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BRIEF ARTICLE

Characteristics of intestinal pseudo-obstruction in patients with mitochondrial diseases

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Abstract

AIM: To reveal the frequency, characteristics and prognosis of chronic intestinal pseudo-obstruction (CIP) in mitochondrial disease patients.

METHODS: Between January 2000 and December 2010, 31 patients (13 males and 18 females) were diagnosed with mitochondrial diseases at our hospital. We conducted a retrospective review of the patients' sex, subclass of mitochondrial disease, age at onset of mitochondrial disease, frequency of CIP and the age at its onset, and the duration of survival. The age at onset or at the first diagnosis of the disorder that led to the clinical suspicion of mitochondrial disease was also examined.

RESULTS: Twenty patients were sub-classified with mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), 8 with chronic progressive external ophthalmoplegia (CPEO), and 3 with myoclonus epilepsy associated with ragged-red fibers (MERRF). Nine patients were diagnosed with CIP, 8 of the 20 (40.0%) patients with MELAS, 0 of the 8 (0.0%) patients with CPEO, and 1 of the 3 (33.3%) patients with MERRF. The median age (range) at the diagnosis and the median age at onset of mitochondrial disease were 40 (17-69) and 25 (12-63) years in patients with CIP, and 49 (17-81) and 40 (11-71) years in patients without CIP. During the survey period, 5 patients (4 patients with MELAS and 1 with CPEO) died. The cause of death was cardiomyopathy in 2 patients with MELAS, cerebral infarction in 1 patient with MELAS, epilepsy and aspiration pneumonia in 1 patient with MELAS, and multiple metastases from gastric cancer and aspiration pneumonia in 1 patient with CPEO.

CONCLUSION: Patients with CIP tend to have disorders that are suspected to be related to mitochondrial diseases at younger ages than are patients without CIP.

Key words: Chronic intestinal pseudo-obstruction; Criteria; Mitochondrial disease; Mitochondrial encephalopathy; Lactic acidosis; Stroke-like episodes; Chronic progressive external ophthalmoplegia

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INTRODUCTION

Intestinal pseudo-obstruction was first reported by Dudley *et al*[1] in 1958, and refers to an uncommon disabling motility syndrome characterized by severe symptoms and signs of intestinal obstruction (abdominal pain, abdominal distention, nausea, and vomiting) and radiographic evidence of a dilated bowel in the absence of any mechanical obstruction. Pseudo-obstruction is primarily considered a small-intestine motility disorder, but it may occur in any portion of the gastrointestinal tract[2-6]. Furthermore, pseudo-obstruction may occur as an acute disease (Ogilvie syndrome[7]) or as a chronic remitting or persistent disorder, and chronic intestinal pseudo-obstruction (CIP) can be caused by and complicate many disorders[2]. Primary CIP can be sub-classified into visceral myopathy, visceral neuropathy and idiopathic CIP based on its histopathological manifestations. According to its etiology, secondary CIP can be categorized as disease-induced (such as connective tissue disorders, muscular dystrophies, infiltrative diseases, mitochondrial diseases, generalized nerve disease, endocrine disease, metabolic disease and others)[8-12] or drug-induced (antidepressant and anti-anxiety drugs, phenothiazines and others)[13-16].

Although an algorithm for the diagnosis of CIP was proposed by Rudolph *et al*[2] in 1997, diagnostic criteria for CIP have not yet been established in Japan or worldwide. Recently, Iida *et al*[17] proposed the diagnostic criteria for CIP shown in Table 1 and reported a diagnostic sensitivity of 85.9%.

Mitochondrial diseases are a heterogeneous group of disorders associated with mutations or deletions of nuclear or mitochondrial DNA[18-22]. Genetic mutations or deletions result in multisystem involvement associated with defects in the oxidative phosphorylation system and impaired production of ATP. The degree of organ dysfunction is contingent on the energy requirement of the organ and the proportion of mutated mitochondrial DNA in the organ[18]. Encephalomyopathy and cardiomyopathy are frequently encountered manifestations of mitochondrial diseases, and recently, gastrointestinal dysmotility has received attention[23-26]. Chinnery *et al*[27] reported that over 15% of patients with mitochondrial diseases complain of dysphagia or constipation, and a small percentage of the cases with constipation develop intestinal pseudo-obstruction. Although Amiot *et al*[28] reported that 19% of 80 patients with CIP had mitochondrial defects, the relationship between CIP and mitochondrial disease has not yet been conclusively established.

