Prodromes as Predictors of Hereditary Angioedema Attacks

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Letter to the Editor

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To the Editor

Hereditary Angioedema (HAE) is a rare genetic disorder, expressed by recurring bouts of edema (swelling) in various organs and tissues.¹ Pre-attack perceptions (Prodromes) are frequently reported by HAE patient's but since they are loosely defined they pose a clinical condundrum.²⁻³ Prodromes are subjective and objective signs and symptoms, preceding attacks by several hours (Table S1).³ They may represent an early pathophysiologic events involving the bradykinin-forming cascade and the vascular endothelium.⁴⁻⁵ HAE patients may use these portending perceptions to predict oncoming attacks.^{2-3,6}

Since specific research instruments are not available, prodromes have not been properly investigated by a methodical manner and their predictive power as an early warning sign is unknown. In view of these unmet needs, we constructed and validated a new HAE specific Patient-reported Outcome (PRO) instrument, capable of assessing the predictive power of prodromes.⁷

The present study is based on reports of 66 HAE patients (Table 1). Prodromes and attacks in relevant body locations (domains) were designated a 'cluster'.^{2,6} Accordingly, 'abdominal cluster' represents all recognizable gastrointestinal (GI) signs and symptoms. This method is easy to comprehend and amenable to statistical analysis.⁷ Clusters included: facial, oropharyngeal, abdominal, extremities (skin) and urogenital domains (Figure S1). They were evaluated by four scalable dimensions: pain, severity, impairment and functionality. Patients rated their recent experience with prodromes and attacks on a Visual Analog Scale (VAS). We received 223 patient reports on attacks, with 92% experiencing a prodrome before at least one attack, and 64% said they are able to predict an oncoming attack by a prodrome. We found significant and consistent differences between dimensions of prodromes and attacks across all clusters. Mean severity of prodromes was approximately half of attacks across all pre-specified clusters (Figure 1). Prodromes could be discriminated from attacks across all clusters, supporting our hypothesis that patients can distinguish between these two events (Tables S2, S3). Highly significant correlations were found between the dimensions and intensity of prodromes and attacks (Figure S2). We also proved that personal variables (i.e. experience and duration of illness) influences patients' perception of a prodrome.⁷ Sensitivity of prodromes as a predictor of attack was 89.5% and Specificity 63.1%.

These results indicate that HAE patients can distinguish prodromes from attacks and that prodromes fortell subsequent attack location and intensity. Although prodromes and attacks are unpredictable and vary in their manifestations, experienced patients are more attentive to their body cues and capable of finding consistency and repetitiveness in prodromes.⁸ Patients can better cope with the challenges of the disease by using prodromes as an early warning sign and take preventative actions to mitigate attacks. Training

patients to recognize early prodromes may be adopted as an efficient strategy for timing self-administration of rescue medication.⁹

We propose that a careful selection of relevant clusters and scaleable dimensions authentically reflect the patients' perception of disease severity and its impact on real-life illness perspective. The new instrument can be applied to other diseases with relapsing-remitting pattern, whose attacks are also antedated by prodromes, such as Epilepsy, Migraine and FMF, allowing fast deployment of therapeutic strategies to preempt attacks.¹⁰

In conclusion, we found that by using a disease specific tool, HAE patients can distinguish prodromes from attacks and predict oncoming attacks. Personal experience is a crucial factor in the patients' perception of a prodrome and ability to respond. This study adds to our knowledge on prodromes and their importance as attack-predicting harbingers. Early detection an attack is expected to assist in clinical decision-making regrading the timing of treatment and may shorten or even avert the attacks. Evaluating prodromes can be helpful in the management of HAE and other chronic illnesses with undulating course.

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Supporting information: Additional supporting information may be found online in the Supporting Information section.

Table 1: Disposition of patients in the study

Variable	Category	Value (%)
Total number		N=66
Age (ys)	M±SD Mean Range	32.4±16.4 30.0 10-70
Age Groups	10-20 21-30 31-40 41-50 51-60	19 (28.8) 11 (16.7) 14 (21.2) 9 (13.6) 7 (10.6) 6 (9.1)
Gender	Male Female	27 (40.9) 39 (59.1)
Type of HAE	Type I Type II	60 (90.9) 6 (9.1)
Family history	Yes No	61 (92.4) 5 (7.6)
Age at 1st attack (ys)	M±SD Range	9.8±7.2 1-48
Age at diagnosis (ys)	M±SD Range	14.5±12.3 1-48
Experience in HAE (ys)	M±SD Range	25.9±19.2 1-66
Country of birth	Israel Europe America	55 (83.3) (12.2) 8 3 (4.5)
HAE in the family*	Parents Siblings Grandparents	49 (74.2) 40 (60.6) 32 (48.5) 20 (30.3)
Triggers**	Uncles	46 (69.7) 31 (46.9) 24 (36.4) 23 (34.8) 18 (27.3) 16 (24.2) 16 (24.2) 14 (21.2) 12 (18.2)
	Injury Stress Pressure, vibration Unknown Other	
	Menstruation Fever Diarrhea	
	Medicines	
Prodrome (Pre-attack)	None At least once Sometimes	11 (16.6) 55 (83.3) 53 (80.3) 42 (63.6)
	Can predict attack	

* Each patient may have more than one affected family member ** Each patient may have experienced more than one trigger of attack

Legend to Table 1. Disposition of patients in the study

Patient's demographics and their past medical history of 66 HAE patients included in the study, is shown on this table. Patients were requested to fill a structured questionnaires (HAE-EPA) relating to their demographic and past medical history and experience with prodromes and attacks (see Methods).

Figure 1. Dimensions of prodromes and attacks according to body locations

[CHART][CHART][CHART][CHART][CHART]

Legend: Attack Prodrome

Legend to Figure 1. Dimensions of prodromes and attacks according to body locations

HAE patients were asked to rate their past experience with prodromes and attacks during the previous 6 month, on a visual analog scale (VAS) ranging from 0 to 10cm. Mean VAS of 223 attacks, involving different body locations (clusters) are illustrated. All patients reported at least one abdominal attack during

the respective period. Intensities of the prodromes were significantly less than those of the attacks, as demonstrated for each scalable dimension (pain, severity, impairment, functionality). Orange bars = attacks, blue bars = prodromes