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The psychosocial well-being of children with Fragile X Syndrome: Psychopathology, autism spectrum disorder comorbidity and the role of caregivers' perceived social support

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Abstract

Aim: Fragile X syndrome (FXS) is a rare genetic disease that can have several intellectual and developmental disabilities. Here, we aim to examine psychopathology in children with FXS and investigate the relationship between children's psychosocial well-being and socio-demographic factors, autism spectrum disorder (ASD) comorbidity, and the type and level of caregivers' perceived social support.

Materials and Methods: Twenty-six children aged 5-18 years with FXS and 26 age- and sex-matched healthy controls (HC) were included. DSM-5-based clinical interviews were conducted with all participants. We also collected parent ratings of health-related quality of life indexes and perceived social support levels and types.

Results: The mean age of children with FXS was 10.9 ± 3.5 years, and the mean age of healthy comparisons (HC, n= 26) was 11.8 ± 2.6 years. In the FXS group, 84.6% had comorbid psychiatric disorders, and 65.3% had intellectual disability. FXS group displayed lower psychosocial and total quality of life scores than the HC group. Also, there was significant positive correlations between children's' psychosocial well-being and "significant others" ($r_p = 0.502$, $p = 0.009$) and total perceived support scores ($r_p = 0.448$, $p = 0.022$). The most influential factor related to the psychosocial well-being in children with FXS was ASD comorbidity ($F= 30.6$, R^2, 0.543, $p<0.001$).

Conclusion: Providing support to mothers of children with FXS may positively affect the children's health outcomes, especially psychosocial well-being.

Introduction

Fragile X Syndrome (FXS), the most prevalent cause of inherited intellectual disability, is caused by increased CGG repeats of the FMR1 [1]. FXS is also one of the most common monogenic causes associated with autism spectrum disorder [2]. The prevalence of FXS is estimated to be one in 5,000 in men and between one in 4, 000 to one in 8,000 in women [3]. Autism spectrum disorder (ASD) co-occurrence is a common condition in FXS, with a prevalence of approximately 50% [4].

Over the lifespan, FXS presents many features of the behavioral and psychiatric phenotype and creates a spectrum of disorders, ranging from neurodevelopmental problems in infancy to neurodegenerative conditions in aging [5]. The most prevalent problems include intellectual disability, autism spectrum disorder, attention-deficit/ hyperactivity disorder (ADHD), anxiety disorders, affective disorders, sleep disturbances, chronic pain and autoimmune problems [5]. Recently, the name Fragile X-Associated Neuropsychiatric Disorders (FXAND) has been proposed to promote the recognition and investigation of these disorders [5]. Recognizing FXAND is essential because it will also be helpful to goal treatments that will be beneficial for such a group of neuropsychiatric disorders.

Health-related quality of life (HRQoL) is a subjective, multidimensional, and multifaceted term that examines psychological and physiological well-being in individuals with intellectual disabilities [6]. Studies showed that individuals with FXS have lower HRQoL scores [7].

Social support helps people manage stress in daily life and express their feelings. Also, perceiving adequate and appropriate support is a protective factor for mental disorders [8]. Having a child with a developmental delay is a challenging condition for parents that causes emotional

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stress and social difficulties [9]. A study revealed that about a third of caregivers of children with FXC received treatment for anxiety, stress, or depression [10]. Moreover, their mothers who perceive inadequate social support may have difficulty meeting the needs of the child, which may affect the child's well-being and social functionality. The perceived social support of mothers of children with FXS is also a growing concern for clinicians.

Thus, we hypothesized that (1) children with FXS will have lower HRQoL and MSPSS scores and higher psychiatric comorbidities than the healthy comparison group; (2) there will be a strong relationship between children's psychosocial well-being and mothers' perceived social support.

Materials and Methods

This study was carried out at Ataturk University, located in the Eastern Anatolia Region of the Republic of Turkey. Totally, 26 children with FXS and their biological mothers and 26 healthy children and their biological mothers were included using convenience non-probable sampling. The sample size of at least 26 in each group was calculated by using the G-Power 3.1 with an effect size of 0.8, power of 0.8, and significant level of α=0.05.

