Annals of Clinical and Medical Case Reports

Case Series

ISSN 2639-8109 | Volume 12

Persistent PTSD among Patients with Fragile X Syndrome: Case Series

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Received: 22 Nov 2023
Accepted: 27 Dec 2023
Published: 01 Jan 2024
J Short Name: ACMCR

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Keywords:

Fragile X syndrome; posttraumatic stress disorder; Behavioral regression; Intellectual disability; Autism spectrum disorder

Citation:

Hagerman RJ, Persistent PTSD among Patients with Fragile X Syndrome: Case Series. Ann Clin Med Case Rep. 2024; V12(9): 1-7

1. Abstract

1.1. Background: Posttraumatic stress disorder (PTSD) affects about 3.6% of the US population and has clear diagnostic criteria and treatment modalities. Individuals with autism spectrum disorder (ASD) and intellectual disabilities (ID) are at an elevated risk for exposure to trauma and development of PTSD. Fragile X syndrome (FXS) is the most common inherited cause of ID, and there is currently need for further research regarding presentation of PTSD among these individuals.

1.2. Case Presentation: We report three cases of individuals with FXS and ID seen at a neurodevelopmental research center who had traumatic experiences leading to severe PTSD symptoms. The details of the traumatic event, patients' social and communicational baselines and subsequent changes, manifestations of different PTSD symptoms, and various psychopharmacological and non-pharmacological interventions are discussed. Compared to PTSD in neurotypical individuals, we find that post-traumatic symptoms in FXS are more severe and very long lasting, even up to 10 years. While the cases exhibited some classic symptoms of PTSD, there were also non-classic behaviors involving significant developmental regression and exacerbation of pre-existing behavior problems in response to trauma. In all cases, there was minimal improvement with classic PTSD treatments, both psychopharmacological and non-pharmacological.

1.3. Conclusion: There is a high risk of developing severe PTSD among individuals with FXS. Given this risk, it is recommended to take measures to avoid creating traumatic situations. Further research regarding how PTSD manifests in FXS and effective treatment modalities for these patients is merited.

2. Introduction

Posttraumatic stress disorder (PTSD) is defined by the American Psychiatric Association as a disorder that may result after an individual witnesses or lives through an event that presents a threat to life and safety, and causes emotions of fear, terror or helplessness [1] (Table 1). The current prevalence of PTSD in the United States

is estimated to be about 3.6%, but for people with intellectual disabilities (ID), the prevalence of PTSD has been reported to be up to 10% [2]. Over the years, there has been concern that the prevalence of PTSD is underreported among those with ID, as measures and screening tools had not been adapted to this population. The Impact of Event Scale Questionnaire was modified for patients with ID in a study by Hall et al in 2014, and a pilot study used the Diagnostic Manual-Intellectual Disability (DM-ID) criteria for PTSD, which showed that a greater number of study participants with ID met criteria for PTSD under these modified guidelines compared to use of the DSM-IV-TR guidelines [3, 4].

Individuals with autism spectrum disorders (ASD) and those with IDs are at a higher risk of trauma exposure and development of PTSD-spectrum symptoms [5]. Higher levels of anxiety, aggression, hyperactivity and social withdrawal were identified in youth with ASD in response to traumatic experiences [6]. Additionally, individuals with ASD demonstrated regressions in adaptive behavior and exacerbation of behavioral problems in response to trauma [7]. A case series by Santoro et al in 2020 identified unexplained regression in patients with Down syndrome [8]. Among these patients, a significant number had other psychiatric co-morbidities (including PTSD) and experienced more life stressors such as trauma/loss/grief. Among individuals with 22q11.2 DS, it was identified that there was a higher risk of developing PTSD (8.0%) compared to the general population (3.6%) [9]. While there is literature regarding PTSD and response to traumatic experiences among individuals with ASD and in those with IDs, information remains sparse for patients with fragile X syndrome. Fragile X syndrome (FXS) is the most common inherited cause of ID. It is known that individuals with FXS experience hyperarousal and greater anxiety than normal patients at baseline and are at higher risk for developing a maladaptive stress response to traumatic or disruptive events. Cordeiro et al. in 2011 identified the prevalence of formal anxiety disorders in FXS. Among 58 males and 39 females with FXS, 86.2% of males and 76.9% of females met diagnostic criteria for an anxiety disorder [10]. One case series described the psychological and functional issues following traumatic experiences among individuals with FXS and ID [11]. In this study, two individuals with FXS and ID presented with severe PTSD symptoms following motor vehicle accidents. Treatment with cognitive behavioral therapy was provided for both patients, but minimal information was discussed regarding treatments for PTSD with FXS. With this in mind, we report three individuals with FXS and ID who developed chronic psychological disturbances and behavioral regression following various traumatic experiences. We also report the different medications and treatment modalities the patients received to address symptoms following their traumatic events, and their effectiveness. Finally, we discuss safety planning and suggestions for preventing traumatic events and improving well-being among individuals with FXS and ID.

