CLINICAL NOTE

Chronic primary intestinal pseudo-obstruction from visceral myopathy

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ABSTRACT

Chronic intestinal pseudo-obstruction is an uncommon syndrome characterized by relapsing episodes suggesting intestinal obstruction during which no mechanical causes are identified to account for symptoms. Etiologic factors may be manifold. Among them a number of neurologic conditions, gastrointestinal smooth muscle myopathies, endocrino-metabolic and autoimmune diseases, and the use of selected drugs stand out. We report a case of chronic intestinal pseudo-obstruction originating in a sporadic, primary intestinal myopathy that corresponds to no type thus far described. A histological study of the intestinal wall showed disrupted muscle bundles and the presence of interstitial edema. Myocytes had severe degenerative changes, and no alterations were seen in submucosal and myenteric plexus neurons. The activity of enzyme complexes in the mitochondrial respiratory chain, and of thymidine phosphorylase was normal. No mitochondrial DNA changes were seen.

Key words: Chronic intestinal pseudo-obstruction. Visceral myopathy.

Muñoz-Yagüe MT, Marín JC, Colina F, Ibarrola C, López-Alonso G, Martín MA, Solís Herruzo JA. Chronic primary intestinal pseudo-obstruction from visceral myopathy. *Rev Esp Enferm Dig* 2006; 98: 292-302.

Recibido: 17-01-06.
Aceptado: 17-01-06.

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INTRODUCTION

Chronic intestinal pseudo-obstruction (CIPO) is an uncommon, high-morbidity syndrome that develops as a consequence of altered intestinal motility, which results in clinical manifestations that resemble intestinal obstruction but in the absence of any obstructive process (1-3). It may be primary, when it exclusively involves intestinal smooth muscle or enteric neural plexa, or secondary to other conditions. Within primary forms, even though familial forms with dominant or recessive autosomal inheritance have been reported, most cases are described as sporadic (4,5). Clinical spectrum is variable and dependent on the cause, site, and involvement extent (6,7). Major diagnostic criteria include suspicion of this condition and exclusion of mechanical obstruction. When suspicion develops, gastrointestinal manometry, radionuclide studies, and histopathological examination of all intestinal wall layers may help confirm the diagnosis, establish a prognosis, and delineate treatment (1,7). The presence of an unexplained association with neuromuscular, gastrointestinal, and other non-neuromuscular symptoms should prompt suspicion of mitochondrial changes as a reflection of mitochondrial ubiquity (8-10). Treatment is aimed at symptom improvement and sustained adequate nutrition (1,7,11). The female subject of this paper initially had sporadic, primary intestinal pseudo-obstruction symptoms, and then developed manifestations suggesting the involvement of striated muscle. However, studies of mitochondrial respiratory chain activity and mitochondrial DNA were all normal.

CASE REPORT

A 37-year-old woman with constipation since childhood and a fecal retention episode in the last six months. Moderate obesity. Her family history included two sib-

lings diagnosed with Crohn's disease. She was first admitted for the study of persistent pain in the right iliac fosse, abdominal distention, and increased constipation. She had also lost 15 kg weight in 2 months, and had nausea and vomiting. Both the basic blood study and biochemical and coagulation tests were normal. Erythrocyte sedimentation rate and C-reactive protein were also normal. Thyroid hormones were within the normal range. No vitamin deficiency was identified. Non-organ-specific antibodies were negative, and fecal microbiologic studies yielded normal results. Abdominal plain X-rays showed dilated small-bowel loops with no fluid-air levels. Doppler ultrasonography and abdominal CT scans were normal. Ileocolonoscopy showed a macroscopically normal terminal ileum with no mucosal lesions in the histological exam. Enteroscopy with gastric, duodenal, and jejunal mucosa biopsy sampling revealed no pathologic findings. An opaque enema could not be assessed because of the presence of feces. Gastrointestinal follow-through revealed no pathologic findings. The study of colonic transit using radiopaque markers showed that after 7 days all of them but three remained in the right iliac fosse, within the cecal region. Gastric emptying was slow when studied using radionuclides. She had food intolerance during admission, which did not improve with the use of prokinetic drugs, and ultimately required total parenteral nutrition. Despite this, clinical manifestations worsened, which led to an exploratory laparotomy to collect transperitoneal tissue. In the days before surgery urinary incontinence developed, which was thoroughly assessed by the Neurology Department—physical examination was absolutely normal. A medullary or radicular lesion was ruled out by lumbosacral magnetic resonance imaging. Intravenous urography as well as cystography showed no pathologic findings.

