8TH C1-INHIBITOR DEFICIENCY WORKSHOP
2013

PROGRAMME
&
BOOK OF ABSTRACTS

THERMAL HOTEL MARGITSZIGET
BUDAPEST, HUNGARY
23-26 MAY 2013

8th C1-Inhibitor Deficiency Workshop 2013
Programme & Book of abstracts

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Lectored by: Henriette Farkas, Lilian Varga
www.haenet2013.hu

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Dear Colleagues,

It is 50 years since DONALDSON & EVANS published their findings, demonstrating that the deficiency of the C1 inhibitor is the culprit behind certain forms of hereditary angioedema (HAE). This rare, life-threatening condition may affect an estimated 140,000 to 700,000 individuals worldwide. Unfortunately, the proportion of diagnosed cases is low and possibly does not exceed 80 per cent, even in the most developed countries. In many regions of the world, however, this disorder still evades diagnosis and treatment, because its existence is not even suspected. Since 1963, medical science has come a long way in studying this disease. Nevertheless, there still are many questions unanswered, and the ultimate remedy – gene therapy – is yet to emerge. The medicinal products available currently to control disease symptoms and to supplement the missing protein are the results of a massive effort invested into decades-long development. Intense research to find the safest and most effective preparations – also offering the most convenient dosing for the patients – continues. However, improved therapy can help only if the disorder has been recognized in the first place. The 8th C1 Inhibitor Deficiency Workshop will be held between 23 and 26 May 2013 in Budapest (www.haenet2013.hu), among the picturesque surroundings of Margaret Island. This event has become a forum for everyone involved with HAE – either as a health care professional or a representative of the patients – to share their experience and join their efforts to enhance screening and diagnosis, as well as to improve the patients' quality of life.

The number and the range of the participants continue to grow event by event. On this occasion, 250 participants have registered from 33 countries – this is the greatest attendance in the history of the Workshop since the start of the series of biennial events in 1999. This welcome expansion is further reflected by the number of the presentations submitted for this 4-day long scientific forum – 89, which is 1.5 times higher than on the last occasion. This time, we have invited three prominent experts, namely FRANCOIS MARCEAU from Canada, COEN MAAS from The Netherlands, and PETER GÁL from Hungary, who will increase our knowledge with their lectures on bradykinin receptors, plasma kinins, and the lectin pathway of complement activation. The scientific agenda of the 2013 Workshop focuses on the pathophysiology of angioedematous attacks, the properties of HAE with normal C1-inhibitor associated with factor XII gene mutation, and the practical experience gained in routine clinical practice. In addition to presenting new research findings, the Workshop will enlarge on issues related to the management of HAE-patients and to the activities of their organizations. The generous support of our Sponsors again enabled us to present the "For HAE Patients" and the "For HAE Research" awards, as well as to give the "Grant for Young Investigators" to four presenters under the age of 35 years.

The submitted abstracts, as well as the review lectures presented by the invited speakers at the Workshop will be published in the *Journal of Angioedema*, to make them available to an even broader range of professionals interested in this subject.

Henriette Farkas and Lilian Varga
Chairs of the 8th C1-Inhibitor Deficiency Workshop

ORGANIZED BY

C1-INH Deficiency Working Group
Foundation for the Prevention and Treatment of Fatal
Angio-oedematous Diseases

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SCIENTIFIC PROGRAMME

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Thursday, 23 May

13:00-16:00 **Registration**

17:00-17:30 **Welcome coffee**

17:30-20:00 **Opening ceremony**

Greeting of the Guests

'*For HAE Patients*' Award Prize-giving ceremony

Opening lectures I-II *Chairs: Anete Grumach, Marco Cicardi*

I-1 Bradykinin receptors: agonists, antagonists, expression, signaling and adaptation to sustained stimulation
Francois Marceau

I-2 The protease storm of angioedema
Coen Maas

20:00 **Welcome Dinner**

Friday, 24 May

08:30-09:10 **Opening lectures III** *Chairs: Christian Drouet, Péter Gál*

I-3 Activation and regulation of the lectin pathway of the complement system
Péter Gál

09:10-10:25 Scientific lectures
NON-CONVENTIONAL DIAGNOSTICS

O-01 Development of a functional assay for diagnosis of types I and II HAE based on inhibition of factor XIIa or kallikrein
Joseph Kusumam, Baby G. Tholanikunnel, Sonia Bains, Konrad Bork, Anette Bygum, Anne Aabom, Claus Koch, Berhane Ghebrehiwet, Allen P. Kaplan

O-02 C1 Inhibitor function with kinin forming enzymes as target: evaluation of a novel assay
Arije Ghannam, Federica Defendi, Bertrand Favier, Denise Ponard, Christian Drouet

O-03 High Molecular Weight Kininogen, an informative angioedema diagnostic tool
Rémi Baroso, Delphine Charignon, Federica Defendi, Françoise Csopaki, Bertrand Favier and Christian Drouet on behalf of the National Reference Centre for Angioedema CREAK

O-04 Enzymatic assays for the biological diagnosis of BK-dependent angioedema
Federica Defendi, D. Charignon, A. Ghannam, R. Baroso, F. Csopaki, M. Allegret-Cadet, D. Ponard, B. Favier, S. Cichon, B. Nicolie, O. Fain, L. Martin and C. Drouet on behalf of the National Reference Centrefor Angioedema CREAK

O-05 Hormone modulation in women with Hereditary angioedema
Anne Gompel, Isabelle Boccon-Gibod, Laurence Bouillet, David Launay, Ludovic Martin, Gisele Kanny, Olivier Fain

10:25-10:55 **Coffee Break**

10:55-12:55 Scientific lectures *Chairs: Francois Marceau, Andrea Zanichelli*

GENES AND CASCADES

O-06 De novo homozygous mutation of the C1 Inhibitor gene in a patient with hereditary angioedema
V. Bafunno, Chiara Divella, F. Sessa, G.L. Tiscia, G. Castellano, L. Gesualdo, M. Margaglione, V. Montinaro

O-07 Hereditary angioedema due to C1 Inhibitor deficiency among Brazilian patients
Camila Lopes Veronez, Nathália Cagini, Márcia Buzolin, Lício Augusto Velloso, Eli Mansour, João Bosco Pesquero

O-08 Modulation of adrenomedullin and Plaur genes in the pathogenesis of angioedema due to inherited C1 Inhibitor deficiency
Giuseppe Castellano, Chiara Divella, Fabio Sallustio, Vincenzo Montinaro, Andrea Zanichelli, Erika Bonanni, Chiara Suffritti, Loreto Gesualdo, Marco Cicardi

O-09 Gene regulation in the pathogenesis of inherited C1 Inhibitor deficiency (Hereditary Angioedema)
Sonia Caccia, Rosaria Russo, Fleur Bossi, Romina Berardelli, Anna Maria Fra, Valeria Rimoldi, Rosanna Asselta, Stefano Duga, Marco Cicardi

O-10 Immunological method for specific measurement of C1 Inhibitor polymers in plasma and C1 Inhibitor concentrate
Daniel Elenius Madsen, Yaseelan Palarasah, Johannes J. Sidelmann

O-11 Activation of the FXII dependent kallikrein-kinin system by C1-inh polymers
Daniel Elenius Madsen, Johannes J. Sidelmann, Jørgen Gram

O-12 Studies of non-contact activation of Hereditary Angioedema plasma types I, II, and III
Joseph Kusumam, Baby G. Tholanikunnel, Sonia Bains, Konrad Bork, Anette Bygum, Anne Aabom, Claus Koch, Berhane Ghebrehiwet, Allen P. Kaplan

O-13 Inhibition of the plasma kallikrein-kinin system activation by DX-2930, a fully human monoclonal antibody inhibitor of plasma kallikrein
Daniel J. Sexton, Ryan Faucette, Jon Kenniston, Christopher TenHoor, Andrew E. Nixon, Burt A. Adelman

12:55-14:25 **Lunch Break**

14:25-15:55 Poster Session *Chairs: Emel Aygören Pürsün, Timothy Craig*

MIXING IT WITH THE AUTHORS – SCIENCE IN THE SHOP-WINDOW I.

P-01 The Hereditary Angioedema Burden of Illness Study in Europe: A Conceptual Model of Patient Impacts
Anette Bygum

P-02 Hereditary angioedema in Switzerland
Urs Steiner, Werner Pichler, Walter Wuillemin

P-03 Leukocytosis and hemoconcentration yield misinterpretation in abdominal emergencies of Hereditary Angioedema
Daisuke Honda, Isao Ohsawa, Seiji Nagamachi, Hiyori Suzuki, Atsuko Hisada, Satoshi Horikoshi, Yasuhiko Tomino

P-04 Influence of psychological factors on Hereditary Angioedema attacks in children and adolescents: the parents' point of view
Raffaella De Falco, Maria Bova, Maria Francesca Freda, Anna Galante, Angelica Petraroli, Livia Savarese, Gerarda Siani, Massimo Triggiani, Paolo Valerio

P-05 New abdominal crisis trigger on patients with Hereditary Angioedema
José E. Fabiani, Marta Villaverde, Fernando Vazquez Godoy

P-06 No evidence for disease-modifier genes in the PBMC expression profile from HAE patients in basal conditions. An RNA-based microarray screening
Alberto López Lera, Fátima Sánchez Cabo, Sofía Garrido, Ana Dopazo, Margarita López Trascasa

P-07 Gallstones in C1 Inhibitor Deficiency – Are they different?
Jimmy Gooi, Dimitra Athanasiadou, Dimosthenis Sokaras, Udo Becker, Elias Chatzitheodoridis, Athanasios Godelitsas

P-08 The new change in the SERPING1 gene in a Brazilian family can be associated to Hereditary Angioedema (HAE)
Nathália Cagini, Camila Lopes Veronez, Márcia Buzolin, Lício Augusto Velloso, Eli Mansour, João Bosco Pesquero

P-09 Severe laryngeal edema and anemia as first symptoms of IgG kappa multiple myeloma – an acquired angioedema (AAE) case demonstration
Marcin Stobiecki, Krystyna Obtulowicz, Artur Jurczyszyn

P-10 Novel disease severity markers in Hereditary Angioedema due to C1 Inhibitor deficiency
Dorottya Csuka, Lea Munthe-Fog, Mikkel-Ole Skjoedt, Andrea Kocsis, Zsuzsanna Zotter, Péter Gál, Lilian Varga, Henriette Farkas, George Füst†, Peter Garred

P-11 Angioedema - not always an allergic symptom
Kristina Lings, Anette Bygum

P-12 Reduced C1 Inhibitor secretion in fibroblasts derived from patients with Hereditary Angioedema
Iben Rose Christiansen, Claus Koch, Anette Bygum, Jacob Giehm Mikkelsen

P-13 Estrogenic hereditary angioedema
Hakim Rahmoune, Nada Boutrid, Belkacem Bioud

P-14 Possible causes of acquired C1 Inhibitor deficiency, based on our 9 patients
Katalin Molnár, Laura Horváth, Szabolcs Benedek, Lilian Varga, Zsuzsanna Zotter, Henriette Farkas

P-15 Elevated adrenomedullin and endothelin-1 levels during HAE attacks
Erika Kajdácsi, Péter Károly Jani, Dorottya Csuka, Lilian Varga, Zoltán Prohászka, Henriette Farkas, László Cervenak

P-16 Age related changes in the severity of Hereditary Angioedema due to C1 Inhibitor deficiency
Nóra Veszeli, Dorottya Csuka, Lilian Varga, Henriette Farkas

P-17 Adverse effects of danazol prophylaxis in female patients with Hereditary Angioedema due to C1 Inhibitor deficiency (HAE-C1-INH)
Zsuzsanna Zotter, Ibolya Czaller, Dorottya Csuka, Kinga Viktória Kőhalmi, Lilian Varga, Henriette Farkas

P-18 Thyroid function parameters in patients with hereditary angioedema due to C1-inhibitor deficiency
Ibolya Czaller, Dorottya Csuka, Zsuzsanna Zotter, Erika Szabó, Edit Takács, Lilian Varga, Henriette Farkas

P-19 Flow-mediated dilation: assessment of endothelial cell function in patients with hereditary angioedema due to C1-inhibitor deficiency
Zsuzsa Nébenführer, Erika Szabó, Katalin Keltai, András Zsáry, Dorottya Csuka, Zsuzsanna Zotter, Lilian Varga, László Cervenak, Henriette Farkas

15:55-16:25 **Coffee Break**

16:25-17:40 Scientific lectures *Chairs: Coen Maas, Avner Reshef*

THE ATTACK IN THE LIMELIGHT

O-14 Early biomarkers are required for better prediction, evaluation and treatment of HAE attacks
Avner Reshef, Mona Kidon-Iancovici, Boris Gilbord

O-15 Activation of the ficolin-lectin pathway during attacks of Hereditary Angioedema
Dorottya Csuka, Lea-Munthe-Fog, Estrid Hein, Zsuzsanna Zotter, Lilian Varga, Zoltán Prohászka, Peter Garred, Henriette Farkas

O-16 A preliminary study into the activation of plasma enzyme systems during attacks of Hereditary Angioedema due to C1 Inhibitor deficiency (HAE-C1-INH)
Dorottya Csuka, Éva Imreh, Zsuzsanna Zotter, Szilvia Walentin, Mónika Kleiber, Lilian Varga, Henriette Farkas

O-17 Endothelial cell activation during edematous attacks of Hereditary Angioedema type I and II
Erika Kajdácsi, Péter Károly Jani, Dorottya Csuka, Lilian Ágnes Varga, Zoltán Prohászka, Henriette Farkas, László Cervenak

O-18 Activation of the Plasma Contact-system in patients with Anaphylaxis
A. Sala Cunill, M. Guilarte, V. Cardona, J. Björkqvist, M. Labrador, K. Nickel, T. Renné

19:15- **Social Programme (including dinner)**

Saturday, 25 May

08:30-09:00 **Prize-winner lecture and Distribution of prize „for HAE Research Award"**
Chair: Bruce Zuraw
Awarded: *Allen Kaplan*

09:00-10:45 Scientific lectures *Chairs: Janne Björkander, Konrad Bork*
SORTING THINGS OUT: HAE-FXII

O-19 Hereditary angioedema with normal C1 Inhibitor: Clinical characteristics of seven families in Catalonia
Maria del mar Guilarte, A. Sala-Cunill, M. Labrador-Horrillo, O. Luengo, V. Cardona

O-20 A deletion in the factor 12 gene analysed in two Turkish families with Hereditary Angioedema with normal C1 Inhibitor (HAE type III): a Turkish *F12* mutant?
Konrad Bork, Karin Wulff, Jochen Hardt, Guenther Witzke

O-21 Mutation in Coagulation Factor XII gene associated with Hereditary Angioedema with normal C1 Inhibitor in Brazilian families
Adriana S. Moreno, S.O.R. Valle, A.T. França, S.A. Levy, F.S. Serpa, N. Monnier, D. Ponard, J. Lunardi, M.D. Mendonça, W.N. Campos, H. Arcuri, M.S. Palma, W.A. Silva Junior, L.K. Arruda

O-22 Hereditary Angioedema-factor XII associated. Clinical and genetic characteristics in an Andalusian cohort (South of Spain)
Macarena Piñero-Saavedra, T. González-Quevedo, R. García-Lozano, B. Saenz de San Pedro

O-23 Hereditary Angioedema patients with normal C1 Inhibitor and factor XII mutation: a French cohort
Isabelle Boccon-Gibod, Anne Gompel, Olivier Fain, Yann Ollivier, Nadia Raison-Peyron, Aurélie Du-Than, Stéphane Gayet, Laurence Bouillet

O-24 Hereditary Angioedema with factor XII mutation: no evidence for contact activation during attack (case report)
Chiara Suffritti, Andrea Zanichelli, Marta Mansi, Christiane Stieber, Giulia Periti, Erika Bonanni, Lorena Maggioni, Romualdo Vacchini, Marco Cicardi

O-25 Kinin catabolism and disease severity in hereditary angioedema with *F12* mutation
Delphine Charignon, Federica Defendi, Arije Ghannam, Denise Ponard, Sven Cichon, Olivier Fain, Ludovic Martin, Christian Drouet on behalf of the CREAK, the National Reference Centre for Angioedema

10:45-11:15 **Coffee Break**

11:15-13:00 Scientific lectures *Chairs: Jonathan Bernstein, Grzegorz Porebski*
MANAGEMENT FINE-TUNED

O-26 Long term prophylactic treatment in Spanish patients with Hereditary Angioedema with C1 Inhibitor Deficiency (HAE-C1INH)
Maria Pedrosa, M. Guilarte, T. González Quevedo, M.L. Baeza, T. Lobera, C. Marcos, B. Sáenz de San Pedro, J. Jurado, T. Caballero

O-27 Anabolic androgen experience and response to nanofiltered C1 inhibitor from the CINRYZE prevention trials in patients with HAE
B.L. Zuraw, D. Mariano, J. Dayno

O-28 HAE Patient experience with short term prophylaxis: Responses to an on-line questionnaire survey
Jonathan A. Bernstein, Umesh Singh, Joyce Wilmot

O-29 Management of Hereditary Angioedema. Real-world experiences from a Danish Specialist Centre
Anette Bygum

O-30 Prospective evaluation of the efficacy of on demand treatments in reducing duration of angioedema in patients with Hereditary Angioedema due to C1 inhibitor deficiency
Giulia Periti, Andrea Zanichelli, Marta Mansi, Romualdo Vacchini, Chiara Suffritti, Lorena Maggioni, Erika Bonanni, Marco Cicardi

O-31 Ruconest in routine clinical practice: UK experience
A.L. Manson, J. Dempster, S. Grigoriadou, M.S. Buckland, Hilary J. Longhurst

O-32 Clinical trial experience of pediatric patients treated with ecallantide for acute attacks of Hereditary Angioedema
Andrew J. MacGinnitie, Mark Davis-Lorton, Leslie E. Stolz, Raffi Tachdjian, Ibrahim Dagher

13:00-14:30 **Lunch Break**

14:30-16:00 Poster Session *Chairs: Anette Bygum, Tom Bowen*

MIXING IT WITH THE AUTHORS – SCIENCE IN THE SHOP-WINDOW II.

P-20 A cross-sectional questionnaire survey to assess physician's approach to short-term prophylaxis in HAE patients
Jonathan A. Bernstein, Umesh Singh, Joyce Wilmot

P-21 Case report of use of Icatibant during pregnancy
Andrea Zanichelli, Marta Mansi, Giulia Periti, Chiara Suffritti, Lorena Maggioni, Erika Bonanni, Romualdo Vacchini, Marco Cicardi

P-22 Experience and current status of the translation and cross-cultural adaptation of the angioedema quality of life questionnaire (AE-QoL)
Karstem Weller, Marcus Maurer, Markus Magerl

P-23 The Romanian Hereditary Angioedema Registry
Dumitru Moldovan, Eniko Mihaly, Noemi Anna Bara, Valentin Nădăşan

P-24 Pilot study and validation of the IHAE-QoL questionnaire
Nieves Prior, E. Remor, E. Pérez-Fernández, C. Gómez-Traseira, M. Caminoa, F. Gayá, A. Aabom, W. Aberer, S. Betschel, A. Bygum, D. Csuka, H. Farkas, A. Groffik, M. Gomide, A. Grumach,I. Leivobich, A. Malbran, E. Mihaly, D. Moldovan, K. Obtulowicz, G. Porebski, C. Rayonne, A. Reshef, P. Staubach, M. Wiednig, T. Caballero

P-25 The US HAE Association: an important partner in a longstanding effort to improve patients' quality of life
Anthony Castaldo, J.F. Long, D.K. Davis, L.I. Perry, D.L. Williamson, P.L. King

P-26 Hereditary Angioedema - how can medicines reach the patient?
Maja Jošt, Mihaela Zidarn, Mitja Košnik

P-27 Comparison of acute angioedema attacks versus breakthrough attacks during a placebo-controlled, crossover study of CINRYZE® (C1 Esterase Inhibitor [Human]) for prophylaxis in patients with Hereditary Angioedema
Jennifer Schranz, D. Fitts, C. Broom

P-28 Feasibility of home infusion and self-administration of CINRYZE® (C1 Esterase Inhibitor [Human]) for routine prophylaxis in patients with Hereditary Angioedema and characterization of a training and support program
David Mariano, L.M. Landmesser, C. Gregory

P-29 Clinical descriptive study and Health Related Quality of Life (HRQoL) as measured by SF-36v2 in adults with Hereditary Angioedema due to C1-inhibitor deficiency in Spain
Teresa Caballero, C. Gómez-Traseira, M. Caminoa, E. Pérez-Fernández, C. Andreu, A. Campos, P. Carretero, L. Fernández-Vieira, A. Ferrer, F. García-González, T. González-Quevedo, M. Guilarte, M.A. Gonzalo-Garijo, C.H. Larramendi, T. Lobera, C. Marcos, A. Salas, P. Sánchez-Payá, M.E. Sanchís, M.T. Soto-Mera, N. Prior

P-30 Benefits of early administration of Icatibant for the treatment of Hereditary Angioedema attacks
Hilary Longhurst, Werner Aberer, Laurence Bouillet, Teresa Caballero, Vincent Fabien, Priscila Valente de Freitas, Andrea Zanichelli, Marcus Maurer

P-31 Treatment of Hereditary Angioedema attacks with Icatibant: A comparison of observational data with clinical trial data
Marcus Maurer, Hilary Longhurst, Michaela Wiednig, Vincent Fabien, William Lumry

P-32 Teaching intravenous self-application in patients with HAE: Experiences by a specialist nurse
H. Mühlberg, Nicole Ettl, M. Magerl

P-33 Different forms of HAE prophylaxis
Murat Bas, Ulrich Straßen

P-34 An indirect comparison of icatibant and four other therapies for the symptomatic treatment of acute attacks of Hereditary Angioedema types I and II
Matthew Helbert, M. Alvarez-Reyes, I. Pearson, L. Diwakar

P-35 The efficacy and safety of self-injected icatibant administered as an acute treatment for Hereditary Angioedema due to C1 Inhibitor deficiency (HAE-C1-INH) in clinical practice
Zsuzsanna Zotter, Dorottya Csuka, Lilian Varga, György Temesszentandrási, Henriette Farkas

P-36 Short-term prophylaxis in a patient with acquired C1-INH deficiency
Kinga V. Kőhalmi, Zsuzsanna Zotter, Dorottya Csuka, Katalin Molnár, Lilian Varga, Henriette Farkas

P-37 Home treatment of attacks with conestat alfa in Hereditary Angioedema due to C1 Inhibitor deficiency (HAE-C1-INH)
Erika Szabó, Dorottya Csuka, Zsuzsanna Zotter, Lilian Varga, Henriette Farkas

16:00-16:30 **Coffee Break**

16:30-17:45 Scientific lectures *Chairs: Laurence Bouillet, Hilary Longhurst*

ANGIOEDEMA AVALANCHE

O-33 Follow-up of patients with drugs targeting the renin-angiotensin-aldosterone system- induced angioedema
Macarena Pinero-Saavedra, Isabelle Boccon-Gibod, Teresa Gonzalez-Quevedo, Laurence Bouillet

O-34 Asphyxiation in HAE due to C1-INH deficiency and HAE with normal C1-INH
Konrad Bork, Jochen Hardt, Günther Witzke

O-35 Clinical survey of different forms of angioedema without wheals
Marta Mansi, Andrea Zanichelli, Giulia Periti, Chiara Suffritti, Erika Bonanni, Lorena Maggioni, Romualdo Vacchini, Marco Cicardi

O-36 Surveys of prodromes preceding acute attacks of Hereditary Angioedema
Avner Reshef, Michael J Prematta, Timothy J. Craig

