

World Journal of *Hepatology*

World J Hepatol 2020 September 27; 12(9): 533-692



REVIEW

- 533** Clinical implications, diagnosis, and management of diabetes in patients with chronic liver diseases
Chung W, Promrat K, Wands J
- 558** Biomarkers for hepatocellular cancer
Singh G, Yoshida EM, Rath S, Marquez V, Kim P, Erb SR, Salh BS

MINIREVIEWS

- 574** Comprehensive review of hepatotoxicity associated with traditional Indian Ayurvedic herbs
Philips CA, Ahamed R, Rajesh S, George T, Mohanan M, Augustine P

ORIGINAL ARTICLE

Basic Study

- 596** N-acetylcysteine and glycyrrhizin combination: Benefit outcome in a murine model of acetaminophen-induced liver failure
Minsart C, Rorive S, Lemmers A, Quertinmont E, Gustot T

Retrospective Cohort Study

- 619** Transaminitis is an indicator of mortality in patients with COVID-19: A retrospective cohort study
Suresh Kumar VC, Harne PS, Mukherjee S, Gupta K, Masood U, Sharma AV, Lamichhane J, Dhamoon AS, Sapkota B

Retrospective Study

- 628** Clinical efficacy of direct-acting antiviral therapy for recurrent hepatitis C virus infection after liver transplantation in patients with hepatocellular carcinoma
Ismail MS, Hassan M, Khaderi SA, Yousry WA, Kamal El-Din MM, Bahaa El-Din MM, El Sayed OA, Kaseb AO, Goss JA, Kanwal F, Jalal PK
- 641** Surgical treatment of gallbladder cancer: An eight-year experience in a single center
Kamada Y, Hori T, Yamamoto H, Harada H, Yamamoto M, Yamada M, Yazawa T, Tani M, Sato A, Tani R, Aoyama R, Sasaki Y, Zaima M

Prospective Study

- 661** Can gadoteric acid-enhanced magnetic resonance imaging be used to avoid liver biopsy in patients with nonalcoholic fatty liver disease?
Amorim VB, Parente DB, Paiva FF, Oliveira Neto JA, Miranda AA, Moreira CC, Fernandes FF, Campos CFF, Leite NC, Perez RDM, Rodrigues RS
- 672** Sofosbuvir plus ribavirin is tolerable and effective even in elderly patients 75-years-old and over
Tamai H, Shingaki N, Ida Y, Shimizu R, Maeshima S, Okamura J, Kawashima A, Nakao T, Hara T, Matsutani H, Nishikawa I, Higashi K

CASE REPORT

- 685** Non-alcoholic fatty liver disease later diagnosed as myotonic dystrophy

Tanaka N, Kimura T, Fujimori N, Ichise Y, Sano K, Horiuchi A

ABOUT COVER

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AIMS AND SCOPE

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INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Li-Li Wang; Production Department Director: Yun-Xiao Jian Wu; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

LAUNCH DATE

October 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Nikolaos T Pylsopoulos, Ke-Qin Hu, Koo Jeong Kang

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5182/editorialboard.htm>

PUBLICATION DATE

September 27, 2020

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Non-alcoholic fatty liver disease later diagnosed as myotonic dystrophy

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Author contributions: Tanaka N, Kimura T, and Ichise Y were the patient's physicians, reviewed the literature, and contributed to manuscript drafting; Sano K performed pathological interpretation and contributed to manuscript drafting; Fujimori N and Horiuchi A supervised the manuscript; all authors approved submission of the final version.

Informed consent statement:

Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement:

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was

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Abstract

BACKGROUND

Myotonic dystrophy (MD) is sometimes accompanied by metabolic/endocrine disorders, including dyslipidemia, central obesity, and hypogonadism. Due to considerable individual differences in the severity and progression of myopathy, MD patients with minimal-to-mild muscle symptoms might be followed as having other diseases, such as non-alcoholic fatty liver disease (NAFLD).

