

THE ORIGIN OF THE CONCEPT OF NEUROPATHIC PAIN IN EARLY MEDIEVAL PERSIA (9TH-12TH CENTURY CE)

IZVORIŠTE POJMA NEUROGENE BOLI U RANOSREDNJEVJEKOVNOJ PERZIJI (9.-12. STOLJEĆE)

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SUMMARY

Neuropathic pain is supposed to be a post-renaissance described medical entity. Although it is often believed that John Fothergill (1712-1780) provided the first description of this condition in 1773, a review of the medieval Persian medical writings will show the fact that neuropathic pain was a medieval-originated concept. "Auojae Asab" [Nerve-originated Pain]

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was used as a medical term in medieval Persian medical literature for pain syndromes which etiologically originated from nerves. Physicians like Rhazes (d. 925 CE), Haly Abbas (d. 982 CE), Avicenna (d. 1037 CE), and Jorjani (d. 1137 CE) have discussed multiple aspects of nerve-originated pain including its classification, etiology, differentiating characteristics, different qualities, and pharmacologic and non-pharmacologic treatments. Recognizing medieval scholars' views on nerve-originated pain can lighten old historical origins of this concept.

Key words: Iranian Traditional Medicine; Medieval History; Neuralgia; Neuropathic Pain; Persian Medicine; Avicenna; Jorjani; Rhazes

INTRODUCTION

Pain management traces its history back to the ancient times. The ancient physicians like those who lived in Egypt, China and Persia, considered pain as an emotion rather than a sensory modality [1]. Ancient Egyptian physicians used opium and *Salix* (*Salicyl* bark from the willow tree) as analgesics ca. 3000 BCE [2]. Evidence of acupuncture practice for pain control was identified on the “Ice Man” who died ca. 3300 BCE [3]. Ancient texts documented medicinal herbs such as *Cannabis* (*Cannabis sativa* L.) as an analgesic in pre-historic times used by Persian physicians [4].

Different theories on pain perception were presented by Ancient Greek scholars. The Greek term *Poinē* [*Punishment*] is known as the origin of “pain” word. Aristotle (384-322 BCE) considered the heart as the point-or-origin for pain. Based on his observations in animals, Galen (130-200 CE) amended Aristotle’s theory on pain and supplanted the heart with the brain as the central organ in pain perception. Galen also suggested nerve tissue as the transferring route of pain to the brain through the invisible psychic pneuma. In his opinion, this pneuma traveled within the hidden hollows of the nerves [5].

In the medieval era, a number of Islamic medical scholars thoroughly discussed pain related topics. Muhammad ibn Zakariyā Razi (Rhazes) (865-925 CE), in his medical book “*Al-Havi*” [*Liber Continens*], first quoted Greek scholars’ theories on pain in detail; then, declared his own observations [6]. He disapproved Galen’s theory that mild pain is not sensed when concomitant with more severe pain [7].

Ali ibn al-Abbas al-Majusi (d. 982 CE), commonly known as Haly Abbas in the West, devoted the 17th chapter of 6th treatise of his medical encyclopedia *Kamil al-Sinaa al Tibbiya* [*Complete Book of the Medical Art*] to the description of his theory on pain [8]. He defined pain as an unpleasant sensation

opposed to natural condition. Haly Abbas believed that all five body senses could be involved in pain perception. He considered five senses for pain perception. These included touch (the most sensitive one to pain), taste, smell, auditory, and vision senses [9].

Later to Haly Abbas, in *Al-Qānūn fī al-Tibb* [*Canon of Medicine*], Avicenna described his theory on pain [10]. Avicenna did not accept Galen's view on the 'interruption of continuity' as the sole cause of pain and described temperamental change (stimulus that alters the physical condition of organs) as a further cause of pain.

Avicenna expanded Galen's classifications of pain from four to fifteen items based on the different qualities of pain, i.e., itching, coarse, pricking, compressing, stretching, disintegrating, breaking, soft, penetrating, stabbing, numbing, pulsating, tiredness, breaking, and heavy quality pain [11]. He described many herbs with analgesic properties, and addressing the aspects of opium and a detailed description of its medicinal use [12].

