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RESEARCH ARTICLE

High Prevalence of Myotonic Dystrophy Type I in a Town of Colombia

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1 | INTRODUCTION

Myotonic dystrophy type I (MD I) is a primary, progressive, systemic and hereditary muscular pathology. (1) Clinical findings include weakness, myotonia, progressive muscle mass loss, (2) and characteristic changes in the electromyogram. (3) As well as, an association with endocrine, cardiovascular, ocular and cognitive alterations. (4)

The worldwide prevalence of MD I is estimated at 1: 20,000 people, being high in Quebec (Canada), as well as in the Basque region (Spain), Guam (USA possession), and in some areas of South Africa and Sweden. (5, 6) In Europe, the prevalence is variable between countries, being lower in Apulia (Italy), intermediate in Norway (7, 8) and higher in Mallorca (Spain) with prevalence ranging between 0.24: 20,000 and 2.2: 20,000. (9)

MD I is inherited in an autosomal dominant pattern caused by a CTG triplet expansion in the 3'-untranslated region (3'-UTR) of DMPK gene, lo-

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cated in chromosome 19q13 .3.1

This study presents an extensive family with five generations of affected individuals in a small geographic location in the Andean region, the largest group described so far, where the highest prevalence of MD I is found in Colombia.

2 | MATERIALS AND METHODS

2.1 | Ethical declaration, consent and permissions

This study was carried out under the guidelines of the Declaration of Helsinki and Resolution 008430 of the Ministry of Health (October 4, 1993) where, framed in Law 10 of 1990, Decree 2164 of 1992, each participant was presented with an informed consent and posteriorly were signed by them.

2.2 | Methodology

A complete medical history and physical exam was performed, along with the elaboration of the family pedigree Figure 2. Since multiple members of the family had similar findings, a genetic pathology was considered. Five family member were examined and, due to economic limitations, just one of the individuals, which showed greater affectation, underwent genetic studies to demonstrate the re-expansion of the CTG triplet, to confirm myotonic dystrophy, however, a clinical diagnosis had already been made. For this, 5 ml of a peripheral blood sample in venipuncture tubes with EDTA and another 5 ml of peripheral blood sample in venipuncture tubes with Heparin were taken for perform DNA isolation and karyotyping as well as amplification of the DMPK gene respectively.

2.3 | Individuals

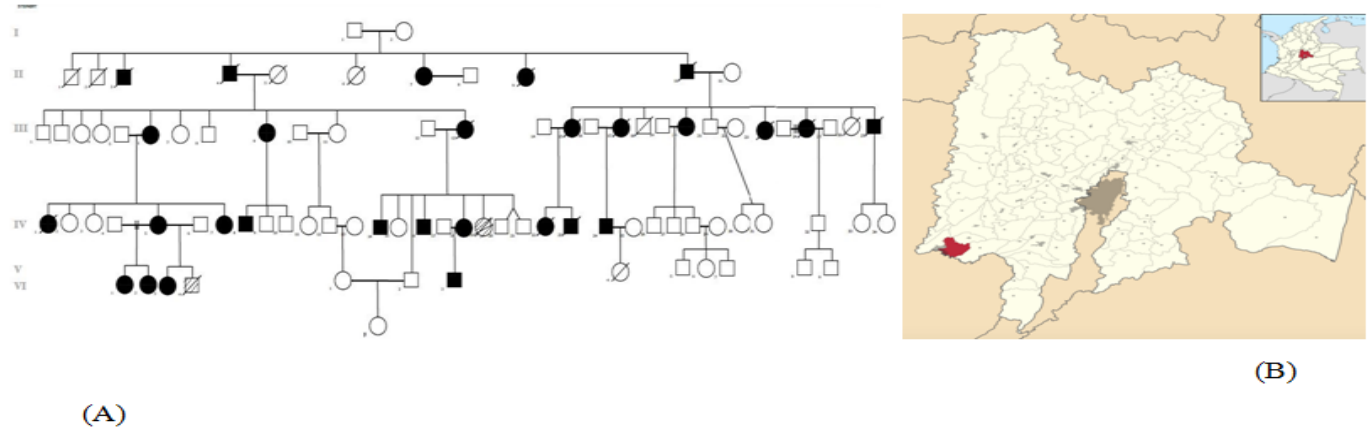
A five-generation family with 28 affected members is presented, of which two cases were selected; *MDI*-Patient1 and *MDI*-Patient2, to perform extended studies. They attended general medicine consultation for presenting myalgias in the upper and lower extremities as well as progressive loss

