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A survey of Neuropathies among Patients with Generalized Joint Hypermobility in View of the Initial Assessment

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Abstract

Background: Patients with symptomatic generalized joint hypermobility is a very vulnerable group in the initial care seeking, as the neuropathic components of the condition may be overlooked. This literature survey aims to contribute to improvement in the initial management of patients with symptomatic generalized joint hypermobility – by describing neuropathies associated with this syndrome.

Methods: A literature review was performed in the electronic databases PubMed, Cinahl, and Web of Science using the two keywords "Hypermobility", and "Neuro-" (Neuropathic, Neurological, and so forth).

Results: There were, as of November 2020, a total of 664 publications for the period 1947 to 2020. Out of these, 62 articles describing peripheral, spinal, and supraspinal nerve involvement and central sensitization in symptomatic generalized joint hypermobility were included in the survey.

Conclusion: Screening for nerve involvement and central sensitization should be part of the assessment for patients who present clinically as with symptomatic generalized joint hypermobility. The patients' narrative is a vital part in the initial management, as perceived symptoms provide valuable additional information to classify the condition, and consequently adds to the factual foundation for the task to identify the cause/diagnosis. We recommend to emphasize the "central sensitivity" diagnose when present, to promote patient empowerment and self-care.

Keywords: Hypermobility; Joint Laxity; Connective Tissue; Spine, Fatigue; Chronic Pain; Central Nervous System Sensitization; Primary Healthcare

Introduction

This report presents an overview of neuropathies and central sensitization in symptomatic generalized joint hypermobility (SGJH) due to defective connective tissue, mainly the Hypermobility spectrum disorders and Ehlers-Danlos syndrome hypermobility type (hEDS), both caused by mutations in genes controlling for collagen structure or biosynthesis [1]. The objective is to draw attention to some of the needs in the clinical assessment of patients. Up until 2009, the broad scientific discussion in this field did not seem to include issues regarding the nervous system. Many years the association of tiredness or lack of energy (fatigue) and muscle weakness with generalized joint hypermobility was seen as an indirect link. This linkage was based on a logic that diminished muscle force and a cautious "motor habitus", not to risk injury, led to a diminished amount of physical activity, in turn leading to fatigue [2]. This might perhaps still be a standard explanation in some care facilities. The last decade, however, more and more researchers have looked at clinical features in the group, not least the most common – pain and fatigue [3].

Prevalence

Prevalence of generalized joint hypermobility is estimated to about 20 % for the entire population (Iraqui and Swedish population) [4], higher among women [5]. In a non-clinical context, a prevalence of 32 % (Swedish population) [6] and 35 % (Caucasian women 20–30 years old) [7] has been reported. Several factors have an effect on joint mobility such as trauma, surgery and physical training. There is also asymptomatic

generalized joint hypermobility [8]. As for EDS (the majority with the hypermobility type), it is often described as a rare disease [9]. However, concerning hypermobility spectrum disorder/hEDS, recent research (2019) with British patients shows a prevalence of 1 in 500 people [10].

Clinical Presentation

Pain is a constant from childhood and onward for a majority of individuals with SGJH [11]. Apart from pain and fatigue, other frequently reported symptoms are headache, heart palpitations, light-headedness and syncope, intestine related problems, and problems with the temperature regulation, [12] all with severe negative effects on functional capacity. Inner organ symptoms linked to SGJH are mainly of a functional gastro-intestinal origin (pain, bloating, diarrhea and constipation) possibly caused by changed mechanical traits of the intestinal wall and decreased gut motility [13,14]. Psychiatric manifestations are more common among individuals with SGJH than in the general population [15,16]– fear, agoraphobia, anxiety, panic attacks, and depression – although causality has not been clarified.

An immense amount of energy is spent in this context, from the patient's side, in navigating the healthcare system and struggling with self-care, and, from the side of the healthcare system, to handle these problems. A more purposive management would ease the situation in many ways by economizing resources and providing patients' safety. Thus, a starting-point of this survey is that SGJH probably is underdiagnosed within healthcare. Possible reasons may be, that

- It has not somehow yet reached the broad public that there are major interpersonal differences in tenacity or solidity in the musculoskeletal tissue
- It, still, might to this day seem suspicious with pain in the absence of an identifiable trauma
- Seemingly vague symptoms are reported by patients, perhaps sometimes even parenthetically – constant tiredness or lack of energy could be perceived to be a natural part of everyday life, not a medical condition
- Specialized healthcare personnel might only pay attention to a certain function or organ system, and miss the whole of the symptomatology or clinical presentation that signals a hypermobility spectrum disorder.