CASE SUMMARY

A 40-year-old non-obese man without a history of regular ethanol consumption was referred to our hospital due to persistent liver dysfunction and hyperlipidemia. His body mass index was 23.4 kg/m². Liver histology demonstrated macrovesicular steatosis, ballooned hepatocytes with eosinophilic inclusion bodies, and perisinusoidal fibrosis, leading to the diagnosis of non-alcoholic steatohepatitis (NASH). Although he had no discernable muscle pain or weakness, persistently high serum creatine kinase (CK) and myoglobin levels as well as the presence of frontal baldness, a hatched face, history of cataract surgery, and grip myotonia indicated the possibility of MD. Southern blotting of the patient's DNA revealed the presence of CTG repeats, confirming the diagnosis.

CONCLUSION

When gastroenterologists encounter NAFLD/NASH patients, serum CK should be verified. If hyperCKemia, frontal baldness, a hatched face, history of cataract surgery, and grip myotonia are noted, the possibility of MD may be considered.

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Manuscript source: Invited manuscript

Received: April 22, 2020

Peer-review started: April 22, 2020

First decision: May 15, 2020

Revised: July 24, 2020

Accepted: August 1, 2020

Article in press: August 1, 2020

Published online: September 27, 2020

P-Reviewer: Vajro P

S-Editor: Wang DM

L-Editor: Webster JR

P-Editor: Wang LL



Key Words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Frontal baldness; Cataract; Creatine kinase

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Core Tip: We describe a patient with non-alcoholic steatohepatitis (NASH) who was later diagnosed as having myotonic dystrophy (MD). Some MD patients with minimal-to-mild muscle symptoms may be misdiagnosed as having non-alcoholic fatty liver disease (NAFLD). Therefore, when gastroenterologists encounter patients with NAFLD/NASH, serum creatine kinase (CK) should be verified. If high serum CK levels persist in the presence of frontal baldness, a hatched face, history of cataract surgery, and grip myotonia, the possibility of MD may be considered.

Citation: Tanaka N, Kimura T, Fujimori N, Ichise Y, Sano K, Horiuchi A. Non-alcoholic fatty liver disease later diagnosed as myotonic dystrophy. *World J Hepatol* 2020; 12(9): 685-692

URL: <https://www.wjgnet.com/1948-5182/full/v12/i9/685.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v12.i9.685>

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a common cause of persistent liver dysfunction and is defined as the presence of hepatic steatosis without regular consumption of ethanol or drugs^[1,2]. For the diagnosis of NAFLD, other causes of chronic liver injury, such as hepatitis virus infection, bacterial and parasitic infection, autoimmunity, drugs and toxicants, hemochromatosis, Wilson disease, and citrin deficiency should be excluded. Additionally, the possibility of secondary NAFLD, including gastrointestinal/pancreatic surgery, hypothyroidism, hyperadrenalism, and pancreatic exocrine insufficiency, needs to be carefully surveyed^[3,4].

Although it is accepted that endocrine/metabolic disorders are closely associated with the development of NAFLD, the relationship between myopathy and NAFLD has not been fully addressed. Among several types of myopathy, myotonic dystrophy (MD) is often accompanied by metabolic/endocrine disorders, such as dyslipidemia, central obesity, insulin resistance, and hypogonadism^[5]. Due to considerable variation in the severity and progression of myopathy, MD patients with minimal-to-mild muscle symptoms may be followed as having other diseases. We herein describe a patient with non-alcoholic steatohepatitis (NASH), a severe phenotype of NAFLD, later diagnosed as having MD.

CASE PRESENTATION

Chief complaints

A 40-year-old non-obese man without a history of regular ethanol consumption was referred to our hospital due to persistent hypertransaminasemia and hyperlipidemia.

History of present illness

It was pointed out that he had liver dysfunction and hyperlipidemia at annual health checkups from 35 years of age. He had noticed easy fatigability, but presumed that it was caused by overwork and insufficient sleep. He had no history of regular ethanol, drugs, or supplements consumption, or smoking.

