SUPPLEMENTAL MATERIAL

Data analysis according to the Rasch model

In contrast to the classical psychometric theory, analysis according to the Rasch analysis model allows a conjoint measurement, where the person and estimated values on items are expressed in the same units and located on the same construct continuum (1,2). The model assumes that the probability of an affirmative answer on an item is a logistic function of the relative distance between the item location and the person location on a linear scale (1). The estimates of person parameters are regarded as measures of unobservable latent traits and the bias standard error of measurement (3). In this study, the person parameter represents the level of disease activity and the item parameter the risk of experiencing consequences related to C1-INH-HAE. According to the likelihood ratio test ($p < 0.001$), the partial credit model for polytomous items was used (4).

Data were considered to fit the Rasch model if the probability of the Chi-square item trait interaction test was not significant with Bonferroni correction ($p<0.05$/number of items) and values of the item and person fit residual followed a standard normal distribution with a mean of 0 and a standard deviation of 1. Besides, items with fit residuals higher than 2.5 are deemed not to fit and may reflect another construct. Items with residuals lower than -2.5 are redundant.. Disordered thresholds were corrected by collapsing adjacent categories (5).

Reliability, based on Person Separation Index (PSI) values, was deemed as satisfactory if higher than 0.7 (6). Items were assumed to have local independence when standardised residual correlations were lower than 0.3 (7). Unidimensionality was checked through principal components of the residuals: the difference in scores between positive and negative-loading items was assessed with independent t-tests, measures with a lower limit of binomial confidence interval (CI) < 0.05 were considered unidimensional (8).

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DIF occurs when different groups respond in a different manner to an individual item, despite equal levels of the underlying construct (1). Items were judged to be free of bias if the analysis of variance for DIF analysis was not significant using Bonferroni correction. If two or more items presented DIF, the top-down purification approach was used (9) by selecting two subtests, one with items with bias (impure items) and the other without bias (pure items), and checking the DIF again. The factors used for DIF analysis were gender, age (split by median, 40 years), family C1-INH-HAE history and type. DIF was not analysed by country due to insufficient sample size in some countries.

Rasch analysis results:

Table S1 shows information about the initial HAE-AS items. The initial Rasch analysis revealed misfitting items which lead to modifications in the model (Table S2). Due to disordered thresholds, the response scale for virtually all items was simplified. Two items with reported estimates that gave distorted pictures of the data were removed: "treatment maintenance in the last 6 months" (fit residual=4.857) and "frequency of attacks in the last 6 month" (fit residual=-4.778). The final analysis with 12 items provided a good fit to the Rasch model, with a PSI of 0.748, absence of local dependency and unidimensionality (Table S2). The item fit statistics had suitable values (Table S3). Items "Days not attending school/work due to C1-INH-HAE in the last 6 months" and "General health in the last month" presented DIF by age, however the bias was filtered out under the top-down purification approach. All other items had no significant DIF, which suggests they were free of bias for the analysed groups. The threshold distribution presented a mean value of -1.924 (SD=1.318), and a few items measured lower levels of disease severity (Figure S1).

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Table S1. Initial item frequency of the clinical activity scale for hereditary angioedema with C1-inhibitor deficiency (HAE-AS).

