



Research

Psychiatric Disorders in Fabry Disease: Investigating the Relationship Between Psychiatric Symptoms, Target Organ Involvement, and Lyso-Gb3 Levels

Fabry Hastalığında Psikiyatrik Bozukluklar: Psikiyatrik Semptomlar, Hedef Organ Tutulumu ve Lyso-Gb3 Düzeyleri Arasındaki İlişkinin Belirlenmesi

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ABSTRACT

Objective: This study aims to evaluate the psychological issues experienced by individuals diagnosed with Fabry disease (FD) and examine whether these issues are associated with serum globotriaosylsphingosine (Lyso-Gb3) levels and target organ involvement.

Methods: This study included 51 individuals: 22 FD patients (FD group) and 29 healthy controls (control group). The FD group comprised 18 adults and four pediatric patients, and both groups were matched for age and gender. The Symptom Checklist-90 (SCL-90) was administered to participants aged 15 years and older, while the Conners' Parent Rating Scale-Revised Long Form (CPRS-R/L) was used for pediatric patients. The FD group was also assessed for organ involvement and plasma Lyso-Gb3 levels.

Results: Somatization was the most prevalent psychiatric symptom among adult FD patients (32%). Compared with the healthy control group, adult FD patients exhibited higher scores across multiple SCL-90 subscales, including somatization, depression, anxiety, interpersonal sensitivity, and anger-hostility. However, a statistically significant difference was only observed in the somatization subscale ($p=0.042$). All SCL-90 subscale scores were significantly correlated with involvement of the central nervous system (CNS) and the cardiovascular system (CVS). No significant correlation was found between SCL-90 subscale scores and Lyso-Gb3 levels ($p>0.05$). Among pediatric patients, CPRS-R/L scores were higher in the FD group than in controls, with a significant difference observed only in the oppositional subscale ($p=0.04$).

Conclusion: Patients with FD exhibit a higher prevalence of psychiatric disorders than age- and sex-matched healthy controls. CNS and CVS involvement appears to be a significant risk factor for psychiatric comorbidities. No significant association was identified between serum Lyso-Gb3 concentrations and the presence of psychiatric disorders.

Keywords: Fabry disease, psychiatric disorders, enzyme replacement therapy, Lyso-Gb3

ÖZ

Amaç: Bu çalışmanın amacı, Fabry hastalığı (FH) tanısı almış bireylerde görülen psikolojik sorunları değerlendirmek ve bu sorunların serum globotriaosylsphingosin (Lyso-Gb3) düzeyleri ile hedef organ tutulumu arasındaki olası ilişkisini incelemektir.

Gereç ve Yöntem: Çalışmaya toplam 51 birey dahil edilmiştir: 22 FH (FH grubu) ve 29 sağlıklı kontrol (kontrol grubu). FH grubunda 18 erişkin ve 4 pediatrik hasta yer almış olup her iki grup yaş ve cinsiyet açısından eşleştirilmiştir. On beş yaş ve üzerindeki katılımcılara Belirti Tarama Listesi-90 (SCL-90) uygulanmış, pediatrik hastalarda ise Conners Ebeveyn Derecelendirme Ölçeği-Gözden Geçirilmiş Uzun Form (CPRS-R/L) kullanılmıştır. FH grubunda ayrıca organ tutulumu ve plazma Lyso-Gb3 düzeyleri değerlendirilmiştir.

Bulgular: Erişkin FH hastalarında en yaygın psikiyatrik belirti somatizasyon olup olguların %32'sinde saptanmıştır. Sağlıklı kontrol grubuna kıyasla erişkin FH hastalarında somatizasyon, depresyon, anksiyete, kişilerarası duyarlılık ve öfke-düşmanlık alt ölçeklerinde daha yüksek skorlar gözlenmiştir. Bununla birlikte istatistiksel olarak anlamlı fark yalnızca somatizasyon alt ölçeğinde saptanmıştır ($p=0.042$). Tüm SCL-90 alt ölçek

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ÖZ

skorları, merkezi sinir sistemi (MSS) ve kardiyovasküler sistem (KVS) tutulumları ile anlamlı düzeyde ilişkili bulunmuştur. Buna karşın, SCL-90 alt ölçek skorları ile Lyso-Gb3 düzeyleri arasında anlamlı bir korelasyon gözlenmemiştir ($p>0,05$). Pediatrik hastalarda ise CPRS-R/L skorları FH grubunda kontrol grubuna göre daha yüksek olmakla birlikte, istatistiksel olarak anlamlı fark yalnızca karşı gelme alt ölçeğinde saptanmıştır ($p=0,04$).