O-37 The influence of age at first clinical manifestation of Hereditary Angioedema (HAE) on the clinical course of the disease
Inmaculada Martinez-Saguer, Eva Rusicke, Carmen Escuriola-Ettingshausen, Emel Aygören-Pürsün, Karin Andritschke, Adrianna Piotrowski, Wolfhart Kreuz

18:30- **Social Programme (including dinner)**

Sunday, 26 May

08:30-09:45 Scientific lectures *Chairs: Iris Leibovich, Alejandra Menendez, Dumitru Moldovan*

THE SHADES OF FREEDOM – Nursing round table discussion

O-38 Living with Hereditary Angioedema – Nursing aspects
Iris Leibovich

O-39 Practical Approach to self-administration of C1-Inhibitor in HAE-Patients
Karin Andritschke

O-40 The Hungarian Patient – Hospitalisation of HAE-patients with diseases different from HAE
Arianna Kitzinger

O-41 Practicalities and barriers to HAE self-administration therapy: discussions from an international HAE expert meeting
Christine Symons, H.B. Boysen, L. Bouillet, S. Neri, J. Hébert, E. Aygören-Pürsün, I. Martinez-Saguer, C. Bethune, A. Sala-Cunill, M. Cancian, O. Rossi, M. Magerl, K. Andritschke, T. Craig

O-42 The building blocks for an effective patient group advocacy program
Anthony Castaldo, H.B. Boysen, M. Rutkowski, S.F. Smith, A. Menendez, H. Mykal, J. Schultz-Boysen, V. Ledbez, P. Hermeling

09:45-10:15 **Coffee Break**

10:15-12:30 Scientific lectures *Chairs: Teresa Caballero, Bernd Rosenkranz*

LIVING WITH HAE AROUND THE WORLD

O-43 International clinical descriptive study of adults with Hereditary Angioedema due to C1 Inhibitor deficiency
Teresa Caballero, M. Caminoa, E. Pérez-Fernández, C. Gómez-Traseira, F. Gayá, A. Aabom, W. Aberer, S. Betschel, A. Bygum, D. Csuka, H. Farkas, A. Groffik, M. Gomide, A. Grumach, I. Leivobich, A. Malbran, E. Mihaly, D. Moldovan, K. Obtulowicz, G. Porebski, C. Rayonne, A. Reshef, P. Staubach, M. Wiednig, N. Prior

O-44 Clinical differences among countries in Hereditary Angioedema due to C1 Inhibitor deficiency
Nieves Prior, Magdalena Caminoa, Elia Pérez-Fernández, Carmen Gómez-Traseira, F. Gayá, Anne Aabom, Werner Aberer, Stephan Betschel, Anette Bygum, Dorottya Csuka, Henriette Farkas, Adriane Groffik, M. Gomide, Anete Grumach, Iris Leivobich, A. Malbran, Eniko Mihaly, Dumitru Moldovan, K. Obtulowicz, Grzegorz Porebski, C. Rayonne, Avner Reshef, P. Staubach, Michaela Wiednig, Teresa Caballero

O-45 Health status utility weights for Hereditary Angioedema attacks and in between attacks
Emel Aygören-Pürsün, Teresa Caballero, Anette Bygum, Kathleen Beusterien, Emily Hautamaki, Zlatko Sisic, Suzanne Wait, Henrik B. Boysen

O-46 HAE – The Situation in South Africa
Bernd Rosenkranz

O-47 Hereditary Angioedema in Latin America: 1st report
J. Fabiani, S.O.R. Valle, M. Olivares, S. Nieto, E.H. Landeros, A. Ginaca, L. Bezrodnik, E. Nievas, M. Oleastro, O.M. Barrera, A.M. Gallardo, A. King, J.R. Galindo, M.J.O. Carabantes, M.M.Alfonso, R. Vilarim, Anete S. Grumach

O-48 Quality of life and productivity loss in patients with Hereditary Angioedema (HAE) in Sweden; results from a retrospective patient registry survey implemented by Sweha-eg (A population based census of HAE in Sweden)
Patrik Nordenfelt, J. Björkander, L. Mallbris, A. Lindfors, S. Friberg, K. Löfdal, L. Nordvall, S. Werner, C.F. Wahlgren

O-49 Hereditary Angioedema in Greece
F.E. Psarros, M. Speletas, N. Koutsostathis, Anastasios E. Germenis

O-50 HAE in Macedonia: Current status
Vesna Grivcheva-Panovska

O-51 Hereditary Angioedema nationwide study in Slovenia
Matija Rijavec, Peter Korošec, Mira Šilar, Mihaela Zidarn, Jovan Miljković, Mitja Košnik

12:30-13:00 **Closing Ceremony** *Chairs: Henriette Farkas, Peter Späth*
Distribution of prizes for „Grant for Young Investigators"
Closing remarks by Peter Späth

13:00-14:30 **Lunch**

14:30- **Farewell & Departure**

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ABSTRACTS - OPENING LECTURES

I-1
BRADYKININ RECEPTORS: AGONISTS, ANTAGONISTS, EXPRESSION, SIGNALING AND ADAPTATION TO SUSTAINED STIMULATION

François Marceau

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Bradykinin (BK)-related peptides, the kinins, are blood-derived peptides that stimulate two G protein coupled receptors, the B_1 and B_2 receptors (B_1R, B_2R). We will succinctly review the pharmacological and molecular identities of these 2 receptor subtypes, with emphasis on drug development, receptor expression, signaling and adaptation to persistent stimulation. Peptide and non-peptide antagonists and fluorescent ligands have been produced for each receptor. The B_2R is widely and constitutively expressed in mammalian tissues, whereas the B_1R is mostly inducible under the effect of cytokines during infection and immunopathology. Both receptor subtypes mediate the vascular aspects of inflammation (vasodilation, edema formation). On this basis, icatibant, a peptide antagonist of the B_2R, is approved in the management of hereditary angioedema attacks. Other clinical applications are still elusive despite the maturity of the medicinal chemistry efforts applied to kinin receptors. While both receptor subtypes are mainly coupled to the G_q protein and related second messengers, the B_2R is temporarily desensitized by a cycle of phosphorylation/endocytosis followed by recycling, whereas the non-phosphorylable B_1R is relatively resistant to desensitization and translocated to caveolae upon activation.

I-2
THE PROTEASE STORM OF ANGIOEDEMA

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Attacks of angioedema are hallmarked by edematous swelling of skin and mucosal tissues, which are painful and sometimes life-threatening. The molecular mechanisms involved the initiation and propagation of these attacks are currently poorly understood. During attacks, a storm of proteolytic activity is generated that mediates this disease. Deficiency in C1 esterase inhibitor is a strong risk factor, but there are many patients that suffer from angioedema without a known underlying cause. This suggests that one or more elusive factors beyond this deficiency increase the susceptibility for developing this disease. Several lines of evidence suggest that the plasma contact system plays an active role in angioedema. This enzyme system is well-known for its capacity to trigger in blood coagulation *in vitro*, but its physiological role *in vivo* is presently unknown. The plasma contact system is also functionally linked to the complement system and fibrinolytic system, both of which are implicated in angioedema. Furthermore, the contact system is responsible for the liberation of kinins from the plasma protein high-molecular weight kininogen. Recent new findings from fundamental studies have identified endogenous activators of the contact system that liberate kinins without concurrent activation of blood coagulation. Interestingly, clinical evidence suggests a similarity with angioedema patients: pathological amounts of kinins form without concurrent clinically overt thrombotic pathology. Detailed biochemical studies are ongoing to help to explain the apparent preference of the plasma contact system for kinin formation in angioedema. This improved understanding of the functioning of the contact system may help to pinpoint therapeutic targets. Finally, recent technological advances have led to the development of analytical methods for determining the activity of contact system enzymes. Hopefully, development of new bioassays will improve diagnosis and guided personalized treatment of patients with angioedema.

I-3
ACTIVATION AND REGULATION OF THE LECTIN PATHWAY OF THE COMPLEMENT SYSTEM

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The complement system, a network of about 35 soluble and cell-surface proteins, is an ancient part of the innate immune system. It can recognize various danger signals provided by pathogens or altered host cells. The complement system can be activated through three different routes: the classical, the alternative and the lectin pathway. The lectin pathway which was discovered at the end of the last century seems to be the most complex among the activation routes. Pattern recognition molecules, such as mannan-binding lectin (MBL) and ficolins recognize arrays of sugars or acetylated compounds on microorganisms and stimulate activation of MBL-associated serine proteases (MASPs), which results in the activation of the complement cascade. Three serine proteases (MASP-1, MASP-2 and MASP-3) and two non-enzymatic components (MAp19 and MAp44) are associated with the pattern recognition molecules with still unknown stoichiometry. The first enzymatic step of the lectin pathway activation is the autoactivation of zymogen MASP-1. Active MASP-1 then cleaves zymogen MASP-2 and MASP-3. MASP-2 is able to generate C3 convertase (C4b2a) by cleaving C4 and C2. MASP-1 has substrates outside the complement system as well, such as high-molecular-weight kininogen, fibrinogen, factor XIII and protease activated receptors. By cleaving these substrates MASP-1 can initiate various pro-inflammatory reactions to mount an even more powerful innate immune response. C1-inhibitor is a natural regulator of the lectin pathway since it can inhibit the activity of both MASP-1 and MASP-2. Another serpin, antithrombin, also can efficiently inhibit the lectin pathway but only in the presence of glycosaminoglycans such as heparin. In the case of HAE when C1-inhibitor is absent or dysfunctional uncontrolled activation of the lectin pathway may contribute to the worsening of the symptoms.

ABSTRACTS - ORAL LECTURES

O-01
DEVELOPMENT OF A FUNCTIONAL ASSAY FOR DIAGNOSIS OF TYPES I AND II HAE BASED ON INHIBITION OF FACTOR XIIA OR KALLIKREIN

Kusumam Joseph[1], Baby G. Tholanikunnel[1], Sonia Bains[1], Konrad Bork[2], Anette Bygum[3], Anne Aabom[3], Claus Koch[3], Berhane Ghebrehiwet[4], Allen P. Kaplan[1]

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Background: Hereditary angioedema types I and II are caused by a deficiency of C1 inhibitor (C1-INH) leading to overproduction of bradykinin. The current functional diagnostic assays employ inhi ition of activated C1s however, an alternative, more physiologic method, is desirable.

Methods: ELISA assays were developed using biotinylated factor XIIa or biotinylatedkallikrein bound to avidin-coated plates. Incubation with plasma was followed by detection of bound C1-INH.

Results: After standard curves were developed for quantitation of C1-INH, serial dilutions of normal plasma were employed to validate the ability to detect known concentration of C1-INH in the plasma as a percent of normal. HAE types I, II, and III were then tested. Thus far, the level of C1-INH in 42 HAE types I and II plasma tested employing an assay for factor XIIa-C1-INH complexes varied between 0 and 23μg/ml plasma, values for 10 samples of type III HAE were 30 - 42μg/ml plasma, while the values in 20 normal controls were 38 to 95 μg/ml. The means and standard deviation for each were: normal, 63.1±12.4; type III HAE, 36.29±5.38 and types I and II HAE, 6.1±5.4. The "P" value comparing types I and II HAE to normal controls was <0.0001, and the "P" values comparing type III HAE to normal controls or types I and II HAE were both<0.0001. The results obtained assaying for kallikrein- C1-INH complexes were strikingly similar with no overlap between groups although the "P" value comparing type III HAE with normal controls were borderline at 0.042.

Conclusions: Diagnosis of HAE types I and II can be ascertained by inhibition of enzymes of the bradykinin-forming cascade. The functional C1-INH level in type III HAE is low, but clearly distinguishable from types I and II HAE. This result suggests C1-INH consumption in type III HAE or an abnormality outside the C1-INH coding sequence.

O-02
C1 INHIBITOR FUNCTION WITH KININ FORMING ENZYMES AS TARGET: EVALUATION OF A NOVEL ASSAY

Arije Ghannam[1,2], Federica Defendi[1,2], Bertrand Favier[1], Denise Ponard[2], Christian Drouet[1,2]

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Background: C1-Inhibitor (C1Inh) controls the activation of complement, contact, and coagulation/fibrinolytic path ways. Besides, the control of the prekallikrein (pKK) to kallikrein conversion by C1Inh is proposed as the major pathophysiologic mechanism to protect HAE patients from angioedema. The serpin function of C1Inh is currently measured in plasma by the residual activity of C1s protease, aC1Inh target not involved in the pathological process of angioedema. We describe a novel enzymatic measurement of C1Inh function relying on contact phase activation and adapted to patient plasma.

Methods: The contact phase is reconstituted by adding the purified components in the presence of the plasma sample, and then the kinetics of the amidase activity is followed using the Pro-Phe-Arg-*p*NAas substrate. The measurement conditions are independent of the alpha2-macroglobulin, a serpin control of the contact phase. To prevent the interference ofa possible high plasma kininogenase activity, the sample is preincubated with di-*iso*-propylfluorophosphate.

Results: The volumes of control samples as low as 1µl result in the decrease of Vmax of 50-55%. As shown by the calibration curve established on purified C1Inh, the remaining Vmax of 45-50% corresponds to the inhibition of pKK activation by100 ng(1 pmol) of C1Inh. The C1Inh function value is determined as the % of C1Inh of the reference plasma and taking the purified C1Inh standard. The samples develop values ofC1 Inh equivalent between 5%(low limit) and 140%.

Conclusion: The performance outcome is evaluated with high analytical sensitivity (5% of the reference) and specificity. It is suitable for an application in routine laboratory for diagnostic of angioedema usinglow volumes of plasma. Established on the kinin formation system and specific of the pathological process, the present assay should advantageously replace the old-fashioned method based on the residual activity of the C1s protease target.

O-03
HIGH MOLECULAR WEIGHT KININOGEN, AN INFORMATIVE ANGIOEDEMA DIAGNOSTIC TOOL

Rémi Baroso[1], Delphine Charignon[1,2], Federica Defendi[1,2], Françoise Csopaki[2], Bertrand Favier[1], Christian Drouet[1,2] on behalf of the National Reference Centre for Angioedema CREAK

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Background: The demonstration of the involvement of kinins could be considered as the ultimate criteria of angioedema. High molecular weight kininogen (HK) and Prekalikrein (pKK) circulate as a complex in plasma. HK is cleaved after pKK activation in heavy (HC) and light (LC) chains, with a release of bradykinin (BK). LC is further cleaved into shorter chain (cLC). Given the short half-life of BK, the best biological marker for BK release is the cleavage of HK with a change from a native, full length status, to cleaved molecules.

Methods: We investigated the plasma HK by western blot, using a peroxydase labeled anti-HK L chain polyclonal antibody. Healthy controls (>20 males, >20 females) and a parallel number of angioedema patient samples were comparatively investigated with the following criteria: established angioedema disease, normal kinin catabolism, no prophylactic treatment. After quantification of each molecular species (ECL, Amersham), and from the receiver operating characteristic (ROC) curves, cut-off, sensitivity and specificity were established.

Results: References values for native HK are 152±37 mg/L (median ± SD) for men (M) and 108±45 mg/L for women (W). We defined the cleavage percentage (%C) as the ratio (LC+cLC)/(all species). The %C is 9±9 % (M) and 18±15 % (W). Plasma HK antigenic levels of angioedema patients are 60±37 mg/L (M), 26±44 mg/L (W). The %C is 32±19% (M) and 68±29% (W). From the ROC curves, the cut-off values are 130 mg/L and 34%C, with 100% specificity (M), and 100 mg/L 40%C with 88% specificity (W). The BK abundance is between 350 and 886 nmol (cut-off 190 nmol).

Conclusions: With its high specificity, this new test gives strategic information for angioedema diagnostic and follow-up. It brings the range of the kinin abundance during the attack.

O-04
ENZYMATIC ASSAYS FOR THE BIOLOGICAL DIAGNOSIS OF BK-DEPENDENT ANGIOEDEMA

F. Defendi[1,2], D. Charignon[1,2], A. Ghannam[2], R. Baroso[2], F. Csopaki[1], M. Allegret-Cadet[1], D. Ponard[1], B. Favier[2], S. Cichon[3], B. Nicolie[1,4], O. Fain[1,5], L. Martin[1,6], C. Drouet[1,2] on behalf of the National Reference Centre for Angioedema CREAK

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Background: The kinins (primarily bradykinin, BK) represent the mediators responsible for local increase of vascular permeability in hereditary angioedema (HAE), HAE I-II associated with alterations of the *SERPING1* geneand HAE with normal C1-Inhibitor function (HAE-nC1INH). Besides C1-Inhibitor function and concentration, no biological assay of kinin metabolism is actually available to help physicians for the diagnosis of angioedema (AE). We describe enzymatic tests on the plasma for biological diagnosis of BK-dependent AE.

Methods: The plasma amidase assays are performed using the Pro-Phe-Arg-*p*-nitroanilide peptide substrate. We analysed data of 872 patients presenting with BK-dependent AE or BK-unrelated diseases, compared to 303 controls. Anti-high MW kininogen (HK) immunoblotwas achieved to confirm HK cleavage in exemplary samples. Receiver operating characteristics (ROC) were used to calculate diagnostic performance of the assays.

Results: Spontaneous amidase activity was significantly increased in all BK-dependent AE, associated with the acute phase of diseasein HAE-nC1INH, but preserved in BK-unrelated disorders. The increase of the amidase activitywas associated to HK proteolysis, indicating its relevance to identify kininogenase activity. The oestrogens, known for precipitating AE episodes, were found as triggers of enzymatic activity. Calculations from ROC curves gave the optimum diagnostic cut-off for women(9.3 nmol·min^-1·mL^-1, areaunder curve [AUC] 92.1%, sensitivity 80.0%, and specificity 90.1%) and for men (6.6 nmol·min^-1·mL^-1, AUC 91.0%, sensitivity 87.0% and specificity 81.2%).

Conclusion: In addition to immediate diagnostic outcomes to help physiciansin the decision to distinguish between BK-related and -unrelated AE, the data argue that the BK-AE illustrated herein refer to conditions of contact phase activation.

O-05
HORMONE MODULATION IN WOMEN WITH HEREDITARY ANGIOEDEMA

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It is well known that women with HAE can experience worsening of their attacks under estrogens. Different situations and treatments can either worsen or improve the course of the disease. It is thus necessary to well-balanced the introduction of any treatment which might impact the delicate equilibrium of the patients. Concerning contraception we recently reported a series of patients who improved with antigonadotropic progestin used as contraceptives. These agents can help to decrease the frequency and severity of the attacks. Other situations can be also managed for the benefits of women with HAE. Anti-hormone therapy in women with breast cancer can also be associated with worsening of the attacks when tamoxifen is given in postmenopausal women or combined with GnRH agonist in premenopausal women. At the opposite, GnRH analogs can help to decrease their attacks in specific situations. This sensitivity to a mild estrogen agonist was observed in patients with all the types of HAE (with C1 inhibitor deficiency, without C1 inh deficiency with or without factor XII mutation) illustrating their equivalent susceptibility to estrogens. Another situation where specific protocol could be developed in these women is IVF. We will report a recent observation using danazol as the antigonadotropic agent which avoid any attacks during the stimulation by gonadotropins and was successful with a leaving child delivery. We thus propose that a multidisciplinary approach for the management of these patients including an expert in hormonal pharmacology will help to improve the quality of life of women with HAE.

O-06
DE NOVO HOMOZYGOUS MUTATION OF THE C1 INHIBITOR GENE IN A PATIENT WITH HEREDITARY ANGIOEDEMA

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Background: Hereditary angioedema (HAE) is an autosomal dominant disease due to mutations in the C1 inhibitor gene (*C1NH*) that affects its protein synthesis (HAE I) or function (HAE II). *C1NH* gene maps onto chromosome 11q12-q13.1 and is organized into 8 exons and 7 introns. At present, more than 300 deficiency-causing mutations in the *C1NH* have been identified. Approximately 25-30% of these mutations occur *de novo*. HAE patients present generally a heterozygous mutation of the C1 INH gene, only recently three subjects from two different families with a homozygous genetic defect on the *SERPING1* locus have been reported.

Aim of this study was to characterize the biochemical profile of a 21 year-old female that shows clinical and laboratory findings typical of HAE and provide evidence for a homozygous *de novo* null mutation (c.646_647insTCAGTGTCGTGdelA, p.Lys216Serfs*4) in the exon 4 of *C1NH* gene.

Methods: Biochemical diagnosis of HAE was confirmed by using direct DNA sequencing of *C1NH* and western blot analysis on the proband and her family. Furthermore, long range PCR, RFLP, SNP genotyping and real-time PCR were performed to identify the possible mechanisms that could explain the homozygous *de novo* mutation in the patient.

Results: The patient showed very low antigenic and functional levels of C1 inhibitor protein and C4, with normal levels of C3 and C1q. Western blot analysis of plasma sample confirmed the absence of native and cleaved forms of the protein. Her parents showed no alterations in complement parameters and did not present the mutation. By using different approaches we could exclude the deletion of exon 4 as the cause for the homozygous *de novo* mutation.

Conclusions: This is the first report of a patient homozygous for a *de novo* null mutation affecting the *C1NH* coding region probably resulting from a small size event of gene conversion. In contrast with the previous homozygous cases, clinical phenotype of the patient resembled typical heterozygous form of HAE.

O-07
HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY AMONG BRAZILIAN PATIENTS

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Background: Hereditary Angioedema (HAE) is a rare autosomal dominant inherited disease caused by C1-inhibitor (C1-INH) deficiency, which leads to acute swelling episodes due to excessive bradykinin release. Severity, frequency and localization of oedema attacks are highly variable between patients, even in members of the same family, and there are few statistics and studies focusing the Brazilian population. The aim of this study was to evaluate clinical symptoms, biochemical data and genetic features of a group of Brazilian patients with HAE.

Methods: We screened the whole C1-INH coding region gene of 17 subjects from 12 unrelated families who reported recurrent episodes of angioedema or abdominal pain attacks without urticaria and presented low levels of C1-INH.

Results: We identified eleven different mutations among which six were not described in consulted databases. We found three new small deletions affecting exon 3 (c.97_115del19), exon 4 (c.553delG), exon 5 (c.775_781del) and one known deletion in exon 8 (c.1353_1354del), all of them producing frameshifts leading to premature stop codons. Among the four missense mutations found, one affected exon 3 (c.550G>C – p.G184R), two affected exon 5 (c.752T>C – p.L251P; c.889G>A – p.A297T) and the other affected exon 8 (c.1431C>A – p.F477L). One nonsense mutation affecting exon 8 (c.1480C>T) was found in one of our patients. We identified two mutations affecting the splice acceptor site in exon 2 (c.51+1G>T; c.51+2T>C), one of them not yet described. Just one patient did not present any alteration in C1-INH coding sequence gene.

Conclusions: Our results show a wide range of alterations in the C1-INH gene in the Brazilian HAE patients. Despite the small amount of participants, these results suggest a more diverse Brazilian population regarding C1-INH mutations responsible for the disease. Our findings will help to elucidate the relationship between symptoms variation of HAE and C1-INH genotype.

O-08
MODULATION OF ADRENOMEDULLIN AND PLAUR GENES IN THE PATHOGENESIS OF ANGIOEDEMA DUE TO INHERITED C1 INHIBITOR DEFICIENCY

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Background: Hereditary Angioedema (HAE) is a rare Mendelian disease that causes recurrent local edema with important negative impact on the patients' quality of life. HAE is mediated by bradykinin, released when a triggering factor, mainly physical and psychological stress, activates the contact system. In this study we followed a high-throughput approach with the goal of identifying genes that are involved in HAE attacks.

