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Abstract

Abstract: Hypothesis: This study represents a second part of a study recently published about a new form of evaluation and flow-up of rare genetic neurodegenerative disease. The objetive is to provide a more global vision of thermography with respect to Emery-Dreifuss pathlogy, through the analysis of the data collection carried out during one year. The basic hypothesis is that thermography could become a valid tool for the diagnosis and follow-up of this pathology because is a very specific tool to register temperature´s changes produced by a constant degenerative evolution of this muscular dystrophy. keyword: Thermography, Emery-Dreifuss, Muscular dystrophy.

Taxonomy	Musculoskeletal Medicine, Medicine, Neurosurgery, Pathophysiology, Pathology

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There are no linked research data sets for this submission. The following reason is given:
No data was used for the research described in the article

August 26th 2020

The Managin Editor

Medical hypotheses

Dear Editor,

Please find attached the preliminary study entitled "**Relationship between infrared skin radiation and functional tests in patients affected by Emery-Dreifuss muscular dystrophy: Part 2.**" This original second part of anterior study published in this journal, is submitted to Medical hypotheses, as part of the research topic: **"Thermographic patterns in people affected by Emery-Dreifuss muscular dystrophy".**

This work has been conducted as one-year observational study in Emery-dreifuss pathology and there aren't other previously works with these characteristics. **The first, the second and the third articles published about this line of research belongs to your magazine.**

There is an urgent need to research different form to asses and follow Emery-Dreifuss muscular dystrophy (EDMD; MIM 310300). The thermography is a rapid, not invasive, easy to use and objective technique, which analyzes the temperature of the examined tissue. Since in the alterations of the skeletal muscle system there are possibility to observe change in temperature, volume and density of the affected area, we hypothesized that the patient with Emery-Dreifuss muscular dystrophy would suffer continue changes of temperature with the evolution of the disease.

The evolution of the disease can be observed with diagnostic machine as thermography or functional test. However, both parameters have not been studied together in patients with this characteristic up to now.

In this study, we compared one year the use of thermography and funtional test in lower extremities in four affected patients of Emery-Dreifuss muscular dystrophy to support and justify the use of this technique for the proposed objective. The main strength of this work is its novelty; since this pathology has scarcely studied with thermography.

The manuscript has been prepared according to the journal's Instructions for Authors. We believe that this new work is within the scope of your journal and makes an important contribution to the future works in this area.

We hope that you will consider this manuscript for publication.

We await your response and the comments of reviewers.

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of Conflicts of Interest: None of the authors has any conflict of interest to disclose.

Yours sincerely,

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August 26th 2020

The Managin Editor

Medical Hypoteses

Dear Editor,

Highlights:

1. It is the first time that thermography and functional test has been used in this type of patient to evaluate one-year of the disease.

2. There is an important correlation of thermography and functional test during one year.

3. The proposed study presents aspects that can be improved through future research in other pathology, work and new theories on which to base others

Title:

Relationship between infrared skin radiation and functional tests in patients affected by Emery-Dreifuss muscular dystrophy: Part 2.

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Abstract: Hypothesis: This study represents a second part of a study recently published about a new form of evaluation and flow-up of rare genetic neurodegenerative disease. The objetive is to provide a more global vision of thermography with respect to Emery-Dreifuss pathlogy, through the analysis of the data collection carried out during one year. The basic hypothesis is that thermography could become a valid tool for the diagnosis and follow-up of this pathology because is a very specific tool to register temperature´s changes produced by a constant degenerative evolution of this muscular dystrophy. **keyword:** Thermography, Emery-Dreifuss, Muscular dystrophy.

Ethical publication statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declarations of interest: none.

Equal contribution: These authors contributed equally to this work.

Abbreviation:

BMI: Body Mass Index
EDMD: Emery Dreifuss muscular dystrophy
TAC: Computed Axial Tomography
IRT: Infrared thermography
TISEM: Thermographic Imaging in Sports and Medical Exercise

