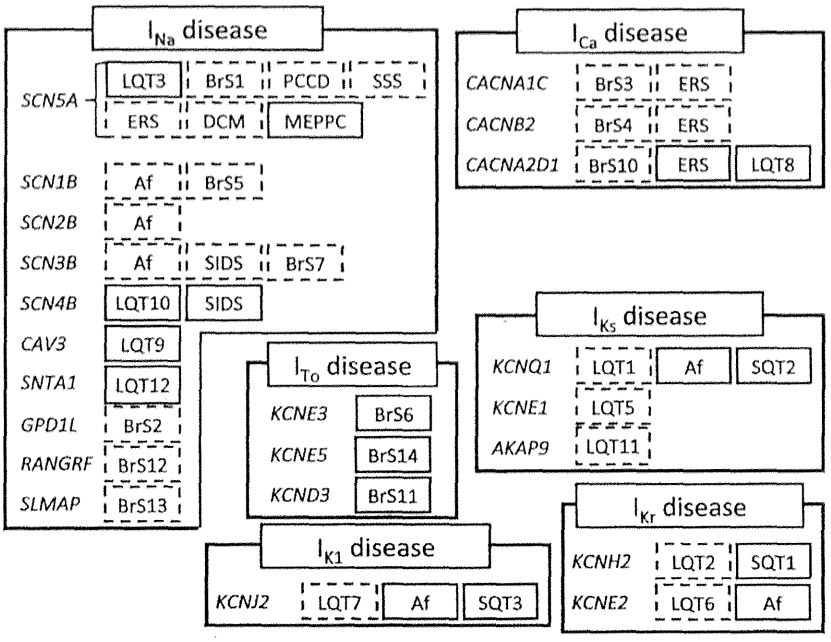

Figure 3 Current-centered classification of inherited arrhythmogenic diseases caused by malfunctions of plasmalemmal proteins.

The clinical phenotypes are grouped according to the specific current that is altered by the genetic defects. Solid line rectangles indicate phenotypes caused by gain-of-function, while dashed-line rectangles indicate loss-of-function.

Abbreviations: Af, atrial fibrillation; BrS, Brugada syndrome; DCM, dilated cardiomyopathy; ERS, early repolarization syndrome; LQT, long QT syndrome; MEPPC, multifocal ectopic Purkinje-related premature contractions; PCCD, progressive cardiac conduction defect; SIDS, sudden infant death syndrome; SQT, short QT syndrome; SSS, sick sinus node syndrome. [Adopted from 16) Ruan Y, et al. Nat Rev Cardiol 2009., 17) Wilde AM, Brugada R. Circ Res 2011 and 18) Wilde AM, Behr ER. Nat Rev Cardiol 2013.]

E. Af

心房が統制のない不規則な興奮状態に陥った状態で，ECG でP 波の消失，RR 間隔の不整，f 波の出現を認める。一般に後天的なものが多いが，遺伝性不整脈疾患としては *SCN5A* 遺伝子の M1875T 変異による家族性 Af の報告がある。また，BrS の 15〜20%の症例で Af を呈するという報告もある[16]。

VI. DM における心筋型イオンチャネルのスプライシング異常

以上の様に，多彩な遺伝子異常で心伝導障害を呈するが，中でも心筋型電位依存性 Na チャネルに関連した疾患（I_{Na} disease）は表現型が多彩で，症状のオーバーラップも見られる（**Fig. 3**）。心筋型 Na チャネルは 6 つの膜貫通領域からなるドメインが 4 つ連なった構造を持つ α サブユニット（Nav1.5）と，一回膜貫通領域を持つ捕捉ユニットと考えられている 4 種の β サブユニット（β1〜β4）からなる。その他にも，様々なチャネル結合蛋白（Channel interacting protein）が存在し，その機能を修飾している（**Fig. 4D**）。Nav1.5 の各ドメインのうち，セグメント 1（S1）からセグメント 4（S4）は電位感受性ドメイン（Voltage Sensing Domain: VSD）と呼ばれ，チャネルが電位を感受する重要な部位である。中でも，S4 は 3 塩基毎に正電荷をもつアミノ酸（アルギニンもしくはリジン）が並ぶ構造を持ち，VSD の中核的な役割を担う。

前述したように Nav1.5 の遺伝子異常で呈する表現系には，PCCD・Af といった，DM1 でみられる心臓伝導異常に類似するものが多く見られる。また，Nav1.5 には幼若型スプライシング産物の存在が知られている[19]。そこで，我々は，Nav1.5 に存在する選

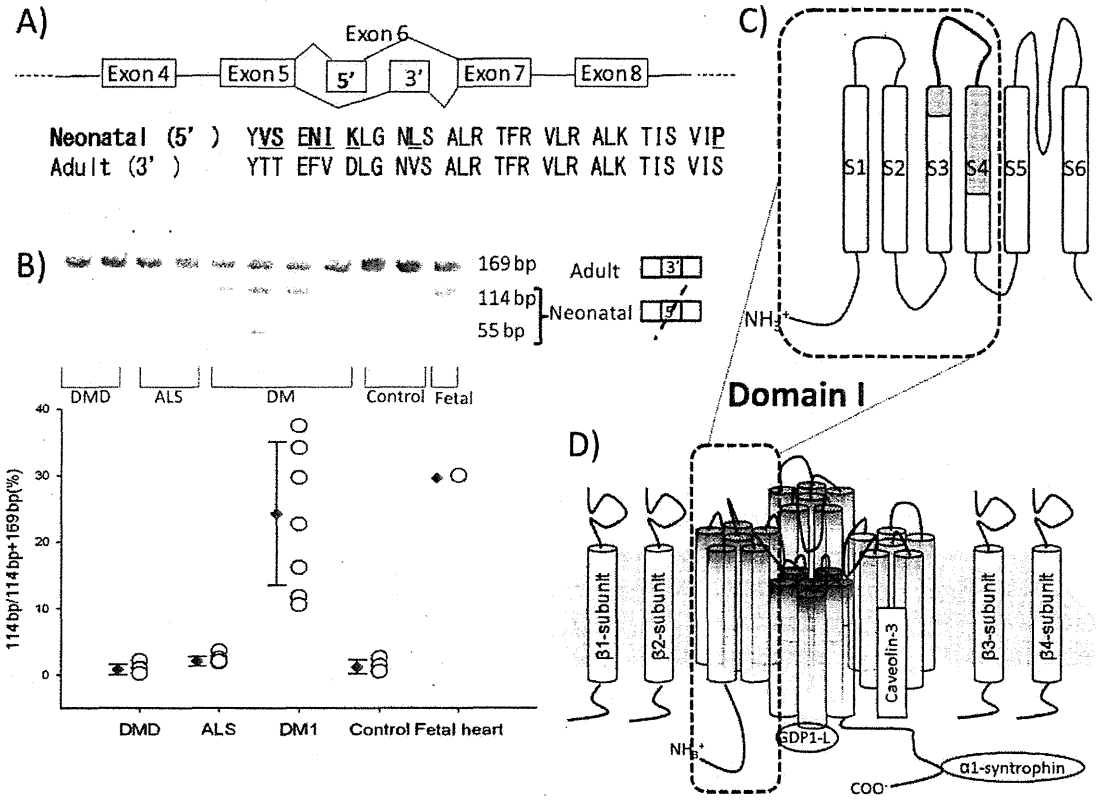

Figure 4 Alternative splicing of *SCN5A* in myotonic dystrophy 1.

A) Schematic diagram of the *SCN5A* gene and amino acid sequences of Nav 1.5 alternative splicing variants, "Neonatal" and "Adult" isoforms. Rectangles indicate translated segments. Exon 6 is shown as two parts, the relative position of the 5′ and 3′. The "Neonatal" isoform is composed of the relative position of the 5′ of exon 6, instead of the 3′ in the "Adult" isoform. Consequently, the "Neonatal" isoform sequence shows a difference of seven amino acids (underlined) from the "Adult" isoform at the protein level.

B) Reverse-transcriptase PCR (RT-PCR) analysis of *SCN5A* splicing in human samples. The "Neonatal" isoform was identified as two shorter bands cleaved by a restriction enzyme. The proportion of the "Neonatal" isoform was significantly increased in DM1 compared to a control and disease controls, including Duchenne muscular dystrophy (DMD) and amyotrophic lateral sclerosis (ALS).

