 doi:10.1111/ene.12542

Endocrine function over time in patients with myotonic dystrophy type 1

J. R. Dahlqvist, M. C. Ørngreen, N. Witting and J. Vissing

Neuromuscular Research Unit, Department of Neurology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Keywords:
endocrine dysfunction, fertility, libido, myotonic dystrophy type 1

Received 28 January 2014
Accepted 23 June 2014

Background and purpose: Patients with myotonic dystrophy type 1 (DM1) have an increased incidence of endocrine dysfunction. In this study, the temporal evolution of endocrine dysfunction in patients with DM1 was investigated.

Methods: Endocrine function was assessed in 68 patients with DM1, in whom endocrine function had been followed, on average, for 8 years. The endocrine function was assessed by measuring the concentration of hormones and metabolites in blood and by validating libido with questionnaires.

Results: At baseline, 30 of the 68 patients presented with at least one hormonal dysfunction. When re-evaluated after 8 years, 57 of 68 patients had endocrine dysfunction. Diabetic patients had increased from one to four. At follow-up, hyperparathyroidism occurred in 25% and abnormal thyroid-stimulating hormone in 21%, compared with 14% and 9% at baseline. Sixteen of 33 men had increased luteinizing hormone levels compared with seven at baseline.

Conclusions: Our findings show that endocrine abnormalities amongst patients with DM1 increase over time. Based on these findings it is suggested that correctable endocrine abnormalities should be monitored periodically in this patient group.

Introduction

Myotonic dystrophy type 1 (DM1) is the most common muscular dystrophy worldwide, with a prevalence of 8–10 per 100 000 [1]. It is characterized by involvement of many different organs. Typical clinical features are myotonia, distal muscle wasting, cataracts, cognitive dysfunction, fatigue, hair loss and various endocrine dysfunctions. The disease is caused by a dominantly inherited CTG repeat expansion on a non-coding region of the dystrophia myotonica protein kinase (*DMPK*) gene on chromosome 19. CTG expansions vary over time and amongst tissues in patients with DM1 [1]. The pathogenesis of the disease is not completely understood, but a central mechanism is that the mutant *DMPK* gene disrupts the normal RNA metabolism resulting in disrupted regulation of alternative splicing, mRNA translation and mRNA stability [1,2]. As an example, myotonia is caused by abnormal splicing of the skeletal muscle-specific chloride channel [2].

Cross-sectional studies have shown an increased prevalence of endocrine dysfunctions, especially hypogonadism, diabetes and hyperparathyroidism, in DM1 patients [3–5]. However, the temporal evolution of endocrine dysfunction has never been described, and knowledge of this is necessary to understand the disease process and to plan clinical follow-up. In this study, the temporal evolution of endocrine dysfunction in DM1 was investigated.

Correspondence: J. Dahlqvist, Neuromuscular Research Unit, Department of Neurology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark (tel.: +45 35456135; fax: +45 35456138; e-mail: juliardahlqvist@gmail.com).

Materials and methods

The study was approved by the Danish National Committee on Health Research Ethics (H-1-2012-121), and all patients consented to participation. A total of 132 patients were identified in whom a comprehensive metabolic and hormonal profile dating back more than 5 years was available (Fig. 1). Sixty-eight (19–68 years of age) consented to participate and were included.

The majority of recruited patients (66.2%) had the adult form of DM1, 22% had the early adult form, and 11.8% were affected by the infantile form [6]. They had 56–1800 CTG repeats (mean 293 ± 44 repeats). Two patients were wheelchair bound at follow-up.

In all included patients, the previous analyses were repeated (follow-up analyses) and additional examinations were made (cross-sectional analyses) in accordance with the development of diagnostic tools.