Methods: Using Illumina microarrays, we determined the effects of HAE attack on the gene expression profile of 8 HAE patients comparing samples collected during (A) and outside the attack (OA) and also from 8 healthy subjects (HS).

Results: The microarray experiments revealed several modulated genes that have a potential function during A. We identified and validated 10 genes that were induced more than 1.5-fold during A. These include genes that are important for the regulation of the vascular tone such as adrenomedullin (ADM). Gene Set Enrichment Analysis identified 10 processes differentially regulated comparing A to OA. The most represented processes ($p<0.05$) resulted in: "response to external stimulus" and "protein processing". Among genes belonging to the group "response to external stimulus", we found genes that are important for the structure or regulation of extracellular matrix such as PLAUR. Moreover, comparing HAE patients in OA to HS, we found the "cell matrix adhesion", and "g protein signaling coupled to camp nucleotide second messenger" gene sets. To validate the genes identified by microarray, we used a RT-PCR approach showing that ADM and PLAUR were significantly up-regulated during attacks.

Conclusions: Since PLAUR can activate the entire bradykinin-forming cascade, and ADM is a pivotal factor in mediating the vascular tone, we hypothesize that these two newly identified genes may have an important role in the pathogenesis of HAE.

O-09
GENE REGULATION IN THE PATHOGENESIS OF INHERITED C1-INHIBITOR DEFICIENCY (HEREDITARY ANGIOEDEMA)

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Background: Hereditary angioedema (HAE) is caused by mutations in the C1-inhibitor gene (SERPING1). As an autosomal dominant disease, HAE patients are mostly heterozygous (only two families with a homozygous mutation have been described). Nevertheless, plasma levels of functional C1-inhibitor in most HAE patients are markedly below the half normal levels that the wild-type allele should provide, suggesting a dominant-negative effect of the mutated allele on the wild-type one.

Methods: We combined total SERPING1 mRNA measurement with allele-specific mRNA dosage in blood of HAE patients carrying different mutations. We confirmed and expanded the results obtained in patients' cells through transient expression of exogenous SERPING1 in stabilized cell lines, looking both at the transcriptional and post-translational levels.

Results and Conclusions: Generally, no difference in mRNA levels was found between controls and HAE patients carrying missense mutations, thus excluding a down regulation of the wild-type allele at the transcriptional level. Nonsense mutations were responsible for a marked allele-specific and position-dependent reduction of SERPING1 transcript level, suggesting proper activation of the Nonsense-Mediated mRNA Decay pathway. Notably, all nucleotide changes mapping in proximity of position 16872 in the last SERPING1 exon were unexpectedly associated with a considerable mRNA degradation, pointing to the presence of an mRNA stability element, which could be destroyed by the mutations.

A better understanding of C1−inhibitor gene regulation and of its role in HAE pathogenesis could be critical to provide targets for new therapeutic approaches.

O-10
IMMUNOLOGICAL METHOD FOR SPECIFIC MEASUREMENT OF C1INH POLYMERS IN PLASMA AND C1 INH CONCENTRATE

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Background: Mutated C1inhibitor (C1inh) in hereditary angioedema (HAE) lacks the inhibitory capacity towards the Factor XII (FXII) dependent kallikreinkinin system, and HAE attacks are caused by overactivation of this system.

Mutations in the SERPING1 encoding C1inh are associated with formation of C1inh polymers in the plasma of HAE patients. Measurement of polymers in patient samples is a challenging task as the available antibodies do not distinguish between polymeric and native C1inh.

To further elucidate the role of C1inh polymers in the pathophysiology of HAE, we developed sensitive monoclonal antibody (MAb) based methods specific for detection of C1inh polymers.

Methods: C1inh polymers were produced by heating of native C1inh at 65C for 35 min at 6.5 g/L. Native polyacrylamide gel electrophoresis (PAGE) was used to validate the presence of polymers.

MAbs were produced by immunizing mice with C1inh polymers.

Polymers were separated using native PAGE, and the reactivity of each MAb was tested in western blotting (WB).

A polymer specific ELISA was establish using a MAb for coating, and the same biotinylated MAb for detection. The assay was calibrated with C1inh polymers, and C1inh as well as C1inh:FXIIa complexes were added in huge excess to study crossreactivity. Finally it was studied whether Berinert P 500 contained polymers.

Results: 15 MAbs recognised polymerised C1inh in native PAGE WB. One was extremely reactive towards polymers, and was used for establishment of a polymer specific ELISA. A calibration curve was constructed in the range from 0.5 to 10 mg/L. Neither native C1inh nor C1inh:FXIIa complexes interfered with measurement of C1inh polymers. No polymers were observed in Berinert P 500.

Conclusions: We produced a new ELISA method specific for C1inh polymers that is not influenced by the presence of native C1inh. This method is promising with respect to determination of C1inh polymers in patient samples and as a quality assurance in C1inh concentrates.

O-11
ACTIVATION OF THE FXII DEPENDENT KALLIKREIN KININ SYSTEM BY C1 INH POLYMERS

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Background: C1 esterase inhibitor (C1inh) is the primary inhibitor of the factor XII (FXII) dependent kallikrein kinin system (KKS), and thus controls bradykinin (BK) formation. Mutations in the C1inh gene can cause misfolding and polymerization of the inhibitor as observed in hereditary angioedema (HAE) patients. HAE patients suffer from recurrent life threatening BK mediated edema attacks, but the trigger of these attacks is so far unidentified. Misfolded proteins can activate the FXII dependent KKS, and we tested if polymers of C1inh show similar effects.

Methods: C1inh polymers were generated by heating native C1inh for 35 min at 65C at 6.5mg/mL. Interactions between C1inh polymers and FXII were investigated by analysing the electrophoretic mobility of FXII in the presence of C1 inh polymers using native PAGE western blotting (WB). FXII activating properties of C1inh polymers were tested in a WB bandshift assay, where C1inh polymers were incubated with FXII and the KKS proteins. All WBs were performed using anti FXII antibodies. C1inh polymer mediated kallikrein formation was studied using enzymatic methods: polymers were incubated with FXII, prekallikrein and a kallikrein sensitive substrate. The inhibitory capacity of the polymers were analysed in a C1s activity assay.

Results: The electrophoretic mobility of FXII was dramatically reduced in the presence of C1inh polymers, demonstrating a specific interaction between FXII and C1inh polymers. Band shift assays demonstrated that C1inh polymers induced kallikrein dependent cleavage and activation of FXII. Enzymatic experiments demonstrated that the polymers activated prekallikrein to kallikrein in a FXII dependent manner. The inhibitory capacity of the C1 inh was lost upon polymerisation.

Conclusion: With the use of immunological and enzymatic methods we demonstrated that polymerisation of C1 inh has dramatic effects resulting in conversion of an inhibitor to an activator of FXII dependent kallikrein generation.

O-12
STUDIES OF NON-CONTACT ACTIVATION OF HEREDITARY ANGIOEDEMA PLASMA TYPES I, II, AND III

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Background: We have previously reported that prekallikrein expresses an active site when it is bound to high molecular weight kininogen (HK). It can digest HK to produce bradykinin and the prekallikrein-HK complex autoactivatesin phosphate buffer to produce kallikrein. We wished to compare factor XII-independent kallikrein formation and HK cleavage in HAE plasma.

Methods: We incubated types I, II and III HAE plasma in polystyrene plates for up to two hours and measured kallikrein activity using a synthetic substrate (pro-phe-argp- nitro anilide).C1-INH was removed from Factor XII-deficient plasma by immunoadsorption.

Results: HK cleavage and kallikrein formation was observedin types I and II HAE,which was corrected by the addition of C1-INH. This is attributable to either traces of activated factor XII present or prekallikrein cleavage of HK or prekallikrein-HK autoactivation.Wereproduced this result in factor XII-deficient plasma upon removal of C1-INH indicating that factor XII is not required for activation when a "surface" is not present. We next questioned whether such an abnormality is present in type III HAE. Kallikreinformationwas demonstrable upon prolonged incubation of 50% plasma (1:2 dilution),which wasalso corrected by addition of C1-INH to twice normal levels. Separately, we demonstrated that the C1-INH in type III HAE is capable of inhibiting both factor XIIa and kallikrein although the functional level (mean)is less than normal. Thus excess C1-INH may bypass the underlying abnormality.

Conclusions: Our results demonstrate intrinsic lability of HAE plasma, types I and II, and a more subtle abnormality in type III HAE, which are reversed by the addition of C1-INH.Bradykinin can be generated in the absence of factor XII due to the intrinsic reactivity of the prekallikrein-HK complex but is prevented in normal plasma by C1-INH.

O-13
INHIBITION OF THE PLASMA KALLIKREIN-KININ SYSTEM ACTIVATION BY DX-2930, A FULLY HUMAN MONOCLONAL ANTIBODY INHIBITOR OF PLASMA KALLIKREIN

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Background: Hereditary angioedema (HAE) is a rare genetic disorder caused by a deficiency in C1-inhibitor characterized by unpredictable and debilitating attacks of angioedema that result from unregulated plasma kallikrein (pKal) activation and exaggerated bradykinin production. Inhibition of pKal is a viable therapeutic option for HAE, as demonstrated by the efficacy of ecallantide, a specific pKal inhibitor for treatment of acute HAE attacks. There remains an unmet medical need for a non-intravenous, long-lasting prophylactic treatment for HAE.

Methods: We used an antibody phage display library to identify DX-2930, a fully human antibody inhibitor of pKal. In vivo efficacy and pharmacokinetic properties of DX-2930 were determined using preclinical rat and cynomolgus monkey models.

Results: DX-2930 is a potent antibody inhibitor of pKal (Ki = 0.14 nM) that does not bind prekallikrein or similar serine proteases. Using surface plasmon resonance, DX-2930 was shown to bind the pKal-high molecular weight kininogen (HMWK) complex through non-catalytic domain residues. DX-2930 injected subcutaneously in monkeys demonstrated a high bioavailability (66%) and a half-life (12.5 days) that allometrically scales to ~28 days in humans. DX-2930 effectively reduced paw edema in rats and inhibited *ex vivo* contact-system-mediated HMWK cleavage in plasma from rats, monkeys, and humans.

Conclusion: DX-2930 is a potent, long lasting and highly specific antibody inhibitor of pKal. These properties suggest it may be an effective prophylactic treatment option for pKal-mediated diseases like HAE.

O-14
EARLY BIOMARKERS ARE REQUIRED FOR BETTER PREDICTION, EVALUATION AND TREATMENT OF HAE ATTACKS

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Background: Plasma proteolytic cascades are being activated in HAE, promoting generation of vasoactive substances and tissue edema. Current hypothesis maintain that loss of inhibitory C1 inhibitor (C1INH) activity result in endothelial instability, and vascular hyper-permeability. Recent data shows that many HAE attacks are often preceded by a variety of 'prodromal' signs and symptoms which may suggest that early activation of subclinical mechanisms precede the overt attacks. Therefore, early detection of such processes may contribute to the understanding of factors that lead to attack progression, which may assist a better timing of targeted treatments.

Methods: We present an extensive review of the current literature, focusing on biochemical agents that are activated during the early stages of attacks, and can therefore serve as early biomarkers of HAE. Reviewed biomarkers included complement fragments, C1INH and complexes, contact cascade and kinin-forming metabolites and their cleavage species, fibrinolysis and endothelial activation markers.

Results: Candidate biomarkers are presented based on established mechanisms and their potential contribution to the evaluation of an ongoing attack. Candidate biomarkers were categorized according to their putative role: diagnostic, predictive, metabolic, outcome. Where possible biomarkers used in clinical drug studies were assessed by their ability to predict an oncoming attack or to differentiate between attacks and remissions. Assay availability and measurability was also considered.

Conclusions: In view of the recent advancements in HAE management, there is an urgent need for early diagnosis of oncoming attacks. Identification of HAE-specific biomarkers might be useful for designing optimal timing of treatments.

O-15
ACTIVATION OF THE FICOLIN-LECTIN PATHWAY DURING ATTACKS OF HEREDITARY ANGIOEDEMA

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Background: The activation of the plasma enzyme systems is insufficiently controlled in hereditary angioedema due to the deficiency of C1-INH (HAE-C1-INH). Recently, a few studies suggested that the ficolin-lectin pathway (ficolin-LP) might play a more predominant role in the pathomechanism of HAE-C1-INH, than the MBL-lectin pathway. As the role of ficolin-LP in the development of edematous attacks is still enigmatic, we analyzed its activity during such episodes.

Methods: 35 HAE-C1-INH patients, who have experienced severe attacks on 112 occasions, were enrolled. We analyzed blood samples drawn during attacks, and 35 samples obtained from the same patients during symptom-free periods. The serum levels of ficolins, ficolin-3/MASP-2 complex, C1-INH, C4, C4d and C3a, as well as the extent of ficolin-3 mediated activation of the lectin pathway (F3-TCC) were measured using ELISA methods.

Results: Levels of functional C1-INH and ficolin-3/MASP-2 complex were elevated ($p=0.0009$ and $p=0.0224$), whereas F3-TCC was lower ($p=0.0002$) during attacks, compared with the symptom-free period of the same patients. During symptom-free periods, F3-TCC was significantly related to the concentrations of ficolin-3 ($R=0.2778$, $p=0.0022$), antigenic C1-INH ($R=0.3152$, $p=0.0006$), and C4 ($R=0.5307$, $p<0.0001$). During attacks, the level of ficolin-3/MASP-2 complex correlated with ficolin-3 ($R=0.5319$, $p=0.0025$), functional C1-INH ($R=0.5391$, $p=0.0066$) and C3a ($R=-0.4981$, $p=0.0096$). The concentration of the ficolin-3/MASP-2 complex was stable in consecutive symptom-free samples of the same patients.

Conclusions: The strong association between C1-INH activity and the level of ficolin-3/MASP-2 complex suggests that the ficolin-LP undergoes activation during HAE attacks. The ficolin-3 mediated activation of LP can lead to the consumption of the small reserve of functional C1-INH and thus, it may contribute to uncontrolled activation of the plasma cascade systems, and thereby to edema formation.

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O-16
A PRELIMINARY STUDY INTO THE ACTIVATION OF PLASMA ENZYME SYSTEMS DURING ATTACKS OF HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY (HAE-C1-INH)

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The activation of plasma enzyme systems contributes to the occurrence of hereditary angioedema attacks. We aimed to study the markers of the activation of the fibrinolytic, coagulation, and complement systems in a larger number of paired samples obtained from the same patients in symptom-free periods and during attacks.

Eleven parameters (Factor XI, XII, and C1-inhibitor activity, as well as the concentrations of the D-dimer, prothrombin fragments 1+2, plasminogen, plasminogen activator inhibitor-1 [PAI-1], thrombin-anti-thrombin III [TAT] complex, fibrinogen were measured along with prothrombin time and aPTT) using commercial kits. We compared these markers in samples obtained during attack-free periods and during 62 edematous episodes from the same 38 patients. Forty healthy subjects, matched for sex and age, served as controls.

Compared with the healthy controls, significantly higher FXI and FXII activity ($p=0.0006$, $p=0.005$), as well as D-dimer ($p<0.0001$), prothrombin fragments 1+2 ($p< 0.0001$), and TAT ($p=0.0303$) levels were ascertained in the patients in the symptom-free periods. The evaluation of samples from symptom-free periods or obtained during attacks revealed the significant increase of FXII ($p=0.0315$) and C1-INH activity ($p=0.0002$), as well as of D-dimer ($p<0.0001$), prothrombin fragments 1+2 ($p=0.0005$), and TAT ($p=0.0028$) concentration during edematous episodes. PAI level ($p=0.0076$), prothrombin time ($p=0.0026$), and aPTT ($p=0.0096$) decreased significantly during attacks, compared with symptom-free periods. C1-INH and FXII activity, as well as D-dimer levels were significantly higher during attacks with multiple (*vs*. a single) location, and/or in episodes of subcutaneous (*vs*. submucosal) edema.

Comparing a large number of paired samples from symptom-free periods or edematous episodes allowed an accurate appraisal of the changes occurring during attacks. Moreover, our study pointed out that the individual episodes may be characterized by different marker patterns.

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O-17
ENDOTHELIAL CELL ACTIVATION DURING EDEMATOUS ATTACKS OF HEREDITARY ANGIOEDEMA TYPE I AND II

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Background: Hereditary angioedema due to C1 Inhibitor deficiency (HAE-C1-INH) is a potentially life-threatening, rare disease caused by the decreased activity of the C1-Inhibitor (C1-INH). The lack of C1-INH leads to the overproduction of bradykinin (BK), a potent vasoactive peptide. Although angioedema is induced by BK, the function and activation of endothelial cells, the targets of BK, have not yet been studied during HAE attacks. We studied whether endothelial cell function is altered during HAE attacks, in comparison to attack-free intervals.

Methods: 46 consecutive 'during-attack' samples of 18 HAE-C1-INH patients were compared with 'inter-attack' samples of the same patients. The patients' sera were tested for von Willebrand factor antigen (VWF:Ag), von Willebrand factor collagen binding activity (VWF:CBA), soluble E-selectin (sE-selectin), and endothelin-1 (ET-1) levels using ELISA and BRAHMS Kryptor technologies. We also analyzed the possible effect of smoking and long-term danazol prophylaxis.

Results: The levels of all four endothelial cell markers (VWF:Ag, VWF:CBA, sE-selectin, ET-1) were significantly elevated during HAE attacks, compared to the symptom-free period of the same patients. Their increases were even more obvious in the subgroup of patients who had no danazol prophylaxis or did not smoke, both of which conditions are possible risk factors for endothelial dysfunction.

Discussion: In this study, we demonstrated that endothelial cells might be activated during HAE attacks. Our results may suggest the need for revising the knowledge on the pathogenesis of HAE-C1-INH, and reconsider the role of endothelial cells as a possible, novel therapeutic target in this disease.

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O-18
ACTIVATION OF THE PLASMA CONTACT-SYSTEM IN PATIENTS WITH ANAPHYLAXIS

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Rationale: Allergen-activated mast cells play a central role in the pathophysiology of anaphylaxis and lead to activation of the plasma contact system, a protease cascade which proteolyzes high molecular weight kininogen (HK) to liberate bradykinin. Bradykinin mediates the inflammatory response. Our aim was to investigate the role of contact system activation in anaphylaxis.

Methods: We compared 10 patients with variable grades of anaphylaxis at the time of admission and during remission with 10 age- and sex- matched controls. We determined proteolysis of HK by immunoblotting. Plasma bradykinin concentrations were quantified by ELISA. Mast cell activation and heparin release were determined by serum tryptase levels and aPTT or anti-Xa-activity. Contact system deficient and inhibitor treated mice were analyzed in anaphylaxis models.

Results: We noted extensive proteolysis of HK in the plasma of all anaphylactic patients at the onset of symptoms but not during remission and in none of 10 controls. Bradykinin concentrations were >30 fold elevated in anaphylactic patients than in control plasma. Degree of HK breakdown correlated with the severity of anaphylactic reactions. aPTT and anti-Xa activity were prolonged and significantly higher during anaphylaxis than in basal conditions or healthy controls. Contact system inhibitors interfered with drops in blood pressure in anaphylaxis models. $FXII^{-/-}$ mice and bradykinin B2 receptor-/- mice were resistant to mast cell-driven hypotension and vascular leak.

Conclusions: Mast cell-driven activation of the contact system is essential for the systemic manifestations of anaphylaxis. Interference with this system can provide an effective strategy for the treatment of allergic reactions.

O-19
HEREDITARY ANGIOEDEMA WITH NORMAL C1INH: CLINICAL CHARACTERISTICS OF SEVEN FAMILIES IN CATALONIA

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Background: Hereditary angioedema (HAE) with normal C1INH is a rare entity often underdiagnosed. It may be classified in 2 subtypes depending on the presence of F12 gene mutations (HAE-FXII and HAE-unknown).

Aim: To describe the clinical characteristics of patients with HAE with normal C1INH.

Methods: Retrospective study of clinical characteristics and triggers of angioedema (AE) attacks. Index cases were included. A family study was performed in all the relatives that could be recruited, including F12 gene mutations.

Results: Seven women were included as index cases; the family study increased the number to 20 patients (17 women/5 men). F12 gene mutations were identified in all. Fourteen (70%), 13 women and 1 man, had symptoms compatible. The other 30%, 2 women and 4 men, were asymptomatic, even in hyperestrogenic situations or on ACE-i. The majority of symptomatic patients (85%; 12/14) suffered an AE attack related to hyperestrogenic situations. One patient had an attack after a trauma and other without any identified trigger. All symptomatic women had developed AE when they were on oral oestrogenic contraceptives (OA). Of 9 patients who had been pregnant, only 3 had attacks during pregnancy. ACE-I were involved in two AE attacks (one in relation to a dental extraction). Dental extractions, major surgeries, intubations or endoscopies were performed in 75% of the symptomatic patients without triggering an attack. Most attacks were located in face and lips, 3 patients had an upper airway attack and four had an abdominal attack. C1INH levels and function were normal in 19/20 (C1INH function was 60% in one patient).Two attacks were treated with tranexamic acid and one with pd-C1INH with partial response. Three patients received icatibant with onset of relief in less than one hour and complete remission in 6h.

Conclusion: In our population, HAE with normal C1INH is associated with F12 gene mutations, affected mainly women and the OA are the precipitating factors.

O-20
A DELETION IN THE FACTOR 12 GENE ANALYSED IN TWO TURKISH FAMILIES WITH HEREDITARY ANGIOEDEMA WITH NORMAL C1 INHIBITOR (HAE TYPE III): A TURKISH *F12* MUTANT?

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In patients and families with hereditary angioedema with normal C1 inhibitor (HAEnCI) coming from West European and other countries, the missense mutations p.Thr328Lys and p.Thr328Arg in the coagulation *F12* gene have been found to be associated with the disease. To investigate whether in two Turkish families with HAEnCI a mutation in the gene coding for the coagulation factor XII could be identified. Family members coming from 2 unrelated Turkish families were investigated for recurrent angioedema, for C1 inhibitor activity and C4 in plasma, for mutations of the *F12* gene, and for the co-segregation of angioedema and mutation. Sequencing of all exons, the exon/intron boundaries, and the 3′ and 5′ flanking regions of the *F12* gene locus was performed. Four women, two women in each of the two families, had clinical symptoms of HAEnCI. In three women the symptoms started or exacerbated after beginning to take oral contraceptives. One woman had never received any estrogens. All 4 women had the novel deletion mutant in the *F12* gene causing the deletion of 72 base pairs (c.971_1018+24del72). The deletion leads to the loss of the 3′ end of exon 9 and the 5′ region of intron 9 of the *F12* gene. In a control group of 71 healthy individuals of Turkish origin the deletion was not present. A novel large deletion in the *F12* gene was found in two Turkish families with HAEnCI. A founder effect for this "Turkish" *F12* gene mutation is likely. The deletion is localised in the same *F12* gene region as the point mutations found in HAEnCI of West European countries.

O-21
MUTATION IN COAGULATION FACTOR XII GENE ASSOCIATED WITH HEREDITARY ANGIOEDEMA WITH NORMAL C1-INHIBITOR IN BRAZILIAN FAMILIES

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Background: Hereditary Angioedema with normal C1 Inhibitor (HAE type III)) is a rare familial disorder, described mostly in women. Mutations in the gene coding for Coagulation Factor XII (*F12*) have been identified a subset of patients with HAE type III, however functional implications of these mutations remain controversial. Our aim was to investigate *F12* mutations in patients with characteristics of HAE type III from Brazil, and to use molecular modelling to gain insights into the role of these mutations in clinical disease.

