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REVIEW

# Gastrointestinal manifestations in myotonic muscular dystrophy

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## Abstract

Myotonic dystrophy (MD) is characterized by myotonic phenomena and progressive muscular weakness. Involvement of the gastrointestinal tract is frequent and may occur at any level. The clinical manifestations have previously been attributed to motility disorders caused by smooth muscle damage, but histologic evidence of alterations has been scarce and conflicting. A neural factor has also been hypothesized. In the upper digestive tract, dysphagia, heartburn, regurgitation and dyspepsia are the most common complaints, while in the lower tract, abdominal pain, bloating and changes in bowel habits are often reported. Digestive symptoms may be the first sign of dystrophic disease and may precede the musculo-skeletal features. The impairment of gastrointestinal function may be sometimes so gradual that the patients adapt to it with little awareness of symptoms. In such cases routine endoscopic and ultrasonographic evaluations are not sufficient and targeted techniques (electrogastrography, manometry, electromyography, functional ultrasonography, scintigraphy, *etc.*) are needed. There is a low correlation between the degree of skeletal muscle involvement and the presence and severity of gastrointestinal disturbances whereas a positive correlation with the duration of the skeletal muscle disease has been reported.

The drugs recommended for treating the gastrointestinal complaints such as prokinetic, anti-dyspeptic drugs and laxatives, are mainly aimed at correcting the motility disorders.

Gastrointestinal involvement in MD remains a complex and intriguing condition since many important problems are still unsolved. Further studies concentrating on genetic aspects, early diagnostic techniques and the development of new therapeutic strategies are needed to improve our management of the gastrointestinal manifestations of MD.

## INTRODUCTION

Myotonic dystrophy (MD) is an autosomal dominant genetic disorder<sup>[1]</sup>. It is caused by an unstable trinucleotide repeat expansion containing cytosine-thymidine-guanosine (CTG)<sup>n</sup>, located in the 3' untranslated region of chromosome 19q13.3. The CTG trinucleotide is repeated in the normal population from 5 to 36 times<sup>[2,3]</sup>, but has been found to be expanded up to 2 000 times in MD patients<sup>[4,5]</sup>. This amplification is correlated to the severity of the disease. Patients can be divided into four groups based on the number of CTG repeats. Group E1 (50-100 CTG repeats) may have either the minor or the classical form of MD, group E2 (500-1000 CTG repeats) have the classical form of MD, group E3 (1000-1500 CTG repeats) have the classical form of MD with onset during childhood, and group E4 (more than 1500 CTG repeats) are affected with the congenital form of MD<sup>[6]</sup>.

Although MD is primarily characterised by myotonic phenomena and progressive muscular weakness, multi-system involvement is often present, taking the form of cardiac conduction abnormalities, cognitive deficits, cataracts and diabetes, as well as endocrine, sexual and reproductive disturbances<sup>[1]</sup>. Involvement of the gastrointestinal (GI) tract is frequent, and may occur at any level from the pharynx to the anal sphincter. Dysphagia, heartburn, emesis, regurgitation, coughing while eating and dyspepsia are the most common complaints involving the upper digestive tract, while abdominal pain and bloating, changes in bowel habits (diarrhoea or constipation) and dyschezia are common signs of impairment of the lower digestive tract<sup>[7-9]</sup>. These clinical manifestations have generally been attributed to motility disorders caused by striated and more rarely, smooth muscle damage<sup>[10]</sup>,

although recent studies suggest that neurological alterations may also play a role<sup>[11,12]</sup>.

There appears to be little correlation between the degree of skeletal muscle involvement and the presence and severity of the gastrointestinal disturbance, but some authors have reported a positive correlation with the duration of the skeletal muscle disease<sup>[13, 14]</sup>. In some patients the impairment of gastrointestinal function is so gradual that they adapt to it with little or no awareness of any disturbance and only a thorough anamnesis may elicit the recall of possible symptoms<sup>[12]</sup>. In such patients, routine endoscopic and ultrasonographic evaluations are of little value and only highly sensitive, targeted techniques such as electrogastrography, manometry, electromyography, functional ultrasonography, compartmental scintigraphy, *etc.* may help to reveal the true extent of the involvement.

