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Laboratory Abnormalities in Patients with Myotonic Dystrophy Type 2

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Abstract

Background—Myotonic dystrophy type-2 (DM2) is a recently discovered adult muscular dystrophy. Similar to DM1, this disease causes progressive debilitating weakness, clinical myotonia, and early cataracts, and is thought to cause widespread physiologic dysfunction of multiple organ systems.

Objective—To analyze and compile the laboratory abnormalities of patients with DM2.

Design—Baseline DM2 laboratory data were compiled representing 68 different types of laboratory tests and 1442 total studies.

Setting—University Medical Center.

Patients—Eighty-three adults with genetically confirmed or clinically probable DM2 were identified. Of these patients, 49 had documented baseline laboratory screening.

Main Outcome Measures—The individual frequencies of abnormal values in the population with DM2 studied.

Results—Of the 1442 studies, results for 359 (24.9%) were outside of their standard reference ranges. Of the 68 types of laboratory tests studied, 43 had values from fifteen or more different patients with DM2. The relative frequency of an abnormally elevated laboratory value was greater than 50% in several tests, including the levels of creatine kinase, total cholesterol, lactate dehydrogenase, and alanine aminotransferase (ALT). In addition, serum levels of immunoglobulin G (IgG) were low in 75% of all DM2 patients tested and absolute lymphocyte counts were low in 54% of all DM2 patients tested.

Conclusion—There is a high frequency of laboratory abnormalities in patients with DM2. These abnormalities provide insight into the widespread pathologic manifestations of DM2 and may form a basis for clinical monitoring and disease screening.

Introduction

Myotonic dystrophy type 2 (DM2) is an autosomal dominant muscular dystrophy discovered in 1994.(1) Although DM2 shares many of the multisystemic clinical features of myotonic dystrophy type-1, it does not carry DM1's characteristic CTG repeat on the 3′ region of the DMPK gene on chromosome arm 19q. Instead, DM2 is genetically linked to a unique CCTG repeat located on intron 1 of the zinc finger protein 9 (ZNF9) gene.(2) Both DM1 and DM2

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have widespread clinical implications. Similar to DM1, patients with DM2 experience muscle pain, progressive extremity and truncal weakness, stiffness, muscle myotonia, male hypogonadism, cardiac arrhythmias, diabetes mellitus, and early cataracts.(3) More recently, cognitive dysfunction, hearing loss, hypersomnia, and tremor have been reported in patients with DM2.(4)

In the past, a large-scale study identified a high frequency of abnormal clinical laboratory values in the DM1 population.(5) Ambulatory DM1 patients were found to have a wide range and a high prevalence of abnormal laboratory values reflecting dysfunction of the endocrinologic, hematologic, hepatic, and renal systems.(5) This study was similarly designed to analyze and compile the baseline laboratory values of a symptomatic group of DM2 patients. This analysis has the potential to: 1) further define the clinical manifestations of DM2; 2) discover previously unrecognized areas of DM2 systemic dysfunction; 3) provide a baseline laboratory profile for physicians caring for patients with DM2; and, 4) identify dysfunction amenable to early therapeutic intervention. Herein we compile the laboratory abnormalities of 1442 separate baseline studies from DM2 patients.

Methods

This study was approved by the University of Rochester (Rochester, New York) Institutional Review Board. Adult DM2 patients previously evaluated in the University of Rochester Healthcare System were identified for participation in this study. All the patients were older than 18 years and had: 1) genetically confirmed DM2; 2) weakness and myotonia with a symptomatic first degree relative with genetically confirmed DM2; or, 3) clinical features consistent with and suggestive of the diagnosis of DM2.

Participants who had not been genetically tested for DM2 were included if they met the following criteria: 1) clinically suspected DM2; 2) medical council weakness of 4 or fewer at an upper or lower extremity; 3) electrodiagnostic or clinical myotonia (as demonstrated through grip contraction, percussion of the wrist extensors, or percussion of the thenar eminence region); and, 4) negative genetic testing for DM1 or negative genetic testing for DM1 in a similarly affected first degree relative.

