Juvenile fibromyalgia: A call for diagnostic refinement, a case report

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Case Report

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Abstract

Background

Fibromyalgia is a clinical syndrome consisting of widespread musculoskeletal tenderness and various somatic complaints including nonrestorative sleep, mood disorders such as anxiety or depression, abdominal pain, and/or headaches. There is a great deal of heterogeneity in its expression which leads to difficulty in identifying predisposing factors. A singular review of patients in an academic pediatric pain clinic reveal immune system dysfunction, mood disorders, infection, postural orthostatic tachycardia syndrome, complex regional pain syndrome, and hypermobility are premorbid conditions. It is unclear if these premorbid conditions confer a distinct fibromyalgia clinical phenotype that can provide insight into targeted therapies. Current diagnostic measures for fibromyalgia do not allow for this level of discrimination and are not validated in children.

Case Presentation

20 children who demonstrated widespread musculoskeletal pain, tenderness to pressure on exam and multiple somatic complaints were diagnosed with fibromyalgia. Average time from start of pain to diagnosis is 2 years. Over half the patients have psychopathology, a third have an immune system dysfunction related to autoimmunity or an infectious exposure, a third with orthostatic intolerance or postural orthostatic tachycardia syndrome, a quarter relating to hypermobility, and a quarter of the cohort with dysmenorrhea were pre or comorbid conditions. Effective therapeutic regimens among patients varied widely from responding to medical monotherapy to multimodal treatment. Trigger point injections worsened pain in one fibromyalgia patient but decreased pain in another. Patients with comorbid autoimmunity report appreciating a difference between a flare in their arthritis as opposed to a flare in their fibromyalgia. Such varying responses within the same clinical syndrome suggest distinct phenotypes within fibromyalgia which is difficult to distinguish using our current diagnostic tools.

Conclusion

There is a need for clear diagnostic criteria for both the recognition of juvenile fibromyalgia and tools to distinguish phenotypes within fibromyalgia. Currently, the recognition of clinical symptoms renders it an often-overlooked neuropathic pain condition. This case series suggest there are different phenotypes within fibromyalgia. Some patients respond remarkably to serotonin norepinephrine reuptake inhibitors alone whereas others require multidisciplinary therapy. A diagnostic tool refined to capture these nuances can facilitate targeted treatment recommendations.

Background

Fibromyalgia (FMS) is a constellation of clinical symptoms characterized by widespread musculoskeletal pain and somatic complaints of at least 3 months duration[1]. There are no gold standards for diagnosing FMS[1] which results in controversy surrounding its validity as a diagnosis. The American College of

Rheumatology (ACR) first established standardized criteria for the diagnosis of FMS in 1990. It was revised in 2010/2011/2016, no longer requiring discrete tender points on physical exam. Instead, cardinal symptoms of FMS now comprise widespread pain, fatigue, sleep disorders, and memory disturbances. The ACR 2016 provisional diagnostic criteria for FMS in adults includes a Widespread Pain Index (WPI), where the patient must endorse pain in 4 of the 5 outlined regions and Symptom Severity scale (SSS), where patients must report symptoms of fatigue, non-restorative sleep, cognitive symptoms, headache, abdominal pain, or depression with symptoms ongoing for at least 3 months[1]. The sum of the WPI and SSS results in a value for the Fibromyalgia Severity (FS) scale where the minimum number must be 12 to satisfy FMS criteria[1]. The FS can be tracked over time to identify response to treatment[1].

The term *fibromyalgia* was developed by Smythe and Moldofsky in the 1970s to reflect chronic condition where there is no accompanying inflammation, but rather a form of pain involving connective tissues. The pain of FMS typically presents diffuse or multifocal, difficult to localize, often waxes and wanes, and migratory in nature[2]. Most patients diagnosed with FMS also display augmented pain or sensory processing to normally painful and nonpainful stimuli[3]. Comorbid conditions reported include irritable bowel syndrome (IBS), chronic fatigue syndrome, tension-type headaches, migraine, temporomandibular disorder (TMJ), interstitial cystitis, chronic prostatitis, vulvodynia, and other functional somatic syndromes[3]. IBS in particular is five times more likely in FMS patients compared to unaffected patients[4–7]. Hypothyroidism, polymyalgia rheumatica, Sjogren syndrome, osteoarthritis, and autoimmune disorders (ie. SLE, rheumatoid arthritis) similarly have been linked to adult FM[2]. It is unclear if these comorbid conditions are due to FMS or provide a predisposition to developing FMS.

