TWENTY YEARS OF NATURAL HISTORY OF MYOTONIC DYSTROPHY TYPE 1

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INTRODUCTION

Myotonic dystrophy type 1, an autosomal dominant disorder caused by expansion of an unstable trinucleotide (CTG) repeat sequence in an untranslated, but transcribed, portion of the 3' untranslated region of the myotonic dystrophy protein kinase (DMPK) gene located on chromosome 19q13.3,is the most prevalent muscular dystrophy and is associated with high levels of morbidity and premature mortality. The age of onset of DM1 is variable and identifies different disease forms. Symptoms onset at birth, with respiratory failure, difficulties in feeding and hypotonia identify the Congenital form; symptoms onset (mainly learning disabilities) after the newborn period and up to18 years of age is typically referred to as childhood-onset myotonic dystrophy (2); symptoms onset in adult age is associated to the so called "classical "DM1 form, characterized by progressive distal muscle weakness, myotonia, early onset cataract, cardiac, respiratory and gastrointestinal disturbancies, and dysfunction in the CNS (1) . Improvements in the comprehension of molecular pathogenesis opened the route to clinical trials. The collection of natural history data is essential either to improve proactive clinical management either to reach trial readiness.

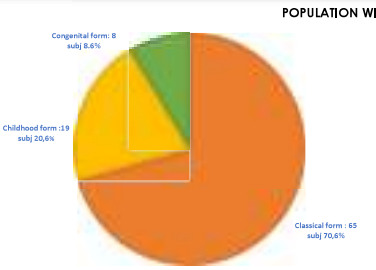
PATIENTS AND METHODS

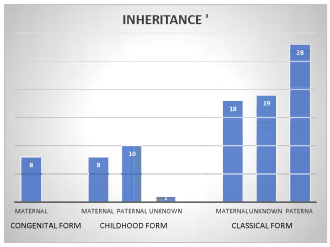
Data from 92 patients with genetically confirmed diagnosis, collected along 20 years of follow up, were retrospectively analyzed database. Demographic and clinical data were collected and patient's motor functional state was monitored, using Medical Research Council scale (MRC), Motor Function Measure(MFM) and 6 Minute Walking Test along 20 years of follow up.

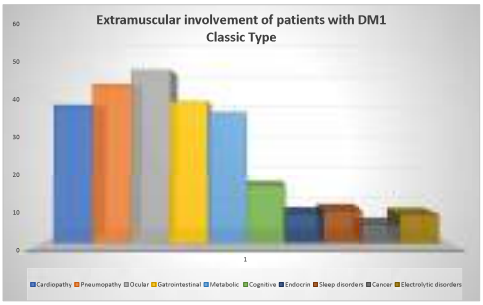
The Motor Function Measure (MFM) is a tool designed to monitor precisely the severity and progression of motor function in most neuromuscular diseases. It is applicable to all degrees of disease severity, in both ambulant and nonambulant patients. Items are rated on a 4-point Likert scale and are grouped into subscores assessing 3 functional areas: standing position and transfers (the D1 subscore; 13 items), axial and proximal motor function (D2; 12 items), and distal motor function (D3; 7 items). The MFM has been validated in terms of reproducibility, construct validity, and concurrent validity in patients aged between 6 and 60 years old with one of the principal neuromuscular disease (3) .