C) Close-up schema of domain I in Nav1.5. Exon 6 corresponds to a part of S3, the S3-S4 linker, and a part of S4 shown in shaded rectangles with a thick line.

D) A schematic of cardiac-type voltage-gated sodium channel composed of the α subunit (Nav1.5), β subunits (β1-β4), and channel-interacting proteins including GDP1-L, Caveolin-3, and α-syntrophin.

択的スプライシングに注目し，剖検患者の心筋サンプルを用いて Reverse-transcriptase PCR (RT-PCR) による解析を行った。その結果，DM 患者群にて Nav1.5 の exon 6 における幼若型スプライシング産物が増加していることを見出した (**Fig. 4A, B**)。この幼若型 Nav1.5 は，成熟型 Nav1.5 と比較すると，ドメイン I の S3，S3-S4 リンカー，S4 に 7 つのアミノ酸変異をもつ (**Fig. 4A, C**)。前述の通り，S4 は VSD の中核的部位であり，また近年の研究で S3-S4 リンカーも VSD の機能に重要な影響を与える事が分かって来ている。この事からも幼若型 Nav1.5 は機能異常を示す事が予想され，その機能異常を検証する為に，幼若型 Nav1.5 を培養細胞に発現させパッチクランプ法を用いて電気生理学的に解析した。

その結果，幼若型 Nav1.5 の activation の電位依存性は脱分極方向へシフトしており，成熟型に比べて興奮性が低下していることがわかった。次に，その機能解析データを用いて心室細胞モデルに基づくコンピューターシミュレーションを行ったところ，不整脈源性を再現することができた。以上の事から，Nav1.5 のスプライシング異常が筋強直性ジストロフィーの心臓伝導障害の病態に関与している可能性が示唆された(unpublished data)。

VII. DM 治療への展望

残念ながら，現時点で DM の根治的治療は存在しない。予後を改善するためには，時期を逸しない NIPPV(非侵襲的陽圧換気)などの呼吸補助の開始や，ペースメーカーや埋め込み式除細動器(ICD)の導入が重要となる。ECG 上 PR 間隔が 240ms，QRS 幅が 120ms を超える場合には，心臓電気生理検査，ペースメーカーや ICD 導入を考慮すべきとされている[20]。しかしながら，本邦での治療現状は確立した共通意識のもと行われているとは言い難い。我々は大阪府下の専門医を対象に，DM の受療動向についてアンケート調査を実施したが，治療方針について神経内科と循環器内科との連携・意見交換は未だ少なく，改善すべき点が見出された[21]。本邦の実情に合わせた適応について神経内科と循環器内科の間で共通認識が形成され，治療体制が整っていくことが期待される。

また近年，RNA-dominant disease である DM において，病態の根源となる異常 RNA をターゲットとした治療法の開発も進んでいる。具体的には，アンチセンス核酸を用いて異常 RNA による MBNL の凝集を防ぐ方法や，異常 RNA 自体を分解する方法でモデルマウスの症状改善に成功している[22][23]。また，モデルマウスに骨格筋の ClC-1 のスプライシング異常を直接是正するアンチセンス核酸を投与することにより，筋強直症状が消失することも報告されている[24]。今後，DM の心臓伝導障害の原因となるスプライシング異常が確定すれば，これらを直接ターゲットとした治療も可能となることが期待できる。

VIII. 結　　語

DM の病態生理と，その中心症状の一つである心臓伝導障害の発症機序について，最近の知見を踏まえて概説した。DM の心臓伝導障害は，その生命予後を左右する重要な症状であり，その分子病態解明を通じて理解が深まり，より良い治療戦略が確立されていくことが期待される。

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ORIGINAL ARTICLE

Simple questionnaire for screening patients with myotonic dystrophy type 1

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Key words
myotonic dystrophy type 1, physical examination, receiver operating characteristic curves, screening, self-administered questionnaire.

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Abstract

Background and Aim: Myotonic dystrophy type 1 (DM1) is a multisystemic disease, and patients often visit a variety of specialists before being correctly diagnosed. Identifying DM1 is not an easy task, particularly for non-neurologists. We tried to develop a simple and useful screener to identify DM1.
Methods: In the present study, we proposed and refined a simple questionnaire for screening patients with DM1. A preliminary study showed that the sensitivity and specificity of a well-designed questionnaire was comparable with that of a physical examination. We developed a nine-item questionnaire that assessed cataract history, dysphagia, myotonia, drop foot, the ability to whistle, lift the head, sit-up and unscrew a bottle cap, and family history.
Results: A total of 95 DM1 patients, 121 healthy controls and 132 disease controls completed the questionnaire. Many healthy controls were family members of DM1 patients; therefore, family history was excluded from statistical analyses. In DM1 patients with mild symptoms, sensitivity exceeded 70% for three items (sit-up, drop foot, myotonia). In healthy controls, specificity exceeded 70% for all items. Receiver operating characteristic curve analysis showed that the combination of lifting the head, sit-up, unscrewing a bottle cap and myotonia items had high capability to distinguish DM1 patients with mild symptoms from healthy controls and disease controls with mild symptoms.
Conclusion: This simple questionnaire might help to identify DM1 patients.

Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominant disorder, and is one of the most common forms of muscular dystrophy. The severity of DM1 is variable, ranging from severe, in the congenital form, to almost asymptomatic. DM1 can involve multi-organ symptoms including cataracts, baldness, leukoencephalopathy, deafness, arrhythmia, sleep apnea, insulin resistance, and hyperlipemia, in addition to muscle weakness.[1] These complications are not always associated with the onset and severity of muscle weakness, and many patients are unaware of their motor dysfunction in the early stages of the disease.[1] As such, many patients visit a variety of specialists before receiving the diagnosis of DM1. In 2009, we surveyed cardiologists, diabetologists, gynecologists and ophthalmologists practicing in Osaka, Japan, and asked them about the medical consultation behaviors of DM1 patients.[2] Over 30% of doctors had experience in the medical management of DM1 patients, and approximately 10% had experience in the diagnosis of DM1. Unfortunately, a few patients were diagnosed only after peripartum or perioperative troubles.[2] Clinical symptoms of DM1 are variable, and identifying DM1 patients with mild symptoms is quite difficult. Specialists with experience in diagnosing DM1 paid more attention to the characteristic features of DM1, such as grip myotonia and hatchet face, than those without experience in diagnosing DM1.[2]

These facts suggest that a simple screen for DM1 would be useful in helping non-neurologists to detect DM1, which would not only increase the likelihood of an early diagnosis, but also prevent complications and aid the construction of a multidisciplinary treatment. The aim of the present study was to develop a simple screen for DM1. As the initial step, we compared the practicality and precision of a physical examination with that of a self-administered questionnaire. The results of the present pilot study suggested that the sensitivity and specificity of a well-designed questionnaire was comparable with that of a physical examination; therefore, we developed and tested a nine-item questionnaire to identify individuals with DM1.

Methods

The ethical review boards of each hospital reviewed and approved both the pilot study and the main study. Studies were registered to the UMIN Clinical Trials Registry (UMIN000008960).

Pilot study. Seven DM1 patients (age 43.0 ± 9.1 years) and six healthy controls (HC; age 48.0 ± 9.2 years) participated in the pilot study. All DM1 patients had mild symptoms and did not require any support for activities of daily living (ADL). Two DM1 patients had minimal or no muscle symptoms. All participants understood the concept of the study and provided informed consent.

We listed the distinctive signs and symptoms of DM1, and selected 21 items for inclusion in the questionnaire and 18 items for inclusion in the physical examination (Table S1). All participants completed the 21-item questionnaire (Table S2). Eight trainee doctors that had not yet received neurology training and two neurologists that were experts in DM1 carried out the structured, 18-item physical examination (Table S3) without any information about the disease status. Some tools, including an examination table, a hammer, a flashlight, a tongue blade, and test food and drinks, were necessary to carry out the physical examination. All participants started the questionnaire simultaneously, and after 10 min we asked whether they had finished or not. Similarly, all trainee doctors started the physical examination simultaneously, and after 10 min we asked whether they had finished or not. The sensitivity and specificity of each item on the questionnaire, and in the physical examination was assessed. Sensitivity was quantified as the positive responses in DM1 patients divided by the total number of responses (including positive, negative and not sure) in DM1 patients, and specificity was quantified as the number of negative responses in HC divided by the total number of responses (including positive, negative and not sure) in HC.