The aim of this study was to determine the frequency, characteristics, and prognosis of CIP in patients with mitochondrial diseases.

MATERIALS AND METHODS

Between January 2000 and December 2010, 33 patients were diagnosed with mitochondrial diseases at the Yokohama City University School of Medicine. Their clinical and treatment data were collected from their medical records and 2 patients were excluded due to insufficient clinical data.

Diagnosis of mitochondrial disease

The plasma and cerebrospinal fluid levels of lactate and pyruvate were measured at rest and then re-evaluated under exercise stress to ensure that the levels were within the normal ranges. Muscle biopsies and genetic analyses were performed in all patients. Examinations for other component disorders of mitochondrial dysfunction, such as glucose intolerance, electrocardiography, echocardiography, and brain magnetic resonance imaging were performed as needed.

Ethical approval

This study was conducted in accordance with the declaration of Helsinki, and with the approval of the Ethics Committee of Yokohama City University School of Medicine. We obtained written informed consents from each of the patients.

Statistical analysis

We conducted a retrospective review of each patient's sex, subclass of mitochondrial disease, age at the onset of mitochondrial disease, age at the establishment of the diagnosis of mitochondrial disease, frequency of CIP and the age at onset, and the duration of survival. The age at onset or at the first diagnosis of the disorder that led to the clinical suspicion of mitochondrial disease was also examined. As controls, we collected the data of 57 patients who were diagnosed with progressive muscular dystrophy at the Yokohama City University School of Medicine between January 2007 and December 2011. Five of the patients were excluded due to insufficient clinical data.

RESULTS

Thirty-one patients with mitochondrial diseases underwent detailed assessment (Table 2). The subjects comprised 13 males and 18 females and were sub-classified as having mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS; $n = 20$), chronic progressive external ophthalmoplegia (CPEO; $n = 8$), or myoclonus epilepsy associated with ragged-red fibers

Table 1 Criteria for the diagnosis of chronic intestinal pseudo-obstruction

Must include
One or more symptoms of ileus[1] onset at least 6 mo prior to diagnosis
One or both of following for the last 12 wk: (1) Abdominal pain; (2) Abdominal bloating
Dilatation and/or air-fluid levels of the intestine on abdominal X-ray, echo and/or computed tomography imaging
No evidence of structural disease (including findings of upper endoscopy, lower endoscopy, computed tomography, barium enema, and small-bowel follow-through) that could explain dilatation and/or air-fluid levels of the intestine
Supportive criteria
Congenital and/or onset under 15 years old must be excluded. Only adult onset is included
Surgical history within the 6 mo prior to diagnosis must be excluded to rule out Ogilvie syndrome, except surgery for CIP
To define CIP at two levels: Primary CIP or secondary CIP. Primary CIP consists of three types: the muscular type, neurogenic type and idiopathic type; Secondary CIP consists of two types: the systemic sclerosis (SSc) type and unclassified type
Family accumulation may exist
Neuropathy such as problems with urination may exist
Some psychosocial disorder may be present

[1]Symptoms of ileus include: Abdominal pain, nausea, vomiting, abdominal bloating, abdominal fullness, lack of defecation and/or passing gas. CIP: Chronic intestinal pseudo-obstruction.

Table 2 Age at the oncet of mitochondrial disease and chronic intestinal pseudo-obstruction

Sex	Subclass	Age at the onset of mitochondrial disease, yr	Age at the diagnosis of mitochondrial disease, yr	Age at the diagnosis of CIP, yr
F	MELAS	Difficulty in walking at 40	40	40
M	MELAS	Glucose intolerance at 13	57	46
M	MERRF	Difficulty in walking at 41	50	50
F	CPEO	Palpebral ptosis at 71	81	-
F	MELAS	Impaired hearing at 45	54	-
M	MELAS	Impaired hearing at 24	29	-
M	CPEO	Palpebral ptosis at 40	69	-
F	CPEO	Impaired eye movement at 30	52	-
F	MELAS	Impaired hearing at 25	40	43
M	CPEO	Palpebral ptosis at 49	49	-
F	MERRF	Muscular weakness at 46	54	-
M	MELAS	Impaired hearing at 47	52	-
M	MELAS	Epilepsy at 11	18	-
M	CPEO	Glucose intolerance at 40	67	-
M	MELAS	Impaired hearing at 24	31	-
F	MELAS	Impaired hearing at 12	17	25
F	MELAS	Impaired hearing at 54	60	-
F	MELAS	Epilepsy at 40	44	-
M	MELAS	Glucose intolerance and impaired hearing at 18	18	-
F	MELAS	-	23	-
F	MELAS	Chronic diarrhea at 26	40	-[1]
F	MELAS	Epilepsy at 18	18	26
F	MELAS	Difficulty in walking and hearing at 63	69	69
F	MELAS	Glucose intolerance at 33	42	55
M	CPEO	Palpebral ptosis at 16	44	-
M	MELAS	Epilepsy at 29	29	-
F	CPEO	Palpebral ptosis at 13	17	-
F	CPEO	Palpebral ptosis at 59	59	-
M	MELAS	Epilepsy at 21	21	34
F	MELAS	Glucose intolerance at 46	48	-
F	MERRF	Difficulty in walking at 20	50	-