The unique parental aspect has further been considered in pediatric FMS, in which youths with FMS come from families described as anxious, disorganized, or with high-degree of parental control, exerting an influence on daily coping mechanisms[8,9]. Family environmental factors are thus unique and salient to understanding pediatric FMS. Whereas a mixed approach of pharmacologic (tricyclics, dual-reuptake inhibitors, alpha-2-delta ligands) and nonpharmacologic (cardiovascular exercise, CBT, patient education) therapies have established strong evidence of efficacy in adults, pediatric-centered and evidence-based treatment is lacking. The management of pediatric FMS currently centers on education, behavioral, and cognitive change. There are few studies focused on pediatric FMS leading to a lack of clarity surrounding diagnostic criteria and treatment approaches. This uncertainty poses clinical challenges for management and prevention of disease progression into adulthood.

It is our aim to elucidate this incongruity and contribute more case-based evidence of pediatric FM to inform further tailored research into diagnostic criteria and treatment. Ultimately, earlier detection is an indication of better prognosis and quality of life[10]. Outcomes are favorable compare with that in adults, with 73% of pediatric FMS patients evaluated after 30-month follow-up reporting remission[11]. But shortcomings in present adult FMS research render our understanding of pediatric FM uncertain. Clarity regarding the most appropriate pediatric criteria to promote identification, pain relief and recovery is paramount. We highlight the need for change in diagnostic and therapeutic approach to FMS.

Case Presentation

A retrospective chart review of 20 patients with a new diagnosis of FMS from a single pediatric pain medicine physician is described. Ages varied from 10yo to 18yo with the mean age of 14.8years, with 18 female, 1 male and 1 transgender male (Tab 1). The duration of pain prior to presentation varied from 2 months to 5 years with mean duration of 25.2 months. Most often patients presented with no diagnosis surrounding their pain but those who did have a diagnosis were told amplified musculoskeletal pain (AMPS), complex regional pain syndrome (CRPS), psychosomatic disorder, Lyme disease, POTS, and growing pains (Fig 1). 3 of the 20 patients presented with a diagnosis of FMS (Fig 1).

Surrounding premorbid conditions, 13/20 patients presents with psychopathology (Fig 2, Fig 3). 7 of the 13 children with psychopathology reported significant familial stressors from parental divorce, illness of parent or sibling, and/or bullying. 6/20 patients have immune dysfunction with one patient each demonstrating one of the following: an idiosyncratic reaction to HPV vaccine, autoimmunity due to juvenile idiopathic arthritis (JIA), spondyarthropathy, psoriatic arthritis, an infectious trigger due to Lyme and EBV exposure and one with pediatric acute-onset neuropsychiatric syndrome (PANS) (Fig 2). Hypermobility was present in 5/20 patients with 2 patients having genetically confirmed Ehlers Danlos (EDS) hypermobility type (Fig 2). Other somatic complaints include headache 11/20 out of which 3 were migraines, 5 were nonspecific cephalgia, and 3 were post concussive. 5/20 patients had abdominal pains with 2 patients who were s/p MALS surgery with persistent pain and 3 with IBS. Fatigue was a universal symptom in this cohort with 20/20 reporting sleep disturbances varying from insomnia to nonrestorative sleep.

Patients described their pain differently with “whole body feels like pins and needles” in the patient EDS-HT versus heaviness and fatigue with infectious triggered FMS, versus “achy” in patient who FMS occurred in the setting of recurrent msk injuries palpation. Patients with history of CRPS reported “burning everywhere you touch” or a “feeling like acid”. Patients with autoimmunity report being able to appreciate a difference between a flare in their autoimmune condition compared to a flare of FMS reporting their inflammatory arthritis pain is usually well defined to their joints and sharp which responds to immunosuppression as opposed to the vague widespread ache attributed to fibromyalgia and responds to neuropathic agents.

