



THE 9TH INTERNATIONAL C1-INH DEFICIENCY WORKSHOP

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BUDAPEST, HUNGARY

MAY 28-31, 2015

Dear Colleagues,

The 9th International C1-INH Deficiency Workshop – a scientific conference taking place every second year since 1999 – will be held between 28 and 31 May (www.haenet2015.hu) in Budapest, the capital of Hungary. The event constitutes a forum for professionals involved in the research and management of bradykinin-mediated angioedema, as well as for the representatives of the patients. This year's workshop will be attended by 260 participants from 36 countries. The conference focuses on hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE); however, hereditary angioedema with normal C1-INH level (nC1-INH-HAE), and acquired angioedema resulting from C1-INH deficiency (C1-INH-AAE) will also be discussed. A ceremonial highlight of the event will be the bestowal of the "For HAE Patients" award to Professor Tom Bowen from Canada, for his life's achievement.

Notwithstanding the substantial progress made in the research of HAE during recent decades, a number of essential questions have been left unanswered. It is currently unknown, how loss-of-function mutations in the *Serping1* gene lead to HAE in heterozygous carriers, and to which extent dominant negative effects of defective C1INH protein are responsible for the cellular and molecular pathogenicity leading to HAE. The Danish researcher, PROF. JACOB MIKKELSEN will read a lecture on novel genetic engineering techniques, which might facilitate the introduction of gene therapy into clinical practice. PROF. ERIK HACK from The Netherlands will outline a model in which the inflammation-induced endothelial BK-receptor (B1R) is presumed to play a major role. This model may elucidate the background of the local manifestations seen during the systemic activation process so characteristic of HAE.

Some of the submitted abstracts promise to disclose new, hitherto unexplored details of the pathomechanism of angioedema related to bradykinin release. Several papers will review the development of improved diagnostic methods. The relative significance of the genetic background, and of the modulating influence by environmental factors, the presence of concomitant disorders, and lifestyle differences will be given emphasis. The presentations will summarize current experience accumulated with recently introduced therapeutic modalities, and pinpoint further therapeutic options suggested by the latest research findings. A session of the conference will be devoted to issues specific to the care of pediatric patients, and the discussion will culminate in the adoption of an international consensus guideline. Another session on the share of nurses in the management of HAE will add a touch of color to the scientific program.

Organizing this Workshop has been aided by the generous sponsorship of the pharmaceutical companies, which have developed medicinal products for the treatment of HAE. The representatives of these manufacturers will attend the conference to join forces with the researchers, physicians, and patients in forthcoming development projects. The major donors to this event are CSL Behring, and Shire. Dyax, SOBI, Pharming also contributed financing, and our welcome to BioCryst Pharmaceuticals, who joined the ranks of our sponsors for the first time this year. For many colleagues, the donations by these companies made it possible to attend



the Workshop by reducing their travel and registration costs – and furthermore, these contributions lent support to organizing the Nurses' Session. Finally, the '*Grant for Young Investigator*' award, established to motivate junior research fellows, will be bestowed by the scientific committee of seven members.

The scientific program of the 9th C1-INH Deficiency Workshop consists of 86 items including lectures by invited presenters, along with oral and poster presentations. It is a great pleasure that just as before, the *Journal of Angioedema* will publish the abstracts of the conference. This will make the essence of the information discussed at the event available also to interested professionals, who could not join us on this occasion. It is to be hoped that the Readers of this issue of the *Journal* will find the abstracts useful and interesting enough to arouse their curiosity to attend the next, 2017 edition of the Workshop in person!

Henriette Farkas

Chair of 9th C1-Inhibitor Deficiency Workshop

Lilian Varga

Secretary of 9th C1-Inhibitor Deficiency Workshop



ABSTRACTS OPENING LECTURES



I-01

HEREDITARY ANGIOEDEMA (HAE) AND PACHYDERMOPHOBIA – EXORCISING SOME DEMON PACHYDERMS - BRINGING BACK SOME BABIES MISSING WITH THE BATH WATER

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As we are trending towards the world's richest 1% owning more than 50% of the world's wealth, it is apparent that distribution of health care benefits for expensive rare disorders like Hereditary Angioedema (HAE) may become less equitable instead of improving. From having only one licensed plasma derived C1-inhibitor replacement product (C1-INH) for the treatment of HAE events in the 1980's, one sees development of more C1-INH plasma and recombinant products, kallikrein inhibitors, bradykinin receptor blockers, and other interventions. We mistakenly thought a free market economy would prevail and HAE prevention and treatment would become more economical. Instead, one sees new products coming to market somewhat more pricey than the products before and not clearly priced by development and production costs as much as what the market will bear. Mergers and acquisitions are skewing the free market economy and some products seem only marketed in countries willing to pay high prices while distribution to less affluent countries limited. Availability to many products seems limited to USA and EU. Poor countries find it difficult to place treatments for HAE on National Essential Medicine Lists that have to balance scarce public funding for vaccines, parasite control and antimalarials with very expensive therapies for rare disorders. Perhaps one has to rethink the extended patent protection for orphan drugs and extension of patent protection granted in free trade agreements between wealthier areas. Product utilization and costs for HAE therapy in some nations is rising exponentially and justification is being sought by many health care systems. Extending patent protection and orphan drug status may prevent dissemination of valuable therapies to less wealthy parts of the world and prevent development of more cost effective therapies. What are the roles of hormonal adjuvant and antifibrinolytic interventions in HAE and as expensive drug sparing agents? Where do androgens for males, progestational agents for females, antifibrinolytics fit in the pharmacoeconomics of HAE. How will prevention and cure strategies evolve including modern reproduction technologies including preimplantation embryo selection, ex vivo and in vivo gene manipulations, stem cell transplantations and who should fund these options? We need to bring some of the babies back that have been thrown out with the bath water and examine our pachydermophobia and exorcise some of the elephants in the consensus rooms. Through independent data base registries and research programs we can improve on prevention and treatment programs for HAE in all of our jurisdictions. We must provide robust independent data on the pharmacoeconomics and quality of life justifications of our HAE management algorithms. We must be willing to tackle our pachydermophobia and re-examine some of the babies thrown out with the bath water. It can be done – it must be done for the sake of our patients!



I-02

GENETIC ENGINEERING FOR CELLULAR MODELING OF HAE DISEASE MECHANISMS IN CELL LINES, PATIENT-DERIVED FIBROBLASTS, AND MICE

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Background: HAE is caused by reduced levels of the C1INH protein encoded by the *serping1* gene. It is currently unknown how loss-of-function mutations in the *serping1* gene lead to HAE in heterozygous carriers and to which extent dominant negative effects of defective C1INH protein are responsible for the cellular and molecular pathogenicity leading to HAE.

Methods: Using a panel of state-of-the-art genetic engineering technologies, which have not been applied previously in the HAE research field, our goal is to study the effect of disease-causing mutations at the molecular level. We aim at providing basic understanding of how the activities of the normal *serping1* allele are disturbed by mutations within the disease-causing allele and how this information can be used in the development of a genetic therapy for HAE.

Results: In patient-derived fibroblasts, we find levels of secreted C1INH corresponding to about 20 % of the amount of C1INH secreted from control fibroblasts from healthy individuals, suggesting that such cells represent a suitable cellular model of the disease. We have initiated studies of lentivirus-based delivery of both the normal and mutated *serping1* gene variants in this model and are currently implementing the CRISPR/Cas9 system for knockout and editing of HAE disease alleles. Also, using novel DNA transposon-based vector technologies, we are creating human liver cell lines that mimic the co-existence of normal and mutated *serping1* alleles in heterozygous HAE patients. Finally, using adeno-associated virus (AAV)-derived vectors, we have established *serping1* gene transfer to mouse liver, resulting in robust and sustained C1INH production (>6 months) after a single vector injection.

Conclusions: Novel genetic engineering techniques facilitate studies of the cellular pathology of HAE. As gene therapy is coming of age, insight into the cellular disease mechanisms may pave the way for genetic intervention as a possible treatment modality.



I-03

ANGIOEDEMA ATTACKS OF HEREDITARY ANGIOEDEMA: LOCAL MANIFESTATIONS OF A SYSTEMIC ACTIVATION PROCESS

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Hereditary angioedema (HAE) due to a deficiency of C1-inhibitor (C1INH) becomes clinically manifest as attacks of acute angioedema. C1INH is the main inhibitor of the contact system. Poor control of a local activation process of this system at the site of the attack is believed to lead to the formation of bradykinin (BK), which upon interaction with BK2-receptors (B2R) on the endothelium increases local vasopermeability and mediates angioedema. However, several observations in HAE patients are difficult to explain from a pathogenic model claiming a local activation process at the site of the angioedema attack. Therefore, we postulate an alternative model for acute angioedema attacks in HAE, which assumes a systemic, fluid-phase activation of the contact system to generate BK and breakdown products. Interaction of these peptides with endothelial receptors that are locally expressed in the affected tissues rather than with receptors constitutively expressed by the endothelium throughout the whole body, explains that such a systemic activation process results in local manifestations of an attack. Particularly the BK-receptor 1 (B1R), which is induced on the endothelium by inflammatory stimuli such as kinins, cytokines and endotoxin, meets the specifications of the involved receptor. The pathogenic model discussed here also provides an explanation why angioedema may occur at multiple sites during an attack and why HAE attacks respond well to modest increases of circulating C1INH activity levels, since inhibition of fluid-phase factor XIIa and kallikrein requires lower C1INH levels than inhibition of activator-bound factors.



O-01

C1-INHIBITOR: THE CONDUCTOR OF EVENTS IN HEREDITARY ANGIOEDEMA

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Angioedema based on the deficiency of the C1-inhibitor (C1-INH) has hereditary and acquired forms (C1-INH-HAE and C1-INH-AAE) that are important subsets within the group of bradykinin-mediated angioedemas.

C1-INH plays a dominant role in the regulation of the enzymes, which constitute the bradykinin-forming cascade. It is thus not surprising that the deficient concentration of this key inhibitor results in the excessive production of bradykinin. The 'deficient' concentration is difficult to define. Apparently, it is not a complete depletion, because in C1-INH-HAE – a heterozygous dominant disorder – one of the pair of genes produces a protein with normal function. The activity of C1-INH is below normal in the blood of the patients with this condition, and substantial intra- and inter-individual differences can be observed over a lifetime. On one hand, the enhanced activation of the target enzymes may increase C1-INH requirements, whereas other inhibitors may act in lieu of – or as add-ons to – C1-INH. Enhancers, such as glycosaminoglycans potentiate the effect of C1-INH, and furthermore, the determination of a 'sufficient' C1-INH concentration might be influenced by additional, hitherto unknown factors. Possibly, the elucidation of the latter can resolve the paradox in C1-INH-HAE, where episodic of edema formation keeps recurring despite the persistent deficiency of C1-INH. According to current knowledge, the time of onset, the severity, and the location of edematous attacks are still unpredictable. The mechanism leading to the spontaneous resolution of edema is similarly enigmatic. The pathophysiology of C1-INH-HAE/AAE resembles the functioning of a symphonic orchestra, where the incompetent conductor is unable to forestall disharmony caused by discordant tunes. In our example, although the whole 'orchestra' listens to C1-INH, the 'musicians' communicate among themselves. That is, the individual enzymes of the cascade can activate each other, and thereby alter the centralized control at various phases of the process.

Better elucidation of the interactions of C1-INH would improve our understanding of the pathomechanism of bradykinin-mediated angioedemas and could take us closer to developing individualized and targeted therapies further. The presentation reviews all hitherto identified interactions of C1-INH.



O-02

IMPORTANCE OF C1 INHIBITOR POLYSACCHARIDES FOR SERPIN FUNCTION AND AUTO-ANTIBODY TITRES

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Background: C1 Inhibitor (C1Inh) is a heavily glycosylated protein with 45% polysaccharides by weight. C1Inh is bearing 6 *N*-linked carbohydrates, 14 potential *O*-glycosylation sites, with 7 verified by carbohydrate analysis. Most of the sugars are present in the *N*-terminal domain; three *N*-linked oligosaccharides are attached to the serpin domain through residues Asn216, Asn231, and Asn330. The precise function of these carbohydrate groups is unknown, whereas it has been demonstrated that affinity to endotoxins and selectins depends on the *N*-glycans.

Objective: We aim to decipher whether *O*- or *N*-deglycosylation could affect (1) the serpin function towards C1s protease or contact phase target and (2) the target of anti-C1Inh autoantibody.

Method: (1) Deglycosylation was performed using neuraminidase, *O*-glycosidase and *N*-glycanase. Serpin function was titrated using the residual amidase activity (Pro-Phe-Arg-*p*NA) for contact phasetarget. Anti-C1Inh immunoblot was used to estimate the C1Inh-protease complexes for both targets. (2) Anti-C1Inh antibodies were titrated by ELISA using native or deglycosylated C1Inh.

Result: (1) Deglycosylation of C1Inh for *O*-linked polysaccharides, but not for *N*-linked polysaccharides, was demonstrated to affect serpin function towards contact phase (amidase activity and serpin-protease complexes) but not C1s target (serpin-protease complexes). (2) The anti-C1Inh autoantibody IgM/IgG titres decreased dramatically after *O*-deglycosylation, and to a smaller extent, after *N*-deglycosylation.

Conclusion: (1) C1Inh function is strongly affected by polysaccharides; in particular the *O*-linked sugars affect the control of contact phase proteases, suggesting an involvement of the *N*-terminal domain in the serpin function. (2) The polysaccharide motif was found to be a target of the anti-C1Inh autoantibodies. These antibodies could be polyspecific immunoglobulins to membrane glycoprotein targets on circulating cells (*e.g.* neutrophil) or endothelial cell.



O-03

ACTIVATION OF ENDOTHELIAL CELLS TO RELEASE HSP90, AN ACTIVATOR OF THE PREKALLIKREIN-HIGH MOLECULAR WEIGHT KININOGEN (HK) COMPLEX

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We have previously demonstrated that Hsp90 release by activated endothelial cells leads to conversion of prekallikrein to kallikrein if prekallikrein is bound to HK. Kallikrein formation is therefore stoichiometric and occurs in the absence of factor XII. Since kallikrein activates factor XII, we theorized that endothelial cell activation might first generate kallikrein which then recruits factor XII. We now demonstrate that estrogen, interleukin 1, and to a lesser degree TNF α can activate endothelial cells to release Hsp90. The dose range tested for each in ng/ml was 0, 0.5, 1.0, 5.0, and 10.0. A dose-response for estrogen or IL-1 was maximal at the 10 ng/ml dose while TNF α was best between 0.1 and 5 ng/ml. A time course for each up to 4 hrs incubation revealed maximal Hsp90 secretion between 30 and 60 min with a significant increase noted by 15 min for each. Our observations are particularly relevant for types I and II HAE (C1 inhibitor deficiency) where estrogen and inflammation are known triggers of angioedema events and for HAE with normal C1 inhibitor (HAE-N) where estrogen exposure is a key precipitant. For the latter, studies of endothelial cell release of urokinase and tissue plasminogen activator are in progress given recent observations regarding inhibitors of fibrinolysis.



O-04

THE ISOLATED HUMAN UMBILICAL VEIN AS A BIOASSAY FOR TISSUE KALLIKREIN (KLK-1) AND PLASMA KALLIKREIN (PK): RESPONSES MEDIATED BY LOCALLY FORMED VASOACTIVE KININS

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Background: the isolated human umbilical vein is a robust contractile bioassay for agonists of the bradykinin (BK) B2 receptor (B2R), applicable as well to antagonists like icatibant. We hypothesized that, as a freshly vascular segment, it also contains traces of plasma proteins that may confer an effect to exogenous proteases via the formation of kinins.