Aim

The current survey aims to provide an overview of nerve involvement in SGJH and, in view of this to highlight recommendations for the initial management of patients who present clinically as with SGJH.

Material and Methods

Article selection

Publications were retrieved from the electronic medical databases PubMed, Cinahl and Web of Science. Criteria for inclusion were: quantitative, peer-reviewed studies with persons ≥ 19 years old. Criteria for exclusion were: studies not answering the research question and doublets. The literature search (latest updated November 13 2020), was based on the research question; Which are the neurological manifestations in generalized joint hypermobility? The search strategy had two key words, hypermobility and neuro*, the last with the conjugations removed (truncated) in order to retrieve everything that concerned neurology (neuropathic, neurological etc.).

Results

Search results

The number of publications generated are shown in Table 1. From the English publications, 62 were selected for reading in full text based on their relevance to the research question. No quality assessment was made since the aim was to screen for all available symptoms and pathogenesis, and not to exclude publications with low scientific quality. The results are presented below (Table 1).

Table 1: The number of studies found in the different databases.

Database	Articles (N)
PubMed	279
Cinahl	72
Web of Science	313

Peripheral neuropathy

Small fiber neuropathy – sensory fibres

Pain in SGJH is mainly reported as joint pain, severe diffuse musculoskeletal pain, [17] headaches [18] and burning pain in hands and feet [19]. As late as 2009, Voermans et al. [20] introduced a neurological phenotype of SGJH. They found small fiber neuropathy (axonal polyneuropathy) to be part of what caused pain in 40 patients with EDS (vascular, classic, classical-like, and hypermobility type EDS caused by TNXB haploinsufficiency). Results also showed impaired sensibility and muscle strength (mainly for classical-like type of EDS, i.e. complete absence of Tenascin X), increased muscle echo intensity, and myopathic changes in the biopsy. Subsequent studies supported that a peripheral neuropathy in this group could trigger both pain and autonomic dysfunction [19,21]. In a study with 80 patients with hEDS, participants' sensory profile (Pain Detect Questionnaire) revealed a high prevalence of neuropathic symptoms: paresthesia, numbness and burning pain [12]. Bénistan and Martinez [11] evaluated pain in 37 French patients with hEDS (clinical examination, Quantitative sensory testing (QST), questionnaires) and concluded that neuropathic pain was prevalent in the joint found most painful to the patient.

In contrast, Di Stefano et al. [22] provided data on unharmed somatic nerves in SGJH (27 Italian patients, hypermobility spectrum disorder and hEDS), despite the majority having

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widespread pain, reduced pain thresholds and an increased wind up-ratio. The authors concluded that central sensitization was present. Impaired muscle contractility is another manifestation in defective connective tissue [23]. Voermans et al. [20] proposed for classical-like EDS, that defects in the interstitial matrix in connective tissue sheaths could lower the muscle function, as well as the function of the peripheral nerve (adding to the muscle weakness). More, they saw a dose-effect relationship – a negative correlation – between the Tenascin X-level and neuromuscular involvement. The authors proposed some neuromuscular phenotypes, and that the differences in neuromuscular involvement reflect the tissue specific distribution of involved molecules: For someone with vascular EDS, the muscle and peripheral nerve involvement could be explained by the wide distribution of collagen type III in the interstitial matrix of both peripheral nerve and muscle; for someone with a hypermobility related to the TNXB-gene (classical-like EDS and hypermobility type from TNXB-haploinsufficiency), the abnormalities in distribution of Tenascin X would affect peripheral nerve and muscle; while, in classic EDS with unaffected peripheral nerves, this would be due to almost no collagen type V in the interstitial matrix of the peripheral nerve [20].

