ORIGINAL ARTICLE

Age of diagnosis of Duchenne muscular dystrophy in Peru 2023: a transversal study

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ABSTRACT

Background: Duchenne muscular dystrophy (DMD), a progressive neuromuscular disease, usually manifests before the age of 5. In low- and middle-income countries, diagnosis is often delayed compared with high-income countries. This difference in the diagnosis timing could influence the disease's management and prognosis.

Objective: The study aimed to determine the age of diagnosis of DMD in Peruvian patients treated in a high-complexity hospital or belonging to independent associations.

Methods: Descriptive study through a survey of patients diagnosed with DMD.

Results: 95 patients were included with a mean age of 12.4 years (range 3-34). The mean age at diagnosis of DMD was 8.1 years (range 7 - 307 months); in patients younger than ten years, the mean age was 4.9 years, and in those older than ten years, the mean age was 9.7 years. The mean age of first attendance to the healthcare system for symptoms related to DMD was 43.34 months (range 5-216), and the most common symptoms that prompted were motor or gait difficulties and frequent falls. At the first consultation, 47.4% were seen by a pediatrician, who dismissed the symptoms in 44.4%, and only 11% requested creatine kinase. The mean time from first consultation to diagnosis was 4.4 years. Genetic findings included deletions in 46.3% of cases, duplications in 16.8%, and point mutations in 36.8%.

Conclusions: The mean age of definitive diagnosis of DMD in Peruvian patients is 8.1 years, although the diagnosis tends to be made earlier in children under ten years of age. This suggests that the detection of DMD in Peru has improved in the last decade, leading to a timelier diagnosis.

Keywords: Muscular Dystrophy, Duchenne; Diagnosis (Source: MeSH)

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Edad de diagnóstico de distrofia muscular de Duchenne en Perú 2023: un estudio transversal

RESUMEN

Introducción: La distrofia muscular de Duchenne (DMD), una afección neuromuscular progresiva, se manifiesta comúnmente antes de los 5 años de edad. En los países de bajos y medianos ingresos, el diagnóstico suele ser más tardío en comparación con los países de altos ingresos. Esta diferencia en la oportunidad del diagnóstico podría influir en la gestión y el pronóstico de la enfermedad.

Objetivo: El estudio se enfocó en determinar la edad de diagnóstico de la DMD en pacientes peruanos atendidos en un hospital de alta complejidad o aquellos pertenecientes a asociaciones independientes. Métodos: Estudio descriptivo mediante encuesta a pacientes con diagnóstico de DMD.

Resultados: Se incluyó a 95 pacientes con edad promedio de 12,4 años (rango 3-34 años). La edad media de diagnóstico de DMD fue 8,1 años (rango 7-307 meses), en los pacientes menores de diez años la edad promedio fue de 4,9 años y en los mayores de diez años fue 9,7 años en promedio. La edad de primera atención en el sistema de salud por síntomas relacionados con la DMD fue en promedio 43,34 meses (rango 5-216 meses), los síntomas más frecuentes que motivaron la primera consulta fueron retraso motor o de la marcha y caídas frecuentes. En la primera consulta al sistema de salud el 47,4% fueron atendidos por pediatras, quienes desestimaron los síntomas en 44,4% de casos y sólo en 11% solicitaron creatina quinasa. El tiempo transcurrido entre la primera consulta y el diagnóstico fue en promedio 4,4 años. En cuanto a los hallazgos genéticos, se observó deleción en 46,3% de los casos, duplicación en el 16,8% y mutaciones puntuales en el 36,8%.

Conclusiones: La edad promedio de diagnóstico definitivo de DMD en pacientes peruanos es de 8,1 años, aunque en menores de diez años, el diagnóstico tiende a realizarse a una edad más temprana. Esto sugiere que, en la última década, la detección de la DMD en Perú ha mejorado, logrando un diagnóstico más oportuno.

Palabras clave: Distrofia muscular de Duchenne; Diagnóstico (Fuente: DeCS)

INTRODUCTION

Duchenne and Becker muscular dystrophy (DMD) results from mutations in the DMD gene located on chromosome Xp21.1. This is the longest gene in the human genome and has 79 exons encoding dystrophin, a protein essential for muscle integrity. In DMD, symptoms and signs usually present before the age of 5 years and most frequently include skeletal muscle and cardiac involvement and sometimes intellectual disability. Delayed gait acquisition, Gowers' sign, pseudohypertrophy of the calves, and increased creatine kinase (CK) levels are commonly observed. During adolescence, patients often develop contractures and scoliosis, facing cardiac and respiratory complications that are often causes of mortality at this stage.