Sonuç: Fabry hastalığı olan bireylerde, yaş ve cinsiyet açısından eşleştirilmiş sağlıklı kontrollere kıyasla psikiyatrik bozuklukların görülme sıklığı daha yüksektir. MSS ve KVS tutulumu, psikiyatrik komorbiditeler açısından önemli risk faktörleri olarak görünmektedir. Lyso-Gb3 düzeyi ile psikiyatrik bozukluklar arasında bir korelasyon saptanmamıştır.

Anahtar Kelimeler: Fabry hastalığı, psikiyatrik bozukluklar, enzim replasman tedavisi, Lyso-Gb3

INTRODUCTION

Fabry disease (FD, OMIM#301500) is an X-linked glycosphingolipidosis caused by a deficiency of the lysosomal alpha-galactosidase A, leading to systemic accumulation of globotriaosylceramide (Gb3) and its derivatives (1). The progressive buildup of these substances in the parenchyma and endothelium triggers inflammatory processes, oxidative stress, and microvascular stenosis, ultimately causing target organ damage (2). FD manifests across a broad spectrum of clinical phenotypes, affecting the skin, eyes, gastrointestinal tract, heart, kidneys, the central nervous system (CNS), and the peripheral nervous system (PNS) (3). While accumulation begins early in life, clinical symptoms of organ involvement typically become apparent within the first decade. Consequently, FD patients span a wide age range, encompassing both pediatric and adult populations.

Previous studies suggest that individuals with FD exhibit a higher prevalence of psychiatric disorders, such as depression and anxiety, compared to the general population (4,5). Regular psychological assessments are crucial for early detection and intervention, which can significantly improve quality of life. However, the underlying causes of these psychiatric symptoms remain unclear. It is uncertain whether they stem solely from the stress of a chronic illness or from a complex interplay of factors (6). The scarcity of empirical research complicates efforts to elucidate the relationship between FD and psychiatric symptoms, thereby hindering the development of targeted interventions.

Globotriaosylsphingosine (Lyso-Gb3), a key biomarker for FD diagnosis and monitoring, has been linked to high-risk complications (7,8). However, no studies have explored the association between neuropsychiatric symptoms and Lyso-Gb3 levels. One major challenge in obtaining conclusive evidence is the difficulty of measuring Lyso-Gb3 in brain tissue. Additionally, while enzyme replacement therapy (ERT) has demonstrated positive effects on various organ systems, its impact on mental health remains inconclusive.

This study aims to assess the psychological well-being of FD patients, investigate the prevalence of psychiatric disorders in those undergoing ERT, and examine potential associations between these disorders, blood Lyso-Gb3 levels, and organ involvement.

METHODS

This cross-sectional descriptive study was conducted between April and June 2024 at the Pediatric Metabolism Outpatient Clinic of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital. The control group comprised individuals without chronic illnesses who sought medical care in general internal medicine and pediatric clinics. Informed consent was obtained from all participants prior to enrollment.

Participants

The study included 22 patients with FB diagnosed using enzymatic and genetic criteria; all were under regular clinical follow-up and were receiving ERT. Patients not meeting these criteria were excluded. The control group consisted of age- and gender-matched individuals with no history of chronic physical or severe psychiatric disorders, including schizophrenia, intellectual disability, autism spectrum disorder, or bipolar affective disorder. Involvement of the CNS and CVS was evaluated by brain MRI and echocardiography, respectively.

Assessment Tools**1. Lyso-Gb3 Measurement**

Plasma Lyso-Gb3 levels were quantified from dried blood samples using liquid chromatography-mass spectrometry, with lyso-ceramide trihexoside (Matreya, Catalog No. 1520) as the reference standard. Organ involvement was recorded without specifying severity. Plasma Lyso-Gb3 levels were measured for each patient at six-month intervals.

2. Sociodemographic and Clinical Data

A structured data collection form was used to obtain demographic information (age, gender) and clinical parameters, including Lyso-Gb3 levels, duration of ERT, and organ involvement.

3. Psychiatric Assessment Tools

- **Symptom Checklist-90-R (SCL-90-R):** A validated self-report questionnaire measuring psychological distress across ten subscales (9). The Turkish adaptation was conducted by Dağ (10). Scores range from 0 to 4, with higher scores indicating greater psychological distress. Scores above 1 suggest clinically significant symptoms.

