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# Mental Problems in Cases with Duchenne Muscular Dystrophy Mutation: Not Only Males, but also Females

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**Abstract**

Dystrophin, the pathogenic variants of which can cause muscular diseases, is a protein mainly distributed under the sarcolemma. However, the protein also exists in the central nervous system and many reports have described neural comorbidities in patients with dystrophinopathy. Duchenne muscular dystrophy (DMD) has been described as being associated with neurodevelopmental disorders, including intellectual developmental disorders, communication disorders, autism spectrum disorders, and attention-deficit/hyperactivity disorders. Patients with dystrophinopathy have also been reported to have depression, anxiety, or obsessive-compulsive disorders. Female carriers of DMD mutations exhibit a wide variety of clinical features from asymptomatic high serum creatine kinase level to severe muscle weakness or dilated cardiomyopathy, and mental disorders including cognitive impairment. Since the mental disorders in female carriers of DMD mutations can be easily overlooked, it is necessary to pay close attention for correct diagnosis.

**Keywords:** Dystrophinopathies; Female carrier; Mental disorders

## Commentary

Dystrophinopathies [1] include a spectrum of X-linked muscular diseases caused by the pathogenic variants of dystrophin gene. Dystrophin is a large protein located under the plasma membrane of muscle fibers and provides mechanical reinforcement to the sarcolemma and stabilizes the glycoprotein complex [2]. In its absence, the glycoprotein complex is digested by proteases, and loss of these membrane proteins initiates the degeneration of muscle fibers, resulting in muscle weakness [2]. Duchenne/Becker muscular dystrophy (DMD/BMD) is the representative dystrophinopathy, characterized by progressive severe muscle weakness and atrophy in male patients [1]. As dystrophin also exists in the central nervous system and there have been many descriptions about the coexistence of dystrophinopathy and mental disorders. Female carriers of DMD mutations are also at a risk of developing mental disorders, despite the absence of muscular symptoms.

The association of intellectual disability with DMD was noted from the era of Duchenne [3]. The males with DMD have been frequently reported to have a lower than average Intelligence quotient (IQ) [4,5]. Several studies have also focused on behavioral problems among the DMD patients, such as learning disability, autism spectrum disorders (ASD), or attention-deficit/hyperactivity disorders (ADHD) [4-6]. Moreover, patients with dystrophinopathy have been reported to have depression, anxiety, or obsessive-compulsive disorders [5,6].

In the study by Banihani et al., 59 boys with dystrophinopathy were investigated. They reported an IQ <70, learning disability, intellectual disability, ADHD, ASD, and anxiety in 27%, 44%, 19%, 32%, 15%, and 27% of the study participants, respectively [4]. They also investigated the association between the presence of comorbidities and disruption of dystrophin isoforms; however, no significant correlation was observed. In the study by Ricotti et al., intellectual disability, ASD, hyperactivity, and inattention were observed in 26%, 21%, 24%, and 44% of the 130 DMD males, respectively [5]. They concluded that males with mutations at the 3' end of the DMD gene affected all the protein isoforms, which resulted in higher number of cases with intellectual disability and clusters of neuropsychiatric symptoms. Felisari et al. suggested that dystrophin deletions, which involve the brain distal isoform, Dp140 are associated with development of intellectual impairment [7].

Juan-Mateu et al. found cognitive abnormalities in 20.8% of female carriers of DMD mutations in isolation or together with muscle weakness [8]. In the report of Mercier et al., 27% of female carriers showed cognitive impairment, and they suggest that cognitive impairment was associated with mutations in the distal part of the dystrophin gene [9].

Moreover, we recently reported a case of a female carrier with DMD mutation, who only manifested asymptomatic hyperCKemia and psychiatric disorders [10]. The case was a 64-year-old woman who experienced difficulties in communication and anxiety neurosis, since adolescence. It was hard to find an employment for her. Consequently, she once attempted suicide. She presented low scores with respect to processing speed and working memory owing to attention/concentration deficit or obsession. She has a nephew with severe dystrophinopathy, and both of them had a duplication of exon 44 of the DMD gene.

Moreover, her mother became a wheelchair user at age 60, and was suspected to have some psychiatric disorders, as she neglected her own ailing child.

## Conclusion

Mental disorders in the males with DMD mutation have been frequently reported. However, in female carriers of DMD mutations, such mental problems can be easily overlooked owing to the wide

variety of clinical symptoms. Thus, careful attention should be paid for correct diagnosis of such patients.

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