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Caregiver Burden in Fragile X Families

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Abstract

Complex caregiving issues occur in multigenerational families carrying the fragile X mutation and premutation. The same family members may care for children or siblings with fragile X syndrome (FXS) and for elderly parents with fragile X-associated tremor/ataxia syndrome (FXTAS). Family caregivers experience anxiety, depression, neglect of personal health care needs, employment difficulties, and loss of social support, leading to isolation and further psychiatric consequences. There is growing awareness of caregiver burden with regard to parents of children with FXS, but much less is known about the needs of informal caregivers of patients with FXTAS. In this paper, we review the available literature to date and provide suggestions for further exploration of caregivers' needs. Evidence-based strategies to address these needs are included. Many more research studies exploring caregiver burden in multigenerational fragile X families are needed, as well as studies aimed at investigating interventions and their impact on reduction.

Keywords

caregivers; dementia; family; fragile X syndrome (FXS); fragile X-associated tremor/ataxia syndrome (FXTAS)

Background

According to the National Alliance for Caregiving, 65.7 million people (28.5% of the U.S. population) provide unpaid care (averaging 20 hours per week) for an adult or a child; 31% of those have taken care of their loved one for five years or more [1]. Most patients with mental illness receive care in the community, placing a considerable burden on their families. Informal caregivers provide extraordinary, uncompensated care, predominantly in the home setting, for months or years [2]. Several definitions of caregiver burden exist in the literature, but the one that captures the main themes refers to “consequences of the activities involved with providing necessary direct care to a relative or friend that result in *observable* and *perceived* (emphasis ours) costs to the caregiver” [3]. Some authors differentiate the objective and subjective aspects of caregiver burden. *Objective burden* concerns the patient's symptoms, behavior, and sociodemographic characteristics, as well as changes in household routine, work, leisure, family or social relationships, and physical health of the caregiver, while *subjective burden* refers to the mental health consequences for carers [4].

Caregiving in the context of dementia

Contextual factors and individual differences impact caregiver experiences, and there may be considerable variation in the way caregivers adapt to caregiving demands. Kinship ties, caregiver age, gender, coping styles, socioeconomic, spiritual, and cultural factors (such as filial obligation), as well as the care recipient's behavioral disturbances are determinants of caregiver burden [5-7]. About half of the caregivers of patients with dementia have significant depressive and anxiety symptoms, while 20-25% of them have major depression [2, 8]. Those with high initial levels of anxiety, anger, and more physical health problems are more vulnerable to burden over time [9]. Chronic stress and depression can affect the caregivers' cognitive status. For example, cognitive processing speed declined 4.5 times faster in caregivers of spouses with Alzheimer's disease (AD) than in non-caregivers, and the decline was mediated by the caregivers' depressed mood [10].

Adult children, especially daughters and daughters-in-law, are the main caregivers for elderly with dementia in about 30% of families (and up to 70% in Asian cultures) [6, 11, 12]. Adult child caregivers may experience a higher burden and worse mental health due to juggling work, child rearing, and caregiving responsibilities, with the inverse correlation between burden and mental health being strongest in daughters [13]. Children of parents with dementias with known genetic etiology may also be concerned about their risk of developing the same disease [14, 15].

Physiological markers of caregiver stress

More recently, psychological well-being outcome research has been complemented with studies of physiological measures. An impaired hypothalamic-pituitary-adrenal (HPA) axis response and dysregulated cortisol patterns have been observed in spousal caregivers of patients with dementia [16] as well as in mothers of individuals with autism spectrum disorders (ASD) and fragile X syndrome (FXS) [17, 18]. Caregivers of children with autism and attention deficit hyperactivity disorder (ADHD) also had higher concentrations of proinflammatory biomarkers than parents of typically developing children [19].