- **Conners' Parent Rating Scale-Revised Long Form (CPRS-R/L):** A parent-reported measure of children's psychological symptoms, including defiance, inattention, hyperactivity, anxiety, and social difficulties. The Turkish adaptation was validated by Kaner et al. (11). Higher scores indicate greater symptom severity.

Statistical Analysis

Statistical analyses were performed using the SPSS, version 22.0 (IBM Inc., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages, while numerical variables were presented as means and standard deviation. The normality of the distribution of quantitative variables was assessed using the Kolmogorov-Smirnov test. For comparisons between two independent groups, the Student's t-test was applied to normally distributed numerical variables, whereas the Mann-Whitney U test was used for non-normally distributed data. The chi-square test was used to compare categorical data. The Spearman's correlation analysis was conducted to evaluate the relationships between variables. Statistical significance was defined as a p-value of less than 0.05.

Ethical Considerations

This study was conducted in accordance with the ethical guidelines outlined in the World Medical Association's Declaration of Helsinki (2000). Ethical approval was obtained from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no: 2022.07.05, date: 04.04.2022).

RESULTS

Adult Population

The median age of adult patients (n=18) included in the study was 44.5 years (range: 20-65 years). Of the total sample, nine individuals (50%) were female. Eight participants (44.4%) were diagnosed with symptomatic organ involvement, while the remaining participants were identified through family screening. Notably, all patients diagnosed through screening exhibited involvement of at least one organ. The mean duration of ERT was 5.8 years (range: 0.6-12 years). Among the 18 adult patients, the most commonly affected organ was the eye (n=15), followed by the kidney (n=14), the skin (n=13), the heart (n=9), the PNS (n=9), and the CNS (n=4) (Figure 1).

The most prevalent psychiatric condition among adult Fabry patients was somatization (32%), followed by depression (27.8%). Anxiety, interpersonal sensitivity, hostility, and other psychiatric symptoms each had a prevalence of 22.2%. The prevalence of obsessive-compulsive symptoms and

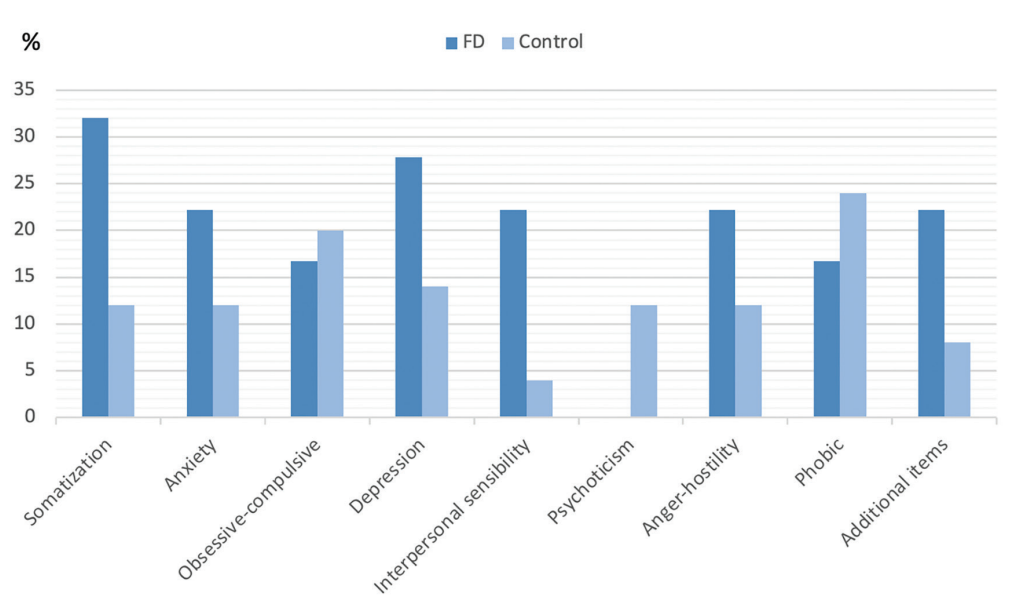


Figure 1. Comparison of the distribution of the SCL-90 subscale scores of FD patients and control group
SCL-90: Symptom Checklist-90, FD: Fabry disease

phobic symptoms was identical, with 16.7% of patients exhibiting both symptoms (Figure 2). Compared with the control group, a statistically significant difference was observed only on the somatization subscale ($p < 0.05$); no significant differences were detected on the remaining subscales (Table 1). Although the differences did not reach statistical significance, the experimental group exhibited higher incidences of depression, anxiety, interpersonal sensitivity, and hostility than the control group (Figure 2). No statistically significant gender differences were observed across psychiatric subscales or overall symptoms.

