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ORIGINAL ARTICLES

Gender effect on onset, prevalence and surgical treatment of cataract in patients with Myotonic Dystrophy type 1

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Myotonic Dystrophy type 1 (DM1) is the most common muscular dystrophy in adults, affecting 1:8000 individuals. It is a multi-systemic disorder involving muscle, heart, endocrine and respiratory apparatus and eye. The eye symptoms can include ptosis, external ophthalmoplegia, epiphora, and early onset cataracts. Cataracts occur at a much earlier age (usually between 30 and 40) than the general population, where females are usually affected more than men. We studied gender differences in cataract prevalence and treatment age in 243 DM1 patients (134 M; 109 F), aged 18 to 70 years, who were subsequently screened at routine follow-up. For each patient, information was collected on age, sex, CTG expansion, age of cataract onset, and age at cataract surgery, when available. Seventy-three patients, 30 females and 43 males, had cataracts, at a mean age of onset of 41.14 ± 12.64 in females, and 40.36 ± 10.03 in males. Sixty-nine of them underwent cataract surgery, males at an earlier age than females (42.8 ± 9.8 years versus 47.3 ± 12.6 years) and in 52.5% of cases before the age of 40, compared to 17.2% of females. The difference was statistically significant. The assumption that females in general and those with DM1 in particular develop cataracts more frequently and earlier than males is not confirmed, at least in this study. A possible explanation for these results could be related to non-advanced age, the protective role of estrogen and the lower prevalence of smoking in the study population.

Key words: Myotonic Dystrophy type 1, Steinert disease, gender, cataract, cataract surgery, prevalence

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Introduction

Myotonic Dystrophy type 1 (DM1) is the most common muscular dystrophy in adults, affecting 1:8000 individuals. It is a multi-systemic disorder involving muscle, heart, endocrine and respiratory apparatus, brain and eye [1-3]. Muscle disease is characterized by myotonia and various degrees of muscle weakness [1-3]. The heart damage [4-5] combines arrhythmias and/or cardiac conduction disorders [6-8], often necessitating of device or heart implantation [7-12]. The disorder may also affect the function of many endocrine glands, with an increased risk for insulin resistance or diabetes, erectile dysfunction, impaired fertility, benign and malignant thyroid

tumors [13-16]. The respiratory involvement is frequent with a progressive decline of vital capacity values and sleep disorders [17-19]. DM1 is often associated with cognitive impairment and developmental behavioural disorders [20-22].

The pattern of inheritance is autosomal dominant, although complicated by the phenomenon of anticipation, where symptoms appear earlier and are more severe in successive generations [23]. Phenotypes range from individuals who are only mildly affected in late adulthood, to severely affected children with the congenital form of the disease [24,25]. DM1 is caused by a CTG expansion in the 3′-untranslated region (UTR) of the dystrophia myotonica protein kinase (DMPK) gene on chromosome 19q13.3 [26]. Small expansions (50 to 80 repeats) may be transmitted for several generations with minor changes. These alleles display greater instability when passing through the male germline [27,28]. Accordingly, the jump from small expansion with minor symptoms to large expansion with classical DM1 is more likely to occur with paternal transmission. In contrast, the massive intergenerational expansions to 1,000 or more repeats are more likely to occur with maternal transmission [28,29]. This explains the near exclusive maternal transmission of congenital DM1 [29]. Anticipation is not an inevitable phenomenon. Occasionally the expanded repeat undergoes an intergenerational contraction (< 5% of transmissions) [30,31].

Myotonic Dystrophy is a unique form of muscular dystrophy which is associated with a variety of ocular manifestations [32,33]. The eye is severely affected and symptoms can include ptosis, external ophthalmoplegia, epiphora, pupillary light-near dissociation, early onset cataracts, pigmentary retinopathy, bilateral optic nerve atrophy and low intraocular pressure (IOP). It has been shown that IOP is related to the detachment of the ciliary body [34] rather than to differences in central corneal thickness or corneal biomechanical properties [35,36]. The lens is particularly affected in DM1 and an early appearance of cataract is often the most common and reliable symptom of the disease, since it is frequently the first occasion for patients to seek medical attention [37].