In this review, the available data on the pathophysiologic mechanisms of GI involvement in myotonic dystrophy, their impact on clinical manifestations of the disease, and the tests that can be used to detect them, are discussed in turn for each segment of the gastrointestinal tract.

## PHARYNX AND ESOPHAGUS

Because most complaints by MD patients focus on the pharynx and esophagus, which can be quite easily investigated, these are the manifestations that have been most thoroughly studied thus far. MD patients often report dysphagia, sometimes associated with coughing while eating, chest pain, regurgitation and heartburn. Different studies have reported a prevalence of dysphagia ranging from 25% to 80%<sup>[9, 12, 15, 16]</sup>. This is usually considered by both patients and doctors to be the most serious symptom of MD, probably because it is associated with a high incidence of recurrent pulmonary infection<sup>[17]</sup>.

Manometry is useful to detect motility disturbances, which show in the form of asymmetric contractions of the pharynx and weak contractions of the upper esophageal sphincter (UES)<sup>[14]</sup>. Studies have reported a reduced basal UES pressure in MD patients compared to controls<sup>[11]</sup>, although the prevalence and duration of UES relaxation during swallowing are similar between the two groups and more significantly, no difference in the residual pressure during relaxation has been found<sup>[11, 12, 18]</sup>.

In the esophageal body significant decreases in the peristaltic amplitude and/or simultaneous waves have often been reported<sup>[12, 18]</sup>. A study of 14 MD patients showed a marked decrease in the median amplitude of the contractions at every level of the esophagus. A higher percentage of non-transmitted and dropped contraction sequences after swallowing has been observed in patients compared to controls, 43% exhibited complete atony of the esophageal body with a scleroderma-like pattern and no detectable esophageal contractions. In this series, although manometry showed impaired esophageal motor function in 71% of the patients, 50% of these were quite asymptomatic<sup>[18]</sup>.

Involvement of the lower esophageal sphincter (LES) is a somewhat more complex matter. Modolell *et al.*<sup>[12]</sup> failed to detect a significant difference in basal LES pressure between patients and controls, only reporting

some cases of incomplete LES relaxation<sup>[12]</sup>. In contrast, other studies have found a significantly reduced resting tone, competence, and area vector volume of the LES in MD patients than in controls<sup>[9, 18]</sup>. These data suggest that some alteration in the smooth muscle may take place, leading to a higher risk of developing gastroesophageal reflux disease (GERD)<sup>[18]</sup>.

Esophageal spasm and segmental dilatation can be seen on x-rays, while radiological and scintigraphic techniques are useful for detecting both a lack of tone and a reduced, ineffective or absent peristalsis<sup>[12, 15, 19]</sup>.

Most authors hold that pharyngo-esophageal myotonia, or problems with post-contraction relaxation, should no longer be considered as a typical feature of esophageal involvement<sup>[12, 18]</sup>. A myotonic response to pharyngeal contractions has been reported by Siegel *et al.*<sup>[20]</sup>, but we now know that this is due to limitations in x-ray technology at the time when the study was conducted.

It has been hypothesized that distal esophageal impairment may be myogenic in origin and abnormalities in both the striated and smooth muscle fibers may play a role in MD. However, the histologic data published to date have failed to demonstrate any alteration in the esophageal smooth muscle fibers<sup>[19]</sup>. Marked atrophy of the esophageal striated muscle, but only small changes in the smooth muscle were observed in a patient reported by Jéquier *et al.*<sup>[21]</sup>. In another case, using electron microscopy to study the esophagus, Ludatscher *et al.*<sup>[22]</sup> detected mild degenerative changes with disoriented filaments of the smooth muscle.