Main study. A total of 95 DM1 patients, 121 HC and 132 disease controls (DC) with neuromuscular disorders or rheumatoid arthritis participated in the main study (Table 1). All DC were receiving medical management at one of our hospitals. Individuals with severe cognitive dysfunction were excluded. All participants understood the concept of the study and provided informed consent.

Based on the sensitivity and specificity determined in the pilot study, we selected an item from each of the nine fields (eye, face, palate and pharynges, neck, trunk, finger, foot, myotonia, and family history) to create a nine-item screening questionnaire (Table 2). All participants completed this questionnaire. No advice or corrections were given from medical staff. Age, sex, primary illness and disability in ADL were noted for all participants. Disability in ADL was classed as mild if the patient was independent in ADL, and advanced if the patient required support in ADL.

A screening tool is most valuable for mild cases, therefore statistical analyses were carried out in two ways: on all participants, and on patients with mild disability. Family members of patients were included in the HC group, therefore item 9 (family history) was not included in the statistical analyses. The sensitivity and specificity of the remaining eight items was quantified, and the area under receiver operating characteristic curves (AUC) was used to explore the optimal combination of items. Student's *t*-tests were used to compare age at the onset of cataracts between DM1 and HC, and between DM1 and DC.

Table 1 Profile of participants included in the main study

Group	*n*	Sex *n* (M/F)	Age, years Mean ± SD (range)	Severity *n* (mild/advanced†)
DM1	95	39/56	44.0 ± 11.7 (14–72)	64/31
Healthy controls	121	33/88	51.1 ± 12.6 (21–78)	121/0
Disease controls	132	81/51	45.1 ± 22.3 (10–89)	53/79
FSHD	13	6/7	42.9 ± 21.3 (15–80)	9/4
Other MD	61	53/8	31.0 ± 15.5 (10–85)	13/48
PD	16	9/7	72.6 ± 9.9 (51–89)	6/10
RA	14	3/11	63.4 ± 14.0 (33–80)	11/3

†Mild severity indicates no support required in activities of daily living. Advanced severity indicates support required in activities of daily living.

DM1, myotonic dystrophy type 1; F, female; FSHD, facioscapulohumeral muscular dystrophy; M, male; MD, muscular dystrophy; *n*, number; PD, Parkinson's disease; RA, rheumatoid arthritis; SD, standard deviation.

Results

Pilot study. Trainee doctors required more than 10 min to assess all 18 items on the physical examination. The specificity of items on the physical examination was generally good for both neurologists and trainee doctors (Fig. 1a). However, many distinctive symptoms were absent in the cases studied, and the sensitivity was variable (Fig. 1a). Sensitivity was less than 70% on all items when the physical examination was carried out by trainee doctors, and exceeded 70% on just five items (hatchet face, nasopharyngeal malocclusion, difficulty unscrewing plastic bottles, percussion myotonia and grip myotonia) when carried out by neurologists. In addition, the discrepancy in sensitivity between neurologists and trainee doctors surpassed 20% for seven items (hatchet face, baldness, high arched palate, nasopharyngeal malocclusion, difficulty lifting the head, difficulty sitting up and percussion myotonia).

All participants completed the questionnaire within 10 min. The specificity and sensitivity of items on the questionnaire were varied; however, specificity was over 70% for 17 items and sensitivity was over 70% for five items (difficulty whistling, difficulty standing still, drop foot, myotonia and daytime sleepiness; Fig. 1b).

Main test. In HC, the specificity was over 70% for all items, and exceeded 90% for four items (difficulty lifting the head, difficulty sitting up, difficulty unscrewing a bottle cap and myotonia; Table 3). In DC, the specificity of items was

Table 2 Questionnaire administered in the main study

1	Have you ever been diagnosed with cataracts? If yes, when were you first diagnosed: () years old	Yes	No	Not sure
2	Can you whistle?	Yes	No	Not sure
3	When you eat food or beverages, do you feel a choking or sticking sensation?	Yes	No	Not sure
4	Can you lift up your head from a supine position without arm support?	Yes	No	Not sure
5	Can you sit up from a supine position without arm support?	Yes	No	Not sure
6	Can you easily unscrew the cap of a plastic bottle?	Yes	No	Not sure
7	Do you experience any difficulty in lifting the toes toward the shin or do you find that ? you often stub your toes against tiny bumps when you walk?	Yes	No	Not sure
8	Do you experience any muscle stiffness, such as difficulty opening your hand immediately ? after you grasp it strongly, or difficulty opening your mouth after you clench your jaw strongly?	Yes	No	Not sure
9	Do any of your blood-related kin have a muscular disorder?	Yes	No	Not sure

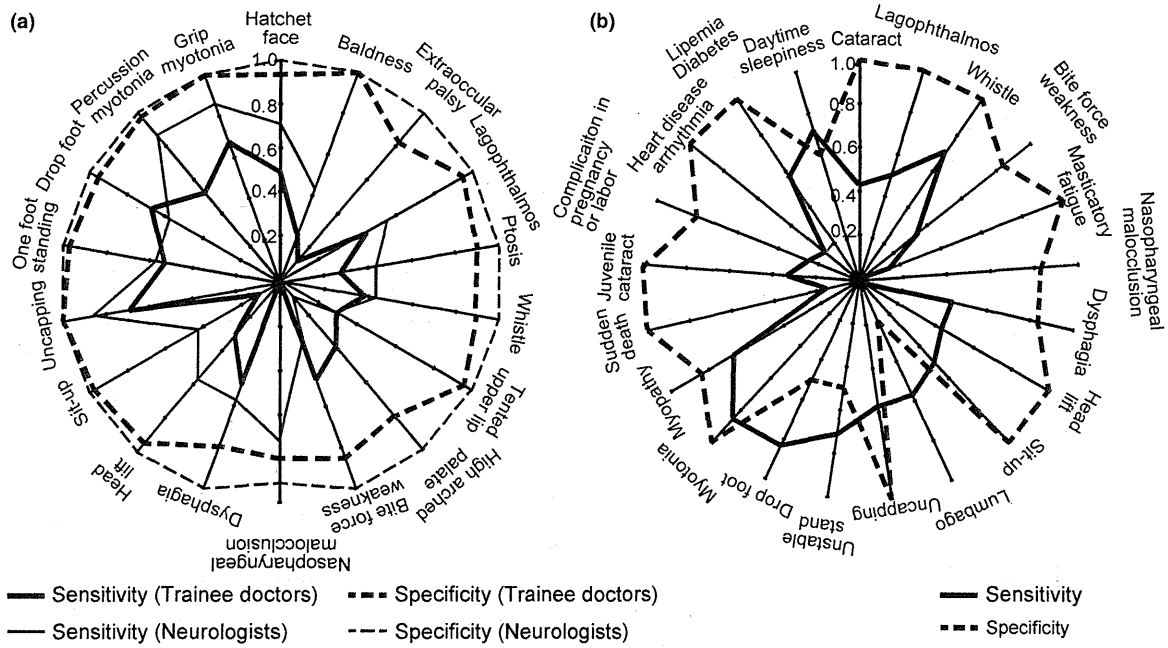

Figure 1 The specificity and sensitivity of each item included in (a) the physical examination and (b) the questionnaire in the pilot study.

not as good as in HC. In DC patients with mild disability, the specificity was over 70% for four items (cataract, difficulty lifting the head, difficulty unscrewing a bottle cap and myotonia; Table 3). The number of cases was not sufficient for statistical analyses, but it is possible that overlapping and/or confusing symptoms influenced the specificity of some items for some diseases. In mild muscular dystrophy, equinus foot could have been regarded as drop foot. In facioscapulohumeral muscular dystrophy, facial and abdominal weakness decreased the specificity of item 2 (difficulty whistling) and item 5 (difficulty sitting up), and in Parkinson's disease, akinesia, small shuffling gait and rigidity decreased the specificity of item 5 (difficulty sitting up), item 7 (drop foot), and item 8 (myotonia). However, confusion of morning stiffness with myotonia in patients with rheumatoid arthritis was not common.

