

## SHORT COMMUNICATION

# When Cold Becomes Hot and Hot Becomes Cold: Unearthing a Historical Report

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We discuss a curious case of abnormal hot/cold sensation recorded by the renowned medieval Persian physician Nurbakhshi. The patient's presenting symptoms imply a neurodevelopmental abnormality; however, the most striking feature of Nurbakhshi's report is the apparent absence of any other pathology, particularly hyperalgesia. This may indicate mis-targeting of A-delta or, more probably, Type 2 C fiber afferents to specific regions of the central nervous system. As far as we are aware, no similar case can be found in the medical literature, medieval or modern. We present a brief biography of Nurbakhshi, a translation of his short report of the case, and a discussion of the possible pathophysiological basis of the condition described. The proposed developmental abnormality may have involved the targeting of unmyelinated afferents to the temperature-responsive regions of the insular cortex, perhaps as a result of defective semaphorin production. The alternative possibilities are mutation(s) of one or more genes encoding thermoTRPs and toxin-mediated phenomena.

**Key words:** Cutaneous, Nerve, Physiology, Sensation, Temperature

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## Biography of Nurbakhshi

*Baha' al-Dawlah* ibn Siraj al-Din Shah Qasim ibn Muhammad al-Husayni Nurbakhshi, a 15-16<sup>th</sup> century Persian physician (renowned as *Rhazes the Second*), is known by a single treatise: *Khulasat al-Tajarib* (Synopsis of Experiences), which was composed in 1501 CE in the village of Tarasht, near Ray (present-day Tehran). Evidence about Nurbakhshi's life is given in Storey and Richter-Bernburg.<sup>1,2</sup> To the introduction of Nurbakhshi, one may quote a statement from Cyril Elgood, a British Orientalist, who mentioned of Nurbakhshi as "the greatest physician who ever lived in Persia after the passing of the golden age of the caliphs of Baghdad."<sup>3</sup>

In *Khulasat al-Tajarib*, Nurbakhshi recounts the following intriguing case. The patient's presenting symptoms imply a neurodevelopmental abnormality. We discuss potential mechanistic aspects of it in light of current understanding of the physiology of the nervous system.

## The Case Report from *Khulasat al-Tajarib*

I saw a person in Astarabad who had [a habit of] sitting in the icy waters during the winter and hanging an ice-made ornament on his neck. In the early morning and when the weather was cold and froze everybody, he walked in the city while putting off his clothes leaving [only] a waist-cloth. He took a pan in one hand and a water vessel in the other, pouring water over his head and blowing air on himself with the fan. There were chains of ice hanging from his beard. However, he insisted that the weather was hot. During the hot summer, he wore several clothes and a fur coat and continually sought fire to keep himself warm, still appearing to be shaking. He lived many years with that condition, but was [otherwise] healthy and happy.

## DISCUSSION

The case appears bizarre, perhaps unique, so fabrication might be suspected. Half a millennium after *Khulasat al-Tajarib* was written, that possibility cannot be excluded. However, Nurbakhshi evidently observed the patient himself rather than giving credence to a rumor or another physician's report. Moreover, the remainder of *Khulasat al-Tajarib* comprises cases that are more readily recognizable today, and Nurbakhshi's status and reputation seem inconsistent with dishonesty. We therefore believe the account to be accurate. Presumably it describes an abnormality of temperature sensation rather than a disturbance of core temperature control, for which a plausible etiology would be hard to imagine.

Even if the abnormal temperature sensation hypothesis is adopted, several aspects of the case are problematical. First, Nurbakhsi's brief account gives no history of the patient, though the symptoms seem to have appeared early in life. Second, we are not told whether other members of the patient's family were affected. Third, additional symptoms are not explicitly excluded, though the final sentence of the report implies there was no hyperalgesia, which might be expected in a neurological disorder affecting cutaneous temperature sensation. Finally, nothing comparable has been reported in the present-day medical literature. What follows is therefore conjectural.

Ochoa and Yarnitsky described 28 cases of cold hyperalgesia associated with cold hypoaesthesia in patients with peripheral polyneuropathy or mononeuropathy of different etiologies.<sup>4</sup> They proposed a mechanism of sensory disinhibition to explain the hyperalgesia and the cold skin, and named the condition the 'triple cold syndrome' by analogy with the triple response.<sup>5</sup> Clearly, Nurbakhsi's patient did not suffer from triple cold syndrome, but an analogous peripheral neuropathy may be plausible. The main difficulty with such an explanation is the apparent absence of further symptoms that would be expected in a peripheral neuropathy, particularly hyperalgesia. Therefore, central nervous involvement seems more probable.

One possibility is a developmental abnormality entailing erroneous targeting of the neurite precursors of the A-delta and/or C fiber afferents from cutaneous receptors on to the dorsal root ganglia or brain centers. During the past decade, the neural pathways involved in the transmission of heat and cold sensation have been studied in detail in both humans and experimental animals.<sup>6-10</sup> The data obtained so far do not directly elucidate Nurbakhsi's case, though they suggest that the bimodal thermoreceptive properties of Type 2 C fibers may be relevant<sup>8,9</sup>, and a region in the insular cortex with a complex role in heat perception could be involved.<sup>10</sup> Nurbakhsi's patient might have suffered a developmental abnormality in this region involving mis-targeted Type 2 C fibers. For example, there may have been a defect in the production of semaphorins – notably semaphorin III – that mediate repulsive and inhibitory guidance of neurons with nerve growth factor receptors, such as A $\delta$  and C fibers.<sup>11</sup>

Alternatively, there could have been a mutation in a thermoTRP gene. The thermoTRPs are transient receptor potential ion channels that are activated by different physiological temperatures, and are crucial in transducing thermal stimuli into chemical and electrical signals within the sensory nervous system.<sup>12</sup> A functional change in one or more of these proteins could, in principle, result in a sensory abnormality of the kind described by Nurbakhsi.

Ciguatera fish poisoning has also been reported to cause paradoxical reversal of hot and cold sensation, but it additionally causes a variety of gastrointestinal and cardiovascular symptoms and pruritus.<sup>13</sup> It has been suggested that this

phenomenon is related to ciguatera-induced persistent opening of the nerve membrane sodium channels causing an exaggerated nerve depolarization originating in peripheral small A-delta myelinated and C-polymodal nociceptor fibers.<sup>14</sup> Ciguatera fish poisoning is relatively common in East Asia and Southeast Asia.<sup>15</sup> Although the possibility of this poisoning is remote in the Caspian Sea region where Nurbakhsi's patient resided, one should bore in mind the plausibility of a similar toxin-mediated phenomenon in that case.

## CONCLUSION

Historical medical reports are often difficult to interpret in present-day terms, but they present a useful challenge to our understanding of physiology and pathophysiology. Current research findings sometimes suggest explanations, as in the case explored here. Conversely, a report such as Nurbakhsi's may present an interesting challenge to researchers in the relevant field. We would be interested to know whether readers of this communication can offer more plausible explanations for the curious abnormality suffered by Nurbakhsi's patient.

## CONFLICT OF INTEREST STATEMENT

The author has no conflict of interest to disclose.

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