Smooth muscle damage could also explain the reduced LES tonic resting pressure and the elevated frequency of heartburn observed in MD patients. Unfortunately, most of the reported cases did not include an upper digestive tract endoscopic examination or a 24-h pH-metry to determine the presence and degree of GERD<sup>[18]</sup>.

Recently some authors have suggested that a combined myopathic - neuropathic etiology could provide a more satisfactory explanation for the pharyngo-esophageal symptoms of MD, but at present this remains speculative<sup>[12]</sup>. One proposed hypothesis is that decrease in the normal amplitude of the peristaltic waves could reflect the inability of the muscle to contract under normal neural control. On the other hand, uncoordinated motor activity in the presence of a normal amplitude contraction could indicate a lack or defect in neural control<sup>[12]</sup>. This hypothesis is not supported by the study of Eckardt *et al.*<sup>[19]</sup>, who failed to detect any neuropathic alterations in MD patients.

However, there are data to suggest that there is no association between the degree of muscular disability and motor abnormalities of the pharynx and esophagus, the presence and severity of dysphagia, or other esophageal symptoms<sup>[12]</sup>. For example, manometric findings are not significantly different between symptomatic and asymptomatic patients or in patients with different degrees of striated muscular involvement<sup>[9, 12, 18, 19]</sup>. In particular, in a study of 18 MD patients Modolell *et al.*<sup>[12]</sup> showed that while severe pharyngo-esophageal abnormalities are present in all patients, symptoms are spontaneously reported by only 30% of them. This figure rose but only to 55%, when the patients were specifically questioned on

this point.

These conflicting reports may be explained by the fact that the tongue and pharyngeal muscles can contract sufficiently to push a bolus through the UES into the esophagus, after which the force of gravity is enough to complete the swallowing process. Moreover, because of the slow evolution of the disease, MD patients may develop compensatory mechanisms and thus gradually adapt to the impairment of their esophageal function<sup>[18]</sup>.

## STOMACH AND DUODENUM

MD patients frequently complain of dyspeptic symptoms such as early satiety, nausea, vomiting, and epigastric pain<sup>[9]</sup>. Radiographic, manometric, ultrasonographic and scintigraphic evidence of decreased peristaltic activity causing the delayed emptying of liquids and solids, visceral dilatation, gastric bezoars and even gastroparesis have been reported<sup>[10, 13, 23-25]</sup>.

Kuiper *et al.*<sup>[23]</sup> have described the case of an MD patient who developed symptoms suggestive of gastric retention. Radiological and endoscopic examination revealed polypoid masses, cytologic washing showed them to be food concretions, probably a consequence of abnormal gastric motility<sup>[23]</sup>. More recently, scintigraphic studies by Ronnblom *et al.*<sup>[25]</sup> indicate a delayed emptying of the stomach in MD patients with dyspeptic symptoms, demonstrated by a prolonged lag phase, a slower emptying rate, and a prolonged T/2.

Bellini *et al.*<sup>[13]</sup> used ultrasound to evaluate gastric emptying abnormalities and their relationship with the severity and duration of the disease in 11 MD patients without dyspeptic symptoms. They found that MD patients and healthy subjects exhibit comparable fasting and maximal antral areas. The findings that (i) the basal and maximal post-prandial values for the gastric antral area between MD patients and controls were quite similar, and (ii) the time required to reach the maximal post-prandial values did not differ in the two groups, are in agreement with the fact that the patients studied were not dyspeptic<sup>[13]</sup>. Analogous results have been reported for a group of non-dyspeptic patients affected by systemic sclerosis<sup>[26]</sup>.

Indeed, increased antral dimensions have been reported in patients with functional dyspepsia<sup>[27,28]</sup>, suggesting that such abnormalities may play a role in the pathogenesis of the dyspeptic symptoms in MD. In Bellini's study<sup>[13]</sup>, the final emptying time of the MD patients was longer than that of healthy volunteers and was clearly correlated with the disease duration, but was independent of both the CTG expansion size and the patients' disability class.