The sensitivity of items was variable (Table 3). Although item 8 (myotonia) had the highest sensitivity, a considerable number (10/95) of patients reported no myotonia. Just three other items, item 5 (difficulty sitting up), item 6 (difficulty unscrewing a bottle cap) and item 7 (drop foot), had sensitivity over 70% (Table 3). For every item except item 8 (myotonia), sensitivity was lower when only participants with mild disability were considered than when all participants were considered (Table 3). Some DM1 patients were unaware of their symptoms, and responded in the negative even when a symptom was present. Although this might have impacted the sensitivity, the answers were not modified.

The largest AUC between mild DM1 and HC (0.998), and between mild DM1 and mild DC (0.915) was obtained by the combination of items 4 (difficulty lifting the head), 6

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Table 3 Sensitivity and specificity of each item in the questionnaire

		Sensitivity	Specificity					
		DM1, % (%)	HC, %	All DC, % (%)	MD, % (%)	FSHD, % (%)	PD, % (%)	RA, % (%)
Item 1	Cataract	45.1 (36.5)	89.0	86.3 (84.6)	93.4 (84.6)	84.6 (100)	75.0 (66.7)	78.6 (81.2)
Item 2	Whistle	34.7 (28.1)	88.0	49.2 (67.3)	55.0 (84.6)	15.3 (22.2)	46.7 (83.3)	71.4 (72.7)
Item 3	Dysphagia	64.2 (57.8)	90.0	52.3 (61.5)	58.3 (61.5)	84.6 (77.8)	43.8 (66.7)	71.4 (81.8)
Item 4	Lift the head	69.5 (60.9)	97.5	39.7 (88.5)	23.0 (76.9)	46.2 (66.7)	56.3 (100)	78.6 (90.9)
Item 5	Sit up	81.1 (73.4)	92.6	27.5 (59.6)	16.4 (46.2)	23.1 (33.3)	18.8 (33.3)	78.6 (90.9)
Item 6	Unscrew a bottle cap	70.5 (60.9)	99.2	36.9 (75.0)	28.3 (69.2)	69.2 (77.8)	37.5 (66.7)	64.3 (81.8)
Item 7	Drop foot	78.3 (73.4)	82.6	34.5 (32.7)	37.3 (7.7)	30.8 (33.3)	0.0 (0.0)	50.0 (63.6)
Item 8	Myotonia	87.4 (92.2)	98.3	68.8 (78.8)	78.0 (76.9)	69.2 (77.8)	37.5 (50.0)	92.9 (100)

Item 9: family history of muscular disorders was excluded from statistical analysis as family members of myotonic dystrophy type 1 (DM1) patients were included in the healthy control (HC) group. The values in parentheses were obtained from patients with mild symptoms.
DC, disease control; FSHD, facioscapulohumeral muscular dystrophy; HC, healthy control; MD, muscular dystrophy; PD, Parkinson's disease; RA, rheumatoid arthritis.

(difficulty unscrewing a bottle cap) and 8 (myotonia; items 4 + 6 + 8). The second largest AUC between mild DM1 and HC (0.995), and between mild DM1 and mild DC (0.902) was obtained from the combination of items 4 (difficulty lifting the head), 5 (difficulty sitting up), 6 (difficulty unscrewing a bottle cap) and 8 (myotonia; items 4 + 5 + 6 + 8). The latter combination also showed the highest AUC between all DM1 and HC (0.996; Fig. 2). With both combinations, the optimal cut-off point for the number of positive items was one to discriminate mild DM1 from HC (items 4 + 6 + 8 sensitivity = 100% and specificity = 98.4%, and items 4 + 5 + 6 + 8 sensitivity = 100% and specificity = 93.4%), and two to distinguish mild DM1 from mild DC (items 4 + 6 + 8 sensitivity = 78.1% and specificity = 84.9%, and items 4 + 5 + 6 + 8 sensitivity = 89.1% and specificity = 81.1%).

A total of 51 participants (37 DM1, eight HC and six DC) reported the age of cataract onset. The age of cataract onset was younger in DM1 (42.1 ± 9.4 years) than in HC (60.4 ± 11.5 years, $P = 0.002$) and DC (56.2 ± 24.1 years, $P = 0.012$).

Although the answers to item 9 (family history) were excluded from the analyses, erroneous answers were noted. Some participants considered only relatives in ancestral/descendent generations, and some participants considered cohabiters when answering this question.

Discussion

Myotonic dystrophy type 1 is a multisystem disorder, and early introduction of multidisciplinary care is important for effective treatment. Non-motor symptoms often appear

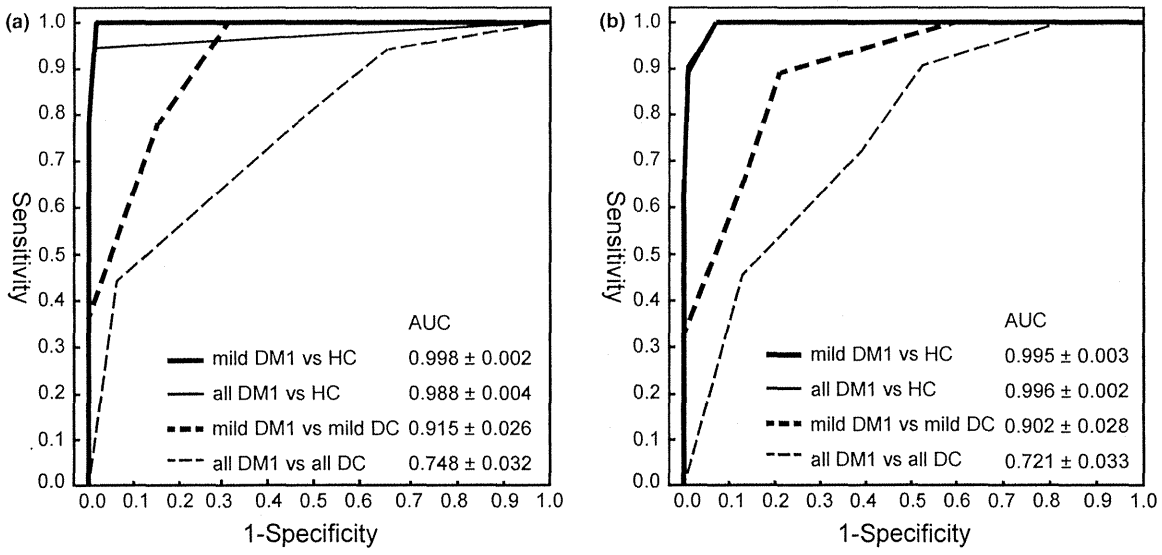


Figure 2 Receiver operating characteristic curve for (a) the combination of lifting the head, unscrewing a bottle cap and myotonia items (items 4 + 6 + 8) and (b) the combination of lifting the head, sitting up, unscrewing a bottle cap and myotonia items (items 4 + 5 + 6 + 8) in the main study. AUC, area under the curve; DC, disease control; DM1, myotonic dystrophy type 1; HC, healthy control.

before motor symptoms, and many patients pay little attention to motor symptoms.[1] Juvenile cataract is an example of a non-motor symptom, and the results of the present study show that the onset of cataract occurred at a younger age in DM1 patients than in HC and DC. DM1 patients often visit a variety of specialists before being correctly diagnosed. Making the correct diagnosis of such patients is important for proper medical management and prevention of complications. However, clinical symptoms of DM1 are variable, and there are no established clinical diagnostic criteria. It is therefore difficult for non-neurologists to identify DM1, particularly in mild cases. A simple screen for DM1 would therefore be of great significance. In the present study, we developed and tested a simple screen for DM1.

One purpose of the pilot study was to compare physical examination and questionnaire methods of screening. We examined mild cases of DM1, because this is the population that will benefit most from a screening tool. The specificity of items on the physical examination was generally high, but the sensitivity was variable, even when specialists carried out the exam. This is likely because the mild cases lacked

Self-questionnaires for screening of myotonic dystrophy

Please check the appropriate boxes(☑) of following questions

1 . Can you lift up your head from supine position without arm support?

☐ Yes ☐ No

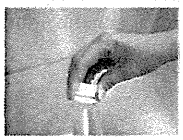
*Your head must take off from floor. You can place your arms beside your body however you must not push floor or grasp your clothes or body

2 . Can you sit up from supine position without arm support?

☐ Yes ☐ No

*You can place your arms beside your body however you must not push floor or grasp your clothes or body. You can stretch your legs.