1. Background and Hypothesis.

Emery-Dreifuss muscular dystrophy (EDMD MIM 310300) is a rare neurodegenerative disease of a genetic nature [1-3]. The etiology and epidemiology of this disease have changed over time with respect to its first appearance, described by Emery AE and Dreifuss FE in the mid-1960s [4-6]. With regard to pathophysiology, research on this disease has shown the presence of joint range limitations, muscle wasting and weakness, and cardiac abnormalities that can lead to death if not treated correctly [1-6]. Since all patients suffer cardiac alterations that in many cases lead to the implantation of an internal defibrillator, quantifying the progress of the disease by means of the most used diagnostic techniques (CT, MRI and ultrasound) is a process in some cases very long and complicated. If, on the one hand, MRI seems to be the most successful technique to show muscle injuries, not all defibrillators are compatible with the electromagnetic field generated by this technique, thus posing a great risk for patients. [7.8]. The CT and ultrasound then seem to be the most successful options, however, the high radiation emissions, the impossibility of analyzing large muscle regions simultaneously, the high cost of these two techniques and the long time they require to perform them, make these two not very functional elements to quantify this disease quickly, economically and objectively. To this end, there is already a growing scientific information regarding the use of thermography in these types of patients. According to these studies, it is possible to quantify the neurodenerative nature of the disease based on the analysis of infrared radiation emitted by the regions analyzed in these patients [7-9]. Considering that infrared radiations are electromagnetic elements common to all bodies that have a temperature above 0 degrees Kelvin and that the higher the temperature of an object, the more infrared radiation it is possible to record [9-12], there is no doubt that the trophic nature of the disease could be quantifiable as vascular scar tissue increases versus normally vascularized muscle tissue. In order to confirm this hypothesis, very recent studies have been carried out regarding the relationships between CT and thermography and thermography with stress tests in these types of patients. Despite the fact that these very recent observational studies use a small sample of patients, they are undoubtedly laying the foundations for a new line of research, so a longitudinal study could represent a further advance in this regard [13, 14]. Accordingly, we have carried out a study of one-year evolution of this disease using thermography in a family of 4 siblings affected by Emery-Dreifuss muscular dystrophy in order to clarify and better explain the possible pre-established correlation between the neurodegenerative nature of the disease with respect to the emission of infrared waves. This study represents a second part of a study recently published by Cabizosu et al. entitled: “Relationship between infrared skin radiation and functional tests in patients affected by Emery-Dreifuss muscular dystrophy” [14]. The objective of this work is then to provide a more global vision of this technique with respect to this disease through the analysis of the data collection carried out during one year.

2. Testing de hypothesis.

This, being a one-year longitudinal study of evolution, in order to be as reliable and precise as possible, we have carefully followed the same work protocol of previous studies [13-15]. As in previous works, with respect to the sample, the machine, the imaging protocol, the organization of the patients, and the tests carried out, we have based ourselves on the TISEM (Thermographic Imaging in Sports and Medical Exercise) and the bibliography already exists [14,15]. As in previous works, with respect to the sample, the machine, the imaging protocol, the organization of the patients, and the tests carried out, we have based ourselves on the TISEM (Thermographic Imaging in Sports and Medical Exercise) and the bibliography already exists [14,15],

• Patients, room, thermographer and functional test:

The study sample and the room have used on this occasion were the same as the one provided for the study by Cabizosu et al. [14]. The only differences registered with the previous study were age, since in this case all the patients are one year older (median age 31 years) and the BMI variable in patient number 2 that suffered an increase in weight of 10.4 kg, being the BMI of the previous study of 34.37 and now 38.27 [14]. In order to eliminate all those aspects that could influence the collection of thermographic data, the same protocol was followed with respect to acclimatization of the patients and the environment, conducting an interview prior to taking the image for 20 minutes at a temperature constant between 23 ° and 24 °, with a room humidity of 40%, (± 0.8) and an atmospheric pressure of 0.98. On the other hand, the thermograph used, the Flir E60 model, and the image analysis program, “Flir researchIR” were the same as the work previously cited [13,14]. In addition to the “Flir researchIR” program, an application created by our group regarding the elaboration and overlapping of the images of the 2 different years was used. The ROIs used were also the same as in the study by Cabizosu et al. [13-14]. In fact, 3 different shots of 4 images of the lower limbs were recorded at the level of the thigh (quadriceps and hamstring region) and leg (tibial and calf region) [13-14]. A researcher specialized in thermography and a doctor specialized in radiological techniques were in charge of the realization and analysis of the images in a blinded manner. Regarding the Chair Stand Test 30-S, the recommendations given, the material, the room and its distribution were the same as the previous study [13-14].

