NEGATIVE SMOKING AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY

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ABSTRACT

Duchenne Muscular Dystrophy (DMD) is the most common hereditary male related disease caused by mutations in the dystrophin gene. It is characterized by muscle weakness in early childhood, causing death before the age of 20 years. Neurobehavioral changes are common in Duchenne muscular dystrophy patients. Attention Deficit Hyperactivity Disorder (ADHD) had been reported in DMD patients. Tobacco smoking use is related later on to offspring behaviour. This study aims to assess the association of exposure to tobacco smoking and behavioural disorders in DMD patients. The present study was conducted on 15 patients who were confirmed to have DMD based on clinical features. SWAN scale (Strengths and Weakness of Attention-Deficit/Hyperactivity Disorder-Symptoms and Normal-Behaviours) was used for ADHD. Smoking questionnaire was done for all patients. Karyotyping was done for the patients to detect any chromosomal abnormalities. We found no statistical significance for negative smoking as a contributing factor for ADHD in DMD patients.

Keywords: Duchenne Muscular Dystrophy, Negative smoking, Attention deficit hyperactivity disease, behavioural disorders.

INTRODUCTION

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive degenerative neuromuscular disorders affecting males and very rarely females with an incidence about 1 in 3600 and 1 in 30,000, respectively (BEYTÍA *et al*., 2012 and Shariati *et al*., 2020). It is caused by alteration of the gene responsible for dystrophin protein, results in loss of function of the DMD protein. DMD gene is one of the largest gene that contains 79 exons located in Xp21. The disease is diagnosed firstly by progressive muscle weakness usually appears during childhood. It causes disability in walking as well as Gowers' sign that indicates proximal muscles weakness (Shimizu-Motohashi *et al*., 2016 and Shariati *et al*., 2020). Usually the patients become wheelchair dependent by the age of 8 to 14 years old (Ryder *et al*., 2017 and Shariati *et al*., 2020). Most of the patients died around their twenties resulted from either cardiac or respiratory failure (Mah *et al*., 2014). DMD can be detected by increasing serum creatine kinase activity, even before muscle affection occurs. Precise genetic testing is needed for better genetic counselling, prenatal diagnosis and gene therapy for these patients who are at risk (Shariati *et al*., 2020).

Attention deficit hyperactivity disorder (ADHD) – characterized by symptoms of hyperactivity, impulsivity and inattention – is a highly widespread neuropsychiatric disorder that continues into adulthood in a large number of affected children of both genders (Biederman, 2005). Moreover, a strong genetic predisposition to ADHD, environmental factors account for

about 10%–40% of the discrepancy in liability to the disorder (Banerjee *et al*., 2007). Stress, alcohol use, cigarette smoking and other lifestyle factors of the mother during pregnancy may represent environmental risk factors for ADHD in children (Thapar *et al*., 2012), but the mechanisms through which those risks factors influence ADHD is poorly understood (Skoglund *et al*., 2014).

Maternal tobacco smoking during pregnancy has negative effects on characteristics of the child birth and perinatal health as increasing the risk of prematurity and low birth weight (Iñiguez *et al*., 2013 and Melchior *et al*., 2015). Children whose mothers smoke may have elevated levels of substance-related and behavioural problems (Roza *et al*., 2009, Gaysina *et al*., 2013 and Melchior *et al*., 2015) particularly symptoms of hyperactivity and attention-deficit hyperactivity disorder (ADHD) (Thapar and Rutter, 2009, Thapar *et al*., 2009, Obel *et al*., 2011 and Langley *et al*., 2012). A wide debate about whether this association is the cause, and the findings from genetic studies suggest that ADHD in children of smoking mothers may reflect the intergenerational transmission of a genetic susceptibility to behavioural difficulties or incomplete confounding factors such as socioeconomic position (Thapar *et al*., 2009, Langley *et al*., 2012, Skoglund *et al*., 2014 & Melchior *et al*., 2015)

We here aim to study the effect of exposure to tobacco smoking in increasing the incidence of ADHD in DMD patients.

MATERIALS AND METHODS

The study was carried out on 15 DMD patients referred from Neurogenetics Clinic, National Research Centre (NRC), Cairo, Egypt. The diagnosis of DMD was based on full family history taking including Pedigree analysis, tobacco smoking questionnaire, and SWAN rating scale followed by complete clinical examination including neurological examination with detailed history of DMD symptoms such as progressive muscular wasting, abnormal walking and Gowers' sign. Peripheral blood samples were obtained for cytogenetics analysis. The study was approved and carried out according to the recommendations of Medical Research Ethics Committee. Informed consent was obtained from patients and/or their legal guardians.

