HAESI
HEREDITARY ANGIOEDEMA SOCIETY OF INDIA

2nd National Conference of HAE Society of India (HAESICON)

May 15, 2022

Advanced Paediatrics Centre
PGIMER, Chandigarh, India

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WELCOME MESSAGES

Prof. Surjit Singh

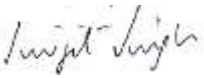
Dear Colleagues,

We are delighted to welcome you to the 2nd National Conference of the Hereditary Angioedema Society of India!

Since its inception in February 2022, the Hereditary Angioedema Society of India has been involved in spreading awareness about HAE in the country. The society has also made attempts in providing better treatment options for patients with HAE in India. As a result, the first line medications for HAE are likely to be available in the country by the end of 2022.

I congratulate the Executive Board of the society and the organizing committee for taking up the initiative and organizing this meeting at PGIMER, Chandigarh.

I wish the conference all success.



Prof. Surjit Singh
Head, Department of Pediatrics and Chief, Allergy Immunology Unit
Postgraduate Institute of Medical Education and Research, Chandigarh

Prof. Sunil Dogra

As president of HAESI, it is my pleasure to welcome you all for HAESICON 2022!

The first conference of HAESI held virtually on 15th May 2021 was a grand success on every count. I am immensely pleased that 2nd Conference of HAESI (HAESICON 2022) is being held in physical mode following ease out of Covid pandemic situation. This is a momentous day to hold conference on Hereditary Angioedema Day – 15th May.

I am grateful to all the faculty for making this conference possible. The faculty includes some of the most distinguished names in the field of hereditary angioedema from India and across the globe - Dr. Hilary Longhurst (New Zealand), Dr. Avner Reshef (Israel), Dr. Anete Grumach (Brazil) and Dr. Markus Magerl (Germany).

The programme includes didactic lectures and panel discussions on various aspects of hereditary angioedema. For the first time, we will have Dr. Hilary Longhurst Oration, award paper presentations by residents, fellows and young faculty, a parallel patient meeting (being organized by Ms. Fiona Wardman, HAE international organization), representation from the International Alliance of Patient Organization and launch of an educational booklet on hereditary angioedema

While going through details of scientific sessions, it is obvious that they are well conceived and designed. My heartfelt appreciation to team scientific for their untiring efforts. Besides scientific feast, hope you will find some time to enjoy tourist attractions at Chandigarh and nearby hill stations. Please follow Covid appropriate behaviour for your and safety of others.

Thanks for joining us in the conference – HAESICON 2022!

Warm Regards

Prof. Sunil Dogra
President
HAE Society of India

Dr. Ankur Kumar Jindal

The Hereditary Angioedema Society of India was founded in February 2021 in Chandigarh with an aim to increase awareness and to promote knowledge about HAE amongst physicians, to improve quality of life of patients and bring better treatment options for HAE in India. Over the last 1 year, society has made a substantial contribution towards improving the life of patients with HAE.

We organized the 1st National conference of HAE Society of India on May 16, 2022 (the international HAE day). This was a virtual conference and was attended by more than 300 delegates across the country.

We are now hosting the 2nd National Conference of HAE Society of India in Chandigarh on May 15, 2022. This is the first ever physical meeting on HAE in the country. We are honored to have Dr. Hilary Longhurst, Dr. Anete Grumach, Dr. Avner Reshef and Dr. Markus Magerl along with national experts on HAE as faculty for this conference. To encourage young talent, we have invited award paper presentations from fellows, students and young faculty.

Such meetings are often incomplete without involvement of patient groups. We are honored to have Ms. Fiona Wardman and Dr. Shaibal Guha who will lead a parallel patient meeting during the conference.

All this work would not have been possible without the able leadership of Prof. Surjit Singh, Head, Department of Pediatrics and Prof. Sunil Dogra, President, HAE Society of India. I wish to thank Prof. Surjit Singh and Prof. Sunil Dogra for providing continuous support throughout this journey. I also wish to thank other executive board members and organizing team of the 2nd National Conference of HAE Society of India for accomplishing this job very efficiently.

I hope that the delegates would benefit from the proceedings of the conference.

Welcome to Chandigarh - The City Beautiful!

Dr. Ankur Kumar Jindal
Secretary General
HAE Society of India

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SCIENTIFIC PROGRAMME

Time	Topic	Speaker/Panellist
09:00 - 09:10 HRS	Introduction and Welcome	Prof. Surjit Singh
09:10 - 09:25 HRS	Inaugural speech	**Chief Guest** Dr. Ratna Devi **Guest of Honour** Dr. Rashmi Sarkar
09:25 - 09:35 HRS	HAE Society of India (HAESI): Past, Present and Future	Dr. Ankur Jindal
Session 1:	**Chairpersons: Dr. Deepti Suri, Dr. M. Sendhil Kumaran** **Repertoire: Dr. Mushtaq Ahmad Bhat**	
09:35 - 10:05 HRS	Recent updates on classification of angioedemas	Dr. Avner Reshef
10:05 - 10:35 HRS	Clinical manifestations and diagnosis of hereditary angioedema (HAE)	Dr. Hilary Longhurst
10:35 - 11:00 HRS	High Tea	
Session 2:	**Chairpersons: Dr. Sunil Dogra, Dr. Ankur Jindal**	
11:00 - 12:00 HRS	1st Dr. Hilary Longhurst oration 'Biomarkers in Hereditary Angioedema'	Dr. Anete S Grumach
Session 3:	**Chairpersons: Dr. Vinay K, Dr. Rashmi Sarkar** **Repertoire: Dr. Suparna Guha**	
12:00 - 12:30 HRS	Disease monitoring tools in HAE	Dr. Markus Magerl
Session 4:	**Chairpersons: Dr. Markus Magerl, Dr. Anete S Grumach, Dr. Avinash Sharma**	
12:30 - 13:00 HRS	Award winning abstract presentations (6)	Dr. Suprit Basu Dr. Reva Tyagi Dr. Spoorthy Raj Dr. Archan Sil Dr. Kapil Jain Dr. Rajni Sharma