- **Images analysis.**

This work analyses the evolution of the temperature at each point of the muscles of the patients. It is important to highlight that the pairs of images have been taken in the interval of one year, thus the exact position of the patients as well as other parameters of the camera can vary in the data acquisition process. Therefore, to apply this longitudinal study, some medical image processing techniques need to be applied to infrared images. First, a histogram equalization is applied to the pairs of images to preserve the mapping between pixel values and temperature values [16]. Second, an intensity-based image registration in intensity is performed to obtain an appropriate similarity between the images acquired in 2018 and 2019 [17,18]. Note that this process applies an affine transformation to the 2019 images to maximize their overlap with the 2018 images. Finally, the difference between the pairs of images is calculated. This allows us to determine the temperature increase, positive or negative, at each point in the muscle during this period.

3. Data of the test.

The following images show the evolution of the diseases according to the thermographic images. Such images are organized from the youngest age of the first patient to the oldest in the fourth.

Figure 1. 2018 (Violet) and 2019 (Green) thermographic images of the anterior and posterior thigh of the 4 patients.

Figure 2. 2018 (Violet) and 2019 (Green) thermographic images of the anterior and posterior leg of the 4 patients.

Table 1. *Data corresponding to the evolution of the average temperature (° C) measured in the regions of interest selected in figures 1 with one year of evolution.*

Table 2. *Data corresponding to the evolution of the average temperature (° C) measured in the regions of interest selected in figures 2 with one year of evolution.*

Table 3. *Data corresponding to the stress test with one year of evolution.*

4. Discussion.

Because our thermograph is capable of collecting a temperature difference of up to 0.5 C, this value has been established as significant in the analysis of the data and observing tables 1 and 2, with respect to the anterior and posterior portion of the thigh and the leg, we observe that, in almost all cases, there is a significant decrease in temperature after one year of disease evolution. If we rely on the existing scientific literature and in particular on the findings of Cabizosu et al. in his studies carried out on this type of patients with CT scan and thermography, and with thermography and strength tests in the lower limbs, we can understand and justify the results obtained in our study [13,14]. As we can see in images 1 and 2, the patient with the lowest mean temperature is patient number 4, and also, as reflected in table 3, is the one who performs the least number of repetitions in the Chair Stand Test. This is probably due, as already expressed by Cabizosu et al, because being the most adult patient and Emery-Dreifuss muscular dystrophy being a neurodegenerative disease, it is the patient with the highest degree of muscle atrophy [13,14]. Numerous authors, who have used this test for the evaluation of strength in the lower limbs, have shown that the greater the number of repetitions, the greater the force presented by the evaluated, in fact, Jones et al, through this test, were the first to mark a functional correlation in healthy patients between the evolution of age and the decrease in strength [19-21]. Recent studies carried out by means of this test and thermography, for the evaluation of Emery-Dreifuss muscular dystrophy, concluded that, the greater atrophy, the lower the motor response, that is to say, fewer repetitions in this type of test [13-14]. Such hypothesis is once again corroborated in this study, where after one year of evolution, as expressed in Table 3, we can see that the tendency of patients is to experience a decrease in temperature accompanied by a decrease in strength as the disease evolves. However, it should be noted that there is an exception represented by patient number 2 who, with a slight increase in temperature and, also as we can see in Table 3, has a decrease in the functional test of strength in lower extremities equal to his respective older brother. This result has already been previously discussed by Cabizosu et al, who in their 2020 study already evidenced, based on the bibliography, how there is a close relationship between a higher BMI and lower strength performance, even this type of patient [14,22-24]. The sudden change in BMI by patient number 2 could be a clear sign of how a weight gain of more than 10 kg influences strength and motor response. For this purpose, because the muscular system, the tendon system and the ligamentous system are the architects of movement and body stability, and that even weight gain affects these structures, there is no doubt that there is no doubt that the relationship BMI - Emery-Dreifuss should be the basis of the evolutionary follow-up of the patients. Due, on the one hand, to the rare nature of the disease, which affects the small number of cases and, on the other, to the different form of expression of Emery-Dreifuss disease, so far it has not been possible to draw an evolutionary line of the disease, however, this study shows some signs that can introduce us to possible evolutionary patterns that must be deepened [13,25]. Accordingly, if we look at tables 1 and 2, we realize that despite patient number 4 being the one with the lowest temperature and logically the one with the fewest repetitions in the strength test, there is a homogeneous pattern with compared to the loss of infrared emission in the lower limbs.