Ismail-e Jorjānī (1137 CE), the author of "*Zakhire Kharazmshahi*" [*The Treasure of King Khwarazm*], added the concept of "itchy pain" to previous types [13]. He also suggested organ warming, functional disturbances and power attenuation as the consequences of pain in a specific organ [14].

Despite the long-lasting historical background of the pain resulting from tissue injury (nociceptive pain), presently, it is often believed that the concept of nerve-originated pain (neuropathic pain) is a post- renaissance medical described entity. However, multiple cases support a medieval origin for this concept. In the present paper, we propose to review case studies in early medieval literature regarding this topic, with emphasis on the most outstanding scholars of that era, Rhazes, Haly Abbas, Avicenna, and Jorjani. We examined the most important medical encyclopedias of that period, the "Al-Hawi fi al-Teb", "Kamil al-Sinaa al-Tibbiya", "Al-Qanun fi-al-Tibb" and "Zakhire Kharazmshahi", respectively. Our focus was devoted to the chapters describing diseases of nerves, and nerve-originated pain and its treatment methods

CURRENT HISTORICAL LITERATURE ON NEUROPATHIC PAIN

Neuropathic pain is defined as "pain initiated or caused by a primary lesion or dysfunction of the nervous system" [15]. It can be associated to abnormal sensations (dysesthesia) or painful response to typically non-painful stimulus (allodynia). In contrast to nociceptive pain, commonly described as

ache, neuropathic pain has different qualities such as burning or coldness, “pins and needles” sensations, numbness or itching.

The earliest description of neuralgia dates back to 1773 when John Fothergill (1712-1780) described trigeminal neuralgia clinically, though he did not use the term neuralgia, which came into use some years later [16-18]. Some years later, in 1829, Sir Charles Bell (1774-1842) differentiated between the functions of the facial and trigeminal nerves, and recognized that trigeminal nerve provides sensibility to the head and face [19].

In the medical articles indexed in medline, the word “*Neuropathy*” was used for the first time by Gordon in an article entitled “*Clinical Lecture on Lead Neuropathy*” published in 1924. However the word neuropathia was defined as a Term for nervous disease, or disease of a nerve by R. G. Mayne Expos. Lexicon Med. Sci. (1860). The changing sensation on malnutrition-induced neuropathy was described by Brigden in 1948 [20]. Dick Metcalf’s study on the numbness, pins, and needle type pain, associated with sensory neuropathy due to lung carcinoma was considered as another milestone in the history of neuropathic pain [21].

THE CONCEPT OF NERVE-ORIGINATED PAIN IN EARLY MEDIEVAL PERSIA

The early medieval age (9-12th century AD) was a significant historical period in Persia’s history of science. This period was accompanied by a great magnitude of growth in the Islamic territory. This flowering initiated an important historical period, known as “*Islamic Golden Age*”, in these countries. Medicine had a significant role in this scientific growth as many universally-known Persian physicians lived in this era such as Rhazes, Haly Abbas, Avicenna and Jorjani. Medieval Persian physicians were familiar with the medical knowledge of ancient Egypt, India, and China. In advance, temperamental medical system theorized by Indians and Persians [22] and then by Greek physicians such as Hippocrates and Galen. Later, medieval Persian physicians added the results of their own medical experiments to this ancient medical knowledge contributing to considerable development of temperamental medical system.

The term “*Vaja al-Asab*” [Nerve-Originated Pain] was used as a term in the medieval medical literature for describing pain syndromes which etiologically originated from nerves rather than the tissues and organs. The term “*Khader*” [Abnormal sensation] was also used by Persian scholars to explain

abnormal sensations such as numbness, moving ant, or piercing needles because of nervous anatomic or functional pathology [9]. Accordingly, some early medieval Persian physicians' views on this topic are presented.

