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EXTENDED ABSTRACT

A25 Development of a comprehensive clinical report form for assessing patients with Myotonic Dystrophy type 1

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Introduction

Myotonic Dystrophy type I (DM1) or Steinert's disease is a rare autosomal dominant genetic disease caused by the abnormal expansion of unstable repetitions of cytosine-thymine-guanine trinucleotide (CTG) in the 3' untranslated region of Myotonic Dystrophy Protein Kinase (DMPK) gene and is the most common muscular dystrophy among adults with European ancestry [1]. The number of CTG expansions can vary in different organs and tissues, contributing to the great phenotypic variability observed in patients with DM1. The clinical phenotype is wide, even for members of the same family, ranging from severe congenital-onset forms to late-onset forms with mild symptoms [1–4]. The reported prevalence of DM1 in Europe ranges from 1 in 7400 to 1 in 10 700, being much higher in some regions of the world, namely in Quebec (Canada) and in the Basque Country (Spain) [1].

DM1 is characterized by myotonia, progressive peripheral muscle weakness and atrophy, involving also multiple organs and systems: cardiovascular, respiratory, endocrine, gastrointestinal, central nervous systems and eye [2–6].

Given the high heterogeneity of disease phenotypic spectrum, the identification and validation of methods and measures for clinical research represents a huge challenge within the field [7]. Therefore, it becomes essential to evaluate patients with DM1 using a structured interview for patients' characterization, not only in clinical terms but also considering patients' sociodemographic conditions, habits, and lifestyles. To date, no published structured clinical report form (CRF) designed for use on Portuguese patients with DM1 was found in the literature. Therefore, the aim of the present study was to create a structured CRF to be used among the clinicians for comprehensive assessment and characterization of these patients. In addition, given that DM1 is a neurological disorder we decided to further explore in detail the neurological examination of patients with DM1.

Methods

Ethics statement

The authorization of the present study was achieved by the Ethics Committee for Health of the Centro Hospitalar do Tâmega e Sousa, EPE (obtained at 14-08-2019 with approval number 31-2019).

CRF design

The structured CRF was developed after an intensive literature review conducted in Web of Science, PubMed and EMBASE with the aim to guide the authors in the relevant aspects to be detailed in different sections of the clinical report form. The protocol used for this review was registered in the International prospective registry for systematic reviews (PROSPERO) (CRD42020143429).

Briefly, the structured CRF includes 5 sections of questions, referent to data collection about the following aspects 1) socio-demographic, 2) habits and lifestyle, 3) neurological examination, 4) other systems and organs examination and 5) additional clinically relevant information. The content validity of the CRF was further assessed by a panel of experts from University of Aveiro and Centro Hospitalar Tâmega e Sousa, EPE, consisting of 2 neurologists that work directly and collected all the information from these patients for the CRF, 1 neuroscientist, 1 pharmacologist, 1 physiotherapist, and 2 biomedical researchers. They assessed the accuracy, clinical terminology, completeness, and the meaning of all statements [8]. This CRF will be applied to patients with DM1 with follow-up at the Centro Hospitalar do Tâmega e Sousa (northern region of Portugal), in the form of a structured interview. This methodology was chosen as data collection instrument rather than the self-administered questionnaire because it is the most accurate method for the clinical situation of the included patients and also because it allows the collection of data

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through consultation of patient clinical file, given that some of the data are unknown by the patients. Furthermore, this type of data collection allows for higher response rates [9]. All data will be collected in paper using the clinical report form (CRF). It includes 87 questions stated in Portuguese given the target audience of the present CRF (see supplementary Figure 1). The questions included are from 2 different categories 1) multiple choice and 2) open answer, to be filled in by the neurologist according to the patients' answer or clinical data information available in patient' database [10,11].