Plasma norepinephrine levels of caregivers of patients with AD in response to a stress task were predicted by their depression symptoms, even when controlling for age, caregiver distress, presence of caregiver hypertension, and care recipient level of cognitive function [20]. On the other hand, personal mastery (i.e., belief that one can manage life's obstacles) was inversely correlated with mean arterial pressure and systolic blood pressure values [21]. The same group later found that high levels of depressive and anxiety symptoms were associated with prolonged sympathetic activation in chronically stressed caregivers [22]. Chronic stress (at work or home) has been linked to higher risk of myocardial infarction in the general population, in a large case-control study in 52 countries [23]. Caregivers may also neglect their own health needs and postpone necessary diagnostic or therapeutic procedures, further compounding their morbidity. Elderly family caregivers who experience strain have a 63% higher mortality risk than age-matched non-caregivers [24].

Caregiving in fragile X families

Complex caregiving issues occur in multigenerational families affected by fragile X gene mutations and premutations. The process of caring for children with FXS (who have full mutations of the fragile X gene) starts in childhood and often continues throughout adulthood. Older adults with premutations of the fragile X gene may develop a neurodegenerative disease, fragile X-associated tremor/ataxia syndrome (FXTAS). Family caregivers play a critical role in managing the complex needs of individuals with FXS and FXTAS. Middle aged family members (some of whom are premutation carriers) may care for both their children with FXS and aging parents with FXTAS. Female carriers are often

involved in caring for their siblings with FXS and may take on an even greater supportive role over time, as their parents age [25].

In this paper we review the subjective burden in family caregivers of individuals with FXS and FXTAS as well as evidence-based interventions that can address caregiver needs. Most studies of caregivers of children with FXS are based on parent surveys. Limited data exist on the needs of informal caregivers of patients with FXTAS therefore the corresponding section is largely based on our research work at the University of California, Davis. Our goal is to highlight the needs of fragile X families and to educate providers about available resources for the caregivers and their care recipients.

Caring for Children with FXS

Caregiver needs

FXS is the leading inherited cause of intellectual disability, estimated to affect 1 in 3,847 individuals in the U.S. [26]. Symptoms of FXS are not evident at birth, but gradually emerge during the first two years of life. In a recent study, the average age when concerns were first noted (developmental delays, poor eye contact, difficulty interacting with others, and behavioral problems) was 12 months old [27]. However, the average lag time between initial concerns and diagnosis was 24 months. Most families reported at least 3-5 visits to a health care professional before genetic testing for fragile X was ordered, and more than 25% needed 10 or more visits. This process caused frustration to parents and, as a result, children often missed the opportunity of an early intervention; 27% of the families with an affected son and 39% of those with an affected daughter had a second child with the full mutation before the first was diagnosed [27].

Almost all boys with the full mutation show clinical and behavioral manifestations, with cognitive impairment being the core feature. Girls with the full mutation are less affected than boys and have a wider variability in phenotype. Children with FXS can have multiple comorbid neuropsychiatric conditions, including ADHD, autism, anxiety, aggressiveness, depression, self-injurious behavior, and seizures [28, 29]. Up to 33% of children with FXS have autism [30, 31]. Among males with FXS, another 30% meet criteria for pervasive developmental disorder not otherwise specified [31]. The combination of FXS and autism can be particularly challenging, leading to poorer family and parent well-being (including pessimism about the child's future and lower maternal perception of reciprocated closeness by the child) [32].

Caring for a child with complex disabilities may have a negative impact on both the physical and the psychological health of the parents. Despite increased interest, only a limited number of studies regarding caregivers of children with FXS have been published; some have small sample sizes or non-representative samples, due to recruitment bias, and most are derived from self-report measures. Mothers of children with FXS had elevated rates of mood disorders (43%) compared to mothers in the general population (13%), almost as high as the mothers of children with autism (59%) [33]. Mothers of adolescents and young adults with FXS displayed lower levels of psychological well-being and higher pessimism and depressive symptoms than mothers of individuals with Down syndrome, but higher well-being levels than mothers of those with autism [34]. Child behavior problems were strongly associated with maternal stress, anger, anxiety, and depressive symptoms, and inversely correlated with mothers' quality of life [35]. In another study, the strongest predictor of maternal stress was the level of marital satisfaction, while the strongest predictor of paternal stress was the extent of the child's adaptive skills [36]. Mothers of children with FXS who reported good social and spousal support were less likely to experience significant levels of stress and depressive symptoms [37].