RHAZES (865-925 CE)

Zakariyā Rāzī, commonly known as Rhazes, was a Persian philosopher, chemist, and physician, and was born in Rey city (Iran). He was the chief physician in Rey and Baghdad hospitals. Known as the father of Islamic medicine, he was considered one of the greatest physicians of the Muslim World. Rhazes' medical encyclopedia "*Al-Hawi fi al-Teb*" [23] known as "*The Large Comprehensive*" or "*Liber Continens*" includes arguments on the Greek philosophers such as Aristotle, Plato and Galen as well as on his own experience with his clinical cases on various diseases [24].

Rhazes classified the various pains according to their point-of-origin and believed that the nerve were the potential originating site of pain contiguous to the viscera, bone, fascia, muscle and blood vessels. Additionally, he described the differentiating properties of the nerve-originated pain in his book the *Liber Continens* [23].

"When an organ has no pain sense and its fascia is sensitive to pain, such as the liver, spleen, lung and kidney, the pain of such organ will be sensed in heavy quality. The longitudinal pain that is similar to painful cord is due to nervous or vascular pathology. The nerve pain is deeper than venous and more superficial than arterial originated pain. The circular pain is due to facial pathology. The twisty pain is muscular origin and the breaking one is from the periosteum. The loose non-stretching pain is due to the pathology in connective tissues. "

HALY ABBAS (949-982 CE)

Ali ibn al-Abbas al-Majusi [Haly Abbas] (982 CE) was born in the city of Arrajan (now in southwestern Iran). He supplemented his own clinical experiences to preceding knowledge and integrated them in his medical encyclopedia entitled "*Kamil al-Sinaa al Tibbiya*" [9] [*The Perfect Book of the Art of Medicine*]. He presented original theories in different fields of medicine such as cardiology and neurology in this book, which had a marked influence on Avicenna (980–1037) [25]. Haly Abbas therefore, is considered the bridge connecting ancient and medieval medicine [26].

Haly Abbas developed Rhazes' theories by introducing numbing, tingling and needle-like forms of pain as insightful criteria of nerve-originated pain [9].

“... and the characteristic of Khader is that the patient sense like the moving ant or penetrating needle in his organ, with the defect in his sensation quality and motor dysfunction, similar to condition that happens in the foots when anyone sit on them or be compressed by other thing for a long time.”

A case-in-point was his discussion regarding pathophysiology of nerve originated pain. Haly Abbas proposed nerve compression at different spinal levels and sensory nerves as the potential etiology for nerve-originated pain. According to him, excessive temperatures and physical cold stimuli on nerve could be the causal agent. His observations on the mentioned pathological conditions were associated with impairment in the nerve conduction leading to an abnormal sensory function. He also theorized a possible motor dysfunction with nerve-originated pains as in the case of sensory and motor innervations of an organ by a single nerve [9].

AVICENNA (980-1037 CE)

The most prominent physician of the Islamic Golden Age, Avicenna also known as *Ibn-e-Sina* was born in Afshaneh, a city near Bokhara (in old Persia) in 980 CE. His medical encyclopedia, *Al-Qānūn fī al-Tibb* [27] (The Canon of Medicine) was translated to Latin by Gerard of Cremona in the 12th century CE and became one of the most renowned medical references in the world until the 16th century [28]. Avicenna rejected many of his predecessors' theories and introduced many original ones in the field of neurology [29].

Avicenna expanded the etiological concept of Haly Abbas on nerve-originated pain. He introduced other kinds of this type of the pain such as toxic and induced snake bite ones. He also suggested natural electrical injury due to touch of the electric fish as another cause of nerve-originated pain [27].

“Khader may be due to ... poisoning, snake or scorpion bite, touch of an electrical fish called Nagher, opium overdose ...”

Avicenna, based on the site, classified the causes of nerve-originated pain into brain, total spinal cord, specific level of spinal cord, and peripheral nerve damage. He also noted the coincidence of nerve-originated pain with stroke, epilepsy, meningitis and tetanus. Avicenna believed that motor neurons are less sensitive than sensory neurons in pathologic conditions, so

chronicity of sensory neuropathies may lead to motor dysfunctions. He also made a description of trigeminal neuralgia [30].