Methods: rings of human umbilical vein, obtained with informed consent after elective caesarean sections, were mounted in organ baths containing Krebs buffer maintained at 37°C. Contractility studies involved introducing highly purified proteases in the bathing fluid along with additional drugs/proteins that permit mechanistic analysis of effects.

Results: human recombinant KLK-1 (provided by DiaMedica, Inc.; 1-10 nM) contracted the isolated vein via the B2R, but in a tachyphylactic, kinin-dependent manner, without desensitization of the tissue to exogenously added BK. Replenishment with low molecular weight-kininogen (LK) restored the response to KLK-1 in desensitized tissues. The lack of effect of metabolic inhibitors suggests that LK is not formed de novo in the isolated tissues. Purified human PK (≤ 5 nM) and plasmin (≤ 10 nM) were not contractile agents in fresh tissues, unless high molecular weight-kininogen (HK, 40-200 nM) replenishment was applied; then PK was the better contractile agent. The effects of KLK-1 and HK+PK are abolished by pretreating tissues with icatibant, but not with tranexamic acid. C1-inh (Berinert) inhibits only HK+PK.

Conclusions: The umbilical vein assay represents a system depleted of HK, but that contains residual LK activated via KLK-1. The pharmacology of KLK-1 and PK+HK is essentially based on the activity of locally generated kinins active on B2Rs. The system models the action of drugs active in angioedema states.



O-05

DECREASED LEVEL OF THE LECTIN PATHWAY SERINE PROTEASE MASP-1 IN SYMPTOM-FREE AND DURING ATTACK PERIODS OF PATIENTS WITH HEREDITARY ANGIOEDEMA

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Introduction: Hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) is an autosomal dominant disease characterized by recurrent bradykinin mediated edematous attacks. C1-inhibitor (C1-INH) is known to form complexes with the lectin complement pathway serine proteases MASP-1 and MASP-2. Previously, MASP-1 has been shown to cleave high molecular weight kininogen into bradykinin that can take place on the surface of the endothelial cells where the local concentration of MASPs can be much higher than in serum. Furthermore, MASP-1 and MASP-2 can be activated during infection or stressful conditions that are known provoking factors of HAE attacks. Based on these studies, we hypothesized that MASP-1 may contribute to the development of edematous attacks.

Methods: 20 C1-INH-HAE patients, who have experienced severe attacks on 34 occasions, were enrolled. Blood samples were collected in 24 hours after the onset of symptoms, before the administration of acute treatment. We analyzed blood samples drawn during attacks, and 20 samples obtained from the same patients during symptom-free periods, as well as blood samples of 26 healthy subjects. The serum level of MASP-1 was determined using an in-house ELISA method.

Results: MASP-1 levels of patients with C1-INH-HAE were lower in the symptom-free period compared to the healthy subjects ($p=0.0004$), and the concentration of MASP-1 decreased even further in the same patients during edematous attacks ($p=0.0313$). A more pronounced, significant difference was observed between the healthy subjects and the patients during attacks ($p<0.0001$). Interestingly, the level of MASP-1 was significantly elevated during attacks with multiple locations, compared to the subcutaneous attacks ($p=0.0217$).

Conclusions: We have shown that C1-INH-HAE patients are characterized by different MASP-1 levels in the symptom-free period or during attacks. Our observations suggest that MASP-1 may play a role in the pathomechanism of C1-INH-HAE.

Supported by the grant OTKA-NKTH 100886 and 112110.



O-06

NEUTROPHIL ACTIVATION DURING ATTACKS OF HEREDITARY ANGIOEDEMA

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Earlier studies have shown that the absolute number of neutrophil granulocytes may increase during the edematous episodes of hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE). Nevertheless, the role of these cells in the attack has not yet been investigated. However, as neutrophil elastase (NE) can inactivate C1-INH, it might be involved in the activation of plasma enzyme cascades. Our study intended to learn whether neutrophil cells undergo activation during edematous attacks.

We studied blood samples, obtained from 26 patients with C1-INH-HAE during symptom-free periods, as well as during edematous attacks and from 26 healthy volunteers. The following parameters were measured: neutrophil granulocyte count, and the levels of NE, myeloperoxidase (MPO), pentraxin 3 (PTX3), C5a, Factor H, interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-alpha).

Neutrophil granulocyte count was higher during attacks than during symptom-free periods ($p=0.011$), and the same was seen for NE ($p=0.003$), MPO ($p<0.001$), and PTX3 levels ($p=0.041$). There was a strong positive correlation between NE and MPO levels during attacks ($p<0.001$, $R=0.709$). Furthermore, IL-8 and TNF-alpha levels were also elevated during attacks, compared with the symptom-free period ($p=0.030$, $p=0.020$). By contrast, C5a and Factor H levels were not different in blood samples obtained during attacks or in the symptom-free period. Similarly, no differences could be detected between the study parameters measured in blood samples from symptom-free patients, or from healthy controls.

Increased neutrophil granulocyte count was associated with elevated NE and MPO levels – this suggests neutrophil activation during edematous attacks. The strong positive correlation between NE and MPO levels along with the elevated PTX3 concentration may indicate the expression of NETs. Elevated cytokine levels also imply systemic activation.

Supported by the grant OTKA-NKTH 10088 and 112110.



O-07

DEVELOPMENT AND CHARACTERIZATION OF AN ANTI-FXIIA MONOCLONAL ANTIBODY FOR THE TREATMENT OF HEREDITARY ANGIOEDEMA

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Background: Hereditary angioedema (HAE) is characterized by recurrent and potentially life-threatening bradykinin-mediated edema. There is an unmet medical need for a safe, effective and long-lasting prophylactic treatment for HAE. We have generated a potent and specific FXIIa blocking antibody and demonstrated that targeting FXII represents a promising therapy for HAE.

Methods: A human phage display antibody library was used to generate a fully human recombinant anti-FXIIa antibody. *In vitro* assays were performed to determine its specific and potent inhibition of FXIIa. The *in vivo* efficacy was investigated in various murine edema models.

Results: The anti-FXIIa mAb 3F7 is a potent and highly specific inhibitor of the proteolytic activity of FXIa. 3F7 binds to rabbit, mouse, non-human primate and human activated FXII. Administration of 3F7 abrogated skin edema induced by contact activation triggered by mast-cell released heparin in mice. 3F7 was also shown to abolish bradykinin-mediated increase of vascular permeability induced by the angiotensin-converting enzyme (ACE) inhibitor captopril in C1-inhibitor deficient mice. Comparison of 3F7 with current HAE therapeutics in these murine edema models revealed that 3F7 has potent and prolonged efficacy. CSL312, an engineered variant of 3F7 with improved affinity and potency, effectively inhibited dextran sulphate-triggered FXII contact activation and bradykinin formation in plasma of healthy donors and HAE patients.

Conclusions: The preclinical data provide strong evidence that CSL312, a potent and specific inhibitor of FXIa, represents an effective acute and prophylactic treatment option for HAE.



O-08

THE GENETICS OF C1-INH-HAE: THE ICEBERG SLOWLY EMERGES

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Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) is caused by SERPING1 mutations and is inherited as an autosomal dominant trait with incomplete penetrance. This gene is a prime example of mutagenic liability resulting to pronounced allelic heterogeneity. Up to 450 different disease-related SERPING1 mutations have been detected scattered over all the 8 exons of the gene. A large variety of mutation types have been observed, including defects representing extremely rare mutagenesis events. However, in ≈5% of the cases no mutation can be detected in the coding region of SERPING1, indicating that a causative defect modifying C1-INH expression may be located in an intronic or an untranslated region. Appropriate functional or segregation studies in kindreds have been carried out only on a fraction of SERPING1 defects, whilst the linkage between most of them and the disease has been deduced from their consequences on the structure/function properties of C1-INH. Therefore, it remains elusive whether the presence of all SERPING1 alterations considered so far as casual, are isolated or expressed in tandem with either functional defects on the genes involved in the function or degradation of bradykinin, or display SERPING1 polymorphisms and mutations of unknown functionality.

The clinical expression of C1-INH-HAE varies widely amongst patients presenting additionally great intra-familial heterogeneity, but responsible factors remain one of the oldest unsolved problems of the disease. Recent evidence indicates that patients carrying missense mutations have significantly lower probability of manifesting C1-INH-HAE attacks before the 10th year of age than those with all other *SERPING1* defects. Moreover, it was recently shown that the *F12-46C/T* polymorphism is an independent genetic factor strongly correlated with the age of disease onset and the need for long-term treatment (negatively). Since patients with an early disease onset display a more severe disease phenotype, carriage of *SERPING1* missense mutations or *F12-46C/T* may represent a significant predictor of disease phenotype. The emerging picture is that C1-INH-HAE genetics disposes a challenging complexity the elucidation of which would not only elucidate the involved mechanisms but also lead to a more effective individualized treatment.



O-09

SERPING1 GENE MUTATIONS IN A BRAZILIAN COHORT WITH HEREDITARY ANGIOEDEMA

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Background: Angioedema is characterized by asymmetric, often recurrent and intermittent swelling of the deeper dermal tissues. Acute episodes can involve the face, tongue, gastrointestinal/ genitourinary tracts, and larynx, which can lead to death due suffocation. Severity, frequency and localization of edema attacks are highly variable among patients, even in members of the same family. Considering that there are few statistics and studies focusing patients affected by HAE in the Brazilian population, the purpose of this study was to determine the disease-causing mutations in the SERPING1 gene.

Methods: The SERPING1 gene promoter and coding region of 52 individuals from 18 unrelated families who reported recurrent episodes of HAE without urticaria and presented low levels of C1INH were sequenced by the Sanger method.

Results: In total we identified 16 different mutations: affecting the splice site in intron 2 (c.51+1G>T; c.51+2T>C), deletions in exons 3, 4, 5, 7, 8 leading to premature stop codons (c.97_115del19; c.553delG; c.775_781del7; c.1075_1089del15; c.1353_1354delGA), missense mutations in exons 3, 5, and 8 (p.N166K; p.G184R; p.L251P; p.A297T; p.A457P; p.A459D; p.R466C; p.F477L) and one nonsense mutation in exon 8 (p.R494X). Eleven mutations are not described in the literature.

Conclusion: Despite the small number of individuals, these results show a wide range of alterations in the SERPING1 gene responsible to the HAE symptoms in Brazilian patients. These findings will help to elucidate the relationship between symptoms variation of HAE and C1INH genotype.



O-10

MUTATIONS OF C1 INHIBITOR (SERPING1) GENE ASSOCIATED WITH HEREDITARY ANGIOEDEMA: IMPACT ON THE TARGET PROTEASES AND BIOLOGICAL PARAMETERS

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Rationale: Mutations in the *SERPING1* gene with subsequent C1Inh deficiency are ones of the major causative factors for Hereditary Angioedema (HAE). The objective was to investigate the mutation impact on the biological markers in symptomatic patients.

Method: Genomic DNA was extracted from EDTA blood samples. Mutation analysis was carried out by direct sequencing and multiplex ligation-dependent probe amplification (MLPA) if necessary. The associated biological phenotypes relevant to C1Inh target proteases were the C1Inh function, the C1Inh cleavage, the plasma amidase activity, the kininogen cleavage and the decrease of C4 antigenic level.

Result: Mutation carrying families have been identified (n=207). The mutations distributed in missense/nonsense (50.2%; 104/207), microdeletions/-insertions (26.6%; 55/207), mutations affecting RNA splicing activity as assayed on monocyte transcripts (7.2%; 15/207), gross deletion/duplication of ≥ 1 exon (8.7%; 19/207), with 4.2% of *de novo* mutations, extending to 478 the number of registered *SERPING1* mutations (URL hae.enzim.hu). Intermediate type HAE with the decreased C1Inh function combined with low antigenic level and the expression of the mutant allele was recognized (9.2%; 19/207). Our methods were unsuccessful for 6.8% (14/207) of index cases investigated with a confirmed HAE condition. Independently of the mutation type, and analysed from index cases, the functional C1Inh deficiency was associated always with an increased amidase activity associated with a kinin forming capacity (100%; 207/207) and a partial to complete kininogen cleavage, and incompletely with a decreased C4 antigenic level (16%; 33/207). Only the mutant L107R exhibited a partial control of contact phase, and the index case was presenting with a normal amidase activity.

Conclusion: A biological phenotype is independent of the mutation type, with permanent uncontrolled contact phase activation, but not always with a control of C1 complex activation.



O-11

THE F12-46C/T POLYMORPHISM PREDICTS THE AGE OF DISEASE ONSET IN PATIENTS WITH HEREDITARY ANGIOEDEMA DUE TO C1-INH DEFICIENCY (C1-INH-HAE)

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Background: Given the clinical heterogeneity of HAE, the prediction of its phenotype is of utmost importance regarding patients' management. Considering that *F12* gain-of-function mutations have been implicated in the HAE with normal C1-INH function pathogenesis and that increased *F12* levels may result in higher bradykinin production, our aim was to investigate the possible contribution of the functional promoter polymorphism *F12-46C/T* (rs1801020) in C1-INH-HAE clinical phenotype.

Methods: 258 patients (28 HAE type II, mean±SD age at analysis 37.8±18 years) from 113 European families with C1-INH-HAE (47 Hungarian, 34 Greek, 18 German, 14 Romanian) were studied. The *F12-46C/T* polymorphism was detected by PCR-RFLP and confirmed by direct sequencing using standard molecular protocols. The possible associations of *F12-46C/T* polymorphism with the clinical features were explored, taking also into account the *SERPING1* mutational status. Given that our patient population consisted of correlated subjects, we implemented generalized estimating equations (GEE), an extension of the generalized linear model that accounts for the within-subject correlations.

Results: 74 patients were heterozygotes and 9 homozygotes for the *F12-46C/T* polymorphism (allele frequency: 17.8%). Carriers of *F12-46C/T* exhibited a significantly delayed disease onset ($p < 0.001$) and did not need long-term treatment ($p = 0.02$). Moreover, in a GEE linear regression model with age at disease onset as dependent variable, the presence of *F12-46C/T* was significantly associated with a 7-year delay in disease onset ($p < 0.0001$) adjusting for sex and ethnicity and regardless of *SERPING1* mutational status.

Conclusions: *F12-46C/T* polymorphism is an independent genetic factor strongly correlated with the age of disease onset in patients with C1-INH-HAE. Bearing in mind that HAE patients with an early disease onset display a more severe disease phenotype, *F12-46C/T* might represent a significant predictor of disease phenotype.



O-12

HIGH HETEROGENEITY OF MUTATIONS IN THE *SERPING1* GENE AND GENOTYPE-PHENOTYPE CORRELATION IN PATIENTS WITH HEREDITARY ANGIOEDEMA DUE TO C1 INHIBITOR DEFICIENCY FROM CROATIA, SERBIA AND SLOVENIA

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Background: Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) is a rare genetic disorder characterized by recurrent oedemas and large heterogeneity in clinical presentation. We aimed to determine the spectrum of *SERPING1* mutations in Croatia, Serbia and Slovenia and to investigate the possible correlations between mutation type and disease phenotype.

Methods: A cohort of 81 well clinically characterised C1-INH-HAE patients from 43 unrelated families from Croatia, Serbia and Slovenia was recruited for genetic analysis, which included sequencing and multiplex ligation-dependent probe amplification of *SERPING1* gene.