In 2013, the prevalence of DMD in England was reported to be 19.5 per 100,000 male newborns (1). A previous European study estimated the incidence of DMD at approximately 1 in 3,500 (2.9 per 10,000) live male births, and for BMD, 1 in 18,518 (0.5 per 10,000) live male births (2). Becker muscular dystrophy is a less severe allelic variant of the disease, characterized by a later presentation and a lower incidence.

The mutations causing dystrophinopathies are single or multiple exonic deletions or duplications, which can be detected by MLPA or multiplex ligation-dependent probe amplification (3). In contrast, small mutations, intra-exonic deletions or insertions, and point mutations (nonsense or missense) are detected by next-generation sequencing (NGS) (4-6). In worldwide studies involving hundreds or thousands of patients, deletions were found in 68 to 72% of cases and duplications in 7 to 11% of cases. In 20% of cases, small deletions, intraexonic insertions, and point mutations (nonsense or missense) detected by next-generation sequencing have been reported (7,8).

In developed countries, neuromuscular diseases are approached by multidisciplinary teams in referral centers where patients can access evaluations by highly specialized personnel and diagnostic support studies such as biochemical studies, histopathological studies, muscle imaging, and molecular-genetic tests. So, in particular, in the case of Duchenne muscular dystrophy, most patients are usually diagnosed between 4 and 5 years of age (9,10). In addition to having a diagnosis at an early age, these countries have an adequate registry of patients with dystrophinopathy, which makes it possible to know the number of affected patients, their geographical distribution, the natural history of the disease, the phenotype-genotype correlation, and to select patients for specific therapies and follow-up by multidisciplinary groups.

The age at which the definitive diagnosis of DMD is reached in developed countries and where there is full access to diagnostic methods is between 4 to 5 years (9,10). In various diagnostic studies, average ages of 41 months are reported in Italy (11), 4.9 years in the USA (12), and 7 years in Brazil (13), while in countries such as Colombia, the average age is 9.45 years (14). In our country, the age of definitive diagnosis reported in 2021 by Guevara-Fujita (15) was 9.8 years, and a sample of patients referred from national hospitals between 2015 and 2018 was included. This delay in diagnosis has been reported in several countries. It is often due to the lack of knowledge of the signs and symptoms on the part of the family and often the lack of suspicion of the disease by health personnel who provide their services at the first level of care (16). Early and accurate diagnosis plays a crucial role in the effective management of the case since it allows early intervention, genetic counseling to the family, a plan to prevent complications, and treatment with specific therapies for the mutation found. However, many of the patients are diagnosed when they are already confined to a wheelchair or complicated with severe scoliosis or cardiac or pulmonary failure. While it is true that these events are part of the natural course of the disease, the treatments available promptly allow for extended ambulation time, prevention of many complications, and a better quality of life. The present research study was carried out to determine the age of confirmatory diagnosis and the clinical characteristics of children treated in the last 5 years in a high-complexity hospital and patients of Peruvian associations related to muscular dystrophies.

Methods

Design

The present descriptive cross-sectional study.

Participants

Patients with a diagnosis of DMD or caregivers of patients with a diagnosis of DMD who are cared for in a high-complexity hospital and those who were on the list provided by the Society of Peruvian patients who have this diagnosis were interviewed. Incidental non-probabilistic sampling was used. The interview was conducted via telephone or video call (via Zoom).

Instruments

During the interview, demographic data were collected, including symptoms present and reasons for which they went to the health system, age at which they went to the health system for symptoms related to DMD, the professional who attended them, the action taken by this professional and the time elapsed from the time they arrived at the health system until obtaining the definitive diagnosis (this was considered the date of the genetic result). For siblings or uncles who did not yet have a confirmatory genetic diagnosis but had symptoms, the age of diagnosis and the date of the genetic result of the patient attended were considered. Creatine kinase levels, the age at which this study was performed, and the type of genetic mutation found were also recorded.

Procedures

All these data were recorded in an anonymized file and entered into a database in RedCap, after which a second

quality control of the data obtained was carried out, ensuring that the database was correctly filled in. The information was collected with prior informed consent from February to July 2023.

