Received: 21 February 2022 | Accepted: 11 October 2022

DOI: 10.1111/ene.15604

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Shedding light on motor premanifest myotonic dystrophy type 1: A molecular, muscular and central nervous system follow-up study

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Funding information
Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Grant/Award Number: PI17/01231 and PI17/01841; Euskal Herriko Unibertsitatea, Grant/Award Number: GU 20/057 and PIF 20/238; Eusko Jaurlaritza, Grant/Award Number: S-PE13UN030; Institute of Health Carlos III; Fondo Europeo de Desarrollo Regional; Basque Government; University of the Basque Country

Abstract

Background and purpose: Myotonic dystrophy type 1 (DM1) is a hereditary and multisystemic disease that is characterized by heterogeneous manifestations. Although muscular impairment is central to DM1, a premanifest DM1 form has been proposed for those characterized by the absence of muscle signs in precursory phases. Nevertheless, subtle signs and/or symptoms related to other systems, such as the central nervous system (CNS), may emerge and progress gradually. This study aimed to validate the premanifest DM1 concept and to characterize and track affected individuals from a CNS centred perspective.

Methods: Retrospective data of 120 participants (23 premanifest DM1, 25 manifest DM1 and 72 healthy controls) were analysed transversally and longitudinally (over 11.17 years). Compiled data included clinical, neuropsychological and neuroradiological (brain volume and white matter lesion, WML) measures taken at two time points.

Results: Manifest DM1 showed significantly more molecular affectation, worse performance on neuropsychological domains, lower grey and white matter volumes and a different pattern of WMLs than premanifest DM1. The latter was slightly different from healthy controls regarding brain volume and WMLs. Additionally, daytime sleepiness and molecular expansion size explained 50% of the variance of the muscular deterioration at follow-up in premanifest individuals.

Conclusions: Premanifest DM1 individuals showed subtle neuroradiological alterations, which suggests CNS involvement early in the disease. Based on follow-up data, a debate emerges around the existence of a 'non-muscular DM1' subtype and/or a premanifest phase, as a precursory stage to other DM1 manifestations.

KEYWORDS
central nervous system, disease progression, follow-up, muscular onset, myotonic dystrophy type 1, premanifest, Steinert's disease

INTRODUCTION

Myotonic dystrophy type 1 (DM1), also known as Steinert's disease, is a progressive and hereditary multisystemic disease that presents an autosomal dominant pattern of inheritance. The diagnosis is established with an expansion length of the trinucleotide CTG (cytosine, thymine, guanine) that exceeds 50 repetitions [1]. DM1 is the most common form of muscular dystrophy in adults, with a global prevalence of 1/7400, and is predominantly characterized by distal muscle weakness and myotonia.

Beyond the impairment of the muscular system, DM1 also implies other systemic alterations, such as ophthalmological, cardiac, endocrine, gastrointestinal and central nervous system (CNS) impairment, amongst others. Regarding the latter, several symptoms have been described (e.g., excessive daytime sleepiness, fatigue and apathy) as well as brain alteration and a variety of cognitive deficits [2]. Although there is growing evidence of a DM1-specific cognitive profile involving an executive and visuo-constructive impairment [3], the nature of the progression of the CNS impairment and the existence of a potential neurodegenerative trajectory of the disease are still the subject of study. In this regard, several studies have revealed neurodegenerative-process-related brain anomalies in DM1 [4, 5], as well as progressive cognitive deterioration [6–10].

A main characteristic of DM1 is its phenotypical variability. The disease varies widely in terms of age of onset, CTG expansion length, muscular impairment, affected body systems and reported symptoms. Thus, various classifications of the disease have been proposed. The most frequently used classification is based on the age of onset of the disease. DM1 can be categorized into five phenotypes: congenital (onset at birth), childhood-onset (1–10 years at the age of onset), juvenile-onset (10–20 years), adult-onset (20–40 years) and late-onset (>40 years). Other classifications [7, 11] have clustered DM1 patients according to their molecular affectation, that is, CTG expansion length.

Similar to other diseases such as Huntington's disease, the premanifest phase has been studied in DM1 and is described as the precursory phase before manifestation of the full disease [12]. Recently, based on muscular impairment, a DM1 subtype has been proposed by van der Plas et al. [13], termed 'motor premanifest DM1'. The authors defined this concept to refer to those individuals with a confirmed DM1 diagnosis without presenting muscular symptoms. Operationally, this implies that clinical examination using the Muscle Impairment Rating Scale (MIRS) reports an absence of motor symptoms (MIRS = 1).

Although in DM1 this precursory phase is characterized by the absence of muscular signs, subtle signs and/or symptoms could emerge and progress gradually during this phase. In this regard, body systems other than the muscular system could be affected in these patients, such as the CNS, as suggested by the abovementioned authors. However, more replication studies—particularly longitudinal studies—are needed to clarify this concept and shed light on the natural progression of this DM1 subtype.

The present study aimed to validate the premanifest DM1 concept and to characterize this patient group transversally and longitudinally in terms of clinical, muscular, neuropsychological and neuroradiological criteria. This would allow for describing DM1 in motor asymptomatic stages and to trace its long-term progression and implicated predictive factors over a 10-year follow-up period.

METHODS

Participants

Participants were part of a larger cohort recruited in the Donostia University Hospital (Gipuzkoa, Spain). When a DM1 patient is identified, it is routine clinical practice to genetically test their

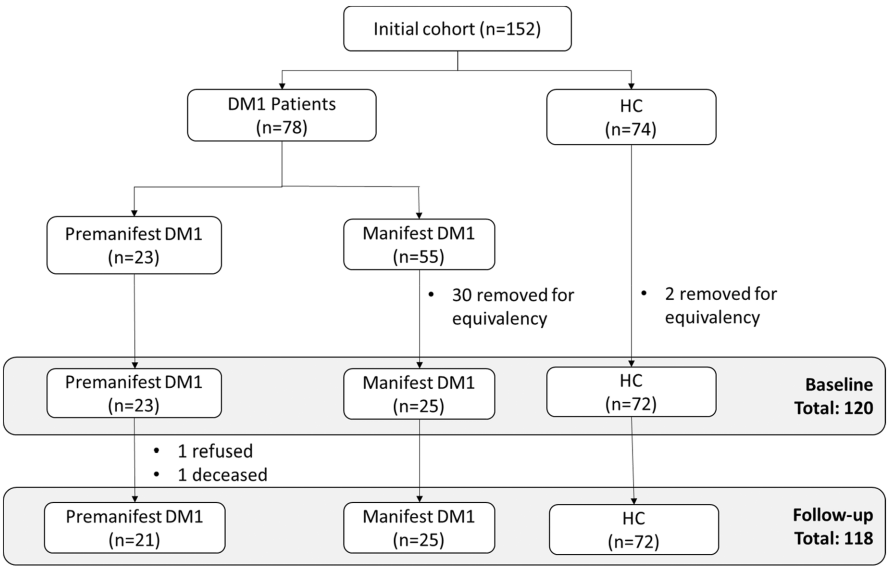

FIGURE 1 Flowchart showing the selection process and the initial and follow-up sample

non-affected relatives for CTG expansion size, and these data are noted in their medical records. For this study, data obtained at two different time points (2005–2007 and 2017–2018) were analysed retrospectively. The inclusion criteria were patients aged 16 years or above and having a molecular confirmation of a DM1 diagnosis. Exclusion criteria were to have a history of major psychiatric or somatic illness (according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition criteria), acquired brain injury, suffering from alcohol or drug abuse, or suffering from a congenital form of DM1.

From the original cohort of DM1 patients with a confirmed genetic diagnosis, those without muscular impairment at baseline (MIRS = 1) were identified by the neurologist of the group and classified as premanifest DM1 ($n = 23$), as proposed by van der Plas et al. [13]. The remaining DM1 patients, that is, those with any degree of muscular impairment (MIRS > 1), were classified as manifest DM1 ($n = 55$). A healthy control group ($n = 74$) of the original cohort was also selected for this study. In order to obtain equivalent groups in terms of demographic variables (sex, age and years of education), certain participants were removed from the study (see Figure 1, flowchart).

The final sample comprised 120 individuals: 23 premanifest DM1 (19.2%), 25 manifest DM1 (20.8%) and 72 healthy controls (60%). All three groups were equivalent in age, sex and years of education. From those, only two participants (premanifest DM1) did not continue to participate at follow-up.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the Gipuzkoa Health Area (DMRM-2017-01). All participants gave written informed consent.

The data were compiled following the method explained below and were retrospectively analysed for this study.

Genetic determination

The CTG expansion size of the DM1 patients was obtained from clinical data at both time points. When recent data were not available (within the last 5 years), genetic assessment was carried out (polymerase chain reaction in *DMPK* alleles up to approximately 100 CTG and southern blot analysis for larger expansions).