Results: We have identified 30 different mutations; 28 in C1-INH-HAE type I, among them 9 missense, 8 nonsense, 6 frameshift, 2 splicing defects, 1 substitution affecting the promoter and 2 large deletions, and 2 mutations in C1-INH-HAE type II both affecting the Arg444. Nine mutations have not been previously described. In one patient only the homozygous variant c.-21T.C was found while in one patient no causative mutation could be identified. To investigate the possible correlation between type of mutation and disease phenotype, patients were divided into two mutation groups: group 1 (nonsense, frameshift, large deletions/insertions, splicing defects, and mutations at Arg444) or group 2 (missense, excluding mutations at Arg444). Significant differences in clinical severity score ($P = 0.02$), based on the age of disease onset, organs affected and long-term prophylaxis ever, were found between two mutation groups, with milder disease in group 2.

Conclusion: Our study identified 30 different, among them 9 novel, disease-causing mutations in C1-INH-HAE patients, highlighting the heterogeneity of mutations in the *SERPING1* gene. Furthermore, it appears that nonsense, frameshift, large deletions, splicing defects, and mutations at Arg444 might be responsible for a more severe disease phenotype in comparison to missense mutations.



O-13

DIFFERENTIAL DIAGNOSES OF ANGIOEDEMA

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Background: Diagnosing angioedema is usually straightforward for angioedema experts but may be more challenging for other healthcare professionals, e.g. emergency room physicians. This means, that patients referred with angioedema may suffer from other diseases.

Methods:an overview of differential diagnoses to angioedema will be presented based on own experiences as a dermatologist combined with a review of the literature.

Results: Cases will be presented suffering from urticarial vasculitis, acute contact dermatitis, acute hemorrhagic oedema in infancy, subcutaneous emphysema, Melkersson-Rosenthal syndrome, dermatomyositis, superior vena cava syndrome, orthostatic oedema, mb. Morbihan, drug rash with eosinophilia and systemic symptoms and dermatitis artefacta.

Conclusions: Patients referred with a diagnosis of angioedema may suffer from other diseases and physicians at angioedema centers need to be aware of possible differential diagnoses.



O-14

DISTINCT CONDITIONS SUPPORT A NOVEL CLASSIFICATION FOR BRADYKININ-MEDIATED ANGIO-OEDEMA

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Background: Angio-oedema (AO) can be attributable to bradykinin (BK) accumulation, as is the case for prototypical hereditary AO (HAO) due to C1 Inhibitor (C1Inh) deficiency. However, our clinical experience in a reference centre has shown that some patients display a clinical history suggestive of HAO, but exhibit normal C1Inh function, have no mutation in the causative genes associated with HAO (*SERPING1*, *F12*), and report no intake of drugs known to promote AO.

Objective: We sought to determine the frequency and distribution of different AO subtypes suspected to be BK-mediated (BK-AO) and defined by clinical criteria, family and patient history, with genetic and biological diagnostic (enzyme activities implicated in BK formation and catabolism).

Methods: All the files of the patients referred to our centre for suspected BK-AO were retrospectively analysed. C1Inh function, amidase activity (for factor XII gain-of-function assay) and kinin catabolism (aminopeptidase P, carboxypeptidase N, angiotensin-I converting enzyme) were performed in plasma as previously described.

Results: The distribution of the patients (n=162) was 16 and 4% with a hereditary condition with a deficiency of C1Inh or a gain of factor XII function, respectively; 2% were with acquired C1Inh deficiency; 4% and 25% were with ACEi/ARB and hormone iatrogenic BK-AO; 21% were with non-iatrogenic defective kinin catabolism; 30% were with idiopathic increased kinin formation and 6% of BK-AO were with no biological abnormality identified.

Conclusion: BK-AO may be caused by multiple inherited or acquired factors triggering BK accumulation. These causes can be identified for the majority of clinical conditions (94% of the BK-AO), e.g. using biological testing, with a small group remaining as BK-AO of unknown origin. Therefore, we propose a novel typology for BK-AO based on the imbalance of production /catabolism of BK.

Dessart P et al. *Dermatology* 2015; doi:10.1159/000371814



O-15

GENETIC VERSUS COMPLEMENT STUDIES FOR THE DIAGNOSIS OF HEREDITARY ANGIOEDEMA IN CHILDREN

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Background: The moment of testing for complement in patients with hereditary angioedema (HAE) suspicion is controversial as it has been suggested that in children aged ≤ 1 year complement testing may lead to misdiagnosis. The aim is to compare the accuracy in diagnosis using complement components level versus the genetic study in children.

Methods: Twenty-nine children studied for HAE were included in the study. Twenty-seven had positive family history. C4 and C1-INH antigenic levels were measured by nephelometry (Dade Behring, Marburg, Germany). C1-INH function was measured by the chromogenic Berichrom C1-Inhibitor assay (Dade Behring). Genetic study was also performed. Agreement between complement results (low vs. normal) and genetic study was measured by Kappa index.

Results: Nineteen children were diagnosed with HAE by means of genetic study. Group 1 comprised 9 children (4 HAE) aged ≤ 1 year. Group 2 included 20 children (15 HAE) aged > 1 year. Complement levels were significantly lower in patients with HAE diagnosis in both groups.

All the patients with HAE showed low levels of fC1-INH and C1-INH in both groups. Four children without HAE in group 1 showed low levels of C4. None of them showed low levels of C1-INH neither f-C1-INH. Kappa index was 1 for both C1-INH and f-C1-INH ($p=0.003$) but 0.18 for C4 ($p=0.34$) in this group. Nevertheless in group 2, only one patient without HAE showed low levels of C4, and 1 patient with HAE showed normal levels of C1-INH. Kappa index in this group was 0.86, 0.88 and 1 ($p=0.000$) for C4, C1-INH and f-C1-INH respectively.

Discussion: The agreement with fC1-INH levels is perfect, and very high with C1-INH in both groups. C4 shows a good agreement with genetic testing in group 2, but poor in group 1. An isolated determination of C4 levels is not sufficient to rule out HAE in children aged ≤ 1 year, whereas f-C1INH is a definite determination.



O-16

A NEW ANGIOEDEMA BIOLOGICAL DIAGNOSTIC C1-INHIBITOR FUNCTION USING CONTACT PHASE PROTEASES AS TARGET

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Background: C1 Inhibitor (C1Inh) function in plasma was commonly evaluated using the residual activity of C1s protease, not involved in the angioedema process. Control of prekallikrein (pKK) activation by C1Inh represents the major mechanism for angioedemapatient protection.

Objective: We aim to validate a biological diagnostic of angioedema using C1Inh function after reconstitution of contact phase. A special interest was on females presenting with oestrogen-dependent angioedema triggered by oestrogen. A secondary interest was on C1Inh mutants with distinct binding properties to target C1s protease or contact phase.

Method: C1Inh function with C1s protease target was performed using conventional method. Reconstitution of contact phase using the purified components, with C1Inh standard or the plasma sample. The kinetics of the amidase activity was followed using Pro-Phe-Arg-pNA, in conditions independent of the alpha2-macroglobulin. Receiver operating characteristics (ROC) were used to calculate the assay diagnostic performance.

Result: The calibration curve was built using C1Inh standard (threshold limit $0.10 \times 10^{-3} \text{U}$, *i.e.* 0.2pmol). The reference interval was established from healthy individuals (n=281; women median: 0.74U/mL; men median: 0.85U/mL). The female values were lower due to estrogen, yet C1Inh function remained within the reference interval. The ROC curves calculation provided the optimum diagnostic cut-off value for women (0.36U/mL; AUC: 0.99; sensitivity: 93.48%; specificity: 99.37%) and for men (0.61U/mL; AUC: 1; sensitivity: 100.0%; specificity: 100.0%). Mutants I271T and R378C developed a better control of C1s protease than that of contact phase, whereas mutant L107R inversely exhibited an active control of contact phase.

Conclusion: The performance outcome provided features suitable for angioedema diagnostic or follow-up. Established by means of the kinin formation process, this assay should be preferred over the method based on a C1s protease target.



O-17

ELISA TO MEASURE NEUTRALIZING CAPACITY OF ANTI-C1-INHIBITOR ANTIBODIES IN PLASMA OF ANGIOEDEMA PATIENTS

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Background: Neutralizing autoantibodies (NAb) against plasma serpin C1-inhibitor (C1-inh) are implicated in the rare inflammatory disorder, acquired angioedema (AAE). There is insufficient understanding of the process of antibody formation and its correlation with disease progression and severity. We have developed an ELISA for detecting neutralizing capacity of anti-C1-inh positive plasma samples that can be used to study changes in NAb repertoire in patient plasma over the course of disease.

Methods: The ELISA is based on the specific interaction of active C1-inh with its physiological substrate C1s. Decrease in the amount of C1s bound to immobilized C1-inh in presence of test samples is proportional to the neutralizing capacity of the sample. Assay specificity, intra- and inter-assay variation and assay cut-off are determined using specific anti-C1-inh antibodies. Assay capability is demonstrated using plasma samples from AAE patients.

Results: The assay is specific to a neutralizing anti-C1-inh antibody and shows no interference by a non-neutralizing anti-C1-inh antibody or by the plasma matrix. Intra-assay and inter-assay variations are determined as 17 and 18 % respectively. Neutralizing capacity of antibody positive AAE patient plasma samples (n = 16) with IgG or IgM type antibodies is readily determined. All antibody positive patient samples show positive neutralization capacity.

Conclusion: We have developed a robust, specific and semi-quantitative assay to detect the neutralization capacity of plasma samples containing anti-C1-inh antibodies. This assay can be an important tool for the study of clinical implications of anti-C1-inh NABs.



O-18

IMMUNOGENICITY OF RHC1INH IN SUBJECTS WITH ALLERGIES TO COW'S MILK OR RABBITS

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Background: Recombinant human C1 inhibitor (rhC1INH) is purified from the milk of transgenic rabbits. rhC1INH contains low amounts (<0.002%) of host-related impurities (HRI). These HRIs could trigger hypersensitivity reactions in subjects with rabbit allergy (RA) or with cow's milk allergy (CMA). We conducted a clinical trial to assess the immunogenicity of rhC1INH in healthy subjects with CMA and /or RA.

Methods: Subjects with CMA and/or RA (medical history) with sensitization confirmed by positive skin prick test (SPT) against cow's milk and rabbit dander were challenged by SPT with rhC1INH (1:10 and undiluted) followed by intracutaneous skin testing (ICT) (1:100, 1:10, and undiluted). Specific IgE (sIgE) was measured at baseline. Blood was also sampled for basophil activation testing (BAT). Subjects who tested negatively to the SPT and ICT returned at least 2 weeks later for a subcutaneous challenge (SC) with undiluted rhC1INH at increasing doses (0.14mL, 1.4mL, 4.2mL, and 8.2mL).

Results: 26 subjects were enrolled; 20 had RA and 11 had CMA (5 had both RA and CMA). Of the 20 subjects with RA and sensitization confirmed by SPT, 18 had sIgE for rabbit dander > 0.35 kU/L. Of the RA subjects, all were negative for SPT with rhC1INH, 18/20 were negative for ICT. 2 subjects were lost to follow up after a negative SPT and ICT. 16 RA subjects were then given SC challenge and had no allergic symptoms. 2 RA subjects had erythema on ICT with standard rhC1INH concentration greater than positive control histamine by 1mm and 4mm, and per protocol did not continue to SC challenge. Of the 11 subjects with CMA and sensitization confirmed by SPT, all had specific IgE > 0.35 kU/L for cow's milk. All 11 subjects with CMA, had negative SPT and ICT with rhC1INH and tolerated the SC challenge. None of the 26 subjects had positive BAT to rhC1INH.

Conclusion: No subjects with rabbit allergy and/or CMA had confirmed clinical allergy and/or lab evidence of hypersensitivity to rhC1INH.



O-19

SAFETY AND EFFICACY OF RHC1INH FOR THE TREATMENT OF HAE ATTACKS IN PEDIATRIC PATIENTS

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Background: Symptoms of hereditary angioedema (HAE) due to C1 inhibitor deficiency usually become apparent in the first two decades of life. Recombinant human C1 inhibitor (rhC1INH) is currently approved as on-demand treatment in adolescent (US only) and adult patients. Despite the need for advanced therapies, there are limited studies in pediatric HAE patients. We conducted a study (NCT01359969) to evaluate the efficacy and safety of rhC1INH for the treatment of HAE attacks in children. An interim analysis of this ongoing study is presented here.

Methods: Patients age 2-13 years old with functional C1INH levels < 50% of normal were enrolled and could be treated when presenting with an attack of at least moderate severity. Patients were treated with rhC1INH 50 U/kg (max 4200 U), with an option for a second dose, and could be treated for up to 10 attacks. Efficacy endpoints were time to beginning of relief and time to minimal symptoms, assessed by the patient (or their parent) using a visual analogue scale (VAS) and by physicians using an Investigator Score (IS). Safety and tolerability evaluation was based on clinical laboratory results and adverse events.

Results: 26 patients from 5 sites in Europe and Israel were enrolled in the study. Eight patients were treated for 28 attacks as of the date of the interim analysis. There were 12 abdominal attacks, 8 peripheral, 4 genitourinary, 2 oro-pharyngeal-laryngeal, and 2 facial attacks treated. Median time to beginning of relief was 60 min by both VAS and IS. Median time to minimal symptoms was 2 hours by VAS and 4 hours by IS. A second dose was provided to 11% (3/28) of treated attacks. No related serious adverse events, including hypersensitivity reactions, were reported. Two patients had transient lymphocyte abnormalities, which resolved spontaneously, and did not recur after repeated exposure to rhC1INH.

Conclusion: The results of this interim analysis support the safety and efficacy of rhC1INH in pediatric HAE patients.



O-20

CAN DANAZOL CAUSE ERYTHROCYTOSIS IN PATIENTS WITH HEREDITARY ANGIOEDEMA?

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Background: Attenuated androgens are used – among other drugs – as prophylaxis for the edematous attacks that occur in hereditary angioedema due to the deficiency of the C1-inhibitor (C1-INH-HAE). A possible undesirable effect of these agents, erythrocytosis, is only barely documented in the literature. We intended to explore the hematological side effects of danazol in a long-term follow-up study of a large number of patients.

Methods: During the initial stage of our retrospective study, we compared the prevalence of erythrocytosis between 51 adult C1-INH-HAE patients not receiving danazol (21 males and 30 females, mean age 38 [18 to 66] years), and 210 healthy, age- and sex-matched controls. In the second stage, we analyzed the hematological parameters (white and red blood cell counts, hemoglobin level, hematocrit, platelet counts) of 41 C1-INH-HAE patients (18 males and 23 females, mean age: 38 [18 to 66] years) after 1-, 3-, and 5-year treatment with danazol 50 to 300 mg/day.

Results: We did not find a statistically significant difference in the prevalence of erythrocytosis between patients not taking danazol and healthy controls. The hematological parameters of male and of female patients remained unchanged after treatment with danazol for one, three, and five years. The only exception was platelet count, which decreased significantly ($p=0.0115$) vs. baseline in female patients who had been taking danazol for 5 years. In the majority of the patients, the measured values were within their reference ranges. Erythrocytosis occurred in a single female patient after 1-year danazol therapy; it persisted after 3 and 5 years of treatment, but did not require discontinuation.

Conclusion: Our findings show that the prevalence of erythrocytosis is not significantly higher in C1-INH-HAE patients after treatment with danazol. Nevertheless, erythrocytosis may occur as a rare adverse effect of danazol and hence, periodic monitoring of hematological parameters is necessary.

Supported by OTKA grant 100886.



O-21

DEVELOPMENT OF A CLINICAL ACTIVITY SCORE FOR HEREDITARY ANGIOEDEMA WITH C1-INHIBITOR DEFICIENCY

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Background: There is need for a disease activity or disease severity score for hereditary angioedema (Hae) with C1-inhibitor deficiency (C1-INH-HAE).

