

The Association between Fibromyalgia, Hypermobility and Neurodivergence Extends To Families: Brief Report

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Received: 11 May 2023; Accepted: 12 Jun 2023; Published: 17 Jun 2023

Citation: Clive Kelly. The Association between Fibromyalgia, Hypermobility and Neurodivergence Extends To Families: Brief Report. Int J Psychiatr Res. 2023; 6(3): 1-5.

ABSTRACT

Objectives: Fibromyalgia is associated with symptomatic hypermobility. People with these conditions have a higher prevalence of neurodivergent conditions. Many fibromyalgia patients with hypermobility also report similar symptoms within their family. This study explores the presence of diagnosed disorders among close relatives of patients presenting with fibromyalgia and hypermobility.

Methods: All patients presenting with both fibromyalgia and hypermobility to the rheumatology clinic were invited to participate. Each of these participants reported all confirmed diagnoses of any of neurodivergence, fibromyalgia or hypermobility among their first- and second-degree relatives. Participants were invited to prepare a family tree detailing these diagnoses. We calculated the incidence of each of neurodivergence, fibromyalgia and hypermobility within these relatives and compared them to the incidence derived from families of case-control patients with osteoarthritis.

Results: Among 13 index patients (all female, median age 38 years), 9 had a diagnosed neurodivergent condition (69%). Among their 163 relatives, 68 (42%) had a diagnosed neurodivergent condition, compared to 4.7% among case-control relatives ($p > 0.00001$). The incidence of diagnosed hypermobility and fibromyalgia in relatives of index cases was 36% and 22%, compared to 8% and 4% in case-control relatives ($p = 0.00001$, $p = 0.00012$).

Conclusion: This self-reported small case-control study confirms the association of fibromyalgia, hypermobility and neurodivergence, and suggests that close relatives also exhibit this association. Females are disproportionately overrepresented within pain populations, in contrast to neurodivergence in other settings where males predominate, perhaps due to underdiagnosis in females. Gene clustering may contribute to these associations, which extend into the community.

Keywords

Fibromyalgia, Neurodivergence, Autism, ADHD, Hypermobility, hEDS, Pain, Genetics.

Introduction

Fibromyalgia (FM) has an estimated lifetime prevalence in the west of 0.2-6.8% [1]. Clinical experience suggests patients are presenting to rheumatology specialists with the combination of FM

and symptomatic hypermobile Ehlers-Danlos syndrome (hEDS) at a younger age than a decade ago. Case studies prompted interest in the potential overlap between fibromyalgia (FM) and attention deficit hyperactivity disorder (ADHD) over a decade ago [2] and high rates of prior ADHD were reported among women who later presented with features of FM [3]. The term 'neurodivergence' incorporates conditions such as ADHD, autism and Tourette's syndrome and further observations confirmed that a quarter of

people with neurodivergence had FM [4], commensurate with a report that the prevalence of ADHD was raised in Dutch women with FM [5]. This association was soon confirmed by van Rensburg who demonstrated that 45% of FM patients also had ADHD [6]. Both conditions are associated with lower circulating levels of dopamine, with evidence of an overlap in the gene coding for dopamine receptor function, which is thought to explain some of the personality traits associated with each condition [7].

A Spanish study highlighted the overlap between autism, hEDS and FM and suggested that neurodivergent conditions in general were associated with both chronic pain and hEDS [8]. A high prevalence of joint hypermobility was recorded among women with ADHD [9], and hEDS itself was linked to the presence of several of the personality traits described among both people with chronic musculoskeletal pain and those with ADHD [9]. Eccles et al. demonstrated that brain structure was different among people with hEDS and suggested that this explained many of the psychiatric features, which mirrored those observed in neurodivergent conditions [10].

Psychological distress in early life was suggested as a predisposing factor for chronic pain, especially if adverse childhood experiences (ACE) included lack of parental support or validation, which were also associated with personality traits seen in neurodivergence [11]. Considering mechanisms by which these diagnoses may occur, Khalil suggested that ADHD may trigger FM via central sensitisation, consequent upon ACEs [12], and that this might explain the pain and motor distress [13] seen in FM. Stimulants given for ADHD have been described as both reducing pain and improving cognitive dysfunction, the latter being a hallmark of FM ('fibrofog') [14]. A French study emphasised the extensive co-occurrence associated with ADHD and the overlap with both widespread musculoskeletal pain and personality disorders. They also noted that fatigue was a major aspect of ADHD, and that associated sleep disturbance was common [15]. They suggested that the prevalence and severity of co-occurring conditions increased with age, and this was supported by Asztely who demonstrated that 77% of neurodivergent women developed chronic musculoskeletal pain in later life [16]. Although most literature on the overlap between FM and neurodivergence has come from Europe, there is evidence that the relationship between these conditions also applies to populations in the Far East [17].

