-nC1INH.

The main limitation of this study is the low number of individuals included. It is very possible that not all individuals treated for this condition in our clinic are accounted for in the study. The diagnosis of NHAE-nC1INH is challenging. It requires a high-level of clinical suspicion, as well as, the patients to be knowledgeable about their family history. Currently, there are no laboratory tests to confirm the diagnosis of NHAE-nC1INH.

## **Conclusions**

Non-hereditary angioedema with normal C1 inhibitor is a rare entity, characterized by recurrent, angioedema affecting the skin, upper airway and gastrointestinal tract, unresponsive to antihistamine, corticosteroid and epinephrine. To date, there are no approved on-demand and prophylactic treatments for NHAE-nC1INH. This small study showed a trend of effectiveness for on demand therapy with pdC1INH, an inconclusive response with pdC1INH prophylaxis and no response with Icatibant.

## **Declarations**

### **Acknowledgements**

The authors for like to thank Jadiann Shore for her administrative assistance.

### **Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### **Availability of data and materials**

The datasets generated and/or analysed during the current study are not publicly available due to individual health data privacy, but are available from the corresponding author upon reasonable request.

### **Ethics approval and consent to participate**

Ethics approval was obtained by the University of Manitoba's Research Ethics Board.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interest.

### **Authors' Contributions**

KH was responsible for data acquisition, analysis, and manuscript drafting. CK assisted in study design, patient acquisition, and review/revision of manuscript.

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