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THE OFFICIAL JOURNAL OF THE EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

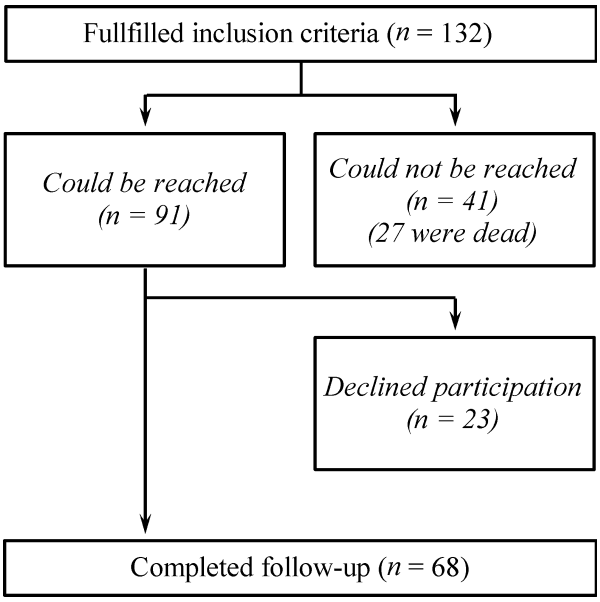

Figure 1 Flow diagram illustrating the identification of participants included in the 8-year follow-up.

Follow-up analyses

The concentration of glucose, free calcium, parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone and prolactin in venous blood was used to assess the endocrine function in the patients. All blood samples were analysed within 4 h after sampling at the Department of Clinical Biochemistry at Rigshospitalet, Copenhagen.

Patients presenting with abnormal calcium values at follow-up were invited for re-testing of calcium, PTH and vitamin D levels after an approximate 6-month interval.

The muscle strength of finger flexion, ankle dorsi flexion and neck flexion was scored using the Medical Research Council scale [7].

Cross-sectional analyses

Hemoglobin A1c (HbA1c) level was measured and an oral glucose tolerance test (OGTT) was performed to investigate the glucose tolerance in patients with DM1 [8].

After an overnight fast, the subjects underwent a standard 75 g OGTT (75 g of anhydrous glucose in 250 ml water). Subjects were instructed to eat a standard diet for 3 days before the test [9]. Subjects with known diabetes did not perform the OGTT but fasting plasma glucose was measured. Glucose tolerance was classified according to the 1999 WHO criteria [10].

Validated self-administered questionnaires were utilized to evaluate relationship status and libido. The questionnaire for women was composed of nine multiple-choice questions, which included the 'sexual desire' and 'arousal' domains of the Female Sexual Function Index (FSFI) [11]. Individual domain scores range from 0 to 6, with a higher score indicating better sexual function and a score of zero indicating no sexual activity during the previous 4 weeks. The questionnaire for men was composed of 11 items, which included the 'sexual desire' and 'erectile function' domains of the International Index of Erectile Function [12]. The sexual desire domain score ranges from 2 to 10, where a higher score indicates higher sexual desire. The total score of the erectile function domain identifies patients with erectile dysfunction (score <25) and without erectile dysfunction (score ≥ 25). A score of zero indicates no sexual activity during the previous 4 weeks. The female results were compared with 131 controls used in the initial validation of the FSFI [11] and the male results with 109 male volunteers without any history of erectile dysfunction [12]. Further, the results were compared with a group of patients with facioscapulohumeral muscular dystrophy (FSHD), recruited from our clinic, with a similar level of physical impairment as the DM1 patients.

Statistical analyses

The Student's t test was used and a P value <0.05 was considered significant. The Pearson correlation test and partial correlation were used to demonstrate correlation between parameters. Values are mean $\pm$ SE.

Results

At baseline, 44% of the 68 DM1 patients included in this study presented with at least one endocrine dysfunction. When assessing the same metabolic parameter in the same patients after 8 years, this number had increased to 84%. The prevalence ratio of at least one endocrine dysfunction at baseline and follow-up was as follows: infantile form (mean age at follow-up 31.6 $\pm$ 3 years), 0.57 and 0.88; early adult form (35.8 $\pm$ 2 years), 0.45 and 0.94; and adult form (42.3 $\pm$ 1 years), 1.20 and 1.04. The prevalence was not significantly different in the three subgroups at baseline or at follow-up.