13:00 - 14:00 HRS	Lunch Break	
Moderators: Dr. Hilary Longhurst, Dr. Anete S Grumach, Dr. Avner Reshef, Dr. Markus Magerl, Dr. Anuradha Bishnoi, Dr. Saniya Sharma		
13:00 - 14:00 HRS	Guided Poster walk	
Session 5:	**Chairpersons: Dr. Shaibal Guha, Dr. Ratna Devi, Ms. Fiona Wardman**	
14:00 - 14:10 HRS	An overview of activities of HAE international organization	Ms. Fiona Wardman
14:10 - 14:30 HRS	A survey on burden of illness of HAE in India	Ms. Deborah Corcoran
Session 6:	**Chairpersons: Dr. Biman Saikia, Dr. M.Sendhil Kumaran Repertoire: Dr. Suman Balan**	
14:30 - 15:00 HRS	Identification of prodromes in patients with HAE: Diagnostic and therapeutic implications	Dr. Avner Reshef
15:00 - 15:30 HRS	Hereditary angioedema with normal C1- inhibitor: An emerging entity	Dr. Anete S Grumach
Session 7:	**Chairpersons: Dr. Sandesh Guleria, Dr. Pratap Patra Repertoire: Dr. G.P. Thami, Dr. (Col.) Ajay Chopra**	
15:30 - 15:50 HRS	Rare dermatologic diseases and HAE landscape in India: gaps and challenges	Dr. Murlidhar Rajagopalan
15:50 - 16:20 HRS	Recent advances in management of HAE	Dr. Markus Magerl
16:20 - 16:45 HRS	Tea/ Coffee Break	
Session 8:	**Chairpersons: Dr. Amit Rawat, Dr. Sagar Bhattad Moderator: Dr. Hilary Longhurst**	
16:45 - 17:45 HRS	Panel discussion: How can we improve the care of patients with HAE in India? **Sponsored by M/s Takeda Pharmaceutical Co.**	Panellists: Dr. Avner Reshef Dr. Anete S Grumach Dr. Markus Megerl Dr. Ratna Devi Ms. Fiona Wardman
17:45 - 17:50 HRS	Concluding remarks and vote of thanks	Dr. Ankur Jindal

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ORAL ABSTRACTS

OA 1-Clinical profile of hereditary angioedema: our experience over 26 years from North India

AUTHORS:

Suprit Basu, Ankur Kumar Jindal, Reva Tyagi, Prabal Barman, Archan Sil, Sanchi Chawla, Anit Kaur, Rahul Tyagi, Rajni Sharma, Deepti Suri, Amit Rawat, Sunil Dogra[1], Anuradha Bishnoi[1], Vinay K[1], Surjit Singh

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Background: Hereditary angioedema (HAE) is a rare genetic disorder. There is limited data in the literature on patients with HAE from developing countries.

Objective: This study was carried out to analyse the clinical manifestations and laboratory features of patients diagnosed with HAE between January 1996 and April 2022 in a tertiary care centre in North India

Methods: Data of patients with HAE were retrieved from medical records of patients registered in the Paediatric Immunodeficiency Clinic, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Results: In this study, we included 145 patients (85 male and 60 female) from 53 families who were diagnosed to have HAE. The median age at onset of symptoms was 14 years (range 1-40 years), and the median age at diagnosis was 27 years (range 2-80 years), with a median delay in diagnosis of 11 years (range 0-44 years). Family history was present in 124/145 (85.5%). The mean frequency of exacerbation was 1.6 attacks/month. Swelling over the face (eyelids and/or lips) was the commonest presentation 93.7% (136/145), followed by extremities and genitalia (Table-1). Laryngeal edema was seen in 45.5% (66/145) cases, 17 of them having multiple attacks. Abdominal symptoms were noted in 62.1% of patients; only one patient presented with the acute surgical abdomen and underwent exploratory laparotomy. No patient in this study had central nervous system complaints. Mean duration of follow-up is 40.2 months (total- 5829 patient-months). Type I HAE was seen in 119 patients, and 18 patients had type-II HAE. Normal C1 INH HAE was seen in 8. Mean serum C4 level and C1 INH were 10.4 mg/dL(Normal-16.7-38.5 mg/dL) and 10.8 mg/dL (Normal-19-37 mg/dL) respectively. Abdominal symptoms and males were significantly more in type-I HAE, whereas laryngeal edema and tongue swelling were higher in type-II HAE(Table-2).

Conclusion: This is one of the largest cohorts of HAE from a developing country, and it shows that there is a median delay of 11 years for diagnosis of the disease. Hence patient awareness about this rare disease is required.