It is not surprising that patients without dyspeptic symptoms may have delayed gastric emptying. Indeed the association between delayed gastric emptying and upper GI complaints is still under debate<sup>[29]</sup>. Other abnormalities in gastric motor function, such as impaired accommodation of the proximal stomach<sup>[30,31]</sup>, abnormal distribution of the gastric contents<sup>[31]</sup>, gastric dysrhythmias<sup>[32, 33]</sup>, and a lack of antro-pyloro-duodenal coordination<sup>[34]</sup>, could play a role in the pathogenesis of dyspeptic symptoms in these patients.

Bellini *et al.*<sup>[13]</sup> have confirmed that a direct relationship

between disease severity and the impairment of GI motor functioning remains to be demonstrated, since there is no significant difference in gastric emptying between patients with different degrees of skeletal muscle involvement. These results appear to agree with previous studies, demonstrating that skeletal muscular damage and gastric motor disturbances can progress independently<sup>[14]</sup>. On the other hand, the direct correlation between final emptying time and disease duration suggests that the impairment of gastric emptying may evolve over time.

The delayed gastric emptying in MD could be explained by the muscular disease itself. Unfortunately no definitive conclusions can be drawn on this point because the histological evidence remains limited. Gastric smooth muscle is only rarely affected<sup>[7, 8]</sup> and as we have already seen in the esophagus, when damage occurs it appears to be similar although earlier and more severe in nature to that occurring in skeletal muscle with severe fatty infiltration<sup>[35]</sup>. However, a sufficiently large study focusing on the gastric smooth muscle in MD patients is still lacking. It would be important to determine whether the two types of muscle tissue may be damaged to different degrees in the same subjects.

Recent reports suggest that, as in the pharynx and esophagus, muscle involvement alone is not sufficient to explain the altered digestive function in the stomach and duodenum of MD patients. Impaired nervous conduction as well as altered GI hormone secretions could be involved in the motor abnormalities<sup>[25]</sup>. For example, changes in the electrical impulses controlling duodenal activity could explain the chronic intestinal pseudo-obstruction occasionally reported in MD. Likewise a reduction in the electrical control of gastric activity could be a possible cause of delayed gastric emptying<sup>[25]</sup>.

An electrogastrographic study carried out by Ronnblom *et al.*<sup>[36]</sup> on 10 patients showed that gastric electric cycling activity manifested as bradygastria, tachygastria and a less stable frequency of the gastric signal are reduced compared with control subjects. The presence of an abnormal EGG in MD patients supports the hypothesis that the disease is a systemic disorder, affecting not only the muscles but also other tissues. Ronnblom *et al.*<sup>[36]</sup> then studied the gut hormone profile in the same group of patients and found that the post-prandial secretion of motilin and glucagone-like peptide-1 (GLP-1) is decreased in MD patients. Since motilin triggers the antral phase III activity of the migrating motor complex and accelerates gastric emptying, reduced motilin secretion could cause delayed gastric emptying. In contrast, low post-prandial GLP-1 secretion is probably a result of delayed gastric emptying, i.e. a consequence rather than a cause of the disease. The patients with the most markedly delayed gastric emptying showed abnormal gastric electric activity and an abnormal post-prandial gut hormone profile. Both factors may contribute to altering gastric functioning. These findings indicate a partial dysregulation of the GI endocrine system in MD patients rather than a disorder of the entire digestive endocrine system. This conclusion is supported by an immunohistochemistry study carried out earlier by the same authors on the different types of duodenal endocrine cells in MD patients affected with diarrhoea<sup>[37]</sup>.

They reported that the duodenal endocrine cell area containing the cells that produce serotonin, gastrin/CCK, secretin, GIP and somatostatin, is significantly increased. There are various possible explanations for this finding. The increased cell area may be a primary phenomenon or a consequence (via a feed-back mechanism) of the synthesis of defective and biologically inactive peptides or the result of a reduced receptor sensitivity of the effector cells and a malfunctioning effector organ.