Patients in this follow-up study were compared with patients who could not be recruited, including those who had died (Table 1). Recruited patients tended to

Table 1 Demographic data at baseline for recruited, non-recruited and deceased DM1 patients

Subject group	*n*	Gender (♂/♀)	Age (years, SE)	CTG_n (mean, SE)	MRC score	Endocrine dysfunctions[a] (%)
Recruited	68	33/35	35 ± 1	293 ± 44	4.3 ± 0.1	44
Non-recruited	37	19/18	39 ± 2	420 ± 58	3.9 ± 0.1[b]	62
Deceased	27	17/10	52 ± 2[c]	523 ± 112	3.5 ± 0.1[b]	67

MRC, Medical Research Council.
[a]Percentage of patients presenting with at least one endocrine dysfunction at baseline; [b]indicates a significant ($P < 0.05$) difference from recruited subjects; [c]mean age at death was 57 ± 2 years.

be younger, stronger and with fewer endocrine abnormalities at baseline.

Calcium metabolism

During follow-up, the prevalence of elevated plasma levels of PTH increased from 14% to 25%, hypocalcaemia increased from 0% to 18% and hypercalcaemia was unchanged at 5% (Table 2; Fig. 2).

Forty per cent of the patients with abnormal values of PTH or free calcium at baseline had normal values at follow-up. Twelve of the 15 patients with abnormal calcium values at follow-up were available for re-investigation and, in these, calcium had normalized in 67% (Table 2).

Vitamin D deficiency was found in four of the patients with hypocalcaemia at follow-up. Twenty-seven patients took vitamin supplements with calcium and/or vitamin D at follow-up. The prevalence ratio of hypocalcaemia in this group of patients was 0.84. There was no correlation between calcium and PTH at baseline and follow-up. Further, there was no correlation between calcium and vitamin D or PTH and vitamin D in patients available for re-investigation at follow-up.

Glucose metabolism

At follow-up, the number of subjects with diabetes had increased from one to four. The OGTT demonstrated impaired glucose tolerance in 11 patients and two with impaired fasting glycaemia (Table 2; Fig. 2). Three of the patients with diabetes and one of the patients with impaired glucose tolerance had HbA1c higher than 6.5%.

Thyroid system

At baseline, 6% had elevated plasma TSH levels and 3% had decreased plasma TSH. Three of the four patients with elevated TSH were diagnosed with hypothyroidism and have been treated with levothyroxine since then. At follow-up, an additional patient was diagnosed with hypothyroidism. Ten per cent presented with decreased TSH and normal T3 and T4, and 4% with increased TSH (Table 2; Fig. 2). None of the patients included in this study was diagnosed

Table 2 Metabolic and hormonal profiles in DM1 patients over an 8-year follow-up

	Baseline	Follow-up	Repeat[a]
Glucose metabolism	*n* = 65	*n* = 68	
Diabetes	1	4	
Impaired tolerance	0[b]	11	
Impaired fasting glycaemia	6[b]	2	
Normal plasma glucose	58[b]	51	
Calcium metabolism	*n* = 63	*n* = 67	*n* = 12
Hyperparathyroidism (high PTH)	10	17	
Low free calcium levels	0	6	2 of 4
Normal free calcium levels	9	10	
High free calcium levels	1	1	1 of 1
Euparathyroidism (normal PTH)	53	50	
Low free calcium levels	0	6	1 of 5
Normal free calcium levels	51	42	
High free calcium levels	2	2	0 of 2
Hypoparathyroidism (low PTH)	0	0	
Thyroid system	*n* = 66	*n* = 68	
High TSH levels	4	7	
Hypothyroidism (low T3 and/or T4)	3	4	
Normal T3 and T4	1	3	
Low TSH levels	2	7	
Sex hormones	♂ *n* = 27	♂ *n* = 33	
High LH levels in male subjects	7	16	
Absolute androgen insufficiency (low testosterone)	1	3	
Relative androgen insufficiency (normal testosterone)	6	13	

PTH, parathyroid hormone; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; LH, luteinizing hormone.
[a]The patients presenting with abnormal calcium values at follow-up were invited to a repeat blood test. Twelve of the 15 patients were available for re-investigation. [b]OGTT was only performed at follow-up, and glycaemic data from baseline are based on a single plasma glucose blood sample. Six patients had plasma glucose between 6.1 and 7.0 mM indicating impaired fasting glycaemia or impaired tolerance.