No significant correlations were identified between Lyso-Gb3 levels and SCL-90 subscales (Table 2). However, CNS involvement demonstrated a significant association with all subscales except paranoia (Table 3). Additionally, cardiovascular system (CVS) involvement was significantly associated with all subscales except obsessive-compulsive symptoms, paranoia, and additional psychiatric symptoms (Table 3). A moderate correlation was observed between PNS involvement and the psychoticism and hostility subscales (Table 3).

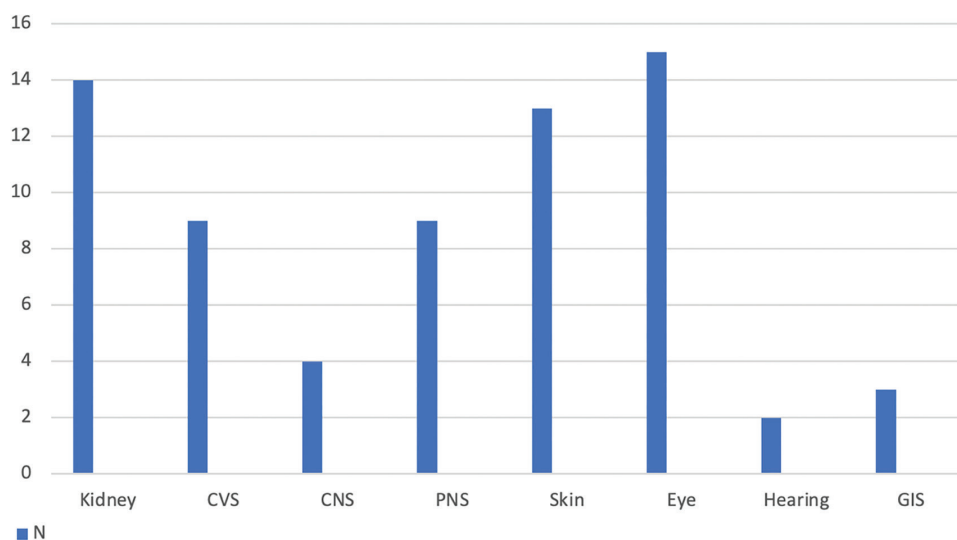


Figure 2. Target organ involvements of Fabry patients
 CSN: Central nervous system, CVS: Cardiovascular system, GIS: Gastrointestinal system, PNS: Periferic nervous system

Table 1. Comparison of SCL-90 and Conners' subscales of Fabry patients and control group

Adults	Fabry patients, n=18	Control group, n=25	p
Somatization	0.88±0.76	0.71±0.59	0.042
Anxiety	0.50±0.40	0.68±0.53	0.366
Obsessive-compulsive disorder	0.80±0.60	0.81±0.59	0.834
Depression	0.72±0.62	0.84±0.67	0.529
Interpersonal sensibility	0.53±0.51	0.45±0.48	0.527
Psychoticism	0.21±0.28	0.48±0.57	0.300
Paranoid	0.42±0.43	0.44±0.48	0.940
Anger-hostility	0.59±0.80	0.69±0.63	0.274
Phobic	0.35±0.40	0.34±0.41	1.000
Additional items	0.74±0.51	0.64±0.52	
Pediatric	Fabry patients, n=4	Control group, n=4	
Oppositional	2.5±1.29	0.8±0.57	0.04
Cognitive problem	3±2.16	2±1.89	0.30
Hyperactivity	1.5±1.29	1.6±1.41	0.55
Anxious-shy	3.5±3.41	2±1.25	0.31

Table 1. Continued

Pediatric	Fabry patients, n=4	Control group, n=4	p
Perfectionism	5.5±3.69	2.8±0.95	0.14
Social problem	1.25±1.89	0.8±0.57	0.75
Psychosomatic	1.5±1.73	0.8±1	0.28
ADH index	1.5±1.73	0.4±0.5	0.15
Global index-restlessness-impulsivity	1±1.41	0.8±1	0.51
Global index-emotional lability	0.75±0.95	0±0	0.13
Conners total	2.25±1.89	0.8±1	0.10
DSM-IV inattention	1.75±0.95	1.6±1.41	0.29
DSM-IV hyperactivity	1.5±0.57	1.2±0.95	0.22
DSM-IV total	3.75±0.95	3.6±2.21	0.30

p<0.05 statistically significant. Significant p-values are shown in bold

ADH: Attention deficit hyperactivity, DSM: Diagnostic and Statistical Manual of Mental Disorders, SCL-90: Symptom Checklist-90