Table 1: Clinical features of HAE patients

Clinical features	Number of patients (n=145)
Asymptomatic	2 (1.3%)
Swelling over face (lips and/or eyelids)	136 (93.7%)
Swelling of extremities	116 (80%)
Swelling of genitalia	15 (10.3%)
Laryngeal edema	66 (45.5%)
Abdominal pain	90 (62.1%)
Tongue swelling	40 (27.5%)
Family history	124/145 (85.5%)
Low serum C4 (Normal- 16.7-38.5 mg/dL)	137 (94.5%)
Low serum C1 INH (Normal-19-37 mg/dL)	119 (82.1%)
Normal C1 INH HAE	8 (5.5%)

Table 2: Comparison between normal and low serum C 1 INH level:

Characteristics	Type-I HAE (n=119)	Type-II HAE (n=18)	p value
Male	76	4	0.001
Frequency of attacks (per month)	1.6	2	
Swelling of genitalia	11	3	0.275
Laryngeal edema	49	15	0.008
Abdominal swelling	84	4	0.001
Tongue swelling	28	10	0.0073

OA 2-Delay in diagnosis is the commonest proximate reason for mortality in hereditary angioedema: our experience at Chandigarh, India

AUTHORS:

Reva Tyagi, Ankur Kumar Jindal, Suprit Basu, Prabal Barman, Archan Sil, Sanchi Chawla, Deepti Suri, Amit Rawat, Surjit Singh

AFFILIATIONS:

Allergy Immunology Unit, Department of Paediatrics, Advanced Pediatrics Centre, PGIMER Chandigarh, India

Objective: To report our experience with mortality in patients with hereditary angioedema and to report factors associated with death in these patients.

Methods: We reviewed the medical records of all patients diagnosed to have HAE in the Pediatric Immunodeficiency Clinic, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India. Medical records of families who reported at least one death attributable to HAE were analysed in detail.

Results: Of the 53 families (145 patients), 13 families (25 patients) reported the death of at least one family member because of HAE. All these family members died because of laryngeal edema. Age at death was known in 20/25 patients. The median age at death was 31 years. Except for one patient who died while she was taking treatment for HAE, the diagnosis was not established prior to death in others. At the time of death of these patients, at least one other family member had angioedema episodes. However, despite a strong family history, the diagnosis could not be established.

In our cohort, only one patient died during follow up. This was a 17-year-old female who was diagnosed at ten years of age and was on long term prophylaxis with stanazolol and tranexamic acid. However, the drug compliance was not adequate because of the adverse effects in the form of amenorrhea and hirsutism. She developed an episode of laryngeal edema and died on the way to the hospital.

We also diagnosed a 21-year-old female during her antenatal period (9 weeks post-conception). Antenatal counselling was done, and the patient underwent chorionic villus sampling for the confirmation of the diagnosis in the fetus. The fetus was also found to have the same mutation in the SERPING1 gene as the patient. She opted for medical termination of pregnancy as there was a history of the death of family members.

Conclusion: Mortality is still a concern for patients with HAE in India. Laryngeal edema is the commonest cause. Delay in diagnosis is the commonest reason for mortality

OA 3-Bumpy journey in the management of HAE: HAE Registry from a Single Centre in South India.

AUTHORS:

Suma Balan[1], Mithun CB[1], Jyothy Srikanth[1], Gopikrishnan Anjaneyan[2], Spoorthy Raj DR[1], Sumanth Madan[1], Nandhetha Sreenivaasan[2].

AFFILIATIONS:

[1]Department of Rheumatology and Clinical Immunology, Amrita Institute of Medical Sciences, Kochi.
[2]Department of Dermatology and Venerology, Amrita Institute of Medical Sciences, Kochi.

Background: Hereditary angioedema is a rare genetic disorder with the autosomal dominant mode of inheritance, caused by mutations in components of the complement-kinin-coagulation family of proteins (SERPING1, Factor XII, Plasminogen) which culminate in enhanced activity of Bradykinin, contributing to episodes of vasogenic edema. Vascular endothelial instability due to mutations in the Angiopoietin gene has also been recently described as a cause of hereditary angioedema1,2. Episodes of angioedema associated with actual or functional deficiency of C1INH, low C4 levels, and familial clustering with associated pathogenic mutations help clinch the diagnosis of HAE.

Objectives: To describe the clinical profile and treatment approaches of HAE kindreds, stressing on the need for early diagnosis and easy availability of targeted therapies.

Results: Here we describe five families of HAE (total affected members = 31) who presented with typical symptoms of angioedema, with few members experiencing life-threatening episodes manifesting as laryngeal edema and distributive shock, with reported mortality in 4 families due to lack of timely diagnosis. The time of disease onset to diagnosis varied from 3 months to 37 years in our group.

All the families had low C1-INH and low C4 except for family 5, who had high C1-INH suggestive of functional C1-INH deficiency.

Most of the cases are managed on attenuated androgens with the use of FFP on a demand basis. One family with less frequent and less severe symptoms is maintained on Tranexamic acid.

Conclusion: Hereditary angioedema is potentially life-threatening in the absence of timely diagnosis and appropriate treatment. Lack of awareness results in undue delay in diagnosis and unwarranted treatment. Episodes of angioedema without associated urticaria, refractory to conventional anti-allergic measures with familial clustering, demands clinical suspicion for the same.

The side effect profile of currently used medications and lack of complete response necessitates the need for easy availability of safer targeted therapies.

References:

1. Zuraw BL, Christiansen SC. HAE Pathophysiology and Underlying Mechanisms. Clin Rev Allergy Immunol. 2016;51(2):216-229. doi:10.1007/s12016-016-8561-8
2. Banday AZ, Kaur A, Jindal AK, Rawat A, Singh S. An update on the genetics and pathogenesis of hereditary angioedema. Genes Dis. 2019;7(1):75-83. Published 2019 Aug 1. doi: 10.1016/j.gendis.2019.07.002

OA 4-Clustering of cases of Hereditary Angioedema in a small district in India: A unique experience with a founder mutation

AUTHORS:

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Background: Hereditary angioedema (HAE) is an autosomal dominant disorder characterised by episodic swelling of the face, limbs, genitals, airway and gastrointestinal tract. Most cases of HAE are caused by pathogenic variants in the SERPING1 gene. The genetic profile of HAE may vary in different countries. However, a founder mutation has not been previously reported in patients with HAE. We, herein, report the clinical and genetic profiles of patients with HAE from one district in India.