The families were recruited through two clinicians. The children with FXS included in this study were collected from the archive records of the Department of Genetics, between November 2020 and May 2021. Children with a previous diagnosis of FXS and their families were invited for a structured interview. Genetic analysis of these cases was conducted at the Department of Medical Genetics. DNA isolation was carried out with the EZ1 DNA blood 200 µL kit (QIAGEN). DNA quality was standardized by NanoDrop (ND-1000, Thermo Fisher Scientific, Wilmington, DE, USA). Per the manufacturer's instructions, PCR amplification was conducted through AmplideX FMR1 PCR/CE reagents (RUO; Asuragen, Austin, TX). CGG repeat analyses were performed with GeneMapper 4.0. CGG repeats of the patients were evaluated as follows; normal <44, intermediate 45-54, premutation 55-200, and full mutation >200 (according to the American College of Medical Genetics Guidelines).

A total of 26 children with FXS mutation (FXS) and their caregiving mothers were included in the study. Inclusion criteria for the Fragile X group were: (a) prior diagnosed FXS (b) age <18 years (c) being in care of the biologic mother. Twenty-six children of similar age (aged 6–18) without a previously known documented illness constituted the healthy comparison (HC) group. For the HC group the inclusion criteria were (a) absence of a psychiatric diagnosis and (b) being in care of the biologic mother. Informed consent was obtained from parents.

The primary endpoint of the study was the description of clinician-assessed psychopathology via "Schedule for Affective Disorders and Schizophrenia for School-age Children-present and Lifetime version (K-SADS-PL)" across the FXS group. A number of secondary endpoints have been chosen to investigate the relationship between the children's psychosocial well-being in different domains and the level of caregivers' perceived social support. The semi-structured psychiatric interviews; K-SADS-PL were conducted to examine children's sociodemographic characteristics and psychopathology by a trained clinician. Also, mothers were requested to complete the Pediatric Quality of Life Inventory (PedsQL) and the Multidimensional Perceived Social Support Scale (MSPSS). Local ethics committee clearance was obtained (Atatürk University Faculty of Medicine Clinical Research Ethics Committee, 01.10.2020/451).

Instruments

1. The Schedule for Affective Disorders and Schizophrenia for School-age Children-present and Lifetime version (K-SADS-PL): It is a clinical interview to define psychiatric problems in children and adolescents.
2. The Multidimensional Perceived Social Support Scale (MSPSS): It is a 12-item Likert-type tool examining the perceived efficacy of social support received from three groups: family members (3, 4, 8, and 11), friends (6, 7, 9, and 12), and significant others (1, 2, 5, and 10). Scores vary from strongly disagree to strongly disagree for each item (1 to 7, respectively).
3. The Pediatric Quality of Life Inventory (PedsQL): It is a 23-item brief scale assessing the HRQoL of children and adolescents. It has five domains that assess well-being on physical, emotional, psychosocial, social, and school functioning indexes.

Statistical analysis

Statistical analyses were conducted using SPPS (Statistical Package for Social Sciences) for Windows 23.0. Descriptive statistics were reported for basic sociodemographic variables. Categorical data were compared with chi-square test and presented as frequencies and percentages. Quantitative data were presented as mean and standard deviation. Shapiro–Wilk test was preferred to determine normality. Depending on the test assumptions, we used both parametric statistical tests to test the hypothesis including the independent t-test for comparing across condition and Pearson's rank correlation coefficient to assess the relationship between variables. A stepwise multiple regression analysis was then conducted to investigate independent factors affecting PRPsHS of children. Statistical significance was defined as $p < 0.05$, two-tailed.

Results

A total of 52 children and adolescents (20 females and 32 males) were recruited for our analysis. The mean age of children with FXS (n = 26) was 10.9 ± 3.5 years, and the mean age of healthy comparisons (HC, n= 26) was 11.8 ± 2.6 years. The groups did not differ significantly in age, sex, average income, and residency. Table 1 presents the sociodemographic features and the comparison of children with FXS group and controls.

In FXS group, the average age at diagnosis was 6.6 ± 3.7. The reason for the genetic examination of children was as follows: six (23.1%) patients were examined by the medical genetics department because of the carrier known history in their family; 12 (46.2%) patients applied to child psychiatry with various complaints and were referred to the medical genetics department by a child psychiatrist

Table 1. Demographic characteristics.