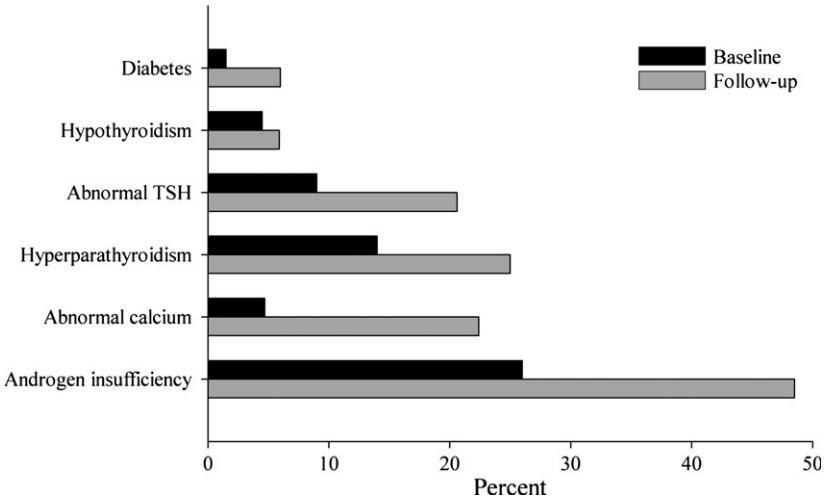

Figure 2 Changes in endocrine dysfunctions over an 8-year period in DM1 patients: *x*-axis, percentage of patients with endocrine dysfunctions at baseline (black) and follow-up (grey).

with a thyroid tumour, but they were not systematically screened.

Sex hormones

During follow-up, the prevalence of elevated LH levels increased from 26% to 48%; absolute androgen insufficiency increased from 4% to 9% and relative androgen insufficiency from 22% to 39% (Table 2; Fig. 2). The prevalence ratio of elevated LH in men at follow-up was for age <20 years, 1.04; 21–30 years, 1.04; 31–40 years, 0.35; 41–50 years, 1.19; and >60 years, 1.25. At follow-up, FSH was measured in addition to LH. With few exceptions, LH and FSH showed concordant abnormalities.

An upper level of LH could not be defined in female subjects since the majority of the women were unable to specify what menstruation stage they were in when blood samples were collected. Furthermore, no lower level of testosterone could be defined since the method of analysis used had a detection limit which was above the normal lower range of the reference interval for testosterone. Fifty-five per cent of the female subjects presented with testosterone levels under the detection limit at baseline and 57% at follow-up.

Libido

Libido data were only assessed at follow-up. Independent of relationship status, the women with DM1 had significantly lower sexual desire and arousal than healthy controls [11]. However, when compared with a group of women with FSHD, with a similar level of physical impairment as the DM1 patients, the sexual desire and arousal did not differ (Table 3). Erectile function score in the entire group of DM1 men was lower compared with healthy controls and men with FSHD [12]. However, DM1 men in a relationship showed similar scores as the controls (Table 3). There was no correlation between the erectile function or sexual desire scores and testosterone concentration in the male patients.

Clinical data

There was a decline in muscle strength from baseline to follow-up ($P < 0.0001$; Fig. 3).

The body mass index (BMI) of all patients was 24.0 ± 0.5 at follow-up. Twenty-three patients were overweight (BMI > 25) but only two patients were obese (BMI > 30).

Table 3 Female Sexual Function Index (FSFI) scores and International Index of Erectile Function (IIEF) scores for women and men with DM1

	All subjects with DM1	Subjects with DM1 in relationship	Patients with FSHD	Healthy controls
Female, FSFI scores	$n = 34$	$n = 22$	$n = 7$	$n = 131$
Desire (1.2–6.0)	3.1 ± 0.2[a]	3.3 ± 0.2[a]	3.1 ± 0.5	4.1 ± 0.1
Arousal (0–6.0)	3.2 ± 0.4[a]	4.0 ± 0.4[a]	3.5 ± 1.0	5.0 ± 0.1
Male, IIEF scores	$n = 33$	$n = 17$	$n = 6$	$n = 109$
Desire (2–10)	6.8 ± 0.4	7.2 ± 0.6	7.7 ± 0.7	7.0 ± 0.2
Erectile function (1–30)	19.0 ± 1.9[a]	23.3 ± 2.4	28.2 ± 1.1	25.8 ± 0.7

FSHD, facioscapulohumeral muscular dystrophy.
[a]Significant ($P < 0.05$) difference from healthy controls.

