DOI: 10.14744/DAJPNS.2019.00052
Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2019;32:359-364

CASE REPORT

# Psychiatric comorbidities in cases with Duchenne muscular dystrophy: a case series

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**ABSTRACT**

Duchenne muscular dystrophy is a hereditary multisystem disease caused by mutations in the dystrophin gene, characterized by proximal muscle weakness in early childhood, generally resulting in death before the age of 20 years. Cognitive and neurobehavioral changes are prevalent in Duchenne muscular dystrophy. Furthermore, psychiatric disorders have been reported. Here we present 12 cases with Duchenne muscular dystrophy, aiming to address psychiatric comorbidities and to examine anxiety and depression levels as well as the quality of life in these cases. Twelve inpatients with Duchenne muscular dystrophy were followed, according to their ages, by an adult psychiatrist or a child and adolescent psychiatrist. Psychiatric examination and detailed psychiatric and medical history-taking were performed. The Hospital Anxiety and Depression Scale (HADS) and the KINDL Questionnaire were administered and family interviews conducted. In 5 cases, comorbid psychiatric diagnoses were present, including depression, obsessive compulsive disorder, and generalized anxiety disorder. Anxiety levels according to the HADS were higher than threshold level in two cases. Alongside cognitive and neurobehavioral changes, psychiatric comorbidities such as depression, obsessive compulsive disorder, or generalized anxiety disorder might be seen in Duchenne muscular dystrophy, as was the case with our patients. At the same time, due to the chronic illness process and disability involved, psychosocial support is needed both for the patient and the family. Therefore, it is important that psychiatry should be part of a holistic treatment approach and that psychiatric support should be provided right from the first years in these cases.

**Keywords:** Anxiety, depression, Duchenne muscular dystrophy, psychiatric care, quality of life

## INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most common heritable fatal male-related disease, occurring in around 1 in 3.500 male babies (1,2). Over the progressive course of DMD, patients show proximal muscle weakness in early childhood; usually around the age of 9-12, they lose their ambulation, and in subsequent years, general muscle weakness and atrophy occur. Over the years, these cases develop respiratory insufficiency, and commonly they die before the age of 20 due to pneumonia or heart failure (2-4).

Etiologically, DMD is caused by mutations in the gene Xp21 that is coding for the protein dystrophin, which plays a role in skeletal, myocardial, and smooth muscle tissues. While most genetic mutations consist of deletions, we also see point mutations and duplications, though less commonly. These mutations

**How to cite this article:** Ozer U, Tufan AE. Psychiatric comorbidities in cases with Duchenne muscular dystrophy: a case series. Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2019;32:359-364.

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**Received:** October 01, 2018; **Revised:** November 13, 2018; **Accepted:** July 08, 2019

damage the function of dystrophin, and the damaged dystrophin causes membrane instability leading to degeneration of the muscle fibers, triggering inflammatory processes and later on muscle defects with necrosis and fibrosis. Cognitive and neurobehavioral changes, reportedly related with the presence of dystrophin isoforms in the central nervous system, have also been observed (2-6).

Psychiatric disorders in DMD cases have been studied in the literature; among the most common psychiatric comorbidities, attention deficit hyperactivity disorder (ADHD), autism-spectrum disorders (ASD), anxiety disorder, depression, and obsessive-compulsive disorder (OCD) have been reported (1,5,7,8).

This report presents 12 cases with a diagnosis of DMD, aiming to examine their psychiatric comorbidities, their anxiety and depression levels, and their quality of life.

## CASES

Twelve inpatients with DMD in our hospital were followed, according to their ages, by adult or child and adolescent psychiatrists. The patients were seen in the hospital rooms, where a psychiatric examination was carried out, a detailed medical and psychiatric history was received, and the Hospital Anxiety and Depression Scale and the KINDL Questionnaire (according to age: Kid-KINDL or Kiddo-KINDL) were administered. In addition, the family member accompanying the patient was also interviewed.

**Hospital Anxiety and Depression Scale (HADS):** This instrument was developed by Zigmond and Snaith (9); a validity and reliability study for Turkey was carried out by Aydemir et al. (10). The scale, consisting of subscales for anxiety and depression, is mainly used for physically ill patients. Cutoff scores are 10/11 for the anxiety subscale and 7/8 for the depression subscale; cases scoring higher are considered to be at risk of anxiety or depression, respectively.