History of past illness

He had no history of past blood transfusion, surgical treatment, or acupuncture.

Physical examination

His body mass index was 23.4 kg/m². He was asymptomatic with no signs of hepatomegaly, xanthoma, or Achilles tendon thickening.

Laboratory examinations

Laboratory findings revealed significant increases in serum aspartate aminotransferase (65 U/L, normal 13-30), alanine aminotransferase (103 U/L, normal 7-23), total cholesterol (298 mg/dL, normal 142-220), and triglycerides (TG; 318 mg/dL, normal 30-150). Hyperinsulinemia and greater index of homeostasis model assessment for insulin resistance indicated the presence of insulin resistance. Hepatitis virus markers and autoantibodies were all negative and immunoglobulins, ferritin and ceruloplasmin were within normal ranges. Laboratory data at the time of liver biopsy are shown in [Table 1](#).

Imaging examinations

Abdominal ultrasonography revealed hyperechogenic liver parenchyma with deep attenuation, indicating the presence of steatosis.

Further work-up

A percutaneous liver biopsy was conducted to evaluate his persistent liver dysfunction. Liver histology showed macrovesicular steatosis, ballooned hepatocytes with eosinophilic inclusion bodies ([Figure 1A](#), arrows), and perisinusoidal fibrosis ([Figure 1B](#)), which led to the diagnosis of NASH. According to the criteria proposed by Kleiner *et al*^[6], the score for steatosis, lobular inflammation, and hepatocyte ballooning were 2 (moderate), 1 (few), and 1 (few), respectively, for a total NAFLD activity score of 4. Bezafibrate (400 mg/d) was commenced for his hypertriglyceridemia.

A blood examination to assess the effects of fibrate treatment 1 mo later revealed elevated levels of creatine kinase (CK; 757 U/L, normal 62-287) and myoglobin. The patient denied any symptoms of muscle pain, weakness, or dark urine. The abnormalities in serum CK and myoglobin persisted despite immediate cessation of the fibrate. Thyroid function was normal.

The patient's face was closely inspected again ([Figure 2](#)). He had frontal baldness at the age of 40 and a hatchet face. Manual muscle testing demonstrated that he was very slow opening his hands after grasping forcefully (*i.e.*, grip myotonia). Careful history taking revealed a prior cataract operation. These findings indicated the possibility of MD.

MD is an autosomal dominant disease that affects the dystrophin myotonia protein kinase (DMPK) gene on chromosome 19^[5]. The expansion of CTG trinucleotide repeats in the 3' untranslated region of this gene results in the retention of an expanded RNA repeat that is directly toxic to myocytes. Southern blotting of the patient's DNA after BamHI digestion detected an additional band caused by CTG repeats ([Figure 3](#)), confirming the diagnosis of MD.

FINAL DIAGNOSIS

The final diagnosis in this patient case was NASH with underlying MD.

TREATMENT

The patient is being treated with eicosapentaenoic acid (2700 mg/d) for dyslipidemia and is under calorie restriction by medical dieticians.

OUTCOME AND FOLLOW-UP

Since the diagnosis of MD, the patient has been followed for 14 years. His hepatosteatosis and mild elevation of serum aminotransferases have persisted, with no findings indicating liver cirrhosis or cancer. However, he has suffered from progressive muscle weakness and reduced physical activity.

DISCUSSION

MD is a relatively common myopathy with almost 100% penetrance that is estimated to afflict approximately 5-7 per 100000 persons worldwide^[5]. The condition is

