Prodromes as Predictors of Hereditary Angioedema Attacks

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Abstract

Background: Prodromes are repetitive complexes of signs or symptoms portending attacks of certain chronic diseases. Recent data suggest that a large majority of patients with Hereditary Angioedema (HAE) have experienced prodromes and able to predict the onset of oncoming attacks. However, prodromes and their clinical significance have not been investigated in a systematic manner and the underlying pathophysiologic basis is unknown. A disease-specific, patient-reported outcome (PRO) instrument suitable for evaluation of prodromes and attacks is an unmet clinical need. We sought to examine and evaluate prodromes and attacks of HAE and its associations, by a new validated PRO instrument (HAE-EPA). *Methods:* HAE patients participated in a preliminary survey addressing their demographics, social and medical status. A cohort of 66 patients was asked to report their recent experience in prodromes and attacks. Domains (i.e. body locations) and dimentions (i.e. severity, impairment, functionality) were pre-defined for both episodes. Robust bio-statistical methods were used to analyze associations and correlations between both events. **Results:** Significant correlations were demonstrated between the two interrelated phenomena. Corrleations in severity were high across all domains. Hierarchical Regression analysis demonstrated an interaction between prodromes and the patients' experience in illness (i.e disease duration). The later can explain associations between patient perception of the intensity of the prodromes and attacks. **Conclusions:** By using the new instrument HAE patients could effectively distinguish prodromes from attacks. The new validated instrument demonstrated high discriminative ability, acceptability, content validity/reliability, and therefore can be used for the investigation and reporting prodromes, attacks and their relationships.

ORIGINAL RESEARCH ARTICLE:

Prodromes as Predictors of Hereditary Angioedema Attacks

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Authores contributions:

ILN: Study design, interviewed patients, data collection and recording, treating HAE patients, writing of the manuscript.

AR : Head of Angioedema Center, treating HAE patients, adviced and guided, assisted in writing and reviewing the manuscript.

RS: Academic supervisor of the study, guided and approved the results, reviewed the manuscript.

HG : Helped to design, assisted and supervised the study, reviewed the manuscript.

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ABSTSRACT

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Methods: HAE patients participated in a preliminary survey addressing their demographics, social and medical status. A cohort of 66 patients was asked to report their recent experience in prodromes and attacks. Domains (i.e. body locations) and dimentions (i.e. severity, impairment, functionality) were predefined for both episodes. Robust bio-statistical methods were used to analyze associations and correlations between both events.

Results: Significant correlations were demonstrated between the two interrelated phenomena. Corrleations in severity were high across all domains. Hierarchical Regression analysis demonstrated an interaction between prodromes and the patients' experience in illness (i.e disease duration). The later can explain associations between patient perception of the intensity of the prodromes and attacks.

Conclusions: By using the new instrument HAE patients could effectively distinguish prodromes from attacks. The new validated instrument demonstrated high discriminative ability, acceptability, content validity/reliability, and therefore can be used for the investigation and reporting prodromes, attacks and their relationships.

Keywords: Attacks, clusters, dimensions, Hereditary Angioedema, Prodromes

Abbreviations/acronyms used:

ANOVA Analysis of variance

BK Bradykinin

C1-INH Complement 1-esterase Inhibitor

GI Gastrointestinal

HAE Hereditary angioedema

HRQoL Health-realted quality of life

MANOVA Multivariate analysis of variance

PRO Patient-reported Outcomes

VAS Visual Analog Scale

INTRODUCTION

Hereditary Angioedema (HAE) is a rare genetic disorder, resulting from either low production or dysfunctional regulatory enzyme (C1-esterase Inhibitor, C1-INH), whose major role is to control biochemical pathways leading to endothelial permeability. [1] It is clinically expressed by recurring bouts of edema (swelling) in various organs and tissues.[2-3] Recurrent and unpredicted attacks may be triggered by tissue trauma, inflammation, hormones or medications. [3] As a lifetime illness, the burden of HAE on individuals, families and health-providing systems is considerably high.[4-5] Moreover, attacks involving the oropharyngeal region, if not promptly identified and treated, may become life-threatening due to asphyxiation.[6]