All selected DM2 participants had previously received care at the University of Rochester in the Muscular Dystrophy Association (MDA) clinic, outpatient setting, electrodiagnostic laboratory, or through their participation in a University of Rochester DM2 clinical trial. Eighty-three DM2 patients were identified; 49 of which had recorded baseline laboratory data. Twenty-nine of these patients were male; 20 were female.

Each participant underwent multiple laboratory studies, although none underwent all 68 separate tests. Patients were divided into male and female study groups. Laboratory reference ranges were defined based on standardized test reference ranges from the University of Rochester Medical Center Clinical Laboratories on April 5, 2010. These ranges are set through varied methods, including local volunteer testing and outside data accumulation. Where ever applicable, sex specific ranges were defined. In instances in which standard laboratory ranges were based on menstrual staging (i.e., levels of follicle-stimulating hormone (FSH) and luteinizing hormone) the reference range was broadened to include all possible premenstrual and postmenopausal values. Sex specific reference ranges were utilized to determine whether a laboratory value was high, low, or normal.

For each selected participant, past laboratory data were recorded in a spreadsheet format. In several instances patients were found to have multiple studies (over time) for one type of test. In these cases, the patient's laboratory result obtained under direct clinical trial supervision was selected. Otherwise, initial baseline laboratory studies were utilized for

patients who did not participate in a previous DM2 clinical trial. Only laboratory tests with input from five or more DM2 patients were reported. Once collected, abnormal laboratory results were tabulated and processed using a commercially available statistical software program (SAS; SAS Institute Inc, Cary, North Carolina) for review, analysis, and display.

Results

Of the 1442 laboratory studies performed, DM2 patients had 359 [24.9%] abnormal laboratory values. Forty-three of the 68 types of laboratory studies had values from fifteen or more different DM2 patients (representing 1271 total studies). For these forty-three different types of laboratory test, 312 of the 1271 studies [24.5%] were outside of their standard reference range. Tests with responses from fifteen or more patients are listed in Table 1 in order from highest to lowest percentage of total abnormal values. For each laboratory test listed, the reference range is included in addition to the mean DM2 value, standard deviation, total number of DM2 patients studied, and number (and percentage) of abnormal values from tested DM2 patients. Tests with responses from fewer than fifteen patients are listed in Supplemental Table 1.

All together, 10 laboratory tests from Table 1 had abnormal values in more than 40% of DM2 patients tested. These tests included the levels of creatine kinase (CK), IgG, total cholesterol, lactate dehydrogenase (LD), alanine aminotransferase (ALT), creatinine, serum glucose, total protein, and the absolute lymphocyte and absolute basophil counts. For some studies, the DM2 values were consistently high (i.e., CK, total cholesterol, and ALT levels), whereas other studies demonstrated frequent low values (i.e., IgG, creatinine, and total protein levels). Still other studies had both abnormally high and low values (i.e., serum glucose level).

Certain laboratory tests showed no abnormalities. These included potassium, sodium, total bilirubin and IgA.

The tabulated data add to previous clinical reports of abnormal laboratory values in DM2. Before this study, the two most commonly reported DM2 laboratory values were creatine kinase and gamma-glutamyltransferase (GGT). In one of the initial clinical descriptions of DM2 (then called proximal myotonic myopathy), 18 of 26 patients [69%] had elevated creatine kinase levels and 14 of 18 patients [78%] had higher GGT levels then their stated reference range.(6) Similarly, Day et al observed that 90% of DM2 patients had elevated CK levels, and 64% had elevated GGT levels. In a population of Italian and American families with DM2, Meola and Moxley reported that 60% of their patients had elevations in CK levels and 58% had increased GGT levels.(7) Although the present study demonstrated a similar elevation in CK levels (31 of 40 patients tested [78%]), only 33% of the patients had elevations in their GGT levels. Compared to a similarly studied myotonic dystrophy type-1 (DM1) population, on average, the present DM2 patients had higher CK levels (DM2: 537 u/L; DM1: 183 u/L) and lower GGT levels (DM2: 61.1 u/L; DM1: 110.4 u/L). (5)

