The Association Between Fibromyalgia, Hypermobility and Neurodivergence Extends to Families: Brief Report

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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.

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Key words: Fibromyalgia; neurodivergence; autism; ADHD; hypermobility; hEDS; pain; genetics.

Key messages:

1. Many patients presenting with fibromyalgia have features of neurodivergence
2. This combination is strongly associated with the presence of joint hypermobility
3. The relatives of these patients also report an increased prevalence of all three conditions

All the data collected for this study were anonymised and are freely available

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 here 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. Data was analysed to assess the prevalence of each of FM, hypermobility and neurodivergence in the families of 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.

Results

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 68 index case relatives with neurodivergence, 43 (25 male) had autism, 23 had ADHD (13 male) and 2 had Tourette's syndrome (1 male). Of the 6 comparison case relatives, 4 (3 male) had autism and 2 (1 male) had ADHD.

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.

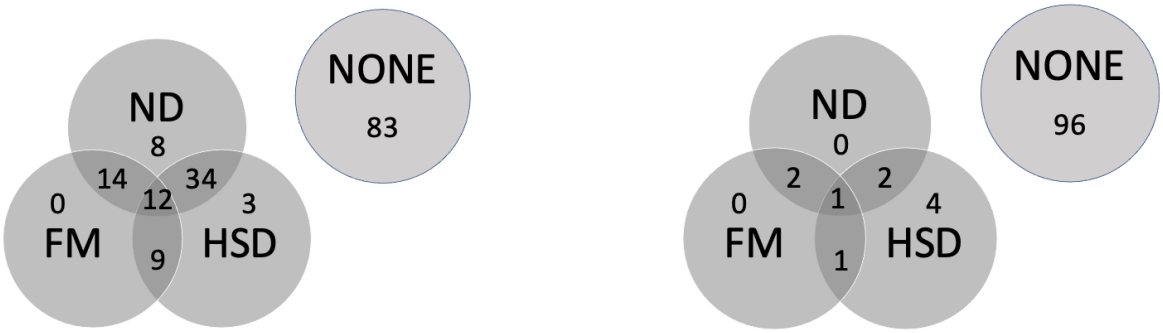

Figure 1. To show frequency and co-occurrence of Neurodivergence (ND), Hypermobility spectrum disorder (HSD) and Fibromyalgia (FM) among 163 first- and second-degree relatives of 13 index cases with both FM and HSD (left), by comparison with 106 relatives of age / gender matched controls (right).

There were 58 (49 female) reported diagnoses of hypermobility among the relatives of index cases, giving a prevalence of 35.6%. By comparison, there were 8 (7 female) 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 (32 female) reported diagnoses of FM among the relatives of index cases, giving a prevalence of 21.5%. By comparison, there were 4 (4 female) 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 neurodivergent conditions 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][4][5][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. This study is very relevant to today's society where many young people are struggling with their identity. Pain in all its manifestations can be associated with this process, and it is important for health-care professionals to recognise this. Understanding how best to respond to young people's emotional and social issues is fundamental to providing an efficient and cost-effective health system.

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 both to explain the differing sex ratios between neurodivergence and fibromyalgia and to confirm the extent of the 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 clinical 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.

Statement and declarations

The author has no conflicts of interest and no disclosures.

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.

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References

1. ^*Marques AP, Santo ASDE, Berssaneti AA, Matsutani LA, Yuan SLK. Prevalence of fibromyalgia: literature review update. Rev Bras Reumatol Engl Ed. 2017 Jul-Aug;57(4):356-363. doi: 10.1016/j.rbre.2017.01.005. Epub 2017 Feb 8. PMID: 28743363.*
2. ^*Young JL, Redmond JC. Fibromyalgia, chronic fatigue, and attention deficit hyperactivity disorder in the adult: A case study. Psychopharmacol Bull 2007;401:118–26.*

