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Correlates of Tumor Development in Patients with Myotonic Dystrophy

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Abstract

Patients with myotonic dystrophy (DM) have recently been reported to be at increased risk of tumor development, but clinical associations related to this observation are unknown. We calculated the odds ratios (ORs) and 95% confidence intervals (CI) of self-reported tumor development by patients' demographic and clinical characteristics to evaluate factors associated with tumor development in DM patients, using data from the National Registry of Myotonic Dystrophy and Facioscapulohumeral Dystrophy Patients and Family Members. Of the 911 participants, 47.5% were male and 85.7% had DM type 1 (DM1). Compared with DM1, patients with DM type 2 (DM2) were older at Registry enrollment (median age =55 vs. 44 years, $p<0.0001$) and at DM diagnosis (median age= 48 vs. 30 years, $p<0.0001$); and more likely to be females ($p=0.001$). At enrollment, 95 (10.4%) DM patients reported a history of benign or malignant tumor. Tumors were associated with female gender (OR=1.9, 95% CI=1.2–3.1, $p=0.007$) and DM1 (OR=2.1, 95% CI=1.1–4.1, $p=0.03$). In a subgroup analysis of patients with blood-based DNA testing results (397 DM1, 54 DM2), repeat expansion size was not associated with tumor risk in DM1 ($p=0.26$) or DM2 ($p=0.34$). In conclusion, female gender and DM1 subtype, but not DNA repeat expansion size, were associated with increased risk of tumors in DM. Follow-up studies are warranted to determine if oncogenes associated with *dystrophin myotonic-protein kinase (DMPK)* are altered in DM, and to determine if repeat expansion size, as in our study, is not associated with tumor development.

Keywords

Myotonic dystrophy; comorbidity; neoplasms; risk factors; repeat expansion size

Introduction

Myotonic dystrophy (DM), also referred to as myotonic muscular dystrophy (MMD), is an autosomal dominant, slowly progressive, multi-system disease characterized by skeletal muscle weakness, wasting, and myotonia [1]. Two major types, DM type 1 (MIM#160900)

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Conflict of interest: None

and DM type 2 (MIM#602668), have been identified that are clinically similar, but genetically distinct [2]. DM1 is caused by a CTG-repeat expansion in the 3' untranslated region of the *dystrophia myotonica protein kinase (DMPK)* gene on chromosome 19q13.3 [3–5], while DM2 results from a CCTG-repeat expansion in intron 1 of the *CCHC-type zinc finger, nucleic acid binding protein gene (CNBP)* (also known as *zinc finger 9* gene) on chromosome 3q21 [6].

Case reports have raised the possibility that DM patients may be at increased risk of benign and malignant tumors. A review of published case reports between 1965 and 2004 found that skin neoplasms (40 of 85 cases), particularly pilomatricomas (benign, calcifying tumors of hair matrix cells), were the most commonly described tumors [7]. We recently published a population-based registry study of 1,658 Danish and Swedish DM patients that provided the first strong quantitative evidence that cancer is part of the DM phenotype [8]. Specifically, DM patients were at excess risk of endometrial (Standardized Incidence Ratio (SIR)=7.6, 95% CI=2.3–10.4), ovarian (SIR=5.2, 95% CI=2.3–10.2), brain (SIR=5.3, 95% CI=2.3–10.4), and colon (SIR=2.9, 95% CI=1.5–5.1) cancers and, possibly, non-melanoma skin cancer (SIR= 2.1, 95% CI=1.2–3.4), and thyroid cancer (SIR, 7.1; 95% CI, 1.8–19.3) [8]. A subsequent clinic-based study of 307 confirmed DM cases identified significant excess risks of thyroid and choroidal melanoma [9]. To our knowledge, no studies have assessed potential clinical correlates of these observed higher rates of tumors in DM.

In the current analysis, we evaluated factors associated with tumor development in a large, well-characterized sample of DM patients including disease subtype, repeat expansion size, and other clinical, lifestyle, and demographic factors.

Methods

Study Subjects and Data Source

We used data collected from DM patients at enrollment in the US *National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members*. The registry was initiated in 2000 and is maintained by the University of Rochester, Rochester, NY (<http://www.urmc.rochester.edu/neurology/nih-registry/>). It collected demographic and clinical information from enrolled patients and their family members, plus molecular diagnostic testing results if available [10]. Patients' DM diagnosis was confirmed based on review of medical records, family history of DM, and genetic testing (when available). The study was approved by the Ethics Committees of the University of Rochester and the National Cancer Institute, and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All study participants or their guardians (for minor patients) provided written informed consent.

Study Outcome and Variables

The study outcome (presence or absence of neoplasm) was determined from patient self-response to the following question: “*Have you ever had or do you have any of these conditions?*” Study participants who responded affirmatively to the option of *Cancer or tumor* were asked to specify the anatomic organ of origin.

The study variables of interest were: 1) DM type (DM1 vs. DM2), which was further classified as: a) *definite*, if the patient was mutation-positive by genetic testing or was clinically diagnosed and had a parent or a child with a DNA-confirmed DM diagnosis; b) *probable*, if the patient lacked DNA testing results, but had clinical signs and symptoms consistent with a diagnosis of DM; and c) *congenital* (in DM1 only), if the patient had clinical symptoms consistent with DM within the first 4 weeks of life, and had either a positive DNA test or a mother with DM1; and 2) demographic, lifestyle, and clinical factors

including sex, age at DM diagnosis, age at registry enrollment, race/ethnicity, current tobacco smoking, and body mass index (BMI). When DNA testing results were available, nucleotide (CTG or CCTG) repeat expansion size was included in the analysis.

Statistical Analysis

In this cross-sectional study, we compared patients' demographic, lifestyle, and clinical factors by DM type and by the presence or absence of neoplasms using chi-square or Fisher's exact test for categorical variables, and Mann-Whitney U test for continuous variables. For descriptive analyses, continuous variables were also categorized into tertiles based on the distribution in all DM patients. To evaluate the strength of association between the age at DM diagnosis and repeat expansion size, we used Pearson's correlation coefficient. To identify factors associated with neoplasm development in DM patients, we developed multivariable logistic regression models, and calculated the adjusted odds ratio (OR) and 95% confidence interval (CI) for each variable, while controlling for the others in the model. The final model included DM type, age at registry enrollment, age at DM diagnosis, and gender. To evaluate the role of leukocyte DNA repeat expansion size in DM tumorigenesis, we performed a sub-analysis of patients who had undergone diagnostic DNA testing and developed multivariable models stratified by DM type. These models included repeat expansion size (CTG in DM1, and CCTG in DM2), age at DM diagnosis, age at registry enrollment, and gender.

Results

Overall, 950 DM patients were enrolled in the *National Registry of Myotonic Dystrophy and Facioscapulohumeral Dystrophy* between 2000 and 2011. We excluded 39 patients who had symptoms of DM, but in whom DM type was not specified, leaving 911 patients in the study (DM1=781; DM2=130). Of these, 499 (63.9%) had definite DM1 (among whom 100 patients had congenital disease), and 87 (66.9%) patients had definite DM2. Of the definite DM patients, DNA test results were available for 79.6% of DM1, and 62.1% of DM2 subjects (Figure 1).

Baseline Patient Demographics, Lifestyle, and Clinical Characteristics by DM Type

Compared with DM2, DM1 patients were more likely to be male ($p=0.001$), younger at both the age at DM diagnosis ($p<0.0001$) and age of registry enrollment ($p<0.0001$), and had lower BMI ($p=0.0003$) (Table 1). However, the prevalence of tobacco smoking was comparable between DM1 and DM2 patients ($p=0.31$). Patient characteristics were similar in those with a definite/congenital DM diagnosis and those found in all DM study participants (Supplementary Table 1). Among DNA-confirmed patients, the median CTG repeat expansion size in DM1 patients ($n=397$) was 450 (range=42–2307) while the median CCTG repeat expansion size in DM2 patients ($n=54$) was 14,000 (range=300–15,600). In DM1 patients, we observed an inverse correlation between repeat expansion size and age at diagnosis ($r=-0.57$, $p<0.0001$), a pattern that was not observed in DM2 patients ($r=0.10$, $p=0.43$) (Figure 2).

Factors Associated with Neoplasm Development in DM Patients

Among study participants, 95 (10.4%) reported a personal history of neoplasm. DM1 patients were more likely to develop tumors at a younger age (<50 years) compared with DM2 patients (43% vs. 6.3%, respectively). The most commonly-reported neoplasms in DM1 patients were those of the skin ($n=32$ including 10 basal cell carcinomas, 6 melanomas, and 16 non-specified), breast ($n=7$), thyroid ($n=5$), cervix ($n=5$), and colon ($n=5$). In DM2 patients, the most commonly-reported cancers involved the breast ($n=4$), thyroid ($n=3$), skin ($n=2$), and ovaries ($n=2$) (Supplementary Table 2). Among patients with

neoplasms, tumors of the skin were more prevalent in DM1 patients (40.5% vs. 12.5%, $p=0.03$); however, endocrine gland tumors (pancreas, parathyroid, pituitary, or thyroid) were more prevalent in DM2 patients (37.5% vs. 6.3%, $p=0.003$).

In the unadjusted analysis evaluating factors associated with neoplasia in DM patients, tumors were more prevalent in females (13.0% in females vs. 7.6% in males $p=0.009$), patients diagnosed with DM at an older age (median=38 years vs. 31, $p<0.0001$), and those who were older at registry enrollment (median=54 years vs. 43, $p<0.0001$). DM type (10.1% in DM1 vs. 12.3% in DM2, $p=0.45$), tobacco smoking (8.4% vs. 9.4%, $p=0.75$) and BMI (median=24 vs. 25 kg/m², $p=0.20$) were not associated with reported neoplasms in this analysis (Table 2).

In the multivariable analysis (Table 2), after adjusting for the other variables in the model, female gender (adjusted OR=1.9, 95% CI=1.2–3.1, $p=0.007$) and older age at registry enrollment (adjusted OR=1.08, 95% CI=1.06–1.1, $p<0.0001$), but not age at DM diagnosis (adjusted OR=0.99, 95% CI=0.97–1.01, $p=0.33$), remained statistically significantly associated with neoplasia. Importantly, DM1 patients had twice the tumor risk compared with DM2 patients (adjusted OR=2.1, 95% CI 1.1–4.1, $p=0.03$). A similar pattern was observed after excluding patients with congenital DM1 ($n=100$) (adjusted OR comparing DM1 with DM2=2.3, 95% CI=1.2–4.7), after restricting the analysis to only adult-onset DM (initial symptoms ≥ 20 years of age) (adjusted OR=1.8, 95% CI=0.9–3.7), and after restricting the analysis to those with definite DM ($n=482$) (adjusted OR=1.4, 95% CI=0.6–3.1).

In a sub-analysis including patients with known DNA test results (397 DM1, 54 DM2), leukocyte DNA repeat expansion size was not statistically significantly associated with tumor risk in either DM1 (OR=0.99, $p=0.26$) or DM2 patients (OR=1.00, $p=0.34$) after controlling for gender, age at registry enrollment, and age at DM diagnosis.

Discussion

In this large cross-sectional study, we found that DMtype 1 and female gender were associated with tumor development in DM patients after controlling for age at DM diagnosis and age at enrollment into the Registry. Yet, there was no apparent association between DNA repeat expansion size and tumor risk.

The observed higher odds of tumor development in female DM patients may be related to the cancer profile associated with DM. Our recently-published population-based registry study demonstrated an excess of female genital cancers in DM patients [8]. In the current study, breast neoplasms were the most numerous in female patients, as we observed in our previous study, although the latter did not translate into a higher quantitative risk of breast cancer when compared with the general population [8].

Among current study participants, skin tumors were the most frequent neoplasms in DM1 patients, as they are in the general population. In the literature, pilomatricoma (benign, frequently-calcified, tumors of the hair matrix) was the most commonly reported neoplasm in DM patients [7]. These case reports included a significant number of DM patients with multiple primary pilomatricoma and/or several other family members with pilomatricoma. Pilomatricoma has also been associated with other inherited cancer-susceptibility disorders, including Rubinstein-Taybi syndrome (caused by mutations in the *CREBBP* gene), and Gardner syndrome, a variant of familial adenomatous polyposis (caused by mutations in the *APC* gene) [13, 14]. Additionally, several reports have suggested that multiple basal cell carcinomas may represent a phenotypic variant of DM [15–18]. Several mechanisms of skin tumor development in DM have been proposed earlier [7, 19]. In the current study, 10 basal

cell carcinomas were reported, but none of the reported skin tumors were specified as pilomatricomas, likely because this diagnosis was not specifically sought in the Registry questionnaire; 18 subjects (16 with DM1, and 2 with DM2) reported only “skin tumor,” without further specification. Thus, quantifying skin tumor risk in DM patients is of importance particularly in light of their high incidence in the general population.

On the other hand, the most commonly-reported tumors in the registry among DM2 patients were endocrine in origin. While endocrine gland neoplasms in DM patients existed in case reports and epidemiological studies [7–9], a relationship between DM2 and endocrine tumors has neither been characterized nor confirmed. This finding warrants additional research to understand if this association is real and, if so, to determine the mechanisms which might underlie this tumor profile variation by DM subtype.

Longer repeat expansion size in DM1 [20], but not DM2 [21], has been correlated with earlier age at DM diagnosis, with which our findings agree, and with more severe disease. In our sub-analysis, however, we did not observe an association between leukocyte DNA repeat expansion size and tumor development in either DM1 or DM2 patients. Past studies of neoplasms from DM1 patients have found that tumors contained longer CTG-repeat expansions than adjacent normal tissue [22–24]. The high degree of tissue mosaicism in DM1 patients may provide an explanation as to why the repeat expansion size measured in peripheral blood DNA is not associated with tumor development in DM patients [25, 26]. Tumor tissues were not available for this study to evaluate the effect of tissue-specific repeat expansion size on tumor development in DM patients. Additionally, the small number of participants with available DNA repeat expansion size information limits our ability to draw definitive conclusions about its role in DM tumorigenesis. A future study with a larger sample size is needed to better characterize whether a relationship between repeat expansion size and tumor development does or does not exist.

Future studies are also needed to explore the possible role for the *dystrophia myotonica-protein kinase (DMPK)* gene in DM-related tumor development, particularly because more oncogenes have been found in the protein kinase gene family compared with the zinc-finger protein gene family [11]. Cancer-susceptibility genes found in the protein kinase gene family include *PRKARIA* (Carney complex), *STK11* (Peutz-Jeghers syndrome), *RAFI* (Noonan syndrome), *BRAF* (in cancers of the ovary, skin, colon, thyroid, and in glioblastomas), and others [12].

To our knowledge, our study is the first to evaluate correlates of tumor development in patients with DM. The use of the *National Registry of Myotonic Dystrophy and Facioscapulohumeral Dystrophy* database provided a large sample of a clinically well-characterized DM patient population, of whom the majority were confirmed. However, the study was limited by the self-reporting of tumor history. Patient self-reported tumor/cancer history has been found to be reasonably accurate when compared with population-based registry reported cancers in most cases (sensitivity ranges from 55 to 90%), particularly for common cancers such as breast and prostate [27–29]. The possibility that tumor history may have influenced patients’ participation in the registry is a theoretical concern, but we would not expect differential biases based on self-reported tumor reporting or the possible influence of tumor history on registry participation. The relationship between DM and cancer has only recently been recognized, and it would not be expected to vary by DM type or gender. Moreover, this study analyzed relative odds of neoplasm in DM1 as compared with DM2 patients. Therefore, while we can say that tumors are significantly more common in DM1 than in DM2, we cannot determine whether DM2 patients are at increased risk of tumors relative to the general population or not.

