**Supplementary Materials**

**Methods**

*Measurements of health-related quality of life*

Measures of health-related quality of life were conducted using the Health-related quality of life questionnaire for hereditary angiodema (HAE-Qol) (1), and the generic Short Form Health Survey (SF-36) (2) or Pediatric Quality of Life Inventory (PedsQL) (3) questionnaires, administered by the Allergist/Immunologist. Psychological conditions were assessed by the Hospital Anxiety and Depression Scale (HADS) (4) and by the Depression Anxiety Stress Scales (DASS) (5), conducted by the Psychiatrist; by the Beck Anxiety Inventory (BAI) (6) and the Beck Depression Inventory (BDI) (7), administered by the Psychologist; and by the Children’s Depression Inventory (CDI) (8) and the Child Stress Scale (SSC) (9), administered by the Pediatric Psychologist. Work-related data were collected using the Work Productivity and Activity Impairment-General Health Questionnaire (WPAI-GH) (10), conducted by the Social Worker.

**Supplementary Figure Legends**

Figure S1. Pedigree of the study family with HAE-C1-INH. Family pedigree was constructed using the Genopro 2016 software.

Figure S2. Effect of the systematic program for HAE patients on SF-36 scores. Boxplot showing median scores, lower and higher quartiles, and minimum and maximal values, for each of the 8 dimensions of SF-36. Significant improvement was observed only for the Role-emotional dimension, with mean increase of 35.68 (95% CrI 16.67;54.42) at 14 months, as compared to baseline. Twenty-two patients underwent evaluation with SF-36. Mean values are represented by (+).

Figure S3. Effect of the intervention on psychological conditions. A. Significant improvement was observed for HADS anxiety, with mean decrease of -4.38 (95% CrI -7.04; -1.57) at 14 months within intervention. B. Significant reduction was seen for DASS depression and stress, with mean decreases of -6.5 (95% CrI -11.99; -1.14) and -8.87 (95% CrI -13.78; -3.85) respectively at 14 months. C. Significant decline was observed for BDI depression, with mean decrease of -6.17 (95% CrI -12.28;-0.18) at 14 months, as compared to baseline. Boxplot showing median scores, lower and higher quartiles, and minimum and maximal values, for HADS, DASS and BDI. HADS questionnaire was applied to 22 patients, and DASS and BDI questionnaires in 25 patients. Mean values are represented by (+).

Figure S4. Effect of the intervention on work-related aspects. Boxplot showing median scores, lower and higher quartiles, and minimum and maximal values, for WPAI-GH. Fourteen patients underwent evaluation with WPAI-GH. Mean values are represented by (+).

**Supplementary Tables**

Table S1. Questionnaires used in the present study to assess heath-related quality of life, psychological disorders and work impairment in patients with HAE.

Table S2. Mean number of angioedema attacks per month (SD) and mean differences of number of attacks per month 8 and 14 months within intervention, as compared to 12 months pre-intervention.

Table S3. Mean (SD) health-related quality of life scores and mean differences at 8 and 14 months within intervention as compared to baseline.

Table S4. Mean (SD) psychological and work related outcome scores and mean differences at 8 and 14 months within intervention as compared to baseline.

**E-References**

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