During the surgical procedure the right colon had a delustered appearance, and the cecum's wall was slightly thickened. There was mild ascites, which once subsequently studied was negative for malignant tumor cells, and showed no elevated tumor markers. A right hemicolectomy plus ileotransverse anastomosis was performed. Upon opening the resected specimen a hardened area 3 x 2 cm in size was macroscopically detected in the colonic wall, with loss of mucosal folds and the presence of two erosions and multiple petechiae. The appendix, ileum, and appendicocolic vessels had no gross changes. A microscopic examination of the cecocolic wall at the indurated area level showed a disruption of smooth-muscle fiber bundles from reduced myocyte size and intercellular edema, which resulted in a frayed aspect mainly of the muscularis propria layer (Fig. 1). Myocytes had irregular borders, alternating vacuolization and condensation in their cytoplasm, and scarcely patent myofibrils (Fig. 2). There were no changes in the myenteric plexus, and both the myenteric and submucosal plexus had their usual neuronal population. Mucosal erosions had no microscopic specificity. No vascular lesions were seen. An ex-

Fig. 1.- The internal muscularis propria layer appears frayed due to myocyte degeneration and intercellular edema. Compare this to the external layer's compact appearance (upper part of the picture) (HE, x 60).

La capa muscular propia interna aparece desflecada debido a la degeneración de miocitos y al edema intercelular. Compárese con el aspecto compacto de la capa externa (zona superior de la foto) (HE, x 60).

Fig. 2.- Internal muscularis propria layer: close-up of myocytes showing poorly dense, vacuolated cytoplasm (HE, x 100).

Capa muscular propia interna: detalle de sus miocitos que muestran citoplasmas poco densos y vacuolados (HE, x 100).

tensive sampling of the colonic wall showed similar patchy lesions with an irregular distribution and extension, which mainly involved the inner muscular layer. The ileum had thinned muscularis propria layers, but no degenerative changes in cecal or colonic myocytes. Neither intercellular fibrosis nor inflammatory infiltration were seen at any level.

Fifteen days after the procedure the patient was admitted for similar manifestations. She had urinary incontinence no more; however, an urodynamic exploration was performed, which yielded normal results. Bacterial overgrowth was excluded using the expired oxygen test. Esophageal and anorectal manometry were both normal. New abdominal X-rays were obtained following the administration of radiopaque markers, which were permanently retained apparently in the colon remnant rather than the small bowel.

Total colectomy plus ileostomy was decided upon. The surgical specimen included 8 cm of ileum. No relevant gross lesions were seen. A histological study of the colonic wall showed lesions similar to those described after the previous hemicolectomy. The submitted terminal ileum has normal characteristics. An ultrastructural study of the small intestine and colon was performed, where myocytes exhibited myofibrillar reduction and disruption in both organs (Fig. 3), as well as segmentarily distributed vacuolization in peripheral and paranuclear areas, and nonspecific mitochondrial changes. The latter had abnormal shapes and occasionally hydropic changes in their matrix (Fig. 4). A histological and ultrastructural study of samples from the gastric wall, a different small bowel portion, and abdominal wall striated muscle yielded normal results. An immunohistochemical study of the cecal wall and the small intestinal wall was performed with the markers listed in table I. Actin 1A4 expression was clearly pathological in the small and great intestinal wall. The inner (circular) muscle layer was only positive in the innermost portion of its bundles, which exhibited a positive border (Figs. 5 and 6). However, the outer (longitudinal) muscle layer was clearly stained. CD117

Fig. 3.- A myocyte with disorganized microfilaments and a peripherally vacuolated cytoplasm (ME, uranyl acetate and lead citrate, x 1000).
Miocytes cuyas miofibrillas aparecen desordenadas y cuyo citoplasma muestra vacuolización en áreas periféricas (ME, acetato de uranilo y citrato de plomo, x 1000).