Methods: A field survey was conducted on March 13, 2022, in the Reasi district of Jammu and Kashmir and HAE cases were traced from 4 families. HAE was suspected depending on the clinical manifestations. Detailed clinical profile of each patient was noted, and samples were collected, stored and transported to our institute for analysis, including genetic tests.

Results: There were 24 patients with HAE from 4 families. Clinical data collection and laboratory investigations could be carried out for 18 patients. The median age at onset of symptoms and the median age at diagnosis were 15.5 (range: 5-25 years) and 33.5 years (range: 6-70 years), respectively. The median delay in diagnosis was 20.5 years (range: 3-50 years) with a male to female ratio of 2:7. Predominant sites of involvement were the face, eyelids, lips, tongue, back, hands, feet and genitalia. While history suggestive of laryngeal edema was elicited from 15/18 (83.3%) patients, abdominal symptoms were present in 14/18 (77.8%) patients. Swelling episodes were characterised by an average frequency of 2 episodes/ month and an average duration of 3 days. Prodromal symptoms varied from mild tingling and itching to pain and redness at the local site. Trauma was the commonest trigger of acute attack, followed by seasonal variation. C4 level was reduced in all the patients with a mean level of 0.058 g/L. However, the C1-INH level was normal in 7/18 (38.8%) patients indicative of type-II HAE, and reports of the rest of the patients are awaited. A pathogenic variant in exon 8 of the SERPING1 gene (c.1396 C>T, p.Arg466Cys) was identified in 3 families, while results of the 4th family are awaited. No link could be established between these four families.

Conclusion: We report a founder mutation in the SERPING1 gene from a small district in India, leading to the clustering of several cases in a small geographical area.

Image 1- With the families affected by HAE

OA 5-Negative pressure flash pulmonary edema (NPPE) in a child with hereditary angioedema (HAE)

AUTHORS:

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Negative pressure pulmonary oedema (NPPE) is an uncommon, however, potentially fatal complication due to rapid-onset upper respiratory tract obstruction. Laryngeal oedema due to hereditary angioedema (HAE) is another potential cause of upper respiratory tract obstruction. Most patients die because of asphyxiation caused by obstruction of the larynx. However, NPPE because of laryngeal edema has not been reported in patients with HAE.

A 14-year-old boy was diagnosed to have HAE at the age of 11 with splice site defect in SERPING1 gene {Exon 7 C.1232 C>G Sel 389 Stop} and was initiated on long term prophylaxis (stanozolol 2 mg per day). However, he had poor compliance to therapy and continued to have episodes of laryngeal oedema, which were managed at a nearby health care facility by using fresh frozen plasma (FFP).

In November 2021, he presented to the emergency room with sudden onset complaints of respiratory discomfort, was initiated on oxygen support and referred to our hospital in view of impending respiratory failure. A possibility of laryngeal oedema was considered, and he was immediately intubated. During the procedure of intubation, it was noted that he had pink frothy secretions with evidence of laryngeal oedema. Fresh-frozen plasma (FFP) infusion was initiated considering an acute attack. However, despite securing the airway, he remained hypoxic with a requirement of very high positive inspiratory pressure and high positive end-expiratory pressure. Chest X-ray showed diffuse air space opacification with air bronchogram suggestive of pulmonary oedema. A clinical possibility of flash pulmonary oedema was considered, and furosemide was started. He was continued on FFP infusions. Repeat chest X-ray after 24 hours of hospital stay was normal. The Extubation trial was deferred in view of the presence of laryngeal edema (on direct video laryngoscopy), and he was initiated on T-piece ventilation along with the continuation of FFP infusions. Repeat direct laryngoscopy at 48 hours of hospital stay showed minimal edema, and he was extubated, though FFP infusions were continued for 24hours after extubation. He was given 20 units of FFP over 84 hours. He was initiated on stanozolol (2 mg per day) and tranexamic acid (1500 mg per day) and discharged. He remains well on follow-up.

Hereditary angioedema (HAE) is an uncommon disorder characterised by recurrent episodes of subcutaneous and/or submucosal oedema predominantly affecting distal extremities, face, gastrointestinal tract and upper respiratory tract. Oedema of the larynx is a potentially life-threatening complication and may affect approximately 50% of all patients. NPPE is another potential complication of upper airway obstruction. Immediate release of this obstruction (either by endotracheal intubation or tracheostomy) with positive pressure ventilation and use of diuretics may lead to resolution within 24-48 hours. Timely recognition of laryngeal oedema in patients with HAE as well as recognition of NPPE may be lifesaving in these situations.

OA 6-Quality of life in patients with hereditary angioedema correlates with angioedema control: our experience at Chandigarh, India.

AUTHORS:

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Background: Hereditary angioedema (HAE) is an uncommon disease characterised by recurrent episodes of subcutaneous and/or submucosal edema. HAE is a chronic disease and leads to a major impact on quality of life(QoL). The lack of first-line medications for the treatment of HAE in India may lead to poor disease control and add to the poor quality of life. However, there are no data on the quality of life in patients with HAE in India. The angioedema quality of life (AEQoL) scale is a valid tool for the assessment of the quality of life in patients with HAE.

Objective: To assess the quality of life of patients with HAE using the AE QoL scale and identify the factors associated with impaired quality of life.