Methods: Five families with index cases of female patients who presented history of recurrent angioedema episodes with normal C1-INH and C4 levels were evaluated for HAE type III. Genomic DNA was isolated from whole blood and PCR was performed with 50 ng DNA. Mutations were detected by sequencing of exon 9 of *F12* and allelic discrimination. Family pedigrees were constructed. Modelling of Factor XII protein with and without mutation was performed using human plasminogen as template. Three dimensional modelling, assessment of quality, molecular dynamics and viewing were performed using appropriate programs.

Results: Genetic analysis revealed a previously identified missense mutation, c.983C>A (p.Thr328Lys), in index cases of four of five families. Relatives with history of episodes of angioedema in two families also bear the *F12* mutation. Comparison of predicted structures of native and mutated protein revealed that the p.Thr328Lys mutation leads to significant changes in the structure of the molecule, with disruption of a putative O-linked glycosylation site.

Conclusion: This study describes a mutation in *F12* as a likely cause of HAE type III in four families, for the first time in Brazil. Molecular modelling suggests that this mutation could disrupt significantly the structure of Factor XII molecule. Further studies will be necessary to investigate whether these structural changes could affect activity of kinin pathways.

O-22
HEREDITARY ANGIOEDEMA-FACTOR XII ASSOCIATED. CLINICAL AND GENETIC CHARACTERISTICS IN AN ANDALUSIAN COHORT (SOUTH OF SPAIN)

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Background: Clinical features of hereditary angioedema with normal C1 inhibitor are very similar to classical forms with C1inhibitor deficiency. A mutation in factor XII of coagulation has been found in a 20% of the patients and suggested to be causative for the disease (HAE-FXII). The aim of this study is to define the clinical and genetic characteristics of HAE-FXII Andalusian cohort.

Method: Patients with recurrent angioedema (AE) and normal C1 inhibitor were closely observed and we selected for the study those with FXII mutation. The items were: sex, age of onset, characteristics of attacks, triggers, estrogen (OE) sensitivity, genetic study, needs for maintenance therapy and some other relevant information. These items are compared with previously published case series.

Results: 7 women (from 5 non-related families) were included, 4 of them with family history of AE. The median age of onset was 23 years. Frequency of attack was 2-14/year. The most frequent localizations of AE were perioral area (100%), abdomen (86%) and face (71%). Laryngeal AE was observed in 43% of patients. 1 patient presented frequent urinary symptoms and another one presented an idiopathic urticaria a frigore which sometimes appeared with AE. 71% of patients required acute treatment with complement C1 esterase inhibitor (pdC1INH) or Icatibant which were very successful. One of our patients has shown only good response from Icatibant (not from pdC1INH). Long-term treatment with tranexamic acid was needed in 46% of patients. Only 26% of patients were OE-dependent. Triggers were OE contraceptives, pregnancy, menstrual cycle, perimenopause and stress. The mutation found in all of them was p.Thr328Lys.

Conclusion: Our HAE-FXII cohort presents similar characteristics to cohorts previously reported but abdominal symptoms have been more frequent in our group. We would remark that the presence of a concomitant urticaria can not completely exclude the diagnosis of HAE-FXII.

O-23
HEREDITARY ANGIOEDEMA PATIENTS WITH NORMAL C1 INHIBITOR AND FACTOR XII MUTATION: A FRENCH COHORT

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Introduction: Mutations in the coagulation factor XII (FXII) gene have been identified in few families with hereditary angioedema(HAE) with normal C1inhibitor (C1Inh). Since 2006, in France, the national reference centre of angioedema, a French multisite network of physician experts has collected data and established a cohort of those patients. The aim of this study is to describe the clinical aspects of this cohort.

Methods: We have conducted a retrospective, observational, cohort study of 27 patients diagnosed with normal C1 Inh with FXII mutation, from 15 families. We collected 18 patients completed records from 6 different reference centresites. We reported clinical features: family history, age, sex, onset of symptoms, attacks (sites, duration, frequency, treatment) and oestrogen sensitivity.

Results: 100% of patients are female with mean age of 36 years old. 53% of them have angioedema family history. Mean onset of symptoms is 22 years old.100% of patients experienced face attacks,73% upper airways attacks, with 60% of laryngeal attacks. Abdominal attacks were observed in 80% of patients and peripheral in 87%. Bladder attacks were described for 20% of them. Over the last year, the mean occurrence of attacks was 7.2. Regarding oestrogen sensitivity, 80% of patients worsened oestrogenic pills or pregnancy, 13% have had symptoms only with oestrogenic pills or during pregnancy and 7% reported no oestrogen influence. 27% of patients were treated at least for one attack with Icatibant, and 7% with C1Inh plasma-derived concentrate. 33% received long term prophylaxis with tranexamic acid and 7% with C1Inh plasma-derived concentrate.

Conclusion: On a small number of HAE patients with normal C1Inh and FXII mutation, we report specific clinical features, compared to HAE patient with C1 Inh deficiency. We want to focus on the fact that in this cohort only women are symptomatic and 93% of them have oestrogen sensitivity. A study with more patients is needed to confirm those data.

O-24
HEREDITARY ANGIOEDEMA WITH FACTOR XII MUTATION: NO EVIDENCE FOR CONTACT ACTIVATION DURING ATTACK (CASE REPORT)

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In hereditary angioedema with factor XII mutation (HAE-FXII) symptoms are similar to those detected in other forms of HAE and it is assumed that they are due to an increased formation of bradykinin through contact system activation.

A 24 years old woman from Morocco was admitted to our Emergency Department for severe angioedema of the face. Standard therapy with corticosteroids and antihistamine was ineffective. The patient reported history of recurrent abdominal pain without identified cause and scattered peripheral angioedema since childhood that increased in frequency in the last three months since starting oral contraceptives. Due to suspected bradykinin mediated angioedema, the patient was treated with icatibant (30 mg/3 ml). Because of absence of symptom improvement icatibant (30 mg/3 ml) was repeated 18 hours later. Since angioedema symptoms did not improve the patient was maintained on tranexamic acid 1 gr every 4 h orally. Symptoms relief started on day 3 and complete resolution was on day 5. Blood samples for complement and contact system analysis were collected throughout these days. Plasma levels of C1-INH, function and antigen, C4 and C1q were always normal. Spontaneous plasma kallikrein amydolytic activity, and the capacity of plasma to inhibit kallikrein amydolytic activity were also normal. The amount of cleaved high molecular weight kininogen did never exceed the normal values. FXII gene analysis revealed the presence of the mutation 1032C>A, p.Thr309Lys.

The case of this patient with HAE-FXII does not support the hypothesis that angioedema symptoms are mediated by bradykinin released from high molecular weight kininogen due to an increased formation of plasma kallikrein.

O-25
KININ CATABOLISM AND DISEASE SEVERITY IN HEREDITARY ANGIOEDEMA WITH *F12* MUTATION

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Background: Diagnosis of hereditary angioedema (HAE) associated with the mutation 983A/G on the exon 9 of the *F12* gene is difficult according to the highly variable penetrance of the disease. The aim of this study was to investigate how critical is the kinin catabolism in the severity of the disease.

Methods: Our analysis was based on retrospective reports of patients affected by HAE associated with *F12* gene mutation compared with healthy donors (2007-2012).

We measured bradykinin (BK) forming activity (based on the amidase activity using the PFR*p*NA substrate) and activities of the three major kinin catabolism enzymes (Angiotensin-I converting enzyme, ACE; Aminopeptidase P, APP; Carboxypeptidase N/M, CPN) in the citrated plasma.

We developed a logistic regression analysis from the enzymatic data to predict the disease severity. Severity score was established according to frequency of attacks, age of disease onset and localization (Freiberger T. *et al Scand. J. Immunol* 2011:*74*, 100–106).

Results: We analyzed 76 symptomatic patients in 37 unrelated families (representing 167 individuals) and 200 healthy donors. 28 patients suffered from mild severity disease, 21 with intermediate severity and 27 with severe disease. The severity was found significantly increased with high amidase activity ($p<0.0001$), with decreased ACE ($p<0.01$) and CPN ($p<0.01$) activities, but not correlated with APP activity ($p=0.7$).

Conclusion: These results support the observation that, in addition to the increased BK production, severe patients exhibit a low kinin catabolism. The disease severity in the *F12* mutation carriers is significantly correlated to amidase, ACE and CPN activities, in contrast to C1 Inhibitor deficient patients where the severity is mainly correlated to APP activity. This suggests a higher responsibility of the enzymes of the BK catabolism in HAE with *F12* mutation than those of the *des*Arg^9-BK catabolism.

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LONG TERM PROPHYLACTIC TREATMENT IN SPANISH PATIENTS WITH HEREDITARY ANGIOEDEMA WITH C1INH DEFICIENCY (HAE-C1INH)

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Background: Long term prophylaxis (LTP) in hereditary angioedema (HAE) patients is indicated when attacks are referred very severe or very often. LTP may be performed with attenuated androgens (AA), antifibrinolytics or replacement with human plasma derived C1 inhibitor concentrate (pdhC1INH)

Methods: Data on LTP regarding current medication and doses from HAE-C1INH types I and II patients regularly controlled in the Spanish Hospitals members of SGAB (Spanish Group of Angioedema mediated by Bradykinin) were recorded.

Results: Data on 357 patients were collected. One hundred and seventy-six (49.30%) patients were taking prophylactic treatment, of whom 137 (77.84%) were taking AAs (Stanozolol: 106 (77.37 %), mean dose: 9.65 mg/week, range: 2-28; Danazol: 31 (22.63%), mean dose: 840.86 mg/week, range: 117-2800). Twenty-seven were taking antifibrinolytics (Tranexamic acid) (mean dose: 8055.57 mg/week, range: 2500-14000) and 12 were under replacement therapy with pdhC1INH (mean dose: 3028.83 U/week, range: 2000-5000U).

Conclusions: LTP was used in half of the Spanish patients, mostly with AAs. When AAs were used low doses were sufficient to achieve the control of symptoms in most patients. Replacement of C1INH was the least commonly used treatment as LTP, mainly in cases with adverse events or contraindications of other therapies.

O-27
ANABOLIC ANDROGEN EXPERIENCE AND RESPONSE TO NANOFILTEREDC1 INHIBITOR FROM THE CINRYZE PREVENTION TRIALS IN PATIENTS WITH HAE

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Background: Historically, the most commonly used HAE prophylactic treatment has been attenuated androgens (AA). Clinical trialshave demonstrated the efficacy and safety of plasma-derived nanofiltered C1 inhibitor (C1INH nf, CINRYZE®) for the long-term prevention of HAE. The effectiveness of AA in preventing attacks is variable, and little is known about the effectiveness of C1INH nf in HAE patients who continue to swell on AA.

Methods: Data analyses were conductedfor subjects who were receiving AA at the time of screening in the two prophylactic clinical trials for CINRYZE.

Results: In the randomized trial, 36.4%of subjects (8 of 22) were using AA for prophylaxis with a mean historical attack rate of 13.88 per 12 weeks. Five of the 8 patients discontinued AA use prior to randomization. Among these 5, the mean number of attacks over the 12-week placebo period was 15 compared to 6.8 attacks during the C1INH nf treatment period (54.7% decrease). The 3 patients who continued on AA throughout the trial had a mean of 14 attacks during placebo treatment and 10 attacks during C1INH nf treatment (28.6% decrease).

In the open-label study, 28.8% of subjects (42 of 146) were using AAfor prophylaxis and23 of them discontinuedAA during the study. The median number of attacks/monthin subjects who discontinued AA was 3.00 (1.25, 11) at entry and 0.00 (0.00, 0.31) during an average of 257 days in the study. 8 subjects continued on a stable dose of AA during open label treatment. Their attack frequency went from 3.5 (2.75, 4) to 0.26 (0.06, 0.71). The other 11 subjects reduced but did not stop their AA. Their attack frequency went from 2 (2, 3) to 0.24 (0, 0.67).

Conclusion: Clinical trial evidence demonstrates the effectiveness of CINRYZE for long-term prevention of HAE, even in patients who had been on AA with variable degree of control. These data are consistent with current evidence based HAE guidelines, given the dosing recommendations andlong-term risk/benefit of AA.

O-28
HAE PATIENT EXPERIENCE WITH SHORT TERM PROPHYLAXIS: RESPONSES TO AN ON-LINE QUESTIONNAIRE SURVEY

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HAEA organization

Rationale: The objective was to assess HAE patient experience with short term prophylaxis (STP) before surgical/medical procedures.

Methods: An on-line questionnaire was distributed to HAE patients to obtain information about STP and efficacy. The first 250 respondents were included however only data from Type I and II HAE patients (n=219) were analyzed using descriptive statistics.

Results: Demographics of respondents were as follows: Average age 40yrs (range 7-82); Type 1-182 (73%), Type 2-37(15%); Average # of attacks/year was 29 involving mostly the extremities and abdomen; 13% were previously intubated; 74% experienced prodromes of which 85% predicted an attack; the most frequent triggers (>50%) were emotions(87%), physical stress(79%), trauma(77%), spontaneous(74%), hormones(54%); the most frequent surgical/medical procedure triggers were dental(40%), surgery(38%), pregnancy(18%), labor and delivery(8%) and endoscopy(5%). Patients receiving prophylaxis included 36%(73/201) on Cinryze and 21%(43/201) on androgens. Patients receiving on-demand treatment included 42(21%) on Berinert, 17(8%) on Kalbitor, 18(9%) on Icatibant and 7 (4%) on fresh frozen plasma. Only 15%(33/219)previously used STP. Short term prophylaxis was used alone in 19/33(58%) and was completely effective in 13/19(68%); STP+one on-demand treatment was used in 14/30(42%) and was effective in 5/14 (36%). Onset and/or progression of swelling was prevented in only 1/8 (12.5%) who required more than one OD treatment.

Conclusion: A small percentage of HAE patients reported experience with STP for surgical/medical procedures likely due to fear of precipitating attacks. 42% receiving STP still required OD treatment supporting current recommendations for STP before surgical/medical procedures and having OD treatment readily available for breakthrough attacks.

O-29
MANAGEMENT OF HEREDITARY ANGIOEDEMA. REAL-WORLD EXPERIENCES FROM A DANISH SPECIALIST CENTRE

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Background: The handling of patients with hereditary angioedema (HAE) differs between countries according to tradition, financial resources and health care systems. This study presents data on swellings and treatment principles in Denmark.

Methods: Prospective data were collected by interviews, medical records and patient diaries from 2001 until 2012.

Results: 80 patients (25 children and 55 adults) from 30 families were included. 41 males and 39 females experienced a total of 7809 attacks recorded over 469 patient years. At the end of the study 75% of patients had been treated with complement C1 inhibitor (C1INH) concentrate and 45% of adults patients had been treated with icatibant on-demand. 39 patients practiced home treatment of acute attacks. 13 patients were on long-term prophylaxis (LTP): 7 males were treated with danazol 50-200 mg daily for 1-32 years, 3 patients used tranexamic acid 1000-3000 mg daily for 6-11 years and 3 patients were treated with nfC1INH concentrate in a dose varying between 1000 IU every third day to about once weekly for 6-9 months. Among patients treated with danazol, 3 patients had hypertension, 2 patients had hyperlipidemia and 1 patient had raised creatinine kinase.

In the study period patients received a total of 8151 vials of Berinert®, 684 vials of Cinryze®, 4 vials of Ruconest® and 554 syringes of Firazyr®. At least 831 acute attacks were not treated. A total of 1006 acute hospital contacts were registered. In the 39 patients practising home therapy a total of 580 acute hospital contacts were registered before home therapy (155 patient years) and 71 acute hospital contacts were registered after learning to self-inject (119 patients years). No tracheotomies or deaths were seen.

Conclusions: Patients are treated primarily with on-demand therapy. Half of the patient population practise home therapy and in this group the average number of acute hospital visits is reduced by 84%. At least 10% of all attacks are untreated.

O-30
PROSPECTIVE EVALUATION OF THE EFFICACY OF ON DEMAND TREATMENTS IN REDUCING DURATION OF ANGIOEDEMA IN PATIENTS WITH HEREDITARY ANGIOEDEMA DUE TO C1 INHIBITOR DEFICIENCY

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Background: Hereditary angioedema with C1 inhibitor deficiency (HAE-C1INH) is characterized by angioedema of the skin,of the gastrointestinal tractand upper respiratory mucosalasting 2 to 5 days. Depending on frequency, duration and severity of symptoms, HAE can be disabling and,in case of laryngeal edema, life-threatening. This prospective study evaluates use and efficacy of on demand therapy in shortening attacks duration.

Methods: Patients followed at our centre recorded data of angioedema attacks reporting on occurrence, duration, location, severity, treatment and time of treatment. 96 HAE patients provided data for a total of 694 attacks. 53 patients had both Icatibant and plasma derived-C1 Inhibitor (pd-C1INH) available at home for treatment, 40 had only pd-C1INH and 3 only Icatibant. Patients were treated in hospital or self-administered the treatments at home.

Results: Abdominal attacks were the most frequent (42%),followed by peripheral and facial(38% and 7% respectively). Laryngeal attacks were less common (6%). 77% of the attacks were moderate to severe.

156 attacks (22%) were not treated; 141(20%) were treated with tranexamic acid orsymptomatic therapies, 225 (32%) with Icatibant (89% at home), 172(24%)with pd-C1INH (48% at home).

The median duration of attacks treated with tranexamic acidwas 32 hours, with Icatibant 11 hours, with pd-C1INH 23 hours, while median duration of non treated attacks was 48 hours. Time from drug administration to complete resolution, recordedin 243 attacks,was 24 hours for tranexamic acid, 8 hours for Icatibant, 13 hours for pd-C1INH. A second treatment was required in 31 (14%) attacks treated with Icatibant and in 4 (2%) treated with pd-C1INH.

Conclusions: Our data confirm that specific on demand treatments for HAE-C1INH are effective in shortening the duration of acute attacks and therefore can be used to minimize the disease related inability. Early administration of treatment reduces the duration of attacks.

Keywords: Hereditary angioedema, C1 inhibitor, Icatibant, tranexamic acid

O-31
RUCONEST IN ROUTINE CLINICAL PRACTICE: UK EXPERIENCE

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Conestat alfa (Ruconest) is a recombinant human C1 inhibitor protein (C1INH) that is extracted from the milk of transgenic rabbits. It was licensed in Europe for the treatment of acute attacks of hereditary angiodema (HAE) in 2010. Here we describe our experiences treating the first 11 adult patients who have received Ruconest outside a clinical trial setting in the UK. Nine patients had HAE type 1, one had HAE type 2 and one had acquired C1INH deficiency.

We have considered the prescription of Ruconest in preference to plasma-derived C1INH (pdC1INH), which is comparatively well established in routine clinical practice, in several clinical situations:- when patients prefer to avoid blood products, for heavier patients, when the licensed dose of Ruconest is more cost effective and for patients showing a sub-optimal response to 20 U/Kg of pdC1INH.

The majority of the patients self administered the drug at home and reported that having fewer vials to prepare was a benefit. Eight patients were treated with 4200 and three with 2100 units of Ruconest. Ruconest appeared effective and was well-tolerated by all patients, and six of the patients chose to continue to use it as their preferred treatment for acute attacks. Some patients reported a more rapid time to initial response and complete resolution of their symptoms following treatment with Ruconest compared to their usual pdC1INH. However, three patients experienced recurrent swellings following treatment with Ruconest:- Two patients with very frequent attacks (occurring more than twice weekly) treated with 4200 and 2100 units reported recurrences after 11 hours and 2 days respectively - these were treated successfully with pdC1INH; The third patient, who has acquired C1INH deficiency associated with mild C1INH resistance, had a recurrence at 7 hours after Ruconest that subsequently resolved with tranexamic acid.

Overall, Ruconest was effective and well-tolerated; it has the potential to improve outcomes in HAE.

O-32
CLINICAL TRIAL EXPERIENCE OF PEDIATRIC PATIENTS TREATED WITH ECALLANTIDE FOR ACUTE ATTACKS OF HEREDITARY ANGIOEDEMA

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Background: Hereditary angioedema (HAE) is a rare genetic disease associated with unpredictable, debilitating and potentially fatal acute attacks of edema. Ecallantide is a plasma kallikre in inhibitor indicated for treatment of acute HAE attacks in patients ≥16 years in the US. We report use of ecallantide in pediatric patients<18 years old.

Methods: Data for patients (9-17years of age) was pooled from 4 clinical studies (EDEMA2, EDEMA3, EDEMA4, and DX-88/19) that evaluated the safety and efficacy of 30 mg subcutaneous ecallantide for the treatment of acute attacks of HAE. Endpoints included Treatment Outcome Score (TOS; minimally important difference [MID] = 30), a validated, HAE specific patient reported outcome measure, and time to near complete symptom resolution.

Results: Overall, 29 pediatric patients were included; 25 of them received ecallantide for 62total HAE attacks and 10 received placebo for 10 total attacks. Patients treated with ecallantide reported greater symptom improvement as measured by TOS at 4 h post dosing (74±36 vs 45±44for placebo). The ecallantide group reached the MID for TOS by 1 h post dosing (32±39 vs -5.0±28 for placebo) whereas the MID for TOS with placebo was not reached until 4h (45±44). Median time (minutes) to near-complete symptom resolution was 181 (interquartile range [IQR]: 84, >4 hours) for ecallantide vs 226 (IQR: 197, >4 hours) for placebo. Treatment-emergent adverse events were similar in both groups. Only 1 serious adverse event was reported: staphylococcal cellulitis in the ecallantide group, classified as unrelated to treatment. There were no potential hypersensitivity reactions in this particular analysis, although it should be noted that hypersensitivity is a known risk of ecallantide in all patients.

Conclusions: In this analysis, ecallantide appeared effective for pediatric patients 9-17 years of age and was associated with a rapid time to near-complete symptom resolution. No new safety signals were identified.

O-33
FOLLOW-UP OF PATIENTS WITH DRUGS TARGETING THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM- INDUCED ANGIOEDEMA

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Background: Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely used in patients with hypertension or ischemic heart disease. ACEIs or ARBs-related angioedema (ACEIs/ARBs-AE) is a well-documented condition, which seems to occur in up to 1% of treated patients. The aim of this study is to describe the clinical aspects of a cohort of ACEIs/ARBs-AE patients

Methods: We conducted a retrospective study of 38 patients diagnosed of ACEIs/ARBs-AE. We studied the items: sex, toxic habits, familial or personal history of angioedema, onset of symptoms, characteristics of attacks, antihypertensive involved, response to stop treatment and other relevant information.

Results: 63% of patients are male and 26% smokers. Personal history of histaminergic AE and/or chronic urticaria was founded in 32%. Just 2 patients presented family history of non-histaminergic AE. Median of onset of symptoms was 64 years old. ACEIs-AE was 68% of the total. Drugs most frequently involved were perindopril and ramipril. Just 8% of patients presented ACEIs plus ABRs-AE. Drug was prescribed from 7 days to 20 years before first attack. Attacks on the ORL region were observed in 97% of patients, with 34% of larynx attacks. Attack frequency was from one single attack to 5 episodes/month during several years. Treatment with corticoids and antihistaminics were ineffective in all attacks. 28% of patients were treated at least for one attack with Icatibant, C1inhibitor concentrate or tranexamic acid with improvement in every case. Icatibant was especially successful with an improvement of symptoms in 1-2h. Only 19% of patients presented symptoms until 9 months after stopping drugs involved. Two patients' attacks were also facilitated by the use of hormonal therapy to treat prostate cancer.

Conclusion: This study shows the clinical characteristics of ACEIs/ARBs-AE, in a French patients' cohort and the efficacy of specific treatments as icatibant or C1Inhibitor concentrate.