Fig. 4.- A myocyte's cytoplasm with hydropic matrix mitochondria and scarce microfilaments (ME, x 2000).
Citoplasma de miocito con mitocondrias de matriz hídrica y escasas miofibrillas (ME, x 2000).

Table I. Results from the immunohistochemical study of intestinal muscle layers					
Topography	Actin 1A4	Vimentin	Actin HHF35	Desmin	S-100 enolase and PGP-9.5
Out. layer	+++	+	+++	++	++
Colon					
Int. layer	-	+	+++	++	(In ganglion neurons)
Out. layer	++	++	+++	+++	Idem
S. bowel					
Int. layer	-	++	+++	+++	
Out. layer	++	+	+++	++	Idem
Appendix					
Int. layer	++	+	++	++	
Out. layer	++	-	+++	+	Idem
Rectum					
Int. layer	++	-	+++	+	

(c-Kit) was positive indicating the presence of normal interstitial cells of Cajal. A study of mitochondrial respiratory chain complex activity was performed in an intestinal muscular homogenate using the previously described

Fig. 5.- Immunohistochemistry with actin 1A4 in the great bowel. Myocytes in the internal muscularis propria layer are poorly stained. Compare this with the staining in the outer muscle layer (upper image) (x 60).

Inmunohistoquímica con actina 1A4 en intestino grueso. Los miocitos de la capa muscular propia interna se tiñen débilmente. Compárese con la tinción de la capa muscular externa (zona superior) (x 60).

technique (12), and results were normal. Using a Southern blot technique the presence of single or multiple deletions in striated muscle mitochondrial DNA was excluded. Lack of signal in the sample prevented a mitochondrial DNA study from being performed.

The patient was again admitted two months later because of pain after food ingestion, which was relieved by cisapride. In the following 6 months she had several predominating painful episodes, and hence required a continual infusion pump implanted that was connected to an intradural catheter for chronic opioid administration. Fifteen months later she remained in an acceptable clinical condition from a gastrointestinal standpoint. However, one year after initial diagnosis she started to develop strength loss in her limbs with a proximal distribution; following a complete striated muscle study and brain MRI scans, both with normal results, the patient was di-

Fig. 6.- Immunohistochemistry with actin 1A4 in the small bowel. Similar defective staining in the internal muscularis propria layer. Compare this to the external muscle and muscularis mucosae layers (x 60).

Inmunohistoquímica con actina 1A4 en intestino delgado. Similar defecto de tinción de la capa muscular propia interna. Compárese con la externa y la capa muscularis mucosae (x 60).

agnosed with progressive, disabling tetraparesis, while the type of muscular involvement could not be documented. Approximately one year later she began with sustained urinary incontinence, and the urodynamic study was pathologic. Subsequent plasma thymidine and deoxyuridine measurements were negative, which suggested a normal thymidine phosphorylase activity.

DISCUSSION

The patient reported here had a history of chronic constipation that had turned more severe in the past few months, in association with abdominal pain and distension. Severely slowed intestinal transit and dilated intestinal loops were seen. The study ruled out any obstructive process. Both CIPO diagnostic criteria were met (1,4).

In such cases, plain abdominal x-rays usually show signs suggesting paralytic ileum or dilated bowel loops similar to mechanic obstruction (7). Contrast radiographic and endoscopic studies may exclude obstruction. Endoscopic biopsies usually provide no diagnostic data –for a histological study to be useful, biopsy samples must include the full thickness of the intestinal wall (13,14), and be collected at various levels within the gut (7,13-15).

The causes of CIPO are manifold, but may be classified in two major groups: a) neuropathies; and b) myopathies. The first group includes diverse conditions, including inflammatory and degenerative diseases (4). The patient reported here could not be included in the inflammatory disease group, as no inflammation changes were revealed by histology.