**Health-related quality of life questionnaire (KINDL):** This scale is used to measure the health-related quality of life of chronically ill children and adolescents and to establish which dimensions of their lives are most affected by their illness or the treatment they receive. A Turkish validity and reliability study was carried out by Eser et al. (11,12). For the questionnaire, in addition to the six subdimensions "physical well-being," "emotional well-being,"" self-esteem," "family," "friends," and "everyday functioning," a total score is calculated as the sum of the six subdimensions. A high score from the instrument indicates good health-related quality of life.

Of the 12 cases (all male), 3 were adults and the remaining 9 children or adolescents. Their sociodemographic and clinical characteristics are presented in Table 1. Cases using a wheelchair were classed as immobile, those walking with support as semimobile, and patients walking without support as mobile.

Five of the cases presented with a comorbid psychiatric disorder. These comorbidities were

**Table 1: Sociodemographic and clinical characteristics of the Duchenne muscular dystrophy patients**

| Case | Age (years) | Education | Duration of education (years) | Number of siblings | Accompanying relative | Age when receiving DMD diagnosis (years) | Mobility |
|---|---|---|---|---|---|---|---|
| 1 | 22 | Formal education | 14 | 3 | Mother | 6 | Immobile |
| 2 | 18 | Formal education | 1 | 1 | Elder sister | 4 | Immobile |
| 3 | 20 | Homeschooling | 8 | 0 | Mother | 2 | Immobile |
| 4 | 15 | Formal education | 10 | 1 | Mother and father | 7 | Immobile |
| 5 | 13 | Formal education | 7 | 1 | Mother and father | 9 | Mobile |
| 6 | 10 | Formal education | 5 | 1 | Mother and father | 7 | Mobile |
| 7 | 15 | Formal education | 10 | 1 | Mother | 8 | Semimobile |
| 8 | 10 | Formal education | 5 | 1 | Father | 8 | Mobile |
| 9 | 12 | Homeschooling | 4 | 0 | Mother | 8 | Semimobile |
| 10 | 13 | Homeschooling | 6 | 1 | Mother | 9 | Mobile |
| 11 | 13 | Formal education | 8 | 0 | Mother | 10 | Mobile |
| 12 | 15 | Homeschooling | 10 | 0 | Mother | 9 | Mobile |

**Table 2: Scale scores of the Duchenne muscular dystrophy patients**

| Case | HADS anxiety subscale | HADS depression subscale | KINDL total score | KINDL physical well-being | KINDL emotional well-being | KINDL self-esteem | KINDL family | KINDL friends | KINDL school |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 16 | 2 | 63 | 6 | 7 | 10 | 16 | 15 | 9 |
| **2** | 6 | 1 | 87 | 13 | 11 | 14 | 20 | 16 | 13 |
| **3** | 19 | 6 | 66 | 7 | 8 | 7 | 19 | 14 | 11 |
| **4** | 2 | 5 | 98 | 19 | 15 | 16 | 17 | 18 | 13 |
| **5** | 4 | 5 | 69 | 15 | 12 | 15 | 10 | 7 | 10 |
| **6** | 0 | 0 | 80 | 8 | 13 | 12 | 19 | 13 | 15 |
| **7** | 3 | 4 | 68 | 10 | 14 | 10 | 10 | 11 | 13 |
| **8** | 3 | 2 | 85 | 11 | 18 | 18 | 15 | 13 | 10 |
| **9** | 6 | 1 | 94 | 14 | 15 | 13 | 19 | 16 | 17 |
| **10** | 2 | 3 | 72 | 11 | 12 | 13 | 12 | 11 | 13 |
| **11** | 1 | 1 | 91 | 15 | 16 | 13 | 12 | 19 | 16 |
| **12** | 2 | 2 | 93 | 13 | 17 | 13 | 19 | 15 | 16 |

HADS: Hospital Anxiety and Depression Scale, KINDL: Health-related quality of life questionnaire.

depression and OCD (case 1), OCD (case 2), OCD and generalized anxiety disorder (GAD, case 3), OCD (case 5), and GAD (case 9).

Our patients had HADS anxiety subscale scores between 0 and 19, and 2 of them scored above the recognized cutoff point of 10. The patients' HADS depression subscale scores varied between 0 and 6; thus, no case scored above the accepted cutoff point of 7. The HADS scores are presented in Table 2, as are the KINDL total score and the scores for the subdimensions physical well-being, emotional well-being, self-esteem, family, friends, and school.