Effective therapeutic regimens, effective as defined as pain severity decreased by 50% and functional improvement, largely included a combination of treatment modalities. Cognitive behavioral therapy (CBT) with medication was effective in 5/20 patients (Tab 2). Medications alone was effective in 5/20 patients (Tab 2). Medications include Serotonin norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), oral contraceptive pills (OCP), tricyclic antidepressants (TCAs), and neuropathic agents such as gabapentin and Lyrica. Physical therapy (PT), CBT, and medications were effective for 3/20 patients (Tab 2). 2 patients benefited from PT and medication (Tab 2). 2 patients had benefit with CBT monotherapy (Tab 2). 1 patient had benefit with medications, trigger point injections, and acupuncture (Tab 2). 1 patient improved with no intervention; her symptoms were self-limited. 1

patient in the cohort due to side effects of neuropathic agents and failure of naltrexone 4.5mg, focus is currently on optimizing medication for psychopathology.

Discussion And Conclusions

In the adult population, the prevalence is 1.5 to 2 times as often in women than men, frequently making its first appearance during menopause[2]. Consistent with the adult literature, an overwhelming proportion in our cohort are female. Unlike adults where symptoms manifest for women surrounding menopause, menstruation was a hormonal trigger that flared pain and/or initially triggered it in this cohort of patients. Dysmenorrhea was an overlooked symptom in almost a third of the 18 girls in the cohort which responded to oral contraceptives. In 3 patients, CBT and OCPs were effective treatments for their FMS.

Similar to reported literature, the mean age of diagnosis in this cohort is 14.8 years which is in line with the mean age of FMS diagnosis in adolescents between 13.7 and 15.5 years[12]. Only 3 of the 20 patients carried a diagnosis of FMS at the time of evaluation despite all patients in this cohort meeting ACR criteria. 4 of the 20 patients carried a preexisting diagnosed of AMPS or CRPS which leads to confusion as these are not the same conditions. AMPS is an umbrella term to describe neuropathic pain that encompasses both CRPS and FMS[13]. CRPS is a diagnosis of exclusion marked by light touch allodynia that is usually isolated to a limb whereas FMS is characterized by widespread pain with pressure allodynia[13]. In the evaluation of a child with widespread musculoskeletal pain, a differential diagnoses distinct from those of adults such as juvenile idiopathic arthritis (JIA) and juvenile ankylosing spondylitis must be considered[11]. Dissimilar associated conditions also include hypermobility syndrome, a well-known clinical association of pediatric FMS. 81% of children diagnosed with FMS met criteria for hypermobility in a study of 338 children[14,15]. A quarter of our cohort has hypermobility.

Surrounding this adult validated criteria, Buskila & Ablin[11] are among a limited number of researchers who have explicitly studied pediatric FMS. As in adults, pain is the cardinal symptom but in pediatric FMS also includes debilitating fatigue, headaches, sleep disturbances, abdominal pain, and a variety of neuropsychiatric problems[11]. All of the patients in this cohort had fatigue and sleep disturbances, over half had headaches, and a quarter had abdominal pain, mainly functional in nature. This correlates with the adult literature, sleep disorders are more common in adult FM patients than in the general population[16,17]. Consequently, worse perceived sleep quality is associated with greater symptom severity[16,17]. Cognitive factors such as catastrophizing (irrational thinking that the pain is worse than it is) and fear of movement have also been found to be poor prognostic factors in FMS[2]. Sleep disorders have also been documented in pediatric FMS patients, occurring in 67% of patients in another study[17].Namely, children with FMS differ in sleep architecture with shortened total sleep time, prolonged sleep latency, decreased sleep efficiency, longer awake periods during sleep, and movement arousal[18]. These concomitant factors cumulatively result in diminished capacity to cope with pain as a child.

FMS is associated with a lifetime prevalence of psychiatric disorders, mainly major depressive disorder (MDD), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD). As many as 86% of adult FM patients are diagnosed with MDD, up to 60% with GAD, and up to 57% fulfil diagnostic criteria of PTSD[3]. 65% of the patients in our cohort were diagnosed with psychopathology. Depression and anxiety prevail in pediatric FMS similar to adults, occurring in 26.6% and 60% of patients in one study (n=94), respectively[19]. In our cohort, 2 patients treated with SSRIs with CBT resulted in resolution of symptom. It is unclear the mechanism behind resolution of symptoms, whether the SSRI addresses pain by acting on the descending modulating antinociceptive arm of the nervous system or by treating the mood disorder, or if it is the influence of both.