Table 1: DSM-V Criteria for PTSD

All the following criteria are required for a diagnosis of PTSD:	
1. Exposure to threatened death, serious injury, sexual violence one (or more) different ways	· Directly experiencing the event
	· Witnessing the event
	· Learning the event occurred to a close family member/friend
	· Indirect exposure to aversive details of the event
2. Presence of one (or more) intrusive symptoms associated with the traumatic event, beginning after the event occurred	· Unwanted, disturbing memories
	· Nightmares
	· Flashbacks
	· Emotional distress to traumatic reminders
	· Physiological distress to traumatic reminders
3. Persistent avoidance of stimuli associated with the event, one (or more) of the following	· Avoidance of distressing memories, feelings related to the event
	· Avoidance of external reminders of the event
4. Negative changes in cognition and mood associated with the event, one (or more) of the following	· Inability to remember key aspects of the event
	· Persistent negative beliefs about oneself/world
	· Exaggerated self-blame, or blaming others for causing event
	· Persistent negative emotional state
	· Decreased interest in activities
	· Feeling isolated
	· Difficulty experiencing positive emotions
5. Marked changes in arousal and reactivity associated with the event, two (or more) of the following	· Irritable behavior, angry outbursts
	· Reckless/self-destructive behavior

	· Hypervigilance
	· Exaggerated startle response
	· Concentration problems
	· Sleep disturbance
Additional criteria:	· Duration of symptoms > 1 month
	· Disturbance causes significant distress/impairment in daily functioning
	· Disturbance not attributed to effects of a substance or alternate medical condition

3. Patient Cases

3.1. Case 1

Case 1 was a 31-year-old male with FXS and ASD. His DNA testing demonstrated a full mutation in FMR1 that was unmethylated in bands from 213 to 280 CGG repeats and methylated in bands from 797 to 1063 CGG repeats. About 10 years prior to presentation, he returned home from work crying, agitated, and vomiting with no clear precipitating event. He was urgently taken to the emergency room by his father. When they arrived at the hospital, the patient's father informed the ED staff of the patient's history of FXS and associated excess sensitivity to sensory stimuli. Despite this caution, an emergency department staff member at the front desk closely approached the patient, and he became overwhelmed and hit her. Police arrived and the patient was physically restrained and tasered multiple times. He became apneic and was admitted to the ICU for two days on mechanical ventilation. While admitted, a urine toxicology screen showed traces of multiple drugs of abuse. Per the patient's parents, it was thought that someone at his job (at a nonprofit organization for people with ID) was providing him illicit drugs, and this could have caused his increased agitation. Following discharge, the patient experienced severe anxiety and global functional regression. He became unable to perform his baseline tasks, such as showering and sleeping independently. He experienced sleep disturbances, often waking multiple times a night saying he "needed to shower". He would avoid leaving home for work and withdrew socially from his "favorite people," like his grandparents. The patient perseverated about his experience of being tasered and expressed a new fear of doctors, actively opposing going to outpatient visits. He was trialed on multiple medications, including citalopram 30 mg BID, guanfacine 2 mg TID, metformin 1000 mg BID, quetiapine 100 mg BID & 200 mg QHS, lithium 300 mg BID, minocycline 200 mg QD, alprazolam 1 mg BID, and cannabidiol (CBD) capsules. Metformin 1000 mg BID was found to slightly improve anxiety [12]. He also tried Eye Movement Desensitization and Reprocessing (EMDR) psychotherapy, received regular individual psychotherapy, and participated in yoga. EMDR was mildly helpful for his PTSD symptoms. Case 1 had previously been friendly and outgoing, but following the incident he became socially withdrawn and unable to carry out his activities of daily life. Ten years following the event, he continued to have ongoing symptoms of severe anxiety, disturbed sleep, and avoidance of social settings. The only improvement was absence of subsequent violent interactions.