Not all health insurance policies cover medical costs associated with FXS and not all families have insurance. Annual medical costs to families, including provider fees, medications, and therapy were estimated at \$17,016 per child [26]. Education-related costs add to the family financial burden, with a quarter of families spending about \$2,000 per year out of pocket [26]. In the National Fragile X Family Survey, half of the caregivers of children with FXS reported increased financial burden and more than 60% stated they had had employment problems (quit working, turned down a job or promotion, or changed work hours) as a result of their caregiving responsibilities. The strongest predictor of economic burden per family was the total number of co-occurring conditions among affected children [38]. Reduced work hours can have long-term impact on caregivers' income, job security, career path, and employment benefits (disability and health insurance). Over time, this translates into lower retirement and social security benefits, affecting the caregivers' long-term care plans and further compounding their financial strain. In addition to the economic burden, caregivers may face stigma and social isolation due to neglect of other relationships outside their families.

Interventions to reduce caregiver burden

While we can readily find studies assessing the stress, burden, and depression in families of children with FXS, few have examined interventions that are aimed at ameliorating that stress. Given the strong correlation between child behavior problems and parental well-being depicted above and available prospective studies showing that parental stress may be child-driven [39], interventions which improve the child's functioning can be expected to decrease the parents' strain. A detailed review of treatment recommendations for individuals with FXS was presented by Hills-Epstein et al. [40]. Treatment approaches include individual therapy, family therapy, behavioral therapy, group therapy, and social skills training programs. Ideally, multidisciplinary teams should be involved in the care of individuals with FXS and their families.

Behavioral plans focus on modifying child behaviors, based on the antecedent-behavior-consequence (ABC) model. The ABC model notes that all behaviors have antecedent stimuli to which the child responds and resultant consequences that further modulate behavior. Some caregiver responses reward and maintain maladaptive behaviors. The goal of behavioral therapy based on the ABC principles is to help parents recognize antecedents and consequences, modify or eliminate those, and to replace maladaptive behaviors with appropriate ones through positive reinforcement. Only one behavior should be targeted at a time [40].

Given the overlap of autism in about a third of children with FXS, established therapeutic approaches for autism such as the Treatment and Education of Autistic and Related Communication-Handicapped Children model, the Denver model, pivotal response training, and applied behavior analysis, may be helpful for those with FXS as well [41]. A 20-week social adjustment enhancement curriculum for boys with ASD resulted in statistically significant improvements in facial expression recognition and problem solving [42]. This curriculum addressed three main areas: emotion recognition and understanding, theory of mind, and executive functions/real life problem solving. Additionally, a pilot trial of the evidence-based parent-child interaction therapy in boys with high functioning ASD and behavioral problems showed reductions in parent perception of child problem behaviors and increases in child adaptability, thus benefitting both parents and children [43]. Parent positive affect and shared positive affect in parent-child dyads also improved in the intervention group [43]. However, these modalities have not been specifically studied in individuals with FXS.

A recent literature review identified several promising interventions for parents of children with intellectual disabilities [44]. Cognitive behavioral group therapy was supported by the strongest evidence base, especially with regard to stress reduction in mothers. Respite care and case management services also helped reduce parental stress. Parent-led support networks were additional valuable resources [44]. Parents' coping styles were also tied to their well-being. Mothers who adjusted to their child's disability by using problem-focused coping experienced less burden and depression than those who relied on emotion-focused coping, in which one simply seeks to manage the emotions surrounding the source of stress [45]. All these results suggest that parental caregiver burden can be mitigated by providing access to psychosocial and psychiatric services for the children with FXS, as well as therapy and resources for the parents.