Small fiber neuropathy – autonomic fibres

Small fiber neuropathy has also been suggested to cause autonomic symptoms (Table 2), such as the orthostatic intolerance common in SGJH, [12] that can limit time in standing position to about 5–15 minutes, and affect daily activities like social events. Sympathetic denervation, especially in the lower extremities, can negatively affect venous constriction capacity. This leads to pooling of venous blood when standing and consequently a decreased stroke volume [24]. De Wandele et al. [21] found autonomic dysfunction in hEDS (39 Belgian patients) and found skin extensibility to be the best predictor of symptom severity; skin extensibility (and Beighton-score) mirrored the extensibility of the blood vessel, as well as an increase in heart rate (both vessel and skin containing a lot of collagen type 1). De Wandele et al. [12] also investigated the severity of autonomic dysfunction in generalized joint hypermobility, by means of survey in a group where 80 respondents had hEDS, 11 classic EDS, 7 vascular EDS, 38 fibromyalgia, and 43 were healthy. Conclusions were that participants with hEDS and fibromyalgia had about the same autonomic profile, and a greater symptom burden than other EDS-types.

Table 2: Features in small fiber neuropathy, from Cazzato D, Castori M, Lombardi R, Caravello F, Dalla Bella E, Petrucci A, et al. [19] Small fiber neuropathy is a common feature of Ehlers-Danlos syndromes. Neurology 2016; 87(2): 155-159.

Changed Sweating	Dry eyes	Hot flashes
Diarrhea	Dry mouth	Sensitive skin
Constipation	Dizziness standing	Burning feet
Micturition problem	Palpitation	Sheet intolerance
		Restless legs

Neurapraxia – blocking from compression or swelling

In generalized joint hypermobility connective tissue around a peripheral nerve might not have the required resistance to stressors, or ligaments securing position of peripheral nerves might be loose. A fragile epi-, peri- and endoneurium can follow from lack of tenascin X protein (responsible gene, TNXB) and collagen (type I, III and V) due to gene mutation [25]. Here, stretch force or compression can cause peripheral nerve involvement such as carpal tunnel syndrome or plexopathy [26,27]. In case of compression or ischemia there is initially myelination changes and later often axon loss.

Spinal neuropathy

A cervical segmental kyphosis is thought to be an effect of disc degeneration. Disc degeneration might be prompted by a constitution with defective connective tissue [28]. A kyphosis adds to the elongation of the spinal cord in head or upper body flexion. This may trigger nerve disturbances. Where spinal segmental degeneration has led to a tethered cord-syndrome, this triggers symptoms of aching and burning pain in the low back and lower extremities, and sensory and motor problems in the legs [29].

A hyperextension trauma to the head, not uncommon in contact sports, causes a segmental posterior translational movement of one vertebra over the one below (typically level C3–C4) [30]. In cases of generalized joint hypermobility, such an event has the spinal cord momentarily pinched, and can cause a "spinal contusion" according to Brigham et al. [30] who stress that there might be no correlation between the symptoms and MRI findings, why symptoms must guide the decisions in care management. Symptoms are of a transient paralysis, and long-term consequences can be cognitive problems [31]. Effects of stretch forces on a neuron are pathological calcium inflow, altered gene expression and cell death [32]. For children it has been shown that tension trauma in the spinal cord led to axonal damage in the dorsal brainstem and the medulla oblongata [28].

Supraspinal neuropathy

Craniocervical kyphosis and cervicomedullary syndrome

Patients with collagenopathy sometimes present with a varying degree of occipitoatlantoaxial hypermobility [33]. Loss of integrity in an upright position in the bone-ligament junctions in the upper neck joints can cause an anterior flexion in the

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atalantooccipital joint (decreased clivoaxial angle), and an anterior flexion atlas over axis, with a simultaneous alteration of the atlas-dens interval [33]. The clivoaxial angle is a radiological criterium and helps in identifying a possible deformation of the brainstem [28]. An angle less than 135 degrees is considered to cause chronic repetitive injury to nerves. This involvement of the brainstem and upper spinal cord (cervicomedullary syndrome) has as main symptoms neck pain and suboccipital headache [33,34]. In case of an unphysiologically vast axial rotation between atlas and axis (restricted by the alar ligaments), the vertebral arteries can be compromised, triggering symptoms due to altered blood flow in the arteries, e.g. visual disturbance and lightheadedness [34].

