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Steinert Myotonic Dystrophy in Valcamonica (Brescia): Report of Three Families

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Abstract: Myotonic dystrophy type 1 (DM1) is a multisystem disorder that affects skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous system. The clinical findings, which span a continuum from mild to severe, have been categorized into three somewhat overlapping phenotypes: mild, classic, and congenital. Mild DM1 is characterized by cataract and mild myotonia (sustained muscle contraction); life span is normal. Classic DM1 is characterized by muscle weakness and wasting, myotonia, cataract, and often cardiac conduction abnormalities; adults may become physically disabled and may have a shortened life span. Congenital DM1 is characterized by hypotonia and severe generalized weakness at birth, often with respiratory insufficiency and early death; intellectual disability is common. It is an autosomal dominant, triplet-repeat expansion disorder that affects between 1 in 3,000 and 8,000 individuals globally. We briefly report three families found affect with Steinert Distrophy, all living in Vallecamonica.

Keywords: Steinert; Dystrophy, Families; Valcamonica.

INTRODUCTION

Myotonic dystrophy (DM) is an autosomal dominant neuromuscular disease primarily characterized by myotonia and progressive muscle weakness. The pathogenesis of DM involves microsatellite expansions in noncoding regions of transcripts that result in toxic RNA gain-of-function [Yum, K. *et al*., 2017]. Each successive generation of a DM family carries larger repeat expansions, leading to an earlier age of onset with increasing disease severity (anticipation phenomenon) [Yum, K. *et al*., 2017]. Progressive muscle degeneration leading to disabling weakness and wasting with myotonia, in combination with multisystem involvement, are the main characteristics of myotonic dystrophy type 1 (also known as Steinert's disease or DM1) and myotonic dystrophy type 2 or DM2 [Thornton, C.A. *et al*., 1994]. DM1 is due to a CTG-repeat expansion > 50 repeats in the non-coding 3' UTR of the DMPK (Myotonic Dystrophy Protein Kinase) gene, located on chromosome 19q13.3. DM2 is caused by a CCTG-repeat expansion to 75 – 11 000 repeats in intron-1 of the CNBP (Cellular Nucleic-Antigen Binding Protein)/ZNF9 (Zinc Finger 9) gene [Finsterer, J. *et al*., 2017].

A healthy individual with normal DMPK alleles has 5 to 37 repeats (35 has also commonly been used as an upper threshold for normal repeat length). DM1 patients who have repeats between 38 and 50 are said to have a "pre-mutation" allele and can be asymptomatic throughout their lifetime [Turner, C. *et al*., 2010]. However, they are at increased risk of having children with larger repeats. Penetrance tends to grow as repeat length increases, but extreme variability in penetrance of specific symptoms exists in the patient population [Martorell, L. *et al*., 2017].

Myotonic dystrophy type 1 may present at birth (congenital myotonic dystrophy), during childhood and adolescence (juvenile myotonic dystrophy), or in young adulthood, usually around the second decade (classic form) [Sansone, V.A. 2016; Wenninger, S. *et al*., 2018]. The most typical appearance of DM1 is the "adult-onset" or "classic" phenotype with a CTG-repeat size ranging from 50 to <1,000. It is characterized by a distinctive combination of muscular symptoms, such as facial weakness, ptosis, grip myotonia, and distal muscle weakness with muscular atrophy. The classic phenotype is typically accompanied by extramuscular symptoms like cognitive impairment, cataracts, and diabetes mellitus. Nevertheless, as this multisystem disorder often presents with a high variability, some patients may primarily show only non-specific extramuscular symptoms like fatigue, daytime sleepiness, gastrointestinal symptoms, or cardiac conduction defects in an early stage of the disease, which could delay the diagnosis [Bird, T.D, 2018].

For DM1, there is a rough correlation between the expansion of CTG-repeats and the onset of symptoms as well as the severity of the disease; nevertheless predictions about the clinical features and the progression of the disease based on CTG-repeat size should be made very carefully [Brunner, H.G. *et al*., 1993; Bouchard, J.P. *et al*.,

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2015]. CTG-repeats will expand in every following generation, and fully penetrant alleles occur with >50 CTG-repeats. [De Antonio, M. *et al*., 2016]. Furthermore, the repeat instability leads notably to premature aging of almost all organs, so DM1 may be counted among the progeroid diseases [Mateos-Aierdi, A.J. *et al*., 2015]. Mildly affected patients with CTG-repeat sizes 50–100 may have normal or only minimally shortened lifespan [Bird, T.D, 2018]. Because of comorbidities, such as cardiac and pulmonary complications, life expectancy is, however, reduced in about 70% of the patients with the classic phenotype [Bird, T.D, 2018].

Before identification of the distinct genetic mutations, the combined prevalence of the myotonic dystrophies was estimated at 1 in 8000 (12·5/100 000), based on clinical ascertainment. However, prevalence estimates vary widely for different populations. High prevalence has been reported in northern Sweden, the Quebec region in Canada, and the Basque region of Spain [Suominen, T. *et al*., 2011]. Findings of a population genetics study in Finland showed that the frequency of the myotonic dystrophy type 2 mutation (1/1830) can be much higher than that for type 1 mutations (1/2760) in the same population. However, it is unknown whether mutation frequencies in the Finnish population reflect those for populations elsewhere of European descent and if the mutation is 100% penetrant in all circumstances [Suominen, T. *et al*., 2011]. Considering the generally earlier onset of symptoms in myotonic dystrophy type 1, these data suggest a prevalence in Finland of about 20 in 100 000 for both myotonic dystrophy type 1 and type 2 disease [Suominen, T. *et al*., 2011].

A study conducted in North West Tuscany and Padova showed a minimum prevalence rate of 9.31×10−5 inhabitants, consistent with epidemiological rates worldwide, and more than two times as high as those of two previous studies conducted in the same areas during the era prior to molecular genetic testing [Siciliano, G. *et al*., 2001].

METHODS

Vallecamonica is a valley located in the Brescia province (Northern Italy), which experienced isolation until the end of World War II; it has an area of 1518,19 km² and a population of 100.161 inhabitants (ISTAT, January 2018), 49.673 men and 50.488 women.

The data collected from DM1 patients were gathered via a detailed examination of hospital records from Esine Hospital (Neurology Unit, Pneumology, Internal Medicine, Department of Emergency) from 2008. We also contacted 60 General Practitioners working in Vallecamonica. We identified three big families with clinical and genetic features of Steinert Distrophy in Valcamonica.

The first family (figure 1) lives in Pisogne (a small municipality in the province of Brescia) and about 16 members have been received diagnosis (8 males and 8 females, of which 6 males and 2 females are already dead) and none of them performs regular follow up.

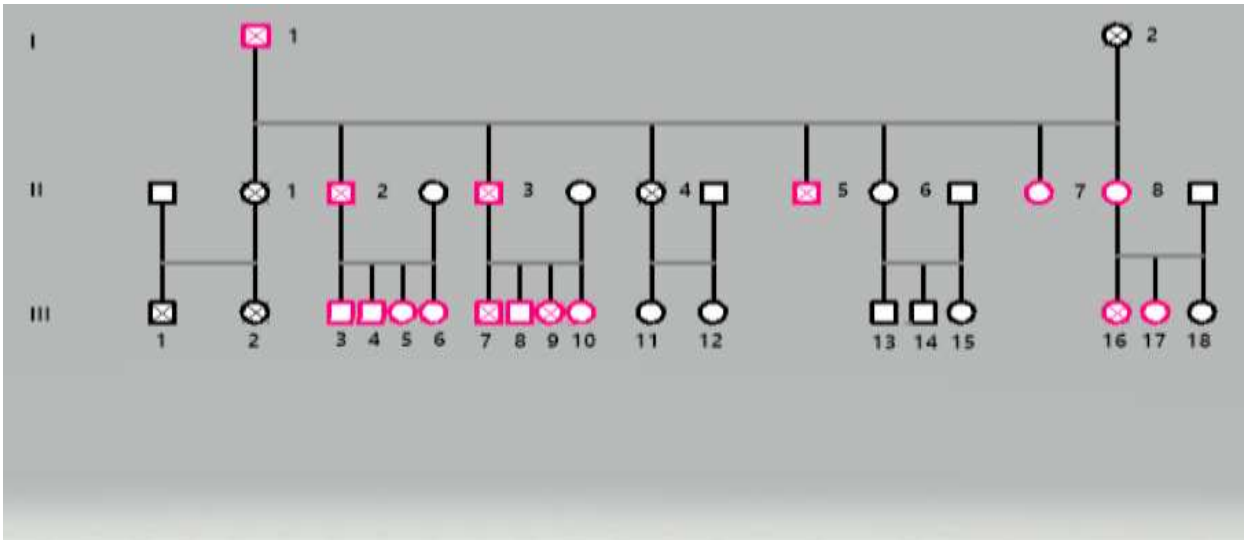

Figure 1: first family living in Pisogne

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The second familial nucleus lives in Berzo Demo (a small municipality in the province of Brescia, in the northern Vallecamonica) (figure 2). About five males and two females have been diagnosed with Steinert Distrophy. Only three of them are regularly followed:

Proband II: 5 a 67 years-old woman who has been genetically diagnosed for Steinert Distrophy. Clinically she presents with alopecia, mental delay, diabetes mellitus, cardiopathy and dyslipidemia. She also suffers from osteoporosis with vitamin D deficiency and bilateral cataract.

Proband III: 5 is the soon of proband II: 5. He has also been diagnosed at birth with Steinert Distrophy and he Is now 37 years-old. He presents intellectual disability and he moves with wheelchair. He present marked myotonic face with spontaneous and percussion myotonic phenomenon.

Proband II: 7 suffered from intellectual disability and moved with wheelchair. He was affected with diabetes mellitus, respiratory insufficiency (for which he refused nocturnal ventilation), hypertrophic cardiopathy, cataract, dyslipidemia. He was a heavy smoker. He recently was hospitalized due to basilar artery thrombosis, for which he developed locked –in syndrome, and then died due to pneumonia at the age of 75.

