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Original article

DUCHENNE MUSCULAR DISTROPHY IN TAFÍ DEL VALLE, TUCUMÁN, ARGENTINA

MARÍA EUGENIA SARANDRÍA[1], ROBERTO REY[2], RODRIGO DE ROSA[3], VANESA CORBALÁN[4], LILIA MESA[5]

[1]Residencia de Neurología, Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI), Buenos Aires, [2]Instituto Argentino de Investigación Neurológica, Buenos Aires, [3]Hospital Elías Medici, Tafí del Valle, Tucumán, [4]Centro de Rehabilitación Los Menhires, Hospital Elías Medici, Tafí del Valle, Tucumán, [5]Sección Neuromuscular Pediátrica, Fundación Favaloro, Buenos Aires, Argentina

Postal address María Eugenia Sarandría. FLENI, Montañeses 2325, 1428 Buenos Aires, Argentina
E-mail: mesarandria@gmail.com
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Abstract

Introduction: Duchenne muscular dystrophy (DMD) is an inherited, X-linked neuromuscular disorder with a global cumulative prevalence of 7.1 cases every 100 000 males. A relationship between consanguinity and DMD has been reported. We aimed to describe the prevalence and the sociodemographic, clinical and genetic characteristics of patients with DMD in an isolated population in Tafí del Valle (Tucumán, Argentina).

Materials and methods: Cross-sectional, descriptive, epidemiological study. Demographic, clinical and genetic data were retrieved from medical records. Pedigree charts were made after an interview with the family group.

Results: Seven male patients with DMD of Diaguita-Calchaquí ethnicity were identified (median age: 14 years old), with a prevalence of 0.12%. Five different mutations were reported. No consanguinity was identified in pedigree charts.

Discussion: An unusual high prevalence of DMD was identified in Tafí del Valle. . In addition, there are 5 different mutations in seven patients suggesting a high number of mutations “de novo”.

Key words: muscular dystrophy, Duchenne, prevalence, Argentina

Resumen

Distrofia muscular de Duchenne en Tafí del Valle, Tucumán, Argentina

Introducción: La distrofia muscular de Duchenne (DMD) es un trastorno neuromuscular hereditario ligado al cromosoma X con una prevalencia global acumulada de 7.1 casos cada 100.000 varones. Se observa una relación entre consanguinidad y DMD. Nuestro objetivo fue describir la prevalencia y las características sociodemográficas, clínicas y genéticas de los pacientes con DMD en una población aislada de Tafí del Valle (Tucumán, Argentina).

Materiales y métodos: Estudio epidemiológico, descriptivo y transversal. Se recuperaron datos demográficos, clínicos y genéticos de las historias clínicas. Se elaboraron genogramas a partir de entrevistas con el grupo familiar.

Resultados: Siete pacientes varones con DMD de etnia Diaguita-Calchaquí fueron identificados (mediana de edad: 14 años), con una prevalencia de 0.12 %. Se reportaron cinco mutaciones diferentes. No se identificó consanguinidad a través de los genogramas.

Discusión: Se identificó una prevalencia inusual y elevada de DMD en Tafí del Valle. No encontramos con-

sanguinidad que explique este hallazgo y se describen en los 7 pacientes, 5 mutaciones diferentes, lo cual podría deberse a un alto número de mutaciones de novo.

Palabras clave: distrofia muscular de Duchenne, prevalencia, Argentina

KEY POINTS
Current knowledge

- Duchenne muscular dystrophy (DMD) is inherited in an X-linked recessive manner. Global prevalence of DMD ranges from 0.9 to 16.8 every 100 thousand males. According to national data, 2000 patients are affected by this disorder in Argentina.

Contribution of the article to current knowledge

- In our epidemiological study, an unusual, high prevalence rate of DMD (0.12%) was found in children of Diaguita-Calchaquí ethnicity. Five different mutations were reported and no consanguinity was identified in pedigree charts.