Aims: To develop an activity scale for C1-INH-HAE (HAE-AS) with sound psychometric properties.

Material and Methods: A prospective multicentre cohort study was performed in 11 countries. A clinical questionnaire was self-administered and completed by 290 adult patients with C1-INH-HAE. Patients also completed two quality of life (QoL) scales, the SF-36v2 and HAE-QoL. Rasch analysis and classic psychometric methods were used in a pre-selection of clinical items: number of attacks by location, treated attacks, emergency room visits, psychological/psychiatric treatment, missed school/work days in the last 6 months; general health; and impairment in everyday work/activities due to pain.



Results: The sample presented a mean age of 41.5 (standard deviation SD=14.7; range: 18-84) years, with 69% females. The final Rasch model with 12 items showed that the HAE-AS presented a satisfactory reliability for group comparisons (person separation index =0.748), local item independence, unidimensionality and no item bias by age or gender. The HAE-AS provided scores in a linear measure, with a mean of 10.3, SD=0.22 (range: 0-29). Further analysis with classic psychometric methods indicated that the HAE-AS linear measure presented a good internal consistency (Cronbach's alpha 0.81), moderate to high convergent validity with two QoL scales ($r = -0.33$ to -0.61) and good discriminative validity by age and gender ($p < 0.05$).

Conclusions: The HAE-AS is a short, valid, reliable and psychometrically sound measure of disease activity for C1-INH-HAE, which may be very useful for further research and clinical studies. Further studies are needed to assess the scale's sensitivity to change.

Funding: FIS PI 060843, CSL-Behring, Jerini AG, HAEi



0-22

MANAGEMENT OF HEREDITARY ANGIOEDEMA IN CHILDREN

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Background: Hereditary Angioedema (HAE) is a rare disorder caused by a deficiency of C1 inhibitor. We describe the clinical features of children with HAE.

Methods: A retrospective review of children with HAE (types I and II) currently followed at Hospital Universitario La Paz, was performed.

Results: Twenty-five children were identified. The median age was 9 years (Interquartile range (IQR) 3-14), 52% female and 92% with HAE family history, 60% paternal. The median age at diagnosis was 30 months (IQR 11-76). The percentage of symptomatic patients was 36%, of whom, 77% had their first attack before turning 10 years old. The first attack was peripheral in 6 patients, abdominal in 1, and laryngeal in another. Symptomatic children had a total of 63 attacks (2001-2015), 39 cutaneous, 19 abdominal, 4 laryngeals and 1 genital. Of all attacks accounted for, 32 had a spontaneous resolution, 1 was treated with steroids and antihistaminic, 1 with anti-inflammatory drugs, 2 increased their LTP doses and the rest with purified plasma-derived C1-inhibitor concentrate (pdhC1INH). Six surgeries were performed, all within the cervicofacial region. In 3 of the procedures, a short-term prophylaxis (STP) was performed with pdhC1INH, 1 with stanazolol and the rest had no STP. No attacks were recorded. No seroconversion was detected after treatment with pdhC1INH. Four patients were under long-term prophylaxis (LTP) with tranexamic acid at different doses. No secondary effects have been detected. The median (IQR) of complement levels at the time of diagnosis was C3 106 (92.8-118), C4 5.86 (3.34-9.14), C1INH 9.73 (7.4-12) and functional C1INH 21 (13.77-25.76). Nowadays, it is C3 102 (91.5-119), C4 5.55 (3.14-7.32), C1INH 7.71 (5.69-10.3) and functional C1INH 17.24 (12.41-22).

Conclusion: In our population the majority of children have a family history and are asymptomatic. LTP is usually performed with AFs, which are secure. STP and treatment of acute attacks are successfully performed with pdhC1INH.



O-23

CAN ALLERGIC DISEASE INFLUENCE THE MANIFESTATIONS OF HEREDITARY ANGIOEDEMA AND COMPLEMENT PARAMETERS?

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The severity and the time of onset of the edematous episodes of hereditary angioedema resulting from C1-inhibitor deficiency (C1-INH-HAE) cannot be predicted in advance. During an allergic reaction, heparin released by mastocytes, as well as the allergen-activated complement system both can influence the occurrence of symptoms. We investigated whether there is any relationship among edematous manifestations, complement parameters, the occurrence of allergic conditions, and IgE levels.

The patients recorded their allergic symptoms on a questionnaire. We measured total IgE level along with inhaled antigen-induced, and antigen-specific nutritive IgE levels (20 forms of each), as well as the eosinophil cell count. These were then compared with the complement levels measured during the actual or the nearest year, and with the frequency of attacks of various locations.

Of the 130 C1-INH-HAE patients (57 males, 73 females, mean age 40 (range: 3-84) years, 72 reported the occurrence of any allergic condition during their lifetime. The annual number of edematous attacks was higher in allergic than in non-allergic patients (12.58 *vs.* 6.64); however, this difference was not significant. Allergic rhinitis correlated with the incidence of facial edema, and we found a relationship between urticaria and total attack number, as well as the number of submucosal attacks. A negative correlation was detected between eosinophil cell count and C1-INH activity. Total and pollen-specific IgE levels were inversely correlated with C1q level. Specific IgE positivity was related to the elevation of total IgE level.

Allergic disorders are more common among C1-INH-HAE patients than in the general population. Organ involvement in allergic disease may influence the location and incidence of edema formation. Eosinophil cells (and the substances released during their activation), as well as the allergen-induced, enhanced complement activation may also have their roles in the occurrence of attacks.

Supported by the grant OTKA-NKTH 100886.



O-24

ASYMPTOMATIC BACTERURIA INCREASES THE RISK OF EDEMATOUS ATTACKS IN PATIENTS WITH HEREDITARY ANGIOEDEMA DUE TO C1 INHIBITOR DEFICIENCY (C1-INH-HAE)

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Introduction: Although urinary tract infections (UTIs) are considered among the most common infectious disorders in humans, these usually follow an uncomplicated course. Various infections may have a role in inducing HAE attacks. Further, danazol treatment has been associated with hematuria. Our study intended to evaluate the abnormalities of the urinalysis of C1-INH-HAE patients.

Methods: Urine specimens contributed by 139 C1-INH-HAE patients at the annual control visits were studied retrospectively (RBC and WBC counts, microorganisms). We analyzed these laboratory parameters in relation of the clinical symptoms and in view of the long-term danazol therapy.

Results: Taking into account 3 randomly selected urine specimens, we found that the cumulative number of edematous attacks was higher in patients with than in those without bacteriuria ($p=0.019$, $p=0.022$, $p=0.014$). Considering the same patients ($n=76$), attack number was significantly higher (14.51 vs. 8.63) in patients with than in those without bacteriuria ($p<0.0001$). The cumulative incidence of microhematuria found upon a single or repeated examination was 74,8% after the annual check-up per patient. Taking into account an observation period of 3 years, the alterations detected in the urinary sediment were unrelated to treatment with or the dose of danazol.

Conclusion: The cumulative incidence of microhematuria was substantially higher compared with the historical data of healthy individuals. As regards the background of this phenomenon, we did not find any relationship with danazol therapy. The main finding of our study was that the increase incidence of edema was associated with bacteriuria. This finding emphasizes the triggering role of bacteriuria in the occurrence of edematous episodes.

Supported by OTKA grant 100886 and 112110.



O-25

HEREDITARY ANGIOEDEMA IN SWITZERLAND: GENDER RELATED CLINICAL CHARACTERISTICS AND THERAPEUTIC MODALITIES IN 2012

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Background: In Switzerland 127 people affected by hereditary angioedema (HAE) are treated in three centers. In a retrospective cohort study we describe disease characteristics and treatment modalities of HAE patients in Switzerland for 2012. As is known, hormones influence the course of disease, therefore we intended a gender-related description.

Method: A questionnaire was sent to each patient including questions about clinical characteristics and treatment modalities.

Result: 104 patients (57 women, 47 men) with a mean age of 43y returned the questionnaire. 100 suffering from HAE type I, 2 from type II, 2 are not defined yet. Mean age at symptom onset was 8.2y in men and 11.4y in women. 79% of women and 70% of men were symptomatic. Women experienced 1300 and men 480 attacks per year. The most frequent localisation of angioedemas for both genders were abdominal, followed by extremities. Women show more symptoms of the trunk, face and complain about more head ache. Men suffer from more genital angioedemas. Larynx was affected in both genders in 15%. 74% indicated factors triggering HAE such as psychological stress/emotions, trauma/physical exertion, foodstuff / allergies and infections. A substantial trigger for women are hormones (74% women, 3% men). Women practised on demand therapy in 46% with C1-INH, in 10% with Icatibant. 33% used prophylactic medication (danazol = 13; TA = 6). Men in comparison used C1-INH in 38%, Icatibant in 2% and prophylactic therapy in 35% (danazol = 13; TA = 4). From the 26 patients with danazol 46% women and 27% men were asymptomatic. Home treatment with C1-INH is practised by 23 women and 15 men.

Conclusion: Female hormones importantly influence the course of disease. Danazol seems to be more effective in women than in men. As clinics is very individual an individualized therapy is required and women need a closer attendance. The fact that 65% of the patients on C1-INH are practicing home therapy indicates a right direction.



O-26

INTER INDIVIDUAL VARIATIONS IN SYMPTOM EXPRESSION AND CLINICAL COURSE IN MONOZYGOTIC TWINS WITH HEREDITARY ANGIOEDEMA TYPE I

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Background: Hereditary angioedema (HAE) is a rare disease with great variability of clinical expression. Variations can occur both intra- and inter-individually, even in twins with the same genetic mutation.

Case Description: We describe the case histories of 3 pairs of female monozygotic twins with type I HAE.

KW and JK had first symptoms of HAE at the age of 11 but were diagnosed 9 years later. Attack characteristics are similar in both with respect to the affected organs but differ in attack frequency. Before 2006, KW had up to 48 attacks/year and JK had approximately 4 attacks/year. Today, KW has 6-24 attacks/year and JK has 1-4 attacks/year. Both receive therapy with a human pasteurized C1 inhibitor concentrate (pdC1-INH).

In EP and SH, first symptoms manifested at the ages of 24 and 27 years, respectively. HAE Type I was diagnosed at the age of 27 years. The course of the disease is more severe in EP, with a higher attack frequency (26-36 attacks/year before 2004, now 0-4 attacks/year, including 8 laryngeal attacks during the last 6 years), compared with SH (6-7 attacks/year before 2009, attack free today). EP and SH receive pdC1-INH since 2004 and 2008.

DP and CZ had their first symptoms at the age of 5 and 3 years, but were not diagnosed with HAE until the age of 21. Both experienced attacks in similar body locations but differed in attack frequency. Whereas DP has up to 55 attacks/year, CZ had between 4 and 15 attacks/year before she died of other causes in 2013. Since 1994, their attacks are/were treated with pdC1-INH on demand.

Conclusions: Monozygotic twins with the same HAE specific mutation have inter-individual variations in symptom expression in terms of frequency and location of attacks. It could be explained by the effect of different polymorphisms or environmental factors which may hamper the elucidation of the background effects of heredity in disease phenotype...



O-27

SUCCESSFUL MANAGEMENT OF HEREDITARY ANGIOEDEMA (HAE) AND THROMBOPHILIA DURING PREGNANCY: A CASE STUDY

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Rationale: The rate of HAE attacks often increases during the second and third trimesters of pregnancy. Therapeutic options during pregnancy are limited, and patients require vigilant care and close monitoring. Hospital delivery is highly recommended, and in the case of caesarean section prophylaxis with C1-inhibitor (C1-INH) is advised. Here we present the case of a 33-year-old woman with type I HAE who suffered seven spontaneous abortions between November 2000 and October 2011.

Methods: Thrombophilia screening and C1-INH self-administration training was performed at the Haemophilia Centre Rhine Main.

Results: The patient presented in March 2013, experiencing ~2 HAE attacks per month. A diagnosis of thrombophilia was initially excluded; however additional screening identified a heterozygous *MTHFR* mutation, which can be associated with spontaneous abortion. The patient was therefore treated with daily subcutaneous low-molecular-weight heparin, which was adjusted during her subsequent pregnancy. The frequency of HAE attacks increased during the second and third trimesters, which were treated with individualised C1-INH replacement therapy. The patient self-administered pdC1-INH concentrate for each attack early, during the prodrome phase. All attacks were treated successfully and safely; the combination of this with the thrombophilia treatment allowed the patient to undergo caesarean section and give birth to a healthy girl at week 39. During the breast feeding phase the frequency of HAE attacks decreased slowly.

Conclusions: This unusual case involved a patient with both HAE and undiagnosed thrombophilia, who suffered from a long history of spontaneous abortions. Correct diagnosis and treatment allowed childbirth, highlighting the importance of multi-disciplinary cooperation in HAE treatment and the need for an individualised management plan during pregnancy.



O-28

LAPAROSCOPIC FINDINGS DURING AN ABDOMINAL ATTACK IN AN UNDIAGNOSED HEREDITARY ANGIOEDEMA PATIENT. A CASE REPORT

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Background: Patients with hereditary angioedema (HAE) are frequently misdiagnosed and often poorly managed because of a lack of sufficient knowledge by the treating physician. Diagnosis remains for a long time undefined, time from start of the symptoms and diagnosis is lasting usually many years. Some HAE patients are probably never diagnosed properly. In undiagnosed cases, abdominal attacks frequently mimic surgical emergencies and are associated with useless investigations and in some instances unnecessary surgical procedures.

Case report: We are reporting a case of HAE patient who underwent multiple gastrointestinal diagnostic procedures. Symptoms started when she was 14 with swellings of her arms. She has got frequent limbs and genital edema and three facial attacks with one suggesting upper respiratory involvement. Her mother reported similar symptoms. Between 2010-2011 she had frequent abdominal recurrent attacks manifested as violent abdominal pain, nausea, vomiting and diarrhea and repeatedly attended ED. Repeated abdominal US examinations detected free peritoneal fluid during attacks. In Nov 2011 it was decided to perform a laparoscopic investigation. A video record was also made. This seems to be the first case report of a short film presenting images of swollen bowels floating in the ascites liquid during an abdominal HAE attack. HAE diagnosis was established only in Dec 2014 when, finally, an allergist was asking for C1inh activity (17%). Now she is pregnant and has her own Berinert for on demand treatment.

Conclusions: Increasing awareness among gastroenterologists by presenting lectures and posters as well as writing case reports and reviews about HAE may help these patients to have a proper diagnosis earlier. Reference to a center that is providing specialized treatment, care and education may improve dramatically their quality of life and prevent further invasive procedures.



O-29

MANAGEMENT OF FERTILIZATION THERAPIES IN PATIENTS WITH HEREDITARY ANGIOEDEMA

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Background: Fertilization procedures are sometimes avoided in patients with angioedema due to C1-INH deficiency because of possible worsening in angioedema attacks related to estrogen increase. We describe the management of fertilization in a group of patients with hereditary or acquired C1-INH deficiency and angioedema (C1-INH-HAE / C1-INH-AAE).

Materials and Methods: Retrospective review of fertilization therapies in patients with C1-INH-HAE or C1-INH-AAE followed-up in our centre in the last five years.