O-34
ASPHYXIATION IN HAE DUE TO C1-INH DEFICIENCY AND HAE WITH NORMAL C1-INH

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HAE attacks involving obstruction of the upper airways (supraglottic edema; laryngeal attacks) are rare but potentially life-threatening; patients are at a risk of asphyxiation during a laryngeal attack (LA). Death from asphyxiation due to an LA was already reported in one of the earliest descriptions of HAE. The mortality in diagnosed and undiagnosed patients with HAE due to C1-INH deficiency (HAE-C1-INH) and in HAE with normal C1-INH (HAEnCI) should be determined. A cohort of 728 patients from 182 families with HAE-C1-INH was evaluated for death cases by analyzing pedigrees and questioning relatives and treating physicians. Of the 214 patients who had died, 70 asphyxiated during a laryngeal attack. Mortality by asphyxiation was 9-fold higher in patients with undiagnosed HAE-C1-INH than in patients with diagnosed HAE-C1-INH. The lifespan of asphyxiated patients with undiagnosed HAE-C1-INH was on average approximately 31 years shorter than for patients with undiagnosed HAE-C1-INH who died of other causes. Five patients with HAEnCI who died by asphyxiated are reported.

The high mortality in patients with undiagnosed HAE-C1-INH underscores the need to identify and diagnose these patients. Patients with diagnosed HAE-C1-INH who are insufficiently informed about the risk for LAs, and who are inadequately trained about emergency treatments and the need for early administration of the appropriate therapy, carry a risk for asphyxiation.

O-35
CLINICAL SURVEY OF DIFFERENT FORMS OF ANGIOEDEMA WITHOUT WHEALS

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Background: Angioedema (AE) without wheals can be hereditary (HAE) or sporadic (SAE) and can be prevented or not by antihistamine (AH). SAE not prevented by AH can be due to acquired C1 inhibitor (C1-INH) deficiency (AAE-C1-INH), angiotensin-converting enzyme inhibitor (ACEi) or unidentified etiology. HAE can be due to C1-INH deficiency (HAE-C1-INH), Factor XII (HAE-FXII) mutations or unidentified etiology.

Methods: This study reports on 1702 patients with AE without wheals referred at our Department between 1993 and 2012 describing in details patients with AE non responding to AH with unidentified etiology.

Results: 353 patients had HAE-C1-INH, 39 had AAE-C1-INH and 2 had HAE-FXII. A specific cause of AE was found in 218 patients. AE occurred during ACEi treatment in 176 patients. Etiology remained unidentified in 465 patients. Based on AH response these patients were divided into histaminergic (379) and non-histaminergic (86). 449 patients were lost at follow-up. Based on presence of family history, 86 patients with non-histaminergic AE were further divided in 2 groups: 68 (M:F 1,17) with non-histaminergicsporadic AE (NH-SAE) and 18 (M:F 2) with non-histaminergichereditary AE (NH-HAE). Median age at onset was 38 and 24.5 respectively. 80% NH-SAE and 58% NH-HAE reported more than 5 attacks/year. AE location in NH-SAE/HAE was: face 86/61%, tongue or oral cavity 59/30%, limbs 54/70%, larynx or gastrointestinal mucosa34/72%. 12 NH-SAEand 2 NH-HAE patients treated acute attacks with tranexamic acid (TA) with rapid resolution; C1-INH concentrate was successfully administered in 2 patients, 1 with NH-HAE and 1 with NH-SAE. Icatibant was effective in 1 patient with NH-HAE. Prophylaxis with TA was effective in 36 NH-SAE and in 6 NH-HAE patients while was not effective in 1 NH-SAE.

Conclusions: Our data indicate that patients with recurrent AE non responsive to AH have analogies in clinical presentation and response to therapy suggesting similar pathogenetic pathways.

O-36
SURVEYS OF PRODROMES PRECEDING ACUTE ATTACKS OF HEREDITARY ANGIOEDEMA

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Background: Premonitory signs and symptoms ("prodromes") may precede the onset of hereditary angioedema (HAE) attacks. They are frequently reported by patients but have a wide variability of subjective and objective manifestations. Data on prodromes is limited to short series and case reports, and it is not clear if they could be reliable indicators for diagnosis and early initiation of treatment.

Methods: Three separate surveys, one prospective and two retrospective, were preformed in the US and Israel. They utilized questionnaires with solicited questions about either overall, or most recent prodromal history as experienced by the patients. A total of 113 patients participated in these studies.

Results: Prodromes were reported by 82.5% to 95.7% of patients. In one survey about 2/3 reported prodromes before all or most acute attacks. Most common types of prodromal symptoms were related to skin/soft tissue and gastrointestinal tract. Prodromes were experienced hours to days before the onset of angioedema. In 69% of cases of two combined surveys (N=402 prodromes), the time lapse between prodromal symptom appearance and the onset of an acute attack was less than 24 hours, and in 39% of attacks this interval was shorter than 12 hours. In one survey most subjects indicated being able to predict an impending attack all or most of the time.

Conclusions: Our data suggest that prodromes in HAE are more common than has been previously reported and that a majority of patients are able to predict their attacks. There is an urgent need to define the specificity, sensitivity and predictive values of physical and perceptual prodromes, and to investigate the clinical efficacy, cost effectiveness, and quality-of-life impact of a prodrome-based treatment approach.

O-37
THE INFLUENCE OF AGE AT FIRST CLINICAL MANIFESTATION OF HEREDITARY ANGIOEDEMA (HAE) ON THE CLINICAL COURSE OF THE DISEASE

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Rationale: Hereditary angioedema (HAE) is a rare disorder caused by functional C1-esterase inhibitor (C1-INH) deficiency and characterized by recurrent episodes of swelling. Initial symptoms usually occur during the first decade of life. There is uncertainty, however, as to whether disease severity is correlated with the age at first clinical manifestation.

Methods: The relationship between age at first clinical manifestation of HAE and frequency of recurrences was retrospectively evaluated for 61 patients, allocated into groups according to their age at first clinical manifestation of symptoms. The course of the disease was defined based on the number of attacks per month(severe: ≥ 4 attacks/month, moderate/mild: <4 attacks/month). Attacks were treated with human pasteurized C1-INH.

Results: Overall, patients with an early onset of symptoms were more likely to suffer from a severe course of the disease. In 6 patients, who suffered from the most severe courses of HAE, the first clinical manifestation was at an age of ≤ 3 years. Treatment with human pasteurized C1-INH concentrate was efficacious and safe irrespective of disease severity. The majority (82%) of 22 patients who were first treated in the context of a pre-procedure prevention received their first treatment at an age of ≤ 6 years. Of 39 patients who were first treated for an acute attack, 56% received their first treatment at an age of ≤ 6 years.

Conclusions: The severity of the course of HAE is associated with the age at first clinical manifestation. The threat of developing a severe course with early onset of symptoms underlines the importance of early diagnosis in families with a history of HAE to allow for an optimal management of the disease. Onset of first clinical symptoms is not associated with early treatment with human pasteurized C1-INH concentrate for pre-procedure prevention.

O-38
LIVING WITH HEREDITARY ANGIOEDEMA – NURSING ASPECTS

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Background: Hereditary Angioedema (HAE) is a chronic rare disease, in which the disease course influences perception of illness trajectory, based on insights accumulated from past experiences. HAE patients endure mental distress, anxiety and negative body image, which may lead to loss of self-confidence and difficulties in personal relationships. Each individual responds to illness differently and adopts personal behaviors and interactions with family and social environment. Coping strategies, like perception-of-control over life events and skills for handling stressful situations are expected to lead to better control and well-being.

Methods: Nurses workshop is planned to provide an interactive forum for debate and discussion regarding the management and education of patients with HAE. The workshop will discuss the following topics: medical and bio-psychosocial problems, difficulties in the perception of illness and its trajectory, rejection and denial, the burden of expensive medical treatments, bureaucratic hardships and health-related quality-of-life. Coping strategies appropriate to disease stage, educating patients on the proper use and timing of treatments, writing treatment plans for acute attacks and prophylaxis will be discussed. The workshop will encourage a productive dialogue between nurses and HAE patients in order to manage expectations and promote mutual understanding.

Conclusion: Nurses and health-care professionals are important in managing chronic diseases like HAE. The nurses have a pivotal role in delivering medical information, integrative care and support. In-line with the new drug treatments, the workshop will deal with methods to empower patients to self-manage their HAE.

O-39
PRACTICAL APPROACH TO SELF-ADMINISTRATION OF C1-INHIBITOR IN HAE-PATIENTS

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Patients suffering from hereditary angioedema (HAE) show recurrent episodes of swelling of the skin and subcutaneous tissue, which might be very painful and in cases of laryngeal attacks even life-threatening. A common treatment option is the i.v. substitution of the missing protein C1-Inactivator (C1-INH). As attacks do not always come slowly, an early substitution is important and may be life-saving. Medically controlled self-administration of C1-INH was identified as an optimal way to intervene early in acute attacks.

In our centre we have extensive experience with medically controlled self-administration in haemophilia since more than 35 years. Several hundred patients or their parents were trained to reconstitute the factor and to inject it intravenously. An experienced nurse is the main person responsible for training and guidance. Since 1982 we offer this treatment option also for HAE-Patients, up to now about 300, which have suitable venous access and which are able to recognize early signs of attacks. The training is repeated, until we are sure that the patient has sufficient practice and is confident with the medical aspects. Patients with bad venous access and a port-system need an extra training with special attention to sterile working. According to our experience self-administration can successfully be introduced for the majority of patients, even for some children and adolescents. The requirements for self-administration and the different steps of the practical training will be explained and discussed in detail.

C1-INH self-administration decreases the time to treatment and the severity of the attack, avoids unnecessary pain and increases quality of life. In addition it increases time to work or to go to school and makes the patients more independent from the physician.

O-40
THE HUNGARIAN PATIENT – HOSPITALISATION OF HAE-PATIENTS WITH DISEASES DIFFERENT FROM HAE

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Although Hungarian HAE-patients enjoy special care and attention from HAE Centre in Budapest, they are not protected from other diseases. Like any other humans they might suffer from an array of diseases from minor ailments to serious illnesses. While some of the symptoms can be treated and cured relatively easily, others need more consideration and professional expertise. If the disease requires hospitalisation, HAE is considered to be the patient's underlying disease which cannot be neglected as it might attack at the most peculiar times and localisation. It may cause surprise not only to the patient but also to the doctors in hospital.

The presentation gives an account of a case study of a patient who underwent a diverticular operation last year. The operation was followed by sepsis; therefore the patient had to be operated for the second time, which prolonged hospitalisation. Two months later, already at home joint meningitis and encephalitis developed which resulted in coma. Within three months the patient happened to be in life-threatening situations twice and for a considerable period. After the second, life saving, surgery, the patient was supplied with an ostomy pouch which was finally removed with intestinal reparation this year. All through his Calvary the patient was firmly accompanied with HAE.

The case has several lessons and raises a number of questions, especially about treatment, medicine supply, cooperation among doctors and relations between hospital staff and the family. The presentation invites doctors and patients to draw conclusions and ask even more questions in order to help other hospitalised HAE-patients in any parts of the world in the future.

Keywords: hospitalisation, treatment, cooperation

O-41
PRACTICALITIES AND BARRIERS TO HAE SELF-ADMINISTRATION THERAPY: DISCUSSIONS FROM AN INTERNATIONAL HAE EXPERT MEETING

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Background: Hereditary angioedema (HAE) treatment options have recently increased with products being licensed for self-administration(SA) for prophylaxis and treatment of acute attacks; however, SA uptake varies. We report results of a survey and an international HAE expert meeting, highlighting the practicalities and barriers to SA of intravenous (IV) C1 inhibitor (C1-INH).

Methods: A 16-question survey was sent to 21 centres in Europe, the United States and Canada. Results were used to stimulate discussion at an international HAE expert meeting to share country-specific experience of SA, focusing on treatment of acute attacks.

Results: The survey, completed by 10 centres, showed SAuse increasing with growing awareness; 5/10 respondents reported 50–74% of patients trained to self-administer (with IV C1-INH or subcutaneous bradykinin receptor blocker). As attack presentation and severity are unpredictable, experts agreed patients should have an acute attack management plan. While there were few concerns in offering SA, trained HAE staff availability, patients' attitude and ability to learn/retain skills should be considered. SA training, provided by all 10 centres, varied between countries. The main barrier to SA with C1-INH was reported as IV injection skills; however, most physicians felt that once learnt, skills were retained long-term by most patients, including children/adolescents. Initiatives to increase SA uptake include IV technique training at a young age and implementation of a 24-hour helpline.

Conclusion: Barriers to SA of IV HAE treatment were identified and practical solutions offered. The international HAE expert panel agreed all HAE patients should be considered for SA as it ensures early treatment and can be life-saving; however, some patients may need more support than others and some may not be eligible. Standardised training, experienced training staff, a 24-hour helpline and individual disease management programmes could encourage further uptake of SA.

O-42
THE BUILDING BLOCKS FOR AN EFFECTIVE PATIENT GROUP ADVOCACY PROGRAM

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The cold reality of difficult economic times and shrinking health care budgets presents huge challenges for patients (like those with HAE) who suffer from a rare, chronic disease that is treated with orphan drugs. Hereditary Angioedema International (HAEi)—the global umbrella organization that represents the worlds HAE patient advocacy organizations—believes that a targeted, well organized, and persistent patient-led advocacy effort can make a difference in efforts to win access to life improving therapies. Clearly, the journey for gaining (or expanding) access to HAE therapies in most countries brings us to the doorstep of the physicians who diagnose and treat HAE, and the health ministries/insurers who must be convinced to pay for HAE therapies.

There are four fundamental building blocks that comprise an effective advocacy program:

1. A group of patients who are passionate about improving the lives of fellow HAE sufferers, and are willing to make a long-term commitment,
2. A physician or group of physicians who are committed to providing guidance and support to the patient group and educating the country's medical community,
3. A pharmaceutical company to provide support for patient advocacy and awareness programs, and
4. A coordinated and systematic approach by all stakeholders to engage insurers and/or government health ministries in a discussion on (1) disability, death, and the low quality of life caused by HAE, and (2) the range of therapies available to prevent and treat HAE attacks, and therefore avoid widespread death and disability.

Unfortunately, we know from experience that the journey to success can be long, frustrating, and full of obstacles. Nevertheless, nothing will ever happen unless patient advocates start the process of "clearing the path" establishing an energetic and well-organized HAE advocacy and awareness program.

O-43

INTERNATIONAL CLINICAL DESCRIPTIVE STUDY OF ADULTS WITH HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY

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Background: An international multicentre study for the development of a specific HRQoL questionnaire for hereditary angioedema with C1-inhibitor deficiency (HAE-C1-INH) (IHAE-QoL) was carried out. We report the demographic and clinical data of the participating sample.

Material and Methods: A self-administered clinical questionnaire was completed by HAE-C1-INH patients in 2008-2010. Recall period was 6 months. Statistical analysis was performed with SPSS.

Results: 290 patients (200 female, 232 type I) recruited from Argentine, Austria, Brazil, Canada, Denmark, Germany, Hungary, Israel, Poland, Romania, Spain. Mean age was 41.5 y. Mean age at onset of symptoms was 11.8 y. Mean delay in diagnosis was 14.4 y. Eight patients (2.8%) were asymptomatic. Intubation/tracheotomy had ever been needed in 34 patients (more than once 31.9%). Attack triggers along life were identified by 89% of patients (stress, traumatisms, infections, menstruation, other). Patients reported at least 2591 edema episodes in the last 6 months: peripheral (39.5%), abdominal (35.4%), genital (9.2%), facial (6.5%), upper airway (5.4%), other (3.8%). Treatment with plasma derived C1INH (pdC1INH) was administered in 911 episodes and fresh frozen plasma (FFP) in 45.139 patients were on long term prophylaxis: 74.1% attenuated androgens (AA), 14.4% antifibrinolytics (AF) and 11.5% pdC1INH. Mean accumulated doses per week were: danazol 1100.2 mg, oxandrolone 43.7 mg, stanozolol 9.6 mg, epsilonaminocaproic acid 21,000 mg, tranexamic acid 11,503 mg, pdC1INH 1,653 IU. Drug side effects were reported for pdC1INH (1.4%), AF (2.1%), AA (14.1%) and other treatments (1.7%). A total of 632 and 259 days had been missed from work and school respectively due to angioedema attacks in the last 6 months.

Conclusions: This study represents demographical and clinical characteristics of a large cohort of HAE-C1-INH patients from eleven countries worldwide.

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O-44
CLINICAL DIFFERENCES AMONG COUNTRIES IN HEREDITARY ANGIOEDEMA DUE TO C1 INHIBITOR DEFICIENCY

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Background: Differences in the health care conditions in different countries may influence the health related quality of life (HRQoL) in hereditary angioedema due to C1 inhibitor deficiency (HAE-C1-INH) patients.

Material and Methods: A self-administered clinical questionnaire was completed by patients from different countries within a study for development of an international specific HRQoL questionnaire for HAE-C1-INH from 2008 to 2010. Data regarding last 6 months were collected. The results were analysed with statistical software SPSS v 9.0.

Results: 290 patients from 11 countries participated: Argentine (AR) 16 patients, Austria (AU) 18, Brazil (BR) 34, Canada (CA) 21, Denmark (DE) 27, Germany (GE) 42, Hungary (HU) 38, Israel (IS) 9, Poland (PO) 22, Romania (RO) 19 and Spain (SP) 44.

Home availability of pdC1INH ranged from 0% (BR) to 97.4% (HU), self-administration of pdC1INH from 0% (BR, PO, RO, AR) to 7.4% (CA), administration of antiallergic drugs for HAE attacks from 0% (CA) to 35.6% (BR), patients with missed work days due to the disease from 21.1% (RO) to 66.7% (AR) and with missed school days due to the disease from 0% (CA) to 18.8% (AR). Patients with long term prophylaxis (LTP) varied from 27.8% (AU) to 73.5% (BR) and taking into account treated patients, drugs were: attenuated androgens 33.3% CA-100% AR, antifibrinolytics 0% (AU, GE, RO, AR)- 50% DK and pdC1INH 0% (HU, DK, PO, RO, AR, BR)- 66.7% (CA). Other data: rate of affected HAE children per patient (mean 23.3% IS-58.3 % BR), age at onset of symptoms (mean 8.5 y. IS-14.0 y. GE), age at diagnosis (mean 11.3 y. IS-34.2 y. RO, BR) and mean delay at diagnosis (2.9 y. IS- 23.3 y. BR).

Conclusion: Although knowledge about HAE C1-INH management have improved in last years, variability between countries still remain. Data presented may be useful to increase awareness of the HAE-C1-INH situation in different countries.

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O-45
HEALTH STATUS UTILITY WEIGHTS FOR HEREDITARY ANGIOEDEMA ATTACKS AND IN BETWEEN ATTACKS

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Background: Utility weights are used to quality-adjust survival in cost-effectiveness evaluations. The objective of this study was to identify utilities for hereditary angioedema (HAE), both for an attack and in between attacks.

Methods: The Hereditary Angioedema Burden of Illness Study in Europe(HAE-BOIS-Europe) was a cross-sectional surveyconducted in Denmark, Germany, and Spain to assess the real-world experience of HAE from the patient perspective. Patients were asked about HAE impacts associated with the most recent attack as well as inbetween attacks. Although the survey did not contain the EQ-5D, a 5 item utility measure capturing pain, mobility, self-care, usual activity, and anxiety/depression, it contained items overlapping with these concepts. Each EQ-5D item has three levels: none, a little, and a lot, each of which has a pre-determined disutility. To estimate utilities for an HAE attack, responses to survey items on worst pain, duration prevented from daily activities, ability to do daily activities, and anxiety about future attacks were mapped to the EQ-5D item weights. For inbetween attacks, survey items used were health in general (from 'excellent' to 'poor'), ability to do daily activities, and distress about HAE. It was assumed that an attack had no impact on self-care, and that inbetween attacks, there was no impact on mobility or self-care.

Results: A total of 111 patients had all relevant item data to incorporate into the mapping exercise (30 Denmark; 40 Germany; 41 Spain). Using UK utility weights, the mean utility for the last HAE attack was 0.444; utilities worsened as attack pain increased: no pain=0.731, mild=0.558, moderate=0.467, and severe=0.080. The mean utility for inbetween attacks was 0.722, suggesting that patients would be willing to trade off 28% of their life to live without HAE.

Discussion: The estimated EQ-5D utilities based on patient-reported data indicate that HAE may cause considerable burden even inbetween attacks.

O-46
HAE – THE SITUATION IN SOUTH AFRICA

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As in most regions, hereditary angioedema (HAE) remains a clinical challenge in South Africa. Although the expected number of HAE patients is about 1000 (population of 50.6 million), only 43 patients are documented at the Lung Institute (University of Cape Town), the main HAE centre in South Africa (personal information, Prof. P. Potter). 36 HAE patients are registered in the Primary Immunodeficiency Registry which has been established in 2006 (personal information, Dr. M. Esser). Of particular interest is a published case report of 6 patients from a Zulu family (E Moran, S Afr Med Journal 99: 40, 2009) who suffered from facial and cutaneous edema (all patients), abdominal attacks and laryngeal edema (1 patient each).

Routine laboratory tests include total complement function assay, C4 and C1- INH antigen. Functional C1-INH is determined outside the country.

HAE patients are treated with danazol or tranexamic acid. C1 esterase inhibitor is not registered, but can be imported on a named patient basis.

There is no dedicated HAE patient organisation. However, the Primary Immunodeficiency Network of South Africa (PiNSA, www.pinsa.org.za) established in 2001 supports and provides advice on a wide range of primary immunodeficiencies.

The first official workshop on "Hereditary and Acquired Angioedema" took place in Durban in December 2012 as part of the 8th Conference of the Federation of the African Immunological Societies (FAIS). Four European and 2 local speakers provided an update on the international and local situation. This event will raise awareness of HAE in the country and ultimately result in cooperation between experts in South Africa and other countries.

O-47
HEREDITARY ANGIOEDEMA IN LATIN AMERICA: 1ST REPORT

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Background: Hereditary Angioedema (HAE) is a rare disease with estimated prevalence of 1:10000 to 1:50000 individuals. According to this incidence, Latin America should have up to 57,000 HAE patients. In order to evaluate LA situation regarding HAE diagnosis and therapy, we developed a registry of confirmed cases.

Methods: The 1st Latin American Meeting on HAE took place on June 2nd, 2012 and the delegates representing LA countries collected HAE data. Clinical data and access to therapy was evaluated.

Results: The following countries participated: Panama, Paraguay, Uruguay, Chile, Peru, El Salvador, Costa Rica, Colombia, Mexico, Brazil and Argentina. The last 4 countries presented data from 20, 34, 276 and 227 cases, respectively. Only 15 HAE patients were identified in the other countries. Difficult access to therapy was detected and fresh frozen plasma is still the therapeutic resource to treat the patients.

Conclusions: Deficient identification of HAE patients as well as knowledge about the disease was identified. The access to laboratorial diagnosis and therapy is restricted in allcountries, with more profound problems regarding drugs and assistance for HAE attacks.The authors propose a plan to action including registry of identified cases, educative programs, laboratorial support with reference centers, and access to prophylactic and attack treatment.

O-48

QUALITY OF LIFE AND PRODUCTIVITY LOSS IN PATIENTS WITH HEREDITARY ANGIOEDEMA (HAE) IN SWEDEN; RESULTS FROM A RETROSPECTIVE PATIENT REGISTRY SURVEY IMPLEMENTED BY SWEHA-REG (A POPULATION BASED CENSUS OF HAE IN SWEDEN)

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Objectives: Hereditary angioedema (HAE) due to C1-INH deficiency is a rare orphan disease characterised by spontaneous attacks of oedema that interrupt the _normal_ attack-free state. HAE is known to impact patient quality of life (QoL) and productivity but, despite a recent increase in treatment options, there remains a shortage of data to quantify these important aspects of the HAE disease. Sweha-Reg, a population based census of HAE in Sweden, implemented a retrospective patient survey to address this data gap and define the burden of HAE in Sweden.