Premonitory signs or symptoms (Prodromes) have been observed as preceding attacks from the early descripitons of HAE.[7]Prodromes are manifested by clinically complex signals, subjective ("symptoms") and objective ("signs"), preceding the physical attacks (Table I).[8] However, their significance has not been sufficiently substantiated so far and the mechanisms of its pathophysiology are yet unknown.[8] Despite this knowledge gap, recent data suggests that a large majority of HAE patients report portending perceptions before attacks and many are able to predict oncoming attacks by experiencing a prodrome.[9-12]. In contrast to the ample data available on HAE attacks, triggers, clinical features and their effect on health-realted quality of life (HRQoL), research of HAE prodromes is lagging, or limited to small series and observational studies. There is paucity of research on prodromes while systematic and validated instruments are not available. Another barrier for investigating prodromes and prodrome-attack associations is the lack of consensual definition of prodromes' main attributes. [12] As a result, prodromes have not been properly investigated by a scientific, systematic and methodical manner and their relation to attacks are not sufficiently established.[8]

Theoretically, if applied in clinical practice, early awareness of a prodrome can alert the patients to oncoming attacks and enable to deploy therapeutic strategies to attenuate the attacks (prodrome-triggered interventions).[12]

To close this gap, we constructed and validated a new HAE specific instrument, capable of assessing the predictive power of prodromes as early warning signs.[13] This instrument, HAE Evaluation of Prodromes and Attacks (HAE-EPA), can now be utilized to assess the critical domains and dimensions of the prodromes and attacks and investigate their associations.

METHODS

Participants

From a total population of 233 HAE patients recruited from four academic expert centers in Israel, 197 patients (84.5%) agreed to participate in a preliminary survey, addressing their medical, ethnic, socioeconomic background, demographics, and health-related items. Out of these, 66 physican-diagnosed HAE patients consented and qualified to join the study (Table II). Main inclusion criteria were: confirmed diagnosis of HAE based on personal and family history of angioedema attacks; antigenic C1-INH below normal range; and/or functional C1-INH <50% and complement C4 below normal range (Type I). Patients with normal antigenic C1-INH, low functional C1-INH and low C4 (Type II) were also included. Angioedema patients with normal C1-INH and normal C4 were excluded. Only Hebrew-speaking patients participated in the study. The study was approved and supervised by the ethics committees of Tel-Aviv University, Sheba Medical Center and Barzilai Medical center. All patients signed an informed-consent form (ICF). Mean age of participants was 32.4 years (SD ±16.4), Median age 30.0 years (age range 10-70(. 22.3% were children and adolescents and 59.1% were females (Table II).

Study design

A new PRO instrument: HAE Evaluation of Prodromes and Attacks (HAE-EPA) was utilized in this study to assess patient reports. Its description and validation process is detailed elsewhere.[13] This instrument consists

of personal and health-related data, evaluation of prodromes and evaluation of attacks, and was powered to collect and analyze recent prodrome/attack data from the participating patients.

For practical purposes, we chose to describe the range of signs and symptoms ocurring in each body system relevant to HAE (domain) as a 'cluster'.[11,12] Accordingly, 'abdominal cluster' represented all the recognizable gastrointestinal (GI) signs and symptoms reported by the patients (i.e. nausea, vomiting, abdominal pains, diarrhea etc.). This method has proven useful and easy to comprehend by both patients and investigators, and is also amenable to statistical analysis.[10-13] Most relevant clusters in this study included: facial, oropharyngeal, abdominal, extremities (skin and subcutaneous tissue) and urogenital domains.. Each cluster of the involved body location is evaluated by specific items, adapted to its unique charachteristics (i.e. abdominal cluster-9 items, Facial-4, urogenital-7, oropharyngeal-8, Extremities-3). Each cluster's involvement was represented by four scalable dimensions, measured by a visual analog score (Likert scale, VAS): pain (scaled), severity (i.e. degree of swelling), impairment (i.e. interference with daily activities) and functionality (i.e. use of a limb).