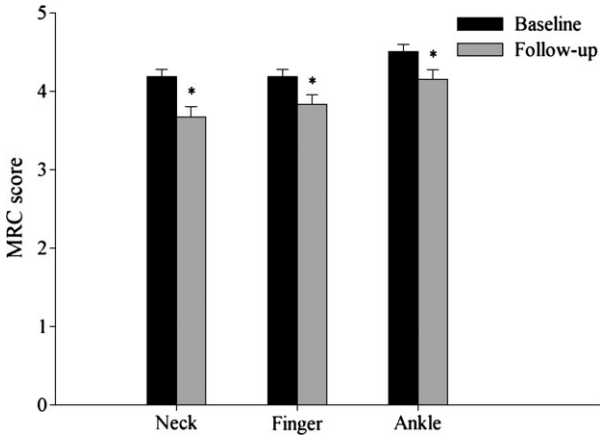

Figure 3 Changes in muscle strength over an 8-year period in DM1 patients. Neck, finger and ankle dorsi flexion were scored on the Medical Research Council (MRC) scale at baseline (black) and follow-up (grey). *Significant ($P < 0.0001$) difference from baseline.

No correlation was found between CTG repeat size and hormonal dysfunction at baseline or at follow-up, or between loss of muscle strength and increase in hormonal dysfunctions at follow-up.

Discussion

The main finding in this study was that the prevalence of endocrine abnormalities amongst patients with DM1 increases over time, suggesting that endocrine dysfunction in DM1 is progressive in nature as is the muscle affection. Hyperparathyroidism increased by 78%, diabetes increased by 300%, abnormal TSH by 133% and male androgen insufficiency by 85%. The increase in hormonal dysfunctions did not seem to correlate to disease severity since there was no correlation between increase in hormonal dysfunction and loss of muscle strength or CTG repeat. Furthermore, the prevalence of hormonal dysfunction was not dependent on onset type of the disease, i.e. infantile, early adult or adult.

These observations have important implications for planning of clinical follow-up and suggest that correctable endocrine abnormalities should be monitored periodically in this patient group.

Calcium metabolism

The number of patients with elevated PTH almost doubled during the follow-up period. Cross-sectional studies have previously reported an increased prevalence of hyperparathyroidism in DM1 patients [3–5]. It has been suggested that patients with DM1 may have abnormal reactivity of the PTH receptor or its signalling pathway resulting in pseudohypoparathyroidism (PHP), with symptoms that include cataract, bone deformities, mental retardation and myotonia. Patients with PHP have low calcium and high phosphate, and a high level of PTH [13]. Kinoshita *et al.* [13] suggested from a cross-sectional study that DM1 patients with high PTH and normocalcaemia will develop hypocalcaemia and PHP over time. Our longitudinal findings do not support an increase in hypocalcaemia over time but instead suggest that the calcium levels seem to fluctuate in patients with DM1. Therefore, repeat blood samples are recommended when screening for abnormal calcium metabolism.

Glucose metabolism

The prevalence of diabetes increased from 1.5% to 6%. This is almost twice the prevalence of 3%–4% in age-matched adults in the Danish background population [14].

At follow-up, all non-diabetic patients performed an OGTT, and impaired glucose tolerance was found in 16% and impaired fasting glycaemia in 3%. These results are supported by Matsumura *et al.* [5] who reported a prevalence of abnormal glucose metabolism of about 24% in 95 patients with DM1 with the same age as our DM1 cohort. In age-matched Danes, 10% have impaired glucose tolerance and 7% have impaired fasting glycaemia [14]. The lower prevalence of impaired fasting glycaemia in our DM1 cohort compared with the background population may possibly be explained by an insulin resistance, as seen in DM1 patients [15], which is compensated for by hyperinsulinaemia. The reduced insulin sensitivity has been explained by altered splicing of the insulin receptor in skeletal muscle, resulting in predominant expression of an insulin receptor with low sensitivity [1,5].