	FX group n=26	Control group n=26	p
Age, year, Mean ± SD	10.9 ± 3.5	11.8 ± 2.6	0.315
Sex, n (%)			
Male	19 (73.1)	13 (50)	0.087
Female	7 (26.9)	13 (50)	
Residence, n (%)			
Rural	15 (57.7)	10 (38.5)	0.165
Urban	11 (42.3)	16 (61.5)	
Economic status, n (%)			
Below minimum wage	11 (42.3)	7 (26.9)	0.244
Above minimum wage	15 (57.7)	19 (73.1)	
Current Education status, n (%)			
Primary school	14 (53.8)	11 (42.3)	
Secondary school	7 (26.9)	12 (46.2)	
High school	1 (3.8)	3 (11.5)	
Dropped out of school	4 (15.4)	0	
Maternal age, Mean ± SD	40.5 (5.7)	40.1 (5.8)	0.831
Paternal age, Mean ± SD	42.5 (5.5)	44.4 (6.7)	0.278
Number of siblings, n (%)	3.2 (1.2)	1.4 (0.8)	<0.001
MSPSS scale scores, Mean ± SD			
Significant others	16.3 ± 5.6	14.5 ± 4.8	0.214
Friends	4.8 ± 1.9	14.0 ± 3.3	<0.001
Family	13.9 ± 4.5	13.5 ± 4.6	0.741
Total	35 ± 9.3	41 ± 8.2	0.009
Pediatric quality-of-life inventory scores, Mean ± SD			
1.Physical health score	709.6 ± 69.6	700 ± 69.5	0.617
2.Psychosocial health score	814.4 ± 302.1	1167.1 ± 116.4	<0.001
Emotional functioning	263.4 ± 103.7	351.7 ± 79	0.001
Social functioning	215.3 ± 137.8	380.7 ± 74.2	<0.001
School functioning	335.5 ± 117	434.6 ± 41.8	<0.001
3.Total score	1523 ± 320.1	1867.1 ± 132.2	<0.001

FX: Fragile X group, MSPSS: Multidimensional scale of perceived social support scale.

because of physical findings; and 8 (30.8%) patients were referred to the medical genetics department due to their application to different departments due to the suspected complaints.

Seventeen of the patients (65.4%) were in the rehabilitation center, and nine (34.6%) were in regular school. While 13 children (50%) of the FXS group had ASD, 13 (50%) children had no ASD. All children with ASD were male, p = 0.003. The sex distribution of those without ASD was as follows: six (53.8%) males and seven (46.2%) females.

In children with FXS, 84.6% (n = 22) of children had a comorbid psychiatric disorder; 17 (65.3%) cases had an intellectual disability; thirteen (50%) cases had ASD; eight (30.7%) cases had sleep disorders; three (7.8%) cases had an anxiety disorder and attention-deficit/hyperactivity disorder (ADHD), and two (7.6%) cases had learning difficulties and anxiety disorders. Children with ASD also had intellectual disability (ID) coexistence. four of the children had three psychopathology coexistences: sleep disorder, ASD, and ID.

The MSPSS comparisons are presented in Table 1. The scores of the "friends" and "total" subscales were significantly higher in HC than in children with FXS (4.8 ± 1.9 vs. 14 ± 3.3, p < 0.001; 35 ± 9.3 vs. 41 ± 8.2, p = 0.009). Children with FXS are also divided into two groups in terms of those with and without ASD. The MSPSS and the psychosocial HRQoL (except physical functioning) scores were significantly lower in children with FXS-with ASD (Table 2).

Functioning in the psychosocial (814.4 ± 302.1, 1167.1 ± 116.4; p <0.001) and total (1523 ± 320.1, 1867 ± 132.2; p<0.001) HRQoL scores was significantly lower in children with FXS compared to HC (Table 1). Also, a significant positive correlation was found between PRPsHS (psychosocial) and "significant others" score (rp = 0.502, p = 0.009); and PRPsHS score and "total MSPSS" score (rp = 0.448, p = 0.022). Also, there was a positive correlation between total HRQoL score and total perceived social support score subscales (rp = 0.441, p = 0.024) in the FXS group. Bivariate correlation analyses between perceived social support subscales and HRQoL indexes are presented in Table 3.

Then, a stepwise multiple regression analysis was performed to identify independent variables (ASD comorbidity and MSPSS subgroup scores included) associated with PRPsHS (dependent variable) in children with FXS. The most influential factor related to PHRQoL of children with FXS was ASD comorbidity (ANOVA: F= 30.6; p<0.001; Adjusted R-square: 0.543).