More recently, hypermobility was observed in over half of a neurodivergent group with an odds ratio of 4.5 compared to a comparison group. The extent of hypermobility mediated the relationship between neurodivergence and both dysautonomia and musculoskeletal pain [18]. Casanova et al. reviewed the evidence linking neurobehavioral and pain syndromes with dysautonomia and dysregulation of the immune system. They reported significant genetic overlap between each of neurodivergence, hEDS and FM, suggesting that hypermobility and pain may even be considered as aspects of autism [19].

Clinical experience has revealed that many patients presenting

with FM and hEDS also report symptoms of chronic pain and mental health issues among their family members. Although the links between these conditions are now recognised among patient populations, we are unaware of any previous studies of the frequency with which they occur within families of those affected. An increased prevalence within close relatives might be expected given the genetic overlap between these disorders. Our objective was to investigate the incidence of diagnosed FM, hEDS and neurodivergence within first- and second-degree relatives of index cases with both FM and hEDS to assess whether this is greater than that observed within a comparison group of index cases attending the same clinical service but with a different musculoskeletal diagnosis.

Methods

Twenty patients were identified with a diagnosis of both FM [20] and hEDS [21], all of whom were attending the rheumatology clinic at the James Cook University Hospital in Middlesbrough. All patients were eligible, independent of sex, gender and age, providing they were at least 18 years of age. After obtaining informed consent, they were invited to prepare a family tree to include themselves and all their first- and second-degree relatives, each of whom were identified only by gender, and to record the presence of any / all confirmed diagnoses of FM, hypermobility or neurodivergent conditions (specifically ADHD, autism and Tourette's) among them. Each index case was asked to discuss this with each of their family members before confirming consent. The rationale for exploring the potential linkage of these conditions was explained, along with the potential benefits of understanding these connections. Given that many of the consultations were remote and the complexity of obtaining written consent from every potential participant, it was agreed that completion and return of the family tree would indicate consent. Five index patients declined to participate because of a breakdown within their family making access to information impossible. Fifteen index cases originally consented to participation but two of these failed to complete the process. The remaining thirteen index patients returned their completed family tree with all data anonymised. Fifteen patients, who were attending the same Department with a diagnosis of osteoarthritis, were also invited to prepare a family tree with identical instructions. These patients were gender matched and aged within five years of the index cases. All these consented to participation and produced their anonymised family tree. Two of these were discounted to ensure a direct 1:1 matching between the two groups. Formal ethical approval for this study was not considered necessary following discussion with the Hospital R&D office and PPI representatives.

Patients were invited to participate over a three-month period from October to December 2021 and were given a three-month window in which to complete and return their family tree. The median (range) age of each group was calculated, along with the female: male sex ratio. The prevalence of each of the conditions recorded among relatives of both groups of patients was calculated and compared using Pearson's Chi squared test for comparison

statistics. The prevalence of each of the conditions in the direct descendants of the index patients was assessed, and the degree of overlapping diagnoses of FM, hypermobility and neurodivergence calculated for the relatives of all index cases.

Results

The 13 index cases (all female) with a median (range) age of 38 (21-53) years, and in the families of 13 comparison cases (all female) with a median (range) age of 41 (26-57) years. Among the 13 index cases, 9 had been diagnosed as autistic (69%), compared to none of the comparison cases. The index cases identified a total

of 163 first- and second-degree relatives, of whom 68 (41.7%) had a diagnosis of neurodivergence, compared to 106 first- and second-degree relatives of comparison cases, of whom 6 (4.7%) had a diagnosis of neurodivergence (Chi squared statistic =41.87, $p=0.00001$) as shown in Figure 1. Among the 52 children and grandchildren of the 13 index cases, 30 reported existing diagnoses of neurodivergence, providing a prevalence of neurodivergence of 58% among their direct descendants.

There were 58 reported diagnoses of hypermobility among the relatives of index cases, giving a prevalence of 35.6%. By



Figure 1: To show frequency and co-occurrence of Neurodivergence (ND), Hypermobility spectrum disorder (HSD) and Fibromyalgia (FM) among 163 first- and second-degree relatives of 13 index cases with both FM and HSD (left), by comparison with 106 relatives of age / gender matched controls (right).

comparison, there were 8 reported diagnoses of hypermobility in relatives of the comparison cases, providing a prevalence of 7.6% (Chi squared statistic =27.26, $p=0.00001$). There were 35 reported diagnoses of FM among the relatives of index cases, giving a prevalence of 21.5%. By comparison, there were 4 reported diagnoses of FM in relatives of the comparison cases, providing a prevalence of 3.8% (Chi squared statistic = 14.80, $p=0.00012$). Prevalence rates for both hypermobility and FM in the 52 direct offspring of index cases were equivalent to the relatives overall at 34% and 22% respectively, despite their relative youth.