If the increase in the number of endocrine cells is a primary disorder, it could play a role in the gastrointestinal manifestations of MD. However, even if it is merely a secondary phenomenon, a possible link can still be hypothesized, because the intestinal peptides may act on many different organs. Further studies are needed to shed light on this intriguing issue. At present, no correlation has been found between the increase in the duodenal cell area and the severity of the disease<sup>[37]</sup>.

Different drugs, particularly prokinetics, have been proposed to treat the dyspeptic symptoms and motor disturbances in MD patients. In their study of 16 patients with delayed gastric emptying of solids and liquids, Horowitz *et al*<sup>[14]</sup> showed that oral administration of 10 mg of metoclopramide 3 times per day can improve the gastric emptying of both a solid and a liquid meal, but has no effect on esophageal emptying. In another study the same authors tested the efficacy of cisapride (10 mg, 4 times per day) and reported that it improves both gastric emptying and digestive symptoms such as nausea, vomiting, early satiety, abdominal distension and pain<sup>[38]</sup>. Metoclopramide also seems to be effective in improving gastric emptying in MD patients with gastroparesis<sup>[24]</sup>. Its effect may be due to the local release of acetylcholine and/or the hypersensitivity of the smooth muscle cells to this transmitter, and/or a reduction in the inhibitory effect of dopamine on gastric motility<sup>[14, 24, 39]</sup>.

Ronblom *et al*<sup>[25]</sup> administered erythromycin (100 mg, 2 times per day, before lunch and dinner) to dyspeptic MD patients over a period of 4 wk. The rationale for the use of erythromycin, which has been proved effective in accelerating gastric emptying in diabetic gastroparesis, lies in its agonistic action on the motilin receptors<sup>[10]</sup>. No effect on gastric emptying and no immediate improvement in symptoms were observed, although by the end of the 4-wk period a slight improvement in nausea and early satiety and a marked improvement in diarrhoea were noted by some patients. The authors reported that overall the treatment is effective possibly due to the positive effects of the drug on other GI symptoms, such as bacterial overgrowth in the ileum, which causes diarrhea by inhibiting the absorption of bile acid<sup>[25]</sup>.

## SMALL AND LARGE INTESTINE

Diarrhea, sometimes accompanied with malabsorption, steatorrhea, and crampy abdominal pain, are frequent complaints in MD patients<sup>[9]</sup>. Paralytic ileus has also been reported<sup>[40, 41]</sup>. The pain may be located in any part of the abdomen, with no specific characteristics or eliciting factors. Episodic diarrhoea is the single most common complaint (present in up to 33% of cases). It

is often disabling and may have a marked impact on the patient's social life, especially when combined with anal incontinence<sup>[9]</sup>.

Diarrhea and possibly malabsorption, have been attributed to reduced peristaltic activity leading to bacterial overgrowth<sup>[10]</sup>. Anaerobic bacteria seem to be the principal contaminating agents. Their ability to deconjugate bile acids, thereby causing defective uptake in the terminal ileum, could be the main cause of diarrhea<sup>[25, 42]</sup>. Norfloxacin, either alone or in combination with cholestyramine, can alleviate this symptom in some patients. Other possible mechanisms of diarrhea, such as the reduced secretion of pancreatic amylase, have been hypothesized but not yet been demonstrated, and further evidence is needed to shed light on this issue<sup>[42]</sup>.

Radiological studies have demonstrated reduced or absent peristaltic and/or segmentary activity with delayed intestinal transit<sup>[43-45]</sup>. Megacolon, sigmoid volvulus and segmental narrowing due to myotonic contractions have also been reported<sup>[43, 46-52]</sup>.