In 2003, Day et al observed that 29% of patients with DM2 had low testosterone levels, 65% had high follicle-stimulation hormone levels, and 75% had insulin insensitivity (elevated basal insulin levels or prolonged insulin elevation).(3) Decreased levels of luteinizing hormone have also been reported.(8) Although endocrinologic laboratory sampling was limited in this study, we found similar trends in this population. Five of twelve patients had elevated follicle-stimulation hormone levels and one of eleven had a low level of luteinizing hormone. In seven patients who had their testosterone tested, one had a low level and three had values higher than the standard reference range. It is unknown, however, whether any of these patient were taking testosterone supplementation at the time of testing. Although none

of the present patients had basal insulin level testing, 9 of 30 [30%] had baseline serum glucose elevations.

An association between autoimmune laboratory dysfunction and DM2 has been previously hypothesized.(9) Day et al reported that although DM2 patients have normal IgA levels, 65% have low IgG levels and 11% have low IgM levels.(3) Similarly, 17 of the present DM2 patients had normal IgA levels, 12 of 16 [75%] had low IgG levels, and 2 of 17 [12%] had low IgM levels. We also found that 5 of 14 [36%] had elevations in their IgE values.

In a 2006 *Archives of Neurology* article we detailed the laboratory abnormalities of myotonic dystrophy type-1 (DM1).(5) Despite the genetic differences between DM1 and DM2, many similarities were noted between the laboratory profiles of these conditions. Both populations were found to have elevated serum cholesterol levels, increased liver and muscle markers, decreases in select hematologic counts, reductions in nutritional markers, and relatively preserved electrolyte studies. Despite these similarities the mean values, and percentage of abnormal values for each study varied per population for each individual test. Several factors may have played a role in this, including but not limited to: 1) the inclusion criteria for the DM1 and DM2 study patients (our previous DM1 population was selected only from ambulatory, mild to moderately affected individuals); 2) the mild variation in laboratory techniques and reference values over time; and, 3) the underlying varying pathomechanisms of these two diseases.

Comment

DM2 is associated with numerous abnormal clinical laboratory results. Although previous articles have described select laboratory abnormalities in DM2,(3,6,7,9) to our knowledge this is the first large scale systematic summary of the abnormal DM2 laboratory values in more than 68 different types of laboratory evaluations. Despite phenotypical overlap between DM1 and DM2, this study demonstrates that these disorders have both overlapping and distinct effects on specific laboratory markers. Overall these data emphasizes that DM2, similar to DM1, is a multisystem disease. Multiple laboratory biomarkers representing muscular, hepatic, renal, hematologic, endocrine, and immunologic function were found to be affected in this population of DM2 patients.

This research provides a deeper glimpse into the widespread clinical manifestations of a relatively rare, recently discovered, and understudied dystrophy. These data may provide an identifiable disease/laboratory profile to assist in the initial identification of undiagnosed cases. Indeed there are clinical reports of DM2 patients being diagnosed presymptomatically secondary to the identification of elevated CK levels during routine blood work.(10) Similarly, the identification of other clinical markers such as elevated total cholesterol, lactate dehydrogenase and ALT levels, or reductions in IgG levels, lymphocyte counts, or creatinine levels may improve a physician’s ability to recognize an undiagnosed case of DM2.

These data also emphasizes the increased frequency of several potentially treatable conditions in the DM2 population. DM2 patients were found to have laboratory markers suggestive of hypercholesterolemia, hypertriglyceridemia, insulin insensitivity, and possibly malnutrition. The presence of such conditions, as manifested by high cholesterol levels, high triglyceride levels, high serum glucose levels, and low albumin and globulin levels may be amendable to early screening, pharmacologic therapeutics, or alterations in diet. The early identification of comorbid states in an at risk DM2 population has the potential to lead to early treatment and improved clinical outcomes for this population. DM2 patients had nearly identical mean albumin levels as their DM1 counterparts.(5) These albumin reductions may correspond to dysphagia, dietary habits, or impaired intestinal absorption in these two

populations.(11) All three of these mechanisms may represent potential avenues for early clinical intervention for these two populations.