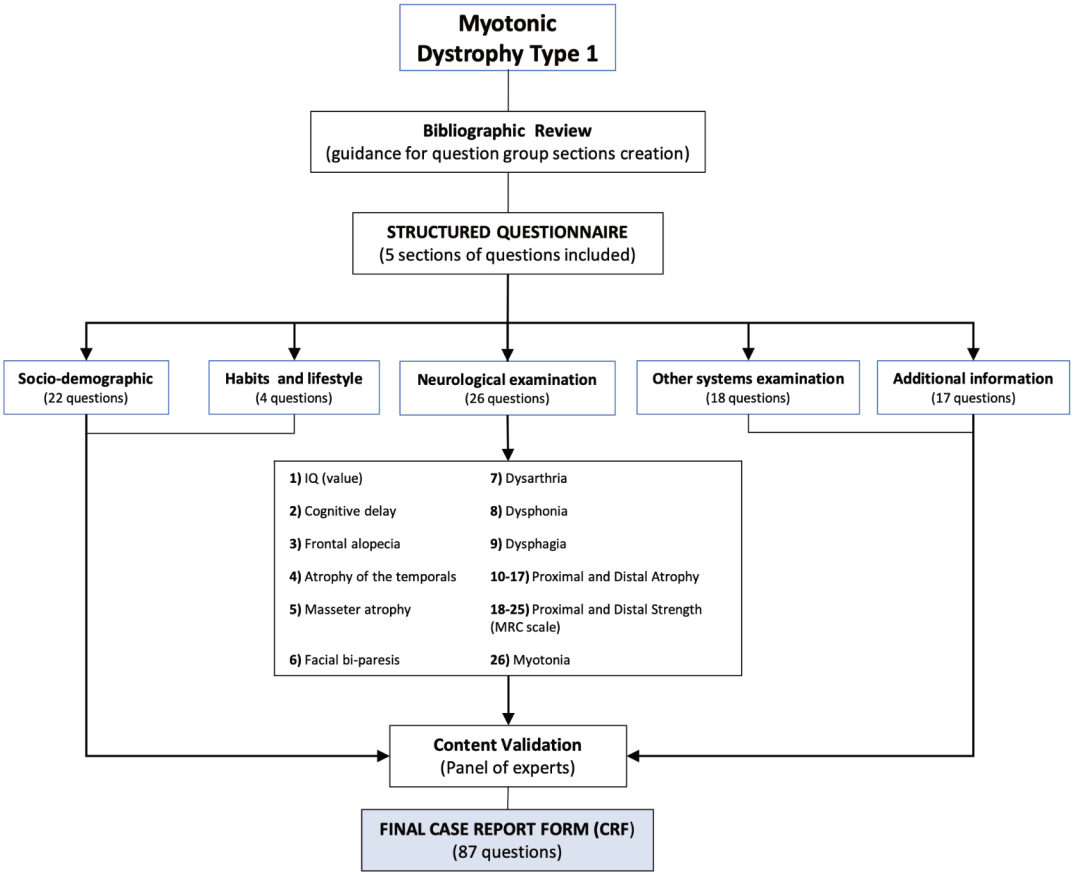

Figure 1 - Schematic representation of different stages of development of the Clinical Report Form to assess patients with DM1.

Results

The different stages of the study are summarized in the Figure 1. A comprehensive structured clinical report form was developed to evaluate and address different aspects of patients with DM1 characterization through 5 different sections of questions. The first one includes 22 questions related with socio-demographic conditions. The second is related to patients' habits and lifestyle and contains 4 questions. The third part refers to the neurological examination and 26 questions are included. The fourth refers to other clinical system and organs examination comprising 18 questions and finally, the fifth section where the other clinical data will be collected (17 questions) (Figure 1). Overall, the final CRF comprises 87 questions divided in the 5 sections mentioned above, which will be applied as a structured interview conducted by a neurologist. The panel of experts mentioned evaluated the accuracy of the questions, the clinical terminology used, the completeness and the significance of all questions included. Further, they also considered that the CRF was well designed, including the relevant issues for patients with DM1 characterization from a clinical, epidemiological, and molecular point of view.

The neurological examination section is composed of 26 open answers to be filled by the neurologist as seen in the summarized Table 1.

Discussion

Developing a comprehensive structured clinical report form for assessing patients with Myotonic Dystrophy type 1 is of paramount importance since to date no robust clinical and epidemiological data referent to DM1 is available in Portugal. To date, only one epidemiological study was conducted in Portugal with the objective to estimate the number of patients with neuromuscular disorders and to determine the prevalence of these diseases in pediatric age [12]. The authors estimated prevalence was 2,8/10,000 inhabitants under 15 years. In addition, the authors also reported that myopathies are the larger group among the neuromuscular disorders [12]. However, to date, many questions remain without answers, namely: 1) What is

Table 1 - Neurological examination in patients with myotonic dystrophy type 1, consisting of 26 open questions to be completed by a neurologist.

Neurological examination			
IQ (value)		Known	Unknown
Cognitive delay		Yes	No
Frontal alopecia		Yes	No
Atrophy of the temporals		Yes	No
Masseter atrophy		Yes	No
Facial bi-paresis		Yes	No
Dysarthria		Yes	No
Dysphonia		Yes	No
Dysphagia		Yes	No
Atrophy MSD	proximal	Yes	No
	distal	Yes	No
Atrophy MSE	proximal	Yes	No
	distal	Yes	No
Atrophy MID	proximal	Yes	No
	distal	Yes	No
Atrophy MIE	proximal	Yes	No
	distal	Yes	No
Strength MSD (MRC)	proximal		
	distal		
Strength MSE (MRC)	proximal		
	distal		
Strength MID (MRC)	proximal		
	distal		
Strength MIE (MRC)	proximal		
	distal		
Myotonia		Yes	No

Abbreviations: MSD- right upper limb; MSE- left upper limb; MID- right lower limb; MIE- left lower limb; MRC- Medical Research Council.

the exact number of patients with DM1 in Portugal? 2) What is the prevalence of DM1 in Portugal and regional differences? 3) How is the quality of life of the patients with DM1? 4) How is the neurological and systemic condition of patients with DM1 in Portugal? Hopefully, these questions will be answered using our structured CRF; it will be applied initially in the Northern of Portugal, and then used in other hospital centers that do the follow-up of these patients.

Concerning the methodology proposed, one of the strengths of the presented structured CRF is that it was built based on an exhaustive review of the literature in different databases and the revision of the CRF by a multidisciplinary team of experts. However, such a detailed clinical report form is time consuming for the clinician who applies it to each patient.

Conclusion:

We successfully gathered information to build a structured CRF with 5 different sections to be used among clinicians to assess patients with DM1. This CRF is of paramount importance, since it addresses multiple aspects of the disease and patients with DM1, and thus helps to better characterize these patients, aiding the clinicians to overcome high heterogeneity of phenotypical expression between patients and families. In addition, our results demonstrated a width variate of question, in particular the neurological examination, composed by 26 questions that have been validated by a panel of experts.

The designed structured CRF represents a step forward and an urgent need to do a better characterization and evaluation of the patients with DM1 niche in Portugal, to aid clinicians and researchers in future clinical trials and interventions.

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