Duchenne muscular dystrophy (DMD) is a severe, progressive neuromuscular disease[1] with no current curative treatment. DMD is caused by mutations in *DMD* gene, which encodes dystrophin[1]. Either frameshift or nonsense mutations in *DMD* cause premature truncation of protein translation, leading to unstable or non-functional dystrophin[1]. These structural alterations lead to sarcolemma instability, increased vulnerability to mechanical stress, and inflammation. The resulting cycles of degeneration and regeneration finally induce depletion of muscle satellite cell pools, replacement with fat, and degeneration of connective and fibroadipose tissues[2].

Clinically, patients with DMD present a progressive degeneration of skeletal muscles. Symptoms appear at around 3 years of age and affected children report difficulty in running, jumping, getting up from the ground, and a characteristic waddling gait with a positive Gowers sign[3]. Cardiac and respiratory complications are the main cause of death in patients with DMD[4].

DMD is inherited in an X-linked recessive manner. The estimated incidence is 1 in 3600 male live-born infants worldwide[5]. Global prevalence of DMD ranges from 0.9 to 16.8 every 100 thousand males[4]. According to national data, 2000 patients are affected by this disorder in Argentina[6].

Several studies have shown a relationship between consanguinity and some genetic disorders, including DMD[7]. Population of Tafí del Valle area, located in a 2000-meter-above-sea-level valley in Tucumán Province (Argentina), is mostly of Diaguita-Calchaquí ethnicity. This district is characterized by a relative geographic isolation, with only two mountain road accesses. These particularities of Tafí del Valle are also linked to a high prevalence of inbreeding.

In this context, our study goals were: 1) to describe the prevalence, and the sociodemographic and clinical characteristics of DMD patients in this population with high levels of consanguinity; 2) to explore the potential genetic relationship among diagnosed patients.

Material and methods

A descriptive, cross-sectional, epidemiological study was carried out in the Tafí del Valle Operational Area (TVOA), which included 10 primary care centers within the scope of Elías Medicci Hospital (Tucumán Province, Northern Argentina). According to the Situational Census of 2019, TVAO population was 147 660 inhabitants. Inclusion criteria were: 1) patients assisted in the local healthcare system; 2) patients permanently living in the TVOA. Subjects relocated from other districts were excluded.

Demographic data included age, gender, current address within the TVOA, and highest level of education attained. Clinical data were retrieved from medical records, including vital signs, pulse oximetry, weight, height, body mass index, nutritional status (according to the standards of the Argentine Society of Pediatrics), and comorbidities.

DMD specific data included confirmation of genetic diagnosis, disease stage (I, pre-symptomatic; II, early ambulatory; III, late ambulatory; IV, early non-ambulatory; V, late non-ambulatory), and therapeutics (drug therapy; rehabilitation; alternative medicine; nutritional support; non-invasive respiratory support, including continuous positive airway pressure devices).

Pedigree charts were developed for all patients according to the Pedigree Standardized Working Group from the National Society of Genetic Counselors recommendations[8]. Data were obtained during a clinical consultation

scheduled at the specialized Rehabilitation Service *Los Menhires* or at the patient's home. The patient, his/her legal representative, and at least the same two interviewers were present at all consultations. Possible DMD cases were considered according to genetic probability, clinical phenotype (progressive muscle weakness or early gait disturbances) and premature death (under 25 years old).

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. All the patients or their parents signed an informed consent before enrollment. Written informed consent was also obtained for the use of audiovisual material related to the study. All data were anonymized, in accordance with Argentinean personal data protection legislation. Authorization was given by the director of the TVOA for operational and statistical management of computerized data from medical records.

Our study was performed in the context of lockdown isolation during the COVID-19 pandemic.

Statistical analysis

The prevalence of DMD was calculated according to the international standards recommended for rare diseases[9]. Anonymized data was tabulated. Depending on its distribution, continuous variables were summarized using the mean, standard deviation (SD), median, range (minimum, maximum), 95% confidence interval, and the eventual number of missing data. Due to the cross-sectional, epidemiological, descriptive study design, a formal sample size calculation was not needed.