Methods: Patients were enrolled from the Allergy Immunology Unit at the Postgraduate Institute of Medical Education and Research, Chandigarh, India. Patients 18 years and above with confirmed diagnosis of HAE were enrolled. All patients were diagnosed to have HAE based on suggestive clinical symptoms, family history and supportive laboratory investigations. Patients were interviewed telephonically by a team of experts(Clinical psychologists and fellows in Pediatric Clinical Immunology and Rheumatology). AE-QoL has 17 items grouped into four dimensions: functioning, fatigue and mood, fears and shame, and food, and items are rated on a 5-point Likert scale. Both overall and dimension scores range between 0-100. Higher scores are suggestive of more impaired QoL. Disease control was assessed by angioedema control test (AECT) within a recall period of 4 weeks. Scores ≤ 10 indicated poor controlled disease.

Results: Seventy-one patients were enrolled in the present study (aged 18-80 years with a median age of 37 years). The median age at onset of disease and at diagnosis was 15years and 34 years, respectively. Approximately 60% of patients reported poor QoL, and 26.8% reported severely impaired QoL. Only 40% of patients reported normal quality of life (Figure). Patients with poor control over their disease reported significantly poorer QoL (p 0.002) than those who had a well-controlled disease. Disease control had a negative association with QoL (poor control over disease predicted poorer QoL). Sixty-five percent of patients reported poor control of the disease. Of these, 19.6% reported mild, 23.9% moderate, and 28.3 % had severely impaired QoL. On average, during the last month, 19 % of patients experienced ≥ 4 attacks, and 39.4% were asymptomatic. 19.7% were much concerned about the unpredictability of the disease, and 35.2% reported that their disease was very well controlled with therapy in the last one month.

Conclusion: This is the first study to report the quality of life in patients with HAE in India. Approximately 2/3rd patients have a poor quality of life, and it negatively correlates with disease control.

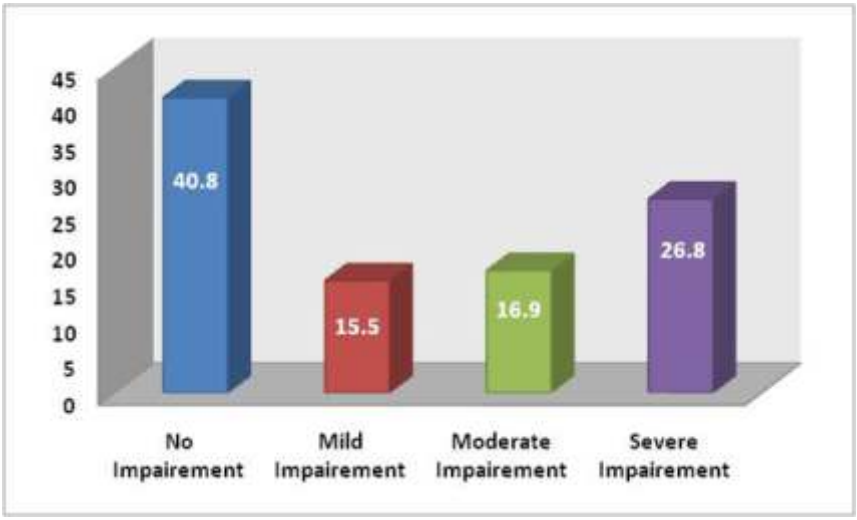

Figure I: Severity of Impairment in AE QoL

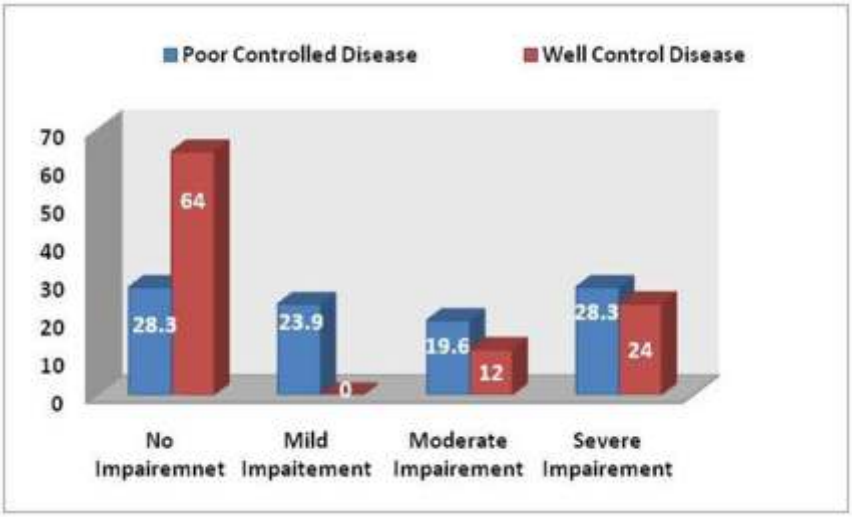

Figure II: Impact of Disease Control on AE QoL

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POSTER ABSTRACTS

PA 1-A retrospective analysis on prodrome in a cohort of Hereditary Angioedema patients from a tertiary care centre in North India.

AUTHORS:

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Introduction: Hereditary angioedema (HAE) is a disorder characterised by recurrent attacks of swelling characteristically involving the periorbital and perioral areas in response to increased production of bradykinin due to functional or quantitative deficiency of C1-inhibitor protein. Typically, the attacks are preceded by prodromes experienced by the patients, of which the most commonly described in the literature are unusual fatigue and erythema marginatum. In this study, we describe the profile of prodromal manifestation in our cohort of HAE patients.

Methods: Retrospective analysis was done using data that was collected from file records of patients enrolled in our clinic. Classification of HAE was made based on C4 and C1 inhibitor levels. Statistical comparisons were done using the chi-square test or Fisher exact test.