Megacolon with the accompanying risk of ileus, volvulus and rupture, is a significant complication and must be kept in mind during the management of MD patients who are usually at higher risk of complications during anesthesia and surgical operations than normal subjects. The pathophysiological mechanisms underlying megacolon are not entirely clear, but probably smooth muscle damage is not the only factor involved. An electron microscopy study of an MD patient with megacolon showed that the myenteric plexus is degenerated with a paucity of neurons and fragmented axons. Glial cells are increased in number with vacuoles containing electron-dense material. Swelling of the mitochondria, distension of the endoplasmic reticulum and the accumulation of free ribosomes in the cytoplasm are also observed. The neurons are described as being "fewer, and the argyrophilic ones smaller, with less prominent processes and poor staining quality." The number of nerve fibers exhibiting reactivity to substance P and enkephalin in the *muscularis externa* is decreased, while normal smooth muscle cells are reported<sup>[52]</sup>.

In concurrence with pregnancy or episodes of gastroenteritis, MD patients have been reported to suffer from recurrent intestinal pseudo-obstruction presenting with nausea, vomiting, abdominal cramps, distension and sometimes, constipation<sup>[53, 54]</sup>. However, such complications may occur during any stage of the disease and may even precede significant skeletal muscle weakness by 15 years. Recently, an MD patient with pseudo-obstruction and partial malrotation of the intestine has been reported<sup>[55]</sup>, although it should be noted that this association has never been observed before and could represent an isolated case<sup>[56]</sup>.

Manometric studies of the small intestine (jejunal manometry) in MD patients have shown low amplitude contractions of the migrating motor complex during phases 2 and 3, with high frequency activity during phase 2 and retrograde propagation and interruption of the contractions during phase 3. Low amplitude post-prandial contractions and myotonic phenomena have also been reported. A disturbance of the mechanoreceptors that link the circular muscle layer with the enteric nerves and

provide the stimulus for the propagation of migrating motor complex phase 3 activity has been hypothesized to explain these phenomena<sup>[57]</sup>.

Very few manometric studies of the colon have been conducted and the results are conflicting. Some report an absence of the normal rhythmic pressure variation in the descending colon<sup>[43]</sup>, while others have failed to detect any motility abnormalities in the sigmoid colon<sup>[58]</sup>. In any case, intestinal motility disturbances are detectable in both symptomatic and asymptomatic subjects, raising doubts as to the actual role they play in the pathogenesis of MD. The absence of a correlation between disease severity and the presence of symptoms has also been confirmed in the intestinal tract<sup>[57]</sup>.

Only a small number of histologic studies of the muscular layer of the small intestine are now available. They describe the cells as being swollen, fragmented, partially destroyed, or decreased in size, and replaced by fats, quite similar to the abnormalities reported for the skeletal muscles<sup>[35, 59]</sup>. Biopsies of the mucosa usually show normal histologic patterns<sup>[37, 43, 60, 61]</sup>, although a case of a patient with intestinal villous atrophy and collagenous sprue has been reported by Woods *et al.*<sup>[62]</sup>. The authors' suggestion that this type of malabsorption may be frequent in MD patients has not yet been confirmed.

## RECTOANAL REGION

Although constipation often associated with dyschezia is common, since some patients represent a serious problem, the most burdensome and disabling problem affecting MD patients may be fecal incontinence<sup>[9, 63, 64]</sup>. Up to 66% of MD patients suffer occasional fecal incontinence, while more than 10% report fecal incontinence one or more times a week. The frequency of urinary incontinence seems to have no difference between MD patients and control subjects<sup>[9, 65]</sup>.

Although the procedure is simple and low in invasiveness, manometric studies of the rectoanal region are not often performed in MD patients. Some studies report a decrease in both the resting pressure (based on the tonic activity of the internal anal sphincter) and the squeezing pressure (exerted by the phasic activity of the external anal sphincter)<sup>[65-67]</sup>. Others have failed to detect any significant modification in the resting pressure and only a slight, statistically insignificant decrease in the squeezing pressure<sup>[11]</sup>.