Results: Three patients with C1-INH-HAE (type I) (patients 1-3) and 1 patient with C1-INH-AAE (patient 4) attended our unit due to problems related to fertilization procedures. Patient 1 suffered an aggravation of angioedema attacks during treatment for successful artificial insemination (AI). Patient 2 had 4 in vitro fertilizations (IVFs). Preimplantational genetic diagnosis was performed in the first IVF with selection of a healthy embryo resulting in pregnancy, which ended with a spontaneous abortion. Ovule donation was required in the other three IVFs: second IVF failed; during the third IVF she had left ovary and ovarian tube extirpation due to an endometrioma. The fourth IVF resulted in a pregnancy with HAE worsening. Patient 3 suffered a tubercular abscess and pelvic inflammatory disease after unsuccessful AI. She was treated with antibiotics. No aggravation of angioedema happened. Patient 4 was diagnosed with C1-INH-AAE due to the beginning of angioedema attacks during IVF. She got a twin pregnancy, but it was not viable.

Attenuated androgens were avoided during IVF and AI (Patient 2) and on demand treatment with C1-INH concentrate (pdC1INH) was prescribed to all the patients. Intermittent long term prophylaxis with pdC1INH 1000 U every 3-7 days was prescribed in Patients 2 and 4.

Conclusions: Fertilization therapies might cause an aggravation of angioedema in patients with HAE-C1-INH, which could be managed by on-demand and intermittent LTP with pdC1INH.



O-30

THE INTERNATIONAL HAE NURSES ORGANIZATION (HAE-INO) – FIRST STEPS

Christine Symons

No abstract has been submitted.

O-31

PRELIMINARY RESULTS OF THE HAE NURSES ONLINE SURVEY

Karin Andritschke

No abstract has been submitted.



O-32

THE RELATIONSHIP BETWEEN PREMONITORY SIGNS AND SYMPTOMS ("PRODROMES") AND THE ONSET OF HEREDITARY ANGIOEDEMA ATTACKS

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Background: Premonitory symptoms ("prodromes") are reported by a majority of patients with hereditary angioedema (HAE). They include subjective and objective signs and symptoms, and may precede the attacks by many hours. Previous studies had confirmed that prodromes are more frequent than previously assumed. It was proposed that they might provide important clues to the understanding of the patients' illness trajectory and may assist in early detection of HAE attacks. This preliminary study was aimed at understanding the association between prodromes and attacks by comparing similar dimensions (i.e. configuration, location, severity, duration, organ dysfunction and emotional burden) in relevant organ clusters.

Methods: Preliminary retrospective study of 15 HAE patients (6 men, 9 women, mean age 26.6 years, range 9-47) was performed by using specific questionnaire, constructed and refined based on previous instruments. Data was obtained on patients' experience with prodromes, predictability of an incoming attack, the disease course and its burden on daily life.

Results: Most patients (%86.6) were able to identify and locate the various dimensions of the prodromes and differentiate them from the attacks. 64.3% could predict oncoming attack based on prodromes in more than half (57%) of the attacks. Personal interviews could discern the patients' personal experience with stress, coping patterns, adaptation and disease management. Prodrome dimensions were correlated with the attack in most organ clusters, in particular within the respiratory ($r=0.50$) and urinary ($r=0.56$) domains. Internal consistency of the various components of the questionnaires was high (Cronbach alpha 0.613 to 0.911). Multiple regression analysis showed good correlation between prodromes and attacks in all organ clusters.

Conclusions: This preliminary retrospective study indicates that prodromes and attacks are correlated in severity, location and degree of dysfunction.



O-33

HEREDITARY ANGIOEDEMA WITH NORMAL C1 INHIBITOR: EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS OF 136 SPANISH PATIENTS

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Background: Data are still limited regarding Hereditary Angioedema with normal C1Inhibitor (nC1INH-HAE). Up to now, Spain shows a rate of cases higher than other Western European countries. The aim of this study is to describe the epidemiological and clinical aspects of nC1INH-HAE patients from five different tertiary Spanish hospitals.

Methods: Retrospective observational study of 136 symptomatic patients belonging to 72 unrelated families; detailed medical histories; complement factors determinations (C4, C1q, C1-Inhibitor level and activity) and screening for mutations in exon 9 of the *F12* gene (asymptomatic carriers not included).

Results: 110 symptomatic patients (55 families) carrying the p.Thr328Lys mutation [FXII-HAE] (95% females [F], 5% males [M]) and 26 patients (17 families) with no FXII mutation [unknown-HAE] (92% F, 8% M). Caucasian 96% and Maghrebi origin 4%. Mean age at onset: F 23.4 years (14-44), M 67.2 years (14-78). Female phenotypes: oestrogen (OE) dependency 67.8%, OE sensitivity 28.8% and OE independent 8.5%. Triggers: OE-containing contraceptives 97.8% (89/91); pregnancy 53.9% (35/65); angiotensin-converting enzyme inhibitors use 100% (6/6), angiotensin receptors blockers 0% (0/6), gliptins 50% (1/2); Others (stress, pressure, trauma, infections) 37.5%. Location of attacks: face/perioral 89%, upper-respiratory tract 44.9% (4 patients required intubation), abdomen 42.7% (9 patients required acute abdominal surgery), limbs 44.9%, genital area 11%. Nine female patients required long-term therapy: 7 with tranexamic acid (TA) (one of them combined with C1 inhibitor concentrate –pdhC1INH-, and another one with desogestrel), 2 of them with desogestrel and another 2 with attenuated androgens. 23 attacks (13 patients) successfully treated with pdhC1INH, 16 attacks (9 patients) with icatibant and 8 attacks (5 patients) with TA.

Conclusions: In contrast to previous reports, our nC1INH-HAE population presents a higher percentage of FXII-HAE (81%).



O-34

HEREDITARY ANGIOEDEMA WITHOUT C1 INHIBITOR DEFICIENCY: EVALUATION OF 21 FAMILIES

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Introduction: Hereditary Angioedema (HAE) without C1 inhibitor (C1INH) deficiency was first described in 2000 and later associated with mutations in the gene *F12*, encoding blood coagulation Factor XII. Clinical manifestations are similar to HAE with C1INH deficiency, including laryngeal edema but hormonal factors may also play a role. Here, we report the clinical and genetic evaluation of 21 families identified in Brazil.

Methods: The inclusion criteria were: clinical history compatible with HAE, normal quantitative and functional C1-INH levels and family history. Differential diagnosis was made. DNA samples were evaluated for the presence of mutations on exon 9 of the *F12* gene.

Results: One hundred twenty seven individuals (33M:94F; mean age: 34.9 years old) out of 21 families were evaluated for HAE without C1-INH deficiency. Eighty nine individuals (70F:19M; mean age: 38.9 years) were symptomatic. Four patients had symptoms and a family history, other family members were not available for evaluation; 2/4 had a known *F12* missense mutation (c.1032C>A). Mean age for first symptoms was 20.7 years. Triggering factors were not identified in 19/94 patients. The following triggering factors were reported among female patients: stress, 30; trauma, 23; contraceptives, 23; menses, 10; pregnancy, 9; ovulation, 2; exercise, 6; dental therapy, 4, weather, 3. Male patients related the attacks to trauma, 7 and stress, 4. The known exon 9 mutation (c.1032C>A; p.T328K) was identified in 12/21 families. Two symptomatic women had no mutation but other family members had factor XII mutated.

Conclusion: Symptomatic female patients are more frequent among the group of HAE without C1-INH deficiency (3.7F:1M). Hormonal causes may be relevant in female patients but trauma and stress also have a role as triggering factor. First symptoms and diagnosis were identified during adulthood. An *F12* gene mutation could be detected in 60% of our families. Most of the families have Portuguese origin (17).



0-35

TREATMENT OF PATIENTS WITH HEREDITARY ANGIOEDEMA WITH NORMAL C1 INHIBITOR AND F12 GENE MUTATIONS

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Background: Hereditary angioedema with mutations in the gene coding for the coagulation factor XII (HAE-FXII) belongs to the forms of hereditary angioedema with normal C1 inhibitor. The efficacy of treatment including the investigational use of various drugs in patients with HAE-FXII is reported.

Methods: One man and 69 women with clinical symptoms of HAE-FXII were included. Efficacy of drugs for acute attacks was determined by recording time to first relief and time to resolution of symptoms and compared to untreated attacks. Efficacy of drugs and other measures for long-term prophylaxis was determined by recording the number of attacks before and during treatment.

Results: Eleven women were treated for 145 acute attacks of HAE-FXII with 500 or 1000 U of C1 inhibitor concentrate. Nine women with 80 treated attacks reported an excellent efficacy. Two of them reported a low efficacy in 13 further attacks. Two patients reported a moderate or low efficacy in 52 attacks. Corticosteroids and antihistamines were ineffective. Discontinuation of estrogen-containing oral contraceptives was performed in 52/69 women and led to complete symptom-freedom in 17 women and to partial improvement in 10 women. Discontinuation of hormonal replacement therapy was performed in 8/69 women and led to complete symptom-freedom in 3 women and to partial improvement in one women. Sixteen women received desogestrel for a total of 85 years. During treatment with desogestrel 15/16 women were symptom-free. Four women received tranexamic acid for a total of 14 years. During this time period the patients were symptom-free. Three women were treated with danazol for a total of 33 years and were symptom-free.

Conclusions: In hereditary angioedema with normal C1-INH and mutations in the *F12* gene various treatment measures are effective in controlling symptoms of disease completely or partially.



O-36

A RETROSPECTIVE NATIONWIDE STUDY OF ACQUIRED ANGIOEDEMA IN FRANCE

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Background: Acquired angioedema (AAE) due to C1-inhibitor (C1-INH) deficiency is rare, and publications report small series.

Epidemiology of AAE and frequency of associated diseases are not well known in France. The treatments of crises, including icatibant and C1-INH concentrates, seem variable. The aim of this retrospective study was to describe AAE in France, its manifestations, associated diseases and response to different treatments.

Methods: A retrospective nationwide study was conducted, on the basis of patients diagnosed in 2 immunology laboratories, in Paris and Grenoble, which are reference laboratories for investigation of complement and angioedema.

Inclusion criteria were a decrease of antigenic or functional C1-INH whether or not associated with anti C1-INH antibody. Exclusion criteria were hereditary and angiotensin-converting enzyme associated angioedema.

Results: Among 64 cases, 59% were women. Mean age at first symptoms of angioedema was 64, and diagnosis was made after a mean delay of 59 months. Oedema of the face and abdominal pain were the most frequent symptoms. Sixteen patients were hospitalized in intensive care unit because of laryngeal oedema, and one patient died. Anti C1-INH antibody was present in 59% of cases. Associated diseases were non Hodgkin lymphoma in 24 patients (16 marginal zone lymphoma), monoclonal gammopathy of undetermined significance (MGUS) in 20 patients. In 24% of cases no associated diseases were detected.

Prophylaxis with tranexamic acid was effective in 77% out of 35 patients, rituximab in 77% out of 27, chemotherapy in 75% out of 9, whereas glucocorticoids response was low: 38% out of 13 patients. Icatibant relieved symptoms in all 36 patients treated, whereas C1-INH concentrate was effective in 80%.

Conclusion: Our results, of the largest series to date, confirm the association of AAE with indolent lymphoma and MGUS. The benefit of rituximab, used alone or combined with chemotherapy, seems promising. Icatibant may not be used enough in this indication.



O-37

TREATMENT OF ANGIOEDEMA WITH ACQUIRED C1 INHIBITOR DEFICIENCY

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Background: Acquired Angioedema with C1-inhibitor deficiency (C1-INH-AAE) is a rarer disease than hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE). Differently from C1-INH-HAE symptom's onset occurs after the fourth decade in more than 90% of patients and family history of angioedema is absent. Plasma-derived C1-INH (pdC1-INH) or Icatibant are used to treat acute attacks, similarly to C1-INH-HAE, although clinical trials to demonstrate their efficacy in C1-INH-AAE have never been conducted. Therefore clinical experience is the only gauge of safety and efficacy evaluation. In this retrospective study we evaluated acute treatments outcomes in C1-INH-AAE.

Methods: Patients diagnosed with C1-INH-AAE and followed up at our centre from 1977 to 2014 were included in the study.

Results: 71 patients (58% female) were studied. Median age was 71 (IQR 64-79). Median age at onset of symptoms was 58 (IQR 50-66). Median age at diagnosis was 63 (IQR 55-72). Delay in diagnosis (from onset of symptoms to diagnosis) was 2.00 years (IQR 1.00–5.00). C1-INH-autoantibodies were detected in 65% of patients. Face edema was the most frequent location reported by 83% of patients; 69% of patients reported peripheral /abdominal attacks and 58% reported oral mucosa and/or glottis attacks. 79% of patients treated acute attack with one of the specific treatments: 86% used pd-C1-INH, 46% used Icatibant. C1-INH-autoantibodies were detected in 71% of patients that used pd-C1-INH; 24% of these patients became non-responsive to pd-C1-INH and switched to Icatibant.

Conclusion: Delay in diagnosis is shorter compared to C1-INH-HAE. Face edema is the most frequent location. A minority of C1-INH-AAE patients with C1-INH-autoantibodies became non-responsive to pdC1-INH treatment. In these patients Icatibant can consider a therapeutic alternative.



O-38

LYMPHOPROLIFERATIVE DISORDERS ASSOCIATED WITH THE SYNDROME OF ACQUIRED DEFICIENCY OF C1 INHIBITOR AND ANGIOEDEMA. RATE OF ASSOCIATION AND RESPONSE TO TREATMENT IN 71 PATIENTS

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Background: Expansion of B cell clones, expressed by anti-C1-INH autoantibodies, monoclonal gammopathies of uncertain significance (MGUS) or lymphoproliferative diseases (LPDs), underlay the vast majority of angioedema due to acquired C1-INH deficiency (C1-INH-AAE).

Methods: We report the long-term follow up of 71 patients with C1-INH-AAE, focusing on associated B cell disorder.

Results: Patients, 30 males, were followed for a median of 5 years (range 1-24). Median age, at present or at death, was 71 years (range 64-79 years) and onset of angioedema symptoms 57.5 (range 50-66). C1-INH autoantibodies were detected in 46 (12/46 IgG, 23/46 IgM, 4/46 IgA, 3/46 IgG-IgM, 2/46 IgA-IgM, 2/46 IgA/IgG). Twentyone patients had MGUS at onset of AAE symptoms, 12 had C1-INH autoantibodies; MGUS and autoantibodies shared the same isotypes in 11 of 12. No MGUS evolved to multiple myeloma (MM). Two patients had CD20⁺, Cyclin D1⁺ Multiple Myeloma, 23 (32.4%) had non-Hodgkin Lymphoma (NHL): indolent in 20 patients (3 Waldenstrom/ lymphoplasmocytic lymphomas, 3 small lymphocytic lymphomas, 11 splenic marginal zone lymphomas, 1 low grade CD 20⁺ CD11⁻ CD10⁻ LPD, 1 follicular lymphoma, 1 unclassifiable low B cell lymphoma), high grade in 3 (2 large B cell lymphomas, 1 mantle cell lymphoma). Fifteen NHL were diagnosed at onset of AAE or thereafter (3 months to 7 years), 8 were already present at onset of angioedema symptoms. C1-INH autoantibodies were detected in 12 patients (52% of LPDs patients). Chemotherapy was performed in 15 patients (1 CEOP, 2 R-CHOP, 1 CEOP + Fludarabine and Cyclophosphamide, 2 Chlorambucil, 4 Bendamustine R, 3 R CVP, 2 CFX / Prednisone). Splenectomy was performed in 2 patients; 2 patients were treated with Rituximab alone. 3 patients received no therapy. 13 patients had clinical and/or complement improvement after chemotherapy.

Conclusions: B cell proliferations associated with AAE present high risk of evolving to LPDs, whose treatment should be thoroughly considered.