Results: Of 145 patients, details of prodrome symptoms were available for 85 patients (46 males, 39 females). The mean age at diagnosis of HAE was 12.07±9.46 years, with a mean delay in diagnosis of 9.4 years. The percentage of types of HAE for type I, II and III were 70%, 25% and 5%, respectively. 46(54%) patients reported a prodrome before their attack of HAE. The most common prodrome reported was the development of an erythematous rash or erythema marginatum (19%) followed by itching at the site prior to the onset of angioedema (14%). In the patients that did not have a prodrome, 56% were children, less than equal to 10 years of age. The males reported significantly less prodrome than the females (p=0.01). Type II HAE was significantly associated with tingling as a prodrome seen in 57% of the subcohort of patients (p=0.01).

Conclusion: About 50% patients in our cohort with HAE reported a prodrome. It is important to identify prodromes so timely therapy can be initiated. Early use of treatment during prodrome may decrease the severity of the attack.

PA 2- Genetic profile of patients with hereditary angioedema at a tertiary care referral hospital in North India

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Background: Hereditary angioedema (HAE) is an uncommon genetic disorder with autosomal dominant mode of inheritance. Most cases of HAE are caused by pathogenic variants in SERPING1 gene. There is a paucity of literature on the genetics of HAE from India.

Objective: To study the genetic landscape of patients with HAE from a tertiary care referral hospital in North India.

Design and Methods: Genetic studies of patients suspected to have HAE were carried out either using SERPING1 gene sequencing or targeted next-generation sequencing or whole-exome sequencing. MLPA for the SERPING1 gene was also carried out in a few patients.

Results: In this study, we included 145 patients from 53 families. Genetic screening of this cohort revealed variants in exon 2 to exon 8 of SERPING1 gene in 25 families. Eight families were found to have variants in exon 7. Mutation in exon 8 was found in 5 families. A single missense variant in exon 8 was reported in 3/5 unrelated families from a village, indicating a possible founder mutation. This was followed by variants in exon 3 and exon 6 with 4 families affected in each. Two families carried mutation in exon 5 of SERPING1 gene. Exon 4 and exon 2 were less commonly mutated with 1 family affected in each. The most common type of variant was missense followed by frameshift, nonsense and small deletion with 14, 7, 3 and 1 families affected, respectively. A total of 7 exonic variants detected were novel. Exon 7 had 4 novel mutations, followed by exon 5, 6 and 8 with 1 novel variant in each.

Intronic variants were also found in 6 families. Most of intronic variants lead to splice donor site defect. Four families had splice site variants located in intron 6. Intron 1, intron 2 was mutated in one family each. No pathogenic variants were detected in 8 families despite doing all investigations. NGS revealed large deletion in exon 8 of 1 family which was confirmed through MLPA. In addition to mutations in SERPING1 gene, variants in XPNEP2 and CPN1 gene were found in one family each.

Conclusion: This is the largest single-centre cohort data of patients with HAE in the country. Genetic profile of patients with HAE in India may be different from that reported from other countries. Most variants are seen in the later part of the gene (i.e. exon 7 and 8).

PA 3-Hereditary angioedema type 2 and Mediterranean stomatocytosis: an unusual association

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Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder characterised clinically by recurrent episodes of non-pruritic swelling, predominantly affecting distal extremities, face, gastrointestinal tract and upper respiratory tract. On the other hand, Mediterranean stomatocytosis/macrothrombocytopenia (MS) is a rare autosomal recessive disorder caused by enhanced gastrointestinal absorption of and reduced excretion of plant sterols (sitosterolaemia) and is characterised by short stature, chronic abdominal discomfort, splenomegaly and laboratory features of chronic haemolysis along with the presence of stomatocytic red cells and macrothrombocytopenia on blood films. To the best of our knowledge, HAE and MS have not been reported together in a single patient. We herein report one such case.

A 25-year-old male, born to a non-consanguineously married couple, along with her younger sister and brother, were diagnosed to have Mediterranean stomatocytosis (intermittent jaundice, failure-to-thrive, epistaxis, spherocytes, variable numbers of stomatocytes, reticulocytosis and thrombocytopenia on peripheral smear, increased osmotic fragility and homozygous mutation in ABCG5 gene [c.727C>T p.Arg243Ter].

Index patient presented with a 2-year history of recurrent episodes of non-pruritic non-erythematous swellings involving lower eyelids and forehead (once every 1-4 weeks and usually subside spontaneously by 2-3 days). His sister had one episode of swelling over her left ankle that subsided in 2 days. A clinical possibility of HAE was considered and was evaluated further. His C4 level was low [7.8 mg/dL (Normal range: 10-40 mg/dL)] and C1-esterase inhibitor (C1INH) level was normal (Normal range:19-37 mg/dL). His sister had normal C4 and normal C1INH levels. C1INH function could not be tested in any of them. A diagnosis of HAE type

PA 4-Normal C1 INH Hereditary angioedema -Our experience from North India

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Background: Hereditary angioedema (HAE) is characterised by sudden, episodic subcutaneous and/or submucosal swelling of the face, limbs, genitals, airway and gastrointestinal tract. It is caused by excess bradykinin production because of defective C1 inhibitor (C1-INH) protein. However, normal C1-INH HAE is a rare entity, and there are no reports from India. We report our experience with normal C1-INH HAE

Materials and Methods: Data of patients with suspected HAE with normal C1-INH were collected from the Pediatric Immunodeficiency Clinic, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh.