Data collection

Data collection was done by using the disease-specific questionnaires of the EPA-HAE instrument[13]. The questionnaires were based on a recent (6 month) experience of the patients with prodromes and attacks. Personal interviews were performed by the principal investigator (ILN). In describing their experience, patients were directed to recount the dimensions of prodromes and attacks (i.e. pain, severity, limitation, functionality) in each affected body cluster (domain). The average time for answering the quesionnaires was approximately 30 minutes.

Statistical Analysis

Data analysis was performed by SPSS® Statistics software V. 21 (IBM®, Chicago, USA).

Mean and standard deviations were calculated for continuous variables (i.e. age, age at onset, duration of illness etc.) and percentages calculated for categorical values. Chi-square test for variance (χ^2) was applied to categorical socio-demographic data, assumed to be normally distributed (i.e. gender/ age differences). Student's t-test was used to analyze statistical significance of differences between the means of continuous variables (i.e. age/gender vs. medication usage, predictability of attacks etc.). Analysis of variance (ANOVA) and multivariate analysis of variance (MANOVA, unidirectional with repeated measurements) were used to assess differences between prodromes and attacks, as related to personal categorical values. Pearsons' correlation coefficient was calculated for associations between continuous personal variables and scalable parameters. Stepwise Hierarchical Regression analysis was used to assess the contribution of health-related personal variables of prodromes to variables of attack, in which the personal health variables were forcedly introduced first, prodrome variables second, and thirdly- the interactions between personal and prodrome variables. Sensitivity and specificity computations assessed the clinical utility of the new instruments.

RESULTS

Patients' Characteristics

The study cohort comprised 66 HAE patients (39 Femles, 27 Males). As expected from an autosomal inherited disorder, high prevalence was found among parents and siblings (74%, 60%, respectively). Half of the adults live with a partner and approximately half are parents. Mean age of onset of HAE was 9.8 years and mean age of diagnosis was 14.5 years (4.7 years diagnosis gap) (Table II).

In this study we received 223 reports on prodromes and /or attacks from the of the 66 patient cohort (attacks and its locations are presented in Figure 1). All the patients experienced attacks during the study period and 94% had their prodromes in the abdominal cluster. A considerable number (81.8%) had prodromes and attacks involving the extremities. The distribution of both events is depicted in Figure 2. More than 5th of the patients (22.7%) reported previous hospital admissions, most of them for facial involvement

(45.2%), mouth-tongue-upper-airway involvement (12.2%), abdominal attacks (7.6%), and genital attacks (4.5%) (Presented in Table I). The vast majority (62/66, 92%) claimed that they experienced a prodromes before at least one of their attacks, and two-thirds (64%) affirmed that they can predict an oncoming attack by having a prodrome.

Evaluating prodrome dimensions

Patients were asked to rate their experience with prodromes in different dimensions measured on a Likert scale (Visual Analog Scale, VAS) of 0 to 10cm. Analysis of variance (ANOVA) demonstrated a significant and consistent difference between dimensions of prodromes in various locations (clusters). Paired t-test showed significant differences between the dimensions of prodromes and attacks across all clusters (Figure 2). Generally, the severity of prodromes in the abdomen and the extremities exceeded the other clusters (urogenital, facial, oropharyngeal). It should be noted that mean severity of prodromes was much less (by half) as compared to attacks across all dimensions (pain, severity and functionality) in all the pre-specified domains (clusters) (Figure 2).

Pain

Significant differences were found in pain severity in the abdominal cluster as compared to other locations. Notable differences were found between the extremities cluster and the other three clusters and between urogenital and facial and oropharyngeal cluster.

Severity

Mean severity reported during the abdominal prodromes was higher than in other clusters. Additionally, significant differences were found between the extremities and three other clusters (urogenital, facial, oropharyngeal)

Limitation

Significant differences were found by paired tests between the degrees of limitiation resulting from a prodrome in the abdomen, as compared to other clusters. Here again, significant differences were also found between the extremities cluster and other clusters (urogenital, facial, oropharyngeal)

Functionality

In particular, paired tests showed a difference between the abdomen and extremities and the other three clusters.