The youngest patient, at the level of the anterior part of the thigh and leg, presented a much more abrupt and significant decrease in temperature than his older brother after one year of follow-up. We believe that this data may depend on multiple variables. On the one hand, the fact that the patient is younger may affect the metabolic evolution of the disease, something that has already been observed in other degenerative diseases [26-29], on the other. On the other hand, it is also possible that as there is a greater presence of muscle tissue, due to the early stage of the disease, there is a greater possibility of it collapsing, which is not possible in a more advanced stage due to the abundant presence of fibrofatty tissue in front of healthy muscle. However, it should also be noted that this pattern does not apply at the posterior level, where, as we can see in Tables 1 and 2, there is a significant difference in the decrease in temperature in favor of the older patient in the thigh (right: + 1.1 °; left: +1.1) but not so significant in the leg (right: + 0.3 ° SX: = 0.0 °). In this regard, it should be noted that certainly the purely anatomical and physiological composition of the muscles located in the anterior part of the thigh is not the same as in the posterior part, in fact, the tendinous portions of the muscles of the posterior region (ischio-tibio-fibulae) they are longer and wider than the anterior portion (quadriceps) with the quadriceps and patellar tendons [30-32]. Since the prognosis and evolution of this type of patient depends to a great extent on the involvement of myotendinous contractures and cardiac involvement and that in general there is a significant lack of information on the biology and functionality of the mechanisms of development and pathogenesis of the tendon, hypotheses about a possible anteroposterior or postero-anterior evolution of the disease cannot be ruled out, depending on age and tissue physiology that undoubtedly need to be clearly and forcefully deepened [33-35]. These results are the first bibliographic information, obtained after one year of evolution, in this disease through the use of thermography and could show how the disease evolves at the level of the lower limbs in this type of patients, however we are aware that further Studies, if possible, more extensive in techniques and numbers of patients in order to better demonstrate and quantify the relationship between muscular dystrophy / BMI / strength in the lower limbs in these types of patients. However, this work further corroborates the aforementioned theories that propose thermography as a monitoring and quantification tool for Emery-Dreifuss muscular dystrophy [7,13,14].

5. Limitations and forces.

This research is the result of a very innovative work and a year of evolution with diagnostic elements very little used before in this disease. However, there are aspects that could be improved. Since the study`s goal was both to describe a possible evolution of the disease and to add more precise aspects about thermography as a valid tool for the follow-up of Emery-Dreifuss muscular dystrophy, a larger sample would be needed, however, when Being a rare disease, the samples available in these cases are usually scarce. Despite the good results obtained, and the advances made in this area of study, more research is needed on the subject to better deepen this new line of research.

