# Brain imaging in myotonic dystrophy type 1 – a systematic review

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## Abstract

**Objective:** To systematically review brain imaging studies in myotonic dystrophy type 1 (DM1).

**Methods:** We searched Embase (index period 1974 to 2016) and Medline (index period 1946 to 2016) for studies in DM1 patients using: MRI, MRS, fMRI, CT, ultrasound, PET or SPECT. From 81 studies, we extracted clinical characteristics, primary outcomes, clinical-genetic correlations and information on potential risk of bias. Results were summarized and we calculated pooled prevalences of imaging abnormalities, where possible.

**Results:** In DM1, various imaging changes are widely dispersed throughout the brain, with apparently little anatomical specificity. We found general atrophy and widespread grey matter volume reductions in all four cortical lobes, the basal ganglia and cerebellum. The pooled prevalence of white matter hyperintensities is 70% (95% CI 64 to 77), as compared to 6% (95% CI 3 to 12) in unaffected controls. DTI shows increased mean diffusivity in all four lobes and reduced fractional anisotropy in virtually all major association, projection and commissural white matter tracts. Functional studies demonstrate reduced glucose uptake and cerebral perfusion in frontal, parietal and temporal lobes, and abnormal fMRI connectivity patterns that correlate with personality traits. There is significant between study heterogeneity in terms of imaging methods, which together with the established clinical variability of DM1 may explain divergent results. Longitudinal studies are remarkably scarce.

**Conclusion:** DM1 brains show widespread white and grey matter involvement throughout the brain, which is supported by abnormal resting state network, PET/SPECT and MRS parameters. Longitudinal studies evaluating spatiotemporal imaging changes are highly needed.

## Background

Myotonic dystrophy type 1 (DM1) is a complex multisystem disease, characterized by significant clinical variability, anticipation and autosomal dominant inheritance.[1] Brain involvement in DM1 has now been irrefutably demonstrated in neuropsychological, neuropsychiatric, and pathologic studies.[2] Salient clinical features like apathy, cognitive deficits in multiple domains (*e.g.* visuospatial, executive) and behavioural disturbances are important determinants of quality of life.[3] At the pathological level, cell loss, neurofibrillary tangles and neuronal inclusion bodies occur at various locations in the brain.[1] Imaging correlates of these clinical and pathological characteristics have been addressed in many studies employing a variety of methods, with sometimes conflicting results. For example, studies have inconsistently found clinical correlates of white matter hyperintensities, in terms of their severity and distribution.[3]

Therefore, the objective of this study was to provide a comprehensive, widely scoped overview of the substantial body of brain imaging literature in DM1 on seven commonly used imaging methods (magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), ultrasound, single-photon emission computed tomography (SPECT), positron emission tomography (PET) and computed tomography (CT)). In addition, we evaluated the reported relationships between imaging and clinical - genetic parameters in DM1 patients. Finally, we evaluated evidence on temporal changes in DM1 brain imaging (*i.e.* longitudinal studies), to assess whether these were in support of the view on DM1 as a progressive neurodegenerative disease.

## Methods

### Search

We searched Embase (index period 1974 to 2016) and Medline (index period 1946 to 2016) for relevant studies. We searched for free text and index terms related to DM1 and imaging methods (Appendix e-1A and e-1B). Our primary search was completed on June 22nd, 2016, with a final update yielding three additional studies performed 1st September, 2016. We also performed cross-referencing to identify articles potentially missed by our search.

**Eligibility criteria**

We selected studies on the basis of predefined criteria for eligibility, considering studies reporting on DM1 patients and at least one brain imaging method (Appendix e-2). We restricted our selection to studies that utilized CT, MRI, MRS, SPECT, PET, fMRI or ultrasound methods. Reasons for exclusion of studies were case reports (on single patients), double reporting, and studies written in a language different from English, French, German or Dutch. We also excluded studies for which we were unable to obtain full-text. Study selection comprised an initial round of title and abstract screening, after which a second round of full-text screening was performed. All (n = 14) conference abstracts were excluded.

**Data extraction**

A data extraction form was piloted on five studies and consequently adapted where necessary. We extracted clinical information such as age, sex, educational level, types of DM1 (congenital, juvenile, adult-onset), main inclusion- and exclusion criteria, and the use of neuropsychological tests and questionnaires for psychiatric disorders. Type of DM1 was arbitrarily defined as presence of first clinical symptoms at birth (congenital DM1 (cDM1)), after birth but before age of 18 years (juvenile (jDM1)) or at 18 years or later (adult-onset (aDM1)). If reported, the estimated age at

onset and disease duration were recorded. Furthermore, we recorded for each study: imaging method used, technical details and the main findings (see section on 'data synthesis').