Many of these CIPO-inducing visceral neuropathies fall within the degenerative type. In such cases there is degeneration of ganglion cells in the myenteric and submucosal plexa, with no inflammatory component (4,16-18). The causes of such neuronal degeneration are manifold, and comprise central nervous system neurodegenerative conditions, including mitochondrial diseases, among others. The latter conditions have mitochondrial changes that disturb oxidative phosphorylation and result in complex clinical syndromes, including multiple system (neurologic, striated muscular, smooth muscular) manifestations. The development of muscle weakness in this patient's limbs led to consider a mitochondrial disease. As can be seen in table II, which lists all major mitochondrial myopathies, most of these conditions manifest with neurologic symptoms. These manifestations have not developed in our patient so far; however, gastrointestinal symptoms occasionally precede in months or years the remaining manifestations of mitochondrial disease (19-25). Moreover, the striated muscle study proved it to be normal both from the histological and ultrastructural standpoint, and in relation to mitochondrial DNA or mitochondrial respiratory chain activity.

Mitochondrial conditions most often manifesting with gastrointestinal symptoms include: 1) mitochondrial neurogastrointestinal encephalopathy (MNGIE); 2) Leigh's syndrome (subacute necrotizing encephalopathy); 3) Kearns-Sayre syndrome (progressive external ophthalmoplegia, pigmentary retinal disease, ataxia, and heart block); and 4) MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, cerebrovascular accidents). Patients with gastrointestinal manifestations failing to meet diagnostic criteria for either syndrome have been reported (24,26). The best known syndrome is MNGIE. This is an autosomic recessive disease resulting from mutations in the thymidine phosphorylase gene (22,27,28), which translates into high plasma thymidine and deoxyuridine levels (29). These changes, which our patient lacked, are of diagnostic value. Secondarily, increased thymidine may result from disturbed mitochondrial DNA

Table II. Mitochondrial myopathies

1. Mitochondrial DNA mutations
—Kearns-Sayre syndrome: ataxia, neuropathy, ptosis, ophthalmoplegia, pigmentary degeneration of the retina, myocardiopathy, short stature.
—Pearson's syndrome: refractory sideroblastic anemia
—Progressive external ophthalmoplegia (PEO): bilateral ptosis, ophthalmoplegia, muscular weakness
—Mitochondrial encephalopathy with lactic acidosis and cerebrovascular insufficiency episodes (MELAS)
—Myoclonic epilepsy associated with "ragged red" fibers (MERRF): cerebellar ataxia, deafness, and dementia
—Neuropathy, ataxia, and retinitis pigmentosa (NARP)
—Deafness, myoclonus, epilepsy, ataxia, myopathy
—Leber's hereditary neuropathy
—Aminoglycoside-induced sensory-neural deafness
2. Diseases from genetically-induced mitochondrial DNA stability disturbance
—Autosomal dominant progressive external ophthalmoplegia (Ad PEG)
—Mitochondrial neuro-gastrointestinal encephalomyopathy (MNGIE)
—Fatal infantile congenital myopathy with or without Fanconi's syndrome
—Fatal infantile liver disease
—Amish congenital microcephaly
3. Diseases from defective nuclear genes coding for CRM enzyme complex proteins
—Leigh syndromes
—Hereditary paraganglioma
—Hyperpotassemia and lactic acidosis
—Ataxia, epilepsy, myopathy
4. Diseases from defective genes coding for proteins indirectly related to phosphorylating oxidation
—Friedreich's ataxia
—X-linked ataxia and sideroblastic anemia
—Hereditary spastic paraparesia
—X-linked deafness-dystonia syndrome
—Autosomal dominant optic atrophy

stability, and lead to muscle depletion (28). In the muscle fibers of these patients a cytochrome *c* oxidase deficiency may be identified. While the full clinical picture includes peripheral neuropathy, leukoencephalopathy, and ophthalmoparesis in addition to CIPO (30), gastrointestinal symptoms develop first in 45 to 67% of patients (23,25). In these patients the most relevant changes are seen in enteric neurons, which exhibit degenerative changes and mitochondrial abnormalities (19). None of this was seen in our patient. However, it has been suggested that degenerative changes may compromise neurons in the autonomic extraintestinal nervous system (26).

The remaining above-mentioned syndromes –Leigh's (31,32), Kearns-Sayre (33), and MELAS (34)– do not correspond to our patient's picture either.