[1]This patient died of uncontrolled epilepsy and aspiration pneumonia 5 mo after the onset of intestinal pseudo-obstruction and did not fulfill the diagnostic criteria. M: Male; F: Female; CIP: Chronic intestinal pseudo-obstruction; MERRF: Myoclonus epilepsy associated with ragged-red fibers; MELAS: Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; CPEO: Chronic progressive external ophthalmoplegia.

(MERRF; n = 3). Of the 31 patients, 9 (28.1%) were diagnosed with CIP based on Nakajima's criteria, including 8 of the 20 (40.0%) patients with MELAS, 0 of the 8 (0.0%) patients with CPEO, and 1 of the 3 (33.3%) patients with MERRF. One patient died of uncontrolled epilepsy and aspiration pneumonia 5 mo after the onset of intestinal pseudo-obstruction and did not fulfill the diagnostic criteria.

The confirmable outcomes were as follows: in December 2010, 14 patients were receiving outpatient treatment, 12 patients had been transferred to chronic care facilities, and 5 patients (4 patients with MELAS and 1 with CPEO) had died. The cause of death was cardiomyopathy in 2 patients with MELAS, cerebral infarction in 1 patient with MELAS, epilepsy and aspiration pneumonia in 1 patient with MELAS, as previously described, and multiple metastases from gastric cancer and aspiration pneumonia in 1 patient with CPEO.

In radiographic examinations for the 9 patients with CIP, small intestinal distention was observed in 6 patients, and large intestinal distention was observed in 1 patients. Both small and large intestinal distention was observed in 2 patients.

The median age (range) at the establishment of the diagnosis of mitochondrial disease was 40 (17-69) years in patients with CIP and 49 (17-81) years in patients without CIP. The median age (range) at the onset or at the first diagnosis of the disorder that led to the suspicion of mitochondrial disease was 25 (12-63) years in patients with CIP and 40 (11-71) years in patients without CIP.

The symptoms of CIP were treated with laxative agents, antidiarrheal drugs, antiflatulence agents, mosapride, dimethicone, pantothenic acid, daikenchuto (Chinese herbal medicine), neostigmine or distigmine, and none of the patients required surgery (Table 3).

As controls, we collected the data of 57 patients with progressive muscular dystrophy (Table 4). The patients consisted of 2 patients with Duchenne muscular dystrophy, 7 patients with Becker muscular dystrophy, 4

Table 3 Characteristics of chronic intestinal pseudo-obstruction in patients with mitochondrial diseases

Sex	Subclass	Type of abdominal discomfort	Area of dilated intestine	Treatment
F	MELAS	Nausea, vomiting, diarrhea, constipation	Small intestine	PEG, neostigmine
M	MELAS	Diarrhea	Small intestine	Antidiarrheal drug
M	MERRF	Pain, diarrhea, distension	Small and large intestines	Mosapride, dimethicone, antiflatulent, daikenchuto, pantothenic acid
F	MELAS	Diarrhea, constipation, distension	Small and large intestines	Mosapride, daikenchuto, magnesium oxide
F	MELAS	Nausea, vomiting, diarrhea, constipation, pain	Small intestine	PEG, antiflatulent, magnesium oxide, antidiarrheal drug
F	MELAS	Nausea, vomiting, constipation, pain	Small intestine	Prostarmon, magnesium oxide, dimethicone, daikenchuto, mosapride, neostigmine, sodium picosulfate hydrate
F	MELAS	Nausea, vomiting, distension	Small intestine	Magnesium oxide, daikenchuto
F	MELAS	Nausea, vomiting	Large intestine	Daikenchuto, sennoside
M	MELAS	Nausea, vomiting, diarrhea, distension	Small intestine	Daikenchuto, mosapride, magnesium oxide, lansoprazole, neostigmine, dimechicone

M: Male; F: Female; CIP: Chronic intestinal pseudo-obstruction; MERRF: Myoclonus epilepsy associated with ragged-red fibers; MELAS: Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; PEG: Polyethylene glycol.