Table 2. Correlation status between SCL-90 subscales and Lyso-Gb3 levels of Fabry patients

SCL-90	r	p
Somatization	-0.096	0.704
Anxiety	-0.137	0.589
Obsessive-compulsive disorder	-0.008	0.974
Depression	-0.158	0.530
Interpersonal sensibility	0.050	0.843
Psychoticism	-0.088	0.729
Paranoid	0.229	0.361
Anger-hostility	0.093	0.713
Phobic	0.149	0.555
Additional items	-0.122	0.630

p<0.05 statistically significant. Significant p-values are shown in bold
SCL-90: Symptom Checklist-90, Lyso-Gb3: Globotriaosylsphingosine

Pediatric Population

The study included four pediatric patients, one of whom was male. The median age was 9.5 years (range: 6-16 years). All pediatric patients were diagnosed through family screening. The mean scores on the Conners' subscale in the pediatric Fabry patient group were higher than those in the control group. However, a statistically significant difference was observed only on the oppositional subscale (p=0.04) (Table 1).

DISCUSSION

Due to the absence of routine psychiatric evaluations in outpatient clinics, individuals with FD often remain undiagnosed and untreated for mental health conditions. Although prior research has investigated psychiatric disorders in FD, most studies have focused on depression and anxiety (4,5). The present study aimed to examine a

broader spectrum of psychiatric disorders in Fabry patients, making it among the first to do so. Moreover, the study's findings on the correlation between psychiatric disorders and CNS and CVS involvement contribute valuable insights to the existing literature.

Although statistical significance was not reached for anxiety, depression, interpersonal sensitivity, and hostility, adult Fabry patients exhibit higher rates of these symptoms than the control group; a significant difference was observed only in the somatization subscale. Somatization is commonly associated with chronic physical illnesses and can serve as a manifestation of depression across different age groups (12). Patients experiencing cardiac discomfort or palpitations in the absence of underlying cardiac pathology may develop heightened anxiety due to the hereditary nature of FD and its potentially life-threatening implications.

Depression and anxiety are more prevalent among individuals with functional somatic symptoms than in the general population (13). If left untreated, depression can adversely affect both the prognosis of the somatic illness and the overall quality of life. The prevalence of depression in adult FD has been reported to range from 15% to 62%, whereas 10-25% of the general population experience at least one major depressive episode during their lifetime (14-17). The prevalence of depression in this study was 27.8%, slightly higher than general population norms, but lower than in previous studies of FD. Variability in findings across studies may be attributed to differences in assessment tools, the administration of ERT, and adherence to treatment (18,19). Given that patients in this study had undergone long-term ERT with high adherence, the observed lower prevalence aligns with findings suggesting that ERT may alleviate depressive symptoms, particularly in pediatric patients.

Table 3. Correlation between system involvements and SCL-90 subscales

	PNS		Eye		Skin	
	r	p	r	p	r	p
Somatization	0.383	0.116	0.368	0.133	0.393	0.107
Anxiety	0.316	0.202	0.308	0.214	0.256	0.305
Obsessive-compulsive disorder	0.287	0.248	0.026	0.919	0.171	0.497
Depression	0.187	0.458	0.345	0.160	0.217	0.387
Interpersonal sensibility	0.178	0.481	0.210	0.404	0.411	0.091
Psychoticism	0.530	0.024	0.237	0.344	0.389	0.110
Paranoid	-0.064	0.801	-0.027	0.914	0.276	0.267
Anger-hostility	0.544	0.020	0.211	0.400	0.364	0.138
Phobic	0.208	0.407	0.242	0.334	0.289	0.245
Additional items	-0.140	0.578	0.149	0.556	0.169	0.503

p<0.05 statistically significant. Significant p-values are shown in bold
 CSN: Central nervous system, CVS: Cardiovascular system, GIS: Gastrointestinal system, PNS: Periferic nervous system, SCL-90: Symptom Checklist-90