Caring for Patients with FXTAS

Background and caregiver needs

FXTAS is a neurodegenerative disease which may occur in up to 75% of male carriers of the fragile X premutation in their 80's and up to 16% of female premutation carriers [46, 47]. Typically, premutation carriers are identified through cascade testing from families of children with FXS. FXTAS manifests clinically with intention tremor, ataxia, parkinsonism, peripheral neuropathy which can result in severe pain, autonomic dysfunction, as well as a myriad of associated medical and psychiatric illnesses [48]. Falls occur later in the course of the disease, leading to dependence on walking aids and wheelchairs. Men with FXTAS often have diabetes, hypertension, and hyperlipidemia, placing them at risk of heart disease and cerebrovascular accidents [48, 49]. Women develop FXTAS less often and may have less severe symptoms when they do, likely due to the protective effects of the second X chromosome [50]. Female carriers may develop chronic muscle pain, migraines, fibromyalgia, thyroid problems, primary ovarian insufficiency, autoimmune disease, and have very high rates of anxiety and depressive disorders [47, 50-54]. Daughters of men with FXTAS have more anxiety and depression and report having received counseling or psychiatric medications more often than daughters of premutation carriers without FXTAS [15].

All of the daughters of a male premutation carrier are obligate carriers, with a 50% risk of having a child affected by FXS. Thus, some female carriers are in the "sandwich generation", taking care of children with FXS but also of parents (often, fathers) with FXTAS. We have also seen both men and women with FXTAS who are the primary caregivers for their grandchildren and who financially, physically, and emotionally support their premutation carrier daughters. Despite their illness, these grandparents remain the central family figures, while at the same time their families are an important source of love and support and a protective factor for them. Another impressive psychological trait in individuals with FXTAS is their altruism, evidenced in the dedication with which they participate in research studies, hoping to help find a cure for illnesses that may affect their children and grandchildren.

As FXTAS progresses, individuals suffer increasing disability related to the neurological symptoms, pain, and/or cognitive decline. Role changes may take place, with patients no longer being the primary breadwinner or the family business leader, while spouses and adult children have to take over these tasks. In time, conflicts may arise between patients and their families as they may misinterpret the family members' intentions. In our work, we have seen patients with FXTAS become convinced of their spouse's infidelity when they forgot the spouse's schedule or feeling "set up" or left out of family decisions, when in fact they forgot these conversations. Rarely do these beliefs reach delusional intensity, but they are hurtful nevertheless to the family members who are unfairly accused. About a third of men and few

women with FXTAS develop dementia in more advanced illness stages [55, 56]. Cognitive deficits involve multiple domains: attention, executive function, and memory recall and retrieval, along with personality changes, impulsivity, disinhibition, lack of insight, and psychomotor slowing [55, 57-58] (also see *Cognitive dysfunction in FMR1 premutation carriers*, in this issue).

There is a dearth of data regarding caregiver burden and subjective needs when caring for individuals with FXTAS. In a study of 24 patients with FXTAS and 18 caregiver spouses, Gane and colleagues found that informational needs were viewed as most important, followed by emotional, and, lastly, instrumental needs [56]. Informational needs referred to learning about disease progression and what to expect in the future; emotional needs included having a close person to talk with, being in contact with other families affected by fragile X spectrum disorders, support groups, and professional counseling. Instrumental needs were more relevant to those in advanced stages of FXTAS and included home health care, help with transportation, and financial support. Patients and caregivers prioritized the same needs, showing that spouses were emotionally attuned to each other. Average patient age in this small sample was 66 years old and 29% had dementia (all those with dementia were men). Most informal caregivers of patients with dementia are women [59]; this was also true in the group described by Gane et al., where 90% of caregivers were patients' wives or long time partners [56].

Interventions to reduce caregiver burden

Studies show that the mood and quality of life of caregivers and patients with motor neurodegenerative diseases are quite similar, therefore educational and therapeutic interventions need to address both groups [60]. Furthermore, interventions that reduce depressive symptoms in patients with dementia have been shown to improve the caregivers' mood [61]. Based on this information and given the caregiver needs described above, multi-faceted interventions will be optimal to help families affected by FXTAS. Specifically, we recommend sensitive genetic counseling, sharing as much information as possible with patients and their family members, education on illness progression and management, and supportive, concrete psychotherapeutic approaches. Couples and family therapy are also options, especially for families with multiple affected members.