Muscular severity

The muscular severity of the DM1 patients was assessed (at baseline and follow-up) by an experienced neurologist through the MIRS [14]. This scale assesses the severity of clinically recognized distal to proximal muscular impairment and ranges from 1 to 5: (1) no muscular impairment, (2) minimal signs, (3) distal weakness, (4) mild to moderate proximal weakness and (5) severe proximal weakness.

Excessive daytime sleepiness

Data for patients' excessive daytime sleepiness or hypersomnolence were gathered through the Epworth Sleepiness Score [15] and were available only at baseline.

Neuropsychological performance

Neuropsychological assessment was conducted at baseline and follow-up by two experienced neuropsychologists blind to the clinical condition of the participants (i.e., premanifest/manifest DM1, disease form, CTG repeats, MIRS or inheritance pattern), in the hospital facilities.

The neuropsychological assessment included the following tests and subtests: Vocabulary, Block Design and Digit Span subtests from the Wechsler Adult Intelligence Scale, third edition (WAIS III) [16], Rey–Osterrieth Complex Figure test (ROCF) [17], Rey Auditory Verbal Learning Test (RAVLT) [18], Stroop colour and word test [19], Raven's Progressive Matrices [20], verbal fluency test (semantic and phonemic) [21, 22] and California Computerized Assessment Package (CALCAP) [23]. Standardized *t* values of all tests were obtained according to Spanish population-based normative data.

For this study, performance on seven cognitive domains was calculated from the converted scores of the administered tests: visuo-construction (block design from WAIS-III and ROCF copy), verbal memory (RAVLT immediate recall, RAVLT delayed recall, total RAVLT), attention/processing speed (Digit Span from WAIS III, Stroop word, Stroop colour and the CALCAP subtests simple reaction time [RT], election RT, sequential 1 RT, sequential 2 RT), executive functions (total Raven, phonemic fluency, Stroop interference), language (Vocabulary from WAIS-III and semantic fluency), visual memory (ROCF delayed recall) and intellectual functioning estimated from a WAIS III short-form composed of Vocabulary and Block Design subtests, based on Sattler and Ryan (reliability $r_{xx} = 0.93$; validity $r = 0.87$).

Neuroimaging

All the magnetic resonance scans—at both baseline and follow-up—were acquired on the same 1.5 T scanner (Achieva Nova, Philips). The current results are based on a high-resolution volumetric turbo field echo series (sagittal 3D T1 weighted acquisition, repetition time 7.2, echo time 3.3, flip angle 8, matrix 256 × 232, slice thickness 1 mm, voxel dimensions 1 × 1 × 1 mm, number of signal averages 1, no slices 160, gap 0, total scan duration 5 min 34 s).

FSL (version 6.01) voxel based morphometry was used [24] to study grey matter (GM) and white matter (WM) volumes. Structural images were brain-extracted and segmented before being registered to the MNI 152 standard space using nonlinear registration [25]. The

TABLE 1 Demographic data of the participants

		Premanifest DM1			Manifest DM1			Healthy controls	
		n (%)			*n* (%)			*n* (%)	
Sex									
Female		13 (53.5%)			13 (52%)			69 (57.5%)	
Male		10 (43.5%)			12 (48%)			51 (42.5%)	
	n	*M* (SD)	Min–max	*n*	*M* (SD)	Min–max	*n*	*M* (SD)	Min–max
Age									
Baseline	23	48.14 (13.49)	(20.41–69.63)	25	43.53 (5.27)	(35.47–56.37)	72	42.29 (12.50)	(18.68–71.07)
Follow-up	19	57.15 (3.09)	(32.08–76.66)	24	55.48 (1.15)	(47.08–69.00)	66	53.00 (1.60)	(27.08–82.74)
Education (years)	23	14.04 (5.60)	(3–23)	25	13.20 (4.63)	(6–25)	72	16.60 (5.23)	(3–26)

Abbreviations: DM1, myotonic dystrophy type 1; *M*, mean.

resulting images were averaged and flipped along the *x*-axis to create a left–right symmetric template. All native GM/WM images were nonlinearly registered to the template and 'modulated' to correct for local expansion (or contraction) due to the nonlinear component of the spatial transformation. The modulated GM/WM images were then smoothed with an isotropic Gaussian kernel with a sigma of 3. To estimate global GM and WM brain tissue volume, normalized for subject head size, the SIENAX tool was used [26].

Data for white matter lesions (WMLs) were assessed according to the Wahlund scale [27]. When lesions >5 mm were identified, severity was rated from 0 (no lesions) to 3 (diffuse involvement). Lesion location was quantified separately across five different regions: (i) the frontal area; (ii) the parieto-occipital area; (iii) the temporal area; (iv) the infratentorial area, including the brain stem and cerebellum; and (v) the basal ganglia, including the striatum, globus pallidus, thalamus, internal and external capsules, and insula.

Statistical analyses

The collected data were analysed using the SPSS statistical package (version 27).

For the transversal analysis, parametric (*t* test) or non-parametric (Mann–Whitney *U* test) statistical tests was conducted where appropriate, at baseline and follow-up. The premanifest DM1 group was compared with both manifest DM1 and healthy control groups.

For the longitudinal analysis, intragroup and intergroup analyses were conducted. To assess intragroup longitudinal differences, parametric (*t* test repeated measures) and non-parametric (Wilcoxon signed-rank) tests were conducted for all three groups. To assess longitudinal intergroup differences, a repeated measures ANCOVA (controlling for time between measures) and repeated measures ANOVA were conducted.

Effect sizes were calculated using Cohen's *d* when parametric tests were used, interpreted as small (0.20), moderate (0.50) or large (0.80) [28], whilst *r* was calculated when non-parametric tests were used and interpreted as small (0.10), moderate (0.30) or large (0.50).

A stepwise multiple regression analysis was conducted to analyse the variables at baseline that could potentially explain the onset of muscular impairment at follow-up in premanifest DM1 patients.

RESULTS

Descriptive analysis

Premanifest DM1 and healthy controls were equivalent in age ($t = 1.92$ [93]; $p = 0.058$), years of education ($t = -1.98$ [88]; $p = 0.050$) and sex ($\chi^2(1) = 0.74$; $p = 0.786$). Likewise, premanifest DM1 and manifest DM1 were also equivalent in age (Mann–Whitney *U* test 192.50; $p = 0.050$), years of education ($t = -0.57$ [46]; $p = 0.571$) and sex ($\chi^2(1) = 0.10$; $p = 0.753$). The mean elapsed time between the two time points was 11.17 years (SD = 0.12).

In the manifest DM1 group, 84% were adult-onset patients and 16% juvenile-onset. Regarding the inheritance pattern, 88% had a paternal inheritance and 12% maternal. The premanifest DM1 patient group was distributed as 58.8% paternal inheritance, 35.3% maternal inheritance and 5.9% (one patient) inheritance of both parents.

Demographic data of the sample are displayed in Table 1.

Transversal analysis

Clinical and neuropsychological functioning

When comparing the premanifest DM1 and manifest DM1 groups, a significantly larger CTG expansion size and worse performance was found in the following cognitive domains in the manifest group: executive functions, attention/processing speed, intellectual functioning domains (both time points) and in the visuo-construction domain (at follow-up) (see Table 2).

No statistically significant differences were found between premanifest DM1 and healthy controls in the neuropsychological

outcomes. Nevertheless, as shown in Table 2, the effect size was close to moderate for the executive functions domain at baseline and attention/processing speed domain at follow-up, with poorer performance in the premanifest DM1 group.

Neuroimaging

Although not statistically significant, moderate to large effect sizes were reported for the differences between the premanifest DM1 and manifest DM1 groups in GM/WM volumes and WMLs (see Figure 2). The manifest DM1 group showed poorer GM/WM volumes, accompanied by WMLs in the frontal and temporal cortex. The premanifest DM1 group showed more lesions in the basal ganglia and infratentorial areas (see Table S1).

As shown in Figure 2, although no significant differences were found for GM and WM volumes between premanifest DM1 and healthy controls, moderate effect sizes were reported for GM volumes at baseline and follow-up, with lower GM volumes in the premanifest DM1 group. Furthermore, premanifest patients showed significantly more WMLs than healthy controls in the total WMLs at baseline, in the left parieto-occipital cortex (at both time points) and in the right temporal cortex and right basal ganglia (only at follow-up) (see Table S1).

Intragroup longitudinal analysis

Clinical and neuropsychological functioning

Regarding clinical data, for the premanifest DM1 group a significant increase in muscular impairment ($Z = -2.12$; $p = 0.034$; $r = 0.46$) was found. Sixteen of the 23 patients (76.2%) maintained an absence of muscular impairment (MIRS = 1) at follow-up, whilst the rest developed a higher degree of muscular impairment. For the manifest DM1 group, a significantly higher CTG expansion size ($Z = -3.39$; $p = 0.001$; $r = 0.69$) was found at follow-up.

Results regarding intragroup longitudinal differences in neuropsychological outcomes can be found in Table S2.

TABLE 2 Transversal intergroup comparisons in clinical and neuropsychological outcomes

	Descriptive analyses: *M* (SD)			Intergroup comparisons					
	DM1 patients		HC	Premanifest DM1 vs. manifest DM1			Premanifest DM1 vs. HC		
	Manifest DM1	Premanifest DM1		*t*	*p*	*d*	*t*	*p*	*d*
Baseline									
CTG	639.44 (400.27)	116.24 (105.38)	–	−5.69	0.000**	1.68	–	–	–
MIRS	2.92 (0.50)	1 (0)	–	−18.65	0.000**	0.36	–	–	–
Epworth	6.29 (4.36)	5.19 (4.07)	–	−0.78	0.440	0.26	–	–	–
Attention/PS	40.72 (7.84)	47.31 (9.74)	48.16 (7.38)	2.59	0.013*	0.75	−0.42	0.677	0.10
Verbal memory	45.13 (12.32)	48.99 (10.97)	48.96 (9.58)	1.13	0.266	0.33	0.01	0.993	0.00
Visual memory	42.96 (14.06)	46.57 (6.93)	44.48 (8.16)	1.07	0.290	0.32	1.02	0.310	0.27
Visuo-construction	43.04 (9.88)	47.65 (8.06)	47.55 (8.97)	1.76	0.085	0.51	0.05	0.962	0.01
Executive functioning	41.61 (8.90)	46.84 (8.21)	50.19 (7.90)	2.08	0.043*	0.61	−1.63	0.108	0.42
Language	47.80 (8.96)	50.37 (8.81)	51.31 (8.12)	1.00	0.322	0.29	−0.45	0.652	0.11
IQ	92.36 (15.10)	100.86 (12.71)	102.58 (15.17)	2.07	0.044*	0.61	−0.47	0.641	0.12
Follow-up									
CTG	902.21 (533.66)	194.95 (292.70)	–	−5.29	0.000**	1.60	–	–	–
MIRS	3.08 (0.64)	1.29 (0.56)	–	−10.01	0.000**	0.61	–	–	–
Attention/PS	38.38 (7.62)	42.78 (5.53)	45.80 (7.14)	2.11	0.041*	0.65	−1.70	0.093	0.44
Verbal memory	47.27 (12.90)	51.87 (10.22)	50.15 (9.40)	1.27	0.211	0.39	0.69	0.491	0.18
Visual memory	43.63 (10.47)	48.26 (7.31)	48.89 (6.68)	1.64	0.109	0.50	−0.35	0.725	0.09
Visuo-construction	40.71 (8.53)	53.18 (6.54)	52.67 (8.59)	5.26	0.000**	1.62	0.24	0.809	0.06
Executive functioning	39.27 (9.58)	47.26 (7.38)	47.55 (7.76)	3.00	0.005**	0.92	−0.15	0.883	0.04
Language	48.88 (8.48)	51.11 (6.52)	52.80 (7.14)	0.95	0.350	0.29	−0.93	0.355	0.24
IQ	94.13 (12.16)	107.79 (11.71)	108.77 (12.82)	3.72	0.001**	1.14	−0.30	0.765	0.08

Abbreviations: CTG, CTG expansion size; HC, healthy controls; IQ, intelligence quotient; *M*, mean; MIRS, Muscular Impairment Rating Scale; PS, processing speed.*$p < 0.05$; **$p < 0.01$.

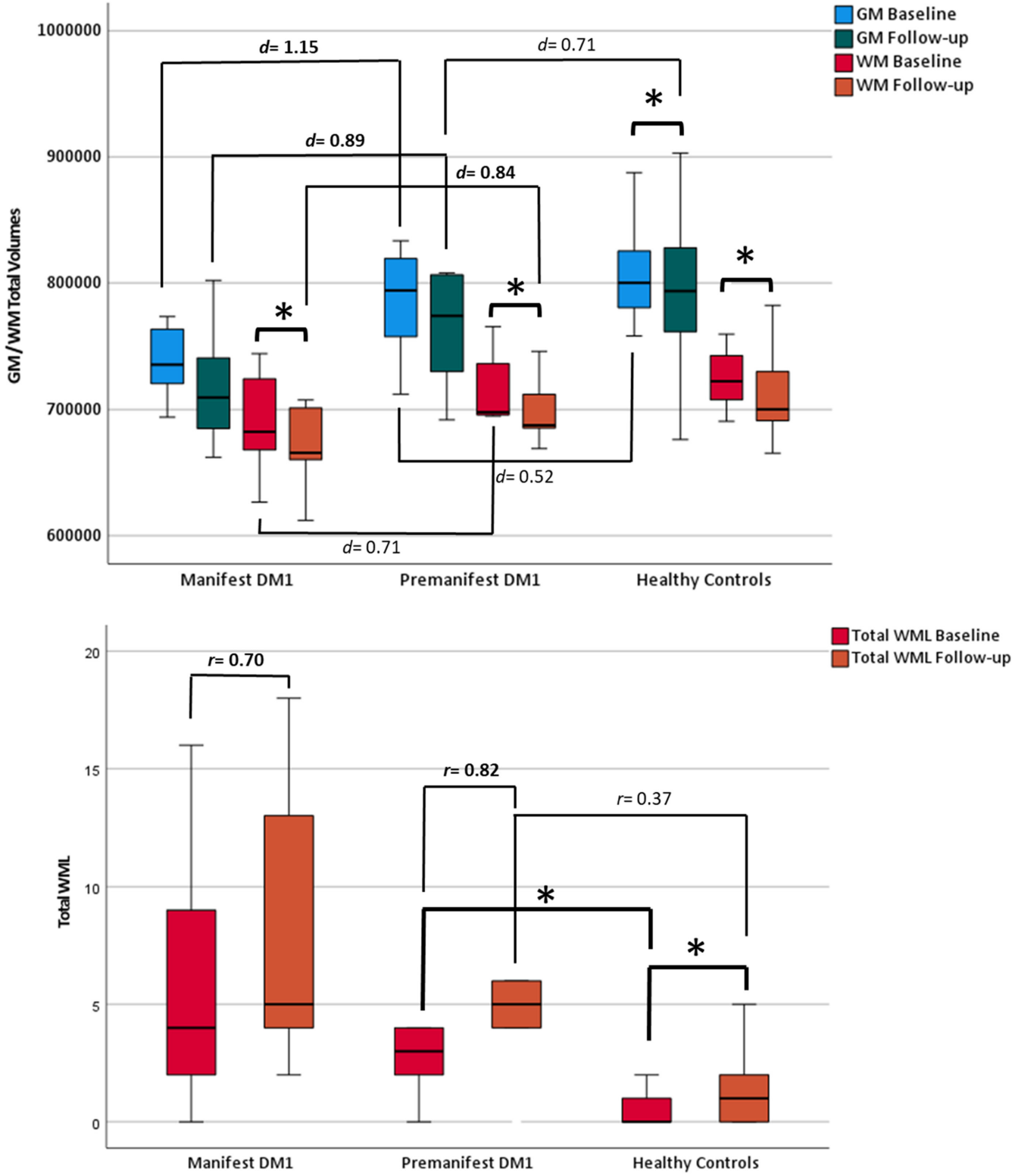

FIGURE 2 Intragroup and intergroup comparisons of GM/WM volumes and total WMLs. GM, grey matter; WM, white matter; WMLs, white matter lesions. Effect sizes were calculated using Cohen's *d* for GM/WM (0.20, small; 0.50, moderate; 0.80, large) and *r* for total WMLs (0.10, small; 0.30, moderate; 0.50, large). $^{*}p < 0.05$

Neuroimaging

Results regarding WM/GM volumes and total WML longitudinal analysis are shown in Figure 2. Additionally, WML localization differences can be found in Table S3.

For the premanifest DM1 group, a significant decline in WM volume was found between the two time points. Regarding WMLs, although not statistically significant, a large effect size was found for the differences in total WMLs. Moreover, more WMLs were reported at follow-up in the parieto-occipital and the right temporal

cortex, with moderate to large effect sizes. In contrast, in the right frontal cortex more WMLs were reported at baseline.

For the manifest DM1 group, a significant decline in WM volume and a higher number of WMLs were reported at follow-up. Additionally, large to moderate effect sizes were reported in the following areas: frontal and left parieto-occipital cortex, right temporal cortex, basal ganglia and infratentorial area. As in the premanifest DM1 group, significantly more WMLs were reported in the right frontal cortex at baseline.

The healthy control group showed significantly lower GM and WM volumes at follow-up. In addition, significantly more total WMLs were found at follow-up. Moderate effect sizes were reported for the left frontal cortex and for the bilateral parieto-occipital cortex, with more WMLs found in these regions at follow-up.

Longitudinal intergroup analysis

Clinical and neuropsychological functioning

Regarding clinical measures, when comparing premanifest and manifest DM1, the latter group showed a significantly greater increase in the CTG expansion size. Additionally, MIRS progression was similar in both groups. Regarding neuropsychological outcomes, no differences were found in the progression of the cognitive domains when comparing either the DM1 patient subgroups or premanifest DM1 with healthy controls (see Table S4).

Neuroimaging outcomes

Regarding GM and WM volumes, no statistically significant longitudinal differences were found between either premanifest DM1 and manifest DM1 or premanifest DM1 and healthy controls. Nevertheless, the premanifest DM1 group showed significantly greater WML deterioration in the right temporal cortex than healthy controls (see Table S4).

Muscular onset predictors in premanifest DM1

The following baseline potential predictors for the deterioration of muscular impairment were included in the regression model: age, CTG, Epworth score and estimated intelligence quotient. From these, only CTG expansion size and Epworth scale score at baseline were statistically significant predictors of MIRS evolution at follow-up in premanifest DM1 patients ($F(2, 11) = 7.50$; $p = 0.009$). This model—which includes two clinical variables—explained 50% of the total variance.

DISCUSSION

Premanifest DM1 refers to the group of patients that are in the precursory/subclinical phase of the full manifestation of the disease. The present study is the first to include a longitudinal follow-up of these patients, which has enabled this form of the disease to be characterized and these patients to be traced over a decade, combining clinical, neuropsychological and neuroradiological approaches.

As reported by van der Plas et al. [13], in the present study premanifest and manifest DM1 patients differ considerably in terms of several disease manifestations, such as brain and cognitive alterations. Specifically, according to the current results, manifest DM1 patients show greater molecular defects, worse performance on almost all neuropsychological domains, and lower GM/WM volumes. Moreover, manifest DM1 patients show WMLs around cortical regions, whilst the premanifest DM1 patients present lesions affecting subcortical structures. Indeed, a meta-analysis of brain imaging in DM1 reported WMLs in frontal, temporal and parietal lobes [29]. Our results suggest the potential importance of analysing different WML patterns in different forms of the disease. Moreover, all these differences between manifest and premanifest DM1 are in accordance with the fact that DM1 is a heterogeneous disease.

Although premanifest DM1 patients are muscularly unaffected and less impaired than other DM1 patients regarding non-muscular symptoms, they cannot be considered a healthy population. In this study, premanifest DM1 patients showed outcomes suggesting brain structural vulnerability, with lower GM volumes and more cortical and subcortical WMLs than healthy controls. So far, our findings support the notion that premanifest DM1 patients are at an intermediate point between manifest DM1 and healthy controls, at least with regard to brain structure, in agreement with van der Plas et al. [13], who also reported WM abnormality in premanifest DM1. Our findings favour the idea that brain alterations occur in the early stages of the disease, when the classic muscular signs of the disease have not yet developed.

Beyond a static picture of the disease, this study provided the opportunity to analyse its natural progression. In this regard, none of the studied clinical, neuropsychological or neuroimaging data revealed differences in the rate of disease progression between the three groups. Specifically, all three groups reported a similar GM/WM volume loss and WML increase over a decade, findings that are most likely related to aging processes. This does not support the idea that DM1 patients—either manifest or premanifest—suffer from neurodegenerative processes, although the possibilities that DM1 might be a slow progressive cerebral disease or could gradually evolve during the later stages of the disease cannot be ruled out [30, 31]. However, the fact that patients differed from healthy controls both at baseline and follow-up suggests that the brain structure of these patients could have distinctive developmental characteristics throughout their life stages and are not clearly associated with aging or neurodegeneration, even in premanifest forms of the disease.

Having described premanifest DM1 individuals, it is now necessary to clarify whether this is a DM1 subtype or just an initial phase of the disease. It should be noted that within the premanifest DM1 group most patients (76.2%) remained muscularly asymptomatic over more than 10 years of follow-up. This raises

the possibility that there are certain DM1 patients who may not develop muscular symptoms and could thus belong to a 'non-muscular DM1' subtype, a term that might therefore be more accurate than 'premanifest'. This idea can only be confirmed by tracing these patients throughout the course of the disease. Nevertheless, other premanifest patients gradually developed muscular symptoms, suggesting that whilst these patients do not show muscular signs during the initial phases (premanifest phase) they will do so in the future.