Lecoite *et al.*<sup>[11]</sup> found that the amplitude and duration of the recto anal inhibitory reflex (RAIR) in response to rectal distension are markedly decreased in MD patients. This could be explained, however, by a prolonged myotonic contraction of the striated external anal sphincter muscles<sup>[67]</sup>, which could obscure the manometric signal indicating the normal internal anal sphincter relaxation response to rectal distension. Due to this myotonic phenomenon, the duration of the rectoanal contractile reflex (RACR) is longer in patients than in controls<sup>[11]</sup>. According to Hamel Roy *et al.*<sup>[68]</sup>, the amplitude of this myotonic response is decreased by pudendal nerve blockade, suggesting the possibility of at least a partial neural reflex response. Pudendal nerve terminal motor

latencies are normal in these patients, confirming the absence of a neurogenic lesion<sup>[67, 69]</sup>. Finally, it was reported that the maximum tolerable volume at rectal distension is significantly lower in MD patients than in controls<sup>[11]</sup>.

Anorectal motility disturbances are as frequent as pharyngo-esophageal disturbances, the degree of involvement of the upper and distal portions of the gastrointestinal tract may be closely correlated both quantitatively and qualitatively<sup>[11]</sup>. It has been shown that anorectal motility and esophageal motility are altered in a similar number of patients<sup>[11]</sup>.

Although the prevalence of altered motility is high, symptoms such as anal incontinence, diarrhoea and/or abdominal pain have been found in a small number of patients, suggesting that there is a close relationship between smooth and striated muscle motor function in MD but only in the gastrointestinal tract, where smooth and striated muscle abnormalities may be interdependent<sup>[11]</sup>. Unfortunately, there are no histologic data to back up this intriguing hypothesis.

Eckardt *et al.*<sup>[66]</sup> studied the external anal sphincter using electromyography and have found myopathic potentials with myotonia. Herbaut *et al.*<sup>[65]</sup> reported a decreased duration and amplitude of the motor units in the external anal sphincter and the puborectalis muscle of MD patients with fecal incontinence, suggesting that there may be a myopathic component to the pathology. In 25% of these patients, polyphasic high-amplitude motor units were also present, indicating the probable presence of a neuropathic lesion. Taken together, the data suggest that both the striated external anal sphincter and the smooth internal anal sphincter may be altered in MD, even if previous histologic examinations have reported pathological findings only in the striated muscle<sup>[66]</sup>. More recently, Abercrombie *et al.*<sup>[67]</sup> used electron microscopy to study the anal sphincter in two siblings with MD and found that the external anal sphincter is atrophic in both patients, with marked fibrosis and a high variation in the diameter of the fibres as well as the striated muscle almost entirely substituted by smooth muscle cells deriving from the internal sphincter. These cells are all different in size and electron density separated by large amounts of fibrous connective tissue. Some show features suggestive of dedifferentiation into myofibroblasts. The puborectalis biopsies revealed an analogous decrease in the amount of normal striated fibres with pronounced fibrosis. Some of the fibres were hypertrophic with increased central nucleation and many showed sarcoplasmic masses. Moreover, type 1 fibres were markedly prevalent (99%). In the ano-rectal region, no close correlation between motor abnormalities and overt symptoms has been found, although defecatory behaviour is often severely altered in these patients.

Constipation in MD patients is usually treated with prokinetics, laxatives and enemas<sup>[15, 70]</sup>, while medical treatment with procainamide (300 mg twice a day) has been proposed for fecal incontinence<sup>[71]</sup>. Surgery to treat fecal incontinence has been attempted, but post-anal repair only temporarily improves the defecatory function<sup>[67]</sup>. Treating and curing defecatory problems in MD patients remain a difficult challenge. Rehabilitation involving a combination

of volumetric rehabilitation, electroanalytical stimulation, kinesiotherapy and biofeedback, can be effective in those patients not suffering from severe damage to the pelvic floor muscle<sup>[72,73]</sup>.

## CONCLUSIONS

Since MD is a relatively rare disease, most of the papers published are hampered by the bias arising from the low number of patients studied. Many report just one or two cases, and very few involve series of more than 10 patients. Gastrointestinal involvement is frequently observed in MD patients and digestive complaints may be the first sign of the disease. According to Ronnblom *et al*<sup>[9]</sup>, 25% of patients consider their gastrointestinal problems as the most disabling consequence of MD, 28% have digestive symptoms that may appear up to ten years before the typical musculoskeletal features. During this period the impairment of the digestive functions may be so gradual that patients unconsciously adapt to them by compensatory mechanisms, thus masking the symptoms<sup>[18,74]</sup>. They may even develop a higher pain threshold (visceral hypoalgesia) similar to that seen in diabetic gastroparesis<sup>[75]</sup>. For these reasons, patients often do not undergo a thorough examination of the digestive tract, while at the same time they may be subjected to a broad battery of other examinations because of multi-system involvement. Thus, a careful assessment of the digestive tract may be performed only when the symptoms have become severe, although reliable, non-invasive or minimally invasive techniques such as ultrasonography, scintigraphy, breath test and cutaneous electrogastrography are available<sup>[13]</sup>.

Little correlation has been found between the degree of skeletal muscle damage and gastrointestinal disturbances<sup>[12,14]</sup>, while there does appear to be a relationship between the severity of GI involvement and the duration of the disease<sup>[13]</sup>. Nevertheless, the pathophysiologic mechanisms of digestive motor disorders certainly suggest that there is damage to the striated muscles in the upper and lower portions of the gastrointestinal tract. Histologic evidence of smooth muscle alterations is scarce and conflicting<sup>[12,14]</sup>, although some authors have hypothesized that smooth muscle damage may occur earlier and is more severe than striated muscle changes<sup>[10]</sup>.

Moreover, some authors suggest that a common mechanism may be the generation of the motor abnormalities in both the smooth and striated muscles. For example, Lecoite *et al*<sup>[11]</sup> studied the esophagus and the rectoanal region of MD patients and found that alteration in the smooth muscle is closely related with that in striated muscle, at least in the digestive tract.

A neural factor could also be involved in the digestive symptoms of MD patients. Neural dysfunctions, such as an alteration in the non-adrenergic, non-cholinergic neuronal control of the GI tract, have been suggested to explain the symptoms and instrumental findings that may be present even in the absence of definite histologic damage. Nitric oxide (NO) can mediate non-adrenergic, non-cholinergic nerve-induced relaxation and hyperpolarization of the smooth muscle in the digestive tract<sup>[76]</sup>. NO is produced from L-arginine via NO synthase,

a key enzyme that is expressed in the myenteric plexus, motor neurons and myenteric fetal interneurons<sup>[77-80]</sup>. Thus, the NO molecule seems to be common in both the striated and smooth muscles, the inhibition of NO synthase could alter the motor parameters in a manner consistent with the observations of Lecoite *et al*<sup>[11]</sup>. This "neuronal hypothesis" can explain the absence of histologic abnormalities in the smooth muscle of MD patients. In addition, it could explain the degeneration and decreased number of argyrophilic neurons in the colonic myenteric plexus of an MD patient affected with megacolon<sup>[52]</sup>.

Gastrointestinal involvement in MD remains a complex and interesting condition. Given the limited data available, there are very few certainties and many important questions to be solved<sup>[81]</sup>. The relationship between myotonic dystrophy, gastrointestinal motility and clinical symptoms needs to be investigated in greater depth. Studies should begin early in their disease course, using non-invasive diagnostic techniques and concentrating on the genetic and histologic aspects of each case. Such efforts can improve our understanding of the pathophysiology of the digestive system involvement in MD and speed up the development of new therapeutic strategies to manage this difficult condition.

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