La diagnostica come sta evolvendo: Quali novità?

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QUALI PAZIENTI?

Angioedema ricorrente e dolore addominale ricorrente di tipo colico e/o laringedema.

Storia familiare positiva per angioedema

Anamnesi e Esame obiettivo

C4

C1 inibitore quantitativo
C1 inibitore funzionale
C1q emocromo e formula leucocitaria

Diagnosis

Clinical criteria

(1) Self-limiting, non inflammatory subcutaneous angioedema without major urticarial rash, often recurrent and often lasting more than 12 hours

(2) Self-remitting abdominal pain without clear organic etiology, often recurrent and often lasting more than 6 hours

(3) Recurrent laryngeal edema

(4) Family history of recurrent angioedema and/or abdominal pain and/or laryngeal edema due to C1 inhibitor deficiency

Diagnosis

Correct treatment of samples to be analyzed is critically important in order to obtain reliable results

Laboratory criteria

(1)C1 inhibitor antigenic levels <50% of normal at 2 separate determinations with patient in basal condition and after the first year of age

(2) C1 inhibitor functional levels <50% of normal at 2 separate determinations with patient in basal condition and after the first year of age

(3) Mutation in C1 inhibitor gene altering protein synthesis and/or function

Diagnosis can be established in presence of 1 clinical criterion and 1 laboratory criterion

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ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy

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Table 1 Demographic characteristics and laboratory assessments of Italian C1-INH-HAE patients

	Type I	Type II	Total
Patients (%)	859 (87%)	124 (13%)	983
Gender (M/F)	407/452	55/69	462/521
Median age (years)	44	45	45
Median age at diagnosis (years)	25	31	26
Antigenic C1-INH, median value (%)	21 (IR 13-25)	96 (IR 64-150)	24 (IR 14-31)
Funcitional C1-INH, median value (%)	20 (IR 10-30)	19 (IR 10-30)	20 (IR 10-30)
Antigenic C4, median value (%)	20 (IR 10-25)	21(IR 12-30)	20 (IR 11-26)

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Misdiagnosis trends in patients with hereditary angioedema from the real-world clinical setting

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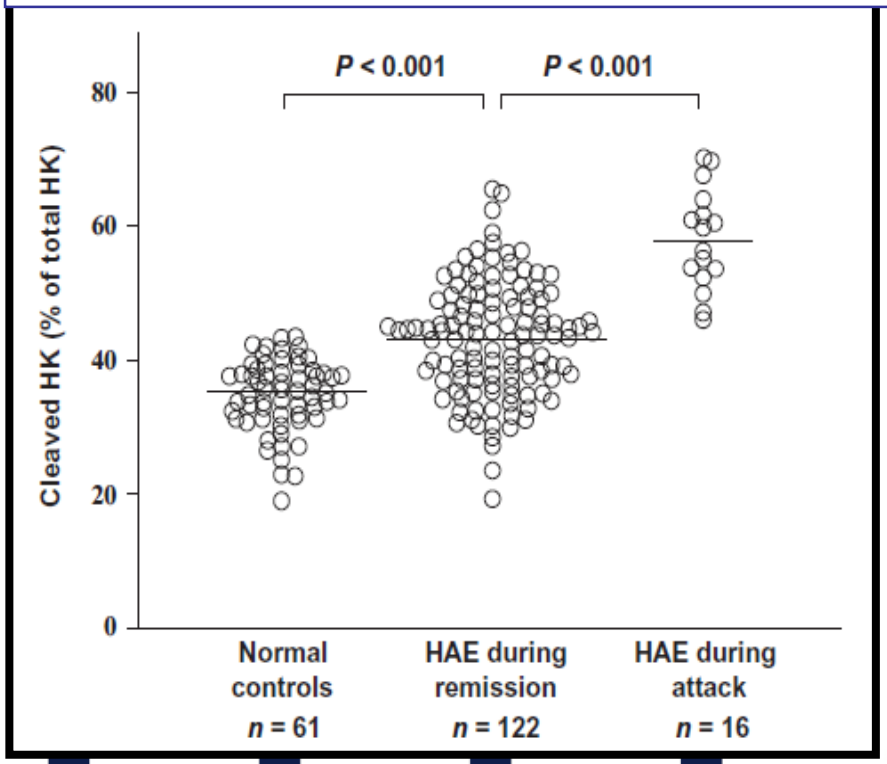
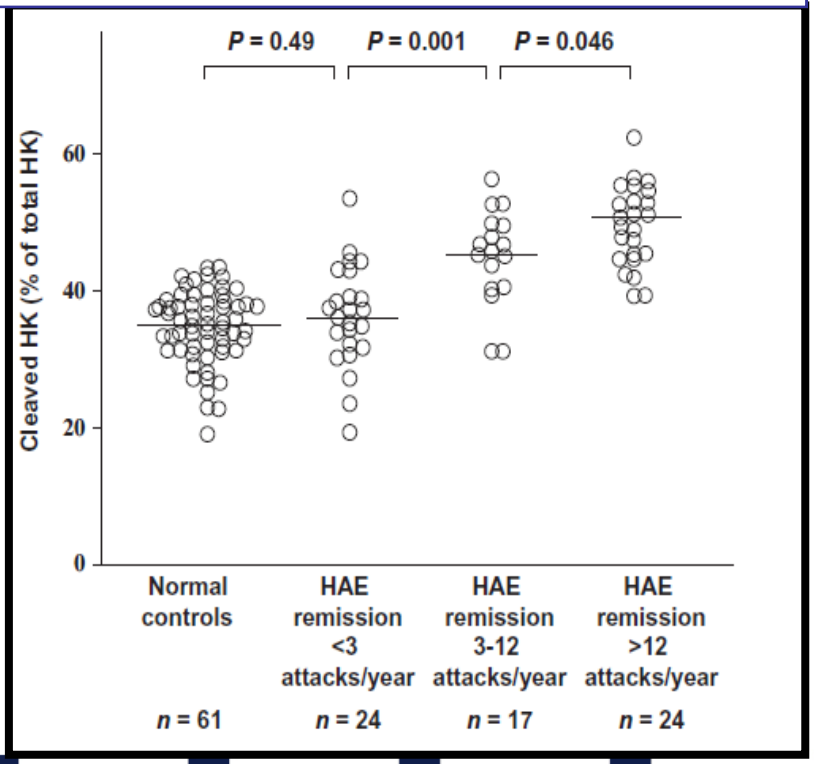
ORIGINAL ARTICLE Clinical Mechanisms in Allergic Disease

High-molecular-weight kininogen cleavage correlates with disease states in the bradykinin-mediated angioedema due to hereditary C1-inhibitor deficiency

C. Suffritti[1], A. Zanichelli[1], L. Maggioni[1], E. Bonanni[1], M. Cugno[2] and M. Cicardi[1]





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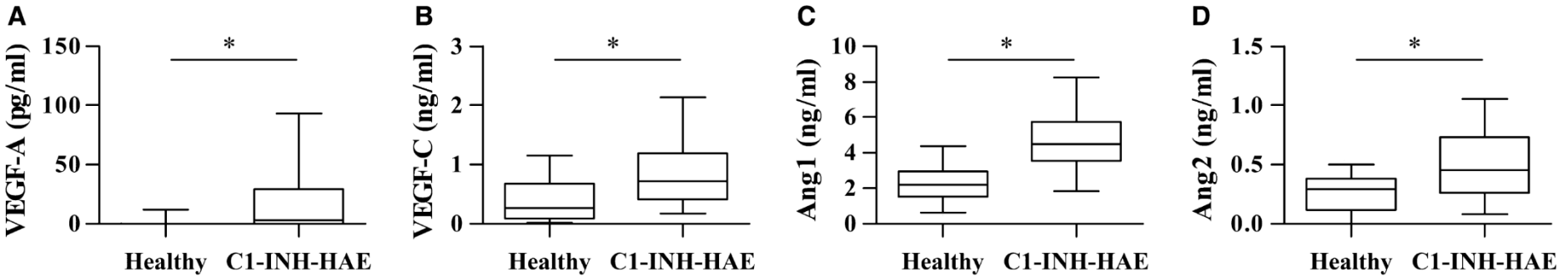
EXPERIMENTAL ALLERGY AND IMMUNOLOGY

Elevated plasma levels of vascular permeability factors in C1 inhibitor-deficient hereditary angioedema

S. Loffredo[1], M. Bova[1], C. Suffritti[2], F. Borriello[1], A. Zanichelli[2], A. Petraroli[1], G. Varricchi[1], M. Triggiani[3], M. Cicardi[2] & G. Marone[1,4]



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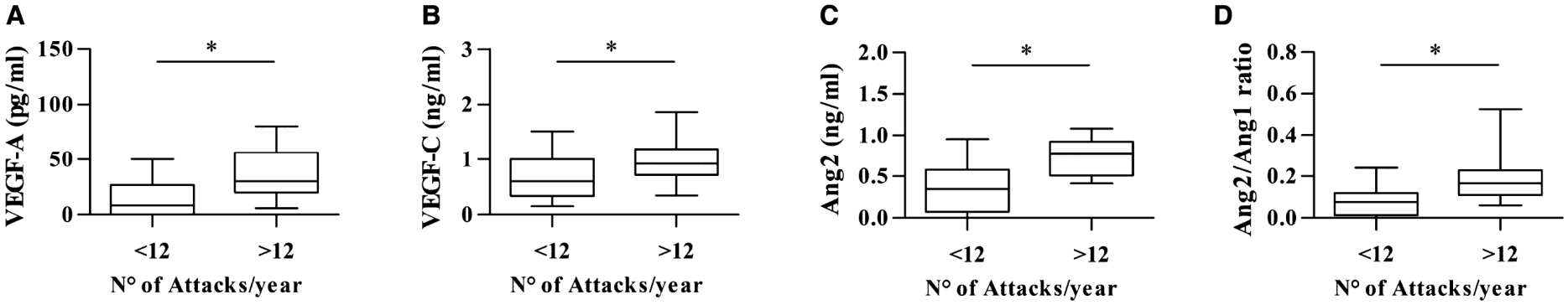

In conclusion, we demonstrate that plasma levels of VEGFs and Angs are increased in patients with C1-INH-HAE, and they further increase in patients experiencing a higher number of angioedema attacks per year. Thus, VEGFs and Angs stand as candidate biomarkers of C1-INH-HAE severity. Based on this observation, we hypothesize that these factors along with an increased release of BK induce a state of 'vascular preconditioning' that may change the threshold for the development of angioedema attacks. Pathways modulating 'vascular preconditioning' could represent new targets for increasing resistance to angioedema recurrences.

Loffredo S et Al Elevated plasma levels of vascular permeability factors in C1 inhibitor-deficient hereditary angioedema. 2016

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Hereditary C1 inhibitor deficiency is associated with high spontaneous amidase activity

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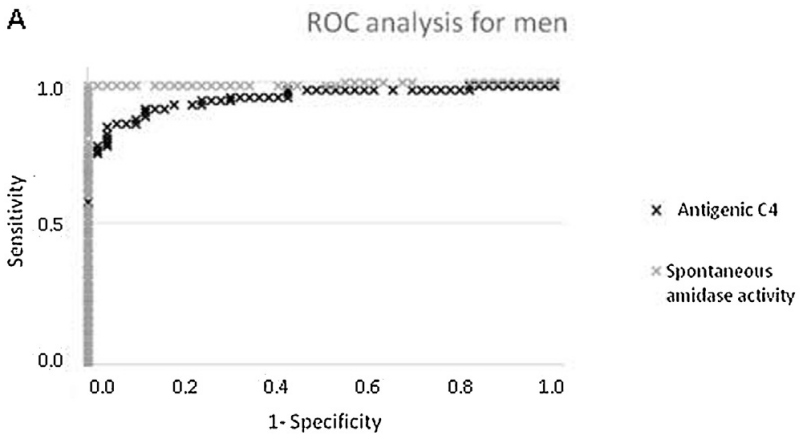