Results: Of the145 patients with HAE, 8 (5.5%) patients were suspected of having normal C1-INH levels. Of these, two patients were siblings. No family history of similar illness was seen in the remaining six patients. Of the eight patients, 62.5% were males, and 37.5% were females, while in the total HAE cohort, the proportion of males and females were 58.6% and 41.4%, respectively. The median age at onset of symptoms and the median age at diagnosis were nine years and four months (range: 8months - 32years) and 10.5 years (range: 3-36 years), respectively. Predominant sites of involvement were eyelids, face and lips. The other involved site that are involved are the tongue, back, hands, feet and genitalia. Other symptoms such as laryngeal edema, tongue swelling, and abdominal symptoms were seen in 25%, 25% and 12.5%, respectively. Prodromal symptoms were seen in 37.5% of the patients, with symptoms ranging from mild tingling, and itching to pain and redness at the local site. Triggers were seen in 37.5%. Trauma was the commonest trigger (in 25%), followed by intake of milk products and pickles. C4 levels and C1-INH levels were normal in all patients. However, the C1-INH function could not be tested. Whole-exome sequencing did not show any pathogenic variants. Six patients are receiving long term prophylaxis with tranexamic acid (3) or stanozolol (3).

Conclusion: We report our experience with normal C1-INH HAE. Limitations include the inability to perform C1-INH function and anti-C1-INH antibodies. Comparison between Type 1 HAE and Type 3 HAE.

Characteristics	Type-I HAE (n=119)	Type-III HAE (n=8)	p value
Frequency of attacks (per month)	1.6	2	
Laryngeal edema	49	2	0.366
Abdominal swelling	84	1	0.0005
Tongue swelling	28	2	0.737

PA 5-Challenging case of Hereditary Angioedema with Central Venous Sinus Thrombosis

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Introduction: Hereditary angioedema (HAE) is an autosomal dominant disease caused by either a lack of C1-inhibitor protein or dysfunctional C1-inhibitor protein. Drugs used in the treatment of HAE, such as danazol and tranexamic acid, are associated with an increased risk of venous thrombosis [1,2].

Case summary: A 41-year-old gentleman was well until the age of 30 years when he developed recurrent episodes of angioedema and abdominal pains. Episodes of angioedema would involve the face and lips lasting for 3-4 days, not responding to treatment with anti-histaminics. He continued to suffer for several years, and at the age of 37 years, he was diagnosed to have Hereditary angioedema type I with very low serum C1 esterase inhibitor levels (0.05 gm/L). He was initiated on prophylaxis treatment with danazol and tranexamic acid. Following treatment, the frequency of episodes of angioedema decreased to 1- 3 episodes per year. However, over the years, he defaulted on treatment and continued to have intermittent episodes of angioedema requiring fresh frozen plasma (FFP) transfusions. A Sanger sequencing, whole-exome sequencing and MLPA failed to identify a mutation (PGI, Chandigarh).

At the age of 40-years, he complained of severe headaches, following which he developed left-sided focal seizures. On evaluation, MR angiography showed the presence of a large-sized hemorrhagic infarct in the right frontal lobar region with thrombosis of the superior sagittal sinus and cortical veins of the right frontal region. He underwent an emergency right frontotemoroparietal decompressive craniectomy at Aster CMI Hospital, Bangalore. Danazol and tranexamic acid were withheld. During the postoperative period, while on mechanical ventilation, he developed marked swelling of the lips and tongue. He was treated with multiple FFP transfusions; however, the angioedema failed to subside. As danazol and tranexamic acid could not be used, and due to the lack of availability of C1 esterase inhibitor, he had to be managed only with FFP transfusions. Subsequently, the angioedema subsided in 3-4 days, and after a prolonged hospital stay, he was subsequently discharged. Recently, he underwent a cranial flap repair, during which he had another episode of angioedema which was managed successfully with FFP transfusion.

Conclusion: We hereby present a challenging case of a gentleman with HAE type 1 on treatment with danazol and tranexamic acid who presented with CVST. Thrombotic complications are very uncommon in patients with HAE. The cause of thrombosis in the index case is debatable as he was on tranexamic acid and danazol, which might have been contributory. This case also highlights the challenges involved in the treatment of life-threatening situations in HAE in the absence of availability of a C1-inhibitor.

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PA 6-HEREDITARY ANGIOEDEMA:- limited experience from a tertiary care centre in Himachal Pradesh

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Introduction: Hereditary angioedema (HAE), also known as Quincke's disease, is an autosomal dominant disease caused by deficiency or dysfunction of the C1 inhibitor. It classically manifests as recurrent attacks of intense, massive, localised edema without pruritis, affecting the skin, bowel, and upper airway. The diagnosis is made based on clinical history, physical findings, and a low level of C4. Positive family history strongly supports the diagnosis. We report two cases of hereditary angioedema over the past 2.5 years.

Case report: A 13-year female adolescent presented with swelling over both forearms for three days. The swelling was painless and non-pruritic. She did not have any significant family history. On examination, we found a non-pitting swelling over the left arm with no signs of inflammation. Based on this history and examination, a possibility of HAE was considered. Investigations revealed low C4 levels. C1 inhibitor levels and SERPIN gene mutation analysis were sent, and she was initiated on tranexamic acid. On treatment, she is doing well and has had only one episode since then, lasting for 2days.

The second case was a four-year boy who presented with recurrent episodes of non-itchy, painless swellings over the face, arms and lips for the last seven months, which were self-resolving and often associated with abdominal pain and vomiting. A family history of similar complaints was not found. Low C4 was documented on two occasions. C1 inhibitor levels and genetic analysis have been planned for this patient.

Conclusion:

- Hereditary angioedema is a debilitating disease with the autosomal dominant mode of inheritance, resulting in sudden onset of non-pitting, non-itchy edema commonly involving extremities, face and intestinal tracts.
- Positive family history is not seen in all cases.
- Laboratory investigations of low C4 levels and low levels or impaired functioning of C1 inhibitors help confirm the diagnosis.

