LETTER TO THE EDITOR

Chronic inducible urticaria: a delayed path to specialist care

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To the Editor,

Chronic inducible urticaria (CIndU) accounts for a substantial proportion of chronic urticaria (CU) cases and is characterized by reproducible, trigger-specific symptoms that require specialized clinical evaluation and, when appropriate, provocation testing for accurate diagnosis (1-3). However, because patients with CIndU often learn to avoid their triggers, including cold, pressure, heat, exercise, sweating, or friction, symptoms may be underrecognized in nonspecialist settings, potentially delaying referral (3-6). The coexistence of chronic spontaneous urticaria (CSU) and CIndU may further complicate phenotype recognition (1,2). Although diagnostic delay has been described in CU and in specific CIndU subtypes (4,5), including differences across CU phenotypes (4), time to first specialist assessment is a distinct endpoint that warrants further study. We aimed to compare the time from symptom onset to first specialist assessment across CU phenotypes.

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We performed a retrospective analysis of patients with CU evaluated at a Urticaria Center of Reference and Excellence (UCARE) in Lisbon, Portugal. Patients were classified as having CSU, CIndU, or mixed CU, defined as coexistence of CSU and CIndU, based solely on the initial specialist assessment. Patient-reported symptom onset was obtained from the clinical history documented at the initial specialist assessment. The interval from symptom onset to that assessment was recorded in months. Interval data were available for all 730 patients included in the analysis. No patients were excluded because of missing symptom-onset information. Sex, age at symptom onset, and age at first specialist assessment were summarized descriptively to provide baseline context. Continuous variables are reported as median and interquartile range (IQR) because of their skewed distributions. Differences in mean time to first specialist assessment across CU phenotypes were assessed using one-way analysis of variance (ANOVA), considering its relative robustness to departures from normality with large within-group sample sizes (CSU, n = 520; CIndU, n = 99; mixed CU, n = 111). The study received approval from the ethics committee.

A total of 730 patients were included (Table 1): 520 (71.2%) with CSU, 99 (13.6%) with CIndU, and 111 (15.2%) with mixed CU. Most patients were female across all groups. Median age at first specialist assessment was 45 years in CSU, 36 years in CIndU, and 42 years in mixed CU. The overall median time from symptom onset to first specialist assessment was 4.5 months. Patients with CSU had the shortest median interval at 4 months (IQR, 1–12). In contrast, patients with CIndU had a median interval of 10 months (IQR, 2–36), and patients with mixed CU had a median interval of 12 months (IQR, 3–36). The overall difference

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in mean time to first specialist assessment across CU phenotypes was statistically significant by one-way ANOVA ($p < 0.001$).

These observations complement the CURE registry analysis by Muñoz et al., which included 4,332 patients and reported longer median diagnostic delay in CIndU than in CSU or combined CSU/CIndU (4, 1, and 2 months, respectively) (4). Their endpoint was time to physician-confirmed diagnosis, whereas ours was time to first specialist assessment. In our cohort, the median interval was longer in mixed CU than in CIndU, whereas Muñoz et al. reported a longer diagnostic delay in CIndU than in mixed CU. These findings are not directly comparable because the studies measured different endpoints. Differences in patient populations and referral pathways may also have contributed.

Several factors may explain the longer intervals observed in patients with inducible features. Trigger-dependent symptoms may not be recognized as urticaria during a routine clinical assessment. In addition, patients may reduce exposure to triggers through avoidance strategies, delaying medical attention or referral until symptoms become more frequent, severe, or difficult to avoid (3-6). Limited familiarity with CIndU in primary care may also lead clinicians to interpret reactions to cold or friction as nonspecific skin sensitivity, overlooking the need for further evaluation (3,4,6). These possible explanations were not assessed in this study.

The prolonged interval observed in mixed CU is noteworthy, because the spontaneous component might otherwise be expected to prompt earlier referral. However, mixed CU was classified at the initial specialist assessment; therefore, the reported symptom duration may include a preceding period during which only spontaneous or inducible symptoms were present or recognized. The observed

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association cannot establish when the mixed phenotype developed or whether inducible features contributed to the longer interval.

The interval measured in this study reflects total time to first specialist assessment and should not be interpreted exclusively as physician-related diagnostic delay. Patient-related delay in seeking care, time spent under nonspecialist management, referral pathway barriers, and access to specialist services may all contribute. Patient-reported symptom onset is also susceptible to recall error, particularly for long disease durations. The comparisons were unadjusted, and differences in age or other unmeasured factors may have influenced the observed intervals. In addition, this was a retrospective, single-center study from one UCARE center in Lisbon, which may limit generalizability to health care systems with different referral structures.

Nevertheless, the findings are clinically relevant because delayed specialist assessment may postpone phenotype confirmation, provocation testing, optimization of antihistamine dosing, and escalation to advanced therapies when indicated (1-3,6). Simple office-based tools, such as stroking the skin for symptomatic dermographism, cold provocation for cold urticaria, including assessment of the critical temperature threshold (CTT) and critical stimulation time threshold (CSTT) when available, and pressure provocation for delayed pressure urticaria, can support earlier recognition of common CIndU subtypes (2,3,6). Incorporating structured trigger questions and appropriate provocation testing into the initial evaluation of patients with chronic wheals or angioedema may help identify CIndU earlier. Whether these measures shorten the time to specialist care requires prospective evaluation.

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In conclusion, patients classified as having CIndU or mixed CU at their initial specialist assessment had longer median intervals from symptom onset to first specialist assessment than those with CSU. These findings support the need for greater awareness of inducible features and systematic trigger screening in nonspecialist settings, while further studies are needed to determine the factors contributing to longer intervals.

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Table 1. Baseline characteristics and time from symptom onset to first specialist assessment according to chronic urticaria phenotype

Characteristic	CSU, n=520	CIndU, n=99	Mixed CU, n=111
Female sex, n (%)	405 (77.9)	63 (63.6)	87 (78.4)
Age at first specialist assessment, median (IQR), years	45 (34–57)	36 (23.5–48)	42 (30–54)
Age at symptom onset, median (IQR), years	42 (31–54)	30 (20–44.5)	39 (25–47.5)
Time from symptom onset to first specialist assessment, median (IQR), months	4 (1–12)	10 (2–36)	12 (3–36)

CSU, chronic spontaneous urticaria; CIndU, chronic inducible urticaria; mixed CU, coexistence of CSU and CIndU; IQR, interquartile range.

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