Conventional cytogenetic analysis by GTG banding technique: The technique was done according to *Verma and Babu,1995.* Twenty-five metaphases were analyzed for each case to detect any chromosomal abnormalities.

Smoking questionnaire: It was obtained from the parents to record whether their child had ever exposed to tobacco products, especially maternal exposure to tobacco smoking during pregnancy either actively or passively *(Braunet al., 2006).*

Behavioural disorders by SWAN Scale: According to *Brites et al., 2015,* SWAN scale was done for each patient to detect weather he/she had ADHD or not and to detect the type of ADHD.

RESULTS

The current study included 15 patients with DMD. The current study included 15 patients with DMD, 14 males and one female. Their ages ranged from 3 to 19 years with median 11 years and mean 10.6 years. The serum creatine kinase (CPK) levels of the patients showed that all patients were having DMD. It was done in 14 patients. It ranged from 1310 to 72000 IU/L (Normal values: male: 39-308, female: 26-192 U/L). Positive parental consanguinity was found in 33.3% of the cases (5 patients), while 10 patients had negative consanguinity. Eight cases (53.3%) were giving positive family history of DMD. Thirty-three percent of patients with positive family history were 1st degree relatives. Second- and third-degree relatives were found in 6.7% and13.3% of patients, respectively. The characteristics of the studied sample is described in Table 1 and Clinical features were emphasized in Table 2.

Karyotyping was done in 10 patients (66.7%). Five patients didn't undergo chromosomal analysis (33.3%). There were 9 males (46, XY) as shown in Figure 1, and only one female (46, XX). No chromosomal abnormalities were detected in the studied patients.

Table (1): Characteristics of the Studied DMD Patients

Characteristics of the studied DMD patients		**No. (15)**	**%**
Sex	Male	14	93.3%
	Female	1	6.7%
Consanguinity	+ve	5	33.3%
	-ve	10	66.7%
Family history	+ve	8	53.3%
	-ve	7	46.7%
Degrees of family history	1st	5	33%
	2nd	1	6.7%
	3rd	2	13.3%
Negative Smoking	Yes	10	66.7%
	No	5	33.3%
Range of Age	3-19 years		
Median of Age	11 years		
Mean of Age	10.6 years		
Range of CPK	1310-72000 IU/L		

Table (2): Clinical Features of the Studied DMD Patients

	No. (15)	**%**
Gowers' sign	13	87
Wheel chair	8	53
Abnormal gait	6	40
Pseudohypertrophy	13	87
Other deformities	4	27
Hypotonia	14	93
Hyporeflexia	14	93
Weakness	14	93
Mental affection	3	20
Chest affection	1	7
Heart affection	2	13
Genitalia	0	0
Sensations	0	0