In patients with DM1 cataract occurs at a much earlier age (usually in the 30s-40s) compared to general population and can also appear even in the lenses of teenagers. Females are usually more affected than men [38,39]. This could be due to a longer survival, and to age-dependent cataract incidence.

We studied the gender differences in cataract prevalence and treatment age in DM1 population.

Patients and methods

A population of 243 patients with DM1 (134 M; 109F), aged 18-70 years (mean 43.3 ± 14.2) and regularly followed at the Cardiomyology and Medical Genetics of the University Hospital of Campania "Luigi Vanvitelli", were subsequently screened at the routine follow-up. For each patient, information was collected on age, sex, CTG expansion, age of cataract onset, and age at cataract surgery, when available.

Consent to the use of data in an aggregate manner was obtained upon admission to the University Hospitals as per established practice.

Statistical analysis

Data are shown as mean ± standard deviation. We performed Student T test for non-paired data, and chi-square test to investigate differences in mean and percentage between the two groups.

Results

The clinical characteristics of the patients enrolled in the study are shown in Table I. Seventy-three out of 243 patients with DM1 (30%) developed cataracts. Of them, 30 were females and 43 were males. The mean age of onset of cataracts was 41.14 ± 12.64 in females and 40.36 ± 10.03 in males. The differences were not statistically different (p = 1.29; Student t test for non-paired data).

Sixty-nine patients (94.5%) had cataract surgery, at an average age of 44.7 ± 11.2 years. However, males underwent the surgery at an earlier age than females (mean age 42.8 ± 9.8 *versus* 47.3 ± 12.6). Furthermore, by dividing the patients - males and females - according to the age of cataract surgery more or less 40 years, we noticed that

Table I. Demographic characteristics of the study population.

	Total	Males	Females	P-value
Patients with DM1 examined (N)	243	128	115	n.s
Mean age in years		39.97 ± 14.85	40.77 ± 14.78	n.s
CTG expansion (Mn ± SD)		495.78 ± 477.95	466.25 ± 416.74	n.s
Smoking (N; % of patients)		57; 45	6; 5	p < 0.001
Insuline resistance/overt type 2 diabetes (N; % of patients)		52; 40.6	45; 39.1	n.s

Table II. Cataract onset and surgery in the study population.

	Males	Females	P-value
Number of patients with DM1 with cataract	43	30	n.s
Mean age in years	40.36 ± 10.03	41.14 ± 12.64	n.s
Patients with cataract surgery (N; %)	40; 93	29; 96.7	n.s
Mean age in years	42.8 ± 9.8	47.3 ± 12.6	< 0.05
Cataract surgery < 40 years (N; %)	21; 52.5	5; 17.2	< 0.001

21/40 (52.5%) males underwent surgery before the age of 40 compared to only 5/29 (17.2%) females. The difference was statistically significant ($p < 0.001$, chi-squared test) (Tab. II).

Discussion

Cataract is a common cause of visual impairment in the elderly [40], and surgery is often effective in restoring vision [39]. Cataract is a multifactorial disease associated with age, female sex, genetic predisposition, smoking, diabetes mellitus, drug intake and environmental exposure to UVB radiation [41-43]. In a study on cataract prevalence and prevention in Europe, Prokofyeva et al. [44] found that the overall prevalence of cataract was higher in Germany and Italy compared to the rest of Europe. They showed an increase with age in 2/3 of cases diagnosed over the age of 70. Sex-specific cataract prevalence was higher in women than in men, although not all of the reviewed studies were consistent in this aspect. Sex-specific cataract prevalence in a Spanish study [45] was higher in men over 64 years of age than in women at the same age, and a case-control study [46] from Athens, Greece, found only borderline significance of female sex to the risk of cortical cataract.

Furthermore, several European epidemiological studies [47-49] showed that former and current smoking [47], a history of cardiovascular disease [48], family history of ophthalmic disease, and higher exposure to sunlight [49] lead to increased risk of cataract, whereas only one study [50] showed an association of increased cataract risk with diabetes duration of 10 years or longer, or with asthma and chronic bronchitis. Importantly, that literature review showed that chlorpromazine, corticosteroids and multivitamin/mineral formulation intake increased the cataract risk depending on dose, treatment application, and duration [51,52].