Additionally, consensus regarding use of the term 'premanifest phase' is still needed. Whilst the premanifest concept has been employed so far to refer to those patients without motor symptoms, it should be reconsidered to include patients who do not manifest other key symptoms. For instance, juvenile-onset DM1 patients are known to present cognitive or psychiatric symptomatology, whilst they might be free of other classic neurological and motor manifestations [32]. Indeed, the heterogeneity of DM1 regarding different subtypes and disease progression could be explained by the pathogenetic profile of DM1, which, even if monogenic, spreads to a larger gene-to-gene interactome, leading to the alteration of many other genes [33].

From a clinical standpoint it is therefore crucial to gain knowledge about the prognosis and predictive variables of the muscular progression of the disease. In this study, it was found that CTG expansion size and the degree of excessive daytime sleepiness at baseline explained up to 50% of the fact of deteriorating muscularly in premanifest DM1, thus evolving from the premanifest phase to the manifest DM1 group. Indeed, excessive daytime sleepiness has been described as a key neurocognitive feature in DM1, present in around 70%–80% of patients [34, 35]. Our study confirms the hypothesis of van der Plas et al. [13] which suggests that this symptom precedes further muscular impairment and could be a useful predictor of muscular onset in premanifest DM1. Similarly, an effect of the genetic defect on muscular deterioration has been previously reported by Mazzoli et al. [36].

The main limitation of this study is the absence of certain data that could be of interest (e.g., cataracts, cardiac and metabolic pathology etc.). Considering that this is a retrospective study, only data available from the selected sample could be analysed. Using the data of other body systems could help elucidate whether the premanifest patients (as defined in this study) are 'non-muscular DM1' patients with other initial symptoms or whether they are completely asymptomatic patients. Participants have been studied from a clinical, neuropsychological and neuroradiological perspective, but future studies should also study potentially affected body systems as early as in the premanifest phase, given the multisystemic nature of the disease. Finally, since this is a rare disease, the small sample size constitutes the other main limitation. However, the large effect sizes obtained in this study encourage conducting a prospectively designed study to replicate our results with a larger sample. Specifically, it would be of special interest to recruit more premanifest DM1 patients to shed light on the premanifest phase/subtype issue as well as to broaden knowledge on the prognosis of DM1. Moreover, recruiting larger samples could allow for separately analysing the different DM1 phenotypes (e.g., childhood, juvenile, adult), since, as previously suggested, the initial symptoms and disease progression may differ between subgroups.

Overall, the results of this study confirm that CNS involvement is present in premanifest DM1 and can be detected early in the disease before muscular deterioration develops. Our findings contribute toward a broader understanding of DM1 in its various forms, depicting early CNS changes and disease progression. This information could help clinical practitioners to achieve a more accurate prognosis and to better manage the health care needs and expectations of patients and relatives.

AUTHOR CONTRIBUTIONS

Joana Garmendia: conceptualization, data curation, formal analysis, methodology, visualization, writing the original draft, writing—review and editing. Garazi Labayru: conceptualization, data curation, formal analysis, investigation, methodology, supervision, visualization, writing—original draft, writing—review and editing. Miren Zulaica: investigation, resources, writing—review and editing. Jorge Villanúa: investigation, resources, writing—review and editing. Adolfo López de Munain: conceptualization, funding acquisition, investigation, resources, supervision, validation, writing—review and editing. Andone Sistiaga: conceptualization, data curation, funding acquisition, investigation, methodology, resources, supervision, writing original draft, writing—review and editing.

ACKNOWLEDGEMENTS

This work was supported by the Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (Ref: 609), from the Institute of Health Carlos III co-founded by Fondo Europeo de Desarrollo Regional (PI17/01231 to A.S.; PI17/01841 to A.L.); Basque Government (S-PE13UN030 to A.S.); and University of the Basque Country (UPV/EHU) (PIF 20/238 to J.G.; GU 20/057 to J.G., G.L. and A.S.).

CONFLICT OF INTEREST

All authors declare no conflict of interest regarding the content of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Garmendia J, Labayru G, Zulaica M, Villanúa J, López de Munain A, Sistiaga A. Shedding light on motor premanifest myotonic dystrophy type 1: A molecular, muscular and central nervous system follow-up study. *Eur J Neurol*. 2023;30:215-223. doi: 10.1111/ene.15604