The second major group of CIPO etiologies includes visceral myopathies (Table III). Histological lesions found at the intestinal wall allow the inclusion of our patient in this etiologic group, since myenteric plexa and ganglion cells were free of involvement but muscle layers were deeply disrupted. These are sometimes intestinal smooth muscle lesions that develop secondary to other conditions (scleroderma, autoimmune disease, amyloido-

Table III. Visceral myopathies

<i>Secondary</i>	
	Scleroderma / lupus / Kawasaki
	Polymyositis
	Amyloidosis
	Ceroidosis (vitamin E deficiency)
	Progressive muscular dystrophy
	Drugs (neuroleptics, haloperidol)
	Pheochromocytoma
<i>Primary</i>	
	Absence of or selective decrease in smooth-muscle alpha-actin
	Familial or sporadic visceral myopathy
	Myopathy from abnormal gut morphogenesis
	Myopathies from primary changes in myocytes
	Autoimmune leiomyositis

sis, myotonic dystrophy, progressive muscular dystrophy, etc.) (18,35,36). On other occasions these are intestinal morphogenesis alterations (presence of additional muscle layers; fusion of muscle layers together) (37), yet in others these are likely primary myocytic changes (atrophy and loss of muscle cells, and their replacement by fibrosis; focal accumulation of nuclei; absence of alpha-actin in the smooth muscle) (37,38). In our reported patient, a reduced expression of alpha-actin was found in the bowel's circular muscle layer. Some authors feel (39) that this represents a useful CIPO marker in the absence of other changes.

Each one of these myopathies, familial or sporadic, has well-defined clinical or histological characteristics. Our patient's manifestations allow her diagnosis with no disease with a potential to secondarily develop a visceral myopathy. Also, histological lesions allow her classification in none of the visceral myopathy groups as defined by Smith et al. (37). While there was vacuolization and degeneration in myocytes, no fibrosis, inflammatory infiltration, or abnormal muscle layer organization was apparent. There is the possibility that muscle cell loss would result from a past autoimmune condition no longer active. However, this seems unlikely, as intestinal areas with less damage had also no inflammatory component, and the corticoid regimen empirically received by the patient (40) resulted in no improvement.

CIPO's association with other disorders suggesting an autonomic neuropathy or extraintestinal smooth muscle dysfunction, including urologic symptoms from ureteral or vesical dysfunction, is not a rare finding (41). The patient reported here had self-limited urinary incontinence during the pre-operative period, but the neurologic and urologic examination yielded normal results. Two years later she started with sustained urinary incontinence and her urodynamic study was pathological, which supports the aforementioned association.

The management of CIPO is intended to improve symptoms and maintain adequate nutrition (1,7,11,42). In more serious, treatment-refractory cases a number of

endoscopic or surgical therapies may be needed, including colectomy (11) and intestinal transplantation (6,7).

In the patient we report here gastrointestinal symptoms are acceptably controlled with measures adopted after colectomy, but limb muscular weakness results in greater disability when compared to gut manifestations. According to data available, we believe this case to be a chronic intestinal pseudo-obstruction syndrome resulting from a primary, sporadic visceral myopathy. Studies performed allow inclusion in no myopathy class thus far described.

ACKNOWLEDGEMENTS

We are grateful to Dr. R. Martí at CIBBIM, Hospital Universitario "Valle de Hebrón", Barcelona, for his measurements of plasma thymidine and deoxyuridine concentrations, and to Dr. M. A. Martínez González at Service of Pathology, Hospital Universitario "12 de Octubre", Madrid, for the ultrastructural examination of the surgical specimen.

REFERENCES

1. Panganamamula KV, Parkman HP. Chronic intestinal pseudo-obstruction. *Curr Treat Options Gastroenterol* 2005; 8: 3-11.
2. Patel R, Christensen J. Chronic intestinal pseudo-obstruction: diagnosis and treatment. *Gastroenterologist* 1995; 3: 345-56.
3. Hirano I, Pandolfino J. Chronic intestinal pseudo-obstruction: pathogenesis, diagnosis and therapy. *Z Gastroenterol* 2002; 40: 85-95.
4. De Giorgio R, Sarnelli G, Corinaldesi R, Stanghellini V. Advances in our understanding of the pathology of chronic intestinal pseudo-obstruction. *Gut* 2004; 53: 1549-52.
5. Miyata M, Watanabe K, Suzuki T, Satoh N, Sasajima T, Yamamoto G, et al. Chronic intestinal pseudo-obstruction ileus in a patient with rheumatoid arthritis: outcome of a stoma construction and its histopathological features. *J Gastroenterol* 2002; 37: 653-7.
6. Cucchiara S. Chronic intestinal pseudo-obstruction: the clinical perspective. *J Pediatr Gastroenterol Nutr* 2001; 32 (Supl. I): S21-S22.
7. Di Lorenzo C. Pseudo-obstruction: current approaches. *Gastroenterology* 1999; 116: 980-7.
8. Mueller LA, Camilleri M, Emslie-Smith AM. Mitochondrial neurogastrointestinal encephalomyopathy: manometric and diagnosis features. *Gastroenterology* 1999; 116: 959-63.
9. DiMauro S, Bonilla E, Zeviani M, Nakagawa M, DeVivo DC. Mitochondrial myopathies. *Ann Neurol* 1985; 17: 521-38.
10. Sokol RJ, Treem WR. Mitochondrial hepatopathies. En: Suchy FJ, Sokol RJ, Balistreri WF, editors. *Liver Disease in Children*. Philadelphia: Lippincott Williams Wilkins; 2001. p. 787-809.
11. Malagelada JR, Distrutti E. Management of gastrointestinal motility disorders. A practical guide to drug selection and appropriate ancillary measures. *Drugs* 1996; 52: 494-506.
12. Pérez-Carreras M, Del Hoyo P, Martín MA, Rubio JC, Martín A, Castellano G, et al. Defective hepatic mitochondrial respiratory chain in patients with nonalcoholic steatohepatitis. *Hepatology* 2003; 38: 999-1007.
13. Greig JD, Miles WF, Nixon SJ. Laparoscopic technique for small bowel biopsy. *Br J Surg* 1995; 82: 363.
14. Tornblom H, Lindberg G, Nyberg B, Veress B. Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. *Gastroenterology* 2002; 123: 2144-7.