Five cases had a previous psychiatric history, and in distinction from the ongoing diagnoses, case 1 had a history of depression and case 3 past diagnoses of panic disorder and depression. Five cases had a history of past and ongoing psychiatric treatment. Only one of the cases (case 5) had a family history of psychiatric illness and treatment.

## DISCUSSION

DMD cases are known to present with comorbidities of intellectual disability, ADHD, ASD, anxiety disorder, depression, and OCD, particularly with psychiatric symptoms such as anxiety and depressive symptoms (1,5,7,8,13). These signs and conditions will be discussed in detail below.

In addition to the dystrophin that fulfills basic functions in skeletal, myocardial, and smooth muscles, in DMD a full-length isoform (Dp427) is expressed in the central nervous system alongside shorter dystrophin derivatives from the dystrophin gene, including Dp260, which is active in the retina, Dp116 in the peripheral nervous system, Dp140 in the brain, retina, and kidneys, and Dp71, which affects brain, retina, kidney, liver, lung, and myocardial tissue. Dystrophin is known to be found in various brain regions, contributing to cognitive functions in the cerebral cortex, the hippocampus, and the cerebellum (1,5). Accordingly, central nervous effects of DMD are being reported (5). While the neuropsychiatric disorders associated with DMD might be explained by these actions, the underlying neurobiological mechanisms are not yet fully understood (1,8).

Intellectual functions in DMD have been studied for many years. The prevalence of intellectual disability in DMD cases is increased compared to the rates in the general population (20.9% vs. 3%) (13). Bresolin et al. (6) reported cognitive impairment in one third of DMD cases. These patients may present with light or moderate mental retardation (2). A number of studies found that the verbal IQ was typically more affected than the performative IQ (1,3,5,14). Some studies reported an increased risk of learning disabilities in DMD cases (5,15). Banihani et al. (5) found learning disability or intellectual impairment in 62.6% of DMD patients, while Hendriksen and Vles (16) detected dyslexia and light mental retardation in ca. one third of DMD cases, reporting symptoms like impairment of the verbal procedural memory and the inability to accomplish automated motor tasks. These presentations can occur in the form of linguistic and general psychomotor

developmental delay in early childhood (3). As no test protocols assessing neurocognitive or intellectual functions were administered to our cases, we could not obtain data in this area.

ADHD has been reported as the most common neurobehavioral comorbidity of DMD (5,8,15). Steele et al. (17) examined 10 DMD cases and found an ADHD comorbidity rate of 50%, while Pane et al. (18) in a study with 103 cases identified a rate of 32% (33 cases). In another study with 351 DMD cases, the ADHD rate was 11.7% (8), and Banihani et al. (5) reported an ADHD rate of 32.2%. In general, these rates are significantly higher than those encountered in population samples. Another comorbidity found in DMD is ASD. Hendriksen et al. (8) found an ASD rate of 3.1% in their study with 351 cases, while Darke et al. (19) reported that 5.4% of DMD patients had previously received a diagnosis of ASD. A study with 158 DMD cases found ASD in 6 cases (20). Recent studies, however, identified rates in the order of 15% (5) to 21% (7), which is far higher than rates in a population sample. None of our cases had a diagnosis of either ADHD or ASD.

Furthermore, anxiety and depressive symptoms are also more prevalent in DMD cases than among healthy individuals (5,21,22). It has been pointed out that especially the loss of ambulation and independence can bring on depressive symptoms (3). The literature also reports more frequent obsessive-compulsive behaviors in DMD cases compared to other children in a similar age group. The OCD rate in Hendriksen and Vles's study with 351 DMD cases was 4.8%. The diagnoses of depression, OCD, and GAD in our cases are thus consistent with the literature. At the same time, it is remarkable that in two cases the anxiety levels exceeded the threshold level.

In addition to the above, it has been pointed out that DMD cases may experience psychosocial problems related to the chronic disease process and physical disability, which may lead to social isolation and withdrawal (23). Studies have reported a significantly reduced quality of life for DMD patients in physical and psychosocial areas compared to healthy peers (24). In particular, the mobility level being defined by wheelchair use and the need for ventilation were found to be determiners low level of quality of life (25).