Analysis plan

Data were analyzed using version 18 of the Statistical Package for the Social Sciences (SPSS). Measures of central tendency (mean, median) and dispersion (standard deviation, 25th percentile, 75th percentile, minimum, and maximum) were calculated for quantitative variables and frequencies and percentages for qualitative variables. In addition, a scatter plot was performed where the X axis is the age in months at which the CK test was performed for the first time, and the Y axis is the value of the CK test. However, statistical hypothesis testing was not performed.

Ethical aspects

The Institutional Research Ethics Committee of the Instituto Nacional de Salud del Niño San Borja approved the study.

RESULTS

The characteristics of 95 patients included in the study were analyzed; 26 came from a high-complexity hospital in the city of Lima, and 69 belonged to a society of patients with a diagnosis of DMD. The mean age of those evaluated was 12.41 years (SD = 5.74; range 3-34 years). The mean age in months at their first consultation with the health system for symptoms related to Duchenne muscular dystrophy was 43.34 months (SD = 36.82; range 5-216 months; Median = 30 months). The most frequent symptoms that motivated that first consultation were motor or gait delay and frequent falls (see Table 1).

Table 1. Analysis of multiple responses on symptomatology that warranted the first consultation in the health system in patients with a definitive diagnosis of Duchenne muscular dystrophy

	n	%
Motor or running delay	46	48,4%
Frequent falls	30	31,6%
Walking on tiptoe	14	14,7%
Difficulty climbing stairs	13	13,7%
Anserine March	12	12,6%
Delayed language development	9	9,5%
Sign of Gowers	5	5,3%
Pseudo hypertrophy of calves	3	3,2%
Autism spectrum	2	2,1%
Others	19	20.0%

***Note**: Percentage of responses calculated based on the total number of cases analyzed (n=95 patients)*

In 19 cases, the reason for the first consultation was due to a history of a relative with a diagnosis of muscular dystrophy (siblings in 11 cases, cousins in 2 cases, and uncles in 5 cases), and in one case increased CK was found incidentally during a digestive episode, after which he was referred to neurological studies.

Most of the patients were seen by pediatricians (n=45; 47.4 %) and traumatologists (13; 13.7 %) at the first consultation. The action taken by the health professionals was to dismiss the symptoms in 24.2 % of the cases, refer to another specialist in 22.1 % of the cases, wait and observe in 36.8 % of the cases, and request CK in 16.8 %. Table 2 shows the analysis of the percentage of cases attended and the action taken according to the professional. We observed that a pediatrician attended 47.4 % (45/95) of the cases, and the action taken by them in this group of children was to dismiss the symptoms present in 44.4 %, wait and observe in 15.6 %, refer to a specialist in 28.9 % and request CK only in 11.1 %.

Table 3 shows the clinical characteristics observed at the time of consultation or present during the evolution of the disease, highlighting the difficulty in climbing stairs (95.8%), Gowers' sign (95.8%), and rocking gait (91.6%).

The average age at trunk control was 10.92 months (SD = 10.36; range 5-96 months). The mean age in months at which patients achieved independent walking was 20.52 (SD = 10.98; range 12-108 months), and the mean age at which they developed language was 21.93 months (SD = 17.08; range 8-96 months).

The age at which the creatine kinase study was performed for the first time was 69.71 months (SD = 43.3; range 6-250 months), and the mean value of creatine kinase found was 14 276.78 U/L (SD = 8 830.25; range 2800-40000 U/L). Figure 1 shows the inverse relationship between age and CK values, i.e., the younger the age, the higher the CK value.

The average age at which they had a definitive diagnosis of DMD/BMD with genetic confirmation was 8.1 years (range 7 months-25 years; Median = 7.3 years). When performing a stratified analysis by age group, for children aged 10 years or younger, the mean age at which they had a definitive diagnosis of DMD/BMD with genetic confirmation was 4.9 years or 58.31 months (SD = 28.16; range 7-106 months; Median = 56 months), while for participants aged 11 years or older, the mean age of definitive diagnosis was 9.7 years or 116.11 months (SD = 63.89 months; range 15-307 months; Median = 108 months). On the other hand, the time between the first consultation and definitive diagnosis was 4.4 years on average. In particular, in patients with 10 years or less, it was 2.7 years or 32.59 months on average (SD = 26.16; range 0-86 months), and in patients with 10 years or more, it was 5.5 years on average or 66.59 months (SD = 48.38; range 0-227 months).

In addition, 10 patients had the Becker phenotype, and 85 had the Duchenne phenotype. The type of mutation found in these patients was deletion in 46.3 %, point mutation in 36.8 %, and duplication in 16.9 %.