With respect to index cases, the 68 relatives who reported having neurodivergence also reported higher rates of comorbidity, with 46 (67.6%) reporting a diagnosis of hypermobility and 26 (38.2%) recording a diagnosis of FM. Data are shown in Figure 1, along with the overlap of diagnoses in both groups.

Discussion

The incidence of diagnosed neurodivergence within first- and second-degree relatives of index cases with both FM and hypermobility was significantly greater than that observed within a comparison group of relatives. We included OA patients and their families as appropriate comparator controls as many immune disorders are increased in prevalence among neurodivergent people. In addition, the incidence of both FM and hypermobility were also increased among close relatives of those with these conditions, with the rates highest among neurodivergent relatives. This supports previous findings of overlap between these disorders and strongly suggests that neurodivergent people are at much greater risk of developing FM [3-6].

Neurodivergent conditions are present from birth and therefore predate the onset of both HSD and FM. However, symptoms arising from these conditions are very varied and may not be recognised as being due to neurodivergence until adult life. This is more often the case for females than males, and within trans and non-binary people, which may increase their psychological distress and promote anxiety. Overlapping psychological features are described among females with FM and ADHD females [9,10]. Chronic pain may be consequent upon central sensitisation, which can develop in more than three-quarters of women with ADHD over time [16] and this study suggests that similar trends are found among their close relatives.

The presence of hypermobility may mediate the relationship between neurodivergence and chronic pain in FM [18]. Psychological distress in early life is suggested as a predisposing factor for chronic pain, especially if adverse childhood experiences (ACEs) included lack of parental support or validation which may produce personality traits resembling those seen in neurodivergence [11,22]. As the present study demonstrated, females are disproportionately overrepresented within these pain populations, in contrast to the distribution of neurodivergent conditions in the community where diagnosis in males is more common, perhaps due to underdiagnosis in younger females. Many females obtain their diagnosis of neurodivergence during their teenage years or in early adulthood, while males are often diagnosed at an earlier age. Further research should focus on screening for neurodivergent conditions among patients referred to services for the management of chronic pain so that appropriate support and intervention can be offered. The association between FM and neurodivergent conditions is under-appreciated by many

clinicians working in these areas and the promotion of greater awareness and understanding of the overlap between these conditions would benefit patients and clinicians alike.

Power calculations prior to the study were performed and the results used to guide the study design. Despite small numbers, the results were highly significant, supporting the validity of this approach. However, we acknowledge that this is a small study with significant limitations, which include the fact that all data relied on self-reporting and that reported diagnoses were not independently verified. The lack of an objective determination of each diagnosis limits the results' internal and external validity. This could have led to an overestimate of the prevalence of neurodivergence, FM or hypermobility because of greater awareness of these conditions within affected families. By contrast, it is also possible that the reported prevalence estimates may be an underestimate, as not all relatives would have undergone diagnostic assessment for their symptoms, which may not have yet evolved in younger family members.

An overlap of genes coding for neurodivergence and for symptomatic hEDS has been reported [19]. This may explain some of relationship between the three conditions although further research is needed to confirm the extent of this association [23]. However, it is becoming evident that the relationship between FM and neurodivergent traits is not confined to patient populations. Recent work has shown a strong correlation between FM and autistic traits in a large, self-selected adult community population [24], mediated by a combination of hypermobility and food intolerance [25]. Clearly, more work is needed to assess the risk factors for chronic musculoskeletal pain among neurodivergent people both in diagnosed populations and in the community if we are to learn how to intervene early and effectively. It is essential that the voices of neurodivergent people are listened to and that their input to this process is sought [26].

Summary

This study confirmed a high prevalence of neurodivergence among patients presenting to a hospital clinic with features of FM and hEDS. Furthermore, close relatives of these patients' self-reported increased levels of neurodivergence, FM and hypermobility among themselves. Those relatives who reported a diagnosis of neurodivergence also reported higher percentages of diagnosed FM and hypermobility.

PPI statement

This study was conceived after several patients with fibromyalgia and hypermobility raised concerns about potential links with neurodivergent conditions within their families. They encouraged me to undertake the work and together provided helpful and appropriate suggestions and advice for its design and structure. They also acted as a conduit for feeding back results to patients and their families in anonymised form.

Acknowledgements

The author wishes to acknowledge advice and support from Dr

David Moore at the John Moore University in Liverpool, along with Dr Jessica Eccles at Brighton and Sussex Medical school. Neither were directly involved in the study, but both helped with the data analysis, interpretation and presentation. In addition, I am grateful for the input of Rem Martin and several other index patients (PPI group) who declined to be identified to maintain their anonymity.

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