Item (response)		N	%
1. Peripheral attacks in the last 6 months (0-4)	No attacks	100	34.48
	1-5 attacks	99	34.14
	6-10 attacks	35	12.07
	11-20 attacks	27	9.31
	>20 attacks	20	6.90
	Missing	9	3.10
2. Abdominal attacks in the last 6 months (0-4)	No attacks	102	35.17
	1-5 attacks	104	35.86
	6-10 attacks	34	11.72
	11-20 attacks	23	7.93
	>20 attacks	17	5.86
	Missing	10	3.45
3. Facial attacks in the last 6 months (0-4)	No attacks	206	71.03
	1-5 attacks	65	22.41
	6-10 attacks	3	1.03
	11-20 attacks	4	1.38
	>20 attacks	2	0.69
	Missing	10	3.45
4. Genital attacks in the last 6 months (0-4)	No attacks	205	70.69
	1-5 attacks	56	19.31
	6-10 attacks	9	3.10
	11-20 attacks	6	2.07
	>20 attacks	3	1.03
	Missing	11	3.79
5. Upper airway attacks in the last 6 months (0-4)	No attacks	230	79.31
	1-5 attacks	43	14.83
	6-10 attacks	4	1.38
	11-20 attacks	1	0.34
	>20 attacks	3	1.03
	Missing	9	3.10
6. Other location attacks last 6 months (0-4)	No attacks	258	88.97
	1-5 attacks	16	5.52
	6-10 attacks	3	1.03
	11-20 attacks	4	1.38
	>20 attacks	1	0.34
	Missing	8	2.76
7. Number of treated attacks last 6 months (0-4)	No attacks	162	55.86
	1-5 attacks	87	30.00
	6-10 attacks	13	4.48
	11-20 attacks	8	2.76
	>20 attacks	17	5.86
	Missing	3	1.03
8. Emergency visits in the last 6 months (0-5)	0 visits	149	51.38
	1-5 visits	70	24.14
	6-10 visits	16	5.52
	11-15 visits	5	1.72
	15-20 visits	5	1.72
	>20 visits	5	1.72
	Missing	40	13.79
9. Psychological and/or psychiatric treatment in the last 6 months (0-1)	No	248	85.52
	Yes	31	10.69
	Missing	11	3.79
10. Days not attending school/work due to C1-INH-HAE in the last 6 months (0-5)	0 day	112	38.62
	1 day	15	5.17
	2-3 days	24	8.28
	4-5 days	26	8.97
	6-15 days	43	14.83
	>15 days	13	4.48
	Missing	57	19.66
11. General health in the last month (1-5)	Excellent	19	6.55
	Very good	37	12.76
	Good	125	43.10
	Fair	87	30.00
	Poor	17	5.86
	Missing	5	1.72
12. Impairment on everyday work and activities due to pain in the last month (1-5)	Not at all	104	35.86
	A little bit	68	23.45
	Moderately	45	15.52
	Quite a bit	51	17.59
	Extremely	17	5.86
	Missing	5	1.72
13. Maintenance treatment last 6 months (1-5)	No	136	46.90
	Yes	146	50.34
	Missing	8	2.76
14. Attack frequency last 6 months (0-4)	No attacks	52	17.93
	1-5 attacks	113	38.97
	6-10 attacks	38	13.10
	11-20 attacks	33	11.38
	>20 attacks	44	15.17
	Missing	10	3.45

Table S2. Fit of the HAE-AS scale to the Rasch model.

		Ideal values	Initial analysis	Final analysis
Number of items			14	12
Item residual	Mean	0.0	-0.772	-0.810
	SD	1.0	2.409	0.886
Person residual	Mean	0.0	-0.315	-0.327
	SD	1.0	0.783	0.918
Chi-square	Value		172.284	59.318
	Prob.	>0.05/number of items	<0.001	0.127
PSI		>0.70	0.808	0.748
Unidimensional test		(LCI <0.05)	12.50	6.97
CI test Binomial			(0.100-0.150)	(0.044-0.095)

SD: Standard deviation; PSI: Person separation index; Prob. probability; CI: Confidence interval; LCI: Lower confidence interval.

Table S3. Individual item fit residual for final Rasch analysis of HAE-AS scale, ordered by item location.

Item (response categories)	Location	Standard Error	Fit Residual	Chi-Square (df=4)	Probability
6. Other location attacks in the last 6 months (0-2)	1.768	0.203	-0.403	1.574	0.814
3. Facial attacks in the last 6 months (0-2)	1.198	0.144	-0.027	0.947	0.918
5. Upper airway attacks in the last 6 months (0-2)	1.068	0.153	-0.823	3.082	0.544
9. Psychological and/or psychiatric treatment in the last 6 months (0-1)	0.606	0.196	-0.566	4.031	0.402
8. Emergency visits in the last 6 months (0-2)	0.407	0.137	-0.841	5.948	0.203
4. Genital attacks in the last 6 months (0-3)	0.404	0.108	-1.286	2.979	0.561
7. Treated attacks in the last 6 months (0-2)	-0.305	0.114	-0.885	6.981	0.137
10. Days not attending school/work due to C1-INH-HAE in the last 6 months (0-3)	-0.770	0.092	-2.38	9.479	0.05
12. Impairment on everyday work and activities due to pain in the last months (0-3)	-0.865	0.085	-0.072	0.398	0.983
2. Abdominal attacks in the last 6 months (0-3)	-0.876	0.087	-1.974	8.334	0.08
1. Peripheral attacks in the last 6 months (0-3)	-0.975	0.085	-1.35	1.625	0.804
11. General health in the last months (0-3)	-1.660	0.1	0.892	13.94	0.007

Figure S1. Item-person threshold distribution in a logit scale.