"The central sensitivity syndrome" – associated disorders

Different diagnostic interpretations have been made for patients with SGJH. Major aspects of the syndrome – constant pain, lack of energy and activity limitations – could alternatively, and have before been named, simply, chronic pain of unknown origin [35]. There are several disorders that in this sense are similar to SGJH: chronic fatigue syndrome, fibromyalgia, whiplash associated disorders, temporomandibular dysfunction and chronic headache [36,37]. These are all non-malignant diagnostic entities that require the same in a clinical investigation: a consideration of disturbance in the processing of sensory information, which Yunus [38] called a central sensitivity syndrome [36]. Normally, such hypersensitivity abates when the triggering stimulus ceases. However, for certain persons it seems individual traits can interact with afferent signaling and lead to a persistent sensory dysregulation [39]. Such an increased responsiveness in central pathways may lead to a bothersome, sometimes gruesome, sensitivity to impressions [40]. This sensitivity is of pain afference (allodynia, hyperalgesia, enlargement of the nerve's receptive field in the periphery, and painful after-sensations), and may develop in regard to all sensory stimuli, as in fibromyalgia (and associated disorders) (Table 3) [41]. In generalized joint hypermobility, central sensitization is considered to develop partly because of the persistent musculoskeletal pain which lead to reduced pain thresholds [42], and partly from a heightened vigilance in the brain with the amygdala lowering neuronal thresholds in sensory systems [43], so that internal and external impressions may be further amplified.

In order for a consistent central sensitization to appear, different kinds of chronic inflammation are a contributing factor, and activation of the congenital immune system has been shown to be a factor, perhaps through an enhanced release of inflammatory cytokines from glial cells [44]. Spinal trauma and emotional stress may contribute to the development of central sensitization [39,44]. Doubtless, these predisposing factors are prevalent in the population with SGJH, and the group share significant symptoms with different "central sensitivity-syndromes", e.g. jaw pain, post exertional malaise, brain fog, and gut or bladder disturbance [45-47]. Fitzcharles [48] suggested that children and young adults with generalized joint hypermobility have a predisposition to develop widespread pain that with time can evolve into what we call fibromyalgia, and a large part of patients with SGJH fulfill the diagnostic criteria for fibromyalgia [17].

Processes in deep brain structures are often activated and altered by central sensitization in different chronic pain conditions [49]. The brain's base activity becomes raised in rest, physical activity or stress is followed by unnormal fatigue after (decreased stress-related hormone production), and there can be a reduced intellectual capacity (hippocampal atrophy) [50-52] similar to chronic fatigue syndrome. Among groups with joint hypermobility, structural and functional brain changes have been reported, in areas of the brain associated to anxiety, that is the amygdala where an increased volume was registered bilaterally and the insular cortex where increased reactivity was shown [6]. Thus, adding to the diagnostic challenges for SGJH is a maladaptive plasticity in central pathways that can progress over time [11] .

Table 3: Central sensitivity syndromes according to Cassisi G, Sarzi-Puttini P, Casale R, Cazzola M, Boccassini L, Atzeni F, et al. [41] Pain in fibromyalgia and related conditions. Reumatismo 2014; 66(1): 72-86.

Fibromyalgia	Migraine	Periodic limb movements in sleep
Chronic fatigue syndrome	Temporo-mandibular disorders	Multiple chemical syndrome
Irritable bowel syndrome	Myofascial pain syndrome	Primary dysmenorrhea
Tension-type headache	Restless legs syndrome	Female urethral syndrome and interstitial cystitis
		Post-traumatic stress syndrome

Discussion

Discussion of methods

We carried out a literature search focusing on symptomatic generalized joint hypermobility. Our review is not comprehensive for all neurological conditions found in this group, [34] but has a choice scope of promoting content and direction in an initial healthcare contact and clinical assessment.

Discussion of results

Defective connective tissue is not limited to joints and muscle and patients with SGJH are predisposed to different neuropathies.

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This review shows an increased awareness of this as of recent in the medical field, as well as an awareness of collagen within the muscle being a factor for muscle force. How over time the neurological phenotype for SGJH did not receive more attention, might in part stem from contradictory research results. Because of lack of insight in underlying pathology, classification for generalized joint hypermobility has been unrefined; when tools have improved to study the underlying molecular mechanisms, a more adequate differentiation of subgroups has helped in designing clinical studies on collagenopathy.

