

The Brain Involvement in Congenital Myotonic Dystrophy: a Review

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Abstract

The congenital variant of Myotonic Dystrophy (MyD) is transmitted by the affected mothers to children with the MyD gene, in the region q13.3 of chromosome 19, carrying a CTG repeat length larger than 1000. We reviewed the brain abnormalities reported to date in series of cases with Congenital MyD and compared them with our data on patients affected by the same disease. Studies of molecular genetics on cases with Congenital MyD were also considered. In our experience and as seen in recent reports, evaluation of intellectual ability in such children clearly indicates that mental retardation of mild or moderate degree affects almost all the patients with the disease. At the neuroimaging evaluation (CT or MRI) the vast majority of them have also been shown to be affected by central white matter changes and ventricular enlargement, usually not of severe degree. Correlation among the degree of mental retardation, the ventricular enlargement and the white matter changes seems lacking. In our experience, it seems inconsistent also the relationship between the size of the CTG repeat expansion in peripheral blood cells DNA and the degree of the clinical and neuroimaging alterations presented by children with Congenital MyD, even though all showing a trinucleotide expansion larger than 1000. Altogether, the congenital variant of the Steinert's disease appears as a myoencephalopathy of the newborn, that is only partially explained by the characteristic large trinucleotide expansion on chromosome 19q13.3.

Key words: congenital myotonic dystrophy, CTG repeat expansion, mental retardation, brain MRI, review.

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The typical form of Myotonic Dystrophy (MyD) usually has its clinical onset in the second or in the third decade of life. The characteristic features of this autosomal dominant disorder are represented by myotonia and progressive muscular weakness, as originally described by Steinert in 1909 [39]. Since the earliest reports [9, 10, 13, 19, 33] it was soon evident that, besides skeletal muscle, other tissues were also variably involved and among them appeared of importance the heart, the brain, the eye, the smooth muscle and some endocrine glands.

In a proportion of these patients, with values up to 13% in some series [19], the disease is evident at birth with a clinical picture different from the typical one, as originally described by Vanier et al in 1960 [45]. This congenital variant of MyD (CMyD) is characteristically transmitted to the newborns only by affected mothers, aside from very few exceptions [13, 19, 29]. The infants with CMyD characteristically present severe diffuse weakness and hypotonia associated with feeding difficulties and respiratory distress: in the first weeks of life, the disease may lead to death, as in half of the 18 cases reported by Aicardi et al.

[1]. The majority of the patients with CMyD, as pointed out by the studies of Harper's group [19], are also affected by bilateral facial weakness that determines a typical shape of the mouth ("tented" or "carp-mouth"). Talipes is the most frequent skeletal deformity that affects newborns with CMyD.

In association with the major clinical signs, in CMyD may be less frequently observed additional disturbances, as reduced fetal movements and polyhydramnios during late pregnancy, undescended testes in males and hydrocephalus [1, 13, 19, 28]. Congenital cataract has only exceptionally been described in newborns with CMyD [36]. If these patients survive the neonatal period of life, their muscle strength appears slowly but steadily improving, even though with evidence of a characteristic delay in motor development. Delayed speech in these children is usually the first evident sign of mental retardation, that is considered among the typical disturbances of the disease [19, 22, 26, 32, 34, 44].

All the major clinical features of CMyD are listed in table 1.

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Table 1. Major clinical and neuroimaging signs of congenital myotonic dystrophy.

A. Clinical features	B. Neuroimaging alterations
Diffuse muscular hypotonia and weakness	Ventricular dilatation
Characteristic facies myopathica	White matter changes
Delayed motor development	Hypoplasia of corpus callosum
Mental retardation	Cortical atrophy
Neonatal feeding difficulties	Others
Neonatal respiratory distress	
Talipes	

The signs are listed according to their frequency

The most amazing aspect of the clinical presentation of the infants with CMYD, as compared to the patients with the adult form of MyD, is the absence of myotonia, a symptom that becomes progressively apparent only after the first years of life. However, accurate evaluation of children with CMYD by EMG may, in some instances, detect myotonic discharges also in the first years of life, before the onset of clinical myotonia [40]. In the same infants, as in adult cases, serum CK is usually normal, as shown in the large number of patients studied by Harper [19]. Also muscle biopsy is not of help in diagnosis of CMYD, since, like in the adult form, it shows only aspecific alterations, as predominance and hypotrophy of type 1 fibers, internal nuclei, ring fibers and sarcoplasmic abnormalities [13, 15, 19]. Altogether, the clinical, electrophysiological and histological signs of CMYD are aspecific and give a reason why, so often, this variant of MyD is recognized only after the first years of life, unless the mother has not yet been diagnosed as suffering from the typical form of the disease. Moreover, it is noteworthy that frequently the young mothers have only very mild symptoms of the Steinert's disease and, if they do not undergo a careful clinical investigation, often they have not detected the disease [13].

Recently, the identification of a CTG repeat expansion in the region q13.3 of the chromosome 19 as the mutational cause of the MyD [7, 8, 16, 18] provided the possibility of an unequivocal diagnostic test for these patients. However, the difficulty in recognising the disease on clinical, electrophysiological and morphological grounds still restrains the possibility of using DNA molecular analysis in infants with CMYD.

Molecular Genetics and Pathogenesis of Congenital Myotonic Dystrophy

Early genetic linkage studies of DNA of patients with MyD [19] showed that the gene of this disease segregated with a group of other genes, which included that of the complement (C3), subsequently located to chromosome 19 [47].

In 1992 Harley et al [18] and Buxton et al [8] reported the identification of an unstable CTG repeat expansion on chromosome 19q13.3 as the mutation underlying the MyD: the trinucleotide repeat expansion was shown by Fu et al [16] and Brook et al [7] to occur at the 3' untranslated region of a locus related to a protein kinase. Recently, Salvatori et al [35] and Shimokawa et al [37] independently observed by immunological studies that this protein kinase was localized to the terminal cisternae of the sarcoplasmic reticulum of skeletal muscle, in the region of the A-I band boundary. However, the function of this so called myotonin protein kinase and the meaning of its abnormality in the pathogenesis of the MyD remains substantially unexplained [25, 35, 37]. On the other hand, a better understanding of the etiopathogenesis of the disease comes from the observation that the mutation underlying MyD was located in a region very rich in genes: because of it, the same mutation could determine dysfunction of other proteins, so giving account for the pleiotropic clinical manifestations of the genetic abnormality [21]. The variable multisystemic expression of the clinical disturbances in MyD seems also linked to the heterogeneity of the size of the CTG triplet expansion in different tissues [2, 24, 27, 41].

Investigation on the length of the trinucleotide repeat in lymphocytes DNA of patients with MyD indicated that, usually, the bigger was the expansion the more severe was the clinical manifestations of the disease [21, 27, 43]. In the study of Tsilfidis et al [43] were also considered 22 cases with CMYD and, on average, they were shown to have a size of the CTG repeat expansion greater than that seen in the non-congenital cases. In the CMYD patients the CTG repeat is usually greater than 1000; in our series of 8 cases it ranged 1300 to 2300 (unpublished data). On average, also the mothers of our patients with CMYD had a CTG repeat expansion (range 500 to 1090) greater than that found in non-congenital MyD cases, in agreement with the data reported by Tsilfidis et al. [43]. This study, however, clearly showed the lack of a clear-cut correlation between the severity of the disease and the length of the CTG repeat in peripheral blood cells DNA, since some cases with the congenital form of MyD had a trinucleotide expansion lower than 500, whereas some non-congenital cases had a number of CTG repeats over 1500. Likewise, in 5 CMYD cases Tachi et al [41] found no correlation between histological alterations of skeletal muscle and the degree of CTG repeat expansion in the same tissue. From these data [41, 43] it appears also that, despite the possibility of prenatal diagnosis of MyD, the size of CTG repeat expansion in the chorionic villus does not let to define a certain prognosis.

The almost exclusive transmission of CMYD by affected mothers has been considered a puzzling issue since the first reports on this type of MyD. Recently, it seems to have found some explanation in the investigation of Jansen et al [24], that detected different lengths of the CTG repeat in different tissues, with particular evidence that sperm cells

may carry in the region q13.3 of chromosome 19 only MyD gene with a number of CTG repeats smaller than 1000. Accordingly, offsprings of fathers with MyD can not receive CTG repeat expansion on chromosome 19q13.3 large enough to determine the congenital phenotype of the disease [3, 24].