FIGURE 1: SMD-Patient1 (A) and SMD-Patient2 (B). Frontal alopecia, a blank face, and palpebral ptosis are observed, as well as distal limb thinning.

of strength. The family is currently located in a Colombian municipality in the department of Cundinamarca, located at 4 ° 16′45 ″ N 74 ° 46′22 ″W Figure 2. Those affected present phenotype variability, ranging from muscle weakness to postration and death, mostly attributed to cardio respiratory arrest.

MDI-Patient1(Figure 2: IV.5.) A 39-year-old woman began to present symptoms at the age of 31. Symptoms consisted of myalgias in the lower extremities that would get worse after walking. She then developed muscle weakness in all four extremities, leading to a walking disability. Physical examination showed: height 158 cm, weight 65.5 kg (body mass index 26.2 kg/m2), head circumference 53.5 cm, wingspan 165 cm, blood pressure 110/72 mm Hg, heart rate 85 bpm. Clinical findings showed frontal alopecia, bilateral ptosis, expressionless face, predominantly distal muscle thinning, and decreased symmetric strength in all four extremities, accompanied by awithsteppage gait (Figure 1:A). Karyotype was normal, 46, XX. (Number of metaphases: 30)

According to data provided by the patient, her grandfather (Figure 2: II.4.) was diagnosed with cataracts from an early age; however, he did not present any skeletal muscle symptoms and he died of cancer. Her mother (Figure 2: III.6.), on the other



(A) (B)

FIGURE 2: A. The Family Genealogy tree. An autosomaldominant pattern can be seen in 4 generations. SMD-Patient1 can be seen atposition IV. 5. and SMD-Patient 2can be seen at position IV.14. B. Municipality of Ricaurte, Cundinamarca in Colombia, where the studied family is located, is shown highlighted in red.

hand, presented similar symptoms to SMDI-Patient2 at the age of 32 years, progressively increasing until causing complete disability. Later she died at the age of 45 years due to MDI, probably due to cardiac arrest. Additionally, the patient's sister (Figure 2: IV.1.) presented the same phenotypic characteristics associated with muscle weakness in the upper and lower limbs and ataxic gait; these symptoms began at the same age as the patient presented as SMDI-Patient1. Likewise, the patient's nephew (Figure 2: V.7.), currently 6 years old, began with muscle weakness in the hands associated with stiffness, hyperflexibility and joint ache in knees as early as 2 years of age.

The Patient *MDI-Patient1* had three daughters but it is not possible to determine if they presented symptoms due to lact of contact. However, the patient refers that they presented certain phenotypic characteristics, such as an ax-shaped face. Moreover, the patient had a son who was born prematurely at 6 months of pregnancy due to decreased fetal movements, and died 4 days after birth (Figure 2: V.4.). Exact cause of death is still unknown. The mother of the patient, who is the aunt of *MDI-Patient2,* had symptoms of progressive limb weakness, causing later disability and death.

MDI-Patient2 (Figure 2: IV.14.) A 32-year-old male began presenting symptoms since he was 20 years old. Symptoms consisted of myotonia in the hands and passive hypermobility in thumbs, followed by progressive muscle weakness in limbs. Additonally, starting at 31 years of age, he presented gait disturbances.

Physical exam showed: height 177 cm, weight 79 kg, (body mass index 25.1 kg / m2) head circumference 55 cm, wingspan 181 cm, blood pressure 92/59 mmHg and heart rate 63 bpm. Clinical findings showed frontotemporal alopecia, bilateral ptosis, decreased facial muscle mass and expressionless face, dysarthria, weakness in all four extremities, myotonia of the right hand, and steppage gait. Karyotype was normal, 46, XY. (Number of metaphases: 30)

3 | RESULTS

The clinical scenario present in *MDI-Patient1* and *MDI-Patient2* compared with the classic clinical findings of MD I described in the literature and are presented in Table 1.