Methods: A retrospective registry study of Swedish patients with HAE (captured by the Sweha-Reg census). Data was collected using a paper-based survey. Patients completed EQ5D-5L questionnaires for attack-free and acute HAE attack states. To be included in the analysis, patients must have suffered an attack in the last 12 months. Questions related to patient demographics (age and sex) and other parameters (such as attack location and severity) were included to better understand the burden of HAE. EQ5D-5L values were estimated for both HAE disease states and then compared with other variables; utilities were also calculated. Patient-reported sick-leave was analysed to understand the factors responsible for productivity loss in patients with HAE.

Results: A total of 105 valid responses were analysed from an initial mailing of 139 surveys (76% response rate). 94% of patients reported an attack in the last 12 months. The total number of attacks reported per patient during one year ranged from 1 to 120. A significant reduction in QoL scores between the attack-free and acute attack states of HAE was observed. Also, attack location and severity had a clear impact on the utility values.

Conclusions: Results from this Sweha-Reg study provide an insight to the significant impact on QoL and productivity loss that HAE has on patients in Sweden.

O-49
HEREDITARY ANGIOEDEMA IN GREECE

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Three years before, a hereditary angioedema (HAE) registry was established under the auspices of the Greek Society of Allergy and Clinical Immunology to offer a source of information useful for improving disease management and to provide a framework for the disease study. This is the first report of the epidemiological and the molecular analysis data of patients recorded so far. 104 patients (55% male, 45% female; mean age 42 years, range 4—88 years) have been registered belonging to 36 families, 83% of which with type I and 17% with type II HAE. The age of disease onset varied from 1 to 57 years of life (median 8 years) and the average delay in diagnosis was 13 years. The patients reported symptoms from larynx, abdomen and skin with frequencies of 66.7%, 87.5% and 92.5%, respectively. Viral infections was the most commonly (50%) reported triggering factor. 24% of the patients had submitted unnecessary abdomen surgery while intubation or cricothyreotomy had been performed in 12.5% of them. A HAE attack was the cause in 6 cases and it was considered as the most possible cause of death in 3 other cases. 62% of patients, regardless of gender, had received long-term prophylaxis with androgens from 6 months to 32 years. By the use of a disease-specific questionnaire, it was found that HAE has moderate to severe consequences in the quality of life of 74% of the patients. Molecular analysis of the *SERPING1* gene has been performed in 74 patients from all families. Missense mutations were found in 31.8%, nonsense mutations in 13.6%, splice defects in 18.2%, frameshift alterations in 18.2%, small deletions/insertions in 4.5% and large deletions/insertions in 9.1% of the cases. Eleven cases with novel *SERPING1* alterations have been detected. In one case, the detected SERPING1 mutation has found by bioinformatic analyses to be not pathogenic. Molecular analysis performed in apparently healthy family members revealed 4 pre-symptomatic cases (mean age: 6 years, range: 2-16).

O-50
HAE IN MACEDONIA: CURRENT STATUS

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In Macedonia there are 16 patients with HAE, 10 of which are adults with verified HAE type I (age 26 - 62 years). 3 are pediatric patients (age 2 - 12) with HAE type I and 3 patients are with HAE type II (33-63 years) and no diagnosed HAE type III so far. Female: 7 HAE type I, 1 HAE type II, age range 9-62 years, male: 3 HAE type I age range 2-48, 2 HAE type II age range 33-63. Majority of the patients are members of one ethnic group, have Macedonian genetic heritage (vs. 1 of 12 patients is ethnic Albanian, 1 is Roma and 1 Turk). All patients' data are in the Macedonian national HAE Registry. The HAE patients are organized in association named HAE Makedonija since year 2008. Main diagnostic and main centre of providing care for adult patients is Unit of Allergology and Immunology within the University Clinic of Dermatology, School of Medicine University "Sts Cyril and Methodius" Skopje. Head of the Macedonian HAE team is Professor Vesna Grivcheva-Panovska MD PhD. We regularly send updates to the regional medical centers with current information on HAE diagnostic and treatment on trimestral basis, but there is still much work to be done. Aims for the future: To further analyze HAE patients regarding immunogenetic studies; to continue educational courses for medical professionals and general population in the forthcoming decade; to pursue registering of C1 inhibitor and/or other highly efficient therapeutics in Macedonia. The authors consider as an important aim to conduct immunogenetic investigation in Macedonian HAE patients to compare the results with the available data. The most valuable achievement: a baby boy being born in year 2009, after his mother has successfully preventively being treated with C1 inhibitor during pregnancy and childbirth.

O-51
HEREDITARY ANGIOEDEMA NATIONWIDE STUDY IN SLOVENIA

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Background: Hereditary angioedema (HAE) is a rare autosomal dominant disease characterized by swelling of the face, lips, tongue, larynx, genitalia, or extremities, with abdominal pain caused by intra-abdominal edema. HAE is caused by mutations affecting the C1 inhibitor gene, SERPING1, resulting in low levels of C1 inhibitor (Type I HAE) or normal levels of ineffective C1 inhibitor (Type II HAE). Estimated prevalence of HAE is one case per 50,000 persons.

Objective: To determine prevalence of HAE in Slovenia.

Methods: All relatives form known patients with HAE were invited to clinical examination and laboratory testing. Also all patients with low C4 or C1 levels found in a database of all measured C4 and C1 levels at tertiary clinic for pulmonary and allergic diseases were invited. A diagnosis of HAE was established in the presence of clinical and laboratory criteria (low C1 inhibitor antigenic levels and/or function), followed up by a positive family history. Genetic studies were carried out using PCR and sequencing to detect SERPING1 mutations in promoter, noncoding exon 1, the 7 coding exons, and exon-intron boundaries.

Results: A nationwide survey identified nine unrelated families with HAE in Slovenia. One family refused further participation in the study. Eleven patients from five families were diagnosed with HAE type I, and six patients from three families with HAE type II. Four patients (24%) had no known family history of angioedema. 17 individuals from eight families were recruited for genetic analyses. A mutation responsible for HAE was identified in patients from seven families with the disease.

Conclusion: The Slovenian prevalence of symptomatic patients is 1:105,000, which is similar to what is reported in Spain, and slightly lower than reported in a Danish nationwide study, in which the prevalence was reported to be 1:71,000, suggesting that this rare disease may still be under-diagnosed.

ABSTRACTS - POSTER PRESENTATIONS

P-01
THE HEREDITARY ANGIOEDEMA BURDEN OF ILLNESS STUDY IN EUROPE: A CONCEPTUAL MODEL OF PATIENT IMPACTS

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Background: Hereditary angioedema (HAE) is a rare but serious disease marked by spontaneous, recurrent attacks of swelling. The objective of this study was to develop a conceptual model illustrating the impact of HAE on daily life from the patient perspective.

Methods: The Hereditary Angioedema Burden of Illness Study in Europe (HAE-BOIS-Europe) was conducted in Denmark, Germany, and Spain to assess the real-world experience of HAE from the patient perspective. A study component included 30 one-on-one interviews with HAE patients (10 per country). Open-ended questions focused on experience living with HAE and health-related quality of life impacts. These qualitative data were evaluated to identify key themes highlighting the impacts of HAE.

Results: Patients reported both short- and long-term impacts of HAE on their lives. Long periods between symptom onset and diagnosis resulted in significant stress and unnecessary medical procedures. HAE attack impacts included inability to perform daily activities, cancelling plans, anxiety and fear, use of medication, and work/school absenteeism and reduced productivity for both the patient and their caregivers. Inbetween attacks, impacts included anxiety about passing HAE to children and about future attacks, stress driven by uncertainty, inability to plan or travel, interference with social activities, medication inconvenience, and limiting exercise to avoid triggering an attack. Career/educational detriments ranged from absenteeism and decreased productivity to limited choices and advancement. Side effects of treatment further impacted patients' lifestyles. HAE impacts were modified by the availability of treatment for attacks and prophylaxis, and patient education and ability to self-administer medication.

Conclusions: HAE has wide-ranging short- and long-term physical and emotional impacts on patients' lives. The conceptual model from this study can be used to informand improve clinical management in HAE.

P-02
HEREDITARY ANGIOEDEMA IN SWITZERLAND

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Background: Hereditary angioedema (HAE) is a rare, autosomal dominant disease due to functional deficiency of C1- esterase inhibitor (C1-INH). About 150 persons with HAE live in Switzerland (prevalence: 1:50'000). More than 100 patients are known and supported by the Swiss Hereditary Angioedema Association www.hae-vereinigung.ch. A retrospective cohort study was initiated to evaluate clinical and treatment data of the Swiss HAE patients. We present the current data from the centers of Lucerne and Berne.

Method: A questionnaire was sent to each patient including questions about symptom onset, localisation, frequency, trigger, familial history and therapy of angioedema.

Result: 94 patients (56 females) answered the questionnaire. Median age is 43 years. Median age at onset of symptoms is 10y. 44 persons had a family history of HAE. In the patients without family history delay from onset of symptoms to diagnosis was 26y. 90 patients suffer from Type I, 3 from Type II,1 from Type III. 89 patients are symptomatic. Abdominal symptoms and edema of the subcutis occurred in 80%, laryngeal swelling in 32%. Main trigger for angioedema is mechanical impulse, followed by stress, infections, hormonal changes and food intake. In 15% the attacks occur weekly, in 48% monthly, in 15% at least once a year. 11% with less frequently, 5% with no symptoms. Women have greater attack frequency. 76 patients need therapy, 50% of which on demand, namely C1-INH concentrate (n=31), Cyclocapron (4), Firazyr (2), and Danazol (1). 30 patients use Danazol and 8 Cyclocapron continuously.

Conclusion: In this retrospective Swiss cohort study we collected data of 94 patients with HAE, which corresponds to ca. 2/3 of all Swiss patients. Gastrointestinal and skin symptoms predominate. Delay of HAE diagnosis is still long in non familial cases (ca. 15y). Half of the patients use therapy only on demand, predominantly C1-INH concentrate. Long term therapy is practiced mainly with Danazol.

P-03
LEUKOCYTOSIS AND HEMOCONCENTRATION YIELD MISINTERPRETATION IN ABDOMINAL EMERGENCIES OF HEREDITARY ANGIOEDEMA

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Background: The low awareness of hereditary angioedema (HAE) and resemblance to other disorders often delays an accurate diagnosis of HAE. In particular, abdominal symptoms increase the risk of unnecessary surgical operations and drug therapy in the undiagnosed HAE. To explore the cause of misdiagnosis in HAE patients, we conducted a comparison study between laboratory findings under normal conditions and those during an abdominal attack.

Methods: Nineteen HAE patients were enrolled in this study. We compared their laboratory data with each case between having an attack and having a normal condition.

Results: Half of the patients had experienced a life-threatening laryngeal attack and/or severe abdominal pain. The number of white blood cells in the peripheral blood at the time of an abdominal attack was significantly higher (10,933 ± 2,900 / mm^3) than that at normal conditions (6,394 ± 2,267 / mm^3) ($p < 0.01$) or an attack involving other parts (7,362 ± 1,933 / mm^3) ($p < 0.01$). However, there was no difference in CRP levels between these conditions. The percentage of neutrophil was significantly increased at the time of an abdominal attack (75.1 ± 12.5 %) compared with that of normal conditions (63.2 ± 12.0 %) ($p< 0.01$). The number of red blood cells in the peripheral blood at the time of an abdominal attack (520 ± 44 x10^4/mm^3) was significantly higher than that of normal conditions (459 ± 38 x10^4/ mm^3) ($p < 0.01$). The levels of hematocrit at the time of an abdominal attack (45.6 ± 2.7 %) and an attack involving other parts (44.1 ± 2.1 %) were significantly higher than that of normal conditions (41.5 ± 2.8 %) ($p< 0.01$, $p < 0.05$ respectively). All of the severe attacks were alleviated with an infusion of the C1-inhibitor concentrate (Berinert P®, Tokyo, Japan).

Conclusions: It appears that leukocytosis and hemoconcentration may be confused as an acute abdomen in patients with HAE. These laboratory findings can mimic surgical emergencies.

P-04
INFLUENCE OF PSYCHOLOGICAL FACTORS ON HEREDITARY ANGIOEDEMA ATTACKS IN CHILDREN AND ADOLESCENTS: THE PARENTS' POINT OF VIEW

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Background: Hereditary Angioedema (HAE) is characterized by unexpected attacks, and its warning signs can vary significantly. However it is considered that stress or emotional and physical traumas are relevant to the development of HAE attacks.

This contribution describes the first stage of a broader research on the influence of psychological factors on the development of HAE attacks in children and adolescents. The first stage of this research aimed at exploring the parents' interpretations of the condition, based on the hypothesis that these interpretations could influence the way in which the parents cope with the condition and work through the experiences connected to it.

Methods: The parents of 14 patients with HAE, between 4 and 18 years of age, who have been referred to Naples's centre for the treatment of HAE, have been involved in the research. During an initial meeting the parents answered the questions of an interview about the history of the children and the meaning attributed to HAE.

During a second meeting the parents completed the test Child Behaviour Checklist (CBCL).

Results: According to the interviews each parent has constructed a more or less complex interpretation in order to make sense of the unpredictability of HAE: 14% of parents reported that the attacks arise in response to physical traumas; 7% reckoned that intense emotions represent a trigger; while 79% offered an explanation that refers both to emotional and physical stressors. Through the CBCL 52% of the parents recorded critical scores on the Activities subscale. Two children appeared to be at psychopathological risk.

Conclusions: The hypothesises provided by parents seem to have the function of filling the void of meaning caused by the extremely variable and unexpected nature of the condition that creates a sense of confusion, which is managed subjectively. This seems to be closely connected to the burden of HAE on the patients, who are significantly limited in their daily activities.

P-05
NEW ABDOMINAL CRISIS TRIGGER ON PATIENTS WITH HEREDITARY ANGIOEDEMA

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Background: The HAE is an hereditary disease for genetic deficiency of the C1 inhibitor. The edema can be on faces, limbs and viscera. The most frequent is abdominal episode in 60% to 70% of the patients. These episodes lead the patient to exploratory laparotomy or misdiagnosis since episodes are dramatically intense. The crises are initiated from the activation of factor XII, mucosal or tissue, releases bradykinin, chemical mediator of the edema. This Bradikinina runs between the 3th and the 5th days, and edema disappears.

Method: It's about an HAE patient woman with 61 years old, member of an HAE big family. She was diagnosed in 1995 with C4 5mg/dl and C1 inh 5mg/dl. Hers recurrent crisis were: limbs edema, face with laryngeal edema, intestinal colic. The average of abdominals edema was 10 to 12 per year. When she was 34 years old, was operated for false acute abdomen appendicitis.In 2010 she began to suffer more frequently episodes, between two and three times per week. The Intravenous injection of 1500 units Berinet P did not reach the expected relief. Gastroenterologist dismissed any abdominal visceral disease.In 2012 she consulted an orthopaedic for lumbar back pain. With magnetic resonance was detected a lumbosacral junction discopathy on T11 -T12 and shows signs degenerative in lumbosacral region L5-S1, generating instability and pain in the spine, that is relief by using a corset.

Conclusion: At this level originate nerve afferents reaching the gray matter of the spinal and then generating efferent autonomic nervous system to reach target organs (viscera) and then trigger the effect of numerous chemical mediators.We have to remark the Charnela syndrome descript by R. Maigne (1978), the discopathy lies on a level thoracolumbar (T12-L1), where described pain pseudoviscerale

P-06
NO EVIDENCE FOR DISEASE-MODIFIER GENES IN THE PBMC EXPRESSION PROFILE FROM HAE PATIENTS IN BASAL CONDITIONS. AN RNA-BASED MICROARRAY SCREENING

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Background: Hereditary Angioedema due to C1-Inhibitor deficiency is characterized by sudden episodes of cutaneous and mucosal swelling due to local deregulation of vascular permeability. HAE exhibits low genotype/phenotype correlation, which hinders therapeutic approach and probably underlies yet unknown genetic and environmental factors.

Methods: Whole-genome RNA expression of PBMCs was analyzed in 3 Spanish HAE type-I families (accounting for 40 individuals), 24 of which carry the R472X mutation in the C1-Inhibitor gene and show large variability in terms of disease expression. Those included in this study were analyzed according to the presence of mutation and their symptoms severity.

Results: Instead of a single, common disease-associated expression pattern, we found different transcriptional signatures in two of the families studied. In one of them (referred to as DR family), symptoms strongly correlate with the upregulation of 35 genes associated to the biological response to viral infections (including RSADs, OAS, MX and ISG pathway members) and immune response. In another family (Q family) disease manifestation is linked to a complex expression pattern accounting for 394 genes with a wide diversity of functions.

Conclusions: We found no evidence for a common altered PBMC expression pattern linked to HAE symptoms. All the data considered, differential gene expression in PBMCs does not seem to play a significant role in the predisposition or protection against HAE in the basal conditions analyzed. None of the a priori candidate pathways for influencing HAE development -e.g. complement, kinin-degradation pathway etc- reached significance in our cohort. Although the RNA expression pattern associated to the response to viral infections in the DR family supports the idea of infectious diseases as a modifying factor for HAE severity, large-scale studies would be needed to statistically associate such expression pattern to the development of this rare disease.

P-07
GALLSTONES IN C1 INHIBITOR DEFICIENCY – ARE THEY DIFFERENT?

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Introduction: Gallstone disease is common in C1 Inhibitor deficiency (C1 Inh D). About 10-15% of the adult population in the developed countries have gallstones and up to 4% become symptomatic each year. Gallstones can be classified by their chemical composition (cholesterol, pigment or mixed). We are interested in the composition of gallstones in C1 Inh D and whether their particular composition contribute to its common occurrence in this genetic disorder.

Materials and Methods: Gallstones from a mother and daughter with Type 1 C1 Inh D, a female with chronic obstructive pulmonary disease (COPD) and a Greek female with gallstone disease were studied using a combination of microscopic, diffraction and spectroscopic techniques (Scanning Electron Microscopy–Energy Dispersive Spectrometry, X-ray Diffraction, Fourier-Transform Infrared Spectrometry, Nuclear Magnetic Resonance and laser micro-Raman). X-ray Fluorescence analytical technique was used to determine the concentrations of trace elements in all cholesterol gallstones. In addition, molecular simulation using the Accelrys Materials Studio® software was used to investigate the position of characteristic biometals such as Zn.

Results: Gallstones from the 4 patients studied were of cholesterol-type composition. All contain essential metals – Calcium, Iron, Manganese, Copper and Zinc as well as potentially toxic metals – Lead, Arsenic and Nickel. The concentration of these metals differs in the studied subjects even between the mother and daughter with C1 Inh D.

Conclusions: This study concerns the chemical composition of gallstones from 4 individuals, 2 of whom have C1 Inh D and another with COPD. Essential biometals were found in addition to the main organic compound, cholesterol. However, the concentration of the different metals differs even in the mother and daughter. The chemical compositions noted do not point to a common pathogenesis. The presence of toxic metals is a cause of concern.

P-08
THE NEW CHANGE IN THE SERPING1 GENE IN A BRAZILIAN FAMILY CAN BE ASSOCIATED TO HEREDITARY ANGIOEDEMA (HAE)

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Background: The hereditary angioedema (HAE) is characterized by sudden oedema episodes. They affect mainly the upper and lower limbs, gastrointestinal tract, genitals and face, and if untreated, can lead to death due to suffocation. The HAE is an autosomal dominant disorder resulting from changes in the C1-inhibitor (HAE types I and II), missense changes in the coagulation factor XII or by unknown factors (HAE type III). The purpose of this study was to determine the disease-causing mutation in a Brazilian family affected by HAE and identify affected relatives through clinical reports and C1-inhibitor gene (SERPING1) analysis.

Methods: The SERPING1 promoter and coding region of 27 individuals of a Brazilian family was analysed by sequencing. Clinical history and enzymatic measurement compatible with HAE was evaluated.

Results: We found one missense mutation affecting exon 8 of SERPING1, c.1369G>C **-** p.A457P in ten members of this family. This mutation was not previously reported in the literature and when analysed by PolyPhen-2 software it was considered probably damaging for protein structure or function. In accordance with this *in silico* analysis, all the members of the family carrying this mutation exhibited clinical characteristics of the disease. From these members, six had their blood evaluated and all of them presented low plasma levels of C4 and C1-inhibitor. Almost all symptomatic patients presented face (4/10), extremities (10/10), abdominal (9/10) and laryngeal oedema (3/10). Two polymorphisms, c.1030-20A>G (26/27) and c.1438G>A (18/27) were also found in most members of the family.

Conclusions: It suggest that the new mutation p.A457P might be responsible for HAE symptoms in this Brazilian family. These findings will help to establish a more precise and early molecular diagnosis of HAE, improve genetic counseling and permit a better and more efficient treatment in potential candidates.

Keywords: hereditary angioedema; C1-inhibitor; SERPING1; Brazil

P-09
SEVERE LARYNGEAL EDEMA AND ANEMIA AS FIRST SYMPTOMS OF IGG KAPPA MULTIPLE MYELOMA – AN ACQUIRED ANGIOEDEMA (AAE) CASE DEMONSTRATION

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Severe laryngeal edema and anemia as first symptoms of IgG kappa multiple myeloma – an acquired angioedema (AAE) case demonstration.

We are reporting a 67- year- old patient who was diagnosed in our clinic four months after an episode of severe laryngeal edema, which was resistant to typical treatment of steroids and antihistaminic drugs. This patient had diabetes t.2 and undiagnosed anemia. No other symptoms of malignancy were presented. We found decreased levels of C1inh=0,18g/l, C4=0,03g/l and C1inh activity= 58,7%, but normal level of C1q=63mg/l. The patient had hematologic consultation due to anemia and edema symptoms suggested AAE. After marrow biopsy an IgG kappa multiple myeloma was confirmed. The MPT chemotherapy was introduced and we observed normalization of C1 and C4 levels with no more edema symptoms.

AAE is very rare but it requires further evaluation (ordiagnostic procedures). In this case as in other cases with B cell clonal disorders angioedema was an early symptom and it helped to diagnose the patient properly.

P-10
NOVEL DISEASE SEVERITY MARKERS IN HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY

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Background: Hereditary angioedema due to C1-inhibitor deficiency (HAE-C1-INH) causes disturbances in the complement system. However, the role of the lectin pathway (LP) of complement in the pathophysiology of HAE-C1-INH is unresolved. Thus, we studied the relationship between the LP parameters and the severity markers of HAE-C1-INH.

Methods: The serum concentrations of ficolin-2, ficolin-3, MBL, MASP-2, MASP-3, MAP-1 and ficolin-3/MASP-2 complex were measured during symptom-free periods in 91 patients with HAE-C1-INH, and in 100 healthy controls. In addition, we also determined the extent of ficolin-3 mediated LP activation.

Results: Compared with controls, the levels of ficolin-2 ($p<0.0001$), MASP-2 ($p= 0.0238$) and ficolin-3/MASP-2 complex ($p=0.0005$) were reduced, while the levels of MBL and MASP-3 were elevated ($p=0.0028$ and $p<0.0001$, respectively) in HAE-C1-INH patients. Furthermore, the extent of ficolin-3 mediated TCC-deposition was reduced in HAE-C1-INH patients ($p<0.0001$). Interestingly, ficolin-2 correlated positively with MASP-3 in patients ($r=0.3443$, $p=0.0008$), while these parameters showed an opposite relationship in controls ($r= -0.4625$, $p<0.0001$). Ficolin-2, -3, and MAP-1 correlated negatively with the annual requirement of plasma derived C1-INH concentrate ($r=-0.2863$, $p=0.0059$; $r=-0.2654$, $p=0.0110$ and $r=-0.2501$, $p=0.0168$, respectively). Level of ficolin-3 and the extent of ficolin-3 mediated LP activation showed negative correlations with almost all disease severity markers.