Similar to DM1, there was a high proportion of elevated liver enzyme levels (ALT, lactate dehydrogenase, GGT, and aspartate aminotransferase) in DM2. Although GGT elevations may suggests underlying hepatocyte involvement, it is possible that the ALT, lactate dehydrogenase, and aspartate aminotransferase abnormalities are, at least in part, due to underlying muscle abnormalities caused by DM2. In the present study no patient with an elevated aspartate aminotransferase or ALT level had a simultaneously normal CK level. In the past, patients have reported being sent for liver biopsies before being diagnosed as having DM2. Such hepatic biopsies generate extra risk, cost, and discomfort to DM2 patient without providing clear benefit. Through additional education regarding the DM2 phenotype and associated laboratory abnormalities it may be possible to limit future unnecessary referrals for hepatic biopsies. Knowledge of liver enzyme abnormalities may also assist physicians and researchers who serially follow DM2 patients. Baseline and periodic monitoring of liver enzyme levels should be considered before implementing any DM2 therapy. Without such testing, potentially helpful treatments could be discontinued secondary to the misperception of drug induced hepatic toxicity.

The results of this study may underestimate the degree and number of laboratory abnormalities in the DM2 community. A substantial portion of the patients included in this research were selected given their previous participation in controlled DM2 clinical trials. Because these clinical trials excluded patients with significant comorbidities it is possible that this dataset represents a “healthier” subset of DM2 patients. In addition, for DM2 participants who did not participate in a clinical trial, their earliest known laboratory studies were utilized when multiple values were available. By selecting these earlier tests results it is possible that these data underrepresented the progressive systemic dysfunction thought to occur as DM2 patients age.(3) Also note that co-existing medication use was not known during each individual laboratory sampling. It is possible that abnormal thyroid, testosterone, or lipid levels were masked by simultaneous drug use in a portion of patients studied.

Ultimately these laboratory results may provide insight into future potential avenues of DM2 research. Of note, 75% of DM2 patients were found to have low levels of IgG. Although at first glance this may suggest an impaired immune response mechanism in DM2, it is interesting that IgA, IgE, and IgM levels did not show similar levels of decrement. Compared with patients with DM1, age and sex matched DM2 patients may have a higher frequency of autoimmune disorders.(9) It is also possible that IgG has an accelerated turnover rate in DM2 and that IgG is selectively impaired (or sequestered) via a RNA mediated process.(12) If this is the case, IgG may have a role as a serum biomarker during clinical trials of agents (such as morpholino antisense oligonucleotides) which may alter the toxic burden of RNA (13) while simultaneously modifying IgG counts. At the very least, the etiology of selective IgG reduction in DM2 deserves more investigation. More studies are needed to determine the true significance, etiology, and therapeutic implications of the numerous laboratory abnormalities of DM2.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