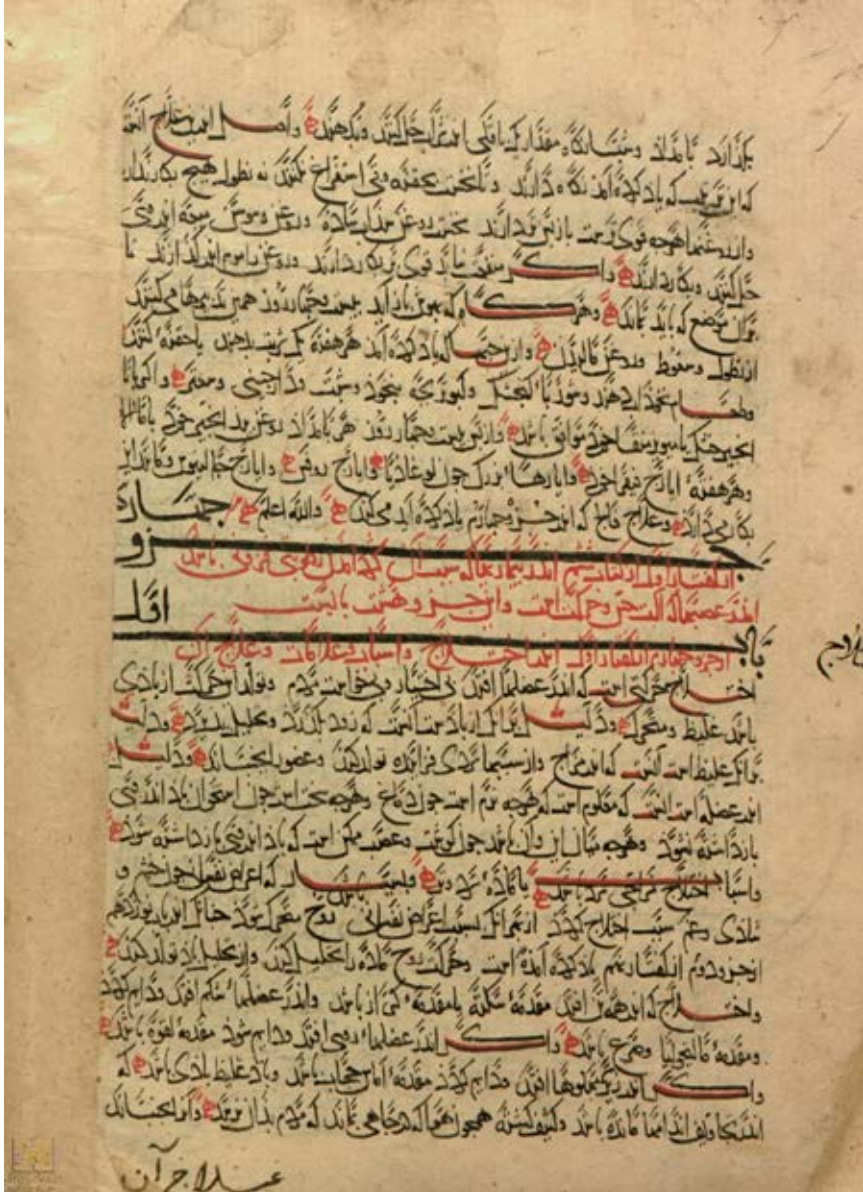


Figure 1. The first page of Chapter of “Nerves Diseases”, from Zakhireye Khwarazmshahi Manuscript, kept in Iran National Library, record number:

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JORJĀNĪ (1040-1136 CE)

Sayyed Ismail ibn Husayn Gorgani (1040–1136 CE) known as Jorjani, was born in Gorgan (Northern Iran). His “*Zakhireye Khwarazmshahi*” [14] [The Treasure of King Khwarazm] is known as the oldest and most comprehensive medical encyclopedia in the Persian language in the medieval era (Figure 1). Although largely influenced by Avicenna, he presented numerous important medical findings, which were not previously reported by Avicenna [31].

