A CASE OF MARFAN SYNDROME AND NEURODEVELOPMENTAL DISORDERS: A TRICKY ASSOCIATION

RALUCA GROZĂVESCU[1], ZEINEB DAKHEL[2*], OANA SAVIN[2], IOANA MORARU[2]

[1]Assistant Professor, Child and Adolescent Psychiatry Department, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Primary Doctor in Child and Adolescent Psychiatry, Child and Adolescent Department, "Prof. Dr. Alexandru Obregia Psychiatry Hospital", Bucharest, Romania

[2]Resident doctor in Child and Adolescent Psychiatry, " Prof.Dr. Alexandru Obregia" Psychiatry Hospital, Bucharest, Romania

Corresponding author email: zeineb.dakhel@yahoo.com

ABSTRACT:

Marfan Syndrome is an autosomal dominant transmitted connective tissue disease caused by mutations in the FBN-1 gene. The most common manifestations of this disorder involve the ocular, musculoskeletal and cardiovascular systems, but since the connective tissue is present all over the body, there are other areas that can be affected too.

Although associations between Marfan's Syndrome and neuropsychiatric disorders have been described in previous research, there is not much scientific data regarding its co-occurrence with ADHD. Here, we present the case of an 11-year-old patient with Marfan Syndrome and Conduct Hyperkinetic Disorder and we aim to start a discussion on the particularities of the treatment plan.

INTRODUCTION

Marfan Syndrome is an autosomal dominant transmitted connective tissue disease caused by mutations in the FBN-1 gene. FBN-1 gene (located on the long arm of chromosome 15) is responsible for encoding fibrillin-1 compounds, which are large glycoproteins that bind to each other in order to form microfibrils. The microfibrils can be found in the extracellular matrix either isolated or associated with elastin fibers [1]. Without proper microfibrils, the connective tissues are abnormal and weakened which leads to multiple clinical manifestations. Not only is fibrillin-1 involved in the proper development of connective tissue, but it is also responsible for binding a growth factor-TGF-β. Due to abnormal fibrillin-1, TGF-β levels are elevated and this, though incompletely understood, seems to be contributing to the pathogenesis of the Marfan Syndrome [2].

According to Gwenaëlle Collod-Béroud & Catherine Boileau, in their 2002 article 'Marfan Syndrome in the third Millenium', there are three types of mutations described in the FBN1 gene: (1) missense mutations, (2) small insertions or deletions, mutations causing premature termination of translation and (3) exon-skipping mutations. Hundreds of different mutations have been found in the FBN1 gene, which is why there is so much clinical variability associated with Marfan`s Syndrome [3].

The estimated prevalence of Marfan Syndrome is 1 per 5000 individuals. About 75% of the patients have the inherited version of the disease, while the others are the first in their families, having spontaneous mutations [4].

The most common manifestations of this disorder involve the ocular, musculoskeletal and cardiovascular systems, but since the

connective tissue is present all over the body, there are other areas that can be affected too. Attention-deficit hyperactivity disorder (ADHD) is a mental disorder characterized by high levels of impulsivity,hyperactivity and a low level of attention [5].

In order to diagnose ADHD, symptoms need to be present for at least six months, alongside with significant changes and problems that arise in multiple social environments (school, workplace, home) [6].

Even though ADHD is one of the most common and widely researched conditions affecting children and teens, there is a lot yet to be discovered now regarding the cause of the disorder.

There is a growing interest in the way genetics and environment contribute to the development of ADHD. There are multiple genes that are thought to play an important role in this disorder. Dopamine neurotransmission is closely influenced by several genes. Directly associated dopamine neurotransmission genes numbers DAT, DRD4, DRD5, TAAR1, MAOA, COMT, and DBH [7,8,9]. Other ADHD related genes are SERT, HTR1B, SNAP25, GRIN2A, ADRA2A, TPH2, and BDNF [10]. Furthermore, siblings of ADHD diagnosed children are 3 to 4 times more likely to manifest the disorder than siblings of children who do not have this disorder [11, 12]. Strong evidence shows that a genetic factor might involve the persistence of ADHD in adulthood [13].