Amplification of the repeated region (CTG) at the 3 ’untranslated end (UTR) of the DMPK gene was carried out by fluorescent and bidirectional TP-PCR in two independent reactions with different primers. Heterozygosity was detected with a normal allele with 19 (± 1) CTG repeats and an expanded allele (> 100 repeats) inthe DMPK gene, confirming the clin-ical diagnosis of type 1 myotonic dystrophy.DMPK: het $CTG^{19}/CTG^{>100}$Figure 3.

4 | DISCUSSION

Myotonic dystrophy type I (MD I) is a genetic muscular dystrophy caused by the expansion of a CTG trinucleotide repeat in the 3’untranslated region of the myotonic dystrophy protein kinase (DMPK) gene on chromosome 19q13.3.1

TABLE 1: Relevant physical examination findings in studied members of the family with suspected or confirmed Steinert's myotonic dystrophy (SMD) ormyotonic dystrophy type I (MD I), compared with classic findings described in literature.

Physical examination findings

	General assesment					Neurologic assesment						
Patient	Age	Palpebral ptosis	Syncope	Cataracts	Constipation	Facies	Alopecia	Strength	Muscle mass	Cranial nerves	Reflexes	Gait
IV. 1	30	NO	DA	DA	DA	Inexpressive	Frontotemporal	4/5	DLT	N	N	Steppage gait
IV. 5 SMD-Patient1	39	YES	YES	NO	NO	Inexpressive	Frontotemporal	3/5	DTL	N	N	Steppage gait
IV. 14SMD-Patient2	32	YES	NO	NO	YES	Inexpressive	Frontotemporal	4/5 upper left limb hypertonia	N	N	N	Steppage gait
IV. 16	24	YES	NO	NO	NO	NO	Frontal	4/5 upper right limb hypertonia	N	N	N	N
V. 7	4	NO	NO	NO	NO	NO	NO	4/5	N	N	+/++++ decreased in lower limbs	N

N: Normal DLT: Distal limb thinning

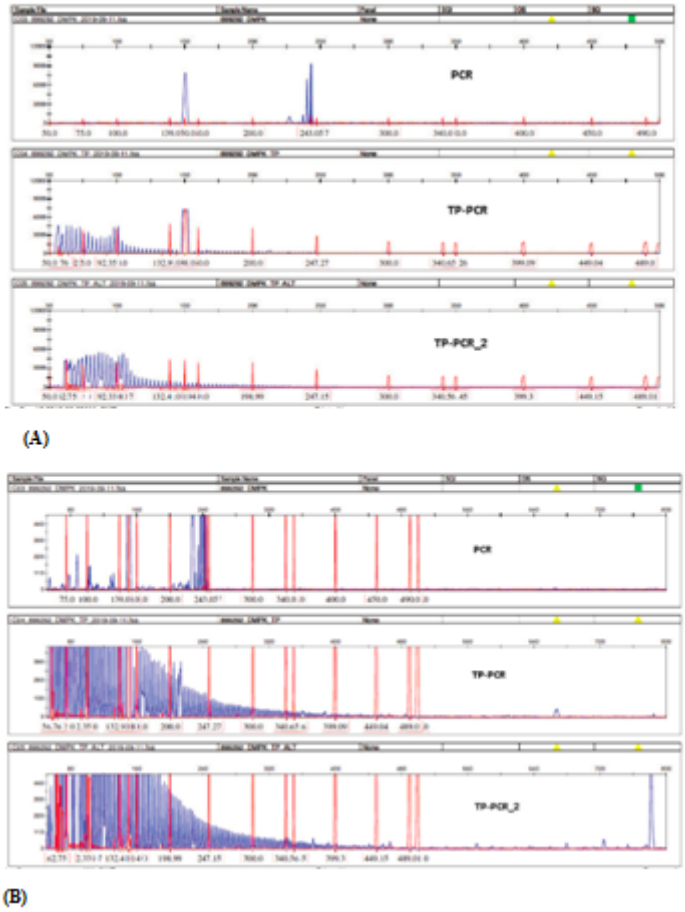


FIGURE 3: Electropherograms of repetitive region amplification $(CTG)^n$ of DMPK gene. Image A. Normalallele. Allele that amplifies in PCR 19 (±1) repetitions. Image B. Abnormal allele from SMD-Patient1. A ladder pattern can be observed for TP-PCR, indicating the presence of an expanding allele that has not been amplified by PCR, suggesting that it is an allele with > 100 CTG repeats.