Table 4 Characteristics of chronic intestinal pseudo-obstruction in patients with progressive muscular dystrophy

Subclass	No. of patients	No. of females	Age at the onset[1]	Age at the diagnosis[1]
Duchenne muscular dystrophy	2	0	1	2 (1-3)
Becker muscular dystrophy	7	0	10 (1-30)	19 (6-43)
Limb-girdle muscular dystrophy	4	1	22.5 (5-40)	49 (10-53)
Facio-scapulo-humeral muscular dystrophy	1	1	NS	NS
Myotonic dystrophy	38	18	30 (5-62)	39 (12-67)
Total	52	20	25 (1-62)	34.5 (1-67)

[1]Data is presented as median age (range). NS: Not stated. None of the patients with progressive muscular dystrophy in this study fulfilled the diagnostic criteria of chronic intestinal pseudo-obstruction.

patients with limb-girdle muscular dystrophy, 1 patient with facio-scapulo-humeral muscular dystrophy and 43 patients with myotonic dystrophy (5 patients were excluded due to insufficient clinical data). The median age (range) at the establishment of the diagnosis of progressive muscular dystrophy was 34.5 (1-67) years and the median age (range) at the onset of progressive muscular dystrophy was 25 (1-62) years. Only 2 of the patients died, while the others were alive at the last hospital visit. Although progressive muscular dystrophy has been considered as one of the etiologies of CIP, none of the patients with progressive muscular dystrophy in this study fulfilled the diagnostic criteria of CIP.

DISCUSSION

Although mitochondrial diseases have been considered as a potential cause of secondary CIP, the frequency of CIP in patients with mitochondrial diseases has not yet been well established. Gastrointestinal dysmotility (including CIP) may be caused by the accumulation of intracellular long-chain fatty acids, activation of extramitochondrial fatty acid oxidation pathways and excessive generation of reactive oxygen species leading to visceral myopathy, possibly as a result of impaired mitochondrial beta-oxidation[29]. Betts *et al*[30] reported that profound COX deficiency was found in the smooth muscle layers of all regions of the gastrointestinal tract in patients with the m.3243A>G mutation despite scarce evidence of morphologic abnormalities within the gastrointestinal tissues of these patients. Parsons *et al*[31] also reported that 80% of patients with MELAS and more than 60% of m.3243A>G carriers have 1 or more autonomic symptoms; gastrointestinal symptoms were especially common in the MELAS group, occurring in 66% of these patients and in almost 40% of the mutation carriers. In mitochondrial diseases, mitochondrial neurogastrointestinal encephalopathy (MNGIE), which is an uncommon autosomal recessive syndrome caused by the reduced activity of thymidine phosphorylase due to a mutation of the nuclear DNA, has also been reported to be particulary associated with CIP along with other symptoms such as malnutrition, progressive external ophthalmoplegia, ptosis, peripheral neuropathy, and leukoencephalopathy[32-34]. Although we have never encountered patients with MNGIE, this study revealed that patients with mitochondrial diseases develop complicating CIP at a relatively high frequency (28.1%), especially patients with MELAS (40.0%). We also examined the clinical data of patients with progressive muscular dystrophy, which is also a known cause of CIP, as controls and found that CIP occurs less frequently in patients with progressive muscular dystrophy than in patients with mitochondrial diseases (0% *vs* 28.1%).

Patients with CIP tend to have disorders, such as glucose intolerance, epilepsy, hearing impairment and palpebral ptosis,that are suspected to be related to mitochondrial diseases at younger ages than are patients without CIP. None of the patients in our study presented with CIP as the initial symptom of mitochondrial disease. This trend indicates that some patients with mitochondrial dysfunction will develop gastrointestinal dysmotility with disease progression, eventually leading

to the development of CIP.

The frequency of CIP among patients with relatively mild mitochondrial dysfunction who do not need advanced treatment at a hospital may also be smaller than that noted in this study. Most patients with mitochondrial diseases die of cardiomyopathy and encephalopathy before the development of severe CIP, and this finding is consistent with a previous report indicating that the degree of organ dysfunction depended on the energy requirement of the organ. Although CIP was not a major cause of death in patients with mitochondrial diseases, it often resulted in impaired oral intake or tube feeding and eventually the critical loss of the activities of daily life. Early detection and treatment of gastrointestinal dysmotility, including CIP, and the maintenance of the nutritional status may be efficacious in the management of patients with mitochondrial diseases.