The prevalence of ADHD in US population ranges between 3 and 5 percent. Knowing that ADHD has a high number of comorbidities, special care needs to be taken when treating these patients.

Associations between Marfan's Syndrome and neuropsychiatric disorders have been described in previous research[13]. The clinical manifestations have been known to produce a variable amount of pain in patients who suffer from Marfan Syndrome.

In a two hundred and forty-five participants study published in 2018 examining the psychological burden of Marfan Syndrome suffering patients, pain was found to be a symptom in eighty-nine percent of the cases. Pain being an initial symptom and spreading across various sites of the body was correlated with psychological problems such as depression, catastrophic thoughts and insomnia [14].

Velvin G and co., in a systematic review investigating the psychosocial particularities of individuals living with Marfan Syndrome, found that people with this disease meet education difficulties, professional and family life challenges, depression and anxiety [15].

Baeza-Velasco C and co. conducted a comprehensive research of scientific online databases and references lists. They found that heritable diseases of connective tissue are correlated with anxiety disorders, depression, schizophrenia, neurodevelopmental disorders (autism, attention deficit/hyperactivity disorder, and developmental coordination disorder), eating disorders, personality disorders and substance use/misuse [16].

There is not much scientific research on the prevalence of ADHD in Marfan Syndrome patients. A 1988 paper evaluating the neurodevelopmental status in 30 school-age children diagnosed with Marfan Syndrome, found that 17% of the cohort had ADHD symptoms [17].

Case Report E.M, 11 years old

E.M an 11 years old male was admitted to the child and adolescent psychiatry ward for the following symptoms: psychomotor agitation, reduced frustration threshold, irritability, mood fluctuations.

Patient History:

E.M had multiple hospitalizations to the psychiatry ward, and he was discharged in 2018 with the following diagnosis according to ICD 10 and DSM 5: Hyperkinetic Conduct

Disorder, Social Communication Disorder, Marfan Disorder.

E.M was diagnosed with Marfan Syndrome in 2016 by a pediatrician.

In his first admission on our ward, E.M. presented, besides the symptoms described above, enuresis and compulsions and rituals which took up to 2 or 3 hours per day "he touches wood multiple times, he hammers nails into wood". No obsessive thoughts were identified. He was diagnosed with OCD, Hyperkinetic Conduct Disorder and Social Communication Disorder. The following treatment was prescribed: Fluvoxamine 50 mg per day and Risperidone 0,5 mg per day.

During the following admission the OCD symptoms maintained, as well as the defiant attitude and the violence towards his mother. The Risperidone dose was raised to 0,75 mg per day, Fluvoxamine was reduced to 25 mg per day and 170 mg of Sodium Valproate where associated to the prescribed treatment.

Under this treatment his OCD symptoms progressively disappeared, and medication was slowly stopped. At his last admission, E.M showed no signs of OCD and his conduct hyperkinetic disorder symptoms had been significantly reduced.

Family history

The mother, aged 48, unemployed, was admitted in the psychiatry ward for a depressive episode, when she received treatment with Gabapentinum, Alprazolam and Escitalopram. Se also declared having multiple allergies.

The father, aged 47, was absent during E.M`s admissions. The mother reports being separated from E.M`s father who was supposedly aggressive with both the mother and the child: "His dad was hitting us and he used to always shout when he arrived home. This is the reason why we decided to separate. I sometimes think the E.M is taking after his dad".

E.M has a 26-year-old brother and an 8-year-old sister, who are healthy.

E.M is a third child, coming from a toxic pregnancy, normal birth, with normal psychomotor development.