Table 1 Laboratory findings at the time of liver biopsy

Item	Value	Item	Value	Item	Value
WBC	4450 / μ L	BUN	10 mg/dL	IgG	1512 mg/dL
RBC	544 $\times 10^4$ / μ L	Cr	0.8 mg/dL	IgA	235 mg/dL
Hb	17.0 g/dL	UA	7.2 mg/dL	IgM	131 mg/dL
Plt	19.9 $\times 10^4$ / μ L	Na	146 mEq/L	ANA	(-)
		K	4.3 mEq/L	HBsAg	(-)
TP	7.4 g/dL	Cl	109 mEq/L	Anti-HCV	(-)
Alb	4.2 g/dL				
T-Bil	0.5 mg/dL	T-Chol	257 mg/dL	TSH	2.1 μ IU/mL
AST	74 U/L	TG	274 mg/dL	FT3	3.2 pg/mL
ALT	102 U/L	HDL-C	76 mg/dL	FT4	1.0 ng/dL
LDH	260 U/L				
ALP	202 U/L	FBS	87 mg/dL	HA	27 ng/mL
GGT	121 U/L	HbA1c	5.0 %	4C7S	4.2 ng/mL
ChE	390 IU/L	Insulin	30 μU/mL		
		HOMA-IR	6.4	Fe	91 μ g/dL
				Ferritin	77 ng/mL
				Cu	89 μ g/dL
				Ceruloplasmin	26 mg/dL

Bold underlined parameters indicate abnormally elevated values. WBC: White blood cell; RBC: Red blood cell; Hb: Hemoglobin; Plt: Platelet count; TP: Total protein; Alb: Albumin; T-Bil: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; ChE: Choline esterase; BUN: Blood urea nitrogen; Cr: Creatinine; UA: Uric acid; T-Chol: Total cholesterol; TG: Triglycerides; HDL-C: High-density-lipoprotein cholesterol; Fe: Iron; FBS: Fasting blood sugar; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostasis model assessment for insulin resistance; Ig: Immunoglobulin; ANA: Anti-nuclear antibody; HBsAg: Hepatitis B virus surface antigen; HCV: Hepatitis C virus; TSH: Thyroid stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine; HA: Hyaluronic acid; 4C7s: Type 4 collagen 7S.

characterized by two different mutations: An expansion of CTG repeats in the 3' untranslated region of the DMPK gene on chromosome 19 and an expansion of CCTG repeats in intron 1 on zinc finger protein 9 on chromosome 3, which are classified as MD type 1 and type 2, respectively. Southern blotting of the present patient led to the diagnosis of MD type 1.

MD is a multisystemic disease exhibiting diverse clinical manifestations, including muscle weakness, myotonia, early cataracts/baldness, arrhythmia, neuropsychiatric symptoms, and gonadal atrophy. The common features of MD type 1 are myotonia and insulin resistance, which are caused by aberrant splicing of chloride channel 1 and insulin receptor RNA in skeletal muscle due to the toxic effect of retained CUG-expanded repeats. Whole-body glucose disposal is reduced by 15%-25% after insulin infusion in MD type 1 patients, and insulin sensitivity, as well as insulin receptor RNA and protein, in the skeletal muscle is significantly decreased. Since peripheral insulin resistance is commonly observed in MD patients, metabolic disturbances, such as dyslipidemia, diabetes, and NAFLD/NASH may co-exist.

Indeed, it was reported that liver test abnormalities were frequent in MD patients^[7-10]. Shieh *et al*^[11] prospectively evaluated the abnormalities in liver enzymes and metabolic parameters of 31 MD type 1 patients. The prevalence of diabetes, impaired fasting glucose, and metabolic syndrome (MetS) was approximately 12%, 21%, and 41%, respectively. Furthermore, 44% of MD patients had liver test abnormalities and 42% had NAFLD, as defined by abnormal liver chemistry tests and ultrasonography findings.