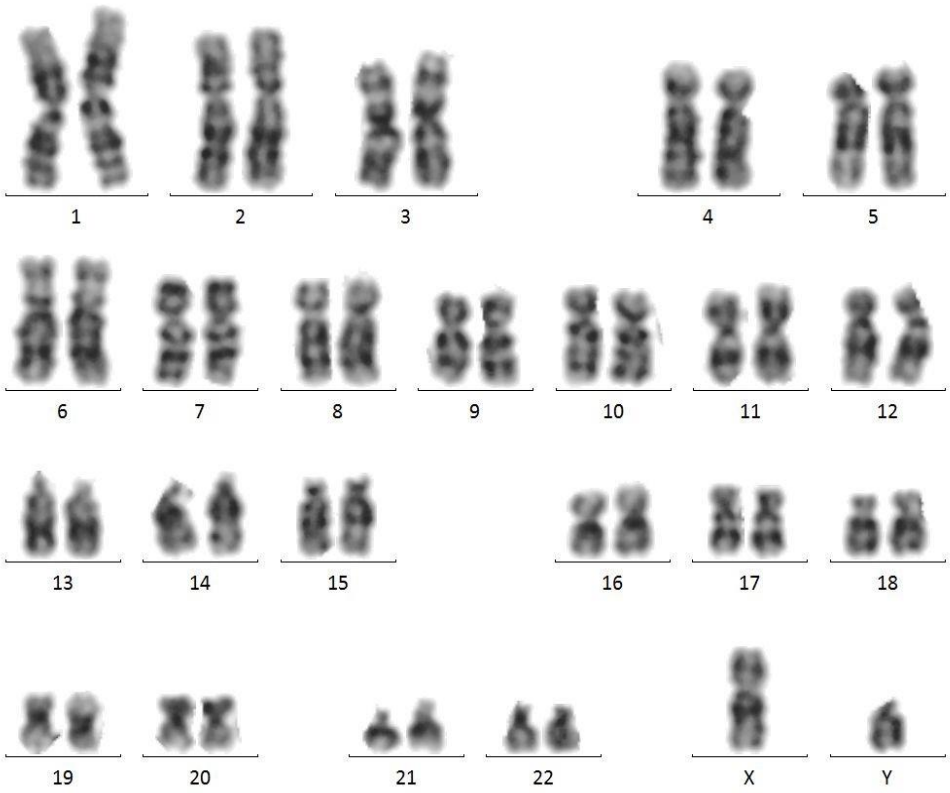

Fig. (1): Normal Karyotype of DMD Male Patient

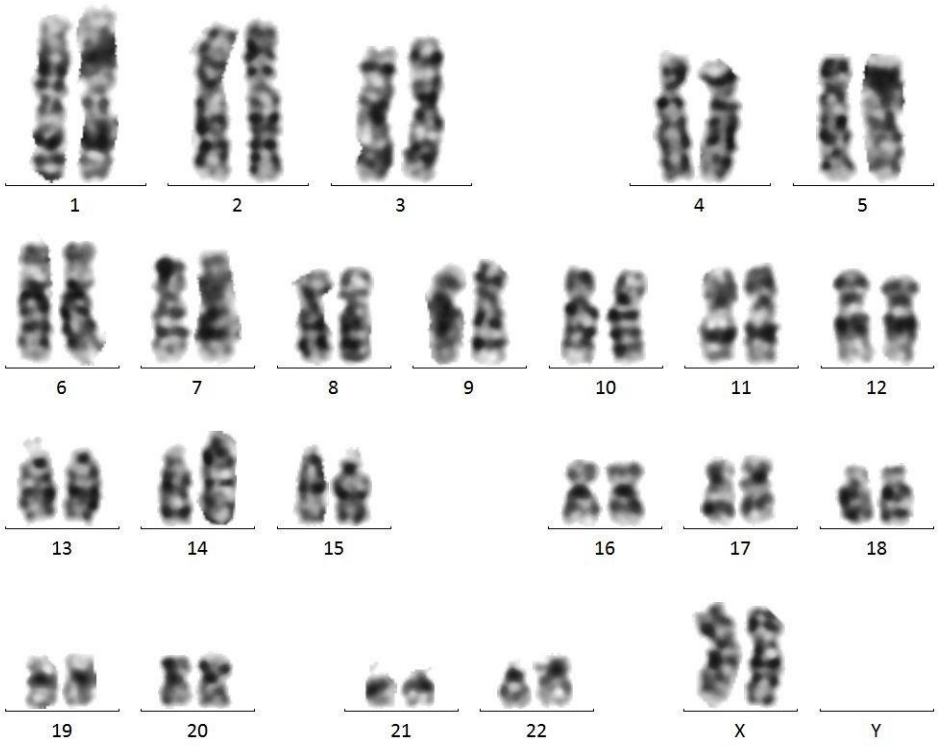

Fig. (2): Normal Karyotype of DMD Female Patient

According to the SWAN scale, 5 patients only were having ADHD (33.3 %). Two of them had ADHD combined type (13.3%) (the score was ≥ 6 in both inattentive and hyperactive types). Three of them had inattentive type (20%) (the score was ≥ 6 in inattentive type only). Ten patients were normal; having no ADHD (66.7%) as shown in Table 3.

Table (3): Results of SWAN Scale

ADHD	No. (15)	%
Normal	10	66.7%
ADHD combined type(the score was ≥ 6 in both inattentive and hyperactive types)	2	13.3%
ADHD inattentive type (the score was ≥ 6 in inattentive type only).	3	20%

The comparison between DMD patients having Attention deficit hyperactivity disease (ADHD) and others who didn't have ADHD according to their exposure to negative smoking showed that 66.7% of the cases were exposed to negative smoking (10 cases), while 5 patients were not exposed to negative smoking (33.3%). Among the 10 cases exposed to the negative smoking, father of one patient was drug addict. Despite that, the negative smoking didn't show any statistically significant difference in Duchenne Muscular Dystrophy patients to get Attention deficit hyperactivity disease. The P-value was 0.101, as shown in Table 4.

Table (4): Comparisons Between DMD Patients with ADHD & Others Without ADHD According to Their Negative Smoking

Patients / Exposure to Negative smoking	No ADHD (n=10)		ADHD (n=5)		P-value
	N	%	N	%	
No Negative smoking	5	100	0	0	0.101
Negative smoking	5	50	5	50	

DISCUSSION

Our study included 15 DMD patients diagnosed both clinically and by CPK. Their ages ranged from 3 years to 19 years with median age of 11 years and mean age of 10.6 years. The age range reported by *Battini et al., 2018* was between 6 and 12 years.