Conclusions: We found significant differences between patients and controls in the levels of some of the molecules belonging to the LP. In view of the negative correlation between the disease severity markers and ficolin levels, our results suggest that reduced levels of ficolin-2 and ficolin-3 may be associated with an increased occurrence of oedematous attacks. This suggests a previously unrecognized involvement of the ficolin-dependent LP in the pathophysiology of HAE-C1-INH.

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P-11
ANGIOEDEMA - NOT ALWAYS AN ALLERGIC SYMPTOM

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Background: HAE is a rare disease and there is limited awareness of the diagnosis and treatment. Missing the HAE diagnosis is a pitfall that may lead to unnecessary morbidity and is potentially fatal. The HAE Center at Odense University Hospital is the only medical center in Denmark providing treatment, care and education of HAE patients.

Methods: The poster gives a short description of the clinical symptoms as well as the less obvious implications for the HAE patients and describes the HAE Center in Odense in order to increase the knowledge of its existence.

Results: Short statements regarding the HAE disease, the symptoms, the patients and the HAE Center as well as our contact information is presented on the poster along with a selection of clinical pictures.

Conclusions: HAE is a rare disease and it is important to increase the awareness on the diagnosis as there are treatments available and because the disease can bring significant morbidity and may be fatal if left untreated.

P-12
REDUCED C1INH SECRETION IN FIBROBLASTS DERIVED FROM PATIENTS WITH HEREDITARY ANGIOEDEMA

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Background: Hereditary angioedema (HAE) is an autosomal dominant hereditary disease caused by one of more than 200 known loss-of-function mutations of the *SERPING1* gene, encoding C1-inhibitor (C1INH). Such mutations lead to reduced blood levels of active C1INH and cause a periodic raise of bradykinin resulting in nonpredictable episodes of swelling of the skin and mucosa. The constant low levels of C1INH in HAE patients do not explain the intermittent character of the angioedema attacks, and the triggering mechanisms are not fully explained. One aspect of the disease that remains unexplored is the dominant negative effect of mutated SERPING1 alleles, causing in many carriers concentrations of active C1INH that are markedly lower than the 50 % that would be expected. To study this effect, often referred to as 'transinhibition', we have initiated studies of C1INH expression in patient-derived fibroblasts.

Methods: We aim at establishing patient-derived fibroblasts as an in vitro disease model. Fibroblast cultures were derived from skin biopsies taken from 6 patients with HAE type I. The concentration of secreted C1INH was measured by ELISA. DNA transposon vectors were utilized for expression of SERPING1.

Results: In 3 out of the 6 fibroblast cultures the level of C1INH secretion is reduced to around 20 % of the level in control fibroblasts from healthy individuals. Increased expression of C1INH is achieved by transfection of C1INH-encoding plasmid DNA. Current efforts seek to mimic the transinhibition phenotype by (i) introducing the *SERPING1* gene in patient fibroblasts and (ii) delivering mutated *SERPING1* gene variants to normal fibroblasts.

Conclusion: A correlation between the amount of secreted C1INH in patient fibroblasts and levels of C1INH in patient blood samples indicates that patient-derived fibroblasts may serve as an in vitro disease model. Ongoing studies based on *SERPING1* gene transfer will aim at mimicking transinhibition in this model.

P-13
ESTROGENIC HEREDITARY ANGIOEDEMA

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Introduction: Estrogen-dependant (type III) is the rarest form of hereditary angioedema, often diagnosed with delay because of a heterogeneous clinical presentation. Before diagnosis, patients frequently present subcutaneous edema or abdominal pain during many years.

Case presentation: A teenage girl of 14 years is admitted for acute swelling of face and feet with abdominal pain. She had been hospitalized several times – during 3 years - for similar conditions, misdiagnosed as acute glomerulonephritis or as severe viral infection. On clinical examination, the patient is on her first day of menses and is free from rash or pruritus. Serology evaluation of C4 and C1-inhibitor is negative; leading to the final diagnosis of type III HAE by pooling clinical and serological elements. "Wait and See" attitude was beneficial and the patient relieves within three days. Further expectation of attacks frequency and severity is needed before long-term prophylaxis.

Discussion: Classic - types I and II - forms of HAE are autosomal-dominant disorders, while no mode of inheritance has been determined yet for this uncommon type III HAE; Factor XII gene mutation is reported in 20% of patients. Its most distinguishable feature is the clinical phenotype as estrogen-dependent; with the serological phenotype corollary of normal C4 with normal C1 INH level and function. Different therapies are available but data is limited, C-1 INH replacement might be the best option.

Conclusion: HAE type III has no specific biological marker; it's diagnostic is mainly clinical, taking into account response to therapeutic test for this peculiar estrogenic form.

P-14
POSSIBLE CAUSES OF ACQUIRED C1-INH DEFICIENCY, BASED ON OUR 9 PATIENTS

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Angioedema due to C1 esterase inhibitor (C1-INH) deficiency is a very rare life threatening diseases, and is characterized by recurrent episodes of regional hard edema. Edema spreads to the subcutaneous and submucosal layer, and laryngeal edema may cause obstruction of the upper airway. Angioedema is classified as either hereditary or acquired. The acquired form has been attributed to various drugs and diseases.

We shall present nine patients with angioedema (5 males and 4 females), mean age: 58.7 years, treated in Angioedema Center of Semmelweis University, Budapest. The mean age of first symptoms of angioedema due to acquired C1-INH deficiency was 53.7 years. The angioedema was attributed to medication in seven patients (5 patients were taken ACE-inhibitor and angiotensin–receptor blockers – 2 patients, 1 patient was receiving anti-depressant). Edema was observed 67 % on the face, 33% in the upper respiratory tract, 56% subcutaneously and 33% in abdominal areas. Four patients suffered hematological diseases (non-Hodgkin's lymphoma – 2 patients, 1 patient had MGUS and multiple myeloma, respectively). Two patients had malignancy, one patient had Chlamydia pneumoniae infection, another one was treated already due to chronic proctosigmoiditis. No other underlying disorder was diagnosed in the last patient. In four cases it was possible to treat the underlying diseases specifically (chemotherapy, immunosuppressant or transplantation). We have started long term treatment with tranexamicacid in two patients. Due to our prophylactic treatment regime or long term therapy the clinical signs of angioedema was blunted or eliminated. In seven cases it was necessary to use C1-INH concentrate to eliminate the acute symptoms.

Based on our results we conclude that the primary task is to verify the underlying disease causing C1-INH deficiency and apply specific therapy if any. Naturally, the acute edema attack has to be treated immediately, as well.

P-15
ELEVATED ADRENOMEDULLIN AND ENDOTHELIN-1 LEVELS DURING HAE ATTACKS

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Background: Hereditary angioedema (HAE) is a vascular disease having impaired bradykinin metabolism in its background. Since the strict regulation of vascular tone is a substantially important physiological process, it is controlled by multiple factors, including small, vasoactive peptides (e.g. adrenomedullin (ADM), arginine-vasopressin (AVP), atrial natriuretic peptide (ANP), and endothelin-1 (ET-1). We previously showed that the level of ANP (but not the other three factors) was significantly lower in the attack-free interval samples of HAE patients than in samples of healthy controls. In our current study we aimed to clarify whether the concentration of these vasoactive peptides changes during HAE attacks.

Methods: We enrolled 18 HAE patients having both inter-attack and during-attack samples. Blood samples were collected then ADM, AVP, ANP, and ET-1 levels were measured by BHRAMS cryptor technology. Other clinical laboratory and complement parameters have been analyzed by Cobas-Integra and by ELISA kits, respectively.

Results: During HAE attacks, ADM and ET-1 levels rose significantly, whereas the levels of ANP and AVP did not change. These alterations of ADM and ET-1 levels were even more obvious in non-smoking or danazol non-treated HAE patients. Moreover, ET-1 concentration correlated strongly with that of ADM in attack-free intervals of HAE patients, and the changes of ET-1 and ADM also correlated during attacks.

Discussion: The changes of ADM and ET-1 during HAE attacks may implicate that compensatory mechanisms are activated in response to vascular leakage and vasodilation. Both factors improve endothelial cell integrity and elevate blood pressure. Since the optimal treatment and prophylaxis are still not fully solved in HAE, our results show another potentially important pathophysiological aspect as well as potential therapeutic targets in HAE.

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P-16
AGE RELATED CHANGES IN THE SEVERITY OF HEREDITARY ANGIOEDEMA DUE TO C1 INHIBITOR DEFICIENCY

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Hereditary angioedema due to C1-inhibitor deficiency (HAE-C1inh) is a rare autosomal dominant disorder characterized by recurrent subcutaneous and/or submucosal angioedema. The prevalence, severity, and the location of the symptoms are variable. Our retrospective study investigated the changes of disease severity over a lifetime.

Among 145 C1inh deficient individuals (79 females and 66 males, including 10 symptom-free individuals), we studied 117 patients whose drug regimen remained stable during the study. The annual number of attacks (ANA) and C1inh concentrate consumption (CCC) were determined and compared with the time of symptom onset. To detect any difference in disease severity during life, we stratified the subjects into 3-3 age groups of males and females. Attack frequencies and locations, as well as CCC were compared among these subsets. In 16 patients followed up for 15 years, ANA and CCC were analyzed in 5-year periods.

ANA and CCC were higher with an early onset of initial symptoms ($p=0.012$, $p=0.049$). In 20- to 40-year old women, all episodes ($p<0.001$), and individual attack types (subcutaneous $p<0.001$, abdominal $p=0.011$) occurred in higher numbers and followed a more severe course than in males, this was mirrored by CCC ($p=0.049$). In male patients aged 40 to 60 years, the total number of attacks ($0=0.031$) – including that of abdominal episodes ($p=0.025$) – was higher than among the 20- to 40-years old. There were no significant differences among the age groups of females. During the 15-year follow-up, the number of abdominal attacks increased with advancing age ($p=0.002$), but only in younger patients.

The earlier the initial symptoms occur, the more severe the course of the disease will be. The disease follows a more severe initial course in women aged 20 to 40 years than in males of matching age. We could not detect any consistent, unidirectional change in the natural course of the disease during a lifetime.

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P-17
ADVERSE EFFECTS OF DANAZOL PROPHYLAXIS IN FEMALE PATIENTS WITH HEREDITARY ANGIOEDEMA DUE TO C1-INH DEFICIENCY (HAE-C1-INH)

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The management of HAE-C1-INH comprises two stages – that is, the therapy of overt attacks, and the prevention of their recurrence. Danazol (an attenuated androgen), commonly used for long-term prophylaxis, has diverse side effects. This study intended to investigate the virilizing effects and the adverse effects of danazol on serum lipid profile, and hepatic function in our female HAE-C1-INH population.

Lipid profile (total cholesterol, HDL, LDL, triglycerides), and hepatic function (bilirubin, GOT, GPT, gammaGT, total protein, ALP, LDH) were compared between patients treated (n=31), or not treated (n=41) with danazol. The 31 danazol-treated patients were interviewed individually, about the type and severity of virilizing effects, as well as their satisfaction with danazol therapy (according to a 10-grade scale).

The duration of danazol treatment was 10.31 years [2 to 23] and a daily dose of 131.7 mg [33 to 250] was administered. The most frequent adverse effect were hirsutism (n=13), weight gain (n=12), menstrual disturbances (n=7).There were no significant differences in the severity of danazol adverse effects in relation to either the duration of dosing, or daily drug dose. The mean level of satisfaction with treatment was 8.47. We performed logistic regression analyses adjusted for age, drug dose, and treatment duration, to evaluate effects of danazol on lipid profile and liver function. HDL levels were lower (p=0.033), in danazol-treated patients, compared with those not treated with danazol. No significant differences were found between the two groups as regards the other parameters we examined

Our findings indicate that long-term treatment with danazol – using the lowest effective dose (max. 250 mg/day) – has a mild virilizing effect. So far, however, this has not led to the discontinuation of danazol therapy in our female patients. Danazol treatment does not alter the lipid profile and liver function of females with HAE-C1-INH.

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P-18
THYROID FUNCTION PARAMETERS IN PATIENTS WITH HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY

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Thyroid hormones control systemic metabolism and upregulate the synthesis of many plasma proteins. We intended to ascertain whether there is a relationship between the parameters of thyroid function and the clinical properties of hereditary angioedema due to the deficiency of the C1-inhibitor (HAE-C1-INH).

Serum TSH, fT3, fT4 levels, as well as anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibody titers and the concentrations of C4 and C1-INH were determined in145 patients with HAE-C1-INH. The per annum number of edematous episodes was ascertained from the patient diaries. Thirteen patients with an autoimmune or other thyroid disorder were excluded from the study. The control group comprised 150 age- and sex-matched, healthy, euthyroid individuals. The statistical analyses were performed using the Mann–Whitney and Fisher's exact tests.

TSH level and anti-TG titer were not different between the patients and the controls. Significantly lower fT4 ($p<0.0001$) and fT3 ($p=0.014$) levels, as well as a higher anti-TPO titer ($p<0.0001$) were seen in the patients. We could not detect any correlation between thyroid and complement parameters of the patients. The fT4 level was lower in patients who experienced a greater number of edematous attacks per year than in those with fewer episodes ($p=0.026$). As regards attack location, facial edema occurred (except for a single subject) in patients whose TSH level was lower than the median of the reference range ($p=0.003$). The fT4 levels were significantly higher in patients on long-term danazol therapy than in those who did not receive this drug ($p=0.021$). Additional correlations with the other thyroid indices could not be ascertained.

Thyroid hormones may influence the occurrence of HAE-C1-INH, and danazol treatment may alter both. Our results suggest that the pathophysiology of HAE-C1-INH has – among others – an endocrine background.

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P-19
FLOW-MEDIATED DILATION: ASSESSMENT OF ENDOTHELIAL CELL FUNCTION IN PATIENTS WITH HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY

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Background: Attenuated androgens such as danazol are commonly used for the prevention of angioedematous attacks in patients with hereditary angioedema due to C1-inhibitor deficiency (HAE-C1INH). Long-term treatment with danazol can have an adverse effect on the lipid profile. The initial phase of atherosclerosis is endothelial dysfunction, which can be investigated *in vivo* by evaluating flow mediated dilation (FMD) of the brachial artery.

Objective: The aim of our study was to compare endothelial function in danazol-treated and non-treated HAE-C1INH patients.

Method: We investigated 33 HAE-C1INH patients without known cardiovascular (CV) disease or diabetes mellitus (mean age 31±8 years, 17 male). Information on the patients' medical history and cardiac symptoms was collected using a questionnaire, and by physical examination. Laboratory tests were performed to evaluate their metabolic status. We investigated endothelial function by measuring FMD, and compared the results of the 13 patients who had been receiving danazol for at least 7 years with those of the 20 patients without danazol profilaxis.

Results: None of the patients had symptoms or signs of CV disease. BMI, total- and LDL cholesterol were significantly higher in danazol-treated patients than in those not treated with danazol. HDL level was significantly lower in the danazol group. By contrast, FMD values were not higher in danazol-treated patients (9.02%) than in danazol non-treated patients (10.04%).

Conclusion: Although the lipid profile of danazol-treated HAE-C1INH patients is much more atherogenic, we could not find any difference in endothelial function, as reflected by FMD measured with high resolution ultrasound. Our results suggest that HAE patients may be protected against endothelial cell dysfunction caused by the atherogenic lipid profile.

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P-20
A CROSS-SECTIONAL QUESTIONNAIRE SURVEY TO ASSESS PHYSICIAN'S APPROACH TO SHORT-TERM PROPHYLAXIS IN HAE PATIENTS

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HAEA organization

Rationale: To assess the physician's treatment approach for HAE patients undergoing elective invasive surgical/medical procedures.

Methods: A retrospective cross sectional on-line survey was administered to physicians to assess use short-term prophylaxis (STP) for Type I or II HAE patients with history or regardless of history of trauma-induced swelling during minimally invasive surgical/medical procedures (dental work, endoscopy), invasive (laporoscopy, surgery, C-section) and normal vaginal deliveries (NVD). Short term prophylaxis and on-demand medications included pdC1INH (Berinert or Cinryze), Ecallantide, Icatibant, fresh frozen plasma, anabolic steroids and anti-fibrinolytic agents. Questionnaire responses were analyzed using descriptive statistics.

Results: 37 respondents treated 177 HAE patients requiring an ER visit in the past year; 46 were hospitalized and 12 intubated. Of these treating physicians, 32/37(86%) routinely prescribed STP and/or on-demand therapy for minimally invasive and invasive surgical/medical procedures. For STP, 14 used Cinryze, 6 anabolic steroids and 1 anti-fibrinolytic agents; for on-demand use, 32 used Icatibant, 5 Berinert, 4 fresh frozen plasma and 2 Ecallantide. For on-demand minimally invasive procedures, on-demand invasive surgical/medical procedures, and on-demand NVD uses, Icatibant, Berinert, fresh frozen plasma and Ecallantide were prescribed from greatest to least frequency. For all STP scenarios (minimally invasive, invasive or NVD without or with a history of trauma induced swelling) Cinryze was most commonly prescribed.

Conclusions: Short term prophylaxis of HAE patients undergoing minimally invasive or invasive surgical/medical procedures was most effective in patients with a history of trauma induced swelling. The best outcome was STP with on-demand therapy readily available for a breakthrough attack.

P-21
CASE REPORT OF USE OF ICATIBANT DURING PREGNANCY

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We report the case of a 31 years woman with hereditary angioedema with C1 inhibitor deficiency (HAE-C1-INH) who self-treated an angioedema attack with icatibant during pregnancy. The onset of symptoms was at the age of 16. The diagnosis of HAE type I was established at the age of 20 based on positive family history of HAE, clinical manifestations of angioedema and laboratory analysis (C1-INH concentration <10%, functional C1-INH 13%, C4 concentration 12%).

During two pregnancies the patients reported an increased frequency of angioedema attacks. She manifested peripheral and abdominal symptoms every two weeks, lasting 2-4 days, not treated with specific therapies. After the second pregnancy the patient started treating gastrointestinal and laryngeal attacks with specific treatments (plasma derived C1-INH or icatibant). Because of the high frequency of attacks, the patient went on long-term prophylaxis with attenuated androgens with clinical improvement. After 6 years androgens were discontinued because of side-effects (headache and amenorrhea).

During the third pregnancy the patient experienced angioedema symptoms every week. She used to treat angioedema attacks with pdC1-INH. During the 4th month of pregnancy the patient experienced a laryngeal edema. After 90 minutes from the onset of the attack the patient self-administered icatibant (30 mg/3 ml subcutaneous) with complete symptoms resolution in 2 hours. During follow-up visit the patient reported the use of icatibant during pregnancy and was advised not to use icatibant till the end of pregnancy. The pregnancy went to full-term and the patient delivered a healthy child. She did not receive short-term prophylaxis before delivering and did not experience angioedema attacks during delivery.

This is the first case report of use of icatibant during pregnancy to treat an angioedema attack. No adverse events on pregnancy and on newborn health were reported.

P-22
EXPERIENCE AND CURRENT STATUS OF THE TRANSLATION AND CROSS-CULTURAL ADAPTATION OF THE ANGIOEDEMA QUALITY OF LIFE QUESTIONNAIRE (AE-QOL)

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Background: Measuring clinical symptoms alone may not adequately assess the disease burden of patients with recurrent angioedema. The use of quality of life (QoL) instruments can help to understand the impact of potentially life-threatening and unpredictable angioedema attacks on patients' lives. The Angioedema QoL Questionnaire (AE-QoL) was originally developed in German and is the first symptom-specific, validated QoL instrument for recurrent angioedema patients. Here, we report our experience and current status in translating the AE-QoL to multiple languages.

Methods: The AE-QoL was translated by two independent translators from German to the target languages. These (forward) translators were native speakers of the target language and fluent in German. Angioedema experts from each country reviewed the two translations and merged them into one consensus version. The AE-QoL was then back-translated to German for review by the AE-QoL original author. The forward and backward translation process continued until a final version was approved by the original author and target language expert.

Results: The original German AE-QoL was translated to American-English, Spanish, French, Hungarian, Romanian, Swedish, Polish, Greek and Azeri. The back-translations to German revealed deviations from the original version in all cases and required at least one revision until a final consensus version could be approved. Critical changes in the AE-QoL structure or questions were not required in any language. Currently, further translations into Italian, Portuguese, Brazilian-Portuguese, Russian and Chinese are underway.

Conclusions: A rigorous process of independent forward and backward translations, verification by local medical experts, and approval by the original authors allowed the generation of multiple language AE-QoL versions. Further work is required to complete a full validation process, most importantly testing these translations in the patients of the target languages.

P-23
THE ROMANIAN HEREDITARY ANGIOEDEMA REGISTRY

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The Romanian Hereditary Angioedema Registry is a population-based registry developed in response to the growing needs of the Romanian Hereditary Angioedema Network which presently enroles a number of 78 hereditary angioedema patients from al over Romania. The access to the database is restricted to authorized personal and the collected data are anonymous. The new patient record includes several forms covering disease and treatment history. The follow-up records include a series of forms that gather information about the location and frequency of the attacks, trigger factors, the consequences of the attacks, the medication used for the treatment of the attacks, the current maintenance therapy and the response to the treatments. The patient records can be retrieved using the patient code, can be sorted by several criteria including the family code and date of registration. Also, they can be saved on the local machine as PDF files and/or printed. The registry provides instant access to basic statistical data such as the number and percentage of patients by type of disease, age, sex, frequency and location of attacks. The database can be exported as a whole in a convenient format that enables further statistical analysis for research purposes. The Romanian hereditary angioedema registry is the result of a collaboration with well known experts in Europe and hopefully will contribute to a better understanding of the disease and the improvement of care of the patients affected by this rare condition.

P-24
PILOT STUDY AND VALIDATION OF THE IHAE-QOL QUESTIONNAIRE

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Background: To the best of our knowledge no specific Health-related Quality of Life (HRQoL) questionnaire for Hereditary Angioedema due to C1 inhibitor Deficiency (HAE-C1INH) is published. After the developmental study, a draft version of an international HRQoL questionnaire for HAE (IHAE-QoL) with 44 items has been achieved.

Methods: International pilot study was performed in 11 countries. Item and psychometric analysis was carried out. First, criteria for item omission were a percentage of no response >10% or corrected homogeneity index (CHI) <0.3. Second, exploratory factor analysis (EFA) was performed to check if theoretical model fitted the empirical data. Items with factor loadings < 0.4 were omitted. In addition, internal consistency and test-retest reliability were calculated. Construct validity evidences were also assessed.

Results: 332 patients from 11 countries participated and accurate data were obtained from 290: Argentine 16 patients, Austria 18, Brazil 34, Canada 21, Denmark 27, Germany 42, Hungary 38, Israel 9, Poland 22, Romania 19 and Spain 44. Retest phase data were obtained from 119 patients.

Item selection process led us to omit one item by a non-response rate above 10% and 3 items by a CHI<0.3. After EFA, three items were omitted due to insufficient factor loadings (<0.40). The final version of the questionnaire included 25 items addressing 7 dimensions: treatment difficulties, physical functioning and health, role-emotional and social functioning, disease-related stigma, concern about offspring, perceived control over illness and mental health. Cronbach´s alpha per dimension varied from 0,63 to 0,88. Regarding test-retest reliability, 37 patients were considered stable and intraclass correlation coefficient was 0.87.