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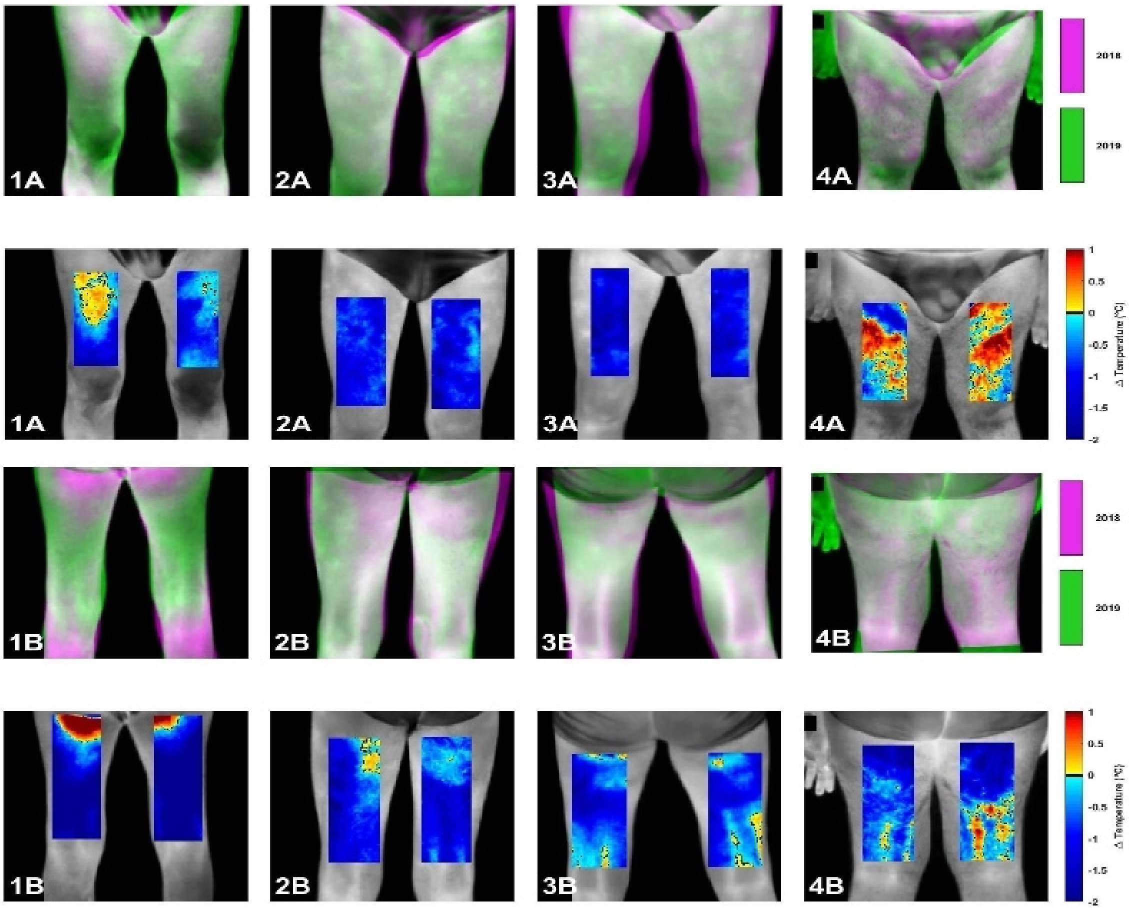
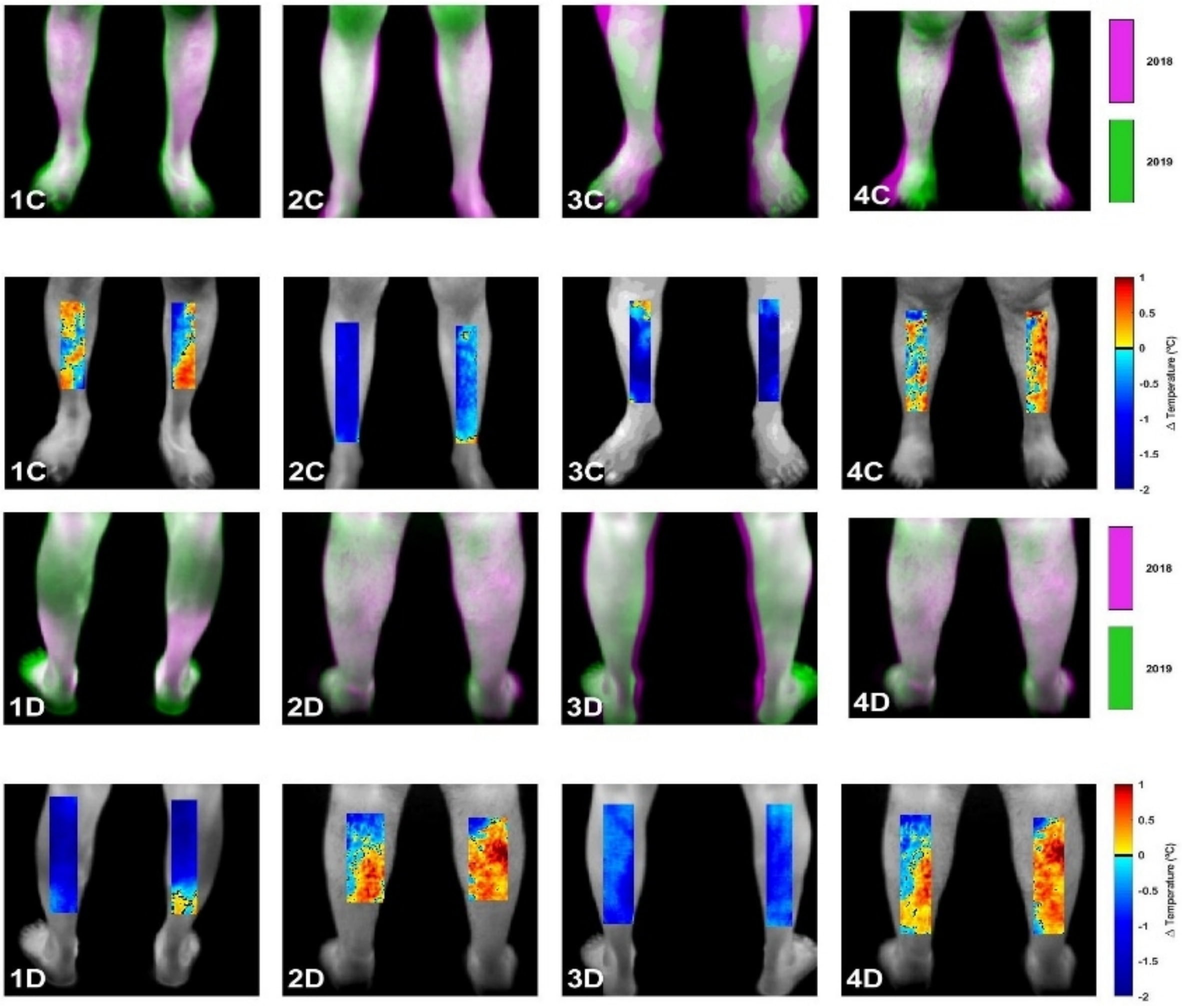
Figure 1. 2018 (Violet) and 2019 (Green) thermographic images of the anterior and posterior thigh of the 4 patients.