Given the multisystem nature of DMD, the management of this condition requires a multidisciplinary and holistic approach (Figure 1) (23). Among the therapeutic approaches are the use of corticosteroids, immunosuppressive agents, utrophin, gene therapy, and stem cell therapy. Genetic

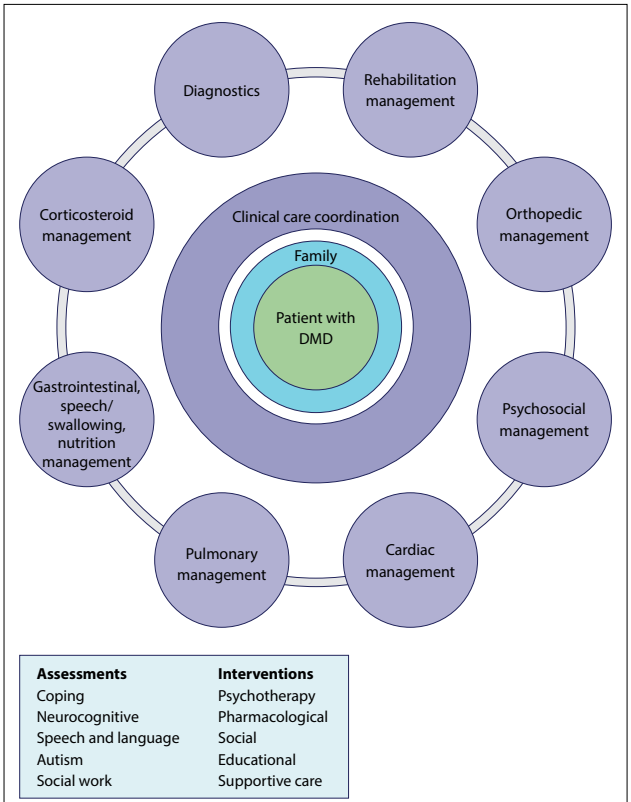


**Figure 1.** Multidisciplinary and holistic approach to DMD (adapted from Bushby et al. [23])

counseling and disease prevention are also important approaches (3). In addition, the use of support products like coenzyme Q10, carnitine, or amino acids has been mentioned, although sufficient evidence is not available. Positive effects of physiotherapeutic applications including light exercise to prevent or reduce contractures and deformities have been reported. In addition, detailed neuropsychological assessment with psychopharmacological and psychotherapeutic treatment approaches can be necessary in DMD cases. It has been noted that the patient's family should be part of a holistic therapy approach. These approaches include individual, group, or family psychotherapy, family education, specific educational programs geared towards cognitive disabilities, and interventions to increase social interaction (23). The fact that only those of our patients who had a current and/or past diagnosis of a psychiatric disorder presented to psychiatry and received psychiatric treatment suggests that the recommended psychiatric assessment as a routine procedure in DMD cases may have been deficient.

Among the limitations of our study, we firstly have to note that we did not administer test protocols

assessing neurocognitive or intellectual functions and thus were unable to collect data in this area. In addition, the past and/or current psychiatric treatments received by our patients have not been specified in detail. In this context, as far as we are aware the effect of pharmacological agents used in the treatment of DMD on psychiatric comorbidities is not sufficiently known; controlled studies in this area appear to be required.

In conclusion, DMD cases display a higher rate of cognitive function disorder, mental retardation, and learning difficulties as well as psychiatric disorders like ADHD, ASD, and OCD compared to a general population sample, and these findings indicate that DMD is not only a muscular disease but simultaneously a neuropsychiatric condition. At the same time, patients as well as family require psychosocial support in the face of the chronic disease process and the related disability. Thus it is evident that psychiatry needs to be a component of holistic treatment, and from the first years of the DMD diagnosis, psychiatric support should be sought.

| Contribution Categories | | Author Initials |
|---|---|---|
| Category 1 | Concept/Design | U.O., A.E.T. |
| | Literature review | U.O., A.E.T. |
| | Data analysis/Interpretation | U.O., A.E.T. |
| | Case follow-up (if applicable) | U.O., A.E.T. |
| Category 2 | Drafting manuscript | U.O., A.E.T. |
| | Critical revision of manuscript | U.O., A.E.T. |
| Category 3 | Final approval and accountability | U.O., A.E.T. |
| Other | Technical or material support | U.O. |
| | Supervision | U.O. |

**Informed Consent:** Written consent was obtained from the patient.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The authors have not stated any conflict of interest.

**Financial Disclosure:** The authors have not received any financial support for this study.

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