Conclusions: The 25-items version of IHAE-QoL, in 11 language versions, shows good reliability and evidences of validity, and is ready to use in research.

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P-25
THE US HAE ASSOCIATION: AN IMPORTANT PARTNER IN A LONGSTANDING EFFORT TO IMPROVE PATIENTS' QUALITY OF LIFE

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The United States Hereditary Angioedema Association (HAEA) leads a nationwide advocacy organization that focuses on increasing HAE awareness and education; empowering patient access to optimal therapy; establishing a presence in the health policy legislative and regulatory environments; and fostering patient-driven clinical and translational research that includes searching for a cure. The HAEA is a growing organization of 4300 members that is governed by a proactive Board of Directors and works closely with a Medical Advisory Board comprised of world-class HAE physician-researchers. The organization is run by an experienced and devoted group of 16 staff members. Notwithstanding the dramatic expansion in the scope of its activities over the past 13 years, the HAEA remains grounded in the fundamental goal espoused since its founding—helping HAE patients achieve life long health by providing unbiased information and highly personalized services. The HAEA's core activities are centered around (1) a website for patients and physicians that serves as the repository for a wealth of authoritative and up-to-date information on HAE diagnosis and treatment, and (2) a caring and compassionate HAEA Patient Services Team which is available around the clock to help patients with HAE-related questions, problems, or emergencies. The HAEA's activities in 2012, and the initiatives it has planned for 2013 reveal that an organized and highly motivated patient organization that partners with interested physician/researchers and industry can be a powerful force in driving programs, activities, and research that improve patient quality of life.

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HEREDITARY ANGIOEDEMA - HOW CAN MEDICINES REACH THE PATIENT?

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Background: Hereditary angioedema (HAE) is a rare hereditary disease, which can be fatal without appropriate treatment of acute episodes. Accessibility of new medicines (conestat alpha and icatibant in Slovenia for the treatment of acute episodes of HAE (AE HAE) has some advantages compared to plasma-derived C1 inhibitor but also huge impact on direct costs. Our main goal was establishment of comprehensive care for HAE patients in order to enhance the quality and unified of care with control of the costs.

Methods: The centralized care model for HAE patients was developed based on data from national lists and recommendations from literature. The data on HAE patients (20) in Slovenia were retrieved regarding supply with rescue medicines for AE, frequency of annual AE and consumption of medicines per patient for each AE for the last two years.

Results: A national widespread network of non-stop access points for supply of conestat alpha in 7 ED in Slovenian hospitals was set up. Patients were gradually switched to icatibant for AE HAE as rescue medicine. A logistic plan to assure sufficient stocks of AE HAE medicines with expired data minimization policy was made. A system for recording treatment outcomes and consumption of medicines on each patient was developed. The safety, quality and unified of care for HAE patients was improved by preparing the documentation: Patient Identification Card, Recommendation for treatment the AE HAE in ED, etc.

Conclusion: Our model was designed in accordance to recommendations for centralized care of patients with rare diseases. It was adjusted to requirements of national health insurance and regional distribution of HAE patients in Slovenia. The comprehensive care model includes non-stop access points for HAE medicines as well as treatment outcomes recording according to medicines consumption. It represents good and necessary base for better management of HAE patients where data from large clinical trials are scarce.

P-27
COMPARISON OF ACUTE ANGIOEDEMA ATTACKS VERSUS BREAKTHROUGH ATTACKS DURING A PLACEBO-CONTROLLED, CROSSOVER STUDY OF CINRYZE® (C1 ESTERASE INHIBITOR [HUMAN]) FOR PROPHYLAXIS IN PATIENTS WITH HEREDITARY ANGIOEDEMA

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Background: The objective was to compare the attributes of angioedema attacks occurring in the presence or absence of prophylactic treatment.

Methods: In a placebo-controlled, crossover study, patients received intravenous CINRYZE or placebo every 3 to 4 days. After 12 weeks on their initial regimen, patients crossed over to the alternate treatment arm for another 12 weeks. Patients could also receive open-label CINRYZE for the treatment of angioedema attacks. Attacks that occurred during CINRYZE or placebo prophylaxis were deemed "breakthrough" or "acute" attacks, respectively. Attacks were characterized by duration and patient-reported maximum severity, rated as mild (1), moderate (2), or severe (3).

Results: Twenty-two patients with an average historical rate of 4 attacks/month completed both treatment arms. All patients reported angioedema attacks during the study. However, 4 had no attacks during the CINRYZE prophylaxis period. A total of 415 angioedema attacks occurred during the study: 135 (32.5%) breakthrough attacks during the CINRYZE period and 280 (67.5%) acute attacks during the placebo period. Breakthrough attacks were of shorter duration compared with acute attacks (mean 2.6 vs. 3.3 days, p=0.007). Breakthrough attacks were also less severe than acute attacks (mean severity score 1.7 vs. 1.9, p=0.007). Forty-nine percent of the breakthrough attacks were not treated with open-label CINRYZE compared to 23% of acute attacks, consistent with the lesser attack severity during prophylaxis. Breakthrough attacks treated with open-label CINRYZE were of shorter duration compared with acute attacks treated with CINRYZE (mean 2.9 vs. 3.4 days, p=0.02).

Conclusion: Breakthrough attacks may occur during prophylactic treatment. However, in this study, breakthrough attacks were of shorter duration and were less severe than acute attacks that occurred without prophylaxis. Breakthrough attacks also appeared to be more responsive to open-label treatment than acute attacks.

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FEASIBILITY OF HOME INFUSION AND SELF-ADMINISTRATION OF CINRYZE® (C1 ESTERASE INHIBITOR [HUMAN]) FOR ROUTINE PROPHYLAXIS IN PATIENTS WITH HEREDITARY ANGIOEDEMA AND CHARACTERIZATION OF A TRAINING AND SUPPORT PROGRAM

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Background: Since hereditary angioedema (HAE) is a chronic genetic disease that may require twice weekly therapy with IV CINRYZE, self-administration is an important option for these patients. An analysis of our dynamic patient-database (N=516) to assess the site of care (SOC) was conducted in June 2010. Six months later, a training and support program led by skilled infusion nurses was implemented to educate eligible patients on self-administration of CINRYZE. The objectives of this study were to evaluate the setting of CINRYZE infusions and the prevalence of self-administration and to describe our experience with the training and support program.

Methods: In early 2012, patient-reported demographic data from the same dynamic CINRYZE database of HAE patients was examined. These results were compared to the 2010 analysis and reflect distributions of SOC for similar lengths of time before and after the initiation of the training and support program. Data was categorized and sorted; the results are based on descriptive statistics.

Results: The SOC for patients receiving CINRYZE (N=789) was 75.8%, 16.1%, 8.1% at home, infusion center, and physician's office, respectively, compared to 49.0%, 23.4%, and 27.5% from the 2010 analysis. Of the patients (75.8%) who infused at home, 57.9% self-administered, 26.6% were infused by a home health agency nurse, 14.7% by a family member, and 0.8% by other. Overall, self-administration was reported in 43.9% of patients compared to 20.3% from the 2010 analysis. The training and support program enrolled 234 patients. Of which, 54.3% were successfully trained and 13.7% were in the process of learning self-administration. Patients required an average of 5 visits to be successfully trained.

Conclusion: Majority of patients received CINRYZE at home and more than twice as many patients reported self-administration as of 2012. A nurse-managed training and support program assisted patients in achieving proficiency in self-administration.

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CLINICAL DESCRIPTIVE STUDY AND HEALTH RELATED QUALITY OF LIFE (HRQOL) AS MEASURED BY SF-36V2 IN ADULTS WITH HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY IN SPAIN

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Background: An international multicentre study for the development of a specific Health Related Quality of Life (HRQoL) questionnaire for hereditary angioedema with C1-inhibitor deficiency (HAE-C1-INH) (IHAE-QoL) was carried out. We report the demographic, clinical data and HRQoL as measured by SF-36v2 in the Spanish sample.

Material and Methods: HAE-C1-INH patients completed a self-administered clinical questionnaire and SF-36v2 survey (2009-2010). Recall period was 6 months for CQ and 1 month for SF-36.

Results: Forty-four patients (63.7% female, 79.5% type I; mean age 41.3 ± 12.1 y.) were recruited. None patient was asymptomatic. Mean age at onset of symptoms was 11.0 ± 9.2 y. Mean delay in diagnosis was 11.8 ± 9.9 y. Attack triggers along life were identified by 93% of patients (stress, traumatisms, infections, menstruation, other). Thirteen patients (29.5%) referred having some family members dead from asphyxia. Intubation/tracheotomy had ever been needed in 4 patients (9.1%). Thirty-one patients (70.1%) were on long term prophylaxis: 80.6% attenuated androgens (danazol 60%; stanozolol 40%), 12.9% antifibrinolytics and 12.9% pdC1INH. Patients reported at least 279 edema episodes in the last 6 months: 114 peripheral, 99 abdominal, 51 genital, 11 facial, 4 upper airway. Seventeen patients referred having visited the emergency room on 103 occasions because of angioedema attacks in the last 6 months. A total of 59 and 21 days had been missed from work and school respectively due to angioedema attacks. Mean time to access the nearest health care centre was 20.9 minutes (SD 13.6; range 3-60). 31 patients (70.5%) had pdhC1-INH available at home. Regarding HRQoL as measured by SF-36v2 the Physical Component Summary was 47.66 ± 9.22 and the Mental Component Summary 46.31 ± 8.86.

Conclusions: A description of patients with HAE-C1-INH in Spain is presented. This disease produces a decrease in HRQoL compared to normal population in Spain.

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P-30
BENEFITS OF EARLY ADMINISTRATION OF ICATIBANT FOR THE TREATMENT OF HEREDITARY ANGIOEDEMA ATTACKS

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Background: Observational studies indicate that early treatment of hereditary angioedema (HAE) attacks may improve attack outcomes. The HAWK Consensus recommends on-demand treatment at attack onset to shorten duration and attack-related inability. We investigated the impact of early treatment on HAE type I or II attacks with icatibant using data collected in the Icatibant Outcome Survey (IOS) registry (NCT01034969), an ongoing, observational study in HAE sponsored by Shire HGT.

Methods: Adult patients ≥18 years were included. Analyses of attack duration (time between attack onset and complete resolution of symptoms) and time to resolution (time between icatibant first injection and complete resolution of symptoms) were performed for 426 attacks treated with icatibant in 136 HAE type I and II patients.

Results: The majority (61.4%) of self-treated attacks were treated within 2 h, compared with 44% of healthcare professional-treated attacks ($p<0.016$). Significantly shorter mean attack duration for attacks treated <1 h after onset compared with those treated ≥1 h (6.1 h versus 16.8 h; $p<0.001$) and mean time to attack resolution (5.8 h versus 8.8 h; $p<0.05$) were observed. Moreover, reductions in mean attack duration were observed for attacks treated <2 h versus ≥2 h (7.2 h versus 20.2 h; $p<0.001$) and <5 h versus ≥5 h (8.0 h versus 23.5 h; $p<0.001$).

Conclusions: Self-administration facilitates early treatment. Observational data from the IOS registry show that early treatment with icatibant reduced the duration of attacks and the time to attack resolution. These data are the first to provide evidence that, in real-life, time to attack resolution is significantly shortened by early treatment.

Keywords: Icatibant, Hereditary angioedema, Patient registry, Self-administration, Early treatment

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TREATMENT OF HEREDITARY ANGIOEDEMA ATTACKS WITH ICATIBANT: A COMPARISON OF OBSERVATIONAL DATA WITH CLINICAL TRIAL DATA

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Background: The clinical efficacy of icatibant in hereditary angioedema (HAE) type I and II was evaluated in a Phase III trial FAST-3 (NCT00912093). We have evaluated whether icatibant used in a real-world setting (Icatibant Outcome Survey [IOS], NCT01034969) provides similar efficacy as in a controlled trial setting.

Methods: In FAST-3, a multicentre, randomised, placebo-controlled trial, 43 adult patients (43 attacks) with moderate to very severe HAE attacks received 30 mg icatibant administered subcutaneously by healthcare professionals (HCP) in the clinic within 6 h of attacks becoming moderate (non-laryngeal attacks). IOS, an observational study with few inclusion/exclusion restrictions, collects data on HAE patients treated with self- or HCP-administered icatibant. IOS data from 129 adult patients with 409 attacks were included. Median time to treatment, time to resolution (almost complete resolution [FAST-3] or complete resolution [IOS]), and attack duration were compared. Data are presented for non-laryngeal attacks.

Results: Median times to treatment with icatibant were shorter in IOS versus FAST-3 (2.17 h [IOS; n=83] versus 6.45 h [FAST-3; n=43]; $p<0.001$). Median time to complete attack resolution in IOS was shorter than median time to almost complete resolution in FAST-3 (4.25 h [n=87] versus 8.00 h [n=43]; $p<0.0001$). The median attack duration was reduced in IOS compared with FAST-3 (13.25 h [n=78] versus 16.92 h [n=43]; $p<0.0001$).

Conclusions: Icatibant was shown to be efficacious in the FAST-3 trial. Data from the IOS registry, in which the majority of HAE attacks were treated earlier with icatibant, show that icatibant reduced the time to attack resolution and attack duration.

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TEACHING INTRAVENOUS SELF-APPLICATION IN PATIENTS WITH HAE: EXPERIENCES BY A SPECIALIST NURSE

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Acute treatment of hereditary angioedema (HAE) is most effective when given early in the course of a swelling. The skill of self-application ensures earliest possible treatment in acute treatment. In prophylactic treatment, the skill of self-application is very useful and time-saving for the patient, as frequent i.v.-injections are required.

18 pts with HAE were trained by experienced specialist nurses until pt and treatment partner have had sufficient practice to be familiar and confident with the self-application. 14 pts received routine prophylaxis with C1-INH-concentrate every 3-4 days, 4 other pts were trained for intravenous acute treatment.

The median age of the pts was 50 years, 7 pts were female, 7 male. The median number of training sessions needed to learn the independent self-application was 5 sessions. Only 3 pts needed more than 10 training sessions, 12 pts were trained 5 times or less. No correlation between the number of needed training sessions and sex, age or anatomical vein conditions was found.

The median number of HAE attacks/month was 8 before prophylactic treatment, decreasing to 0.5 attacks/month under prophylactic treatment, and 7 out of 14 pts were completely free of symptoms. The delay in therapy (time between the decision to treat and the start of i.v. treatment) was markedly reduced in all pts after the training. As trained pts were no longer constrained to seek medical help from healthcare professionals, the delay in therapy could be reduced in median from approx. 2.5 hours to 12.5 minutes.

Conclusion: Individual training of self-application by specialist nurses was successful in almost all pts. 12 out of 18 pts needed 5 or less training sessions until they could administer i.v.-medication safely and independently. Age or anatomical vein conditions were not impedimental. Pts with the skill of self-application minimize the delay in therapy, thus optimizing the efficacy of the overall treatment.

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DIFFERENT FORMS OF HAE PROPHYLAXIS

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Several forms for prophylactic treatment of HAE are possible. We have used in our angioedema center three forms of prophylaxis: 1. Short term prophylaxis before surgery, 2. Long term prophylaxis and 3. On demand prophylaxis. We used for the three prophylaxis forms following drugs: Icatibant in short term prophylaxis and on demand prophylaxis, C1 inhibitor concentrates in all prophylaxis forms. All prophylaxis treatment forms were successful.

Patients with short term prophylaxis were treated with icatibant or C1 INH 30-60 minutes pre surgery, 2 hours post-surgery and 12 h post-surgery. In long surgeries with more than 2 h or large blood-loss an additional application of icatibant or C1 INH was given. Long term prophylaxis was possible with Ruconest, Berinert and Cynrize. We have used all three C1 INH options in long term prophylaxis. Patients get 2 times in the week the C1 INH concentrates for 12 weeks. Our results demonstrate here a significant reduction of angioedema attacks.

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AN INDIRECT COMPARISON OF ICATIBANT AND FOUR OTHER THERAPIES FOR THE SYMPTOMATIC TREATMENT OF ACUTE ATTACKS OF HEREDITARY ANGIOEDEMA TYPES I AND II

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Background: Hereditary angioedema (HAE) is a rare and potentially life-threatening condition. The efficacy of acute HAE treatments has not been assessed in head-to-head comparative studies. This study aimed to establish the relative efficacy of icatibant [Shire HGT] versus C1-esterase inhibitor concentrate (C1-INH) [CSL Behring], C1-INH [ViroPharma], rh-C1-INH [Pharming], and ecallantide [Dyax].

Methods: Nine relevant randomised clinical trials were analysed. Indirect comparison (IC) hazard ratios (HR) between treatments were calculated using the methods of Bucher (1997) and Song (2003). To account for trial heterogeneity, five sets of icatibant data were considered separately; three clinical endpoint definitions (time to onset of primary symptom relief, time to initial symptom improvement [subject-assessed], and time to onset of symptom relief based on composite VAS score); and three rescue medication (RM) censoring methods (no censoring [RMs ignored], censoring subjects who took RMs prior to onset of symptom relief, and resetting time to onset of symptom relief to 24h for censored subjects) were considered separately in the ICs.

Results: The IC considered each of the 45 icatibant data/endpoint definition/RM censoring combinations. HR estimates favoured (HR ≥1) 37/45 icatibant combinations versus C1-INH [CSL Behring] 20 IU/kg (Median HR = 1.39 [minimum 0.72, maximum 2.10]), 45/45 (29 statistically significant) versus C1-INH [CSL Behring] 10 IU/kg (Median HR = 2.19 [minimum 1.07, maximum 3.39]), 32/45 versus C1-INH [ViroPharma] (Median HR = 1.36 [minimum 0.63, maximum 2.22]), 24/45 versus rh-C1-INH 50 IU/kg (Median HR = 1.04 [minimum 0.48, maximum 1.70]), and 43/45 versus ecallantide (Median HR = 1.67 [minimum 0.75, maximum 2.66]).

Conclusions: Icatibant showed improved time to symptom relief when compared with C1-INH [CSL Behring] 10 IU/kg. No clear differences were evident versus either C1-INH [CSL Behring] 20 IU/kg (SmPC dosing) or the three other HAE treatments.

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THE EFFICACY AND SAFETY OF SELF-INJECTED ICATIBANT ADMINISTERED AS AN ACUTE TREATMENT FOR HEREDITARY ANGIOEDEMA DUE TO C1-INH DEFICIENCY (HAE-C1-INH) IN CLINICAL PRACTICE

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The bradykinin B2 receptor antagonist icatibant is suitable for the relief of edematous attacks in patients with HAE-C1-INH as a drug licensed for self-administration by subcutaneous injection. This review describes the experience accumulated with the use of icatibant in clinical practice.

Thirty icatibant-treated edematous episodes, occurring in 4 patients with HAE-C1-INH, were analyzed. The patients self-injected icatibant in their homes and then, recorded the following: the expected effectiveness of icatibant; the time of the onset of the attack and of the self-administration of icatibant; time to the improvement and to the complete resolution of symptoms; undesirable effects. The severity of symptoms and patient satisfaction were measured with a visual analogue scale (VAS).

Mean attack severity was 56.3 (VAS). The time between the onset of the attack and the administration of icatibant was 1.91 (0.45-5.9) hours [median (25^{th}-75^{th} percentiles)]. Time to the cessation of worsening was 0.33 (0.25-0.5) hours, whereas a noticeable improvement occurred after 0.5 (0.4- 0.76) hours. Icatibant was ineffective in a single case. The complete resolution of symptoms took 10.98 (4.16-15.86) hours. In two patients, 11 attacks recurred within 48 hours of the administration of icatibant. A statistically significant relationship between these attacks and any of the study parameters could not be established. The patients did not experience systemic adverse reactions. Mild and transient reactions occurred at the injection site, but not in all patients/attacks. Mean patient satisfaction with the effectiveness of icatibant during a specific attack was 8.93 on a 0-10 scale.

Patient satisfaction was excellent testing under real-life conditions proved that icatibant is a reliable remedy for the relief of attacks.

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SHORT-TERM PROPHYLAXIS IN A PATIENT WITH ACQUIRED C1-INH DEFICIENCY

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In acquired C1-INH deficiency, limited experience is available with short-term prophylaxis, which we used with success in a 66-year old female patient. She has been receiving ACE inhibitors for hypertension since 15 years. In 2009, she started to experience gastrointestinal symptoms recurring every other week – on four occasions with limb edema. Abdominal US and CT imaging detected free peritoneal fluid and edema of the intestinal wall. The complement screen confirmed acquired angioedema due to C1-INH deficiency, without anti-C1-INH antibodies.

As the known trigger factors of angioedema attacks include ACEIs, we replaced enalapril with bisoprolol. The patient had a single, mild abdominal attack during the next 6 months. Iliac crest biopsy, performed to investigate pancytopenia, confirmed Non-Hodgkin lymphoma of the splenic marginal zone type. In 2010, splenectomy was performed after pre-treatment with erythropoietin, as the patient rejected blood transfusions for religious reasons. Notwithstanding this, plasma-derived pdC1-INH concentrate was at hand, but surgery and the postoperative course were uneventful. The patient's hematological parameters have been checked regularly since then. A monoclonal protein of the IgG λ type, which has not been detectable in 2009, appeared in the serum (3.34 g/L). Edematous attacks have not recurred during the last two years. Two dental procedures have been performed. Pre-treatment with pdC1-INH one hour before the event prevented edema formation both during and after the interventions. In 2013, she had cataract surgery. By this time, rhC1-INH had become available and was used upon the patient's request with similar success.

Short-term prophylaxis would be justified in acquired C1-INH deficiency, just as it is in the hereditary form, because invasive procedures may provoke edema-formation also in the former. Both pdC1-INH and rhC1-INH proved effective: the invasive procedures and postoperative wound healing were all uneventful.

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HOME TREATMENT OF ATTACKS WITH CONESTAT ALFA IN HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY (HAE-C1-INH)

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Ruconest, a recombinant C1-inhibitor concentrate (rhC1-INH) was licensed in 2010 in Europe, for the acute treatment of HAE-C1-INH. So far, its efficacy and safety have been evaluated only in clinical trials. The information on the use of rhC1-INH for home therapy is limited.

We analyzed 19 edematous episodes requiring intervention and occurring in 2 female HAE-C1-INH patients. The patients were treated at home by a physician, with the exception of four attacks. During these, the patients self-injected an intravenous dose of 2100 U rhC1-INH per occasion. The patients recorded the following data: the expected efficacy of rhC1-INH; time of rhC1-INH administration; time to the onset of the improvement as well as to the complete resolution of symptoms; and side effects. Symptom severity and patient satisfaction were measured with a visual analogue scale (VAS).

Twelve HAE attacks occurred in abdominal viscera, 2 on the extremities, 1 on the genitals, and 4 had multiple locations. RhC1-INH was administered 90 (5-610) [median (min-max)] minutes after the onset of the attacks, with a severity (upon injecting) of 68 (49-98) on a visual analogue scale. Fifteen (5 to 30) minutes after dosing, the patients felt that the attack stopped worsening. Clinical symptoms improved within 30 (15-225) minutes after rhC1-INH administration, and the complete resolution of symptoms took 350 (100-3525) minutes. The time between the onset of the attack and the administration of rhC1-INH was not related to the times to improvement/complete resolution of the symptoms, or to the severity of the attack.

None of the patients experienced a recurrence of the HAE attack within 48 hours. No drug-related systemic adverse events were reported. The VAS mean score of patient satisfaction (as reflected by the data from 19 episodes) was 93.

RhC1-INH was effective and generally well-tolerated as a therapy for cutaneous and/or abdominal HAE attacks. Home treatment with rhC1-INH completely resolved the attacks in these patients.

AUTHORS' INDEX

NOTES: