No pain, no gain- and no itching either
Two patients with a hereditary sensory and autonomic neuropathy
Proposal of the term «hypoknesis» (impaired pruriception)

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Background

Insensitivity to pain is a hallmark of hereditary sensory and autonomic neuropathies (HSANs)1. C- and Aδ-fibers are the major nerve fibers to conduct pain- and itch alike. In contrast to pain, however, it is largely unknown whether HSAN patients also have impaired perception of itch (“pruriception”)2,3. We report two patients with a clinical phenotype resembling HSAN type VII whose medical history and diagnostic work-up revealed an exteroceptive insensitivity including (histaminergic) itch.

Case reports

- A 31-year-old man and his 2-year-old daughter were referred to our institution due to their remarkable medical history summarized in Table 1.
- Despite normal nerve conduction studies, quantitative sensory testing (father only as not feasible in toddlers) revealed markedly abnormal thresholds of pain (heat- and mechanical pain), temperature, touch and vibration (Table 1).
- Histamine skin prick (father) induced only a minimal erythema but no itch (Figures 2 and 3).

Table 1: Summary of patient history and neurofunctional diagnostic work-up

<table>
<thead>
<tr>
<th></th>
<th>Hyposensitivity to pain</th>
<th>Hyposensitivity to itch</th>
<th>Hyposensitivity to temperature</th>
<th>Other symptoms/signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient history</td>
<td>• Repeated painless injuries (e.g. nose fracture)</td>
<td>• No scratching lesions on atopic eczema (daughter)</td>
<td>• Delayed and impaired discrimination of hot and cold</td>
<td>• Repeated gastro-intestinal painful cramps (father)</td>
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<td></td>
<td>• No pain during Thai-boxing (father)</td>
<td>• Itchy sensation to contact with stinging nettles (Urtica dioica)</td>
<td>• Repeated burns</td>
<td>Chronic night sweats/hyperhidrosis (father)</td>
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<td></td>
<td></td>
<td>• Insect bites barely itch</td>
<td>• No perception of fever</td>
<td>Pain causing behaviour towards playmates (daughter)</td>
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<td>Functional diagnostic</td>
<td>No heat pain felt at maximum temperature applied by QST (52°C)</td>
<td>Histaminergic «hypoknesis»</td>
<td>Cold detection threshold -30°C</td>
<td>Tactile hypoesthesia (vibration detection limit 4/8)</td>
</tr>
<tr>
<td>work-up (father)</td>
<td>Elevated mechanical pain threshold (724 mN)</td>
<td>No pruriception following a histamine skin prick</td>
<td>Warm detection threshold +17°C</td>
<td>Mechanical detection threshold (445.72 mK)</td>
</tr>
</tbody>
</table>

Figure 1: 10-min. course of the itch intensity (father) induced by a histamine 1% skin prick onto the volar forearm in comparison to healthy, age- and sex-matched controls. Itch intensity measured on a 0-10 NRS.

Figure 2: Only minimal local reaction to the histamine skin prick (left volar forearm)
+++: Histamine 1% in aqueous solution
+-: Sodium chloride 0.9%

* Based on the patient history and neurofunctional testing an autosomal dominant subtypes HSAN appears suggestive with type VII being most suitable. An important differential diagnosis is congenital insensitivity to pain (CIP). There is considerable clinical overlap with HSNA disorders. However, genetic testing for the 14 genes most commonly affected in HSANs and CIP has not revealed a pathogenic sequence variant or gene dosage change.

Discussion

These two cases indicate that in HSAN patients not only the perception of pain, but also to itch may be impaired- a fact possibly not adequately addressed in these patients. To our knowledge, only a single case of combined insensitivity to pain and itch has been published, lacking itch induction and QST3. Thus, this is the first report to demonstrate impaired pruriception in patients with a HSAN phenotype.

We propose to use the term “hypoknesis” (as an antonym to “hyperknesis”) to describe impaired pruriception in this context. Whether the absence or presence of “hypoknesis” might help to classify HSANs and whether it also applies to non-histaminergic itch remains to be elucidated. While insensitivity to pain is more of a disadvantage due to continuous risk of injuries, insensitivity to itch may rather be an advantage for HSAN patients.

CIP are caused by mutations in voltage-gated sodium channel genes, SCN9A, SCN11A, ZFHX2 or in the pseudogene FAAH-OUT. The FAAH-OUT pseudogene has recently been recognized to be involved in insensitivity to pain via the endocannabinoid system4. Microdeletions in the pseudogene and long non-coding RNA are causative5. Unfortunately, this analysis has not yet been completed in our patients. Even if no genetic cause should ultimately be proven in the father and his daughter, an autosomal dominant pain loss syndrome can be assumed.

References


QST: Quantitative sensory testing

Histamine flare

<table>
<thead>
<tr>
<th>Histamine flare</th>
<th>Erythema (mm)</th>
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<tr>
<td>0</td>
<td>2</td>
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</tbody>
</table>

Sex- and age-matched controls

| Sex- and age-matched controls | 7.93 | 43.6 |

Figure 1: 10-min. course of the itch intensity (father) induced by a histamine 1% skin prick onto the volar forearm in comparison to healthy, age- and sex-matched controls. Itch intensity measured on a 0-10 NRS.