Family members have to learn basic caregiving skills, such as dealing with an angry, impulsive individual or assisting him/her with activities of daily living. Psychoeducational programs delivered in person (typically in groups), by telephone, or in video format, have been beneficial in reducing caregiver stress, improving disease understanding and ability of coping, improving the quality of the relationship with care recipients, and increasing caregiver support [62-65]. These approaches have been effective for caregivers of various cultural backgrounds. As in caring for children with FXS, a problem-focused coping style has been associated with lower dementia caregiver burden [6, 66].

Problem solving therapy (PST) is one approach we suggest for individuals with FXTAS and their caregivers. PST has led to improvement of depressive symptoms in elderly depressed patients, both cognitively intact and with executive dysfunction [67-69]. PST consists of 6-8 sessions, 30-60 minutes long, which can be delivered in the primary care setting by trained providers (e.g., nurse care managers). The focus of PST is to learn how to solve problems, in a seven-step approach: define the problem, set goals, brainstorm solutions, select, then implement solutions, review the implemented plan, and schedule activities [70].

When treating patients with more advanced FXTAS, physicians can assist patients and families with decision making and formulating appropriate advance care plans, supporting home care, and attending to family grief and bereavement [71]. Patients grieve their loss of

stamina, independence, and identity. Even though FXTAS is an ultimately fatal disease, it is very important to remain optimistic, since targeted therapeutic trials are ongoing, while symptomatic treatments are readily available [72].

Another psychosocial approach which has been shown to help reduce caregiver strain in dementia care is cognitive reframing, which may also be indicated for carers of patients with FXTAS dementia. A cognitive-behavioral therapy component, cognitive reframing focuses on the caregivers' maladaptive, self-defeating or distressing cognitions about their relative's behavior and their own performance in the caring role [73]. A recent systematic review found beneficial effects of cognitive reframing over usual care with regard to caregiver stress, anxiety, and depression, but no effects on burden, coping styles, self-efficacy, reaction to the care recipient's behavior, or institutionalization [73].

Multidimensional interventions consist of a combination of psychoeducation, behavioral problem-solving approaches based on the ABC model, and family meetings. In a study by Zarit et al., caregivers who received the multidimensional intervention had the best outcomes in terms of subjective burden and emotional distress [74]. Caregiver support groups are also popular. A multimodal intervention for patients with dementia, consisting of exercise and support groups, also benefited caregivers who chose to participate. The caregivers who received the intervention had less negative feelings toward their care recipients, compared to the control group [75]. A combination of individual and group therapy, support groups, and ad-hoc telephone counseling also yielded significant positive effects on caregivers' physical health, benefit which was maintained for two years [76]. In addition to these strategies that may be applicable to fragile X families, online support is available through the National Fragile X Foundation (www.nfxf.org). Table 1 summarizes interventions which may help diminish the caregiver burden in family members of individuals with FXS and FXTAS, based on available evidence to date [40-44, 62-65, 70, 73-76].

Conclusion

Many family members provide informal caregiving for individuals with FXS or FXTAS, thus it is important to assess and address their needs. Providers should be aware of caregiver needs and offer appropriate resources. Multidisciplinary interventions are optimal, given the challenges of caring for children with complex disabilities or elderly with movement disorders and associated dementias. Little is known about the trajectory of caregiver burden over time, especially with regard to FXTAS, which was only discovered a decade ago. Longitudinal studies would allow researchers to characterize the progression of caregiver experiences over time, as well as to examine the impact of selected interventions on caregiver mental health. Further research is much needed to explore the caregiver burden in multigenerational fragile X families and to develop and evaluate therapeutic interventions aimed at reducing this burden.

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Table 1

Suggested interventions for family caregivers of patients with FXS and FXTAS.

Caregivers of individuals with FXS	Caregivers of individuals with FXTAS
Psychoeducation	Psychoeducation
Supportive therapy (individual, groups)	Supportive therapy (individual, groups)
Cognitive-behavioral group therapy	Problem-solving therapy
Behavioral therapy (ABC model) ^a	Behavioral therapy (ABC model) ^a
Social skills training ^a	Cognitive reframing
Couples/family therapy	Couples/family therapy
Multidisciplinary team management	Multidimensional interventions
Parent-led support groups	Family support groups

^aThese interventions target the patient and may indirectly reduce caregiver burden ABC = antecedent-behavior-consequence.