Laboratory Abnormalities in Patients With Myotonic Dystrophy Type 2

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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 laboratory 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 15 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. In addition, serum levels of IgG were low in 75% of all patients with DM2 tested, and absolute lymphocyte counts were low in 54% of all patients with DM2 tested.

Conclusions: 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.

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Myotonic dystrophy type 2 (DM2) is an autosomal dominant muscular dystrophy discovered in 1994. Although DM2 shares many of the multisystemic clinical features of DM1, 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. Both DM1 and DM2 have widespread clinical implications. Similar to patients with DM1, patients with DM2 experience muscle pain, progressive extremity and truncal weakness, stiffness, muscle myotonia, male hypogonadism, cardiac arrhythmias, diabetes mellitus, and early cataracts. More recently, cognitive dysfunction, hearing loss, hypersomnia, and tremor have been reported in patients with DM2. In the past, a large-scale study identified a high frequency of abnormal clinical laboratory values in the DM1 population. Ambulatory patients with DM1 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. This study was similarly designed to analyze and compile the baseline laboratory values of a symptomatic group of patients with DM2. 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 therapeutically intervention. Herein, we compile the laboratory abnormalities of 1442 separate baseline studies from patients with DM2.
This study was approved by the University of Rochester (Rochester, New York) institutional review board. Adult patients with DM2 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 participants with DM2 had previously received care at the University of Rochester in the Muscular Dystrophy Association clinic, outpatient setting, or electrodiagnostic laboratory or through their participation in a University of Rochester DM2 clinical trial. Of 83 patients with DM2 identified, 49 (29 men and 20 women) had recorded baseline laboratory data.

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 various methods, including local volunteer testing and outside data accumulation. Wherever applicable, sex-specific ranges were defined. In instances in which standard laboratory ranges were based on menstrual staging (ie, levels of follicle-stimulating hormone and luteinizing hormone), the reference range was broadened to include all possible premenstrual and postmenopausal values. Sex-specific reference ranges were used 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 1 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 used for patients who did not participate in a previous DM2 clinical trial. Only laboratory tests with input from 5 or more patients with DM2 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, patients with DM2 had 359 (24.9%) abnormal laboratory values. Forty-three of the 68 types of laboratory studies had values from 15 or more different patients with DM2 (representing 1271 total studies). For these 43 different types of laboratory test, 312 of the 1271 studies (24.9%) were outside of their standard reference range. Tests with responses from 15 or more patients are listed in the Table 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 (SD) DM2 value, total number of patients with DM2 studied, and number (and percentage) of abnormal values from tested patients with DM2. Tests with responses from fewer than 15 patients are listed in the eTable (http://www.archneurol.com).

Altogether, 10 laboratory tests in the Table had abnormal values in more than 40% of patients with DM2 tested. These tests included the following: creatine kinase (CK), IgG, total cholesterol, absolute lymphocyte count, lactate dehydrogenase (LD), alanine aminotransferase (ALT), creatinine, absolute basophil count, serum glucose, and total protein. For some studies, the DM2 values were consistently high (ie, CK, total cholesterol, and ALT levels), whereas other studies demonstrated frequent low values (ie, IgG, creatinine, and total protein levels). Still other studies had both abnormally high and low values (ie, serum glucose level). Certain laboratory tests showed no abnormalities, including the levels of potassium, sodium, total bilirubin, and IgA.

The tabulated data add to previous clinical reports of abnormal laboratory values in DM2. Before this study, the 2 most commonly reported DM2 laboratory values were CK and γ-glutamyltransferase (GGT) levels. In one of the initial clinical descriptions of DM2 (then called proximal myotonic myopathy), 18 of 26 patients (69%) had elevated CK levels and 14 of 18 patients (78%) had higher GGT levels than their stated reference range. Similarly, Day et al observed that 90% of patients with DM2 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. 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 with a similarly studied DM1 population, on average, the present patients with DM2 had higher CK levels (DM2: 537 U/L; DM1: 183 U/L [to convert to microkatal per liter, multiply by 0.0167]) and lower GGT levels (DM2: 61.1 U/L; DM1: 110.4 U/L [to convert to microkatal per liter, multiply by 0.0167]).

