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Benign and Malignant Tumors in the UK Myotonic Dystrophy Patient Registry

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Abstract

Introduction.—In light of recent evidence that cancer is part of the myotonic dystrophy (DM) phenotype, we assessed the prevalence of benign and malignant tumors among 220 patients enrolled in the UK Myotonic Dystrophy Patient Registry, and evaluated factors associated with their development.

Methods.—A survey was distributed to collect tumor history and lifestyle information. We used multinomial logistic regression for the analysis.

Results.—Thirty-nine benign (30 patients), and 16 malignant (15 patients) tumors were reported. Increasing age (OR=1.13, 95%CI=1.05–1.21, $p=0.001$) and earlier age at DM diagnosis (OR=1.06, 95%CI=1.00–1.13, $p=0.04$) were associated with benign and malignant tumors (OR=1.20, 95%CI=1.10–1.30, $p<0.001$; OR=1.08, 95%CI=1.01–1.15, $p=0.02$, respectively). Female gender was associated with benign tumors only (OR=6.43, 95%CI=1.79–23.04, $p=0.004$). No associations were observed between tumors and smoking ($p=0.24$), alcohol consumption ($p=0.50$), or BMI ($p=0.21$).

Discussion.—Our results confirm previous findings suggesting a limited role for common lifestyle factors, and a potential genetic contribution, in DM tumor predisposition.

Keywords

Myotonic dystrophy; tumor; cancer; risk factors; lifestyle factors; smoking

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Introduction

Myotonic dystrophy type I (DM1) and type II (DM2) are complex autosomal dominant, nucleotide repeat expansion disorders characterized by progressive muscle weakness, myotonia, and multi-system involvement.^{1, 2} Published case reports have speculated that patients with myotonic dystrophy (DM) are at increased risk of benign and malignant tumors, most commonly, pilomatricoma (a rare benign calcifying cutaneous neoplasm).³ Recent large epidemiological studies provided evidence that patients with DM are at increased risk of cancers of the endometrium,⁴⁻⁷ ovary,^{5, 6} eye,^{6, 8} thyroid,^{5, 6, 8} brain,^{5, 6} and testes.^{4, 8} Excess risk of colon, lung, and possibly melanoma and non-melanoma skin cancers were also reported.⁴⁻⁹ The molecular mechanism behind DM-tumorigenesis is yet to be discovered. Proposed mechanisms include possible modified expression of tumor suppressor genes or oncogenes due to RNA spliceopathy, altered protein-coding mechanisms, and/or upregulation of β -catenin.^{3, 10-13}

Previous studies of US and Italian DM patients suggested a limited role of smoking, alcohol consumption, and obesity in DM-related tumor predisposition.^{14, 15} In this study, we assessed factors associated with benign and malignant tumors separately, using data we collected from patients enrolled in the United Kingdom Myotonic Dystrophy Patient Registry (UK DM Registry).

Methods

Study population

The UK DM registry is a self-enrollment registry targeting patients living with DM in the United Kingdom. It collects clinical and genetic information that are subsequently validated by medical professionals.^{16, 17} In February 2015, we distributed a web-based survey to adult (≥ 18 years old) UK DM registry enrollees (n=409), followed by a mail survey to non-responders. We collected information on patient history of benign and malignant tumors, and lifestyle factors. These data were linked to patient demographics and DM-related clinical factors collected by the registry. Research activities of the UK DM registry are approved by the UK National Research Ethics Service. Patients provided informed consent through an online portal, and data were de-identified before performing the analysis. This study was approved by the National Institutes of Health Office of Human Subjects Research.

Study variables

Tumor history was ascertained via patient self-response to the questions: “Have you ever been diagnosed with any benign (non-cancerous) tumor?” and “Have you ever been diagnosed with any type of cancer (a malignant growth or invasive tumor)?” Patients who indicated a history of benign or malignant tumor diagnosis were requested to specify the type of tumor and indicate the date or age of diagnosis. For this analysis, DM patients were categorized into: patients with no history of any tumor (benign or malignant), patients who reported a history of benign tumors only, and patients who reported at least 1 malignant tumor (irrespective of their benign tumor history). Lifestyle factors of interest included self-reported regular smoking (at least one cigarette per day for 3 months or longer) and alcohol

consumption (number of days/week at least one alcoholic drink was consumed in the past year). Demographic and clinical factors were available from the registry and included: patient gender, year of birth, body mass index (BMI) and age at DM diagnosis.

Statistical Analysis

We used multinomial logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI) of benign and malignant tumors, separately, in relation to the study variables of interest. Due to the small number of DM2 patients (n=10), we restricted the multivariable analysis to patients with DM1. Age at study enrollment and age at DM diagnosis were modeled as continuous variables, while patient gender, smoking status, alcohol consumption, and BMI (per World Health Organization BMI classification) as categorical variables. Two-sided tests were used and statistical significance was determined at p-value <0.05. Statistical analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 409 DM patients invited to participate in the study, 261 (64%) responded to the questionnaire (231 with DM1, 10 with DM2, and 20 with unknown DM type). Demographic and clinical characteristics of the DM1/DM2 patients with known tumor status (n=220) are summarized in Table 1. Approximately 50% of the patients were genetically confirmed, 33% reported ever regularly smoking (11% current smokers), 48% were overweight or obese, and 32% reported drinking an average of 2 alcoholic drinks more than once a week in the past 12 months. Among current smokers, an average of 10 cigarettes per day were reported and approximately 13% reported smoking 20 or more cigarettes per day.

Thirty-nine benign tumors in 30 patients, and 16 malignant tumors in 15 patients were reported. All malignant and 92.3% of benign tumors occurred in DM1 patients. Median age at cancer diagnosis was 52 years (Interquartile range=19 years). Skin cancers were the most commonly reported malignant tumors, followed by breast cancer. Tumors of the female reproductive system were the most commonly reported benign tumors (Table 2).

In the multivariable analysis, including only DM1 patients with available tumor and study variables (n=198), we found statistically significant associations with increasing age, and earlier age at DM diagnosis in both benign and malignant tumors. Yet, an association with female gender was only observed with benign tumors. Smoking, alcohol consumption, and BMI were not associated with benign or malignant tumors in this analysis (Table 3).

Discussion

In this cross-sectional study, 12.4% of the DM1/DM2 patients reported at least one benign tumor, and 6.2% reported at least one malignant tumor. Similar to prior studies,^{14, 15} skin cancers were the most commonly reported malignant tumors in this study. Possible mechanisms of tumor development in DM, specifically skin tumors, have been discussed in previous literature.^{3, 12} Notably, only one patient reported having a pilomatricoma. Pilomatricoma is the most frequently reported benign tumor in DM literature.³ However, our

study population was derived from the UK DM registry, which is intended to recruit DM patients for research purposes and therefore may not be representative of the overall DM population. Thus, population-based studies are warranted to ascertain the true prevalence of benign and malignant tumors in DM patients.

Results from this study confirm previous findings suggesting a limited role for smoking, alcohol consumption, and BMI in tumor predisposition among DM1 patients.^{14, 15} It is important to note that most reported malignancies were not among cancer types for which smoking or alcohol are known risk factors. Additionally, the reported smoking and alcohol consumption behavior of those patients is modest. Large longitudinal studies are warranted to elucidate risk factors by cancer type. A recent study suggested that the risk factors of skin cancer in DM patients resemble that of the general population.¹⁸

Similarly, previous studies have reported elevated odds of tumors in older patients^{14, 15} and in females,^{5, 6, 14, 15} which are consistent with our findings. Interestingly, the association with female gender in this study was observed for benign tumors only. This association may be in part explained by the numerous tumors of the uterus (fibroids=6) and ovary (ovarian cysts, not otherwise specified=4, 3 of which required surgical treatment); however, after excluding individuals who reported tumors in reproductive organs, our conclusions remained unchanged.

We observed a significant association between earlier age at DM diagnosis and both benign and malignant tumors after controlling for age at study enrollment, findings that have not been previously observed. In fact, Das et al. (2012) and Bianchi et al. (2015) reported no significant associations between tumors and age at DM diagnosis or disease duration, respectively.^{14, 15} Our observed association may indicate that patients with a more severe DM phenotype, which is inversely correlated with age at diagnosis, are more likely to develop tumors. Alternatively, it is possible that patients with severe DM phenotype are under close medical observation and therefore more likely to get diagnosed particularly with benign tumors. This finding may be of clinical importance and should be further investigated in larger and more comprehensive DM populations.

This study faces several limitations. As with all cross-sectional analyses, causation cannot be inferred and larger longitudinal studies are warranted. Additionally, our study may have been underpowered to detect statistically significant associations between reported tumors and the evaluated lifestyle factors; nonetheless, our results are consistent with previous findings. The use of a voluntary registry to collect information may have resulted in a non-representative subset of DM patients possibly influenced by tumor status; however, the mean age and gender distribution were similar between responders and all adult registry participants ($p>0.05$). Further, misclassification in self-reported tumor status is a possibility, though personal cancer history via self-report has been previously validated and found to be reasonably accurate.¹⁹⁻²¹

Better understanding of tumor burden and factors that impact tumorigenesis in DM patients will inform clinical care and provide insight into the etiology of tumor development in this unique population. In light of the current knowledge, it is important to incorporate

population-based cancer screening guidelines into DM patients' clinical care, and to carefully evaluate new symptoms that may be indicative of cancer. Further research is needed to elucidate factors associated with tumor development in DM.