Evaluating Attack dimensions

Patients were asked to describe the degree of severity, pain, limitation and functional impairment of a recent typical angioedema attack. They rated their experience on a Likert scale (VAS) of 0 to 10cm. Figure 2 represent the patient evaluation of the above dimensions as related to the pre-determined body locations. Analysis of variance (ANOVA) demonstrated a significant and consistent differences between dimensions of attacks in various the clusters.

Pain

As in the prodrome, significant differences were showen in pain severity between the abdominal cluster as compared to other clusters, and between urogenital and facial and oropharyngeal cluster.

Severity

The mean severity of the abdominal attacks was higher than in other clusters. Additionally, significant differences were found between the abdominal and three other clusters (urogenital, facial, oropharyngeal), and between the extremities to other clusters.

Limitation

The differences between the five clusters in the patient's perceived degree of limitation follow a similar pattern. Significant differences were found between the limitation casused by abdominal attacks and other clusters, the extremities and other clusters, and between facial to the other clusters. The limitation caused by oropharyngeal attacks was evaluated as very significant as compared to the abdominal and the extremities.

Functionality

The mean in affected functionality was higher in the abdominal attacks as compared to the other clusters. Additionally, significant differences were found between the abdominal and the three other clusters (urogenital, facial, oropharyngeal) and between the extremities to the other clusters. In particular, paired tests showed a difference between the abdomen and extremities and other 3 clusters.

As a rule, attacks experienced in the abdomen were consistently perceived as extremely challenging for the study subjects. The intensity of pain in the attacks was very high and reached a level of 7-8 on a scale of 0-10 (Fig 2). The standard deviations in dimensions of the attacks were relatively small, which indicates a consistency in individual observations across all the clusters.

Discriminating prodromes from Attack by location

The Eta^2 values performed in each Analysis of variance (MANOVA), for all the clusters together and separately, were found very high in all dimensions. The severity of the prodromes is significantly lower (twice or more) compared to the the attacks in all dimensions and in all clusters. These findings support the studys' hypothesis that it would be possible to differentiate between the dimensions of the prodromes and attacks and to establish their relationship. (Figure 2).

Abdominal cluster

A significant difference was found between the abdominal dimensions of the prodromes and the attacks. However, the means of the prodrome indices were twice lower than the means of the attacks.

Extremities cluster

Significant differences were found between dimensions of the extremities during the prodromes and the attacks. Here again the means of the prodromes were significantly lower than the means of the attacks in this cluster. Similarly, the mean values of the attacks were about twice of the attacks. The means of the degree of functionality and limitations during the attacks in this cluster were higher than in other body clusters.

Facial cluster

Significant differences were found between the facial dimensions of the prodromes and the attacks. The prodromes means were significantly lower (2-3 times) than the means of the attacks in all dimensions.

Oropharyngeal cluster

Significant difference were found between the oropharyngeal dimensions of the prodromes and the attacks, and here too the means of the prodromes were significantly lower, about twice less than the attacks in all dimensions.

Urogenital cluster

A significant difference was found between the urogenital dimensions of the prodromes and the attacks. The means of the prodromes were significantly lower than the means of the attacks in this cluster, in all dimensions. The aggrevation during attacks were more than three times of the prodromes, which was the highest gap of all the clusters studied.

Correlations between attacks and prodromes

Highly significant correlations were found between the dimensions of prodromes and attacks (i.e. functionality in the abdominal cluster, $r = .68$, $p < 0.001$, Fig 3a). In all clusters, except for the extremities, positive and

significant correlations were found between the severity of the prodromes and the attacks. It shoulc be noted that in most clusters, as the severity of the prodromes increased, so does the severity of the attacks (Figure 3 a-d).