O-39

ACE-INHIBITOR INDUCED ANGIOEDEMA (ACEI-AAE) IN THE EMERGENCY ROOM: CASE SERIES AND TREATMENT ALGORITHM

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Background: Acute angioedema poses a considerable challenge in the emergency room (ER). Recently, more cases of Angiotensin-converting enzyme-inhibitor induced Angioedema (ACEI-AAE) are being presented to the ER with acute upper airway obstruction (UAO), necessitating fast assessment and treatment. Consequently, there is a need for greater awareness among ER healthcare professionals for the symptoms and causes of acute angioedema, as well as clear algorithms for optimal management.

Methods: Hospital records of ER visits in a large tertiary academic medical center were searched to calculate the incidence of angioedema from all causes. Additionally, we present a case series of acute UAO associated with the intake of ACE-I. A practical treatment algorithm was constructed, based on expert opinion and existing guidelines.

Results: Angioedema diagnosis (ICD-9-CM code 995.1) was recorded in 31 of 118,367 ER visits (0.26/1,000) in 2013; and 60 of 120,902 (0.5/1,000) in 2014. Fifteen cases of severe UAO (9 male, 6 female, mean ages 70.9, range 51-87 years) are presented. Seven patients required endotracheal intubation and respiratory assist. One patient died of in-hospital complication. ACE/ARB brands used: ramipril=9, enalapril=3, cilazapril=1, losartan=2 cases. Subcutaneous icatibant was administered at the ER in 8 cases, resulting in fast response and relatively shorter hospitalization period. We present a practical Israeli ER guidelines, developed by a team of angioedema and emergency medicine experts, intended to improve the ER diagnosis and treatment nationwide.

Conclusions: The incidence of acute angioedema and ACEI-AAE in a tertiary center in Israel has doubled, most likely due to increased awareness of the medical teams. Consensus guidelines are expected to harmonize the treatment and improve the outcomes.



O-40

ANGIOEDEA TRIGGERED BY EDUCATION BLOCKING THE RENIN/ANGIOTENSIN SYSTEM: RETROSPECTIVE STUDY USING THE FRENCH NATIONAL PHARMACOVIGILANCE DATABASE

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Introduction: Bradykinin-mediated angioedema (AE) is a rare side effect of some medications, including angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB). In France, side-effects to treatments are reported to the national pharmacovigilance database. We used data from this database to determine the clinical characteristics and prognosis for this disease.

Methods: The national MedDRA database was searched using the term "angioedema". Patients were included if they met the clinical criteria corresponding to bradykinin-mediated AE (isolated AE without urticaria, lasting at least 12 h, resistant to treatment with anti-histamines), if their C1-inhibitor levels were normal, and if they were treated with an ACEi or an ARB.

Results: 7998 cases of AE were reported between 1994 and 2013. Among these, 436 patients met the criteria for bradykinin-mediated AE, 324 with no data on C-inhibitor and 112 (69 men, 43 women; mean age 65 years) with normal C1-inhibitor levels. On the 112 drug-AE, patients were treated with an ARB in 21% of cases (24 patients), or an ACEi in 77% of cases (88 patients), in combination with another treatment in 17 cases (mTORi for 3 patients, iDPP-4 for 1 patient, hormonal treatment for 7 patients). ENT involvement was reported in 90% of cases (tongue: 48.2%, larynx: 23.2%). The median duration of treatment before the first attack was 720 days, and the mean duration of attacks was 36.6 h. 41% (19/46) of patients relapsed after discontinuing treatment. 23 patients were efficiently treated with the bradykinin receptor antagonist icatibant.

Conclusion: It is important to sensitise the medical community to the need to report all incidences of AE to allow better characterisation of this side effect.

Keywords: angioedema, bradykinin, angiotensin converting enzyme inhibitor, angiotensin II antagonist



ABSTRACTS POSTER PRESENTATIONS



P-01

ROADS TO DIAGNOSIS IN DANISH CHILDREN WITH HEREDITARY ANGIOEDEMA

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Background: Subcutaneous and abdominal attacks are common in children with hereditary angioedema (HAE), and laryngeal attacks may occur. Establishing diagnosis early is essential. However, early complement measurements are often equivocal and genetic testing is not first choice. Original studies of paediatric HAE are few. Our aim was to survey the Danish paediatric HAE cohort and non-affected siblings for diagnostic and clinical features.

Methods: A retrospective study was conducted at the Danish HAE Comprehensive Care Centre from January 2013 to July 2014. All children with HAE and their non-affected siblings were included. The entire HAE cohort was then surveyed for other non-affected children. Information about diagnosis and symptoms was collected.

Results: We included 19 HAE patients and 18 non-affected children. Fourteen patients had developed symptoms, and age at onset ranged from 1-11 years (median 4 years). In six cases first attack was abdominal, whereas the other involved hands, feet, face, or ear, back and arms. Age at diagnosis ranged from 0-14.9 years (median 3.2 years). Ten children were diagnosed after onset of symptoms; three of these were *de novo* mutations. Median time from onset to diagnosis was 1.2 years (range 0.4 – 3 years). Nine affected and all non-affected cases were diagnosed before any symptoms. Their diagnostic roads were nearly evenly distributed in three categories. One subgroup was diagnosed by two complement measurements, one after the age of one year. The second subgroup comprised children who for various reasons were only tested once. Over time they showed no signs of HAE and were considered non-affected. The third subgroup was diagnosed by genetic testing. In some of the youngest cases this was first choice. Others had several complement measurements with borderline results.

Conclusion: Roads to diagnosis and clinical features of the Danish paediatric cohort were outlined. An emerging shift towards early genetic testing was traced.



P-02

THE DIFFERENCE OF CLINICAL AND LABORATORY CHARACTERISTICS BETWEEN HEREDITARY ANGIOEDEMA AND OTHER TYPES OF ANGIOEDEMA

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Background: Early diagnosis and treatment is key in patients with hereditary angioedema (HAE), however the diagnosis of HAE is often delayed due to the low awareness of this condition. Since distinguishing HAE from other causes of angioedema (AE) is a critical problem in emergencies, the objective of the present study was to clarify the differences between HAE and other forms of AE.

Methods: A single-center study was performed in 72 patients with AE. All patients were divided into four groups, then the medical history and laboratory data of patients with HAE at the first visit were compared to those with other types of AE.

Results: Subjects included 23 patients with HAE, 33 with mast cell-mediated AE, 5 with drug-induced AE and 11 with idiopathic AE. The age of AE onset in the HAE group (19.5 ± 8.0 years old) was significantly lower than that of other groups. A family history of AE was noted in 82.6% of HAE patients, which was significantly higher rate than that of other groups. Extremities and gastrointestinal (GI) tract AE were noted in the majority (60 to 80%) of HAE patients, in comparison to other AE types (10 to 20%). Laryngeal edema was most frequently observed in the HAE group (39.1%) compared to other groups. Suffocation was observed in 30.4% of HAE patients. Patients with low CH50 levels were limited to the HAE group. In 95.6% of HAE patients serum levels of C4 were less than the lower limit of the normal range. In our study, low C4 levels have a high sensitivity and specificity for a diagnosis of HAE (95.6% and 93.8%, respectively).

Conclusions: Consideration of the likelihood of HAE is important to distinguish HAE from other cause of AE when patients have early onset, family history, recurrent AE in the extremities and GI tract, and suffocation. A low serum level of C4 is a useful marker for the differential diagnosis of HAE over other type of AE.



P-03

EVALUATING ASSAYS OF THE CONTACT SYSTEM AS CLINICAL BIOMARKERS OF THE FXIIA ANTAGONIST ANTIBODY CSL312

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Background: Assays of the contact system such as FXIIa and kallikrein enzymatic activities and high molecular weight kininogen (HMWK) cleavage have previously been used to characterise Hereditary Angioedema (HAE) patient plasma. The aim of these assays is to represent reliable biomarkers of disease and pharmacodynamic outcomes. These assays are also useful for defining in vitro potency of candidate therapeutics. CSL312 is a human antibody targeting FXIIa with potential as a therapy in HAE and other FXII-mediated pathologies. The propensity for *ex vivo* contact activation of HAE plasma poses assay development challenges.

Methods: Plasma samples were diluted in buffer containing dextran sulphate to initiate contact activation. Chromogenic substrate, H-D-Pro-Phe-Arg-pNA (S-2302) was used to monitor enzymatic activities in normal human plasma (NHP) and HAE samples, in the presence of varying CSL312 concentrations. HMWK cleavage was monitored in plasma by western blotting and densitometry using an anti-HMWK light chain antibody. Activation in protease inhibitor-infused plasma was compared with citrated plasma samples.

Results: S-2302 slowed the rate of FXIIa-mediated activation consistent with competitive FXIIa inhibition. Maximal kallikrein activity in HAE plasma was reached within 2 minutes of activation. In plasma, kallikrein was the predominant enzyme cleaving S-2302. Pre-kallikrein activation was mediated via FXIIa as CSL312 blocked activation. Kallikrein levels were estimated by calibration with kallikrein spiked into prekallikrein-deficient plasma. CSL312 inhibited FXIIa-mediated pre-kallikrein activation with an IC_{50} in the range 20 – 40 nM. HMWK cleavage products in contact activated NHP and HAE plasma showed up to 5-fold increase within 5 minutes. CSL312 inhibited this cleavage.

Conclusions: CSL312 is highly potent in assays of FXIIa-mediated kallikrein activity in HAE plasma. These biomarker assays show promise for monitoring CSL312 pharmacodynamic effects.



P-04

BIOTECHNOLOGICAL FLUORESCENT PROBES FOR BOTH TYPES OF BRADYKININ RECEPTORS

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Background: bradykinin B2 receptors (B2R), and perhaps B1 receptors (B1R) as well, are key molecular actors in the physiopathology of mast-cell independent angioedema states. In the absence of validated anti-receptor antibodies and in accord with docking models of ligands to each receptor, we developed high affinity fluorescent probes that are fusion proteins composed (from N- to C-terminus) of a 27-28 kDa fluorescent protein (FP), a spacer and a specific ligand for either the human B2R or B1R.

Methods: conventional molecular biology methods were exploited to construct vectors. Fusion protein constructions were expressed in the cytosol of HEK 293a cells, characterized with immunoblot and ELISA for FPs (concentration determination in lysates) and pharmacologically evaluated using radioligand binding assays, microscopy and cytofluorometry. Recombinant human B1R, B2R and ACE were expressed in HEK 293a cells.

Results: Enhanced green FP-maximakinin (EGFP-MK) contains an extended amphibian sequence that includes BK at its C-terminus. EGFP-MK is an agonist that binds to and is internalized via B2R in cells (endosomal labeling). The best design for a B1R ligand was the agonist FP-(Asn-Gly)_n-Lys-des-Arg⁹-BK, n = 15 being superior to 5. Cell labeling concerned mostly the plasma membrane. The binding of each probe is antagonized by a cognate non-peptide antagonist and they don't bind to recombinant ACE, contrary to small ligand peptides conjugated to chemical fluorophores. The FP can be interchanged (EGFP, mCherry, infrared fluorescent proteins) for a maximal signal/noise ratio.

Conclusions: The fusion protein probes for the B2R and B1R are tools of interest to study BK receptor expression and cycling in angioedema states, notably in a biomarker approach involving blood mononuclear leukocytes.



P-05

ARE COMPLEMENT LEVELS IN THE FOLLOW-UP OF HEREDITARY ANGIOEDEMA PATIENTS AGE-DEPENDANT?

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Background: The levels of complement components have been established as a criterion for the diagnosis of Hereditary Angioedema (HAE). Our aim was to study the association between complement levels and the age of patients with HAE.

Methods: Twenty-one children diagnosed of HAE, 28% symptomatic and 47% female, regularly followed up at Hospital Universitario La Paz (Madrid), with a mean age of 8.0 years of age (± 5) were included. The mean age at diagnosis was 21.0 months (± 41.4). They had had a bianual blood test performed from their diagnosis until the age of 14. We compared levels of C1-Inhibitor (C1-INH), functional C1-Inhibitor (f-C1-INH) and C4 at different timepoints. None of the patients had attenuated androgens as long term prophylaxis.

Results: Median C1-INH (mg/dL) at 2 years (N=12) was 10,65 (IQR 9,23-11,85), median f-C1-INH (%) was 22,11 (IQR 14,18-30,51) and median C4 (mg/dL) was 6,58 (IQR 3,42-9,03). Median C1-INH at 4 years (N=9) was 9,7 (IQR 6,42-12,85), f -C1-INH 20,64 (IQR 13,49-32,42) and C4 6,85 (3,19-11,35). Median C1-INH at 6 years (N=6) was 10,25 (IQR 9,64-11,7), f-C1-INH 21,83 (IQR 13,81-34,86) and C4 8,84 (IQR 6,57-10,70). Median C1-INH at 8 years (N=11) was 6,61 (IQR 4,69-8,43), f-C1-INH 17 (IQR 10-26,07) and C4 4,97 (IQR 3,34-6,66). Median C1-INH at age 10 (N=6) was 4,7 (IQR 3,93-6,78), f-C1-INH 15,89 (IQR 10,72-22,32) and C4 3,20 (IQR 1,74-6,40). Median C1-INH at 12 years (N=6) was 7,12 (IQR 4,48-12,73), f-C1-INH 16,78 (IQR 9,08-32,78) and C4 3,8 (IQR 2,80-6,93). Finally at 14 years of age (N=6) the median C1-INH was 9,66 (IQR 5,47-14,97), f-C1-INH 15,51 (IQR 8,28-22,84) and C4 4,12 (IQR 2,47-6,81). We performed a comparative bivariable correlation between each of the timepoints without obtaining any statistically significant results.

Conclusions: We observed no variation of complement component levels depending on the patients' age for all the studied timepoints. Given the small sample, no further statistical analyses were permitted. No clear trend was appreciated.



P-06

BIOBRAD: STUDY FOR ACUTE BRADYKININ AND MAST CELLS MEDIATED ANGIOEDEMA ATTACKS BIOMARKERS

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Background: Angioedema (AE) is characterized by localized swelling; two main subtypes could be identified: bradykinin and mast cells mediated AE. We propose to carry out a prospective study evaluating the diagnostic value of different biomarkers in AE attacks.

Methods: Inclusions were made prospectively and patients were divided into 3 groups : bradykinin-mediated AE attack (group 1), mast cells mediated AE (group 2), or abdominal pain of known etiology (control group or group 3). Clinicals parameters and laboratory tests were collected at each sampling (7) : baseline (H0), 3, 6, 12, 24, 48 hours and 7 days after the beginning of the attack. Markers explored were complement components (C1 inhibitor activity and weight, C4 fraction), D-dimers, and serum VE-cadherin, a marker of vascular stress.

Results: 33 patients were included, 11 in each group. For the group 1, level of D-dimer was higher during the crisis than inclusion ($p < 10^{-3}$), D7 ($p < 10^{-3}$) and than control patients ($p = 0.01$). There were no changes in the rate of complement components. Moreover, the study of the kinetics of the VE-cadherin showed a significantly increased level during attacks in group 1 ($p = 0.01$) compared to baseline. The rate of VE-cadherin was correlated to the intensity of the attack ($\rho = 0.749$, $p = 0.04$). For the group 2, level of D-dimer was significantly higher during the crisis compared to D7 ($p = 0.04$) ; as expected, exploration of complement component was in normal value. Study of VE-cadherin rate was unremarkable for this group.

Conclusions: These results showed that D-Dimer level could be a biomarker for bradykinin-mediated AE attacks, as previously described; As expected, fraction of complement does not vary during the crisis. Finally, a marker of endothelial stress, VE-cadherin, could be considered as a biomarker for bradykinin-mediated AE attack, especially in abdominal crisis, which diagnosis is often difficult. These data need to be validated in larger cohort of patients.