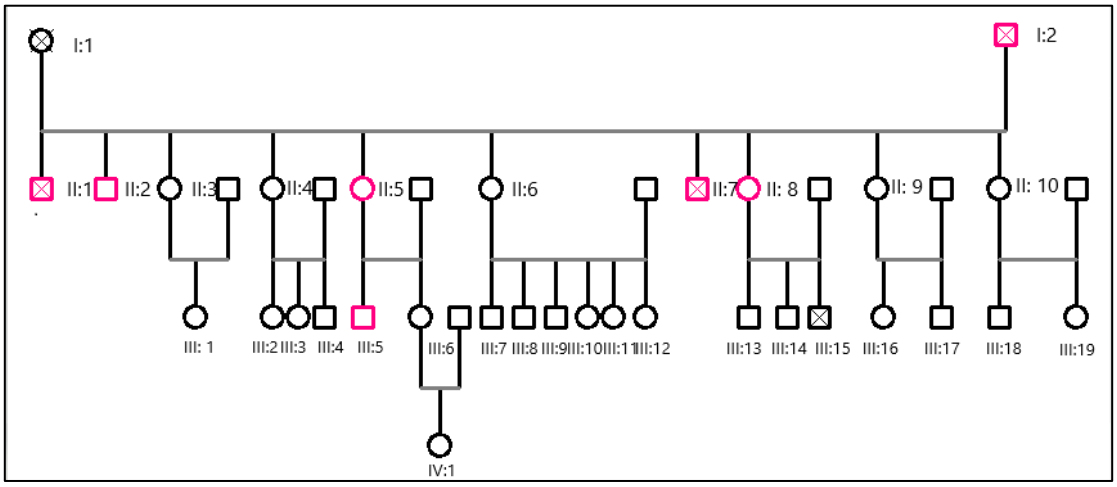

Figure 2: five males and two females have been diagnosed with Steinert Distrophy

In the third familial nucleus (figure 3), coming from Malonno (Brescia, northern Vallecamonica) all three sons resulted affected with Steinert Disease and are regularly followed.

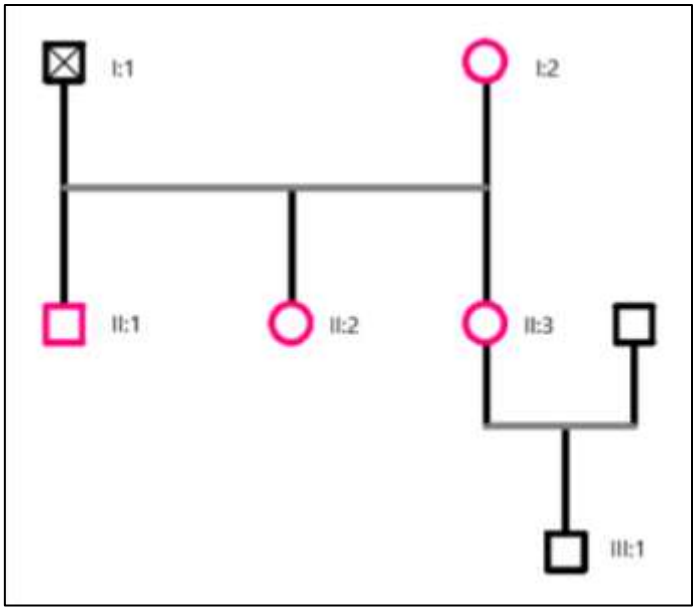

Figure 3: Familial nucleus coming from Malonno (Brescia, northern Vallecamonica)

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Proband II: 1 is a 57 years –old Caucasian man with Steinert Distrophy range E3. He suffers from mental retardation, severe proximal weakness (he uses wheelchair), diabetes mellitus, respiratory insufficiency, alopecia, bilateral cataract, hypertrophic cardiopathy, severe osteoporosis, dyslipidemia. He is also heavy smoker and recently suffered from deep venous thrombosis for which he started anticoagulation therapy.

Proband II: 2: 52 years –old woman, genetically diagnosed for Steinert Dystrophy. She presents relevant intellectual impairment with prominent myotonic face and intellectual delay. She also suffers from respiratory insufficiency, dyslipidemia, bilateral cataract and was recently diagnosed with papillar thyroid carcinoma.

Proband III: 3: a 47 years-old Caucasian woman, genetically diagnosed for Steinert Dystrophy. She presents with marked myotonic face with spontaneous and after percussion myotonia, mild intellectual delay, alopecia, mild respiratory insufficiency, dyslipidemia, bilateral cataract.

DISCUSSION

Myotonic dystrophy type 1 (DM1) is a multisystem disorder that affects skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous system (4).

Particularly, we collected three big families affected with DM1. Most of our patients affected refuse to perform regular follow up, so it is difficult to obtain precise clinical data. We report, however, the peculiarity of the presentation of basilar artery stroke in our II:1 patient, poorly evaluated in literature (16).

CONCLUSIONS

We performed the first attempt to collect patients with diagnosis of Steinert Distrophy in Valcamonica and we have been able to identify three families, one living in middle valley, one in the northern. The next attempt will be to convince all the affected patients to perform regular follow up in order to collect epidemiological data.

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