3. [a, b]*Reyero F, Ponce G, Rodriguez-Jimenez R, et al. High frequency of childhood ADHD history in women with fibromyalgia. Eur Psychiatry 2011; 268:482–3.*
4. [a, b]*Golimstok A, Fernandez MC, Garcia Basalo MM, et al. Adult attention-deficit and hyperactivity disorder and fibromyalgia: A case-control study. Neuro Open J 2015;22: 61-6.*
5. [a, b]*Derksen MT, Vreeling MJW, Tchetverikov I. High frequency of adult attention deficit hyperactivity disorder among fibromyalgia patients in the Netherlands: Should a systematic collaboration between rheumatologists and psychiatrists be sought? Clin Exp Rheumatol 2015; 33(1 suppl 88): 141.*
6. [a, b]*van Rensburg R, Meyer HP, Hitchcock SA, Schuler CE. Screening for Adult ADHD in Patients with Fibromyalgia Syndrome. Pain Med. 2018 Sep 1;19(9):1825-1831. doi: 10.1093/pm/pnx275. PMID: 29099955.*
7. [^]*Buskila, D., Cohen, H., Neumann, L. et al. Erratum: An association between fibromyalgia and the dopamine D4 receptor exon III repeat polymorphism and relationship to novelty seeking personality traits. Mol Psychiatry 9, 973 (2004). https://doi.org/10.1038/sj.mp.4001568*
8. [^]*Baeza-Velasco C, Sinibaldi L, Castori M. Attention-deficit/hyperactivity disorder, joint hypermobility-related disorders and pain: expanding body-mind connections to the developmental age. ADHD Attent Defic Hyperact Disord. (2018) 10:163–75. doi: 10.1007/s12402-018-0252-2*
9. [a, b, c]*Dogan SK, Taner Y, Evcik D. Benign joint hypermobility syndrome in patients with attention deficit/hyperactivity disorders. Arch Rheumatol. (2011) 26:187–92. doi: 10.5606/tjr.2011.029*
10. [a, b]*Eccles JA, Beacher FD, Gray MA, Jones CL, Minati L, Harrison NA, et al. Brain structure and joint hypermobility: relevance to the expression of psychiatric symptoms. Br J Psychiatry. (2012) 200: 508–9. doi: 10.1192/bjp.bp.111.092460*
11. [a, b]*Burke NN, Finn DP, McGuire BE, Roche M. Psychological stress in early life as a predisposing factor for the development of chronic pain: Clinical and preclinical evidence and neurobiological mechanisms. J Neurosci Res 2017; 956:1257–70.*
12. [^]*Khalil R, Khoury E, Richa S. The Comorbidity of Fibromyalgia Syndrome and Attention Deficit and Hyperactivity Disorder from a Pathogenic Perspective, Pain Medicine, Volume 19, Issue 9, September 2018, Pages 1705–1709, https://doi.org/10.1093/pm/pny1*
13. [^]*Stray LL, Kristensen Ø, Lomeland M, et al. Motor regulation problems and pain in adults diagnosed with ADHD. Behav Brain Funct 2013; 9:18.*
14. [^]*Bell T, Trost Z, Buelow M, Clay O, Younger J, Moore D and Crowe M. (2018). Meta-analysis of cognitive performance in fibromyalgia. Journal of clinical and experimental neuropsychology, 40(7), 698-714.*
15. [^]*Weibel S, Menard O, Ionita A, Boumendjel M, Cabelguen C, Kraemer C, et al. Practical considerations for the evaluation and management of Attention Deficit Hyperactivity Disorder (ADHD) in adults. Encephale. 2020 Feb;46(1):30-40. doi: 10.1016/j.encep.2019.06.005. Epub 2019 Oct 11. PMID: 31610922.*
16. [a, b]*Asztély K, Kopp S, Gillberg C, Waern M, Bergman S. Chronic Pain And Health-Related Quality Of Life In Women With Autism And/Or ADHD: A Prospective Longitudinal Study. J Pain Res. 2019 Oct 18; 12:2925-2932. doi: 10.2147/JPR.S212422. PMID: 31695481; PMCID: PMC6804669.*
17. [^]*Kasahara S, Niwa S-I, Matsudaira K, Sato N, Oka H, Yamada Y. Attention-deficit/hyperactivity disorder and chronic*

pain. Psychosom Med. (2020) 82:346–7. doi: 10.1097/PSY.0000000000000789

18. [a, b]*Csecs J, Iodice V, Rae C et al. Joint Hypermobility Links Neurodivergence to Dysautonomia and Pain. Front. Psychiatry, 02 February 2022 | https://doi.org/10.3389/fpsyt.2021.786916*
19. [a, b]*Casanova EL, Baeza-Velasco C, Buchanan CB, Casanova MF. The Relationship between Autism and Ehlers-Danlos Syndromes/Hypermobility Spectrum Disorders. J Pers Med. 2020 Dec 1;10(4): 260 https://doi.org/10.3390/jpm10040260*
20. [^]*Wolfe F., Clauw D.J., Fitzcharles M.A., Goldenberg D.L., Häuser W., Katz R.S., Mease P., Russell A.S., Russell I.J., Winfield J.B. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: A modification of the ACR preliminary diagnostic criteria for fibromyalgia. JRheumatol. 2011; 38:1113–1122. doi: 10.3899/jrheum.100594.*
21. [^]*Juul-Kristensen B, Schmedling K, Rombaut L, Lund H, Engelbert RH. Measurement properties of clinical assessment methods for classifying generalized joint hypermobility-A systematic review. Am J Med Genet C Semin Med Genet. 2017 Mar;175(1):116-147. doi: 10.1002/ajmg.c.31540. PMID: 28306223.*
22. [^]*Sinibaldi L, Ursini G, Castori M. Psychopathological manifestations of joint hypermobility and joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type: the link between connective tissue and psychological distress revised. Amer J Med Genet C Semin Med Genet. (2015) 169:97–106. doi: 10.1002/ajmg.c.31430*
23. [^]*Alsiri N, Alhadhoud M, Alkatefi T, Palmer S. The concomitant diagnosis of fibromyalgia and connective tissue disorders: A systematic review. Semin Arthritis Rheum. 2023 Feb; 58:152127. doi: 10.1016/j.semarthrit.2022.152127. Epub 2022 Nov 17. PMID: 36462303.*
24. [^]*Ryan L, Thomson E, Beer H, Philcox E and Kelly C. Neurodivergent traits correlate with chronic musculoskeletal pain: a self-selected population-based study. OBM Neurobiology 2023, Volume 7, Issue 1, doi:10.21926/obm.neurobiol.2301155*
25. [^]*Thomson E, Beer H, Ryan L and Kelly C. Food sensitivities may mediate the relationship between chronic pain and neurodivergent traits. In press at Rheumato Feb 2023*
26. [^]*Dwyer P. The Neurodiversity Approach (es): What Are They and What Do They Mean for Researchers? Hum Dev. 2022 May;66(2):73-92. doi: 10.1159/000523723. Epub 2022 Feb 22. PMID: 36158596; PMCID: PMC9261839.*