Compared to adults with FMS, stress and distress play important trigger roles in its development. Imbieterowicz[19] specifically cites sexual abuse, learning disability, maternal substance abuse, parental separation, and domestic financial difficulties before the age of 7 years to be major predisposing factors. In our cohort, 35% of patients had significant psychosocial stressors; the age at which these events occurred was not acquired. In children and adolescents, this can be especially frustrating at a crucial stage of their physical and emotional development, which further disrupt social and educational achievements causing concern for patients and their parents. Criteria for pediatric FMS still need to be identified.

Whether the purported bidirectional relationship of these associated somatic conditions can be attributed to shared pathophysiology or common triggers, potentially modifiable risk factors exist for developing FMS – sleep, obesity, stress, nutrition, physical inactivity. The relationship between predisposing environmental factors and genetics fuel further epigenetic studies of this diagnosis as FMS is found at increased prevalence in adult individuals who have experienced specific infections (EBV, Q-fever, hepatitis B, hepatitis C, HIV, mycoplasma), trauma (psychological and physical), and wartime military service[2,3].

Surrounding the medical management of fibromyalgia, effective regimens for fibromyalgia included a medication in our cohort. Duloxetine, milnacipran, and pregabalin are FDA approved for fibromyalgia[20]with duloxetine for use in children as young as 7 years of age[21]. Use of pregabalin for the treatment of fibromyalgia in pediatrics has not been established, a placebo controlled trial in adolescents as young as 12 years old demonstrated pregabalin to be as safe as its use in adults[22]. Duloxetine was either not effective or not tolerated in 4 of the 17 patients and they were switched to a tricyclic antidepressant, pregabalin, or milnacipran with better result. Although both duloxetine and milnacipran are both SNRIs, they differ in their reuptake inhibition as duloxetine is more selective for serotonin reuptake and milnacipran for norepinephrine reuptake[23]. Milnacipran is not currently FDA approved for use in pediatrics[24]. SNRIs, SSRIs, neuropathic pain agents have a black box warning for increased risk of suicidal thoughts[24]; families should be made aware of this warning as FMS have high association of comorbid depression.

Due to the wide range of symptomatology and subjectivity, there is a clear need for uniform consistent diagnostics to capture the heterogeneity of expression of FMS so the pathology is not disputed. Major gaps for the utility of this diagnostic criteria in the pediatric population persist. Yet without validated measures for children, clinicians have no alternative. This poses a challenge in optimal management of FMS in a group of individuals with entirely different social, biological, physical, behavioral, developmental, and emotional biospheres than that of the adult.

Improved diagnostics could ideally lead to targeted treatment plans thus decreasing the time to for treatment and improving quality of life.

Abbreviations

FMS	Fibromyalgia syndrome
POTS	Postural Orthostatic Tachycardia Syndrome
EDS	Ehlers Danlos syndrome
OI	Orthostatic Intolerance
JIA	Juvenile idiopathic arthritis
IBS	Irritable Bowel Syndrome
WPI	Widespread Pain Index
ACR	American College of Rheumatology
SSS	Symptom Severity Score
FS	Fibromyalgia Severity scale
CAM	Complementary Alternative Modalities
PANS	Pediatric acute onset neuropsychiatric syndrome
CBT	Cognitive behavioral therapy
PT	Physical therapy
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
OCP	Oral contraceptive pills

Declarations

Conflict of Interest

The authors did not report any potential conflicts of interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of Children's National Hospital.

Ethics Approval and consent to participate

This study qualified for a waiver of HIPAA authorization, it was reviewed by internal IRB and classified as exempt

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

EEP made a substantial contribution to the design of the work and a major contributor in writing.

CY made a substantial contribution to the draft of the work.

SS made a substantial contribution in the interpretation of data.

JCF made a substantial contribution to the conception of the work and substantively revised it.

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Tables

Due to technical limitations, table 1 and 2 is only available as a download in the Supplemental Files section.