The effect of personal variables

Stepwise Hierarchical Regression analysis was employed to assess the contribution of health-related personal variables on the association between prodromes and attacks. Methodically, the personal health variables were forcibly introduced first, the prodrome variables second, and thirdly- the interactions between personal and prodrome variables. Using this analysis we found that personal variables (i.e. experience and duration of illness) influences the patients' perception of the prodrome (β=.44, p< .001). This means that the association among those with the shortest experience in the disease is much noteable than among the experienced patients. In less experienced patients an intense prodrome predicts stronger attack. It should be noted that in our previous survey of 197 HAE patients, a positive association was also found between the intensity of the prodromes and the intensity of the attacks.[13]

Sensitivity and Specificity

Sensitivity and specificity were calculated by pre-determined rules whereby true positive linkage represent a prodrome followed by an attack. Sensitivity of the prodrome as a predictor of attack was 89.5%, Specificity 63.1%, Positive Predictive Value was 75.0% and Negative Predictive Value = 83.0%. These findings support our basic theory regarding the utility of prodromes as predictors of oncoming attacks.

DISCUSSION

Pre-attack perceptions has been reported by HAE patient's from the early descriptions of this rare genetic disorder, but are still loosely defined and therefore pose a clinical condundrum.[7-12]Some prodromes are charchterized by objective physical signs, even at the same location of the attack, which helps to fortell its development (i.e. Erythema Marginatum rash on the abdomen), but some are manifested by subjective sensations reflecting high variability in individual perceptions.[8] At the present time, a large body of evidence supports the observation that prodromes are an intergral part of the edematous attacks, and may even represent a continuity of pathophysiologic events invlovling the bradykinin-forming cascade as well as the vascular endothelium. [14-17]

HAE is a life-long illness and prodromes with its recurring nature are having a profound effect on the patient's perception of their illness-trajectory and burden of disease.[5,8] The present study indicates that personal variables such as age, gender, and experience in illness, can affect patient's perception of prodromes and their ability to predict oncoming attacks. So far the main obstacle to the investigation of prodromes' clinical significance has been the lack of reliable scientific methods that can capture the essential elements of the prodromes and their association with consequent attacks.[9-12] Clearly, there is an unmet need for a unified definition of prodromes, its temporal relations to attacks, its predictive power as an early warning sign, and its use in mitigating cosequences of attacks.

A newly developed disease-specific evaluation instrument (HAE Evaluarion of Prodromes and Attacks, HAE-EPA), was chosen for this study.[13] This investigational tool is based on the principles of patient-reported outcome measures (PRO) that have already shown its effectiveness in clinical research and medical practice.[18-19] HAE-EPA is the first tool to measure both prodromes and attacks, while other HAE instruments are focusing on either attack attributes, or disease-related quality of life (HRQoL) or both (reviewed in ref. 13). The dimensions and domains selected for evaluation of the attacks and prodromes in our study are meant to authentically reflect the patients' perception of disease severity and its effect on their daily routine, and therefore represent their real-life illness prespective.

The present study is an exploratory pilot which applied the HAE-EPA instrument to a cohort of 66 patients who were willing to share their experience on both prodromes and attacks, out of a total of 197 HAE patients surveyed in Israel.[20]

The statistical analysis presented in this study demonstrates significant differences in the dimensions of prodromes and attacks (i.e. pain, severity, limitation, functionality) across all pre-defined body domains ("clusters"). This means that patients could clearly distinguish between these two events. The positive correlations support our basic assumption that prodromes could predict attack location, severity and degree of impairment and functionality. These correlations indicate that high intensity prodromes can predict high severity of the subsequent attacks, which was particulary emphasized in the abdominal location. Moreover, the relationships seems not to be based on compensatory response during the attack (i.e. intense prodrome results in mild attack), but on a predictive principle (i.e intense prodrome predicts intense attack). As expected, prodromes were far less intense than attacks on all dimensions.

In this study we tried to comprehend how personal characteristics affect the interactions between prodromes and attacks in individual patients. Personal experience seems to be an essential asset when it comes to coping with chronic illness.[21] Even though prodromes and attacks are unpredictable and vary in their manifestations, experienced patients are more attentive to their body cues and capable of finding some consistency and repetitiveness in the prodromes, enabling them better coping skills than the less experienced patients (i.e. newly diagnosed or with fewer attacks) who, according to our study, perceive more intense prodromes and attacks. Experience in illness is strongly associated with the patients' ability of to predict attacks, distinguish them from the prodromes and employ these insights as a coping strategy. Experienced patients are expected to better endure the challenges of the disease by using the prodromes as an early warning sign and prepare to take preventative actions to mitigate the attacks. These finding are in-line with the observation that experienced patients are coping better with chronic disease and able to utilize their individual resources more efficiently[21]. In chronic diseases, patients develop their own perception of illness as a limitation and cultivate their own individual coping strategies. [22-23] More experienced and trained patients can recognize the early warning signs and use them as an efficient strategy in the management of attacks (i.e. timing of self-administration of rescue medication). [24]