PA 7- Identifying triggers in patients with Hereditary Angioedema – Our experience from developing nation

AUTHORS:

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Background: Hereditary angioedema (HAE) is characterised by non-urticarial, non-pruritic subcutaneous and/or submucosal swelling of the face, limbs, genitals, airway and gastrointestinal tract. The attacks are unpredictable, but people can sometimes associate them with various triggers, most commonly being mental stress, physical exertion, and temperature changes, amongst others. Here we describe a cohort of patients from a developing nation who had symptoms of HAE with various identifiable triggers.

Materials and Methods: Data of patients with HAE with various triggers related to edema attacks were collected from the Pediatric Immunodeficiency Clinic, Allergy Immunology Unit, Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Results: Of the 145 patients with HAE in our cohort, 38 (26.2%) patients could identify a trigger for their attacks. Twenty of the 38 patients (52%) had more than one trigger. Common triggers were trauma (65%), change in weather (36%) and stress (31%). Undue exertion (13%), mosquito bite (2%), wet clothes (2%) and menstruation (2%) were other less commonly identified triggers. Food was a trigger in 15% of patients. The same trigger was not associated with every edema attack for a particular patient. The patients who could identify the triggers could temporally correlate their attacks with triggering factors.

Conclusion: In our cohort, approximately 1/4th of all patients identified triggers for their attacks. It is important to identify triggers for most patients with HAE so that these can be avoided and angioedema attacks can be prevented in a proportion of cases. This is especially important for India as none of the first-line treatment options are available.

PA 8-Management of Severe Acute Attack of Hereditary Angioedema in Resource limited setting -A retrospective Analysis

AUTHORS:

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Introduction: Hereditary angioedema (HAE) is an autosomal dominant disorder due to low functional levels of C1-Inhibitor characterised by recurrent attacks of swelling involving the periorbital and perioral areas due to decreased inhibition of complement, kallikrein, clotting and fibrinolytic pathway. Typically, the attacks are benign but can also present as life-threatening laryngeal oedema requiring urgent in-patient management. We hereby present the management of the patient with severe HAE attack in our cohort.

Methods: Retrospective analysis was done using data that was collected from file records of patients enrolled in our clinic. Classification of HAE was made based on C4 and C1 inhibitor levels. Statistical comparisons were done using the chi–square test or Fisher exact test.

Results: Of 145 patients, 17 patients (12%) required in-patient management for acute severe attack of HAE (10 males,7 females). The mean age at diagnosis of HAE was 12.07±9.46 years, with a mean delay in diagnosis of 9.4 years. The percentage of types of HAE for type I, II and III were 70%, 25% and 5%, respectively. In comparison, males (66.7 %) were more predisposed as compared to females (33%) for recurrent severe attacks. Most of the patients (80%) were on a combination of Stanozolol and Tranexamic acid for prophylaxis and did not have more than one attack as compared to those who were on danazol alone. Patients who had the early age of onset of disease i.e., less than five years of age, were also more predisposed to have recurrent attacks i.e., more than two attacks (53%). It was also observed that delay in diagnosis of disease of more than ten years from the onset was also associated with recurrent attacks. We observed that response to Fresh frozen plasma was better with higher volume (15-20ml/kg) per attack (p=0.016).

Conclusion: Acute severe attacks of Hereditary Angioedema were managed in a tertiary centre with FFP infusions which replace the deficient C1 INH. The response is usually adequate in decreasing the duration and severity of the attack and prevents advanced airway management. FFP may be a good alternative treatment modality in a resource limited setting.

PA 9- Dermographism in patients with urticaria and angioedema- more than just skin deep

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Introduction: Markers like elevated serum IgE, D-dimer, and decreased Vitamin D3 and abnormal TSH are associated with refractory urticaria. However, the question remains whether the same holds true in patients with both angioedema and urticaria.

Materials and methods: We retrospectively reviewed charts of 50 patients with both angioedema and chronic spontaneous urticaria (Group-A) and 50 patients with only urticaria (Group-U). These patients had regular follow up in our clinic for at-least 3 months over the past 12 months and also had their serum IgE, serum vitamin-D, serum d-dimer level and serum TSH.

Results: The mean age of the patients and disease duration was not significantly different (A Vs U: 31.7 ± 11.3 Vs 34.7 ± 15.1 years (T test, p=0.28), 45.8 ± 83 months Vs 32.91 ± 33.9 months (T test, p=0.35). Both had a male: female ratio was 2:3.

There was no significant difference in the average serum IgE (A Vs U- 349.7 ± 379.9 IU/mL Vs 550.13 ± 504.9 IU/mL), average serum Vitamin D (19.8 ± IU/ml Vs 28.2 ± 34.9 IU/ml, A Vs U, T test, p=0.45) , average TSH (3.5 ± 2.1 IU/ml Vs 2.08 ± 0.62 IU/ml, T test, p=0.44) nor d-dimer (198.8 ± 126.1 ng/mL Vs 145 ± 136.4, A vs U, p=076).

Dermographism was likely to be absent in those patients of urticaria and angioedema with normal serum IgE (Chi square test, p=0.028). Same association was seen in urticaria alone (Chi square test, p=0.056). These patients had a 50% reduction in UAS with 5 mg levocetirizine at 8 weeks (p=0.013, Chi square).

Conclusion: We found that serum IgE levels tend to be lower in those patients of angioedema and urticaria who do not have associated symptomatic dermographism. The same may serve as a useful and non-invasive marker in resource poor settings.

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