The patients' clinical manifestations, illustrated in Table 1, are closely related to the same expansion of the CTG triplet of the DMPK gene in different tissues, especially skeletal and cardiac muscle. The main clinical manifestation in these tissues is myotonia, moreover being the main reason of consultation. Although repeated expansions are found in genomic regions that do not encode proteins, a direct relationship between allelic expansion of CTG for the DMPK gene and phenotypic characteristics of the disease has been documented in literature. Evidence supports a unifying theory that both MD I and MD II have an RNA-mediated pathogenesis in which both disorders result from repetitive RNA toxicity. The expanded repetition, specifically; in DM I is found in the terminal part of the DMPK gene, close to the polyadenylation signal. This results in the production of a mutant mRNA containing several thousand CUG repeats, the cells with large expansion and high levels of DMPK expression aremuscle fibers, smooth muscle cells, cardiomyocytes, and neurons, resulting in muscle, cardiac, and neuronal manifestations. (1)

Multiple studies have been conducted to test the role of DMPK in the patho physiology of the disease. DMPK is expressed mainly in skeletal and cardiac muscles. In skeletal muscle there is a functional involvement of DMPK in the generation and / or maintenance of this muscle type. In a study carried out in transgenic mice, it was shown that the overpro-duction of the protein originating from a DMPK with 11 CTG repeats, or its respective mRNA, caused cytoarchitectonic disorders and distortion of ionic homeostasis in the heart, skeletal muscle and smooth muscle cells. These animals also showed alteration of normal skeletal muscle

function, indicated in vivo by difficulty in walking, atrophy of type I fibers with moderate hypertrophy of type II fibers, accumulation of mitochondria in the subsarcolemmal space and between myofibrils and an increase in the number of fibers with central nuclei. Similarly, over expression of DMPK in the myogenic C2C12 cell line of mice inhibited terminal differentiation. Taken together, these data suggest that the DMPK protein is relevant to the proper structure and function of skeletal mus-cle. (1)

Proteins of the MBNL family bind to expanded RNA with high affinity. Specifically, this family of proteins normally acts to regulate the splicing of several hundred transcripts, these functions are lost when MBNL proteins become entrapped in the nuclear foci of CUG repeats,resulting in the expression of many incorrect splice products and protein isoforms. For example, incorrect splicing of the ClC-1 chloride channel leads to reduced chloride conductance in muscle fibers, a physiological alteration known to cause myotonia.These effects also explain the other neuromuscular manifestations presented in the patients described, such as palpebral ptosis and dysarthria in *MDI-Patient2* individual. On the other hand, muscle weakness is due to sequestration of MBNL by mutant RNA repeats (CUG), leading to T tubules disorganization and excitation-contraction coupling impairment. (2)

In these patients, other systemic manifestations are also present in addition to myotonia; cardiovascular manifestations represent a frequent complication in patients with this pathology. Cardiac conduction disorders can occur due to induction of toxic RNAs transcription and production of cardiac transcription factor NKX2-5, (3) which can lead to early heart attacks and cardiac death. (10) Brain alterations, on the other hand, are both structural and functional, with imaging evidence of diffuse changes in the white matter, being more prevalent than brain atrophy. Dysphagia in these patients has been the greatest concern since it can be found associated with aspiration and aspiration pneumonia. (11) Endocrine changes have also been widely described as insulin resistance, hypogonadism, infertility, and miscarriages. (4, 5)

The age of onset and severity of the symptoms also depend on the form of presentation. There are 4 documented clinical presentations: mild, childhood, classic and congenital disease.

The mild form manifests with cataracts and mild myotonia (sustained muscle contraction). However, the repercussions on the patient's daily life are minimal and they usually lead a normal life. (6)

However, the most frequent clinical presentation is the classic form. About 75% of patients with the classic form develop symptoms in the second, third, or fourth decade of life. The cardinal finding on physical examination is myotonic myopathy, consisting of myotonia, weakness, and muscle wasting in a characteristic distribution; with preferential selection of the cranial, trunk, and distal limb muscles, most commonly the forearm, hand, tongue and jaw. All cranial muscles are potentially affected, producing a characteristic appearance of ptosis, wasting of temporal and masseter muscles and facial weakness resulting in an inexpressive face. In contrast to most other dystrophies, including type 2 muscular dystrophy, MD I causes obvious weakness of the tongue, and there is often a modest limitation of ocular motility. (1) This is probably the clinical presentation of the two patients presented in this paper, where the onset of symptoms in both individuals occurred in the third decade of life, in addition to the presence of a selective compromise of distal limb muscles, ptosis and dysarthria, these features being characteristic of patients with DM I.

