

## Pain in Ehlers-Danlos syndrome: a diagnostic and therapeutic challenge

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### Abstract

*EDS patients shows chronic and frequently debilitating pain described from different authors as multifactorial. Pain has been described as neuropathic in some individuals but probably the persistent nociceptive input due to joint abnormalities probably triggers central sensitization in the dorsal horn neurons and causes widespread pain. The knowledge of the correct type of pain is necessary for the correct management in particular for the rehabilitative approach.*

**Keywords:** *Ehlers-Danlos, Hypermobility, Pain, Rehabilitation.*

Ehlers–Danlos syndrome (EDS) comprises a growing range of hereditary connective tissue disorders primarily affecting skin, ligaments, joints, blood vessels and internal organs. The widely agreed EDS classification identifies six major variants, the most common being the hypermobility type (EDS-HT) [1]. The lack of specific clinical signs and laboratory confirmatory tests makes EDS-HT merely a tentative diagnosis. EDS-HT also shares identical clinical features with the joint hypermobility syndrome (JHS). Some authors therefore consider these two disorders as a unique and indistinguishable condition (JHS/EDS-HT) [2].

In the last two decades, a growing number of studies pointed out the impact of EDS on quality of life in term of symptom chronification in those patients who skip catastrophic events, and then reach adulthood and the old age. Accordingly, musculoskeletal pain [3] and chronic fatigue [4] are highly reported in various forms of EDS and are both important possible determinants of disability in EDS-HT [5].

Sacheti et al. [6] firstly described the characteristics of pain in EDS patients, showing that chronic and frequently debilitating pain of early onset and diverse distribution was a constant feature in most individuals affected with different types of EDS. They showed that individuals with EDS suffer moderate to severe pain that starts early in life and evolves over time; pain problems associated are described as complex and varied with pain in several locations. They showed that pain was often chronic and multifocal and suggested to have several causes: secondary to frequent dislocations, resulting from repeated soft tissue injury, or related to multiple operations with peripheral nerve injury.

This multifactorial basis was assumed to cause a variable course of pain in EDS: pain related to repeated soft tissue injury or multiple operations with peripheral nerve injury was thought to cause a constant level of pain, whereas hypermobility and dislocations may lead to additional peaks of pain.

Successively Voermans et al [7] made a study in a large

group of EDS patients that shows 1) chronic pain is highly prevalent in EDS and is associated with regular use of analgesics; 2) pain is more prevalent and more severe in patients with the hypermobility type than in those with the classic type and vascular type; 3) pain severity is related to hypermobility, dislocations, and previous operations but not to other disease-related factors; 4) pain is related to sleep disturbances; and 5) pain is related to functional impairment in daily life, independent of the level of fatigue.

The high prevalence of pain and add the finding that pain is most common and most severe in patients with the hypermobility type of EDS. Furthermore, this study shows that myalgia is reported by most patients, and that pain is predominantly localized in neck, shoulders, hips, and legs but not in the head or abdomen. Most severe pain is correlated to hypermobility, dislocations, and previous surgery. Together, these findings may indicate that pain in EDS has a compound origin: a constant level of pain may originate in the musculoskeletal system, and additional peaks of severe pain may be related to recurrent (sub)luxations and/or dislocations. Furthermore, pain severity in EDS was found to be independently related to functional impairment.

In the 2011 Camerota et al. [8] made a study that attempted to assess the type of pain in EDS. Their preliminary findings were apparently in contrast with common sense, that is, in EDS, pain is directly linked to primary joint damage and, consequently, is mainly nociceptive in origin. In fact, their results suggest that pain was frequently neuropathic. This implies that the pathophysiology of pain in EDS may be more complex than expected, and that musculoskeletal involvement cannot explain the entire spectrum of pain. Accordingly, it is likely that pain symptoms in EDS are the result of different pain-triggering mechanisms. The absence of significant differences between the classic and hypermobility types of EDS suggests that the two forms should equally be considered for a high risk of pain, and that they very probably share the same pathophysiology related to pain.

Voermans [9] suggested that compression neuropathy also may cause neuropathic pain in EDS, as founded by her group.

Recently, in order to clarify the kind of pain affect the EDS-HT patients Di Stefano et al. [10] underwent a detailed clinical examination, including the neuropathic pain questionnaire DN4 and the fibromyalgia rapid screening tool associated to quantitative sensory testing methods, included thermal-pain perceptible thresholds and the wind-up ratio and recorded a standard nerve conduction study to assess non-nociceptive fibres and laser evoked potentials, assessing nociceptive fibres.

Clinical examination and diagnostic tests disclosed no somatosensory nervous system damage. Conversely, most patients suffered from widespread pain, the fibromyalgia rapid screening tool elicited positive findings, and quantitative sensory testing showed lowered cold and heat pain thresholds and an increased wind-up ratio. While the lack of somatosensory nervous system damage is incompatible with neuropathic pain as the mechanism underlying pain in JHS/EDS-HT, the lowered cold and heat pain thresholds and increased wind-up ratio imply that pain in JHS/EDS-HT might arise through central sensitization. Hence, this connective tissue disorder and fibromyalgia share similar pain mechanisms. Authors finally concluded that in patients with JHS/EDS-HT, the persistent nociceptive input due to joint abnormalities probably triggers central sensitization in the dorsal horn neurons and causes widespread pain and manifest signs compatible with central sensitization.

All these data suggest the importance of the correct management of this syndrome with particular regard to the rehabilitative approach that may play an important role in the prevention and treatment of symptoms related [11].

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