3.2. Case 2

Case 2 was a 21-year-old female with FXS, ADHD, and generalized anxiety disorder (GAD). Her FMR1 DNA testing demonstrated a full mutation that was 100% methylated with bands at 597 and 1030 on one X and 19 CGG repeats on the second X and her activation ratio was 0.5. At age 20, the patient was on an airplane with her father when a flight attendant asked her if she wanted to have something to eat. She was very shy and turned her head away while the flight attendant continued to address her, even though her father said she was shy and did not want to respond. When they landed, the police were present at the gate and arrested the father on suspicion of human trafficking. The patient was placed in another room for questioning, and she eventually communicated that the man was her father. The situation was determined to be a misunderstanding and the pair was released. Following this event, the patient's anxiety escalated substantially. She subsequently refused to travel on airplanes and resisted leaving home. She experienced sleep disturbances and nightmares, only falling asleep with a parent by her side. She became unable to attend her special needs academic classes and participate in recreational activities such as swimming, because she could not be separated from her parents for long periods of time. The patient received ongoing psychotherapy and was trialed on metformin 1000 mg BID, sertraline 75 mg QD, desvenlafaxine 100 mg QD, and baclofen 40 mg BID, which all somewhat improved her anxiety. A trial of quetiapine 25 mg QD was not helpful and was discontinued. After a year, the patient was eventually able to attend classes at a secondary school, but only half-time because she continued to exhibit parent separation anxiety. She was not able to go on family trips due to her fear of airplanes and continued to require parent presence to fall asleep.

3.3. Case 3

Case 3 was a 10-year-old male with FXS, ADHD and ASD. His DNA testing demonstrated a full mutation in FMR1 with >200 CGG repeats. At age 9, he was scheduled for a dental procedure. Prior to induction of anesthesia the patient's mother attempted to set expectations for the procedure; however, the patient panicked with anesthetic mask placement and required five people to im-

mobilize him while sevoflurane was administered. Immediately post-anesthesia, the patient aspirated vomit and required brief endotracheal tube placement. After respiratory stabilization, the patient was extubated and discharged with prophylactic antibiotics. Arriving home, he continued to vomit with minimal food intake, and displayed significant behavioral changes and regression in language and behavior. The patient became non-verbal, and parents found him having moments of non-interactive, blank staring. After two weeks of minimal nutritional intake, the patient was admitted to a local children's hospital, and a nasogastric feeding tube was placed. Diagnostic workup including an EEG, ECG and CT scan were unremarkable. The patient spent several more days in the hospital before his nutritional status improved and he began eating small amounts. However, his behavior changes persisted. He became increasingly disruptive (e.g., opening cabinets, throwing plates and other household items) and with parent intervention he would scream and become physically violent. The patient could not be taken to public spaces like department stores, because he would knock items off shelves and damage property. He became behaviorally oppositional and violent with peers in academic settings, to the point he was not allowed to return to classes. The patient became fearful of all medical settings. He could not sleep more than 3 hours/night due to nightmares. He lost bowel control (a developmental milestone he had gained at 12 months) and required restarting the use of diapers. The patient refused all forms of therapy and continued to have episodes of minimal nutritional intake, such that he eventually required G-tube placement. The patient was previously treated with guanfacine 1.5 mg BID, clonidine 0.2 mg QHS, melatonin 3 mg QHS, methylphenidate 27 mg QD, and multivitamins. Two months following the event, he was tried on sertraline 25 mg daily, which improved his behavior, sleep quality and regaining of toilet training skills. Following G-tube placement, he experienced improved nutritional and weight status.

4. Discussion

Through the cases presented in this report, we illustrated the varying manifestations of traumatic experiences among individuals with FXS and ID. All three patients experienced significant developmental regression and worsening behavior problems is similar to the presentation of patients with ASD and PTSD described by Mehtar and Mukaddes in 2011 [6]. In this study, patients with ASD and PTSD were found to express increased anxiety, aggression, hyperactivity, and behavioral regression. It is notable that both case 1 and case 3 had a prior co-diagnosis of ASD, and up to 67% of males and 23% of females with FXS are also diagnosed with ASD [13]. Therefore, there may be significant overlaps in how PTSD presents in patients with FXS+ASD and those with ASD alone. Treatment modalities for patients with PTSD and ASD could be considered for populations with FXS+ASD. All cases also exhibited some classic symptoms of PTSD, including sleep disturbances, avoidance of trauma-associated situations, anxiety, and hyperarousal and they met diagnostic criteria for DSM-IV and DSM 5. Compared to PTSD in neurotypical individuals, we find that symptoms are more severe and persistent in these individuals with FXS – even up to 10 years with minimal improvement from standard therapies such as SSRIs, EMDR and psychotherapy. Case 1 and 2 experienced developmental and social regression and were not able to attend school and go to work independently, nor leave the home and be separated from their primary caregivers for extended periods of time.