Aging is known to affect glucose metabolism, and the prevalence ratio of abnormal glucose metabolism in patients aged >40 years was 1.4 at follow-up. Another major predisposing factor to diabetes is obesity. The BMI of the included patients was 24.0 ± 0.5 at follow-up. The four patients with diabetes were all overweight with a BMI of 26.4 ± 0.7, but none of them was obese. The prevalence ratio of abnormal glucose metabolism at follow-up in patients with BMI > 25 was 1.6. Overweight may therefore play a role in patients with DM1 as well. Relative immobility caused by the muscle disease may also influence the prevalence of abnormal glucose metabolism.

The increased incidence of diabetes and impaired glucose tolerance suggests that glucose metabolism should be investigated regularly in patients with DM1. Since glucose metabolism cannot easily be disclosed by fasting plasma glucose measurements,

and OGTT is inconvenient in general clinical practice for DM1 patients, HbA1c can possibly be used as a marker in accordance with the newest guidelines on diagnosing diabetes [8]. Exercise should also be encouraged since it has been proved safe for DM1 patients and improves fitness and insulin sensitivity and reduces overweight [16,17].

Thyroid system

At baseline, the prevalence of an abnormal TSH level of 9% was comparable with the background population at the time. At follow-up, the prevalence had doubled to 21%, which is slightly higher than in the age-matched Danish background population [18,19]. The majority of the patients with abnormal TSH levels had normal T3 and T4 levels. Collectively, and in agreement with previous studies [20], the results do not indicate major disturbances in the thyroid gland axis in DM1 patients. It is therefore suggested that this patient group should not be subjected to more frequent thyroid dysfunction screening than the background population.

Sex hormones and libido

It was found that the prevalence of androgen insufficiency in male patients increased by 85% during the 8-year study period. This is in line with cross-sectional studies, indicating a high prevalence of hypogonadism in men with DM1 [3].

In the background population a decrease in androgen levels occurs with age, and approximately 20% of men older than 60 years have hypogonadism [21]. The mean age of the men with DM1 investigated at follow-up was 44 years, and only five of them were over 60 years old. It is therefore unlikely that the deterioration of androgen status is solely due to aging.

Hypogonadal men generally have lower sexual desire [22] and a higher prevalence of erectile dysfunction. Antonini *et al.* [23] investigated hypogonadism and erectile function in 30 men with DM1 and found hypogonadism in 60%. Almost 90% of the hypogonadal men had erectile dysfunction compared with 42% of those who were eugonadic. An erectile function score indicating erectile dysfunction was found in 73% of the hypogonadal DM1 men in our cohort and in 39% of the eugonadic. However, the DM1 men in our study did not have decreased sexual desire, and there was no correlation between testosterone level and sexual desire score.

The sexual desire and arousal scores were lower in women with DM1 than controls. However, the lower sexual desire may reflect physical disability, since FSHD women with a comparable disability to the DM1 women also had a lower sexual desire (Table 3).

Conclusion

In this first follow-up study of endocrine function in patients with DM1, it is demonstrated that the prevalence of endocrine dysfunction increases over time, especially diabetes, hyperparathyroidism and androgen insufficiency. Our findings suggest that endocrine function should be screened regularly and that the treating physician should be aware of emerging symptoms. Abnormal calcium levels should be confirmed with repeat blood tests, since the concentrations seem to fluctuate without clinical significance.

In the future, it would be interesting to investigate the temporal changes of hormonal dysfunction in a larger cohort of patients and over a longer follow-up period. To be able to do so, a multicentre study is necessary. That would introduce other problems, e.g. measurements carried out in many different laboratories, which should be taken into account when designing the study.

Acknowledgements

Thanks to AnnaMaria Giraldi from Sexological Clinic, Rigshospitalet, for her helpful input. We thank the Augustinus Foundation for financial support.

Disclosure of conflicts of interest

Dr Vissing has received research support and honoraria from Genzyme Corporation. He is a member of the Genzyme Pompe Disease Global Advisory Board. None of the other authors declare any financial or other conflicts of interest.

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