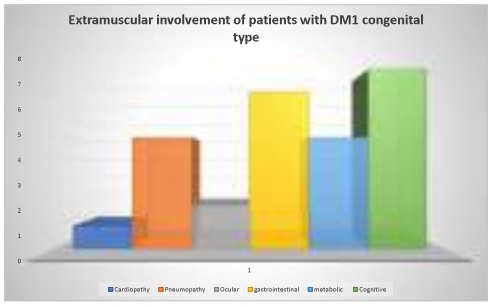
RESULTS

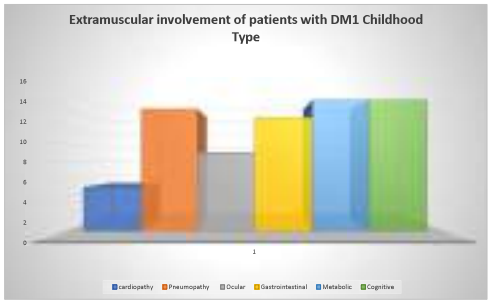
65 patients present classical form with mainly paternal inheritance ,onset age of 34,3+/- 12,5; after 19 years +/- 8,9 from diagnosis,11 out of 65 are wheelchair bound. The most frequent symptoms, beyond neuromuscular, are: cataract (49), gastrointestinal disorders (40), pneumopathy (45), cardiopathy (39) metabolic disorders (37) and central nervous system involvement (16);5 presented cancer (gastrointestinal tract).
8 subjects with congenital form (mean age at last evaluation 22,7 +/-12,2), presented neonatal severe multiorgan involvement with a positive evolution in 7 of them (acquisition of autonomous walking at the age of 23.6+/-5.2 months, autonomous feeding and weaning from respiratory support); Central nervous system disorders were present in all, and did not change along time.
19 patients are presenting childhood form, with onset age of 8,4+/- 3 with learning disabilities with various degrees of mental retardation but no other clinical disturbances. At last evaluation (31,8+/-9,9) they are all ambulant, but present metabolic disorders (15), pneumopathy (14) and gastrointestinal disorder (13%).



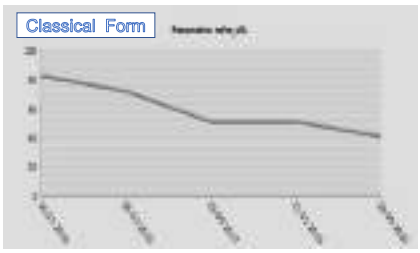


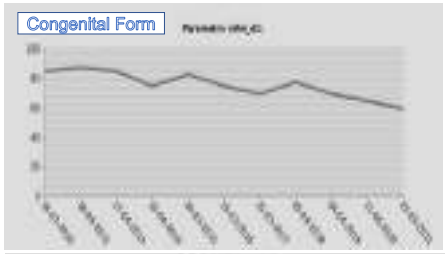


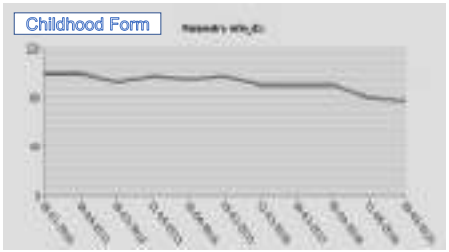


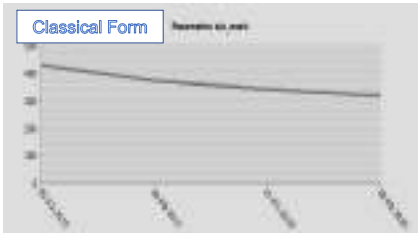


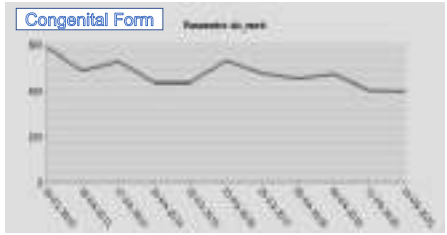
Motor functional state and endurance valuation along more than 10 years of follow up considering 3 walking patients affect by classical , congenital and childhood forms of DM1 respectively, monitored using MFM in his D1 subscores and 6 Minute Walking Test as outcomes measure, shows a decrease in parameters for all the subjects, in particular for the parameter D1 a more rapid decrease over time is observed in the classical form.

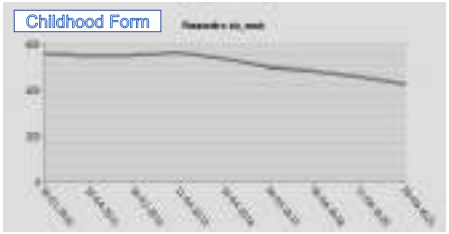












CONCLUSION

Our population presents characteristics comparable to those described in literature. The value of our data lies in the collection overtime and in the attempt to identify clinical milestones of multisystemic disease progression. The rapid advances in the identification of possible target for genetic treatments also in DM1 brings the need to identify outcome measures able to demonstrate the efficacy of the therapy.

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