In 2003, Day et al observed that 29% of patients with DM2 had low testosterone levels, 65% had high follicle-stimulating hormone levels, and 75% had insulin insensitivity (elevated basal insulin levels or prolonged insulin elevation). Decreased levels of luteinizing hormone have also been reported. Although endocrinologic laboratory sampling was limited in this study, we found similar trends in this population. Five of 12 patients had elevated follicle-stimulating hormone levels and 1 of 11 had a low level of luteinizing hormone. In 7 patients who had their testosterone tested, 1 had a low level and 3 had values higher than the standard reference range. It is unknown, however, whether any of these patients 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. Day et al reported that although patients with DM2 have
normal IgA levels, 65% have low IgG levels and 11% have low IgM levels. Similarly, 17 of the present patients with DM2 (100%) 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 patients (36%) had elevations in their IgE values.

In a 2006 Archives of Neurology article, we detailed the laboratory abnormalities of DM1. 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 2 diseases.

**COMMENT**

Myotonic dystrophy type 2 is associated with numerous abnormal clinical laboratory results. Although previous articles have described select laboratory abnormalities in DM2, 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 emphasize that DM2, similar to DM1, is a multisystem disease. Multiple laboratory biomarkers representing renal, hepatic, muscular, endocrine, hematologic, and immunologic function were found to be affected in this population of patients with DM2.

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 patients with DM2 being diagnosed presymptomatically secondary to the identification of elevated CK levels during routine blood work. Similarly, the identification of other clinical markers, such as elevated total cholesterol, LD, and ALT levels and reductions in IgG levels, lymphocyte counts, and creatinine levels, may improve a physician’s ability to recognize an undiagnosed case of DM2.

These data also emphasize the increased frequency of several potentially treatable conditions in the DM2 population. Patients with DM2 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. Patients with DM2 had nearly identical mean albumin levels as their DM1 counterparts. These albumin reductions may correspond to dysphagia, dietary habits, or impaired intestinal absorption in these 2 populations. All 3 of these mechanisms may represent potential avenues for early clinical intervention for these 2 populations.

Similar to DM1, there was a high proportion of elevated liver enzyme levels (ALT, GGT, LD, and aspartate aminotransferase) in DM2. Although GGT elevations may suggest underlying hepatocyte involvement, it is possible that the ALT, LD, 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 patients with DM2 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 up patients with DM2. 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 data set represents a healthier subset of patients with DM2. In addition, for participants with DM2 who did not participate in a clinical trial, their earliest known laboratory studies were used when multiple values were available. By selecting these earlier test results, it is possible that these data underrepresented the progressive systemic dysfunction thought to occur as patients with DM2 age. Also note that coexisting medication use was not known during each individual laboratory sampling. It is possible that abnormally high levels of IgG have an accelerated turnover rate in DM2 and that IgG is selectively impaired (or sequestered) via an RNA-mediated process. If this is the case, IgG may have a role in mediating the toxic burden of RNA while simultaneously modulating 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.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Heatwole, Goldberg, and Moxley. Acquisition of data: Heatwole, Goldberg, Martens, and Moxley. Analysis and interpretation of data: Heatwole, Johnson, Martens, and Moxley. Drafting of the manuscript: Heatwole, Johnson, Martens, and Moxley. Critical revision of the manuscript for important intellectual content: Heatwole, Goldberg, and Moxley. Statistical analysis: Heatwole and Martens. Obtained funding: Heatwole and Moxley. Administrative, technical, and material support: Heatwole, Johnson, Goldberg, Martens, and Moxley. Study supervision: Heatwole and Moxley. Financial Disclosure: None reported. Funding/Support: This research received support from grant 1K23AR055947 from the National Institute of Arthritis and Musculoskeletal and Skin Disorders (Dr Heatwole), the Muscular Dystrophy Association (Dr Heatwole), and the University of Rochester Clinical Translational Science Institute (Dr Heatwole). Online-Only Material: The eTable is available at http://www.archneurol.com.

REFERENCES


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