P-07

MUTATIONS AND EXPRESSIONS OF C1 INHIBITOR GENE IN PATIENTS WITH HEREDITARY ANGIOEDEMA

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Background: Hereditary angioedema is an autosomal dominant disorder disease. Type 1 and 2 hereditary angioedema are due to the mutations on C1 inhibitor gene. We aim to detect C1 inhibitor gene mutations in nine probands from nine different hereditary angioedema families.

Methods: Nine probands from nine different HAE families and 53 healthy controls were recruited in this study. Peripheral blood was collected for genome DNA and mRNA extraction. All eight exons and intron-exon boundaries of the C1 inhibitor gene were amplified by PCR and sequenced. The expression level of C1 inhibitor mRNA was measured by real time PCR.

Results: Nine mutations were identified: c.289 C<T, c.538 C<T, c.794 G<A, c.44 delT, c.939 delT, c.1214_1223 delCCAGCCAGGA, c.1279 delC, c.296_303 delCCATCCAA and c.786_787insT. All mutations formed a premature stop codon that might result in the deficient expression of C1 inhibitor. None of the detected mutations was observed in the controls. The expression of C1 inhibitor mRNA was significant reduced in patients. Compared with that in controls, C1 inhibitor mRNA was 19% on average.

Conclusion: We detected nine different mutations in the C1-INH gene in nine probands with hereditary angioedema (three nonsense and six frameshift), six of which are reported for the first time. All the detected mutations led to a reduced expression of C1 inhibitor mRNA in peripheral blood and produced truncated protein without reactive central loop. Thus, these mutations were responsible for the pathogenesis of hereditary angioedema.



P-08

MUTATIONAL SPECTRUM OF *SERPING1* GENE IN THE SWISS HEREDITARY ANGIOEDEMA COHORT

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Background: The *SERPING1* gene is located on chromosome 11q12 - q13.1 and involves eight exons and seven introns. It encodes for C1-INH, a serine protease inhibitor, regulating among others the contact activation pathway. Mutations in *SERPING1* result in reduced levels (type I) or impaired function (type II) of C1-INH and cause hereditary angioedema. We aim at elucidating the mutational spectrum of *SERPING1* in the Swiss HAE cohort including 140 affected individuals.

Method: In nineteen patients from nine unrelated Swiss families affected by HAE the coding region of *SERPING1* was analyzed by next generation sequencing (Ion Torrent Personal Genome Machine). Identified mutations were confirmed by Sanger sequencing. Quantitative methods were applied to screen for structural mutations (deletion, duplications). Family specific screening methods were designed with either DNA fragment analysis or Sanger sequencing.

Results: We identified a mutation in the *SERPING1* gene in eight families. Four nucleotide substitutions: families B (Exon 4, g.9518T>A), G (Exon 6, g.13918C>G), H (Exon 8, g.22026T>C) and I (Exon 8, g.21922G>A). Two nucleotide duplications: families A (Exon 3, g.7807_7808dupTT), and E (Exon 8, g.21875dupA). One short nucleotide deletion: family F (Exon 3, g.7625delC) and one large nucleotide deletion: family C (Δ Exon4, g.8569_9924del). In one family no mutation could be identified with the applied methods. Mutations result in one nonsense (G), three frameshift (A, E and F), three missense (B, H, and I) mutations and a large in-frame deletion.

Conclusion: It is a first large HAE - population in Switzerland that is genetically characterized. Three of the identified mutations (family B, C, and G) have not been published previously. The mutations detected in families E, F, G, H and I are de novo mutations. The diversity of the identified mutations in the Swiss HAE families is in line with the allelic heterogeneity observed in studies of other populations.



P-09

UNUSUAL NOVEL MUTATION OF *SERPING1* GENE IN FAMILY WITH HEREDITARY ANGIOEDEMA TYPE 1

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Complement system represents an essential part of innate immunity and its activation is precisely regulated. One of the most important regulatory proteins with inhibitory functions is C1-inhibitor (C1-INH). This unique protein plays an important role in complement, bradykin-kallikrein and fibrin-plasminogen system. Hereditary angioedema (HAE) is a rare, life-threatening disorder caused by deficiency of C1-inhibitor. Three subtypes of HAE have been identified and well characterized.

We report a family with 11 members affected by HAE. Four males died before determination of HAE diagnosis due to laryngeal oedema. In the rest of the living family members (3 males and 4 females), the dominant location of angioedema is gastrointestinal tract. Laboratory examination revealed significant decline of C4, C1-INH concentration and function. Molecular genetic analysis was also performed. Mutation c.1371_1373delTGC, p.(Ala459del) in exon 8 of the *SERPING1* gene was detected using PCR and sequencing. No other mutation was found in coding regions and adjacent intronic sequences of the gene, including large gene rearrangements analysed by fluorescent multiplex PCR. This frameshift deletion has not been described so far, however, there are several factors in favour of presumption that it is rather a pathogenic variant. Missense mutations in neighbouring codons leading to HAE (II) phenotype have been published, all missense variants in codon 459 are predicted as damaging using SIFT and Polyphen2 prediction tools and mutation detected in our family segregates clearly with a clinical and laboratory phenotype. Based on the laboratory findings, this mutation can be connected with the typical laboratory pattern of HAE type I although it is close to the typical region of HAE type II.

We identified and described novel, previously non-described unusual mutation in *SERPING1* gene causing typical phenotype of hereditary angioedema type I in family with 11 affected members.



P-10

INCREASED PLASMA LEVELS OF ANGIOGENIC AND LYMPHANGIOGENIC FACTORS IN PATIENTS WITH ANGIOEDEMA

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Background: Angioedema (AE) is a swelling of the subcutaneous/submucosal tissue, due to a temporary vascular leakage. Different underlying mechanisms and patients' clinical characteristics allow to distinguish histamine- and bradykinin-mediated AE. C1-inhibitor (C1-INH) deficiency is found in two forms of bradykinin-mediated AE, that are Hereditary and Acquired AE. The etiopathogenesis of AE is not completely clear. There are no data on the role of angiogenesis/lymphangiogenesis in the development of AE. Angiogenesis and lymphangiogenesis, the formation of new blood and lymphatic vessels respectively, play a prominent role in pathological processes inducing the production of several mediators including Vascular Endothelial Growth Factors (VEGFs) and Angiopoietins (Angs). The aim of the study was to analyze the plasma level of angiogenic factors in patients with different forms of AE compared to healthy controls.

Methods: We evaluated 35 patients with AE due to C1-INH deficiency (A1), 25 with AE not due to C1-INH deficiency (A2) and 25 healthy donors. Concentration of angiogenic (VEGF-A, Ang1, Ang2), anti-angiogenic (VEGF-A165b) and lymphangiogenic (VEGF-C) factors was evaluated by ELISA.

Results: Level of VEGF-A, Ang1 and Ang2 was higher in AE patients than in controls. No significant difference was observed between patients of group A1 and A2. Similarly, VEGF-C was increased in A1 and A2 patients compared to controls. On the contrary, the anti-angiogenic factor, VEGF-A165b, did not differ among the 3 group. The concentration of these mediators was not related to sex, age and different clinical phenotype. Now we are investigating whether the level of angiogenic factors changes during acute attacks compared to asymptomatic periods.

Conclusions: The results of this study suggest a possible role of angiogenesis/lymphangiogenesis in the pathogenesis of AE, paving the way for the identification of new biomarkers and/or therapeutic targets for this disorder.



P-11

VASOREGULATORY ASPECT OF HEREDITARY ANGIOEDEMA: ADRENOMEDULLIN, ARGININE VASOPRESSIN AND ENDOTHELIN-1 LEVELS IN PATIENTS AND CONTROLS

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Background: Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is an autosomal dominant disorder having impaired bradykinin metabolism in its background. We previously demonstrated that endothelin-1 (ET-1) level also increases during HAE attacks. Both BK and ET-1 are potent vasoactive peptides, their vasoactive role and other vasoactive peptides have only been preliminarily studied in a fraction of our C1-INH-HAE patient cohort. In the present study we evaluated vasoactive peptide levels in an extended population assessing their vasoregulatory aspects.

Methods: The levels of ET-1, arginine vasopressin (AVP), adrenomedullin (ADM) and were measured in the plasma of 100 C1-INH-HAE patients in inter-attack periods and of 111 control subjects, using BRAHMS Kryptor technologies. In 18 of the 100 C1-INH-HAE patients, the levels of vasoactive peptides were compared in 46 blood samples obtained during attacks, and 18 blood samples obtained in inter-attack periods.

Results: There was no difference between the levels of ET-1, ADM and AVP in inter-attack samples from C1-INH-HAE patients and in the samples of controls. The levels of all three vasoactive peptides increased during HAE attacks.

Conclusion: This study demonstrated that vascular regulation during HAE attacks is affected by vasoactive peptides. Our results suggest that the cooperation of several vasoactive peptides may be necessary to counterbalance the actions of excess BK, and to terminate the attacks. Since the optimal treatment and prophylaxis are still not fully solved in HAE, our results show another important pathophysiological aspect as well as potential therapeutic targets in HAE.

Supported by OTKA 100886, 112110.



P-12

HEREDITARY ANGIOEDEMA LARYNGEAL ATTACKS: REPORT FROM THE CZECH NATIONAL REGISTRY

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Background: Hereditary angioedema (HAE) is a rare genetic disorder caused by deficiency of C1 inhibitor (C1-INH) function. Laryngeal attacks are potentially life threatening, the patients are at risk for suffocation during the attack.

The goal of this study was to analyse laryngeal attacks from the Czech national registry of primary immunodeficiencies.

Methods: We present data collected between March 2012 and December 2014. Data were collected in 4 centres intended for the diagnosis and treatment of HAE.

Results: The data of 139 HAE patients (77 females, 62 males, 120 patients (86.3%) with type I HAE; 19 patients (13.7%) with type II HAE) were available. 109 laryngeal attacks in 30 patients (19 females, 11 males; 24 patients (80%) with HAE type I patients, 6 patients (20%) with HAE type II) were recorded. The triggering factors described by the patients included stress in 8 (7.3%) attacks, infection in 7 (6.4%) attacks and injury in 2 (1.8%) attacks. However, in 80 attacks (73.4%), the triggering factor was not identified. 81 (74.3%) of laryngeal attacks were treated with icatibant, 21 (19.3%) with recombinant C1-INH, 3 (2.7%) with plasma derived C1-INH, 1 (0.9%) with fresh frozen plasma, 2 (1.8%) by increase in androgens dose. Treatment had to be repeated in 11 attacks (10.1%). The drug was self-administered in 76 (69.7%) of the laryngeal attacks, 22 (20.2%) attacks was treated in the local hospital and only 3 cases (2.8%) were treated in HAE centre. Hospitalization in intensive care unit was necessary in 2 attacks (1.8%), Emergency medical service (EMS) was used in 2 attacks (1.8%).

Conclusions: Laryngeal oedema is the most serious manifestation of HAE. In our experience it comprises more than 10% of HAE attacks. The analysis of laryngeal attacks gives further insight into their course. To prevent fatal outcome, it is essential to instruct patient how to identify the first symptoms of laryngeal attack and how to use appropriate emergency procedures.



P-13

HISTORY OF MISDIAGNOSIS IN PATIENTS WITH HEREDITARY ANGIOEDEMA PARTICIPATING IN THE ICATIBANT OUTCOME SURVEY

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Background: Hereditary angioedema (HAE) causes swelling in the skin and upper airways and pain in the abdomen due to mucosal swelling. HAE is frequently unrecognized and misdiagnosed, leading to delays in diagnosis, inadequate treatment, and potentially unnecessary procedures. We evaluated the history of misdiagnosis in patients who are participating in an international registry, the Icatibant Outcome Survey (IOS; NCT01034969).

Methods: IOS is an ongoing, observational study in which the safety and effectiveness of icatibant has been evaluated since 2009. As part of IOS, patients record any misdiagnoses received before being diagnosed with HAE.

Results: In April 2014, 318 of 512 (62.1%) patients with HAE type I/II enrolled in IOS responded to a question regarding HAE misdiagnosis. Of these, 151/318 (47.5%) had received ≥ 1 prior misdiagnosis. The most common misdiagnoses were allergic angioedema (n=86/151, 57.0%), appendicitis (n=46/151, 30.5%) and other forms of non-allergic angioedema (n=35/151, 23.2%). A wide variety of other misdiagnoses were reported, with approximately 20% being gastrointestinal disorders (excluding appendicitis). There were no substantial differences in misdiagnoses between males (46.6%) or females (48.1%), or for HAE type I (46.9%) vs HAE type 2 (53.8%). Having family members with HAE reduced the likelihood of misdiagnosis vs those without (45.2% [n=114/252] vs 62.0% [n=31/50]; p=0.030). Patients with a prior misdiagnosis had longer median delay to HAE diagnosis (13.3 years) than patients without (2.3 years; p<0.001).

Conclusions: From this large database, almost 50% of patients with HAE type I/II have previously been misdiagnosed, most commonly with allergic angioedema or appendicitis, with an increased delay in diagnosis.



P-14

SMOKING IS ASSOCIATED WITH A HIGHER INCIDENCE OF LARYNGEAL EDEMA IN PATIENTS WITH HEREDITARY ANGIOEDEMA

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Background: The factors contributing to the manifestations of hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) are many, whereas their exact underlying causes are unknown. Our study explored the relationships between smoking and the clinical characteristics of C1-INH-HAE.

Methods: We analyzed the smoking history of 120 C1-INH-HAE patients over 14 years of age, and determined the annual numbers of edematous episodes from entries recorded in the patient diaries. The study analyzed the data accumulated during the year 2012.

Results: The total number of attacks recorded by the 38 smoker and 82 non-smoker patients were not significantly different. However, the analysis of the symptoms by location revealed that over a year, smokers experienced laryngeal edema significantly more often than non-smokers did (mean frequencies: 0.9 *vs.* 0.2 attack/patient-year; $p < 0.05$). Nine patients were ex-smokers. Comparing these with non-smokers, we did not detect any significant difference in the occurrence of laryngeal edema. We analyzed the proportions of the patients who have never *vs.* those who have ever experienced laryngeal edema (once or on multiple occasions). The proportion of patients with symptomatic laryngeal edema was higher among smokers than in the non-smoker subset (11/38 *vs.* 10/82; $p < 0.05$). The risk of experiencing laryngeal edema was 2.9 times higher among smokers than in non-smoker patients with C1-INH-HAE. Multivariate logistic regression adjusted for age, gender, and type of HAE showed that active smoking status significantly ($p < 0.05$) increases the occurrence of laryngeal edema, regardless of the number of pack-years smoked, or daily cigarette consumption.

Conclusion: Smoking is a possible risk factor of laryngeal edema associated with C1-INH-HAE. It may alter the manifestation of the disease as well as its symptoms and their incidence. Therefore, quitting smoking appears to have a beneficial impact on the clinical course of C1-INH-HAE.

Supported by the grant OTKA-NKTH 100886.



P-15

EXAMINATION OF HUMORAL IMMUNE RESPONSE IN PATIENTS WITH HAE BY PNEUMOCOCCUS-, HAEMOPHILUS INFLUENZAE B -, TETANUS TOXOID AND DIPHTHERIA TOXOID SPECIFIC IGG LEVELS

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It occurs that in HAE C1 inhibitor deficiency may change the humoral regulation via the complement system. To test this, we examined HAE patients and healthy donors Pneumococcus (PCP) specific IgG, Haemophilus influenzae type b (Hib) specific IgG, Tetanus toxoid (Tet) specific IgG and Diphtheria (Diph) specific IgG levels in serum.