Contributions of the study

This study adds to the current knowledge about HAE prodromes and their importance as attack-predicting harbingers. It presents a new robust, sensitive and specific instrument that employs the attributes of prodromes, its expressions, typology, consistency and power to predict the occurrence of attacks. Early detection of impending attack is expected to assist in clinical decision-making regrading the timing of an early response ("prodrome-triggered intervention") expected to shorten or avert the attacks. The study findings can be applied to similar conditions with relapsing-remitting patterns, whose attacks are also antedated by prodromes. [25-28] A similar approach was recently employed in the treatment of acute Familial Mediterranean Fever (FMF) attacks by Babaoglu et al. [29] This strategy can improve the patients' self-management skills and contribute to improved quality of life. The newly developed PRO instrument can be used to alert patients to approaching attacks and allow fast deployment of therapeutic strategies to preempt the attack. It can be used by HAE patients worldwide as an internet-based application after cross-cultural translation and validation, to monitor prodromes and attacks over time, transmit real-time data, obtain treatment directions and communicate with the medical staff. [30] We propose to include prodrome reports in disease registries data and management guidelines of diagnosis and treatment of HAE.[31-33]

Limitations of the study

The study was performed in a single country, with its unique cultural and linguistic charchteristics. Patients who consented to participate represent only 33.5% of the total studied HAE patients.[20] Additionally, patient reports are mostly subjective and diverge considerably depending on each patient's experience. Despite being based on a recent (6 month) experience with prodromes and attacks, the retrospective design may involve recall bias, which we hope to address by a prospective study, in which at least several consequtive prodromes and attacks will be reported.

Conclusions

Taken together, the study establishs that patients can distinguish prodromes from attacks across all relevant

body locations and an intense prodrome can predict the severity and location of an oncoming attack. Personal experience is a crucial factor in the patients' perception of a prodrome and his/her ability to respond. Evaluating prodromes can be helpful in the management of HAE and other chronic illnesses with undulating course.

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Legends/captions to Tables

Table I. Definition of a proderome

A proposed definition of pre-attack signs and symptoms (prodromes) of Hereditary Angioedema (see Ref. 8)

Table II. Disposition of patients in the study

The table depicts the demographic and past medical history of a population of HAE patients included in the study (N=66). Patients were requested to fill structured questionnaires (HAE-EPA) relating to their demographic and past medical history and experience with prodromes and attacks (see Methods).

Legends/captions to Figures

Figure 1.

Distribution of patient reports on body locations and systems (clusters) involved in their attacks during the previous 6 month. All patients reported at least one abdominal attack during the respective period.

Figure 2.

The bars (brange=attack, blue=prodrome) represent the intensity of attacks and prodromes in different body locations (clusters). HAE patients were asked to rate their experience with prodromes on a visual analog scale (VAS) scale ranging from 0 to 10cm. Intensities of the prodromes were significantly less than those of the attacks, as demonstrated for each scalable dimension (pain, severity, impairment, functionality).

Figure 3.

HAE patients were asked to rate their experience with prodromes and attacks. Scalable dimensions (Pain, intensity, impairment, functionality) were recorded on a visual analog scale (VAS) ranging from 0 to 10. Pearson's correlation coefficient was used to calculate the associations between prodromes and attacks in different

body locations (clusters)**.** The **X-axis** represents the magnitude of prodromes and the **Y-axis** represents the attacks. Four representative correlations are graphically depicted: **a)**Abdominal pain (Pearson's= .68, p<.001); **b)**Urogenital function (Pearson's= .61, p<.001); **c)**Oropharyngeal impairment (Pearson's= .73, p<0.001);**d)** Oropharyngeal function (Pearson's= .68, p<.01).

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