Results

Seven male patients from Diaguita-Calchaquí ethnicity were diagnosed with DMD. Median age at data cutoff was 14 years old (range: 7 to 22). Demographic data available are summarized in Table 1.

Genetic diagnosis was confirmed in all patients as shown in Table 2. General prevalence of DMD was 0.06% (7 confirmed cases for 11 521 total TVOA inhabitants). Prevalence among male population was 0.12% (7 confirmed cases for 5680 TVOA live-born males).

Three patients were categorized as stage V (late non-ambulatory), 2 subjects as stage IV (early non-ambulatory), one patient as stage II (early ambulatory), and the remaining case as stage III (late ambulatory). Height and weight were normal in 4 patients, while two were obese and the remaining subject was underweight (according to national standards). Neurological comorbidity was diagnosed in two patients: one with speech disorder and the other with mental retardation.

Current treatment is summarized in Table 3. Patients were not receiving alternative medicine, respiratory support, or nutritional support.

Five pedigree charts were performed; two pairs of patients were siblings. Data are shown in Figure 1. No family relationship was identified among the five pedigree charts. Patients #1 and #2 shared the same maternal lineage and had no

Table 1 | Demographic data of Duchenne muscular dystrophy patients

Patient	#1	#2	#3	#4	#5	#6	#7
Age (years)	14	10	21	7	22	9	12
Gender	Male	Male	Male	Male	Male	Male	Male
Highest level of education attained	Primary school (*)	Primary school	Primary school (*)	Primary school	Primary school (*)	Primary school	Primary school (*)
Address within Tafí del Valle Operational Area	El Complejo, Los Cuartos	El Complejo, Los Cuartos	El Churqui	El Potrerillo, El Mollar	Barrio Naranjita, El Mollar	Las Las Carreras	Las Las Carreras

(*) Not completed according to chronological age

DMD family history. Patient #3 had a maternal uncle with a history of DMD; his age at death was unknown. Patient #4 had no family history of DMD. Patient #5 had a second uncle with a possible diagnosis of DMD in the maternal lineage. Patients #6 and #7 were siblings and their granduncle had a possible diagnosis of DMD.

Discussion

In our descriptive, cross-sectional, epidemiological study, prevalence of DMD in TVOA was higher than globally reported. In our population, the general prevalence rate was equivalent to 60.75 cases every 100 000 inhabitants (or 123.23 every 100 000 males), at least 7 times higher than informed in current literature[4]. The highest prevalence rate was reported in Western Sweden, with 16.8 cases every 100 000 live-born males[4].

Table 2 | Genetic diagnosis of Duchenne muscular dystrophy patients (multiplex ligation-dependent probe amplification)

Patient ID	Mutation
#1	Deletion of exons 45 to 54
#2	Deletion of exons 44 to 54
#3	Deletion of exon 68
#4	Duplication of exons 2 to 25
#5	Deletion of exons 49 to 54
#6	Deletion of exons 1 to 44
#7	Deletion of exons 1 to 44

International biomedical literature describes the association of genetic disorders with consanguinity[7]. TVOA has several characteristics that would contribute to a higher probability of consanguinity, including the low number of inhabitants, its geographic isolation, and the lack of knowledge about the epidemiology of genetic disease transmissions. In addition, the low level of family planning and late diagnosis of DMD might have also contributed to the presence of more than one case per family group. Nevertheless, no consanguinity was identified among the five pedigree charts and respective mutations were identified. It is worth noting that patient #5 had deletion of exons 49 to 54 of *DMD* gene, closely resembling genetic variants of siblings #1 and #2. However, deletion clusters between exons 45 to 55 have been reported as mutational hotspots in large epidemiological samples[10], reducing the probability of a common ancestry of these subjects. We hypothesized that populational or environmental factors could be involved. In addition, potential similarities with other local populations with similar ethnical distribution should be evaluated.