4.1. Neurobiology of FXS and Trauma

There are molecular factors associated with FXS that increase vulnerability for developing a maladaptive stress response to trauma. GABA receptors are involved in anxiety and stress responses, and the GABAergic system (specifically the amygdala) has been found to be disturbed and deficient in FXS [14]. Poor sensory gating with abnormal processing of external stimuli in response to stress may further magnify the impact of traumatic experiences in FXS [15, 16]. Studies have identified that the fragile X messenger ribonuclear protein (FMRP) and the FMR1 gene have a role in modulating PTSD and acute stress. In rodent models, FMRP and fragile X related protein 1 (FXR1) was decreased in the hippocampus of rats following a stressful stimulus, and miR132 was an upstream modulator that regulated FMRP and FXR [17]. Response to acute stress was assessed between a FMR1 knockout (KO) and wild-type control mouse. Both were exposed to acute stress, and the KO mice exhibited a longer corticosterone response compared to WT mice, suggesting that the stress response is dysregulated in FMR1 KO mice as in FXS patients [18]. The Big Potassium (BK) channel is dysregulated in the absence of FMRP. Therefore, in FXS, excess stimulation with trauma can lead to overactivation of the BK channel, causing a more dramatic behavioral response and perhaps amplifying PTSD symptoms [19].

4.2. Treatment of PTSD in FXS

Given that the pathophysiology of posttraumatic disorder involves brain regions like the amygdala, hypothalamus and hippocampus, along with changes in various neurotransmitters systems and the inflammatory process, pharmacological interventions targeting these areas provide positive effects in diminishing posttraumatic symptoms [20]. Current monotherapy for treating PTSD involve SSRI/SNRIs, as well as the antipsychotic quetiapine. Prazosin and risperidone had positive effects for augmentation. There was no evidence of superiority for these medications over one another [21]. There is currently no information regarding effective pharmacological interventions for individuals with commingled PTSD and FXS. In regards to improving behavior and cognition in individuals with FXS alone, studies have identified the effectiveness of sertraline, CBD, metformin and guanfacine [12, 22–25]. CBD has been found to be useful in improving social avoidance and anxiety among individuals with FXS [22, 26]. Research is recommended to explore the role of these pharmacological treatments to improve

PTSD symptoms in FXS. A systemic review of non-pharmacological interventions for individuals with ID and trauma symptoms reported effectiveness of both cognitive behavioral therapy (CBT) and EMDR, with greater benefit from EMDR [27]. Trauma-focused CBT(TF-CBT) could improve symptoms of aggression and depression associated with trauma in some individuals with ID [28–30]. However, it is worth noting that the self-awareness, cognitive reconstruction, and imagination skills required for therapies like CBT may limit the use of TF-CBT among individuals with severe ID and FXS. EMDR may be particularly useful for some people with ID, as it does not require identification or articulation of a traumatic event to have a therapeutic effect. Adaptations to EMDR interventions to increase accessibility for individuals with ID have included splitting the traumatic event into smaller components, increased verbal input by the psychotherapist, and the use of bilateral tactile and auditory in addition to visual stimulation [31]. Further research is required to assess the use of EMDR to address PTSD symptoms among individuals with FXS, although it was only minimally helpful in Case 1.

5. Conclusion

5.1. Safety Planning

The events surrounding our patients' traumatic experiences are notable. Two of the cases involved police intervention, and two involved intensive hospitalization. Case 1 was tasered by police and Case 2 witnessed her father arrested and interrogated. In both cases, escalation could have been avoided with better understanding and awareness of the behavioral and social deficits that individuals with FXS experience. Escalation to a painful physical immobilization with a taser by law enforcement has been frequently reported among individuals with ID, with negative consequences that can be lifelong. Aggressive "challenging behavior" in individuals with ID leads to frequent contact with mental health services, ED admissions, and involvement with law enforcement [32]. There have been training programs designed for staff working at residential/care facilities for individuals with ID. These programs were found to improve understanding about people with ID, promote effective communication, and establish appropriate crisis intervention plans [33, 34]. These interventions lead to not only the reduction of traumatic crises, but also benefits in the well-being of the patient, family members and frontline workers. Therefore, further training for frontline workers in the community such as police, teachers, community care providers is warranted. Both Case 1 and 3 were acutely hospitalized for apneic and aspiration events respectively and for Case 3 it is possible that the sevoflurane could have contributed to toxic brain injury and exacerbation of PTSD symptoms [35]. Intensive hospital experiences are a major form of trauma for individuals with ID, and greater efforts need to be made to optimize inpatient care and procedures (such as anesthesia) for individuals with neurodevelopmental disorders. One approach is to take the patient's ID history early in hospitalization and establishing the baseline symptoms such as communication and social abilities, sensory sensitivities and repetitive behaviors [36]. For operative and other sedative procedures, the provider should consider using alternative anesthetic agents to minimize impact on cognitive function [35]. There is a large role for multi-disciplinary special needs support teams and mental health expertise in hospital settings to improve experiences and outcomes for hospitalized patients with ID [37].