On the whole, the recent data about molecular genetics of CMyD seem to explain much of the etiopathogenesis of this variant of the Steinert's disease. Some aspects, however, remain obscure, as the peculiar clinical course of the disease that appears characterized by an improvement of weakness during childhood, followed, during adolescence, by a second phase characterized by a progressive multi-form syndrome, similar to that typical of the adult form of MyD [19, 28, 32, 34]. In order to explain this bimodal clinical expression of the congenital variant of the disease, in its etiopathogenesis the influence of a maternal unknown factor acting "in utero", in addition to the CTG expansion, was therefore suggested [13, 19, 20, 46]. Up to now, however, it remains a pure hypothesis, since it has never been substantiated [13, 19].

Clinical and Neuroimaging Data on Brain Involvement in Congenital Myotonic Dystrophy

The myotonin protein kinase, the product of the MyD gene, is expressed in all the human tissues evaluated and it was found in higher levels in skeletal muscle, heart and brain [2, 21, 24]. Accordingly, in patients with MyD, signs of central nervous system (CNS) involvement in association with the muscular and heart disturbances, have been recognized as characteristic of the disease since the earliest investigations [5, 9, 10, 19].

The main clinical signs of the brain abnormalities usually observed in adults with MyD were apathy and somnolence. Mental retardation was also detected: in the large number of cases studied by the Harper's group [19] in 12% it was the presenting sign. The first systematic studies based on psychometric tests in series of adult patients with MyD showed, however, heterogeneous results [6, 30, 31, 48], with evidence of 10 to 24% of cases with the I.Q. below 0.70. However, a significant impairment of the cognitive functions, even if associated with an I.Q. higher than 0.70, was reported in a greater number of patients with percentage up to 60% [6, 11, 30, 31, 48].

Differently, in CMyD mental retardation was soon recognized as a definite clinical characteristic of the children affected by this form of the disease [1, 9, 19, 45]. By psychometric tests, mild to moderate degree of intellectual deficit was found in 7 out of 8 patients with CMyD studied by us [26], in all the 4 cases studied by Wesstrom et al [46] and in the 5 cases evaluated by Tuikka et al [44]. In other investigations on the mental abilities in patients with CMyD, cases with severe degree of mental retardation were also detected [1, 22]. Longitudinal studies showed that in CMyD this cognitive disturbance is non-progressive [19, 22]. In some cases of CMyD mental retardation may also be the only clinical symptom for several years [14,

38]. According to Tuikka et al [44] many adult cases of MyD with clear-cut mental retardation could be unrecognized cases of CMyD. This hypothesis has recently found consistency in the report by Spranger et al [38] who found in lymphocytes DNA of two of such cases a CTG triplet expansion larger than 1500, as usually observed in the congenital variant of the MyD. These data [14, 38, 44] also indicate that mental retardation in CMyD is not correlated with the muscular deficit.

We studied the relationship between the degree of mental retardation and the size of the CTG expansion in peripheral blood cells DNA of our cases with CMyD [26], but we could not find a clear correlation between the two param-

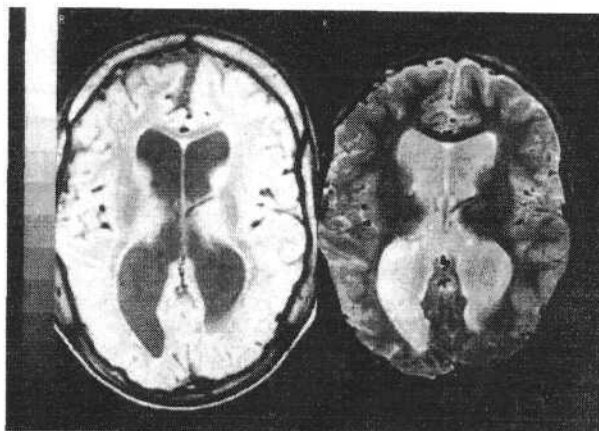


Figure 1. Brain MRI of a 4-year-old boy with Congenital Myotonic Dystrophy: axial proton density (left) and T2 (right) weighted images show clear-cut ventricular dilatation, without evidence of white matter changes. CTG repeat expansion in his peripheral blood DNA was 1576 (from Martine Ho et al.: *Child Nerv Syst*, submitted).