We reviewed the clinical data of 7 MD type 1 patients with NAFLD who underwent liver biopsy, including this case, and summarized the pathological features in Table 2^[11-14]. Ballooned hepatocytes were detected in 5 patients, who were all histologically diagnosed as having NASH. Our case did not receive a repeated liver biopsy. However, he did not show gradual decreases in platelet count or serum albumin, nor

Table 2 Summary of previously reported liver pathology in 7 myotonic dystrophy type 1 patients with non-alcoholic fatty liver disease

Item	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Steatosis (0-3)	3	1	1	2	1	3	2
Lobular inflammation (0-3)	0	0	0	1	1	3	1
Ballooning (0-2)	1	1	0	ND	1	2	1
NAFLD activity score (0-8)	4	2	1	ND	3	8	4
Diagnosis	NASH	NASH	SS	ND	NASH	NASH	NASH
Fibrosis (0-4)	2	1a	1a	1	1a	4	1a
Ref.	Shieh <i>et al</i> ^[11]	Shieh <i>et al</i> ^[11]	Shieh <i>et al</i> ^[11]	Bhardwaj <i>et al</i> ^[12]	Yamada <i>et al</i> ^[13]	Ariake <i>et al</i> ^[14]	Our case

Pathological findings were scored according to the criteria proposed by Kleiner *et al*^[6]. ND: Not determined; NASH: Non-alcoholic steatohepatitis; SS: Simple steatosis (non-alcoholic fatty liver).

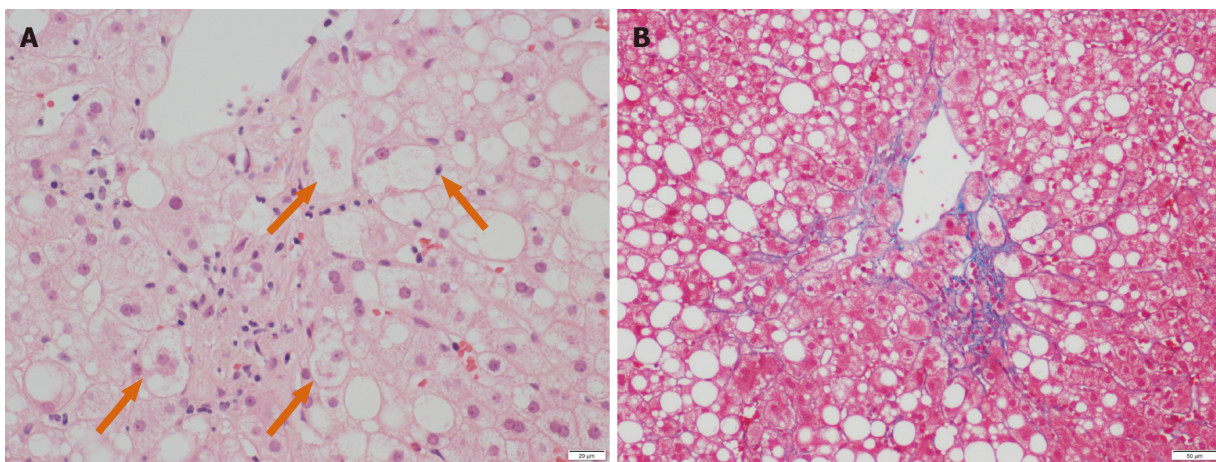


Figure 1 Pathological findings of liver biopsy. A: Liver specimen stained by hematoxylin and eosin exhibited moderate macrovesicular steatosis mainly around the central vein with occasional focal lobular inflammation. Some ballooned hepatocytes were detected (orange arrows). According to the criteria proposed by Brunt *et al*, the score for steatosis, lobular inflammation, and hepatocyte ballooning were 2 (moderate), 1 (few), and 1 (few), respectively. The calculated NAFLD activity score was 4. Scale bar represents 20 μ m; B: Liver specimen stained by the Azan-Mallory method showed pericentral/perisinusoidal fibrosis (score 1a). Scale bar represents 50 μ m.

did he exhibit remarkable values for indicators of liver fibrosis progression or imaging findings suggestive of liver cirrhosis, such as splenomegaly, enlargement of the left lobe, or liver surface irregularity, during his 14-year follow-up. One report described a case of MD type 1 progressing to NASH-derived liver cirrhosis (Case #6 in Table 2)^[14]. Additionally, a case of MD type 2 manifested as myopathy, mild myotonia, cataract, diabetes, erectile dysfunction, gastrointestinal dysmotility, dysarthria, mild myocardial thickening and non-alcoholic and non-hepatic liver cirrhosis was documented^[15]. Therefore, regular monitoring of laboratory indicators of liver synthesis ability (*e.g.*, serum albumin and prothrombin time) and liver fibrosis (*e.g.*, platelet count and serum type 4 collagen 7S) as well as liver imaging is advised for MD patients with NAFLD. In patients with cryptogenic non-alcoholic cirrhosis, the possibility of MD may be considered.

