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**Letter to the Editor**

**A visual analogue scale for itch and pain in 23 cases of cholinergic urticaria**

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Dear Editor,

Cholinergic urticaria (CholU) was described first by Duke<sup>1</sup> in 1924. CholU is a skin disorder characterized by highly pruritic wheals, 1–2 mm in size, with surrounding erythema. CholU is a chronic inducible urticaria<sup>2</sup>, and usually appears after sweating, which can be induced by hot baths, physical exercise, and/or emotional stress<sup>3</sup>.

CholU can be classified into four groups<sup>4,5</sup>: (i) conventional sweat allergy-type CholU; (ii) follicular-type CholU with a positive autologous serum skin test (ASST) result; (iii) CholU with palpebral angioedema (CholU-PA); (iv) CholU with acquired anhidrosis and/or hypohidrosis (CholU-Anhd). (i) and (iii) have type-I allergy to their own sweat, so they can be included as sweat allergy-type (SAT). (ii) is too rare to investigate, so we excluded it from this survey. Therefore, CholU was classified into two subtypes in this study: SAT and CholU-Anhd. The former is thought to hail from sweat “leaking” from sweat ducts to the dermis and stimulating mast cells to release histamine. CholU-Anhd is characterized by a reduced amount of sweat without a clear cause and can be considered as acquired idiopathic generalized anhidrosis accompanied with CholU<sup>6</sup>. It is presumed that sweat glands show poor responses to stimulation from nerves, including acetylcholine, and that excessive acetylcholine stimulates mast cells directly<sup>7</sup>. In certain conditions, the symptoms of CholU are characterized by “stinging or tingling pain and/or itching” in comparison with other types of urticaria. These feelings disturb the quality of life of patients with CholU markedly<sup>8</sup>. However, few scholars have studied these characteristic subjective symptoms quantitatively. We sought to distinguish two types of CholU by describing itch and pain symptoms quantitatively.

Twenty-three patients diagnosed with CholU at Kobe University (Kobe, Japan) participated in this study. They were asked to answer questions about their pre-treatment itch and pain scores using a visual analogue scale (VAS; 0–100 mm). Then, according to a flowchart<sup>4</sup> (Fig 1), patients with a positive autologous sweat test were defined as SAT (n=16). Patients with anhidrosis/hypohidrosis and a negative autologous sweat or negative basophil-activation test using semi-purified sweat antigen<sup>9</sup> were defined as CholU-Anhd (n=7) using the criteria of Fukunaga et al.<sup>10</sup> and Munetsugu et al.<sup>11</sup>

There were 16 cases of SAT and 7 cases of CholU-Anhd. The mean VAS score for itch before treatment was 89.1 points and 42.2 points for the SAT group and CholU-Anhd group, respectively. The mean VAS score for pain before treatment was 36.8 points and 72.6 points for patients with SAT and CholU-Anhd, respectively. The VAS score for itch was significantly higher for SAT patients (Fig 2a) than that for CholU-Anhd patients. The mean VAS score for pain was significantly higher for CholU-Anhd patients (Fig 2b) than that for SAT patients.

Next, we defined the Pain–Itch Index as the VAS score for pain divided by the VAS score for itch. The Pain–Itch Index was significantly higher in the CholU-Anhd group than that in the SAT group (Fig. 2c).

In CholU-Anhd, it is thought that reduced expression of muscarinic acetylcholine M3 receptors on sweat glands leads to excessive secretion of acetylcholine, which in turn

acts on peripheral nerves to cause pain<sup>7</sup>. Collectively, our data showed that patients with CholU-Anhd tended to feel more pain than itch whereas, for SAT cases, the opposite was true. Hawro and colleagues stated that different pruritic inducers evoke different and unique sensory qualities<sup>12</sup>. Our main study limitation was exclusion of follicular-type CholU with a positive ASST result.

Therefore, obtaining VAS scores for itch and pain before CholU treatment might be a useful tool to help differentiate between CholU subtypes, and could aid selection of future therapeutic methods.