During the physical examination, the patient exhibited pectus excavatum, extreme ligamentous laxity, skeletal deformities (kyphoscoliosis, left inferior leg 2 cm shorter than the right leg, genu varum, deviated septum), muscular hypotrophy, ophthalmological problems (anopsia, amblyopia and astigmatism), frequent sore throat episodes, and a systolic murmur.

Mental state examination

At his last admission, E.M arrived at the hospital with his mom, wearing adequate clothing and had a good personal hygiene. During examination, the patient exhibited good mental orientation and he was cooperative with the examiner. E.M made good eye contact, no difficulties in establishing and maintaining it. Facial expression and gestures where consistent with his cheerful disposition. His discourse was mainly focused on family conflicts and school related issues, especially in terms of conflicts with his colleagues.

He had difficulties maintaining attention and he showed signs of distractibility. No qualitative or quantitative perception disturbances. He had no alterations of appetite or sleep pattern disturbances. Hyperkinetic behavior was visible during the examination. EM`s mother describes him: "he is always in motion, always doing something different, he keeps breaking down the bike, and then he repairs it.

E.M`s mother describes defiant behavior which leads to frequent arguments between her and her son regarding his tendency to disobey house rules, push limits and neglect homework. E.M`s mom also describes

episodes of violence: "he sometimes becomes aggressive when something is not as he wants it to be".

Regarding E.M`s academic life, he is in the 5thgrade with satisfactory academic results. His mother describes E.M as having difficulties in terms of social interaction and social communication, which are more prominent and problematic in his relationship with his classmates: "he has multiple friends, he goes out and plays with them, but sometimes he loses his temper so easily that he picks on fights. He doesn`t understand jokes, when his colleagues make jokes with him, he gets angry and sometimes hits them."

Investigations:

Psychological examinations were carried out, E.M. exhibiting average intellect, (a score of 95 in the RAVEN IQ test) and according to his mother, his school results were satisfactory.

Because Marfan Syndrome is associated with cardiovascular complications, during E.M`s admissions an electrocardiogram was performed, and a right bundle branch block was discovered. The echocardiography results came back normal. Also, an electroencephalogram was performed, and no abnormalities could be seen.

DISCUSSION

Since E.M showed hyperkinetic behavior, high impulsivity and difficulties during classes and homework that impaired his functioning in social and home environments, typical ADHD medication should be recommended. E.M has a right bundle block and has a further risk of cardiovascular complications (such as cardiac aneurysm and aortic dissection), typical ADHD medication should not be prescribed. Antipsychotic medication also has limitations considering the risk of QT interval prolongation and cardiometabolic adverse effects which means a lot of care is requested before deciding upon the treatment plan with these patients. Considering risk/benefits of dopamine blocking medication, a short course at a minimal effective dose was considered for this patient, and upon the disappearance of aggressive behavior and compulsions and rituals, dopamine blocking medication was stopped.

Nonpharmacological treatment should be considered for severe ADHD, Social Communication Disorder and Marfan Syndrome. A combination of behavioral intervention, family counseling, social skills group sessions and adequate educational support is necessary in order to ensure an increased quality of life and reducing further need for medication. Pharmacological treatment should only be considered in extreme situations and for a short time only, in order to reduce exposure to potential adverse effects.

As literature indicates, psychotic disorders might be a component of Marfan Syndrome`s phenotype, especially in female patients, even though most of the scientific sources are represented by case reports. Moreover, associations of Marfan Syndrome, anxiety and depression were described in a few studies, further close psychiatric supervision is necessary. Instructing family members for early signs of these disorders is beneficial for early intervention thus reducing the need for aggressive medication.

The association between neurodevelopmental disorders, such as ADHD/ASD and connective tissue disorders -Marfan-like syndromes- was previously described in literature. The association between two neurodevelopmental disorders and Marfan syndrome is a unique presentation. Further research is needed in order to establish if there is a distinct phenotype of Marfan syndrome and the appropriate treatment plan to ensure the best quality of life.

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