15. Smith VV. Chronic intestinal pseudo-obstruction: the pathologist perspective. *J Pediatr Gastroenterol Nutr* 2001; 32 (Supl. I): S23-S24.
16. De Giorgio R, Guerrini S, Barbara G, Cremon C, Stanghellini V, Corinaldesi R. New insights into human enteric neuropathies. *Neurogastroenterol Motil* 2004; 16: 143-7.
17. De Giorgio R, Camilleri M. Human enteric neuropathies: morphology and molecular pathology. *Neurogastroenterol Motil* 2004; 16: 515-31.
18. Krishnamurthy S, Shuffer MD. Pathology of neuromuscular disorders of the small intestine and colon. *Gastroenterology* 1987; 93: 610-39.
19. Perez-Atayde AR, Fox V, Teitelbaum JE, Anthony DA, Fadic R, Kalsner L, et al. Mitochondrial neurogastrointestinal encephalomyopathy: diagnosis by rectal biopsy. *Am J Surg Pathol* 1998; 22: 1141-7.
20. Miyabayashi S, Narisawa K, Iinuma K, Tada K, Sakai K, Kobayashi K, et al. Cytochrome c oxidase deficiency in two siblings with Leigh encephalomyopathy. *Brain Dev* 1984; 6: 362-72.
21. Shaker R, Kupla JI, Kidder TM, Arndorfer RC, Hofmann C. Manometric characteristics of cervical dysphagia in a patient with the Kearns-Sayre Syndrome. *Gastroenterology* 1992; 103: 1328-31.
22. Verma A, Piccoli DA, Bonilla E, Berry GT, DiMauro S, Moraes CT. A novel mitochondrial mutation associated with prominent initial gastrointestinal symptoms and progressive encephaloneuropathy. *Pediatr Res* 1997; 42: 448-54.
23. Teitelbaum JE, Berde CB, Nurko S, Buonomo C, Pérez-Atayde AR, Fox VL. Diagnosis and management of MNGIE syndrome in children: case report and review of the literature. *J Pediatr Gastroenterol Nutr* 2002; 35: 377-83.
24. Chitkara DK, Nurko S, Shoffner JM, Buie T, Flores A. Abnormalities in gastrointestinal motility are associated with diseases of oxidative phosphorylation in children. *Am J Gastroenterol* 2003; 98: 871-7.
25. Gillis LA, Sokol RJ. Gastrointestinal manifestations of mitochondrial disease. *Gastroenterol Clin* 2003; 32: 789-817.
26. Chinnery PF, Jones S, Sviland L, Andrews RM, Parsons TJ, Turnbull DM, et al. Mitochondrial enteropathy: the primary pathology may not be within the gastrointestinal tract. *Gut* 2001; 48: 121-4.
27. Nishino I, Spinazzola A, Hirano M. Thymidine phosphorylase gene mutations in MNGIE, a human mitochondrial disorder. *Science* 1999; 283: 689-92.
28. Nishino I, Spinazzola A, Papadimitriou A, Hammans S, Steiner I, Hahn CD, et al. Mitochondrial neurogastrointestinal encephalomyopathy: an autosomal recessive disorder due to thymidine phosphorylase mutations. *Ann Neurol* 2000; 47: 792-800.
29. Marti R, Spinazzola A, Tadesse S, Nishino I, Nishigaki Y, Hirano M. Definitive diagnosis of mitochondrial neurogastrointestinal encephalomyopathy by biochemical assays. *Clin Chem* 2004; 50: 120-4.
30. Hirano M, Marti R, Spinazzola A, Nishino I, Nishigaki Y. Thymidine phosphorylase deficiency causes MNGIE: an autosomal mitochondrial disorder. *Nucleosides Nucleotides Nucleic Acids* 2004; 23: 1217-25.
31. Triepels RH, van Den Heuvel LP, Trijbels JM, Smeitink JA. Respiratory chain complex I deficiency. *Am J Med Genet* 2001; 106: 37-45.
32. Miyabayashi S, Narisawa K, Iinuma K, Tada K, Sakai K, Kobayashi K, et al. Cytochrome c oxidase deficiency in two siblings with Leigh Encephalomyopathy. *Brain Dev* 1984; 6: 362-72.
33. Johns DR. Seminars in Medicine of the Beth Israel Hospital, Boston. Mitochondrial DNA and disease. *New Engl J Med* 1995; 638-44.
34. Hirano M, Ricci E, Koenigsberger MR, Defendini R, Pavlakis SG, De Vivo DC, et al. MELAS: an original case and clinical criteria for diagnosis. *Neuromuscul Disord* 1992; 2: 125-35.
35. Schuffler MD, Rohrmann CA, Chaffee RG, Brand DL, Delaney JH, Joung JH. Chronic intestinal pseudo-obstruction: a report of 27 cases and review of the literature. *Medicine* 1981; 60: 173-96.
36. Rohrmann CA, Ricci MT, Krishnamurthy S, Schuffler MD. Radiologic and histologic differentiation of neuromuscular disorders of the gastrointestinal tract: visceral myopathies, visceral neuropathies and progressive systemic sclerosis. *Am J Roentgenol* 1984; 143: 933-41.
37. Smith VV, Milla PJ. Histological phenotypes of enteric smooth muscle disease causing functional intestinal obstruction in childhood. *Histopathology* 1997; 31: 112-22.
38. Smith VV, Lake BD, Kamm MA, Nicholls JR. Intestinal pseudo-obstruction with deficient smooth muscle alpha actin. *Histopathology* 1992; 21: 535-42.
39. Knowles CH, Silk DB, Darzi A, Veress B, Feakins R, Raimundo AH, et al. Deranged smooth muscle alpha-actin as a biomarker of intestinal pseudo-obstruction: a controlled multinational case series. *Gut* 2004; 53: 1583-9.
40. Smith VV, Gregson N, Foggensteiner L, Neale G, Milla PJ. Acquired intestinal aganglionosis and circulating autoantibodies without neoplasia or other neural involvement. *Gastroenterology* 1997; 112: 1366-71.
41. Verne GN, Sninsky CA. Chronic intestinal pseudo-obstruction. *Dig Dis* 1995; 13: 163-81.
42. Emmanuel AV, Shand AG, Kamm MA. Erythromycin for the treatment of chronic intestinal pseudo-obstruction: description of six cases with a positive response. *Aliment Pharmacol Ther* 2004; 19: 687-94.