Figures

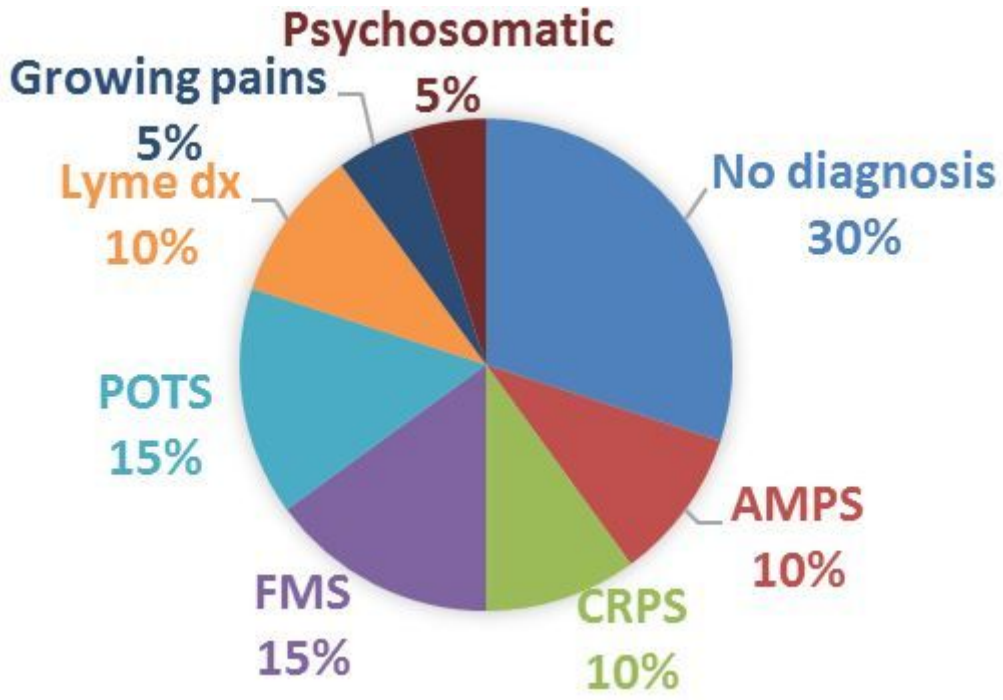

Figure 1

Diagnosis prior to presentation

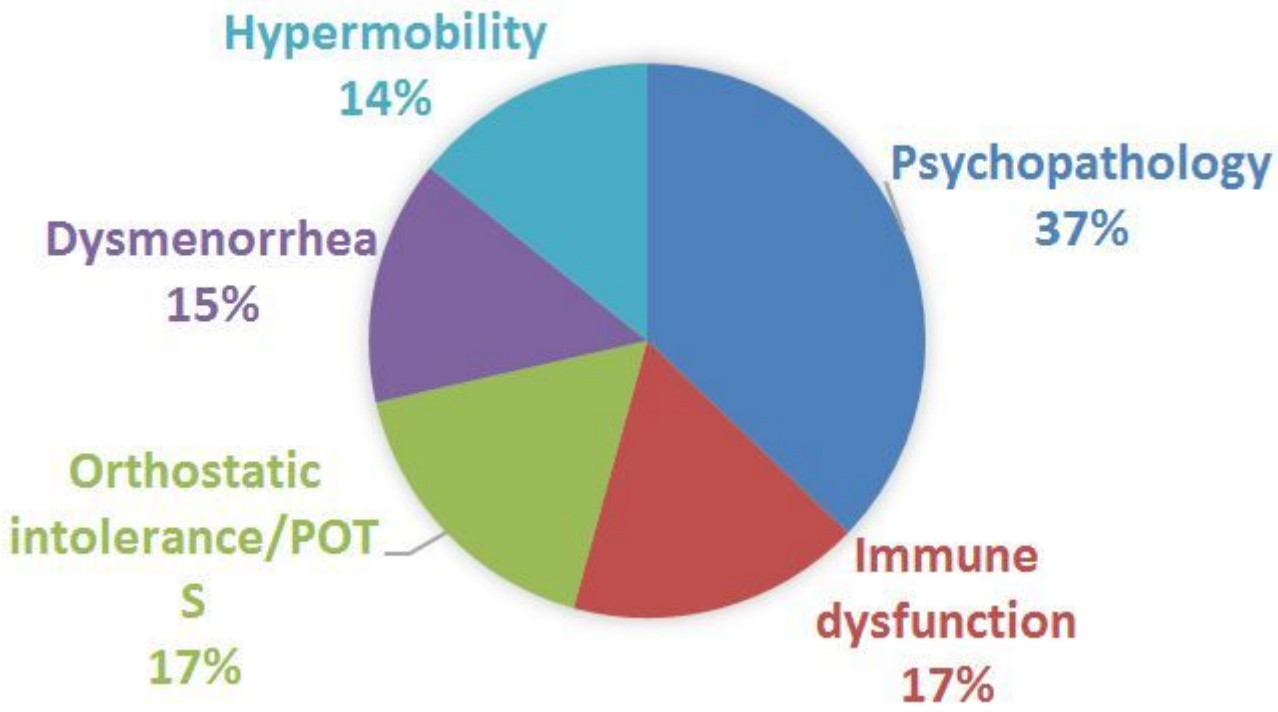

Figure 2