Traumatic nerve pain is another concept of nerve-originated pain that is discussed by Jorjani. Iatrogenic nerve injuries were prevalent in medieval Persia as a complication of bloodletting by venesection. Jorjani believed that nerve injury is more painful than other tissue injuries due to functional and anatomic connection between nerves and brain. He also considered sciatica [*Erghonaasa*] as a nerve-originated pain that could lead to motor dysfunction [14].

TREATMENTS FOR NERVE-ORIGINATED PAIN IN MEDIEVAL PERSIA

Different therapeutic strategies were used for management of nerve-originated pain in medieval Persia. Topical oil-based ointments’ of herbs with hot temperaments (based on temperamental theory of ancient Persian medicine which divided herbs to hot and cold temperaments) such as pepper, chamomile, thyme, colocynth and flax were used for nerve-originated pain. Lavender syrup was the most popular systemic treatment suggested for nerve-originated pain by medieval Persian scholars.

Warm compress (*Takmid*) was also used as non-pharmacologic treatment in that era [23]. Cauterization (burning the nerve by special instruments) was considered as the last option for some kinds of severe nerve-originated pain resistant to other treatments [27]. Some of herbal remedies used in the treatment of nerve-originated pain and potential mechanism of their effect in light-of current medical literature are summarized in Table I.

Table I. Medicinal plants mentioned in the medieval Persian medical books for managing the nerve originated pain.

| COMMON NAME | TRADITIONAL NAME | SCIENTIFIC NAME | ROUTE OF ADMINISTRATION | PHARMACOLOGIC EFFECT |
|-------------|------------------|--------------------------|---------------------------------------|---|
| Pepper | <i>Felfel</i> | <i>Capsicum annum</i> L. | Oral, Topical (Oil based formulation) | Antinociceptive, Antiinflammatory, Antioxidant, Neuroprotective [32,33] |

| COMMON NAME | TRADITIONAL NAME | SCIENTIFIC NAME | ROUTE OF ADMINISTRATION | PHARMACOLOGIC EFFECT |
|---------------|---------------------------|------------------------------------|---------------------------------------|--|
| Colocynth | <i>Hanzal</i> | Citrullus colocynthis (L.) Schrad. | Topical (Oil based formulation) | Analgesic, Antiinflammatory, Antioxidant [34] |
| Olive | <i>Zeyton</i> | Olea europaea L. | Topical (Olive oil) | Anti-inflammatory, Antioxidant, Neuroprotective [35] |
| Castor | <i>Karchak</i> | Ricinus communis L. | Topical (Castor oil) | Anti-inflammatory, Antioxidant [36] |
| Flax | <i>Katan</i> | Linum usitatissimum L. | Topical (Flax oil) | Analgesic, Antioxidant, Neuroprotective [37] |
| lavender | <i>Iranian Ostokhudus</i> | Nepeta menthoides Boiss. & Buhse | Oral (Syrup) | Anti-inflammatory [38,39] |
| Shirazi Thyme | <i>S'atar</i> | Zataria multiflora Boiss. | Oral (decoction) | Analgesic, Antiinflammatory [40] |
| Garlic | <i>Sir</i> | Allium sativum L. | Oral, Topical (Oil based formulation) | Analgesic, Antioxidant [41] |
| Citron | <i>Balang</i> | Citrus medica L. | Topical (Oil based formulation) | Analgesic, Antiinflammatory [42] |
| Saffron | <i>Zaferan</i> | Crocus sativus L. | Topical (Oil based formulation) | Antinociceptive, Antiinflammatory [43] |