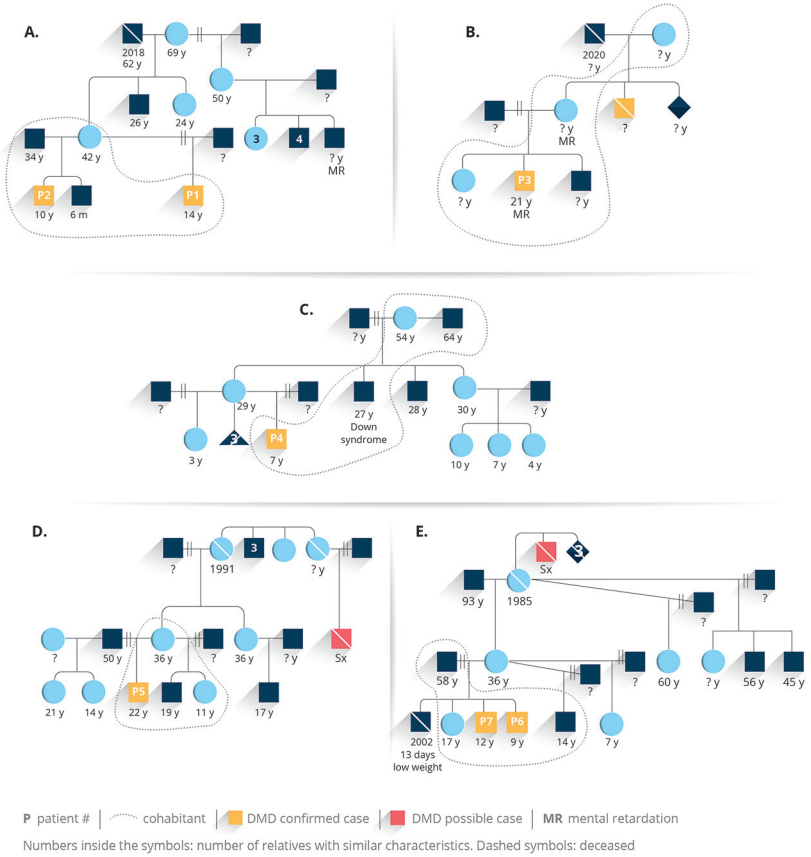
DMD should be diagnosed as early as possible in order to start interventions on the patient. Multidisciplinary management should be adapted to the patient's profile and the clinical stage[11]. The current approach includes systemic corticosteroids and physiotherapy, as well as nutritional, respiratory, cardiac, and orthopedic support[1,11]. Even though a number of pharmacological treatments aimed to restore the miss-

Table 3 | Treatment modalities

Patient ID	Rehabilitation	Drug treatment	Orthopedic treatment
#1	Telemedicine	None	Short orthotics (*)
#2	Telemedicine	None	Short orthotics (*)
#3	Integral rehabilitation	Deflazacort, vitamin D, calcium carbonate	Permanent wheelchair
#4	Integral rehabilitation	Not current (approval pending)	Short orthotics
#5	Telemedicine	Methyl prednisone, calcium, vitamin A	Permanent wheelchair
#6	Low adherence	None	Short orthotics (*)
#7	Low adherence	None	No data

(*) Wheelchair approval pending

Figure 1 | Pedigree charts for A: Patients #1 and #2 (siblings); B Patient #3; C: Patient #4; D: Patient #5; E: Patients #6 and #7 (siblings)



ing dystrophin protein or to address secondary alterations have received regulatory approval, their utility is still limited. Most patients were not receiving current recommended treatment. Family adherence and late diagnosis, among other factors, may contribute to this issue.

DMD treatment improvement has led to better life expectancy, and caregiving of affected patients is also evolving. As a consequence, families and caregivers need to receive the required information to manage care strategies and improve DMD quality of life[12].

Limitations of this research include the cross-sectional design and sample size. Nevertheless, this study shows clinically and genetically characteristics of a population with a high prevalence of DMD, an infrequent neuromuscular disorder with severe complications that leads to premature death. There is no current cure for this disease, but multidisciplinary strategies may delay the natural progression of DMD and the onset of complications. Our study adds new data about local DMD epidemiology, highlighting the importance of early diagnosis.

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Conflicts of interest: None to declare

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