Table 2. Type of personnel who attended patients with a definitive diagnosis of Duchenne muscular dystrophy in the health system and action taken (n=95)

Health personnel who attended	Total		Action taken by health personnel who attended for the first time							
			Disregarding symptoms		Waiting and watching		Refer specialist to another level of care		Request CK	
	n	%	n	%	n	%	n	%	n	%
Pediatrician	45	47,4%	13	28,9%	20	44,4%	7	15,6%	5	11,1%
Traumatologist	13	13,7%	1	7,7%	5	38,5%	7	53,8%	0	0.0%
Nurse	7	7,4%	3	42,9%	3	42,9%	1	14,3%	0	0.0%
General Practitioner	5	5,3%	3	60,0%	1	20,0%	1	20,0%	0	0.0%
Physician of Physical Medicine and Rehabilitation	5	5,3%	0	0,0%	1	20,0%	3	60,0%	1	20,0%
Others	20	21,1%	3	15,0%	5	25,0%	2	10,0%	10	50,0%

***Note**: CK = Creatine kinase*

Table 3. Multiple response analysis of symptomatology present in patients with a definitive diagnosis of Duchenne muscular dystrophy at the time of consultation or in the evolution of the disease

Symptoms and signs present	n	%
Sign of Gowers	91	95,8%
Difficulty climbing stairs	91	95,8%
Tilting gear	87	91,9%
Frequent falls	83	87,4%
Walking on tiptoe	81	85,3%
Pseudohypertrophy of calves	73	76,8%
Motor or running delay	73	76,8%
Delayed language development	38	40,0%
Autism spectrum	11	11,6%

***Note**: Percentage of responses calculated based on the total number of cases analyzed (n=95 patients)*

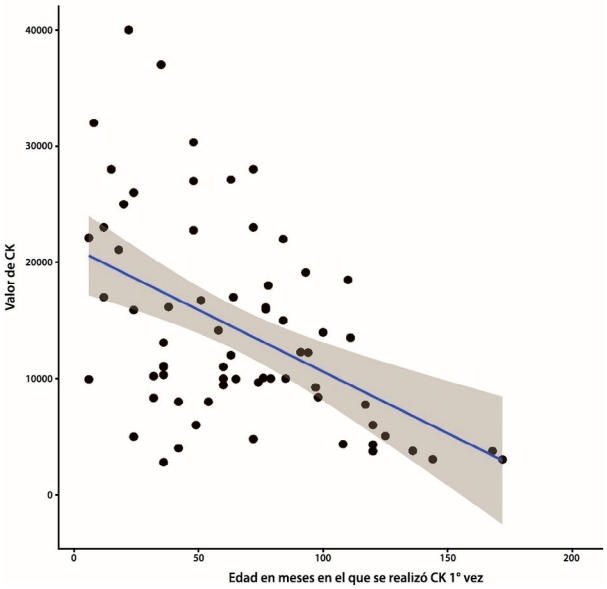

Figure 1. Relationship between creatine kinase (CK) value and age (in months) in patients with DMD

DISCUSSION

Duchenne muscular dystrophy (DMD) is an X-linked hereditary disease and is the most common muscular dystrophy in childhood. It starts with symptoms within the first years of life and is progressive. In their natural course toward adolescence, they lose their gait; in addition, they present cardiac, orthopedic, and respiratory complications. In developed countries, DMD is usually diagnosed between 4 and 5 years of age (9,10). Our study identified that the age of diagnosis was 8.1 years; although it is a late age, it is a little below what was recently reported by Guevara-Fujita et al. (15) in a research study at San Martin University conducted between August 2015 and June 2018, showing average age of diagnosis 9.8 years. This delay in diagnosis is shared with other countries, such as Colombia, where the average age of diagnosis is 9.45 years (14), while in Brazil, the age is 7 years (13). However, it is essential to highlight that in the group of patients included in our study, the age of diagnosis in patients aged 10 years or less was 4.9 years, which suggests that in recent years in Peru, DMD has been diagnosed earlier. The present study is the first in the country that attempts to analyze the factors of delay in the diagnosis of DMD. According to the results, a high percentage of patients presented late for consultation, with an average of 3.6 years or 43.34 months (5-216 months). On the other hand, in 24.2% of the cases in this study, the signs observed by the parents were disregarded by the health personnel who chose to wait and observe, which led to a delayed diagnosis. We emphasize that most of them went to a pediatrician, and in 28.9% of the cases, the symptoms were dismissed, and creatine kinase levels were only requested in 11.1% of the cases in the first consultation.