Table 3. Continued

	CNS		CVS		Kidney		GIS	
	r	p	r	p	r	p	r	p
Somatization	0.628	0.005	0.722	0.001	0.428	0.076	0.441	0.067
Anxiety	0.725	0.001	0.689	0.002	0.414	0.088	0.577	0.012
Obsessive-compulsive disorder	0.553	0.017	0.306	0.216	0.207	0.409	0.103	0.685
Depression	0.811	<0.001	0.568	0.014	0.380	0.120	0.539	0.021
Interpersonal sensibility	0.715	0.001	0.542	0.020	0.092	0.717	0.419	0.083
Psychoticism	0.713	0.001	0.571	0.013	0.365	0.137	0.419	0.083
Paranoid	0.214	0.393	0.024	0.925	0.480	0.044	0.149	0.556
Anger-hostility	0.592	0.010	0.615	0.007	0.320	0.196	0.454	0.058
Phobic	0.812	<0.001	0.625	0.006	0.287	0.249	0.596	0.009
Additional items	0.774	<0.001	0.267	0.283	0.027	0.914	0.575	0.013

p<0.05 statistically significant. Significant p-values are shown in bold
 CSN: Central nervous system, CVS: Cardiovascular system, GIS: Gastrointestinal system, PNS: Periferic nervous system, SCL-90: Symptom Checklist-90

The etiology of depression in FD remains debated. Some researchers propose that chronic pain, particularly acroparesthesia, plays a role, while others suggest that microvascular dysfunction affecting cerebral blood flow contributes to psychiatric symptoms (14,19-21). In the present study, a statistically significant correlation was found between depression and both CNS and CVS involvement. Fear of mortality associated with FD-related complications may further contribute to depressive symptoms, even among patients receiving ERT.

Previous research has demonstrated that FD frequently results in milder symptoms that manifest later in females. However, some studies suggest a higher prevalence of mental disorders, particularly depression, among female patients with FD (4,22). This phenomenon may be attributed to the generally higher prevalence of depression among females rather than to the disorder itself (23,24). Contrary

to the prevailing notion, recent findings indicate a higher prevalence of this phenomenon among males (25). In our study, we did not observe significant gender-related differences in psychiatric symptoms. As noted by Ali et al. (6) in a meta-analysis on this subject, establishing a definitive gender-related association appears challenging.

Anxiety is a frequently reported psychiatric symptom in FD, with prevalence rates ranging from 20% to 37% (17,25). In this study, the prevalence of anxiety was 22.2%, mirroring trends observed for depression. A significant association was found between anxiety symptoms and involvement of the CNS and CVS, similar to findings for depression.

Psychoticism has been reported in FD patients, albeit infrequently (26). The increasing number of case reports suggests a need for further large-scale studies to assess its true prevalence.

Chronic illnesses characterized by persistent pain and high morbidity and mortality risks may contribute to elevated interpersonal sensitivity and hostility scores. Despite the limited pediatric sample size, the study found a significantly higher prevalence of oppositional defiant disorder in pediatric patients than in controls.

Higher attention deficit hyperactivity (ADH) index scores were observed in pediatric FD patients. Given the well-documented interrelation between psychiatric disorders and ADH, ADH is also frequently associated with anxiety and depression (27). Future research should incorporate additional psychological assessments to investigate ADHD in pediatric patients with FD.

No correlation was found between Lyso-Gb3 levels and psychiatric symptoms, suggesting that psychiatric manifestations in FD may not be solely attributable to biological factors.

Study Limitations

This study has several limitations. The lack of pre-ERT assessments prevents baseline comparisons. Additionally, the rarity of FD limits the sample size, potentially affecting correlation analyses.

CONCLUSION

A strong correlation was observed between CNS involvement and various psychiatric disorders in adult FD patients. Additionally, the association between CVS involvement and psychiatric symptoms suggests that severe organ complications contribute to psychological distress. Given the chronic, multisystemic nature of FD, patients with neurological involvement may be at higher risk for mental health conditions. Regular psychiatric assessments and timely interventions are essential to mitigate the psychological burden associated with CNS and CVS involvement.

Since no significant association was found between Lyso-Gb3 levels and psychiatric manifestations, its use as a biomarker for follow-up in this context is not recommended.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no: 2022.07.05, date: 04.04.2022).

Informed Consent: Informed consent was obtained from all participants prior to enrollment.

FOOTNOTES

Authorship Contributions

Concept: M.E., S.Y., H.P., Design: M.E., S.Y., H.P., Data Collection or Processing: M.E., A.Ç., Analysis or Interpretation: M.E., S.Y., H.P., Literature Search: M.E., S.Y., A.Ç., Writing: M.E., S.Y., H.P., A.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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