The presentation in childhood, on the other hand, generates systemic involvement of the muscular-skeletal, cardiac, gastrointestinal, ocular and respiratory systems, similar to the classic form, but its age of onset oscillates around the first decade of life. In this form of myotonic dystrophy, the muscle weakness is not as severe as in the classic presentation and its hallmark is the cognitive deterioration that leads to learning difficulties, and a lower performance in relation to adaptive behaviors, communication, socialization and daily life tasks. (7)

Finally, there is a congenital myotonic dystrophy, being the most severe form of the disease, which manifests prenatally with decreased fetal movements and polyhydramnios.1 At birth, patients will have

difficulty swallowing, hypotonia in the face and extremities, and respiratory distress that can lead to respiratory failure. Mental retardation is frequent and myotonia can be manifested, but to a lesser extent.1 It is probable that the descendant of *MDI-Patient1* Figure 2 (Figure 2: V.4.) had this clinical presentation of the disease; however, more information about the cause of death is needed to confirm this finding.

The heritability pattern of the disease is autosomal dominant1 where the phenomenon of anticipation occurs characteristically. This refers to a greater expansion of the triplet in the pedigree. (8) This phenomenon has been reported in both types of myotonic dystrophies; however, it is more prominent in MD I. Anticipation phenomenon causes an increase in severity and / or a lower age of onset as the generations advance. This behavior is explained by the transmission of an allele with a higher number of CTG repeats to the offspring secondary to a high variability of expansion, also seen in different tissues of the same individual. On average, CTG expansion increases by more than 200 repeats when passed from one generation to the next. It has been shown that the size of the expansion is closely linked to the phenotype of the disease and therefore its severity. (9) Within the case presented, anticipation can be observed from the second generation. The first case documented case of the family is *MDI-Patient1* and *MDI-Patient2* grandfather, who probably presented a mild form of the disease, with cataracts from an early age without significant muscular affectations described. On the other hand, the affected individuals in the third generation, such as *MDI-Patient1* mother, presented similar symptoms at age of 32 years, progressively increasing until causing complete disability and probable cardiac death. The individuals in the fourth generation *MDI-Patient1* and *MDI-Patient2* presented a larger range of clinical features with more severe progressive muscle weakness. Finally, in the fifth generation, the affected people present symptoms of muscle weakness in the hands from the first decade of life. Although it is not possible to confirm the presence of a congenital form of MD I as the cause of the premature delivery and subsequent early death of the MDI-Patient1's baby, there is a probability that he has presented a congenital form of this muscular dystrophy and in turn, has presented intrauterine manifestations of the disease due to the decrease in fetal movements, as reported by the mother. (12)

In the case of *MDI-Patient1* and *MDI-Patient2,* it was documented that they are heterozygous carriers for the DMPK gene mutation. Given the inheritance pattern is autosomal dominant, the risk of transmission of the allele with expansion is 50%, being a fairly high risk for the expression of the disease. As reported in the literature, penetrance is high (close to 100% at 50 years of age) when all manifestations of the disease, even the most subtle, are present. (10) Based on all the above, it is appropriate to perform a genetic study in apparently asymptomatic relatives to have an early diagnosis and treatment of cardiac manifestations, diabetes mellitus, and cataracts. According to information provided by the community where the family resides, there is suspicion of consanguinity within it but it was not possible to verify it; however, a direct relationship between consanguinity and increased expression of the disease has not been demonstrated in the literature. Additionally, consanguinity as a risk factor for syndromes of genetic origin is more associated with diseases with autosomal recessive inheritance. (11) Since this is an autosomal dominant inheritance pattern, it is believed that consanguinity might not be a significant risk factor to explain the high prevalence of the disease within the family group, but rather the inheritance pattern itself.