Gait delay, frequent falls, and tiptoeing were frequent signs reported by parents and are signs of early and frequent presentation in DMD. In the evaluation of developmental

milestones, we observed that the average age at which gait was achieved was 20.5 months (12-48 months), a sign that stands out and, therefore, an opportunity to evaluate these cases with the suspicion of a neuromuscular problem.

The creatine kinase study, a very useful diagnostic support study in this disease, of low cost and available in almost all level II and higher care centers, was requested in only 16/95 (16.8%) patients in the first consultation. According to the personnel who attended this first consultation, CK was requested in only 11.1% (5/45) of the patients attended by a pediatrician. No CK analysis was requested when a traumatologist or general practitioner provided the first care; none requested CK, and CK analysis was only requested in one patient when the evaluation was performed by a physical medicine and rehabilitation physician.

The mean age at which the CK study was requested was 69.71 months. The creatine kinase value in DMD is expected to be elevated by 10 to 100 times the average value, and in this series, the range was from 2800 to 40000 U/L. We should mention that the high variation in CK value could be due to age, as previous studies show an inverse relationship between CK value and age (17).

The time between the first consultation and the definitive diagnosis was 53.3 months, with an average delay in diagnosis of 4.4 years once parents brought their children to the Peruvian health system. We should mention that in the state health system only from 2019, the San Borja National Institute of Child Health will perform the multiplex ligation-dependent probe amplification study, the molecular genetic test used for definitive diagnosis, and in the case of this test being negative, sequencing is performed outside the institution. Before 2019, access to these diagnostic tests was restricted to sending samples to laboratories abroad or entering research studies that offered them. Regarding genetic results, a difference in point estimation was observed in relation to what was reported globally (7,8), in which 66-69 % of cases were due to exonic deletions, 11 % of cases to exonic duplications, and 20 % point mutations. In our study, 46.3 % of cases were due to exonic deletions, 16.8 % to exonic duplications, and 36.8 % to point mutations.

The genetic variation in our study varies with that reported by Guevara-Fujita et al. (15), whose study was carried out in a Peruvian population. In that group, 41.6 % correspond to deletions, 16 % to duplications, and 27.2 % to point mutations, with the most significant difference with our study being noted in the percentage of point mutations. Efforts are currently being made in other institutions to have molecular-genetic testing available for DMD and other diseases on the list of rare and orphan diseases. Therefore, the clinical practice needs to recognize the signs and symptoms that these patients present at early ages to have an accurate and timely diagnosis, thus establishing a crucial role in the effective management of the case since it allows early intervention and genetic counseling to the family, a plan for the prevention of complications and treatment with specific therapies about the mutation found.

The main limitation of this study is that the results are not generalizable to other settings where adequate equipment and supplies for the genetic diagnosis of DMD are unavailable.

In conclusion, the age of diagnosis of Duchenne/Becker muscular dystrophy in Peruvian patients is late (8.1 years), although lower than that observed in a previous study (9.8 years) (15). The factors for delay in diagnosis identified were late visits to the health care system, non-recognition of the disease by health care personnel, failure to perform the CK study, and late confirmatory studies. Point mutations are more frequent than in studies reported in other countries (7,8). This first study will serve as a tool to propose solutions at those levels where work must be done to achieve adequate access to the health system; early recognition and diagnosis of the disease by health personnel will generate the opportunity for a multidisciplinary approach to managing this pathology.

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Authorship contributions: PCME conceptualized, designed, conducted the study research methodology, analyzed the data, drafted, reviewed, and edited the final report. WMOA collaborated in the data analysis, drafted and revised the final report. The authors approved the version submitted for publication.