The most common abnormalities detected in our study were weakness, hypotonia and hyporeflexia which represent 93% of the patients. *Shariatiet al., 2020* found that most of the patients manifested by Gowers' sign and calf muscle pseudohypertrophy.

Our study revealed that attention problems together with hyperactivity had been found in 33.3% of them while 20% had inattentive type. *Battini et al., 2018* noticed that 19% of the patients were having ADHD. *Pane et al., 2012* had the same results (37%) of the patients met the criteria for ADHD. ADHD did not appear to be related to level of motor ability as ADHD was present in both ambulatory and non-ambulatory patients. The same results were obtained by *Pane et al., 2012.*

In our study, patients were assessed for ADHD criteria. All the patients were screened by using SWAN scale criteria. The diagnosis of ADHD in DMD was confirmed in 33.3% of patients, compared with 3–7% of ADHD in the general population (*Rappley, 2005).* ADHD was reported as the most common neurobehavioral comorbidity of DMD *(Hendriksen and Vles, 2008).*

Previous studies *(Ernst et al., 2001)* found an association between maternal smoking during pregnancy and children with ADHD symptoms.

Langley et al., 2012 noticed that ADHD symptoms in children were associated with paternal smoking during pregnancy explaining that by hypothesis of fathers do not give the intrauterine environment but they share the genes and environmental factors with their offspring.

Langley et al., 2012 also found that the exposure to negative smoking at home and at a smoky working environment revealed a lack of association between passive smoking and offspring ADHD so they concluded that these associations between maternal smoking during pregnancy and ADHD symptoms of the children were due to unmeasured familial factors rather than direct intrauterine effect. In our study we found that, 66.7% of the cases were exposed to negative smoking (10 cases), while 5 patients were not exposed to negative smoking (33.3%). According to the SWAN scale 5 patients only were having ADHD (33.3%). There was no statistical significance between smoking and ADHD due to small number of cases, genetic predisposition for ADHD in DMD patients and other familial cofactors.

CONCLUSION

ADHD is the most common neurobehavioral comorbidity associated with Duchenne muscular dystrophy. The percentage of individuals with ADHD among patients with Duchenne muscular dystrophy was reported to be up to 50% in some studies. Unmeasurable familial factors may play a role in the development of ADHD in the offspring of smoking pregnant women rather than to a direct intrauterine effect. Yet, there are many negative consequences

of smoking during pregnancy. This should not alter advice to pregnant women regarding smoking. So, in this study we demonstrate that smoking during pregnancy has no direct risk effect on all offspring outcomes, including ADHD, and alternative risk factors should be put into consideration.

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التدخين السلبي وفرط الحركة وتشتت الانتباه في مرضى ضمور العضلات دوشين

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المستخلص

يعتبر مرض ضمور العضلات دوشين هو المرض الوراثي الأكثر شيوعًا المرتبط بالذكور، والذي تسببه الطفرات في جين ضمور العضلات. يتميز بضعف العضلات في مرحلة الطفولة المبكرة، مما يسبب الوفاة قبل سن ٢٠ سنة. وتعد التغيرات السلوكية العصبية شائعة في مرضى ضمور العضلات دوشين. كما تم تسجيل اضطراب نقص الانتباه وفرط الحركة في مرضى ضمور العضلات دوشين. يرتبط تدخين التبغ بسلوك النسل لاحقًا. تهدف هذه الدراسة إلى دراسة تأثير التعرض للتدخين في زيادة حدوث اضطراب تشتت الانتباه وفرط الحركة في مرضى ضمور العضلات دوشين. أجريت الدراسة الحالية على ١٥مريض تم تأكيد إصابتهم بمرض ضمور العضلات دوشين على أساس السمات الإكلينيكية. تم استخدام مقياس (SWAN) لمرضى اضطراب تشتت الانتباه وفرط الحركة. تم أيضاً عمل استبيان التدخين لجميع الحالات. تم إجراء تحليل الكروموسومات باستخدام طرق مزارع الدم التقليدية للكشف عن أي تشوه بالكروموسومات. لم نجد أي دلالة إحصائية للتدخين السلبي كعامل مساهم في اضطراب فرط الحركة ونقص الانتباه لدى مرضى ضمور العضلات دوشين.

الكلمات الدالة: مرض ضمور العضلات دوشين، التدخين السلبي، اضطراب تشتت الانتباه وفرط الحركة، الاضطرابات السلوكية.