3 . Can you unscrew caps of new plastic bottles using your fingers?



☐ Yes ☐ No

*You must use unopened plastic bottles. Please check "No" if you have to use any tools or body parts except your fingers.

4 . Do you feel delay of muscular relaxation after forced grasp of your finger, clench of your jaw, closure of your eyelids, and so on.?

☐ Yes ☐ No

This picture shows residual muscle contraction after forced grasp

5 . Do you have any patients of myopathies in your blood-related kins (brothers, sisters, parents, children, grandparents, grandchildren, uncle, aunts, cousins, etc.)?

☐ Yes ☐ No

* You can check "Yes" even if you do not know the accurate diagnosis. Your partners and blood-related kins of your partner are not included.

Thanks you for your cooperation

Figure 3 The final version of the self-report questionnaire to be used to screen for myotonic dystrophy type 1.

distinctive symptoms. The physical examination also required more time than the questionnaire, and required some tools.

The sensitivity and specificity of items on the questionnaire were also quite variable; however, the sensitivity and specificity of some items were equivalent to that of items in the physical examination. The short time and lack of equipment required to complete the questionnaire was a distinct advantage. We expected that a questionnaire would be able to identify patients with DM1 from the general population, and carried out a large study to determine the sensitivity and specificity of a questionnaire in a large group of participants.

To reduce the time and effort required of the participants, just nine items were included in the questionnaire used in the main study. In addition to DM1 patients and HC, we tested this questionnaire in DC to evaluate the capability of the questionnaire to distinguish DM1 from other disorders. In HC, the specificity of each of the eight items that were statistically analyzed was generally high. In DC, the specificity was poor, except for the item regarding cataract history; however, the specificity of four items exceeded 70% when only mild cases were considered. Overlapping symptoms appeared to influence the specificity of some items in some diseases. The sensitivity of each item was insufficient to identify DM1 by a single item. For all items except myotonia, the sensitivity was lower in mild DM1 patients than in all DM1 patients, likely because patients with mild disability were unaware of, or were free from, distinctive symptoms.

Receiver operating characteristic curve analyses showed that the combination of items 4 + 6 + 8 and items 4 + 5 + 6 + 8 had high detection capability for DM1. Both combinations showed an excellent capacity to detect DM1 from HC, and the AUC between mild DM1 and mild DC was over 0.9 for both combinations. The AUC between mild DM1 and HC, and between mild DM1 and mild DC was slightly higher for items 4 + 6 + 8 than for items 4 + 5 + 6 + 8, but one DM1 patient responded negative to all three items. In contrast, all DM1 patients had at least one positive item in the items 4 + 5 + 6 + 8 combination, and the sensitivity of at least two positive items was higher for items 4 + 5 + 6 + 8 than in items 4 + 6 + 8. Thus, we propose the use of the items 4 + 5 + 6 + 8 combination as a screen for DM1. In addition, we recommend including family history in the screen, because it would provide an opportunity to detect asymptomatic patients.

There were some instances where participants responded incorrectly to an item, either because they misunderstood the question or they were unaware of the presence of a symptom. To improve the quality of the questionnaire for future use, we have revised the text to use simple expressions and figures (Fig. 3). We hope that this screen will improve the diagnosis, and subsequent medical management, of DM1 patients. If an individual gives multiple positive answers, we recommend a consultation with a neurologist. In the case of only one positive answer, we recommend an examination of neurological findings, serum creatine kinase level and an electromyogram test. A detailed family history of muscular disorders and information about complications including juvenile cataracts, premature baldness and cardiac conduction block might be helpful. If any suspicious signs are detected, consultation with a neurologist should be considered. DM1 patients are high-risk for general anesthesia, and female DM1 patients are at high risk of abnormal pregnancy, congenital myotonic dystrophy and ritodrine-induced rhabdomyolysis.[1–5] Thus, if any operations requiring general anesthesia are considered, consultation with a neurologist is strongly recommended. If the female subject is expected to be married or pregnant, genetic counseling should be carried

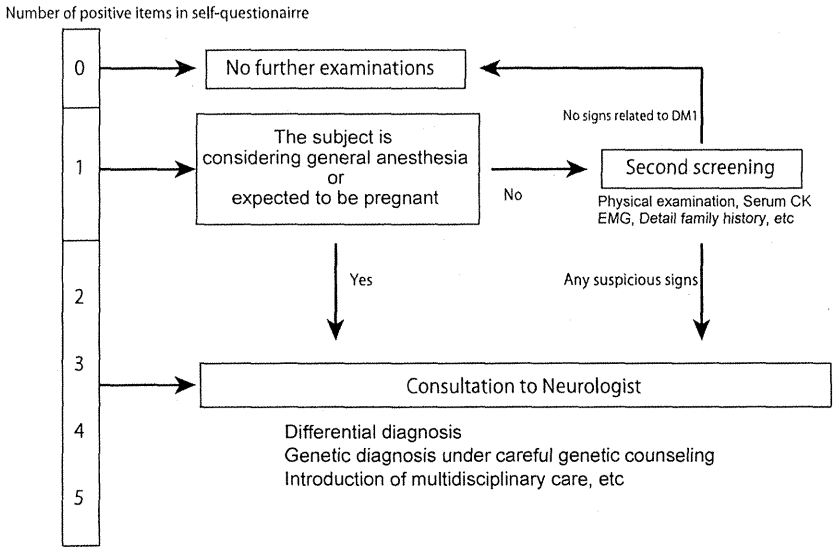


Figure 4 The flow chart of screening for patients with myotonic dystrophy type 1. CK, creatine kinase; DM1, myotonic dystrophy type 1; EMG, electromyogram.

out so that she understands the risk of her pregnancy and baby (Fig. 4).

The proposed screen should be used carefully in young children, elderly people and persons with disability. No children under the age of 10 years were included in the present study; therefore, we have no data for this population. The specificity of items was generally low in DC patients with severe symptoms; that is, patients requiring support for ADL. Thus, the capability of the screen to identify DM1 in these populations might be low.

In conclusion, a small, self-administered questionnaire can be a simple and efficient method to identify individuals with DM1. To determine the power of this tool, we aim to re-evaluate the sensitivity and specificity in clinical practice after dissemination to clinicians.

Acknowledgments

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Signs and symptoms of myotonic dystrophy type 1.

Table S2. Questionnaire administrated in the pilot study.

Table S3. Check-list for physical examination in the pilot study.

＜Symposium　14-4＞　今開かれる筋ジストロフィー治療の扉

筋強直性ジストロフィー症の治療開発

高橋　正紀[1)]　中森　雅之[1)]　望月　秀樹[1)]

要旨：筋強直性ジストロフィーの遺伝的原因は非翻訳領域におけるリピートの異常伸長である．本症の病態は，リピートの伸長したRNAが核内で蓄積し，スプライス因子の量・質の変化を惹起し，結果生じる多様なスプライス異常であることが判明した．この機序の各段階を標的として治療法開発が進行している．なかでもリピート伸長RNAを標的としたアンチセンス核酸治療がモデル動物で有効であったことから，米国で治験が開始されている．臨床試験にあたり，希少疾患の患者集積性に加え，本邦では既存治療の標準化・均てん化も問題であり，近日運用開始される患者登録の活用が期待される．

（臨床神経 2014;54:1077-1079）
Key words：mRNA，スプライシング，リピート伸長，患者登録

はじめに

筋強直性ジストロフィー（DM）は有病率8/10万人程度と成人でもっとも頻度の高い筋ジストロフィーである．本症は白内障，糖尿病，高次脳機能障害，消化器症状，良性・悪性腫瘍など数多くの症状を有し，全身性疾患であるという特徴を持つ．本症はくりかえし配列（リピート）の異常伸長によるいわゆるリピート病であるものの，ハンチントン病や多くの脊髄小脳変性症などポリグルタミン病とはことなり，非翻訳領域におけるリピート伸長が原因であるため，病態機序が長らく不明であった．しかしながらRNA病としての本症の病態理解が進むとともに，精力的に治療開発がおこなわれ，治験が海外で開始されるまでにいたり，ようやく本症にも希望の光がみえてきた．本稿では，近年の病態機序解明の進歩，治療開発の現状を概説し，新規治療薬の臨床応用に向けた課題についても述べることとする．