Pre-morbid/comorbid conditions

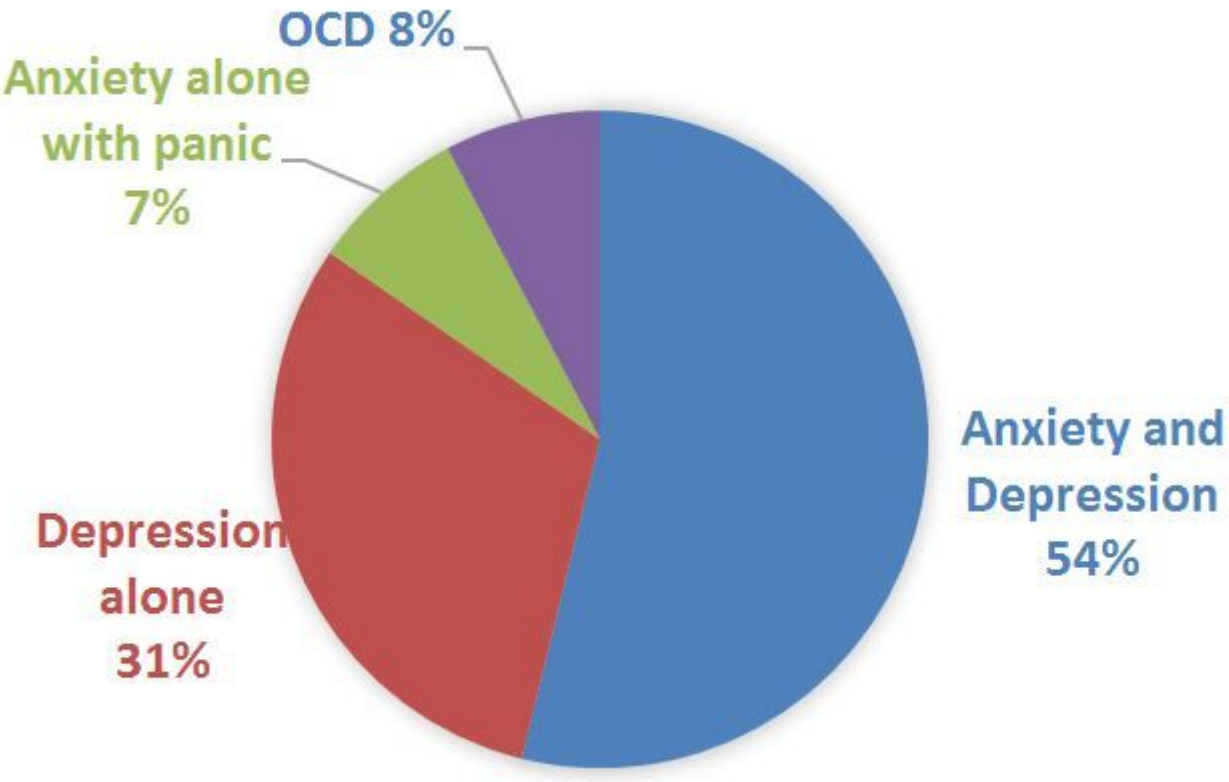

Figure 3

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