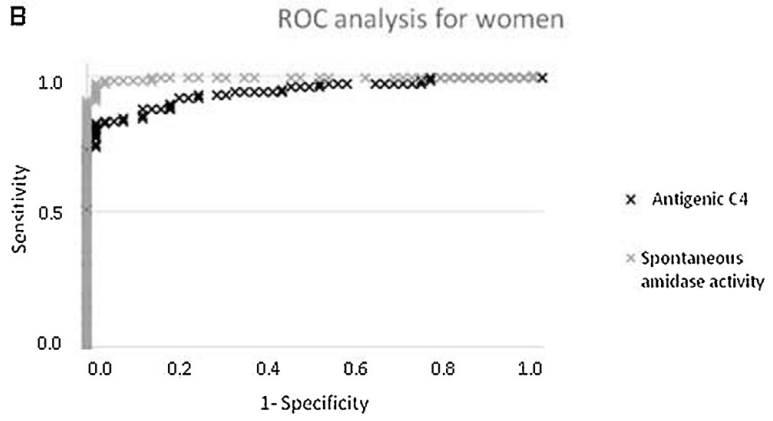

Conclusion: The spontaneous amidase activity assay should replace antigenic C4 level testing and should be tested along side the C1Inh function for both AE screening and follow up of HAE

Regarding the established cut-off values, 50 false negatives were associated with the established antigenic C4 levelcut-off, and 3 false positives and 4 false negatives were associatedwith the spontaneous amidase activity assay cut-off.

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Shortened Activated Partial Thromboplastin Time May Help in Diagnosing Hereditary and Acquired Angioedema

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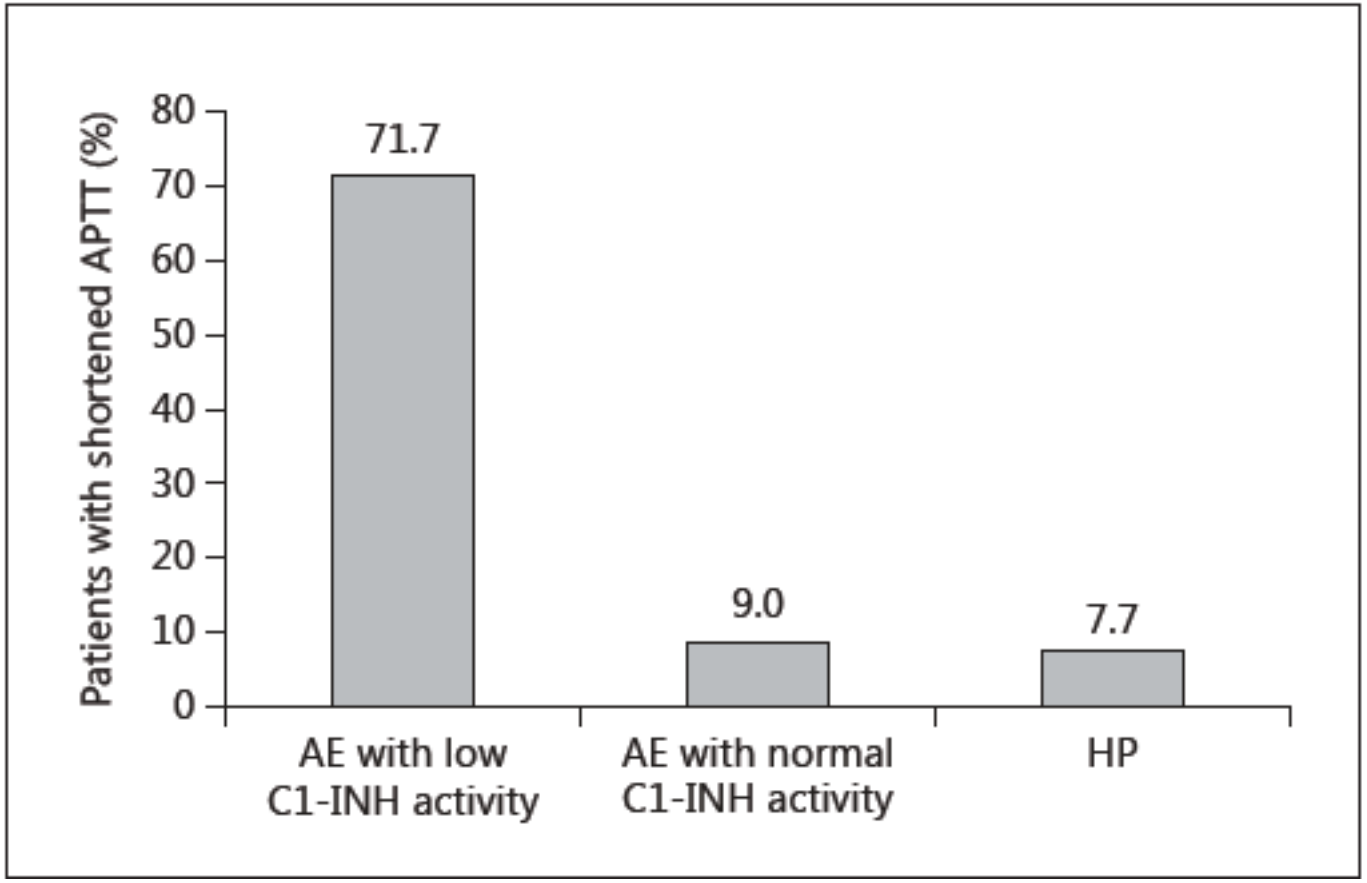
Table 1. Laboratory results (citrated plasma) of patients with various forms of angioedema during attack-free intervals and HP