Discussion

To the best of our knowledge, this is the first study that specifically examined the effect of caregivers' perceived social support and ASD comorbidity on HRQoL in children with FXS. Considering that individuals with FXS have a complex phenotype, they may present to the clinic with complaints such as intellectual disability, ASD, hyperactivity, social and communication difficulties, anxiety, aggression, and sleep problems [11]. In our study, we examined mental problems of children with FXS and found the rate of having any psychiatric disorder in the FXS group as 84.6% (n = 22). The psychopathologies observed in the order of frequency were as follows: ID, ASD, sleep disorder, anxiety disorder, ADHD, and learning disability. FMR1 full mutation is associated with a high rate of ID comorbidity [12]. In our sample, ID was observed at a rate of 65.3% in the FXS group. In addition, double or even triple coexistence of psychiatric diseases was observed in the FXS group. We compared the groups in terms of PedsQL scores and found that PRPsHS and total health scores were significantly lower in children with FXS than in the control group. Also, we examined the relationship between the level of social support provided to caregivers by different groups (family, friends, and significant others) and the child's psychosocial well-being. We found positive associations between children's psychosocial well-being and MSPS (significant others score and total score) scores. Further,

Table 2. Comparison of scores with and without ASD in the FX group.

		With ASD (n=13)	Without ASD (n=13)	
		Mean ± SD	Mean ± SD	p
MSPSS Scores	Significant others	12.9±4.8	19.7±4.2	0.001
	Friends	3.7±1	5.9±2	0.002
	Family	12.1±2.5	15.6±5.3	0.043
	Total	28.6±6.1	41.3±7.6	<0.001
PedsQL Scores	1. Physical health score	713.4±76.1	705.7±65.4	0.785
	2. Psychosocial health score	592.3±197.2	1036.5±211.5	<0.001
	Emotional functioning	217.3±97	309.6±91.5	0.02
	Social functioning	107.6±35.9	323±114.7	<0.001
	School functioning	267.3±129.2	403.8±40.6	0.001
	3. Total score	1303.8±237.3	1742.3±230.3	<0.001

ASD: Autism spectrum disorder, FX: Fragile X group, MSPSS: Multidimensional scale of perceived social support scale, PedsQL: Pediatric Quality of Life Inventory.

Table 3. Bivariate correlation analysis between PedsQL and MSPSS.

			PRTS	PRPhHS	PRPsHS	PRPef	PRPsf	PRPscf
Multidimensional scale of perceived social support	Significant others	F	0.494*	0.085	0.502**	0.437*	0.588*	0.217
		C	0.367*	0.326	0.247	0.343	-0.143	0.197
	Friends	F	0.388*	0.162	0.372	0.031	0.559**	0.276
		C	-0.024	0.236	-0.167	-0.095	-0.065	-0.114
	Family	F	0.137	0.006	0.146	-0.006	0.153	0.202
		C	0.242	-0.048	0.317	0.266	0.176	0.045
	Total	F	0.441*	0.079	0.448*	0.256	0.550**	0.283
		C	0.313	0.218	0.246	0.311*	-0.041	0.114

F: Fragile X group, C: Control group, MSPSS: Multidimensional scale of perceived social support scale, PedsQL: Pediatric Quality of Life Inventory, PRTS: Parent-proxy report total score, PRPhHS: Parent-proxy report physical health score, PRPsHS: Parent-proxy report psychosocial health score, PRPef: Emotional functioning, PRPsf: Social functioning, PRPscf: School functioning. All values represent Pearson correlation coefficient. *Correlation is significant at the 0.05 level. **Correlation is significant at the 0.01 level.

stepwise regression analyses revealed that the most critical variable of a child's psychosocial well-being was ASD comorbidity in children with FXS.

ASD-related symptoms are more common in FXS [4]. FXS cases with ASD comorbidity have a lower cognitive ability (e.g., IQ) compared to those without ASD, and this ability persists throughout life [13]. Further, some comorbid problems such as anxiety, hyperactivity, and social interaction difficulties are more common in individuals with ASD comorbidity. Behavioral characteristics and accompanying psychiatric problems have negative impacts on health and well-being in children with ASD [13]. Autism spectrum disorder comorbidity can significantly affect the overall well-being of the affected child and parents [14]. In our study, when the FXS group was examined in terms of ASD comorbidity, caregivers' perceived social support levels decreased significantly in each index (Table 2). This highlights the importance of behavioral problems that increase the need for social support. It is known that pediatric psychopathology affects child-raising styles and parents' coping skills. Also, many negative effects on children's psychosocial well-being are known [15]. Our study found that the well-being of pediatric FXS with ASD comorbidity also decreased in all health indexes except physical index. FXS-ASD comorbidity not only impairs the child's psychosocial and total quality of life but also increases the social support needs of caregivers. Also, our findings revealed that the most critical factor predicting better psychosocial well-being in children with FXS was ASD comorbidity.