**Quality assessment**

We adopted a quality assessment form from Kmet and colleagues, with modifications to better suit the requirements of this review (Appendix e-3).[4, 5] A single author (KO) scored all studies for quality and risk of bias on a scale of 0, 1 or 2 (0 representing the worst and 2 representing the best score).

**Data synthesis**

We classified studies by their reporting of either structural or functional imaging data, or both. Structural data comprised structural MRI, CT and ultrasound studies; whereas fMRI, SPECT, PET and MRS were classified under functional imaging. For structural MRI studies, we subdivided and separately aggregated data into three categories: whole brain (atrophy and/or ventricular enlargement), grey matter (volume; cortical thickness), and white matter (white matter hyperintensities (WMH) and integrity of normal-appearing white matter (NAWM)). We clustered results per brain region (*i.e*. brain lobes versus deep brain structures and cerebellum; cortical versus subcortical). CT studies were evaluated for information on atrophy (focal or global), ventricular dilatation and skull hyperostosis. We evaluated ultrasound studies for findings of ventricular dilatation, and changes of brainstem echogenicity. Results were assessed in a qualitative manner for all modalities, except WMH on MRI, which allowed a pooled analysis. We estimated pooled WMH prevalence across brain regions using metaXL (version 5.3, EpiGear International Pty Limited, Queensland, Australia), giving a random-effects weighted mean prevalence with 95% confidence

intervals (95% CI). We calculated the $I^2$ statistic as a measure for statistical heterogeneity. For functional imaging studies, aggregation of data was unfeasible due to a limited number of studies per imaging technique and heterogeneous methods.

## Results

Search and selection results

Our search and selection process yielded a total of 81 included studies (table 1). The most important reasons for excluding studies were double reporting (n = 11), non-availability of full-text (n = 15) or unsuitable publication type (n = 13) (supplemental Appendix e-4). Language restrictions applied to most studies for which full-text was unavailable.

Demographics and disease characteristics

Eighty-one studies included a total of 1,663 DM1 cases (Appendix e-5A). Twenty-three studies only analyzed DM1 cases, whereas 58 studies included a total of 1,334 unaffected controls. In studies reporting sex, there was an excess of male DM1 cases (865 males (53.4%) versus 754 females (46.6%), $\chi^2 = 7.62$, $p = 0.006$). The median of average ages across the studies was 38.5 years, interquartile range (IQR) of 5.9 years and total range of 5 to 56.6. Median age at onset was 25.7 years (IQR 5.8 years). In 31 studies reporting modal CTG repeat length, median repeat length was 582 repeats (IQR 177 and total range 534 to 719 repeats). For 27 studies providing information on the muscular impairment rating scale (MIRS), median score was 3.1 (IQR 0.43), which indicates distal but no proximal weakness. Forty-one imaging studies (51%) performed neuropsychological testing (Appendix e-7D). Regarding disease classification, presence or absence of cDM1, jDM1 and aDM1

was reported in respectively 57, 60 and 60 studies. Nineteen studies reported presence of cDM1 patients, whereas jDM1 and aDM1 patients were included in 48 and 52 studies, respectively. With the exception of MRS, functional imaging studies did not include cDM1 patients. In structural studies, cDM1 participants often comprised a minority of included participants (data not shown).

Quality analysis

Our analysis demonstrated that most studies had a clearly described research question (*i.e.* score 2, n = 70), included participants with firmly established diagnosis (both before and after gene identification in 1992) (*i.e.* score 2, n = 70), and provided sufficient details on participants characteristics (*i.e.* score 2, n = 72), imaging protocol and analysis (*i.e.* score 2, n = 71)(Appendix e-5B). Twenty-two studies (27%) gave a full (*i.e.* score 2) description of the recruitment procedure, and six (7%) provided information on the rates of participation. In- and exclusion were provided (*i.e.* score 1 or 2) in 54 studies (67%); 53 studies took into account (*i.e.* score 1 or 2) possible confounding factors. We found discussions of study limitations in a minority of the publications included in our review (*i.e.* score 1 or 2; n = 27, 33%).

Structural imaging studies

A total of 1,247 DM1 cases and 1,015 healthy controls were included in 65 and 46 structural MRI studies, respectively (summary of outcomes parameters, methods of assessment and most salient findings in table 2, figures 1 and 2).[6-69] Of note, only one MRI study had a longitudinal design.[18]

*Whole brain.* Irrespective of the method of analysis, the large majority of studies found generalized atrophy in DM1 participants compared to healthy controls (table 2).

*Grey matter.* Grey matter volumes were mostly assessed with semi-automated or fully automated methods (voxel-based morphometry (VBM)) (table 2). Nine studies used voxel-based morphometry in DM1, showing a pattern of widespread reduction of grey matter volume in DM1 cases compared to controls. Reduction of grey matter volume was found in frontal (n = 9 out of 9), temporal (n = 7 out of 9), parietal (n = 8 out of 9) and occipital cortices (n = 7 out of 9), as well as to deep grey matter structures (n = 8 out of 9) and cerebellum (n = 3 out of 4). The data did not allow for analyses of atrophy in areas within lobes, or within specific deep grey matter structures. Comparing cortical thickness between DM1 and control brains (n = 1 study comprising 24 patients), reduced cortical thickness was demonstrated in parietal-occipital cortex bilaterally, as well as in unilateral (left or right) frontal and temporal cortex.[68]

*White matter.* We calculated the pooled prevalence (pp) of WMH across 49 studies that provided sufficient data for analysis. We found a pp of 70.4% (95% CI = 63.8 to 76.5%), with substantial statistical heterogeneity ($I^2$ = 77%). Fifteen studies also reported the prevalence of white matter hyperintensities in (age- and sex matched) controls, with a pp of 6.4% (95% CI = 2.5 to 11.7%). WMH in DM1 patients were located in periventricular and subcortical white matter, preferentially in frontal (pp 52%, 95% CI = 38 to 65%, $I^2$ = 54%), temporal (pp 44%, 95% CI = 31 to 58%, $I^2$ = 49%) and parietal lobes (pp 31%, 95% CI = 23 to 40%, $I^2$ = 12%), although they were also noted to occur in the occipital lobe in eight studies. Anterior temporal pole (*i.e.* 'deep temporal'; Figure 2)) WMH were reported in 12 studies, of which 10 provided sufficient information to calculate a pooled prevalence of 30.3% (95% CI = 17.3% to 45.0%; $I^2$ = 82%). WMH volume/lesion load across studies was difficult to aggregate because of differences in methodology and reporting (summarized in Appendix e-6).

Besides WMH, enlarged Virchow-Robin spaces were shown to be more prevalent in DM1 cases than in unaffected controls in four studies (data not shown).

The structural integrity of the normal-appearing white matter was mostly evaluated by means of diffusion tensor imaging (table 2). Studies utilizing region-of-interest (ROI) approaches and tract-based spatial statistics (TBSS) demonstrated widespread reduction of fractional anisotropy (FA) and increase in mean diffusivity in DM1 patients compared to controls. Specifically, ROI approaches demonstrated FA reduction in all four lobes and some predefined fiber tracts (*e.g.* inferior and superior longitudinal fasciculus, uncinate fasciculus, forceps minor and major, cingulum). TBSS studies showed mostly symmetrical decreased FA in all major association, projection and commissural fibers.

Ten CT studies (1983 to 2013) included a total of 162 DM1 cases and 122 unaffected individuals.[12, 58, 70-77] These studies studies focused on the presence of ventricular dilatation (present in 1 out of 19 to 6 out of 7 patients), general atrophy (present in 3 out of 19 to 22 out of 37 patients) and frontal hyperostosis (10 out of 37 to 14 out of 16 patients). Two uncontrolled ultrasound studies examined 24 newborn congenital DM1 patients and found ventricular dilatation and macrocephaly in the majority of patients (11 out of 14 and 8 out of 10, respectively).[78, 79] Two ultrasound studies reported increased third ventricle diameter and mixed results for brainstem echogenicity in (mostly) adult DM1 cases versus controls.[41, 80]

Functional imaging studies

Seven PET studies demonstrated a consistent global decrease in glucose uptake as well as regional reductions (*i.e.* lobe specific) compared to unaffected controls (table 3).[45, 63, 69, 81-84] Controlling for possible volumetric differences in two of these studies

did not alter the results.[63, 69] Five SPECT studies demonstrated a picture in line with findings from PET studies, demonstrating both globally and regional decreases (*i.e.* lobe specific) in cerebral perfusion in DM1 cases compared to unaffected controls (table 3).[16, 53, 60, 84, 85] In fMRI studies, an altered activation pattern in bilateral motor regions was demonstrated in DM1 patients during a motor task and in the presence of clinical myotonia.[13, 86] Abnormal resting-state functional connectivity in default-mode and 'theory-of-mind' networks was also noted in relation to personality traits and social cognition in DM1 (table 3).[56, 87] The most consistent finding in MRS studies was a decrease in N-acetylaspartate (NAA) (table 4).[8, 17, 35, 62, 88]

Correlation of imaging with genetic and clinical parameters

Twenty-seven studies examined a total of 53 correlations between imaging findings and modal CTG repeat length in blood, with 15 significant correlations found in 10 studies (Appendix e-7A). In general, longer CTG repeats were associated with greater structural and functional changes of the brain. However, variations in imaging modalities and statistical tests (*e.g.* linear regression, parametric or non-parametric correlation coefficients) limited comparisons between studies. We found correlational analyses between imaging findings with age and duration of disease in 28 and 27 studies, totaling 43 and 45 associations, respectively (Appendix e-7B and e-7C). Significant simple (*i.e.* Pearson or non-parametric equivalent) correlations for age (16 out of 43) and disease duration (20 out of 45) with imaging changes ranged from small (~0.3) to strong (~0.7) and most frequently concerned white matter lesions. Evaluation of correlations with neuropsychological testing failed to yield consistent relationships (Appendix e-7D). For example, neuropsychological studies in DM1 have shown consistent deficits on visuoconstruction domain as demonstrated by the Rey-Osterrieth Complex Figure Copy Test (ROCF-C) (authors' data, unpublished).

However, only three out 15 correlational analyses employing the ROCF-R found significant relations between imaging findings and tests results (Appendix e-7D).[11, 53]

## Discussion

In DM1, there is a broad spectrum of imaging changes that are widely dispersed throughout the brain, with apparently little anatomical specificity. Our findings are in line with the wide range of clinical, molecular and histopathological brain alterations previously reported.[89, 90] Significant between study heterogeneity in terms of imaging methods, together with the established clinical variability of DM1 may explain divergent results. At the structural level, we found evidence for general brain atrophy, which corroborates histopathology studies demonstrating diffuse cerebral atrophy.[91, 92] Partly, brain atrophy can be attributed to volume loss of grey matter, which is evident in all lobes, deep grey matter and cerebellum in VBM studies. Notably, VBM is best suited for the evaluation of cortical changes, less so for deep grey matter structures for reasons mainly related to tissue segmentation.[93, 94] In addition, the cerebellum is often not analyzed in VBM studies. Also, age factor, corrected in 5 out of 9 studies may have influenced the results. Possible explanations for grey matter volume loss are speculative, but may include neuronal loss and loss and/or decreased genesis of dendritic spines and synapses.[92, 95] The possibility of neuronal loss is corroborated by MRS studies that show decreases in [NAA] in grey matter, a marker for neuronal density.

White matter involvement in DM1 involves T2/FLAIR hyperintensities preferentially located in frontal, temporal and parietal lobes at periventricular and subcortical locations. Compared to matched healthy controls, DM1 patients have a higher frequency of WMH. The temporo-polar WMH, reported to be relatively specific for DM1, are present in approximately one third of patients. Divergent prevalence (70.4%

(95% CI = 63.8 to 76.5%); $I^2$: 77%) of WMH across studies may be the result of study characteristics such as field strength (*e.g.* 1.5 T versus 3 T), imaging sequence (*e.g.* T2 versus FLAIR), voxel-sizes and other methodological parameters.[96] More importantly, differences between studies might relate to variations between study populations in terms of age, DM1 disease class and severity and CTG repeat length. Besides WMH, there is now substantial evidence for diffuse involvement of NAWM, as mainly demonstrated by DTI techniques. Notably, all DTI studies used a similar method of controlling for family-wise error at the $p < 0.05$ threshold. Future studies applying more stringent thresholding might theoretically uncover a more focal pattern of white matter involvement. Nonetheless, it is likely that damage to structural brain networks results in alterations in functional connectivity that has recently been demonstrated in DM1.[56, 87] These studies are critically important for better understanding of imaging correlates of neuropsychological involvement in DM1. The lack of consistent correlations found to date may result from limited power due to small sample sizes, and from the fact that cognitive functions are not anatomically set to one particular brain region, but rather are a consequence of complex network interactions.[97]

With regard to the etiology of white matter damage, we cannot exclude a role for 'traditional' vascular risk factors as less than half of the studies took into account these confounders and some risk factors (*e.g.* smoking, hypercholesterolemia) have been shown to be highly prevalent in DM1.[98, 99] However, the presence of temporal and temporo-polar WMH argue against a solely cardiovascular etiology of WMH in DM1. Interestingly, the pattern of WMH concurs with the predominantly frontal, temporal and parietal anomalies observed with PET and SPECT imaging, suggesting a possible role for decreased perfusion in the etiology of WMH. An important caveat

is the fact that none of the SPECT and only two out of the seven PET studies corrected for atrophy. Nevertheless, these studies are notable for the fact that changes in frontal perfusion corroborate clinical frontal lobe involvement, such as apathy and disorders of executive functioning.[3] It remains speculative whether perfusion deficits are a cause or consequence in DM1 pathophysiology: neuronal dysfunction/loss may lead to decreased metabolic demands; alternatively perfusion deficits may be causal to tissue damage and dysfunction.

The paucity of longitudinal imaging studies (3 out of 81) in DM1 is striking given the chronic nature and relatively long survival in the disease and especially because many of the neuroimaging findings discussed here (e.g. brain atrophy, WMH) are associated with age in the general population.[100-102] Whether imaging anomalies in DM1 have a specific spatiotemporal pattern (*i.e.* start in certain anatomical region(s) and disseminate over the brain with time) should be tested in future studies. Such progressive nature of brain involvement in DM1 is suggested by neuropsychological studies documenting cognitive decline in some (*e.g.* attention, psychomotor speed, executive functions) but not all cognitive domains over many months to years.[103, 104]

Complex interrelations between clinical and genetic parameters may explain the lack of an effect of age, disease duration and length of repeat on neuroimaging findings one would expect in a neurodegenerative disease. Anticipation in DM1 is extreme, with age at onset typically decreasing by 20 to 30 years per generation.[105] Coupled with the sex-dependent mutational dynamics, anticipation in DM1 leads to a family structure that is highly non-random in terms of age, inherited CTG repeat length and disease severity.[105-108] Thus, individuals recruited from the first generation of known DM1 families have only a mild presentation of disease despite that fact that they are usually relatively old before the disease is diagnosed in their family. Conversely,

individuals from later generations, despite being younger, usually have inherited a much larger CTG repeat and thus present with a more severe form of the disease. As a result, the true effects of age and inherited CTG length are masked by their inverse relationship in the patient population. Moreover, somatic instability of the *DMPK* CTG repeat that is age- and tissue-dependent and expansion-biased, could lead to longer modal CTG repeats in blood DNA of older individuals and have a negative impact on the precision of genotype-phenotype relationships.[109-112] The CTG repeat is also somatically unstable in other tissues, including post-mitotic tissues (*e.g.* brain) and it has been suggested that somatic expansion may contribute, at least in part, to the tissue specificity and progressive nature of the symptoms.[109-112] It should be noted that with the exception of cerebellum, average CTG repeat lengths are thousands of repeats longer than the inherited allele length in various regions of the brain.[92, 113, 114] Thus, it may not be surprising that pathology in the DM1 brain is widespread and diffuse.

Limitations and future directions

Our study has several limitations. A single author performed literature search and selection. Although we also performed cross-referencing by two authors, we cannot exclude the possibility of missed studies. Selection preferences of reviewed studies may have biased recruitment towards participants with obvious CNS involvement or away from individuals with apathy, thus limiting the generalisability of our findings. Moreover, selection preferences and the sampling biases discussed earlier preclude the identification of relevant differential phenotypes in the DM1 population that could help to explain heterogeneity in our results. The latter is also impeded by the absence of a universally accepted and adopted disease classification (*e.g.* congenital, childhood, juvenile, adult, late-onset DM1) across studies.

Our study underlines the need for a large, imaging study of long duration (*i.e.* preferably ≥10 years) including genetically and clinically well characterized participants. Ideally, recruitment and source of participants would be carefully described and potential sources of confounding (*e.g.* vascular risk factors) accounted for. International collaboration, as exemplified by the European OPTIMISTIC trial in DM1, will increase generalisability of results and statistical power.[115] Not only will such a study provide better insight into natural history, but it will also allow to determine which imaging parameters are suitable as outcome markers in future clinical trials.

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**Table 1**

Search and selection results

| Imaging method | Embase hits (22/06/2016) | Medline hits (22/06/2016) | Remaining after de-duplication and title and abstract screening | Included after full-text evaluation and cross-referencing | Included after search update and exclusion of conference abstracts |
|---|---|---|---|---|---|
| **CT** | 169 | 85 | 23 | 10 | 10 |
| **MRI** | 365 | 173 | 94 | 75 | 64 |
| **MRS** | 40 | 51 | 7 | 5 | 5 |
| **Ultrasound** | 11 | 6 | 5 | 4 | 4 |
| **fMRI** | 10 | 5 | 4 | 4 | 4 |
| **PET** | 19 | 15 | 6 | 6 | 7 |
| **SPECT** | 33 | 23 | 6 | 6 | 6 |

**Legend**. Search and selection results. Studies found in search and remaining after deduplication and title and abstract screening. The numbers in the final column do not add up to 81 as some studies utilized more than one imaging method.

**Table 2**

Summary of structural MRI studies in DM1

| **Parameter** | **Study ID** | **Main findings** |
|---|---|---|
| **Whole brain volume** | | |
| Unknown method of assessment (n = 7) | 9, 14, 35, 37, 53, 56, 69 | *Generalized brain atrophy in DM1 patients compared to healthy controls in almost all studies.* |
| Subjective visual assessment (n = 9) | 18, 21, 27, 38, 42, 47, 67, 68, 77 | |
| Ventricle brain-ratio or comparable brain measurements (n = 13) | 2, 7, 9, 13, 17, 19, 20, 22, 23, 24, 36, 49, 72 | |
| (Semi-) automated segmentation methods (n = 8) | 3, 8, 33, 39, 44, 45, 74, 76 | |
| **Grey matter** | | |
| (Semi-automated) segmentation methods (n = 2) | 29, 33 | *Reduction of grey matter volumes in frontal, temporal, parietal and occipital cortex. Reduction of grey matter volume in deep grey matter structures and cerebellum. Reduced cortical thickness in parietal, frontal and temporal lobes.* |
| Voxel-based morphometry (n = 9) | 5, 8[a], 12[a], 51, 54, 63[a], 64, 76, 81[a] | |
| Cortical thickness analysis (n = 1) | 81 | |

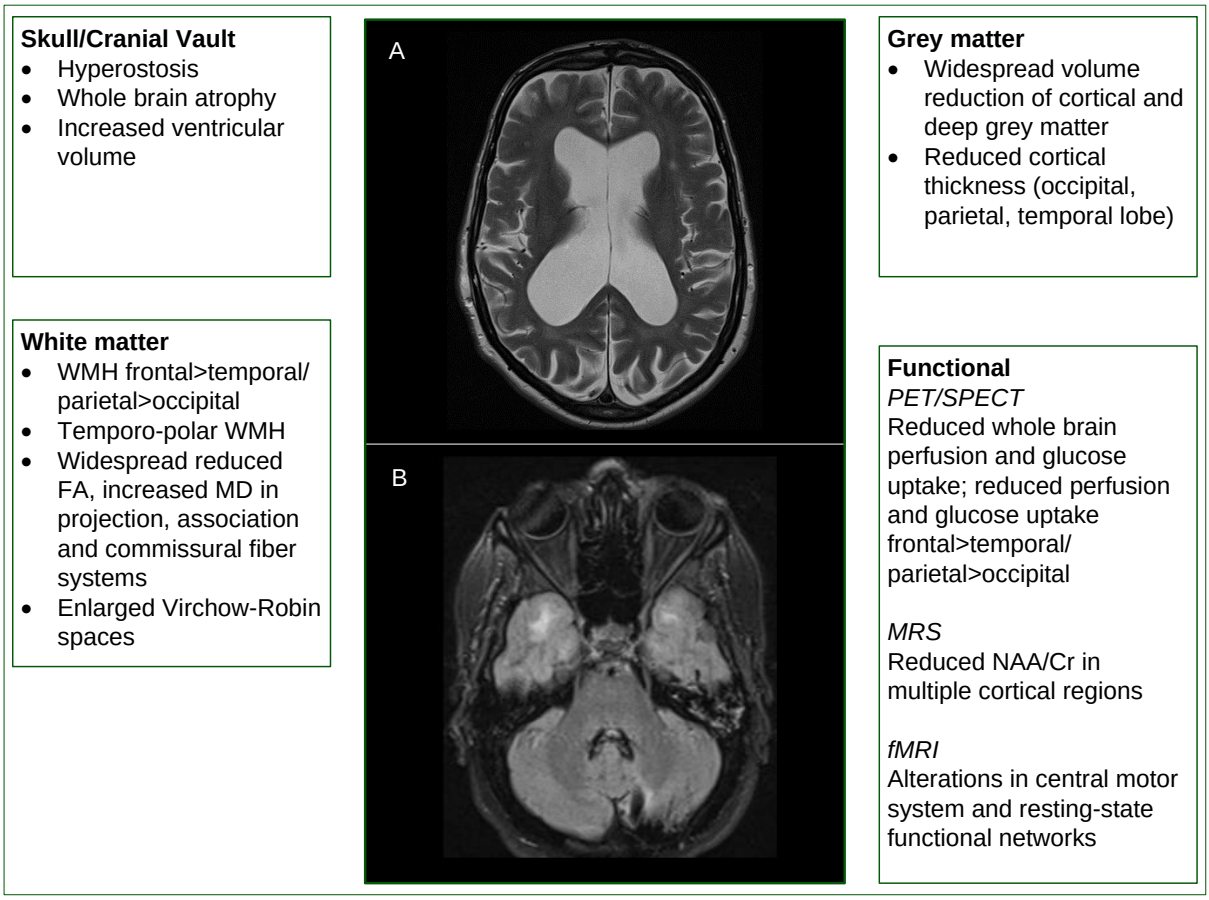
| | | |
|---|---|---|
| **White matter -** *White matter hyperintensities* | | |
| Prevalence of white matter hyperintensities (n = 49) | 1, 2, 3, 5, 7, 9, 11-14, 17-27, 30, 33 - 37, 40, 41, 42, 44-47, 49, 53, 56, 58, 62, 66-69, 71, 72, 74, 76, 77, 81 | *Increased prevalence of WMH (subcortical, deep white matter, periventricular) in DM1 patients compared to healthy controls, particularly in frontal>temporal>parietal lobes. Temporo-polar WMH in one third of participants. Increased lesion load in patients versus healthy controls.* |
| Total lesion load (TLL) or total lesion area (TLA) of WMH (n = 8) | 5, 7, 8, 11, 12, 63, 64, 81 | |
| Fazekas scale (n = 2) | 8, 77 | |
| ARWMC/ Wahlund scale (n = 6) | 12, 51, 62, 63, 64, 65 | |
| **White matter -** *Normal appearing white matter evaluation* | | |
| T2-relaxometry (n = 1) | 23 | *Widespread reductions in FA and increase in mean diffusivity throughout white matter: projection, association and commissural fibers. Alterations of T2 relaxation demonstrated throughout white matter. Mixed results of magnetization transfer ratios of white matter.* |
| Magnetization transfer (n = 2) | 33, 52 | |
| DTI – ROI approach (n = 6) | 29, 30, 54, 78, 79, 80 | |
| DTI – TBSS (n = 5) | 8, 12, 51, 64, 81 | |

**Legend.** Summary of structural MRI studies in DM1. MRI studies evaluating whole brain volume/atrophy; grey matter volumes/atrophy and white matter integrity. ARWMC: age-related white matter change scale; DTI diffusion tensor imaging; ROI: region of interest; TBSS tract-based spatial statistics; prevalence

denotes the ratio of patients with WMH versus total number of patients; TLL and TLA refer to automated methods to detect WMH volume. For study ID, please refer to Appendix e-5. Superscript [a] denotes VBM studies that corrected for age.

## Figure 1

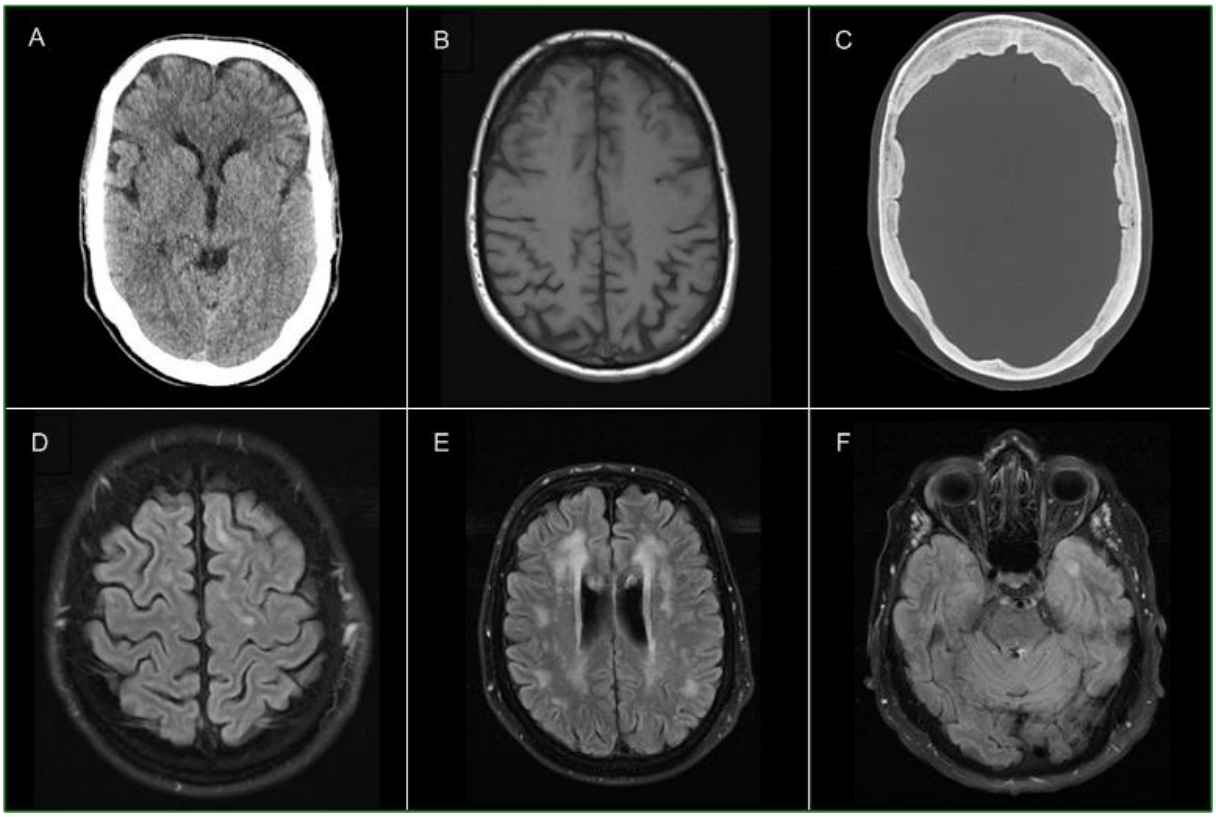
Summary of imaging findings in DM1




**Legend.** Summary of structural and functional imaging findings in DM1. A: T2-weighted transversal MRI of a 54-year old male adult onset DM1 patient with demonstrated hydrocephalus. B: Transversal FLAIR MRI in a 30 year old female adult onset DM1 patient showing bilateral temporo-polar WMH. This patient also had posterior fossa surgery for hemangioblastoma. WMH: white matter hyperintensity; FA: fractional anisotropy; MD: mean diffusivity; NAA: N-acetylaspartate; Cr: creatine; PET: positron emission tomography; SPECT: single photon emission computed tomography; MRS: magnetic resonance spectroscopy; fMRI: functional MRI.

## Figure 2

Illustrative images of structural DM1 imaging




**Legend.** Illustrative CT and MRI images of DM1 patients from our centre. A: CT-scan showing frontal atrophy in a 20-year old male juvenile onset DM1 patient. B: T1-weighted axial MRI demonstrating frontoparietal atrophy in a 60-year old male adult onset DM1 patient. C: Hyperostosis (most prominently frontally located) in a 46-year old adult onset female DM1 patient. D+F: Subcortical and periventricular WMH in a 53-year old adult onset DM1 patient without known risk factors for cardiovascular disease. Note the guirlande-shaped WMH at the convexity (D) and left temporo-polar WMH (F) which argue against a chronic ischemic etiology.

**Table 3**

Functional imaging studies in DM1

| Method | ID | No. of studies | No. of cases/ controls | Main findings |
|---|---|---|---|---|
| **PET** | 4, 28, 47, 50, 58, 61, 76 | 7 | 97/121 | Decreased whole brain glucose uptake; decreased uptake in frontal and parietal lobes, and temporal lobes, basal ganglia and hypothalamus |
| **SPECT** | 15, 48 , 61, 62, 71 | 5 | 108/42 | Decreased whole brain perfusion; decreased perfusion in frontal, temporal and parietal lobes |
| **fMRI** | 11, 65, 66, 73 | 4 | 78/49 | Alterations in central motor system activation and resting-state functional connectivity (DMN and 'theory-of-mind' networks) |

**Legend.** Functional imaging studies in DM1. ID: study identification numbers (Appendix e-5). No.: number, PET: positron emission tomography, SPECT: single photon emission computed tomography, fMRI: functional MRI, DMN: default mode network

**Table 4**

Magnetic resonance spectroscopy findings in myotonic dystrophy type 1

| ID | No. of patients | Region/volume of interest | Field strength | Echo time | Main findings |
|---|---|---|---|---|---|
| **37** | 5 | right parietal region, occipital and frontal | 1.5 T | 270 ms | NAA/Cho↓ and NAA/Cr↓ |
| **14** | 14 | midoccipital grey matter, temporoparietal grey matter | 1.5 T | 30 ms | NAA =, MI↑, Cho↑, Cr↑; NAA/Cr↓, Cho/Cr = |
| **3** | 21 | insular cortex (frontal, temporal, parietal opercula) | 1.5 T | 19 ms | NAA/Cr↓; NAA/Cho ↓; Cho/Cr = |
| **74** | 14 | midoccipital grey matter, temporoparietal grey matter, frontal white matter | 1.5 T | 135 ms | NAA ↓, Cr =/↓, Cho =/↓; Naa/Cr↓, Cho/Cr = |
| **70** | 14 | White matter: frontal, corona radiata, parietal; posterior internal capsule<br><br>Grey matter: basal ganglia, thalamus, limbic cortex | 3.0 T | 24 to 30 ms | grey matter: NAA↓, Cho↑, Cr =; NAA/Cr↓<br><br>white matter: NAA↓, Cho↓, Cr=; NAA/Cr↓; Cho/CR = |

**Legend.** Magnetic resonance spectroscopy findings in DM1. NAA N-acetylaspartate; MI: myo-inositol; Cr: creatine; Cho: choline; = not different from controls; ↓/↑ decreased or increased compared to

controls; T: Tesla; ms: milliseconds; only the most frequently evaluated metabolites are presented in the table.