A concern is that the investigation for this population is directed toward psychological status, or that a too strenuous physical training regimen is recommended. These paths of management may trigger exacerbation. For example both youths and adults with generalized joint hypermobility should be discouraged from contact sports, stretching (yoga) and overly strenuous physical training. Someone with generalized joint hypermobility often has a youthful and healthy appearance, from the experience of the authors of this review. This may somewhat camouflage their serious pain and a substantially decreased capacity. Also, the magnitude of seemingly unrelated symptoms could perhaps, quite understandably, challenge healthcare personnel's commitment to engage in targeted interventions. Anecdotally, we have also been told a couple of times by patients, that the joint flexibility itself has been "held against" the patient in healthcare contacts; the patient has been considered to be in good physical shape. This may contradict the narrative about major daily difficulties, and research has shown the patient-caregiver interaction to be lacking for patients with persistent pain of unknown origin [53,54]. According to Shaw et al. [55] 77% out of about 3 400 patients had gotten a psychiatric or psychological explanation to their illness from a physician before they were diagnosed with orthostatic intolerance, whilst only 28% considered themselves having some sort of psychiatric or psychological disorder before the orthostatic intolerance-diagnose.

Pain can be of nociceptive and neuropathic origin, and in SGJH the pathogenesis is often not clear [11]. For instance, Glans et al. [6] described how generalized joint hypermobility often includes musculoskeletal pain, gastrointestinal, and heart symptoms. All which could be symptoms of neurological dysfunction [56,57] where focus would shift to the nervous system in diagnostics. As such, these are persistent non-malignant somatic nervous disorders, perceived to occur in organs and limbs, although they are generated from affected nerves: spinal nerve disturbances, sometimes widespread nerve loss due to molecular defects, and not least central sensitization.

These improved considerations also mean that clinical praxis is in the process of developing, foremost in an approach where the caregiver focuses to differentiate between several neurological pathomechanisms for the patient, i.e. an inflammatory pain mechanism, versus a functionally compromised central nervous system. Diagnosing generalized joint hypermobility is done only by means of a clinical assessment [58]. Gold standard for assessment are the Beighton-score [59] and the Five-part questionnaire (5PQ), [60] the latter a rapid tool to investigate historical joint hypermobility. In regard to a clinical assessment of neuropathies, to the authors' knowledge, no previous study has explicitly focused on recommendations for the group with SGJH. The methods/tools to collect the required information, must be those available in any primary care facility, i.e. – questionnaires [61] and a clinical bedside examination of the patient. Recommended clinical evidence-based methods for screening for neuropathies are shown in Table 4.

Table 4: The primary tools (not limited to the below mentioned) for a primary health care setting for screening for neuropathies and central sensitization for patients presenting in the clinic as with generalized joint hypermobility.

* Pain drawing to document pain localization and distribution (indicating for example widespread pain, peripheral polyneuropathy, or headache), as is recommended in the investigation of fibromyalgia [62,63]
* A self-reported questionnaire for quantifying autonomic symptoms, e.g. (COMPASS)-31 [64]
* Central sensitization inventory (CSI), [46] a psychometrically sound patient-reported tool for confirming the presence of central sensitization
* A focused spinal examination (myelopathy, nerve involvement from spinal segments, if any from the upper cervical joints) that include a sensory examination [62] (touch, pinprick sensation, thermal sensation and vibration sensation).

Haanpaa [61] commented on the challenges of the bedside neurological examination due to the complexity of the nerve net as a whole, for example fluctuations in intensity and distribution of nervous symptoms, making test results approximate. Identifying central sensitization is vital, as to collect support to perhaps refrain from certain treatments, make the patient's problems more intelligible and lay grounds for a better management. If possible, it is likely in the patient's best interest to settle with the diagnosis central sensitization/central sensitivity, to evoke all relevant considerations as easy as possible, and not reach for other more hard-to-grip explanatory models/diagnoses. For example, Neblett [46] is unambiguous in stating, "… when symptoms are related to central sensitization, or represent a central sensitivity syndrome, the primary target for treatment should be the central nervous system, not the periphery […]. For patients with central sensitization-related disorders, medical interventions targeted in

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the periphery are often unnecessary, unhelpful and potentially harmful" [46]. In regard of interventions, the patient's education is perhaps most important. Persistent pain is a diagnose in itself, and should be kept keenly in mind in the management of patients presenting in the clinic as with generalized joint hypermobility.

Conclusion

Screening for nerve involvement and central sensitization should be part of the assessment for patients who present clinically as with generalized joint hypermobility. The patients' narrative is a vital part in the initial management, as perceived symptoms provide valuable additional information to classify the condition, and consequently adds to the factual foundation for the task to identify the cause/diagnosis. We recommend to emphasize the "central sensitivity" diagnose when present, to promote patient empowerment and self-care.

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Conflict of Interest

The authors declare no conflict of interest in this study.

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