The need for social support is a complicated term that can vary according to the expectations, challenges, personality features, and culture [16]. Children with FXS constitute an especially high burden for caregivers [17]. A meta-analysis examined the relationship between caregivers' perceived and received social support and subjective burden, and found that perceived social support was an important determinant of subjective burden. The accompanying clinical, emotional, and behavioral problems in children with FXS may increase the need for social support among caregivers. We found a significant difference in "friends" and "total" score indexes. Mothers of children with FXS reported receiving less social support from their friends. This result may be related to less social interaction with their friends. Caregivers with better social connections with their environment report fewer symptoms when caring for a child with special needs [18]. This communication is likely to provide some relief to caregivers in daily

life's strengths and difficulties [19]. There is ample evidence showing the benefits of social connections for caregivers of children with special needs. This study presents findings on relationships between caregivers' perceived social support types and levels and the child's psychosocial well-being. Therefore, the child's psychosocial well-being may be an essential outcome measure for caregivers' perceived social support. Since having a child with special needs is challenging for parents in many areas, more social support may be needed. In this respect, the caregiver's social support can contribute to the awareness of the child's shortcomings and disabilities.

Maternal maladaptation predictors for caregivers with children with FXS often include child behavior problems and inadequate social support systems [20]. It is known from previous studies that mothers caring for children with FXS are at high psychosocial risk. The deficiency of social support perceived by caregivers also has a negative impact on children [21]. This study found significant correlations between caregivers' perceived social support and children's psychosocial well-being. We thought that the perceived social support levels of mothers of children with FXS might be lower than those of mothers of HC due to the difficulties they experienced. Considering these findings, we suggest that caregivers of children with FXS need a higher level of social support than their perceived or received social support. The stress experienced by caregivers can also notably affect the child's well-being and management. In this sense, it is believed that the social support perceived by the caregiver is an essential psychosocial factor and will directly benefit the caregiver and indirectly the child. It is possible that the inadequacy of social support perceived by the caregiver negatively affects the child's well-being on several indexes.

Considering the complex and unpredictable nature of the symptoms associated with FXS, caregivers' perceived level of social support can make it easier for the person to cope with strain, increase adaptation skills, and indirectly improve the child's psychosocial well-being. Therefore, perceived social support may positively affect the child's well-being, especially on the psychosocial indexes. Individuals suffering from FXS tend to have low psychosocial well-being due to various factors such as clinical symptoms, level of social communication, and emotional and behavioral problems. It is known that having a child with emotional and behavioral problems also has some difficulties for caregivers, such as family conflict, economic hardship, loss of liberty, and negative psychiatric or health effects [22]. Perceived social support of caregivers by significant others positively correlated with the child's psychosocial quality of life. Therefore, we strongly suggest that the social support provided by fathers to mothers is critical regarding the children's psychosocial well-being in children with special needs.

This study includes some limitations. The mental disorders of caregivers were not examined. Caregivers' psychopathology may have an impact on perceived social support. Further, our sample size was small due to the rare nature of FXS. Thus, it has to be noted, that this cohort seems not to be representative of the general FXS population, as the number of cases with FXS was relatively limited. In the future, it is recommended to address this relationship with multicenter studies.

Conclusion

Despite the low incidence of FXS, it appears to have important implications for patients and caregivers. In this study, we investigated the perceived social support in mothers of children diagnosed with FXS and children's psychosocial well-being. We observed a positive relationship between mothers' perceived social support and children's psychosocial well-being. Organizing community-based professionals to assist caregivers' needs and strengthen their social support will aid the psychosocial well-being of pediatric FXS. Our results suggest that in addition to the accompanying psychopathologies, the caregivers perceived social support should also be questioned to evaluate the child's psychosocial well-being in clinical practice.

Ethics approval

This study was approved by Atatürk University Faculty of Medicine Clinical Research Ethics Committee (01.10.2020/451). All procedures in this study were performed in accordance with the ethical standards or comparable ethical standards specified in the 1964 Declaration of Helsinki.

Patients' consent

Participants were informed fully of study procedures and provided signed consent.

Competing interest

The authors declared no competing interest. Authors' Contributions: HD: Wrote the paper, data acquisition and analysis, interpretation, critical revision, drafting, and final approval. CYK: Conception and design, data acquisition and analysis, interpretation, literature search, critical revision, and final approval.

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