There is still no sufficiently effective treatment for CIP today. A number of medicines were used in this study, and none were especially effective when comparing these treated patients with CIP patients without mitochondrial diseases. Surgery has been reported to be effective in patients with normal small intestinal motility[35], although surgery was not performed in this study (8 of 9 patients with CIP in this study had small intestine dysmotility).

Selection bias is one of the major limitations of our study. Patients receiving outpatient treatment at a university hospital like ours may have more severe symptoms than general patients presenting to primary care practitioners may have. This limitation could have resulted in an over-estimation of the CIP prevalence in patients with mitochondrial diseases. In addition, the 31 patients with mitochondrial diseases in this study included 20 patients with MELAS (64.5%), 8 patients with CPEO (25.8%) and 3 patients with MERRF (9.7%), indicating a larger prevalence of MELAS patients in our study compared with that from an epidemiological study conducted in Japan (64.5% *vs* 25.5%)[36]. This selection bias may also have contributed to an over-estimation of the CIP prevalence. Moreover, patients with MELAS often use antiepileptic drugs regularly, which may cause drug-induced intestinal pseudo-obstruction. In our study, 5 patients with CIP regularly used antiepileptic drugs (phenytoin, carbamazepine, carbamazepine and sodium valproate, and for 2 patients, carbamazepine and clonazepam). Although it may be difficult to precisely distinguish between mitochondrial and drug-induced gastrointestinal symptoms, the regular use of these antiepileptic drugs alone rarely results in CIP, and mitochondrial dysfunction was considered the main cause of the severe intestinal dysmotility of these 5 patients.

In conclusion, patients with mitochondrial diseases (especially MELAS) sometimes develop CIP. In cases characterized by the adequate control of fetal mitochondrial dysfunctions such as cardiomyopathy and encephalopathy, CIP may present as a prominent problem. The possibility of the development of gastrointestinal dysmotility, including CIP, should be considered at all stages of the clinical course of all patients with mitochondrial diseases.

COMMENTS

Background

Chronic intestinal pseudo-obstruction (CIP) is characterized by severe symptoms and signs of intestinal obstruction without mechanical obstruction. Although mitochondrial diseases have been considered as a potential cause of secondary CIP, the frequency, characteristics, and prognosis of CIP in patients with mitochondrial diseases has not yet been well established.

Research frontiers

Mitochondrial diseases are a heterogeneous group of disorders associated with mutations in or deletions of nuclear or mitochondrial DNA. The degree of organ dysfunction depends on the energy requirements of the organ and on the proportion of mitochondrial DNA in the organ. In the treatment of mitochondrial patients with CIP, current research now focuses on how mitochondrial dysfunction develops into CIP and what the differences between the patients with CIP and without CIP are.

Innovations and breakthroughs

The relationship between CIP and mitochondrial diseases has not yet been firmly established. In the present study, authors conducted a retrospective review of each patient's sex, subclass of mitochondrial disease, age at the onset of mitochondrial disease, age at the establishment of the diagnosis of mitochondrial disease, frequency of CIP and the age at its onset, and the duration of survival. The age at the onset or at the first diagnosis of the disorder that led to the clinical suspicion of mitochondrial disease was also examined.

Applications

The study results suggest that patients who have certain disorders, such as glucose intolerance, epilepsy, hearing impairment and palpebral ptosis, that are suspected to be related to mitochondrial diseases at younger ages tend to develop gastrointestinal dysmotility with disease progression, eventually leading to the development of CIP.

Terminology

CIP is an uncommon disabling motility syndrome characterized by severe symptoms and signs of intestinal obstruction (abdominal pain, abdominal distention, nausea and vomiting) and radiographic evidence of dilated bowels in the absence of any mechanical obstruction; Mitochondrial diseases are a heterogeneous group of disorders associated with mutations in or deletions of nuclear or mitochondrial DNA.

Peer review

This is a good descriptive study in which the authors retrospectively reviewed the frequency, characteristics and prognosis of chronic intestinal pseudo-obstruction in mitochondrial patients. The study revealed that patients with CIP tend to have disorders that are suspected to be related to mitochondrial diseases at younger ages than patients without CIP.

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