DM2 Laboratory Data

Test	Units	M Norm Range	F Norm Range	Mean	Std Dev	N (F)	High	Low	% Abn
Creatine Kinase	u/L	46–171	34–145	537.6	671.8	40 (16)	31	2	83
Immunoglobulin G	mg/dL	751–1560	751–1560	667.2	290.4	16 (7)	0	12	75
Total Cholesterol	mg/dL	< 200	< 200	212.2	38.8	24 (11)	15	0	63
Lymphocytes #	thou/uL	1.3–3.6	1.2–3.7	1.4	0.6	24 (10)	0	13	54
Lactate Dehydrogenase	u/L	118–225	118–225	322.6	208.4	18 (10)	9	0	50
Alanine Transaminase	u/L	0–50	0–35	44.2	26.0	16 (6)	8	0	50
Creatinine	mg/dL	0.67–1.17	0.51–0.95	0.7	0.2	27 (9)	1	12	48
Basophils #	thou/uL	0–0.1	0–0.1	0.5	0.6	16 (8)	7	0	44
Glucose	mg/dL	74–106	74–106	102.3	43.3	30 (13)	9	4	43
Total Protein	g/dL	6.3–7.7	6.3–7.7	6.3	0.6	23 (9)	0	10	43
Red Blood Cells	mil/uL	4.6–6.1	3.9–5.2	4.6	0.8	43 (19)	2	12	33
Hematocrit	%	40–51	39–45	41.9	5.4	43 (17)	3	11	33
Gamma-glutamyltransferase	u/L	8–61	8–61	61.1	92.8	15 (6)	5	0	33
White Blood Cells	thou/uL	4.2–9.1	4.0–10.0	5.6	2.2	42 (18)	4	9	31
Calcium	mg/dL	9.0–10.5	9.0–10.4	9.2	0.6	29 (13)	0	9	31
Albumin	g/dL	3.5–5.2	3.5–5.2	3.7	0.4	30 (13)	0	8	27
Neutrophils #	thou/ul	1.8–5.4	1.6–6.1	4.6	5.9	26 (10)	4	3	27
Triglycerides	mg/dL	0–200	0–200	149.2	67.5	19 (10)	5	0	26
Lymphocytes	%	21.8–53.1	19.3–51.7	27.3	10.6	32 (15)	0	8	25
Eosinophils	%	0.8–7	0.7–5.8	4.0	2.7	31 (16)	6	1	23
Partial Thromboplastin Time	sec	22.5–35.3	22.5–35.3	25.2	3.7	30 (14)	0	7	23
Mean Corpuscular Volume	fL	79–92	79–95	89.4	4.9	46 (19)	9	1	22
Monocytes	%	5.3–12.2	4.7–12.5	9.4	3.2	32 (15)	6	1	22
Red Cell Distribution Width	%	11.6–14.4	11.7–14.4	12.8	1.2	43 (19)	5	4	21
Prothrombin Time	sec	11.9–14.7	11.9–14.7	12.4	0.8	29 (14)	1	5	21
Carbon Dioxide	mmol/L	20–28	20–28	25.3	2.9	29 (13)	5	1	21
Basophils	%	0.2–1.2	0.1–1.2	0.9	0.7	27 (11)	3	2	19

Test	Units	M Norm Range	F Norm Range	Mean	Std Dev	N (F)	High	Low	% Abn
Platelets	thou/uL	150–330	160–370	212.2	65.6	42 (18)	1	6	17
Aspartate Transaminase	IU/L	0–50	0–50	36.3	18.1	30 (14)	5	0	17
Neutrophils	%	34–67.9	34–71.1	53.7	15.4	28 (13)	2	2	14
Hemoglobin	g/dL	13.7–17.5	11.2–15.7	14.3	1.9	41 (17)	1	4	12
Immunoglobulin M	mg/dL	46–304	46–304	105.6	62.4	17 (7)	0	2	12
Mean Corpuscular Hemoglobin	pg/cell	27–33	27–33	30.8	2.1	46 (19)	3	2	11
Thyroid Stimulating Hormone	uIU/mL	0.35–5.5	0.35–5.5	2.9	3.9	32 (13)	3	0	9
Chloride	mmol/L	96–108	96–108	104.8	2.7	29 (13)	2	0	7
Urea Nitrogen	mg/dL	6–20	6–20	12.9	8.8	29 (12)	2	0	7
Alkaline Phosphatase	IU/L	40–130	35–105	88.3	55.7	27 (12)	2	0	7
Monocytes #	thou/uL	0.3–0.8	0.2–0.9	0.5	0.2	24 (10)	0	1	4
Mean Corpuscular Hemoglobin Concentration	g/dL	31–36	31–36	34.3	1.1	46 (19)	1	0	2
Potassium	mmol/L	3.3–5.1	3.3–5.1	4.2	0.4	30 (14)	0	0	0
Sodium	mmol/L	133–145	133–145	139.8	2.3	29 (13)	0	0	0
Total Bilirubin	mg/dL	0–1.2	0–1.2	0.6	0.2	24 (9)	0	0	0
Immunoglobulin A	mg/dL	82–453	82–453	158.2	52.7	17 (7)	0	0	0
						1,271 (551)	**160**	**152**	**24.5**
N = 43									