病態機序解明の進歩

最近の研究の結果，DMでは，リピートが異常に伸びたRNAが，病態の主因であることがわかってきた．転写された異常なRNAは，伸長したリピート部分がヘアピン構造と呼ばれる立体構造を作ることから核内で凝集し，細胞質に輸送されなくなる（Fig. 1中段）．こうして核内に蓄積したRNA凝集体により，CUGなどのRNA配列に結合能力を有するスプライス因子が一緒にからめとられる．その結果，核内で正常に働くべきスプライシング因子が不足し，二次的にさまざまなRNAが正常にスプライシングされず，その産物であるタンパクに異常が生じてしまう．このように，タンパク非翻訳領域の遺伝子の異常にもかかわらず，二次的に様々なRNAに影響を与え，本症でみられる多くの臓器のさまざまな症状につながるわけである．

たとえば，骨格筋型塩化物イオンチャネル*CLCN1*のスプライシング異常が生じ塩化物イオンチャネル電流が低下することから，興奮性が上昇し筋強直現象が生じることがわれわれの研究で明らかになった[1)]．また耐糖能異常の原因となるインスリン受容体のスプライシング異常をはじめ，その他に30以上のスプライシング異常が本症で障害される臓器でみつかっている[2)]．しかしながら，筋力低下・筋萎縮の主因となる異常はみつかっておらず，いくつかのスプライシング異常が複合的に関与している可能性が考えられる．

治療開発の現状

病態機序の解明に加え，エクソンスキッピング療法や，ゲンタマイシン・アルベカシンなど既存薬のdrug repositioningといった，デュシェンヌ型筋ジストロフィーでの研究戦略の影響を受け，本症の治療開発が急速に進んでいる[3)]．現在研究されている治療戦略としてFig. 1に示すような4つのアプローチがある．

まずは，一番下流の現象である，個々のスプライシングを正常化しようという試みである（Fig. 1①）．これは，標的が判明しているもの，たとえば筋強直の原因となる塩化物イオンチャネルのスプライシングなどには有効で，実際にモデルマウスに人工核酸（モルフォリノ）を投与し症状改善が報告されている．しかしながら，標的となるスプライス異常が多いため，それぞれに対応した薬物が必要になるということに加え，筋萎縮の原因となる異常がまだはっきりしていないという問題もある．

やや上流のステップに対するアプローチは，スプライス因

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（受付日：2014年5月23日）

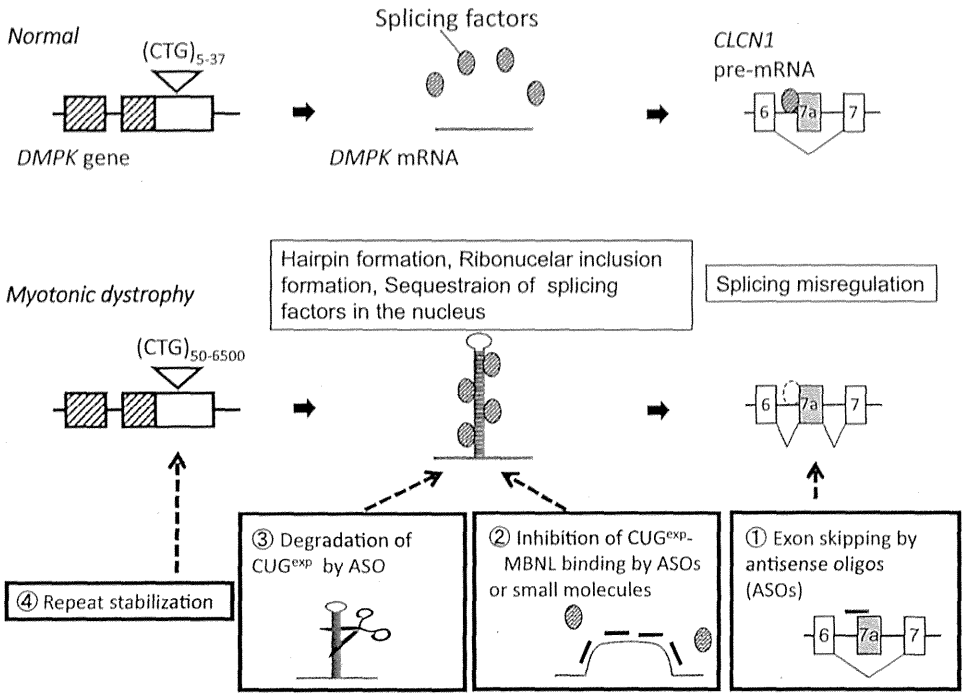

Fig. 1　Schematic illustration of the disease mechanism and therapeutic strategies of DM1.
Expanded CUG repeats (CUGexp) in the mutant DMPK mRNA form hairpin structures and ribonuclear inclusions, and subsequently sequester splicing factors in the nucleus. Loss of the splicing factors causes misregulation of alternative splicing. Mis-splicing of CLCN1 exon 7a induces a frame shift and premature termination codon in exon 7, resulting in loss of functional CLCN1 protein on the sarcolemma and myotonia in DM1. Therapeutic strategies which are currently under development for DM, includes (1) induction of exon skipping of individual target by antisense oligonucleotides (ASOs), (2) neutralization of the toxicity of CUGexp by preventing splicing factor sequestration with ASOs or small molecules (3) degradation of the toxic RNA by ASOs and (4) stabilization of expanded repeats. Figure modified from reference 9.

子がRNA凝集体に結合してしまうのを防ぐという試みである（Fig. 1②）．カリニ肺炎治療薬のペンタミジンが，リピート伸長RNAへアピンとスプライス因子との結合を妨げ，モデルマウスでの症状改善が実際に確認されている[4]．ペンタミジンをリード化合物として，長期投与でも安全性の高い薬剤の開発が期待される．

さらに上流のステップに対するアプローチとして，異常伸長したリピートを持つRNAを分解し核内での蓄積を減らすというものがある（Fig. 1③）．Nakamoriらはギャップマーオリゴと呼ばれる人工核酸が，異常に伸びたRNAを分解することを示した[5]．ギャップマーオリゴは，両端は安定な人工核酸，中央部は天然核酸で構成されており，結合した相補的RNAは中央部では天然型の二重鎖を形成し，内在性のRNaseHの基質となり分解される．Wheelerらは*DMPK* RNAに特異的な人工核酸を，モデル動物に投与し治療効果を確認している[6]．なお，この薬剤は非臨床安全性試験が終了し治験がアメリカで開始されており，ヨーロッパでも類似の核酸医薬が開発中である．

別の角度からのアプローチとして，④のリピート長の制御がある．リピート長は，一生不変ではなく，とくに脳・筋肉・心臓など本症で障害される臓器で伸長する傾向がある．リピート長は重症度とも関係することから，体細胞におけるリピート長不安定性の機序を解明し，改善させることは症状軽減につながると想定される．

新規治療薬の臨床応用へ向けて
—標準的治療確立・患者登録

このように新規治療法開発への動きが種々あるが，いくつかの課題がある．ひとつは，既存治療の標準化・均てん化の問題である．いかに画期的な治療でも，既存治療を十分に適用した上でなければ意味がない．デュシェンヌ型筋ジストロフィーでは人工呼吸器や心不全の薬物治療により予後が大幅に改善したが，DMでは20年前からほとんど変化がない．以前われわれは大阪府の循環器科専門医に対し，DM患者へのペースメーカーなどの適応についてアンケート調査をおこなったが，「積極的に考慮」するという回答はほとんどなく，「適応なし」という回答すらあった[7]．フランスのDM患者登

録の解析によると，心電図異常を有する患者にペースメーカーなどの積極的治療をおこなうと，突然死が著明に少なかったと報告されている[8]．今後，ペースメーカー，人工呼吸器，抗不整脈薬など，既存治療の適応とその標準化をおこなうことが非常に重要であると考える．

もうひとつは，稀少疾患に共通する問題で，臨床試験における対象患者把握の困難さである．そこで症例蓄積性の向上のため患者登録が推進されている．日本では国立精神・神経医療研究センターが患者登録システム（Remudy）を構築し，ジストロフィン異常症などの登録をおこなっており，その情報はヨーロッパを中心としたTREAT-NMDの国際登録にも提供されている．DMは比較的患者数は多いが，重症度や合併症の出現・程度などはさまざまなため，特定の重症度や合併症の合致する患者を集めるのはかなり困難である．DMについても，われわれ大阪大学と国立精神・神経医療研究センターが中心となり，全国の専門家の協力をえて患者登録の準備を進めている．2014年10月ごろ登録開始で，大阪大学神経内科やRemudyのサイトに詳細が掲載される予定である．この登録は臨床試験だけでなく，自然歴の解明，既存治療の標準化など臨床研究への活用が期待されている．