Myotonic cataract is a posterior sub-capsular cataract, detectable as red and green iridescent opacities on slit lamp examination. Its characteristic multi-colored "Christmas tree" appearance (Fig. 1) is present in nearly all affected individuals, so that, in the absence of any evident clinical features, identification of typical sub-capsular opacities in subjects at risk for Myotonic Dystrophy, can be an indicator of a minimally affected gene carrier before the characterisation of the DMPK mutation [39].

Several factors may influence the gender differences observed in the cataract onset and prevalence. Hormonal differences between women and men represent one of the most commonly cited factors [53] as advanced age at menarche, younger age at menopause and a shortened fertile period were significantly associated with an increasing incidence in cataract surgery in several studies. These data suggest that estrogen deficiency may contribute to the cataract development and that estrogen may play a protective role in the human lens [53]. Several observations may support this suggestion: (i) women using postmenopausal estrogen seem to have less cataracts compared to postmenopausal women non using estrogen; (ii) the antioxidant properties of various estrogen, used in hormone replacement therapy, have been shown to protect lens proteins from the oxidative damage, that has been implicated in the pathogenesis of some forms of cataracts; (iii) alfa-estrogen mRNA has been found in human lens epithelial cells, suggesting a possible mechanism for a direct estrogen effect on lens; (iv) estrogen has been shown to protect against TGF-beta-induced cataract in a rat model of cataractogenesis [54]. However, evidences for this hypothesis remain controversial, and it appears that sex hormone levels could be regarded as a risk factor for cataractogenesis more than as a key factor.

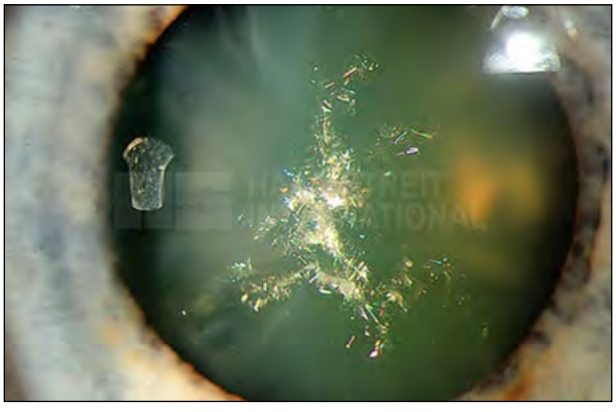

Figure 1. Myotonic cataract presenting as red and green iridescent opacities on slit lamp examination, with the characteristic multi-colored "Christmas tree" appearance.

A second influencing factor could be the insulin resistance [13,14], an endocrine abnormality often associated with DM1, or the presence of an overt type 2 diabetes [55]. Muscle insulin sensitivity is reduced by about 70% in patients with DM1, compared to those of controls [1]. Dysregulation of alternative splicing of the insulin receptor (IR) pre-mRNA in skeletal muscles has been recently indicated as one of the causes [56-58].

Diabetes type 2 is a chronic systemic disorder affecting nearly one in eight adults worldwide. Ocular complications, such as cataract can lead to significant visual impairment. Patients with diabetes have an increased incidence of cataracts which mature earlier compared to the rest of the population, and cataract surgery is a common and safe procedure to treat such a complication [59-60]. However, no differences were found in the prevalence of insulin resistance or overt type 2 diabetes in our patients.

Conclusions

The assumption that females in general and those with DM1 in particular, develop cataracts more frequently and earlier than males is not confirmed, at least in this study. A possible explanation for these results could rely on the non-advanced age, as women are more affected in older ages, the protective role of estrogen (none of females was in menopause) and the lower prevalence of smoking among females. However, further studies are necessary to better clarify this particular aspect in DM1 population.

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Conflict of interest statement

The Authors declare no conflict of interest.

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Author' contribution

MS, LPa, RP: performed the clinical investigations; ML, MDB, NR: performed eye exams and cataract surgery; LP: conceived, wrote and supervised the manuscript. All Authors have approved the current version of the manuscript.

Ethical consideration

This study was performed in line with the principles of the Declaration of Helsinki. Consent to the use of data in an aggregate manner was obtained from patients upon admission to the University Hospital, as per established practice.

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