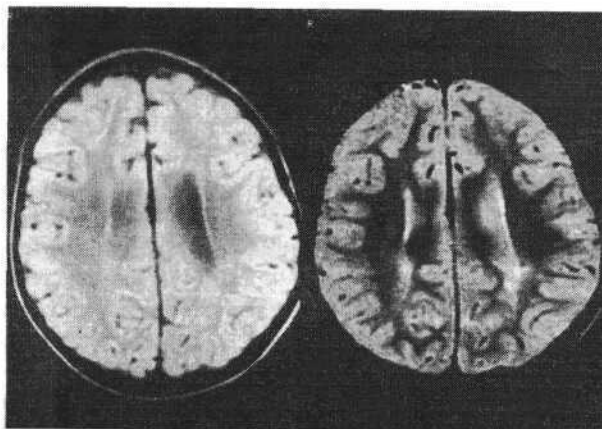


Figure 2. Brain MRI of a 4-year-old boy with Congenital Myotonic Dystrophy: mild periventricular white matter changes are evident in the posterior regions (proton density and T2 weighted images). The size of his trinucleotide expansion was very large (2154) in spite of the minor brain alterations detected (from Martinello et al.: *Child Nerv Syst*, submitted).

ters, even if all the patients had a CTG repeat expansion greater than 1300 [26].

Differently from mental retardation, epilepsy is not reported in CMYD [19] aside from some exceptions [46]. In our experience electroencephalography is usually normal in these children as in cases with the adult form of MyD (unpublished data). Barwick et al [5] found some minor EEG abnormalities in 61% of a series of adult patients, but their results were questioned [19] because they had evidence of similar alterations also in many controls.

Since the introduction of ultrasonography in the CNS evaluation of newborns, in patients with CMYD some degree of ventricular enlargement was soon evident [19]. Previously, similar alterations were also detected in adults with MyD by pneumoencephalographic studies [33]. Brain evaluation by CT scan or MRI of 8 of our cases with CMYD detected ventricular dilatation (fig.1) and some degrees of cortical atrophy in 6 [26], in agreement with the previous study of Garcia-Alix et al [17], who found variable ventricular enlargement in the majority of their neonatal patients by ultrasonographic studies. Subsequently, the investigation of Hashimoto et al by MRI [22] showed similar degrees of ventriculomegaly in all their 7 cases with CMYD. The same study pointed out in 4 of them hypoplasia of the corpus callosum and in 6 white matter changes either in the centrum semiovale or in the periventricular areas. In our experience these white matter alterations are usually of mild degree (fig. 2) and never reaching the wide extension of the leukoencephalopathy that characterizes Congenital Muscular Dystrophy with merosin deficiency [42].

The main alterations found by brain MRI in CMYD are listed in table 1.

Correlation between the ventricular enlargement or the white matter changes found in children with CMYD and their degree of mental retardation appears inconsistent either in our experience [26] or in the report of Hashimoto et al. [22]. Also the size of the CTG repeat length found in lymphocytes DNA, even if consistently larger than 1000, does not correlate with the neuroimaging findings or the degree of the mental retardation [26]. Frequent white matter changes in supratentorial areas were found also in the adult form of MyD in different studies [11, 22, 23]. The same investigations, however, showed that only in few instances the patients with the typical MyD present clear-cut ventricular enlargement, as also shown in a previous neuroimaging study by CT scan [4]. The same reports [4, 11, 23] indicated also that MyD patients have skull thickness and brain atrophy indexes significantly greater than in controls, even if mild in degree.

Altogether, the available data about the CNS involvement in CMYD both in terms of mental retardation and in terms of neuroimaging findings, clearly indicate that this variant of MyD should be considered a form of myoencephalopathy of the newborn. Accurate post-mortem histopathological studies of the brain of such patients are still lacking, in spite of several reports of autopsy of

cases with CMYD [19]. By now, are available only data on histology of adult MyD cases: the main finding was the detection of cytoplasmatic inclusions within neurons of the thalamus [12], but these alterations are still considered of uncertain significance. Possibly, biochemical and immunocytochemical evaluation of the cerebral cortex of patients with CMYD will give a better insight into the pathogenesis of the CNS involvement in this type of MyD.

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