Diagnosis	C1-INH activity, %	C1-INH protein, mg/dl	C4 protein, mg/dl	APTT, s	INR	FXI clotting activity, %	FXII clotting activity, %	TAT, µg/l
HP (n = 26)								
Mean ± SD	94.1±17.5	21.7±5.6	21.5±8.7	29.5±2.4	0.97±0.07	108.2±16.4	113.2±28.9	2.8±1.4
HAE-C1-INH type I (n = 41)								
Mean ± SD	13.5±12.8	6.0±2.8	6.6±3.1	25.2±2.4	0.98±0.09	131.3±21.6	127.8±25.5	5.8±7.1
p value	<0.0001	<0.0001	<0.0001	<0.0001	0.5952	<0.0001	0.0329	0.0418
HAE-C1-INH type II (n = 4)								
Mean ± SD	10.6±19.1	28±3.7	4.8±0	25.1±1.9	0.95±0.06	121.3±8.2	114.2±38.4	4.2±1.8
p value	<0.0001	0.0389	0.007	0.0017	0.6231	0.1336	0.9498	0.1067
HAE-FXII (n = 13)								
Mean ± SD	98.7±16.6	21.8±2.9	22.8±5	29.6±3.5	0.95±0.09	106.9±19.1	102.1±23.2	4.7±7.1
p value	0.4356	0.9357	0.6114	0.9361	0.5672	0.8252	0.2386	0.1949
HAE-unknown (n = 14)								
Mean ± SD	96.8±17	21.7±6.6	27.6±7.6	29.1±3.2	0.98±0.08	117.2±16.1	107.6±30.7	6.5±5.7
p value	0.6408	0.9976	0.0317	0.6461	0.7125	0.1041	0.5745	0.0031
AAE-C1-INH (n = 15)								
Mean ± SD	10.5±11.4	7.8±3.7	4.8±0	24.5±2.8	0.94±0.05	137±19.4	132.7±31.5	9.8±14.8
p value	<0.0001	<0.0001	<0.0001	<0.0001	0.1817	<0.0001	0.0506	0.0212
IAE-h (n = 32)								
Mean ± SD	91.3±19	21.8±4.2	24.4±18.8	30.2±2.4	0.98±0.07	103.3±12.4	109.1±25.9	4.1±3.3
p value	0.5625	0.9443	0.4669	0.3501	0.4347	0.1987	0.5706	0.0913
IAE-nh (n = 30)								
Mean ± SD	99.9±23.7	21.3±4.7	25.1±10.3	28.5±2.5	0.96±0.06	124.5±18.2	117.4±21.5	3.6±1.98
p value	0.3013	0.7987	0.1619	0.1077	0.6128	0.001	0.5351	0.1050
RR	70–130	15.4–33.8	16.4–31.3	26–36	0.8–1.2	70–120	70–150	1–4.1

Lower detection limit of C1-INH and C4 protein = 4.8 mg/dl; lower detection limit of C1-INH activity = 1%.



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Results:

Mean APTT was significantly shortened in HAE-C1-INH type I ($p < 0.0001$) and type II ($p = 0.0017$) and in AAE-C1-INH ($p < 0.0001$) compared to the HP.

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