5.2. Recommendations

For parents and caregivers, the initial steps for avoiding traumatic experiences for individuals with FXS involve anticipation (Table 2). Maintaining predictable routines and setting expectations contributes significantly to emotional stability. It is important to maintain consistent communication and allow space for frequent questions. When entering new situations, we recommend providing abundant time for the event, and ensuring other aspects of life remain routine. Development of PTSD in individuals with FXS can occur even after what seems to be an innocuous event. If an event leads to a posttraumatic stress response, the focus should be on processing and healing. It is important to ensure that the individual with FXS re-enters a familiar environment to comfortably respond to the recent experience. It is important to recognize when an individual with FXS has gone through a traumatic experience and early therapeutic intervention is recommended. For those encountering individuals with FXS, their responses to stressful situations can manifest in different ways, including agitation, screaming, and physical violence. We recommend avoiding immediate immobilization, and creating a safe space where the individual with FXS can eventually be calmed. Parents or close relatives are the most ideal members to intervene and defuse these situations. In all cases, we advise talking to the agitated individual in a calm tone and approaching them slowly, being aware of their safety and one's own. Our strongest recommendation is to avoid violent intervention whenever possible and never use immobilization measures such as a taser unless faced with a life-threatening situation. For psychiatrists, management of patients with FXS after traumatic experiences is manifold. In patients with known FXS, ASD, and/or ID, physicians need to be aware of a possible high risk of PTSD, even following routine medical/surgical procedures. Diagnosis of PTSD is difficult with any patient with communication barriers, especially if the onset of PTSD further impairs communication. For patients with neuropsychiatric conditions requiring operative or sedative procedures, their responses to anesthetic agents may be excessive and put them at risk for further compromise. Patients with ID may not respond well to routine psychotherapy approaches. Creative use of off-label psychopharmacology may be needed for both the neuropsychiatric symptoms of the baseline FXS as well as new-onset PTSD due to subsequent, disruptive (including medical-surgical) events.

Table 2: Recommendations for addressing PTSD in FXS

Parents, Caregivers, Family Members	
Anticipation	
Diverse methods of communication	Verbally, visually with pictures/drawings
Allow space for numerous, frequent questions	Leading up to the event, right before the event, following the event
Familiarize the new experience	Visiting the new space, allowing family to stay with patient throughout hospitalization
Maintain routines	Maintaining sleep schedule, meal times, school/work activities
Stress management	
Place the individual in a familiar environment	
Allow for various forms of expression, both verbal and non-verbal	
Provide early therapeutic interventions	
General Public	
Avoid immediate immobilization	
Create a safe space to reduce agitation	
Allow for parents/caregiver intervention	
Speak in a calm voice, and approach slowly	
Avoid physical immobilization or tasers	
Consultation-Liaison Psychiatrists	
Recognize high risk for developing PTSD in FXS	
Recognize varying presentations of PTSD in FXS	
Caution in regards to anesthetic agents in FX related disorders	
Awareness of the lack of evidence-based treatment for PTSD in FXS and consider creative use of off-label psychopharmacology	

6. Acknowledgement

YT, IMP and MC conceptualized this manuscript, reviewed primary literature, collected patient case data, drafted the initial manuscript, and reviewed and revised the manuscript. AS proofread the initial manuscript and critically reviewed the manuscript. FT provided the molecular data of the cases, proofread the initial manuscript and critically reviewed the manuscript. RJH conceptualized this manuscript, proofread the initial manuscript and critically reviewed the manuscript. JAB critically reviewed and edited the manuscript, adding psychiatry-specific content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

7. Funding

This research was partially supported by the Azrieli Foundation and private donors in addition to the MIND Institute Intellectual and Developmental Disability Research Center funded by NICHD (P50 HD103526)

8. Conflict of Interest/Disclosures

RJH has received funding from Zynerba for clinical trials of CBD in FXS and from the Azrieli Foundation for a metformin study in FXS. The other authors have no conflicts.

9. Patient Consent Statement

Parents/legal guardian of all cases provided verbal and written consent for the writing of this case series.

10. Ethical Publication Statement

The study was approved by the local ethics committee and conducted according to the principles of the Declaration of Helsinki. All patients and their guardians gave written informed consent.

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