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Abbreviations

BMI	Body mass index
CI	Confidence interval
DM	Myotonic dystrophy
DM1	Myotonic dystrophy type I
DM2	Myotonic dystrophy type II
OR	Odds ratio
UK	United Kingdom

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Table 1:

Characteristics of 220 DM patients who completed the tumor history questionnaire

	No Tumor (N=178)			Benign Only (N=27)			Malignant (N=15)*		
Patient Characteristics	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
Age (years)									
At study enrollment	178	45.63	(12.67)	27	52.93	(10.19)	15	60.53	(12.74)
At DM diagnosis	174	34.25	(14.38)	23	35.09	(11.03)	15	41.80	(13.49)
At first DM symptom	167	28.44	(15.20)	22	32.55	(12.65)	15	34.53	(14.39)
	N	%		N	%		N	%	
Disease Duration (years)									
1–9	83	46.63		5	18.52		4	26.67	
10–19	62	34.83		8	29.63		4	26.67	
20+	29	16.29		10	37.04		7	46.67	
Missing	4	2.25		4	14.81		0	0.00	
DM Type									
DM1 (incl. congenital n=7)	174	97.75		25	92.59		15	100.00	
DM2	4	2.25		2	7.41		0	0.00	
Gender									
Female	85	47.75		21	77.78		9	60.00	
Male	93	52.25		6	22.22		6	40.00	
BMI (kg/m²)									
Underweight/Normal (<25)	82	46.07		16	59.26		4	26.67	
Overweight (25–29.99)	57	32.02		5	18.52		8	53.33	
Obese (30+)	31	17.42		2	7.41		3	20.00	
Missing	8	4.49		4	14.81		0	0.00	
	N	%		N	%		N	%	
Regular Smoking									
Never	118	66.29		18	66.67		12	80.00	
Former	40	22.47		5	18.52		3	20.00	
Current	20	11.24		4	14.81		0	0.00	
Alcohol consumption									
Never	22	12.36		5	18.52		3	20.00	
<4 times a month	65	36.52		6	22.22		3	20.00	
Once a week	35	19.66		6	22.22		5	33.33	
2–3 days per week	34	19.10		4	14.81		2	13.33	
4–7 days per week	22	12.36		6	22.22		2	13.33	

* Includes 3 patients with both benign and malignant tumors.

Table 2:

Self-reported benign and malignant tumors in 220 DM1 and DM2 patients.

Site	Benign		Malignant	
	N*	(%)	N*	(%)
Skin [†]	4	(10.3)	4	(25.0)
Breast	2	(5.1)	3	(18.75)
Female Reproductive System [‡]	11	(28.2)	2	(12.5)
Colon & Rectum	2	(5.13)	1	(6.25)
Head, Neck & Throat	0	(0.0)	1	(6.25)
Male Genital System	0	(0.0)	1	(6.25)
Hematological	0	(0.0)	1	(6.25)
Endocrine	6	(15.4)	0	(0.0)
Salivary gland/Parotid	4	(10.3)	0	(0.0)
Other/Unspecified	10	(25.6)	3	(18.75)
Total	39		16	

* Number of tumors, not patients. For patients with more than one tumor, both tumors are listed.

[†] Benign: pilomatricoma (n=1), pilar cyst (n=1) and unspecified (n=2); malignant: basal cell carcinoma (n=2), melanoma (n=1), and unspecified (n=1)

[‡] Benign: uterine fibroids (n=7) and ovarian cysts (n=4); malignant: endometrial cancer (n=1), and cervical cancer (n=1).

Table 3:

Adjusted odds ratios for benign and malignant tumors by clinical and behavioral factors in 198 DM1 patients.

Variable	Benign			Malignant		
	Adjusted OR*	95% CI	p-value	Adjusted OR*	95% CI	p-value
Age (years)	1.13	1.05, 1.21	<0.01	1.20	1.10, 1.30	<0.01
Age at DM diagnosis [†] (years)	1.06	1.00, 1.13	0.04	1.08	1.01, 1.15	0.02
Gender						
Male	Ref			Ref		
Female	6.43	1.79, 23.04	<0.01	1.88	0.53, 6.65	0.33
BMI (kg/m²)						
Underweight/Normal (<25)	Ref			Ref		
Overweight (25–29.99)	0.36	0.10, 1.22	0.10	2.66	0.60, 11.77	0.20
Obese (30+)	0.44	0.08, 2.32	0.33	2.68	0.42, 16.98	0.29
Regular Smoking						
Never	Ref			Ref		
Ever	2.00	0.68, 5.90	0.21	0.47	0.10, 2.26	0.35
Alcohol Consumption						
Over a week	Ref			Ref		
> Once a week	2.48	0.77, 7.97	0.13	1.2	0.30, 4.85	0.80
None	1.44	0.25, 8.47	0.69	2.51	0.44, 14.48	0.30

* Adjusted for age, age at DM diagnosis, gender, smoking status, alcohol consumption, and BMI.

[†] Modeled as negative age to evaluate every 1 year **decrease** in age at DM diagnosis