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REFERENCES

1. Moat SJ, Bradley DM, Salmon R, Clarke A, Hartley L. Newborn bloodspot screening for Duchenne muscular dystrophy: 21 years experience in Wales (UK). Eur J Hum Genet. 2013;21(10):1049-53. doi: 10.1038/ejhg.2012.301
2. Emery AE. Population frequencies of inherited neuromuscular diseases-a world survey. Neuromuscul Disord. 1991;1(1):19-29. doi:10.1016/0960-8966(91)90039-u
3. Sellner LN, Taylor GR. MLPA and MAPH: new techniques for detection of gene deletions. Hum Mutat. 2004;23(5):413-9. doi: 10.1002/humu.20035
4. Wang Y, Yang Y, Liu J, Chen XC, Liu X, Wang CZ, et al. Whole dystrophin gene analysis by next-generation sequencing: a comprehensive genetic diagnosis of Duchenne and Becker muscular dystrophy. Mol Genet Genomics. 2014;289(5):1013-21. doi: 10.1007/s00438-014-0847-z
5. Wei X, Dai Y, Yu P, Qu N, Lan Z, Hong X, et al. Targeted next-generation sequencing as a comprehensive test for patients with and female carriers of DMD/BMD: a multi-population diagnostic study. Eur J Hum Genet. 2014;22(1):110-8. doi: 10.1038/ejhg.2013.82
6. Okubo M, Minami N, Goto K, Goto Y, Noguchi S, Mitsuhashi S, et al. Genetic diagnosis of Duchenne/Becker muscular dystrophy using next-generation sequencing: validation analysis of DMD mutations. J Hum Genet. 2016;61(6):483-9. doi: 10.1038/jhg.2016.7
7. Bladen CL, Salgado D, Monges S, Foncuberta ME, Kekou K, et al. The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. Hum Mutat. 2015;36(4):395-402. doi: 10.1002/humu.22758

8. Aartsma-Rus A, Van Deutekom JC, Fokkema IF, Van Ommen GJ, Den Dunnen JT. Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule. Muscle Nerve. 2006;34(2):135-44. doi: 10.1002/mus.20586
9. Aartsma-Rus A, Hegde M, Ben-Omran T, Buccella F, Ferlini A, Gallano P, et al. Evidence-Based Consensus and Systematic Review on Reducing the Time to Diagnosis of Duchenne Muscular Dystrophy. J Pediatr. 2019; 204:305-13.e14. doi: 10.1016/j.jpeds.2018.10.043
10. Vry J, Gramsch K, Rodger S, Thompson R, Steffensen BF, Rahbek J, et al. European Cross-Sectional Survey of Current Care Practices for Duchenne Muscular Dystrophy Reveals Regional and Age-Dependent Differences. J Neuromuscul Dis. 2016;3(4):517-27. doi: 10.3233/JND-160185
11. D'Amico A, Catteruccia M, Baranello G, Politano L, Govoni A, Previtali SC, et al. Diagnosis of Duchenne Muscular Dystrophy in Italy in the last decade: Critical issues and areas for improvements. Neuromuscul Disord. 2017;27(5):447-51. doi: 10.1016/j.nmd.2017.02.006
12. Ciafaloni E, Fox DJ, Pandya S, Westfield CP, Puzhankara S, Romitti PA, et al. Delayed diagnosis in duchenne muscular dystrophy: data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). J Pediatr. 2009;155(3):380-5. doi: 10.1016/j.jpeds.2009.02.007
13. Prufer de Queiroz Campos Araújo A, Castro de Deco M, de Sá Klôh B, Rangel da Costa M, Veiga de Góis F. Diagnosis delay of Duchenne Muscular Dystrophy. Rev Bras Saude Mater Infant. 2004;4(2):179-83. doi:10.1590/S1519-38292004000200008
14. Eslava-Otálora A. Registro de pacientes con distrofinopatías en Colombia [Tesis de Maestría en Internet]. Bogotá: Universidad del Rosario; 2016 [citado el 20 de octubre de 2021]. Disponible en: https://repository.urosario.edu.co/bitstream/handle/10336/12351/REGISTRO%20DE%20PACIENTES%20CON%20DISTROFINOPAT%c3%8dAS%20EN%20COLOMBIA.pdf?sequence=1&isAllowed=y
15. Guevara-Fujita ML, Huaman-Dianderas F, Obispo D, Sánchez R, Barrenechea V, Rojas-Málaga D, et al. MLPA followed by target-NGS to detect mutations in the dystrophin gene of Peruvian patients suspected of DMD/DMB. Mol Genet Genomic Med. 2021;9(9):e1759. doi: 10.1002/mgg3.1759
16. Van Ruiten HJ, Straub V, Bushby K, Guglieri M. Improving recognition of Duchenne muscular dystrophy: a retrospective case note review. Arch Dis Child. 2014;99(12):1074-7. doi: 10.1136/archdischild- 2014-306366
17. Zatz M, Shapiro LJ, Campion DS, Oda E, Kaback MM. Serum pyruvate-kinase (PK) and creatine-phosphokinase (CPK) in progressive muscular dystrophies. J Neurol Sci. 1978;36(3):349-62. doi: 10.1016/0022-510x(78)90043-6