On the other hand, when the consanguinity factor is considered, a double mutation expression phenomenon could occur in the offspring of two affected people, and this could explain the appearance of a more severe form of the disease. At first it was believed that due to a possible consanguinity in the family, some of the affected members could have been a clear example of this phenomenon, as is the case of the patient with probable congenital myotonic dystrophy Figure 2. However, as mentioned

above, the presence of consanguinity within the family group is not clear, nor has it been shown that the appearance of a double mutation for the DMPK gene can cause a more severe phenotype in an affected individual. More studies are needed to corroborate the relationship between genotype and phenotype.

In Colombia, case reports of MDI have been published. In 1981 a case report was published in Antioquia, (13) in 1983 a report of 17 cases from two families was published in Santander (14) and a report of 37 cases in Bogotá. (15) To date, there are still no reports of the exact prevalence and incidence of the disease in Colombia; however, it is believed to be a rare pathology in our environment. Unlike previously documented cases, this report shows an earlier onset of the disease and a more rapid progression of symptoms. The clinical course of the disease is similar, in terms of the type of symptoms, in relation to those described in the literature and national studies.

The prevalence of MD I varies between countries, but a number close to 13 / 100,000 population worldwide is the most found. (16) The municipality where this family livesFigure 2 has a population of 9844 people according to the latest figures published by the 2019 National Planning Department (24), so the prevalence of MD I in this region is 27/10,000 population, which would represent the highest prevalence documented to date worldwide. This finding is believed to be secondary to the geographic isolation that can be observed in the region. In Colombia, a predominant health determinant is geographic isolation, due to the settlement of small villages as part of the country's political-territorial order, whose inhabitants do not exceed 1,000 individuals and, due to the same phenomenon of geographic isolation, have less access to health services. (17,18, 19)

Regarding the diagnostic methods, this study uses the technique based on the polymerase chain reaction (PCR), the TP-PCR (triplet repeat primed PCR). However, there is another widely spread method that is the southern blot. The latter is in disuse since it is an expensive study and requires a larger DNA sample compared to other methods. The PCR-based method and its variant the TP-PCR (triplet repeat primed PCR) is faster, easier to perform and requires less DNA. (20–22) Both diagnostic techniques have a high correlation in terms of the size of the ex-pansion, its relative heterogeneity and the pattern of bands. The current recommendation suggests the use of PCR-based methods initially, leaving the use of southern blotting in cases where the first one gives ambiguous results. (11) In this case, the di-agnosis was made by means of PCR, finding that these patients were heterozygous for the DMPK gene mutation and had more than>100 CTG repeats.

Due to the heterogeneity of the disease, no specific treatment can be indicated. Therefore, it should consist on treating each patients' individual comorbidities independently. Additionally, in patients with respiratory system involvement it is important to consider the risk of respiratory failure, especially in the context after receiving general anesthesia. (23) On the other hand, skeletal muscle weakness, leading to immobility, respiratory failure, dysarthria, and dysphagia, is the leading cause of severe disability and death. (24)

Currently the treatment is symptomatic, but not curative; it requires a multidisciplinary approach by psychiatry, physical and occupational therapy, orthopedics and neurology. However, an attempt is made to maintain the independence of the patient as long as possible and to avoid complications derived from weakness, being the reason why physical therapy stands out. Often, most cases are mild and rarely require treatment, unlike the cases presented in this article where severe and disabling symptoms, as well as early onset, are documented. People who suffer from MD I require genetic counseling and specific prenatal diagnosis, as well as performing CTG repeat detection tests in cases where father and mother of the affected patient plan to have more children and siblings of the patient who plan to have a pregnancy in the future. (25, 26) Finally, this family was clarified the diagnosis and was given genetic counseling.

5 | CONCLUSIONS

The present work documents the case of a Colombian family with myotonic dystrophy type I (MD I), where the phenomenon of anticipation and the high penetrance of the disease are also evidenced. This disease was not previously documented in this region of the country, and according to data collected during the study and literature review regarding to epidemiology of the disease, this region has the highest prevalence of MD I worldwide estimated to date, being this case the largest group described so far. Due to the heterogeneity of the disease, there is no specific or curative treatment, so it is recommended to approach the comorbidities and complications of the disease independently and individually. Given the features of this disease, and the remoteness of the village in which the family is located it is important to highlight it as a concern for public health. As well as, genetic counseling is of vital importance to educate and prevent the risk of recurrence, and thus to provide the patients the best quality of life possible.

6 | ACKNOWLEDGEMENTS

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