Methods: IgG levels of serum sample from 74 HAE patients older than 17 years and 41 healthy volunteer donor older than 17 years serum was measured using commercially available ELISA kits.

Results: In adults significantly higher PCP IgG and Hib IgG results obtained in HAE group, while the Tet IgG and Diph IgG levels showed no significant difference compared to the control values. The ratio of individuals with protective IgG levels (due to cut off values consistence with literature data: PCP IgG: 30 mg/l, Hib IgG: 1 mg/l, Tet IgG: 0,15 IU/ml, Diph IgG: 0,1 IU/ml) was found equal in the HAE and healthy group for the PCP, Tet and Diph, but for Hib HAE group showed higher proportion for patients with protective titres. The rates of individuals with protective IgG levels (%) of HAE, and healthy group: PCP: 93/83, Hib: 75/51, Tet: 97/95, Diph: 63/59.

Conclusions: Significantly stronger serological response (IgG) found in the HAE group produced against polysaccharide types PCP and Hib antigens. In contrast specific IgG levels due to Tetanus and Diphtheria toxoid vaccine with protein type antigens did not show significant difference when the patients older than 17 years. Specific IgG decays with time in the absence of booster vaccination or natural infection. Decay may hide difference between HAE and healthy groups. It is also conceivable that the responses of HAE patients against polysaccharide and protein type antigens are not equally different from the healthy subjects.

Supported by OTKA grant 100886.



P-16

HEREDITARY ANGIOEDEMA WITH C1 INHIBITOR DEFICIT DURING PREGNANCY, CHILDBIRTH AND POSTPARTUM (BREASTFEEDING) IN BRAZIL

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Background: Hereditary Angioedema (HAE) is an autosomal dominant disease caused by C1-esterase inhibitor deficit. Hormonal changes are common triggering factors. In pregnancy and postpartum, the use of prophylactic and acute treatments are restricted. Plasma derived C1 inhibitor was not available until recently and there are no previous studies reported in Brazil.

Objectives: To evaluate HAE course during pregnancy, childbirth and postpartum (symptoms and triggers factors) and the therapies indicated in these periods.

Methods: Pregnancies in the last 10 years, older than 18 years old and confirmed HAE diagnosis were selected from ABRANGHE files. Patients with associated diseases that could complicate the pregnancy or using drugs to other conditions not related to HAE were excluded. Questionnaires were applied to the patients after their consent. Ethical Committee approved the protocol.

Results: 45 questionnaires were distributed and 14 were completed with a total of 34 pregnancies: 23 deliveries and 11 abortions. Clinical characterization showed: age of initial symptoms 2-26y (mean 15.3y); age of pregnancies 15-37y (mean 27.1y); triggering factors during pregnancies and post partum were: stress (n=15) and trauma, 15/14 and 9/8, respectively. Symptoms during pregnancy were: gastrointestinal such as abdominal pain (n=10), vomiting (n=9), diarrhea (n=9) and nausea (n=9); Headache was also an important symptom (n=8). During postpartum period, abdominal pain was most prevalent (n=10). The pregnancy and postpartum periods present differences from the prior pregnancy. Prophylactic therapy was maintained during pregnancy in 21% of the women: tranexamic acid (25%) and danazol (75%). In 34 pregnancies, 32.3% were abortions (83% miscarriage). No fetal malformations were reported.

Conclusions: Abdominal edema was the most frequent symptom during pregnancy and postpartum. Each pregnancy had a different course. Frequency of abortion was higher than in non-HAE carriers.



P-17

MANAGEMENT OF HEREDITARY ANGIOEDEMA IN PREGNANT WOMEN

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Background: Pregnancy can worsen the clinical course of hereditary angioedema (HAE). We describe the management of pregnancy in a series of patients with HAE.

Methods: A retrospective review of pregnancies in patients with HAE due to C1-INH deficiency (HAE-C1-INH) (type I and II) or with *F12* gene mutation (HAE-FXII), followed at Hospital Universitario La Paz (Madrid) between 2007 and 2015, was performed.

Results: Eleven patients (9 HAE-C1-INH Type I, 1 HAE-C1-INH Type II, 1 HAE-FXII) had 13 successful pregnancies (11 spontaneous, 2 after in vitro fertilization); 2 of them are currently pregnant. Five patients were under long-term prophylaxis (LTP) prior to pregnancy: 2 with tranexamic acid (TA) (withdrawn during pregnancy) and 3 with attenuated androgens (2 stanozolol, 1 danazol) which were discontinued before pregnancy. The patient with danazol changed to TA before attempting conception, went on this drug until week 19 of pregnancy and then changed to LTP with C1-INH concentrate (pdhC1INH). Two more patients had LTP with pdhC1INH. All patients treated acute attacks with pdhC1INH, only 1 patient treated an attack with icatibant acetate during the first days of pregnancy and another patient treated some attacks with oral TA. In the 6 months prior to pregnancy the patients showed a mean of 1.1 attacks per trimester, whereas it was 8.3 in the 1st pregnancy trimester, 3.8 in the 2nd and 4.0 in the 3rd. The most common locations of the attacks were abdominal and peripheral. Eleven pregnancies came to term. In 5 of the 7 vaginal deliveries (1 of them instrumental) and in the 4 cesarean sections short-term prophylaxis was performed (pdhC1INH) without developing angioedema. One of these patients had an allergic reaction 24 hours after cesarean delivery unrelated to HAE. The 11 newborns were 8 female and 3 male and 4 out of the 10 studied had AEH.

Conclusions: The frequency of angioedema attacks increased during pregnancy. pdhC1INH was effective and safe for the treatment of HAE during pregnancy.



P-18

REAL LIFE PARADOX: THE UNAVAILABILITY OF STANDARD TREATMENT, PROVED SAFE THE USE OF THE RECOMBINANT C1-INH DURING PREGNANCY IN HEREDITARY ANGIOEDEMA PATIENT TREATMENT

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During the pregnancies of many of the hereditary angioedema (HAE) patients, an increasing number and severity of attacks is observed. The treatment is limited to plasma derived C1 inhibitor (pdC1-INH).

The aim of the study was to describe two cases of pregnant women: D.H. 26 y.o. and J.C. 23 y.o. treated during the period from Aug. 2013 to Sept. 2014 from indications of severe HAE attacks. Due to changes in the Polish pharmaceutical law, the one and only available and reimbursed treatment at the time was recombinant C1-INH (rC1INH) (Ruconest®). Since March 2014 pdC1-INH (Berinert®) has also become available. As a consequence, both of the patients were treated with rC1-INH in the first trimester, later with pdC1-INH.

Both women from families with previously diagnosed disease. The first symptoms occurred: J.C.-16 y.o., D.H.-18 y.o. In the years before the pregnancy both had very mild intensity of disease with a frequency of 1-2 attacks per year requiring treatment.

Patient D.H had an increased number of attacks to two per week and maintained that number during the pregnancy. She had abdominal attacks, accompanied in some cases with peripheral attacks. The number of attacks did not change in spite of the prophylactic treatment with tranexamic acid and rC1-INH until the 22nd week and pdC1-INH between the 22nd till 35th week. She had a premature natural delivery in the 35th week, of a healthy girl.

J.C. patient had an increased number of attacks to two per month during the pregnancy. She received on demand treatment. She used rC1-INH till the 16th week and following till delivery used pdC1-INH. In the first trimester we observed prevalence of facial and laryngeal attacks, in second and third prevalence of abdominal attacks. She had a caesarian section in the 42nd week, and a healthy boy.

No impact on the frequency of attacks was observed after switching from rC1-INH to pdC1-INH in both cases. Both recombinant and plasma derived C1-INH are safe during the pregnancy.



P-19

COEXISTENCE OF HEREDITARY ANGIOEDEMA IN A CASE OF FAMILIAL MEDITERRANEAN FEVER WITH PARTIAL RESPONSE TO COLCHICINE

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Background: Hereditary angioedema (HAE) is a very rare and potentially life-threatening genetic disease characterized by episodes of edema in various body parts including the extremities, face and airway. The disease is usually associated with attacks of abdominal pain. On the other hand, Familial Mediterranean fever (FMF) is an inherited condition characterized by recurrent episodes of painful inflammation in the abdomen, chest or joints.

Methods: In this report, we present a 15-year-old girl with FMF and undiagnosed HAE which made him partial responder to colchicine treatment.

Results: Because of the family history of HAE in her mother and aunts, recurrent swelling attacks in her extremities and partial response to colchicine treatment, we evaluated our patient for HAE. C4: 6 mg/dl (reference value: 10-40 mg/dl) and C1 inhibitor level: 0,05 g/L (reference value: 0.14-0.35 g/L) were determined low. The patient was diagnosed with hereditary angioedema type 1 and prophylactic treatment was initiated. The attacks apparently decreased.

Conclusions:HAE must be considered in differential diagnosis of the cases from whom partial response is obtained for the treatment FMF, particularly in countries where FMF is frequently encountered, because early diagnosis of HAE can facilitate prevention of life-threatening complications, such as upper airway obstruction. To our knowledge our patient is the first patient reported in the literature with the diagnosis of HAE and FMF together.



P-20

NEUROLOGICAL SYMPTOMS AND HEREDITARY ANGIOEDEMA

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Background: Local cerebral edema caused by C1-inhibitor deficiency has been considered responsible for transient neurological symptoms, but convincing pieces of evidence for direct causality between hereditary angioedema (HAE) and these symptoms are still missing.

Methods and Results: A 21-year-old woman with a confirmed diagnosis of HAE was presented to our hospital. She suffers from episodic peripheral swellings typical for HAE and a variety of neurological symptoms: seizures, limbs' weakness, nystagmus, dizziness, balance, and gait problems for last 13 years. Moreover, there is a progressive loss of vision in both eyes within last 5 years. The treatment with systemic corticosteroids and antiepileptics does not control sufficiently her symptoms. 500 units of plasma-derived C-inhibitor administered during an exacerbation temporarily diminished symptoms. Serial magnetic resonance imaging of her brain showed partially reversible hyperintense signals on T2-weighted images, located mainly in the white matter supra- and infratentorially with concomitant edema. In the report we present and analyze further results of extensive neurologic diagnostic procedures which had been performed, as well as previously proposed laboratory markers for identifying angioedema attacks, especially in case of hidden locations.

Conclusions: There are only a few reports describing seizures or hemiparesis in patients with HAE. Whether there is a true causal relationship between HAE and brain damage remains an open question and requires meticulous differential diagnosis in patients with C1-inhibitor deficiency.



P-21

SUSPICION OF MOSAICISM IN A FAMILY WITH HAE - CASE STUDY

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Background: Two half-sisters having the same father and the only daughter of one of these sisters suffer from hereditary angioedema type I. Family history regarding C1-inhibitor (C1-INH) deficiency was negative of the two half-sisters.

Methods: Samples were collected from all genetically related family members that were as follows: two half-sisters and their father, two mothers of these half-sisters, daughter of one of the half-sisters. DNA was isolated from blood and sequenced using Sanger sequencing for the *SERPING1* gene (from exon 1 to exon 8) encoding C1-INH. Copy number of each of the *SERPING1* exons was analysed by multiplex ligation-dependent probe amplification (MLPA).

Results: We found a duplication of exons 5 and 6 of the *SERPING1* gene in DNA from both half-sisters and the daughter of one of them, nonetheless no mutation was found in this region either in DNA from the father or in DNA from either mothers.

Conclusions: We suppose that mosaicism in cells of the father explains his asymptomaticity and the fully-symptomatic HAE type I in both of his daughters and in his granddaughter.



P-22

AAE TYP II CLOSELY MIMICKING HAE AS A PREMONITORING PRESENTATION OF SLE

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Authors report a case of acquired angioedema type II as a rare, possibly premonitoring presentation of systemic lupus erythematosus (SLE).

Female patient, aged 43, with late onset of angioedema, manifesting as peripheral and abdominal swelling, was admitted upon developing acute laryngeal edema in 2012. Complete examinations excluded allergic edema and HAE, and AAE was set as a possible diagnosis, most probably elicited by upper respiratory tract viral infection.

Under further in depth investigations, diagnosis of SLE was confirmed, fulfilling BILAG and SELENA / SLEDAI criteria. Further treatment included steroids and immunosuppressant.

Patient was responsive to therapy and is in stable remission with no occurrence of angioedema so far. AAE mimicking HAE is a rare syndrome; however it must be taken into consideration and thoroughly investigated.



P-23

ASCITES AS MANIFESTATION OF HEREDITARY ANGIOEDEMA - A CASE REPORT

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A 27-year-old Caucasian woman rushed into the Emergency Department with abdominal distention and pain associated with dyspnea. Her medical history revealed only hiatal hernia and lactose intolerance. At admission vital parameters were normal apart from mild tachycardia and tachypnea. Abdominal tenderness and ascites (confirmed by abdominal ultrasound) were detected. Blood tests were negative. A gynecological exam resulted negative. The patient was hospitalized and underwent diagnostic paracentesis with negative results. Colonoscopy was normal. She was treated with antibiotic and anti-inflammatory therapy. A second abdominal ultrasound showed complete resolution of ascites. She was discharged with a presumptive diagnosis of ascites secondary to "regional enteritis". Two years later the patient was hospitalized for similar clinical symptoms. Ascitic fluid exam was negative. Esophagogastroduodenoscopy showed erosive gastritis due to use of anti-inflammatory drugs. Abdominal CT scan revealed thickening of the walls of the distal duodenum and jejunal loops. The patient was discharged with a diagnosis of serositis and recurrent ascites of unknown origin. Since C4 levels were low (0,04 g/L), hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) was suspected and the patient was evaluated in our center. Quantitative and functional C1-INH resulted 9% and 19% respectively. Finally she referred episodes of post-traumatic skin edema since childhood and was diagnosed with C1-INH-HAE. Family members were also screened. Specific treatments were prescribed. She experienced further recurrent abdominal pain (2 attacks/month) and two severe attacks were self-treated with Icatibant with prompt resolution. When gastrointestinal symptoms are the dominant manifestation, C1-INH-HAE diagnosis is challenging. C4 test is a sensitive marker for C1-INH-HAE. In patients with C1-INH-HAE self-administration of specific treatments leads to a substantial improvement of the quality of life.



P-24

INTRODUCING THE INTERNATIONAL HEREDITARY ANGIOEDEMA NURSES ORGANISATION (IHNO)

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The International Hereditary Angioedema (HAE) Nurses Organisation (IHNO) was established in May 2013, during the 8th C1-Inhibitor Deficiency Workshop, in Budapest, Hungary.

All participating nurses have an extensive experience with patients with Hereditary Angioedema (C1 inhibitor deficiency) in our countries. The main purpose of this initiative is to increase the impact of expert nurses on patient management and implementation of new treatment protocols. Professor Henrietta Farkas from Hungary kindly agreed to become the Honorary President of IHNO.

The main issues discussed were:

- Is there a need for a nurse-specialist in HAE? What would be her role ?
- Does self-treatment introduce a real revolution in patients' life ?
- Was a decrease in hospitalization obtained in countries where self-treatment is implemented ?
- Is it the role of professional teams to interact with HAE support groups ?

Goals:

- To help as many HAE patients as possible to lead independent and productive lives
- To develop training programs directed at self treatment with the available intravenous and subcutaneous medications.
- To help HAE patients get easy access to all available therapies
- To raise awareness of this rare genetic disease
- To work hand-in-hand with national and international HAE and Immune Deficiency experts, and with patient associations (i.e. HAEi)

We realise that nurses who work with HAE patients comes from different disciplines such as Dermatology, Haemophilia, and Allergy etc. We would like to encourage other nurses, working across these settings to join us in our new initiative.