Vujnic *et al*^[16] examined the prevalence of MetS components in 66 MD type 1 patients and found dyslipidemia to be the most frequent [hypertriglyceridemia (67%) and low HDL cholesterol (35%)]. On the other hand, the prevalence of hypertension, central obesity, and hyperglycemia was relatively low (18%, 13%, and 9%, respectively). This observation indicated that hypertriglyceridemia often co-existed in MD type 1 patients and that some MD patients with minimal-to-mild muscle symptoms might be mistaken as having hypertriglyceridemia and/or NAFLD. Insulin resistance enhances hepatic TG synthesis and the secretion of very-low-density lipoprotein particles, but reduces the activity of lipoprotein lipase, consequently leading to raised circulating TG levels. Fibrates are commonly available for treating hypertriglyceridemia, but myotoxicity and rhabdomyolysis are possible adverse



Figure 2 Photograph of the patient. Frontal baldness and a hatchet face were noted.

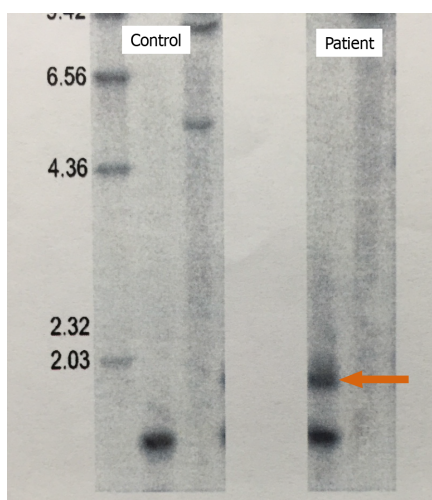


Figure 3 Southern blotting of patient DNA. DNA samples were digested with BamHI. Compared with the control sample, an additional band caused by CTG repeats was detected (arrow), confirming the diagnosis of myotonic dystrophy.

effects. Before commencing fibrate administration for NAFLD/NASH patients with hypertriglyceridemia, serum CK levels should be checked to rule out the possibility of latent MD.

Recent studies documented the contribution of small intestinal bacterial overgrowth and disrupted bile acid metabolism to the pathogenesis of NAFLD/NASH^[1,2,17,18]. Tarnopolsky *et al.*^[19] documented that 65% of MD type 1 patients with gastrointestinal symptoms exhibited small intestinal bacterial overgrowth using glucose breath hydrogen testing. Additionally, it was reported that specific bile acids, such as dihydroxymono-oxocholanic acid and dihydroxycholanic acid, were detected in the serum of MD type 1 patients and biliary ursodeoxycholic acid was reduced^[20], indicating bile acid abnormality accompanied by MD. Although the pathogenesis of NAFLD/NASH is multifactorial, these factors might be associated with NAFLD/NASH in MD.

CONCLUSION

MD is a relatively common congenital myopathy accompanied by peripheral insulin resistance. However, some MD patients with minimal-to-mild muscle symptoms might be followed as having other diseases associated with insulin resistance, such as hypertriglyceridemia, postprandial hyperglycemia, and NAFLD/NASH. In patients with abnormal liver function tests, muscular diseases might be hidden at all ages^[21-24]. When gastroenterologists encounter NAFLD/NASH patients, serum CK should be

verified. If hyperCKemia is detected, the possibility of MD may be considered and careful observation of the patient's face, and history taking for cataracts may help uncover subclinical MD.

ACKNOWLEDGEMENTS

We thank Mr. Trevor Ralph for his editorial assistance.

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