The images show the overlap of the thermographic patterns of the patients for the years 2018 (violet) and 2019 (green). The “A” images show the anterior thigh region, while the “B” images the posterior thigh region. The images marked with ROI show the differences between the 2 years.

Figure 2. 2018 (Violet) and 2019 (Green) thermographic images of the anterior and posterior thigh of the 4 patients.



The images show the overlap of the thermographic patterns of the patients for the years 2018 (violet) and 2019 (green). The "C" images show the anterior leg region, while the "D" images the posterior thigh region. The images marked with ROI show the differences between the 2 years.

Table 1. *Data corresponding to the evolution of the average temperature (° C) measured in the regions of interest selected in figures 1 with one year of evolution.*

THERMOGRAPHY				
THIGH				
	ANTERIOR		**POSTERIOR**	
	2019	**2018**	**2019**	**2018**
01	DX:32.9° SX:32.9°	**DX: >1.3° SX: >1.4°**	DX:32,4° SX:32,8°	**DX:>1.1° SX:>1.5°**
02	DX:32.3° SX:32.5°	**DX:<0.2° SX:<0.4°**	DX:32,4° SX:32,7°	**DX:<0.2° SX:<0.4°**
03	DX:32.6° SX:32.6°	**DX:>0.7° SX:>0.5**	DX:32.3° SX:32.3°	**DX:>1.4° SX:>1.4°**
04	DX: 31.1° SX:31.0°	**DX: >0.8° SX:>1.1°**	DX:30.8° SX:30.6°	**DX:>2.2° SX:>2.6°**

DX: Derecha; SX: Izquierda; >:Mayor; <: Menor

Table 2. Data corresponding to the evolution of the average temperature (° C) measured in the regions of interest selected in figures 2.

THERMOGRAPHY				
SHANK				
	ANTERIOR		**POSTERIOR**	
	2019	**2018**	**2019**	**2018**
01	DX:32,3° SX:32,4°	**DX:>1.6° SX:>1.2°**	DX:31.7° SX:32.0°	**DX:>1.6° SX:>1.7°**
02	DX:32,5° SX:32,9°	**DX:<0.1° SX:<0.4°**	DX:32.4° SX:32.6°	**DX:<0.5° SX:<0.6°**
03	DX:33.2° SX:32.7°	**DX:>0.6° SX:>0.8°**	DX:32.1° SX:32.0°	**DX:>0.8° SX:>0.9°**
04	DX:31.9° SX:32.1°	**DX:>0.5° SX:>0.5°**	DX:30.4° SX:30.6°	**DX:>1.9° SX:>1.7°**

DX: Derecha; SX: Izquierda; >: Mayor; <: Menor

Table 3. *Data corresponding to the stress test with one year of evolution.*

CHAIR STAND TEST

	2019	2018
01	11	>2
02	7	>3
03	11	>3
04	4	> 4

<: Menor

Title:

Relationship between infrared skin radiation and functional tests in patients affected by Emery-Dreifuss muscular dystrophy: Part 2.

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Abstract: Hypothesis: This study represents a second part of a study recently published about a new form of evaluation and flow-up of rare genetic neurodegenerative disease. The objetive is to provide a more global vision of thermography with respect to Emery-Dreifuss pathlogy, through the analysis of the data collection carried out during one year. The basic hypothesis is that thermography could become a valid tool for the diagnosis and follow-up of this pathology because is a very specific tool to register temperature´s changes produced by a constant degenerative evolution of this muscular dystrophy. **keyword:** Thermography, Emery-Dreifuss, Muscular dystrophy.

Ethical publication statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declarations of interest: none.

Equal contribution: These authors contributed equally to this work.

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The Managin Editor

Medical Hypoteses

Dear Editor,

Ethical publication statement: We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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