※本論文に関連し，開示すべきCOI状態にある企業，組織，団体はいずれも有りません．

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Abstract

Therapeutic development in myotonic dystrophy

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Myotonic dystrophy (DM), the commonest form of muscular dystrophy in adults, is a multisystem disease caused by repeat expansions located in untranslated regions of the affected genes. Its pathogenesis results from expression of RNAs with these expanded repeats, which causes sequestration of splicing factors and thus series of splicing misregulation. An increased understanding of the disease mechanism has accelerated the development of therapeutic strategies, including correction of individual missplicing by antisense oligonucleotides (ASOs), ASO- or small molecule-mediated neutralization of the RNA toxicity by preventing sequestration of splicing factors, degradation of the toxic RNA by ASOs, and stabilization of the expanded repeats. ASOs targeting the toxic RNA have exhibited promising results in animal models, and a clinical trial has recently been launched. With the advent of clinical trials, we are confronting several challenges. As with other rare diseases, we must identify eligible patients. It may be more important in Japan to establish a standardized best practice management of currently available approaches (e.g., pacemaker use) followed by nationwide dissemination. The national DM registry, about to be launched shortly, might be a promising tool to overcome these issues and lead to improved management of DM.

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Key words: mRNA, splicing, repeat expansion, patient registry

Evaluation of Examinations of Higher Brain Function Disorder in Patients with Myotonic Dystrophy

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Abstract

The patient with myotonic dystrophy (MyD) is known to be often accompanied by a higher brain function disorder, and there are some reports showing visual space cognitive impairment or frontal lobe dysfunction found in such patients. In this study, for the MyD patients of this hospital, we performed four examinations including Alzheimer's disease assessment scale-cognitive component-Japanese version (ADAS-jcog), frontal assessment battery (FAB), yaruki-score and self-rating depression scale (SDS), and investigated the characteristics of these examinations. From the statistical analysis with Pearson's correlation coefficient test, there was no correlation among results of total number of points of ADAS-jcog, FAB, yaruki-score and SDS. On the other hand, a total number of points of ADAS-jcog showed a correlation to its comprising subjects such as word recall task, constructional praxis, ideational praxis and orientation. Especially, very high coefficient of correlation was seen to a constructional praxis, and therefore a disorder of this ability seemed to be one of specific features of this disease.

In the future, we are going to examine the time course of these findings and the comparison of the finding to the brain function image. For the higher brain function evaluation of the MyD patients, it is important to capture its future change widely including mental status examination. Further, it is necessary to consider the approach of the rehabilitation along the change of the symptom of the patient.

Key Words: myotonic dystrophy, higher brain function, visual space cognitive impairment

1. Introduction

Myotonic dystrophy (MyD) is autosomal dominant hereditary muscle disease assumed to be with progressive muscular dystrophy, muscle weakness, myotonia, and cardinal symptom. Other than a skeletal muscle symptom, intellectual disturbance, a cataract, heart conduction disorders, many

organs are affected. There are some reports that show visual space cognitive impairment or frontal lobe dysfunction found in MyD patients[1,2]. In order to examine a higher brain function disorder of MyD patients, we this time performed Alzheimer's Disease Assessment Scale-cognitive component-Japanese version (ADAS-jcog) and Frontal Assessment Battery (FAB). Furthermore, to examine association with a higher brain function disorder and psychic disorder, we also performed the Yaruki-score, one of motivation scores, and self-rating depressive scale (SDS).

2. Methods

The subjects were fifteen MyD type 1 patients hospitalized in our hospital (six women, nine men), and the patients with congenital disease were excluded. The patient ages ranged 38-66 at the examination, and the averages were 54 for men and 51 for women. Two patients of them had a tracheotomy. All patients ware right-handed.

As test batteries, we performed 1) ADAS-jcog; by operating in accordance with the touch panel, the inspection results are automatically aggregated. Data for each patient is stored in a dedicated cloud, 2) FAB, 3) Yaruki-score, 4) SDS. Each test was composed of several subjects. ADAS-jcog is comprised of eleven tasks; word recall task, language, comprehension of spoken language, word finding difficulty, commands, naming objects and fingers, constructional praxis, ideational praxis, orientation, word recognition task, remembering test instructions. When patients were not able to answer these questions, it is added points and shows that it is severe cognitive function disorder as high score. FAB is one of the testing to examine a frontal lobe function and is comprised of conceptualization, mental flexibility, motor programming, inhibitory control, GO/NO-GO, environmental autonomy. If an answer is right on this test, it is added points, this test is added and shows that there is not disorder so that points is low.Yaruki-score is a kind of the examinations for apathy. When the points are 16 points or more, we judge it to be "low motivation". The SDS is a depressive standard of the self-assessment type. This conducts four phases of evaluations from the question of 20 items. We consist of the questions about feelings (two items), a physiological symptom (eight items), and the psychological symptome (ten items). This test shows severe depressive state as a low score. In addition, we assayed four above-mentioned examinations by Pearson's correlation coefficient test.

3. Results

We show the results of all patients for four examinations in Fig 1, and also show the average total points for each test in Table 1.

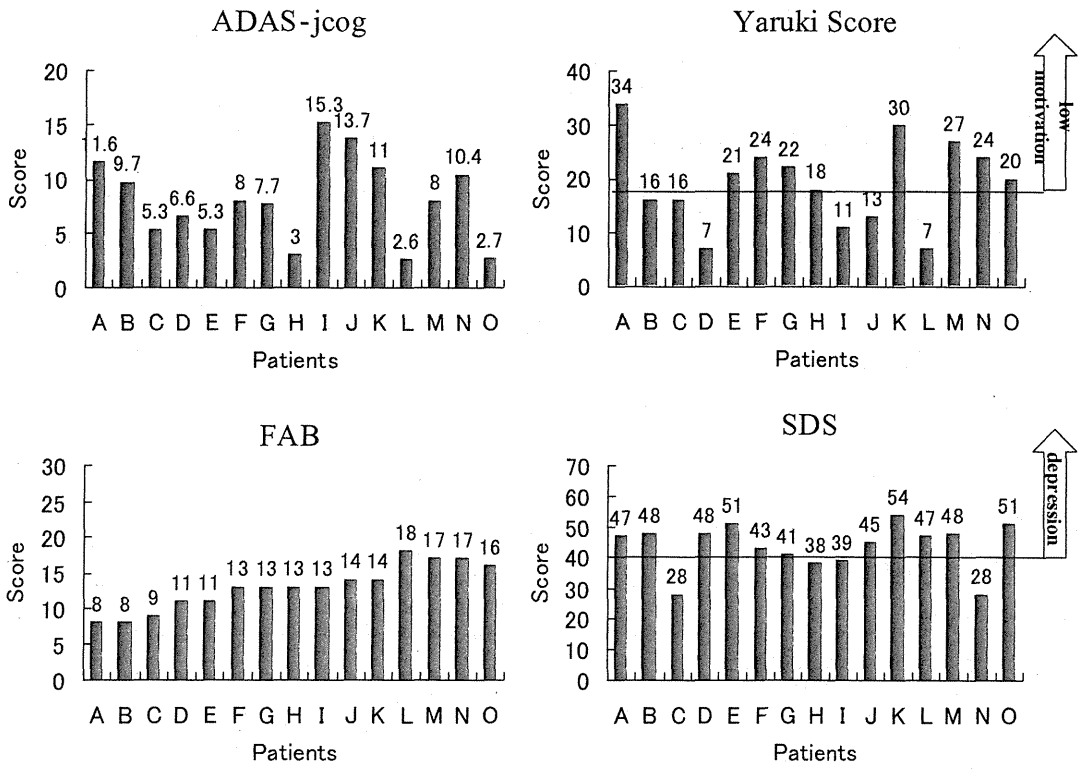

Fig. 1. Results of each patient on the examinations of ADAS−jcog, FAB, Yaruki score and SAD.