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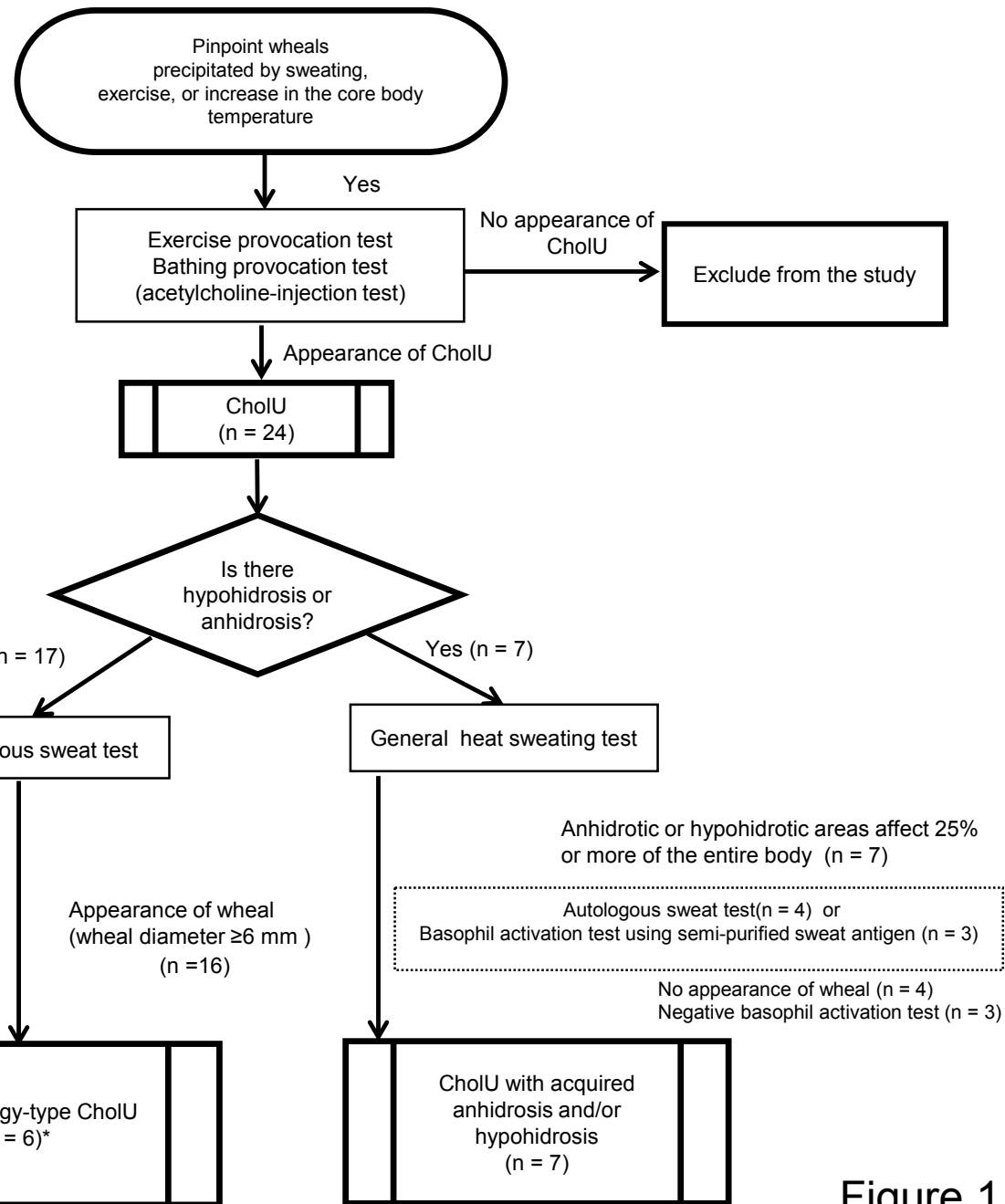
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## Figure legends

Figure 1. Study flowchart. Twenty-four patients diagnosed with cholinergic urticaria (CholU) were classified as sweat allergy-type (n = 16), CholU with acquired anhidrosis and/or hypohidrosis (n=7) or follicular-type CholU with a positive autologous serum skin test result (n=1).

Figure 2. Visual analogue scale (VAS) scores for itch (a) or pain (b), and Pain–Itch Index (calculated as the VAS score for pain divided by the VAS score for itch (c)). A recall period of question for VAS score was unspecified. Statistical analysis was carried out using the Mann–Whitney *U*-test (Prism 7.03; GraphPad, San Diego, CA, USA).