In conclusion, our study suggests that DM patients who are female or who have DM1 are more likely to develop tumors *versus* those who are male or who have DM2. This study is an initial step in advancing our understanding of the possible factors that affect neoplasm development in DM patients. Further research is needed to confirm our results and to elucidate the underlying biological/molecular mechanism for such an association. Recognition of possible risk factors for neoplastic activity in DM patients has implications for medical surveillance and management, including the initiation of appropriate cancer screening. Additional research is required to determine whether DM type plays a critical role in the risk and tissue type of neoplasms observed in this context.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Flowchart summarizing study participants.

Figure 2. Correlation between repeat expansion size and age at myotonic dystrophy diagnosis in (A) DM1 patients, and (B) DM2 patients.

Table 1

Patients' demographic, lifestyle, and clinical factors by DM type.

	DM1 (N=781) N (%)	DM2 (N=130) N (%)	P-value *
Sex			
Male	388 (49.7)	45 (34.6)	0.001
Female	393 (50.3)	85 (65.4)	
Age at Initial DM Symptoms (Yrs)			
0–19	331 (43.8)	21 (16.7)	<0.0001
20–34	260 (34.4)	37 (29.3)	
35+	164 (21.7)	68 (54.0)	
Age at DM Diagnosis (Yrs)			
0–24	269 (34.4)	5 (3.8)	<0.0001
25–39	313 (40.0)	28 (21.5)	
40+	191 (24.5)	96 (73.8)	
Age at Enrollment (Yrs)			
0–39	337 (43.1)	15 (11.5)	<0.0001
40–49	226 (28.9)	30 (23.0)	
50+	218 (27.9)	85 (65.4)	
Race			
White, non-Hispanic	716 (91.7)	126 (96.9)	0.04 **
Other	54 (6.9)	3 (2.3)	
Current Tobacco Smoking			
Yes	76 (9.7)	9 (6.9)	0.31
No	705 (90.3)	121 (93.1)	
Body Mass Index			
Underweight (<18.5)	118 (15.1)	6 (4.6)	0.0003
Normal (18.5–24.9)	335 (42.9)	47 (36.2)	
Overweight (25.0–29.9)	208 (26.6)	45 (34.6)	
Obese (≥ 30)	120 (15.4)	32 (24.6)	

Abbreviation: DM=myotonic dystrophy

* P-value calculated by Chi-square-test unless otherwise specified.

** P-value calculated by Fisher's Exact test.

Table 2
Odds ratios of neoplasia associated with DM patients' demographic and clinical characteristics.

Characteristics	History of Neoplasms		Odds of neoplasm by patients' characteristics			
	Yes N=95	No N=816	Unadjusted		Adjusted*	
DM Type	n(%)	Median (Range)	OR (95% CI)	P-value	OR (95% CI)	P-value
DM1	79 (10.1)	702 (89.9)	0.80 (0.45–1.42)	0.45	2.11 (1.10–4.10)	0.03
DM2	16 (12.3)	114 (87.7)	Ref.		Ref.	
Sex						
Female	62 (13.0)	416 (87.0)	1.81 (1.16–2.82)	0.009	1.92 (1.20–3.10)	0.007
Male	33 (7.6)	400 (92.4)	Ref.		Ref.	
Age at Diagnosis (Yrs)	38 (0–69)	31 (0–70)	1.04 (1.02–1.05)	<0.0001	0.99 (0.97–1.01)	0.33
Age at Enrollment (Yrs)	54 (18–80)	43 (0–80)	1.07 (1.05–1.09)	<0.0001	1.08 (1.06–1.11)	<0.0001

Abbreviations: DM=myotonic dystrophy, OR=Odds Ratio, CI=Confidence Interval

* Adjusted for all other variables in the table