Table 1. Average points in each test.

examination	average points	SD	severeness criteria
ADAS-jcog	8.1	3.9	high score
FAB	13.0	3.2	low score
Yaruki-score	19.3	7.9	high score
SDS	43.7	7.8	low score

In the Pearson's correlation coefficient test, there was no correlation among total scores of ADAS-jcog, FAB, Yaruki-score and SDS. In Table 2, we show the subjects comprising the ADAS-jcog and the value of coefficient of correlation of the total points of ADAS-jcog to each subject. The total points of ADAS-jcog showed a correlation to its comprising subjects including word recall task, constructional praxis, ideational praxis, orientation. In particular, the coefficient of correlation between the total scores and constructional praxis was extremely high (coefficient of

correlation = 0.675, p value=0.006).

Table 2. Results of the examination of ADAS-jcog

task	average	SD	coefficient of correlation	p value
(1) Word recall task	3.3	0.9	0.63	0.011
(2) Language	0	0	—	—
(3) Comprehension of spoken language	0	0	—	—
(4) Word finding difficulty	0.1	0	0.17	0.557
(5) Commands	0.3	0.7	0.35	0.197
(6) Naming objects and fingers	0	0	—	—
(7) Construction praxis	1.9	0.7	0.68	0.006
(8) Ideational praxis	1.5	2.8	0.56	0.030
(9) Orientation	0.8	0	0.59	0.020
(10) Word recognition task	1.4	1.1	0.54	0.036
(11) Remembering test instructions	0	0	—	—

In Fig. 2, we show the results of constructional praxis task, and in Fig. 3, we show some drawings of several cases the alphabetical cords of which correspond to those in Table 2. We have conducted four kinds of figure copying that are a circle, two rectangles, a lozenge and a cube by the problem of "constructional praxis". The results showed the imperfect copying of the cube, enclosure or the copying of the line of the sample. Four patients drew five squares as a combination in it without recognizing two rectangular overlap (patient B, D, E, K). This sign was the abnormal findings common to four of 15 patients.

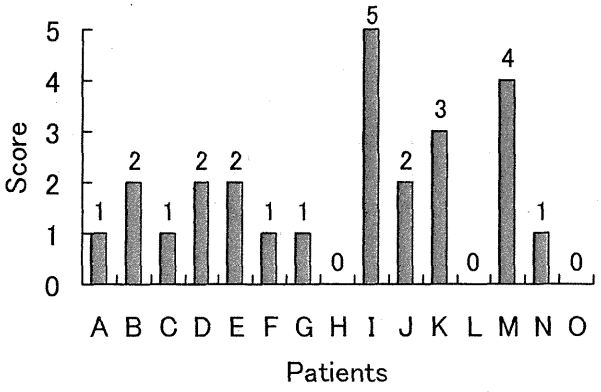

Fig. 2. Results of each patient on the constructional task.

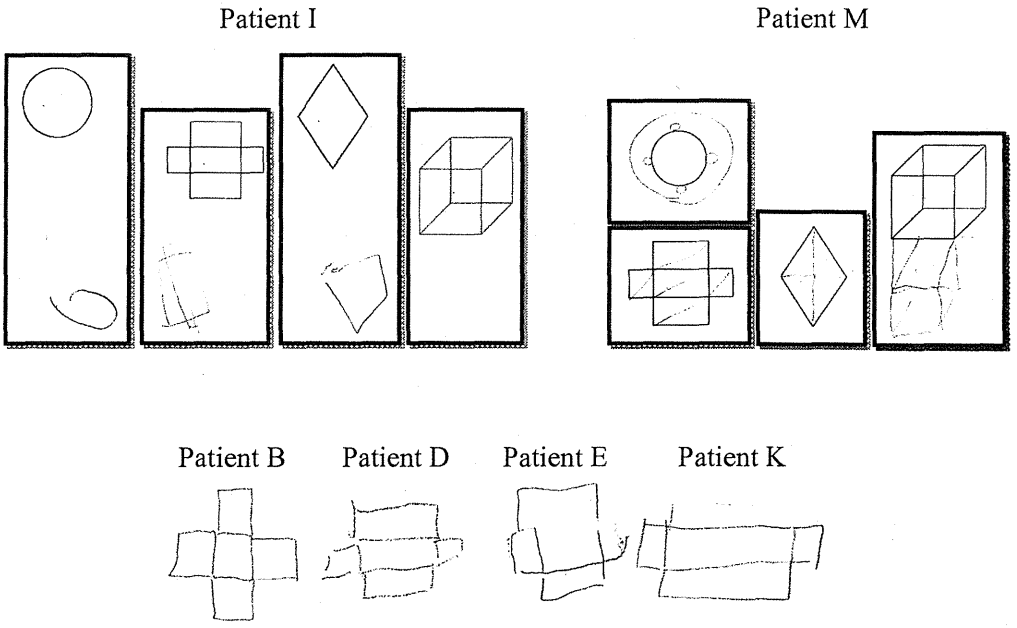

Fig. 3. Drawings by six patients on the constructional task.

We show the results of FAB on Fig. 4 and Table 3. In FAB, a total number of points correlated to behavior program, choice of the response and GO/NO-GO.

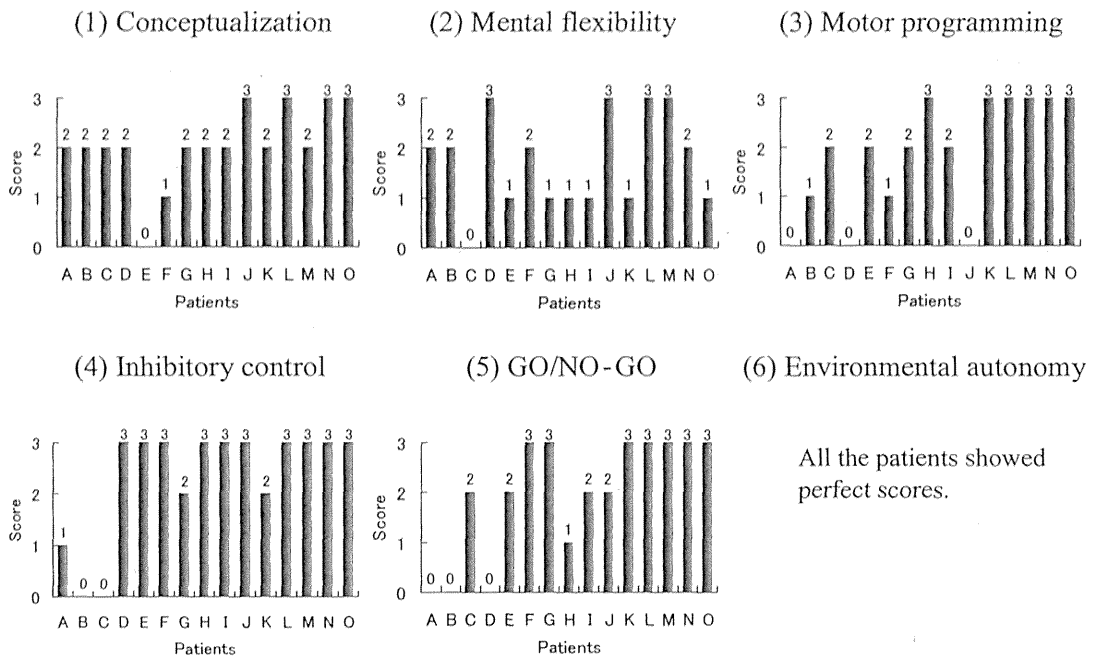

Fig. 4. Results of each patient on the examination of FAB.

Table 3. Average point for each item in the examination of FAB.

item	average points	SD	coefficient of correlation	p value
(1) Conceptualization	1.9	0.7	0.48	0.072
(2) mental flexibility	1.6	0.7	0.33	0.235
(3) Motor programming	1.8	2.1	0.64	0.010
(4) Inhibitory control	2.1	1.4	0.73	0.002
(5) GO/NO-GO	1.7	2.1	0.77	0.001
(6) Environmental autonomy	3	0	—	—

4. Discussion

It is known that MyD patients are often accompanied by a cognitive dysfunction, and there are reports indicating visual-spatial agnosia and frontal lobe dysfunction found in such patients[1,2]. Because the score of the problem of "constructional praxis" was high in ADAS-jcog, and characteristic results were obtained by two rectangular copying problems common to four of 15