SAT, sweat allergy-type CholU. CholU-Anhd, CholU with acquired anhidrosis and/or hypohidrosis



\* Including both conventional sweat allergy-type and CholU with palpebral angioedema

Figure 1



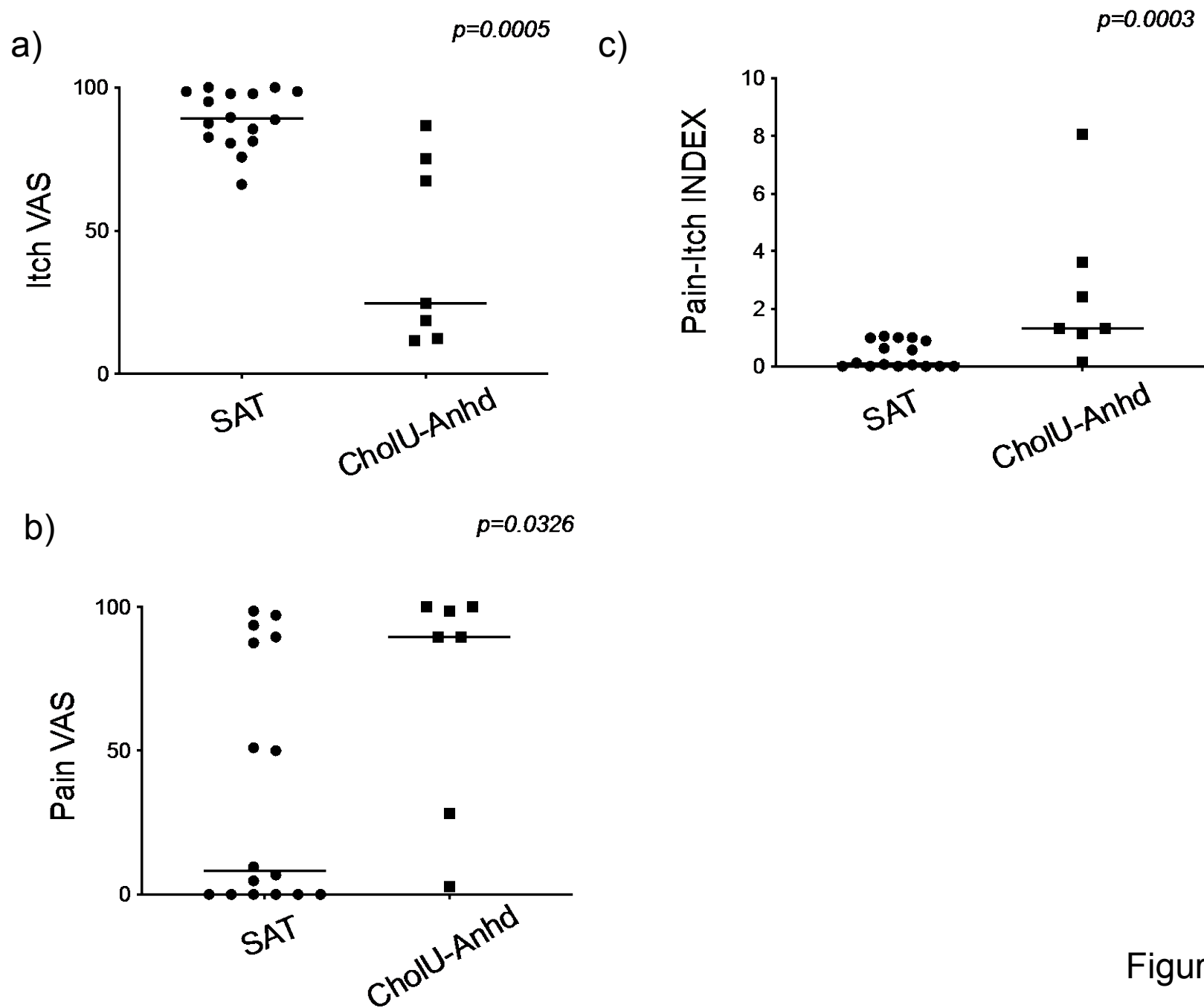


Figure 2