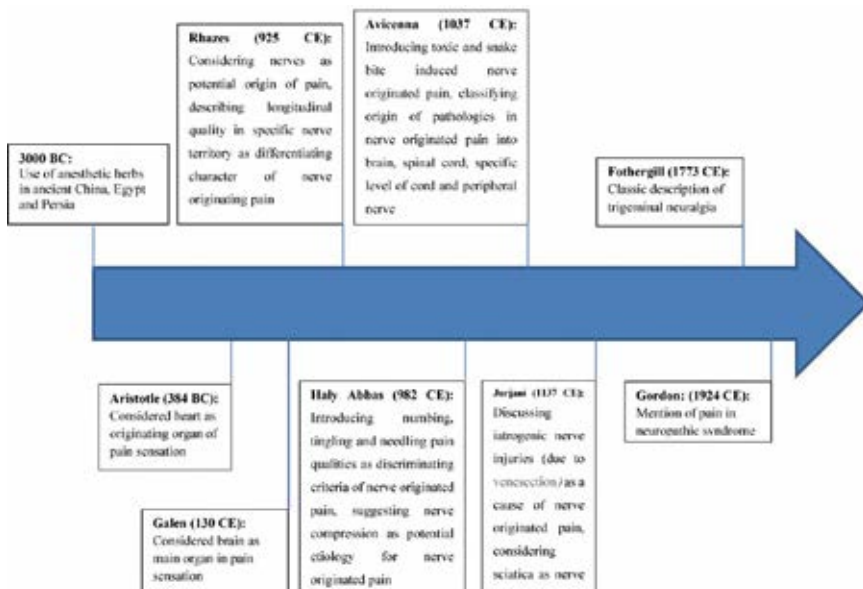


Figure 2. Time table of historical findings on the concept of neuropathic pain

DISCUSSION AND CONCLUSION

Persian physicians of Islamic Golden Age have contributed incalculably to the medical sciences. They were familiar with many medical concepts which supposed to be described in post-renascence decades for the first time [44,45]. Neuropathic pain is also a present-day medical term with old origins which has remained uncovered.

In spite of this fact that the current concept of neuropathic pain is a new entity in medical literature, the concept of origination of pain from the nervous system itself, without any stimulating pathology in other organs, seems to have old medieval Persian origin. The Persian medieval medical scholars named this type of pain specifically as "*vaja al asab*", described its numbing, tingling and needling quality, and discussed its etiology and the differentiating characteristics of this kind of pain in comparison with other types of pain. Although their knowledge on this topic which definitely was not fully compatible with current findings on neuropathic pain, it is historically valuable for their time and can be considered as the first preliminary description of neuropathic pain in the history of medicine.

Along with lightening the hidden aspects of the development of medical science, another importance of such historical reviews on medieval medical literature is popularity of their practice as a traditional medical system in Middle East and India [46]. Familiarity with the concept of this system which known as "Unani medicine" in India and "Persian medicine" in Iran, can help us to better understand of traditional Persian medicine practitioner's practice for investigating potential benefits and harms.

Introduction of new options and findings for the drug discovering systems may well be another benefit of these historical surveys. An additional and significant source of information for medical research are the herbal drugs which have thousands of years of history, that have been and are currently in use and administered by the different practitioners from Greece to India. Suggested by medieval scholars, an example of this is the drug capsaicin a popular topical ointment prescribed for neuropathic pain among other uses, and has an herbal origin, which has its roots in medieval medicine, and a medieval medical historiography.

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SAŽETAK

Smatra se kako je neurogena bol medicinski entitet opisan u postrenesansnom dobu. Mada se često vjeruje kako je ovo stanje prvi opisao John Fothergill (1712.–1780.) 1773. godine, prikaz perzijskih srednjovjekovnih medicinskih zapisa pokazuje da je neurogena bol pojam koji potječe iz srednjeg vijeka. Termin *Auojae Asab* [Bol koja potječe iz živca] bio je korišten u perzijskoj srednjovjekovnoj medicinskoj literaturi za sindrome boli koji su etiološki potjecali od živaca. Liječnici poput Rhazes (u. 925.), Halyja Abbasa (u. 982.), Avicenne (u. 1037.) i Jorjanija (u. 1137.) razmatrali su više aspekata boli koja potječe od živaca, uključujući njezinu klasifikaciju, etiologiju, diferencirajuća obilježja, različita svojstva, farmakološki i ne-farmakološki tretman. Uvažavanje stajališta srednjovjekovnih znanstvenika može rasvijetliti staro povijesno izvorište ovog pojma.

Ključne riječi: Iranska tradicijska medicina; srednjovjekovna povijest; neuralgija; neurogena bol; perzijska medicina; Avicenna; Jorjani; Rhazes.