*Review Article*

# Chronic Intestinal Pseudo-Obstruction

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## Abstract

*CIPO (Chronic Intestinal Pseudo-Obstruction) is an uncommon heterogeneous clinical syndrome of variable severity, featured by disordered GI (gastrointestinal) motility, and its presentations simulate those of recurrent partial or complete intestinal obstruction in the form of radiologically dilated small or large intestine with air-fluid levels in the absence of any identifiable mechanical cause. It results from a complex disordered interaction amongst the altered gut flora/microbiota, the enteric smooth musculature (myopathies), the enteric nervous system (neuropathies), the intestinal endocrine system (endocrinopathies) and mesenchymopathies, etc. It poses a definite challenge to the treating physicians, despite some improvement in diagnostic and therapeutic strategies. Because of non-specific symptoms and the clinician's lack of discretion, there is every possibility of misdiagnosis. Commonly imaging, manometry and sometimes histopathological examination of biopsy specimens are undertaken as diagnostic tools. With surgical advancements, small gut transplantation is an expected treatment option for advanced CIPO. In general, the CIPO patients have increasingly worsening chronic symptoms, with poor prognosis, warranting nutritional and surgical interventions. This review article explains the features of CIPO and the latest avantgarde management strategies, with a view to upgrading clinicians' knowledge about CIPO, categorically summarizing the diagnostic tools and other issues to enlighten the clinicians, resulting in easy, quick, accurate and exact diagnosis of this clinical syndrome for proper and adequate treatment without delay, improving the patients' quality of life, minimizing sufferings. This review, in addition further focuses to the significance of continued research for more elaborately searching the etiology and the more effective management strategies of CIPO patients.*

***Key words:*** *Chronic Intestinal Pseudo-Obstruction, Enteral and Parenteral Nutrition, Gut Microbiota, Intestinal Motility, Intestinal Transplantation.*

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## Introduction

CIPO (Chronic Intestinal Pseudo-Obstruction) is an uncommon heterogeneous clinical syndromic process featured by recurrent episodes simulating intestinal obstruction with imaging findings of dilated small and/or large gut having air-fluid levels in the absence of any mechanical or anatomical obstructive lesion/s. There is often a permanent irreversible process of changes in neural, muscular, or mesenchymal components of the gut, or its extraneous neural control, or chronically jeopardized tonic and propagative motor functions in one or more segments of the gut. It is an example of variably severe form of gastrointestinal motility disorder having substantial morbidity and mortality if untreated.[1-3] Dudley HA in 1950 first reported the case of intestinal pseudo-obstruction, describing it as a disorder of intestinal peristalsis, simulating cases of intestinal obstruction, having no distinct mechanical cause.[2] Christensen J in 1978 proposed the phrase 'chronic intestinal pseudo-obstruction' (CIPO) for the then said intestinal pseudo-obstruction lasting for more than 6 months. Owing to uncommonness, non-specific symptoms, lack of knowledge and land of early suspicion by the attending physicians, it is more commonly misdiagnosed. It is now known to affect both pediatric and adult population. It may be primary,

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secondary or idiopathic. The histopathology may identify variety of such lesions as neuropathy, myopathy, endocrinopathy, mesenchymopathy or a combination of one or more of these.[3-5] Normally, gut motility is regulated by the ENS (Enteric Nervous System). The ENS works in harmony with the EECs (Entero-Endocrine Cells). The EECs secrete bioactive chemical messengers or hormones to control multiple intestinal functions that include the gut peristalsis, motility, and the monitoring of the ecosystem of the gut. There are more than100 trillion microbes living in harmonious mutualism in the gut. These gut microbes interfere with the gastro-intestinal motility, physiology, metabolism, nutrition and immune functions etc. Gut microbial ecosystem have Bacteria, Eukaryotic archaea, Eukarya and Viruses that are evolved together with the host over several thousands of years from the pre-historic time immemorial, establishing a complex symbiotic relationship. Comprehensive reviewing the most recent medical literature on CIPO, we can update our knowledge as regards to its etiology, diagnosis, treatment, and prognosis about this disease. [4-6]

## Epidemiology

The exact incidence and prevalence of CIPO is unknown. It was systematically studied in many countries of the world. The pediatric CIPO may have an incidence of about 1 per 40,000 live births in accordance to Vargas JH (1988). About 100 infants are said to be born with congenital pseudo-obstruction every year in the United States (1999). In Japan, the prevalence may be 3.7 (about 1 in male adult & 8 in female adult) per 10 lac (2014), and out of that 56.5% of cases having a neonatal onset; 91.1% having no pathological abnormalities are described as idiopathic, in accordance to different studies. In another study in Japan, it has been found that in age groups of more than15 years as determined on clinical and radiological features, the prevalence of CIPO was found to be 1.0 and 0.80 cases per 1 lac in respective males and females. The cause of extraordinary male preponderance is unknown.[1,3]

## Etiology and Classification

On the basis of histopathological features, CIPO may be classified into different such varieties as neuropathic, myopathic, mesenchymopathic or a combination of two or more. Commonly, more than one histopathological abnormalities are found in a single CIPO patient. In other acceptable way, CIPO is classified into: 1. Congenital (or primary); 2. Acquired (orsecondary), and 3. idiopathic varieties.[3] Primary ones are usually identified in chilhood, that is further divided into two subtypes: a) sporadic and b). familial. CIPO cases that are detected mostly in children are said to be sporadic that don't have definite positive family history. Some CIPO cases in children having positive family history are thought to possess such genetic features as autosomal dominant, autosomal recessive, and sex chromosome related inheritance etc. CIPO is a commonly identified in several types of such mitochondrial myopathies as MNGIE (Mitochondrial NeuroGastroIntestinal Encephalomyopathy), that develops as a result of mutation in the TYMP (thymidine phosphorylase) gene. MMIHS (Megacystis–Microcolon–Intestinal Hypoperistalsis Syndrome) that develops following mutation in the ACTG2 gene and CAIDS (Chronic Atrial and Intestinal Dysrhythmia Syndrome) following mutations in the SGOL1 gene -all these are belonging to this group of genetic CIPO. Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome or Alpers' disease that develops following POLG gene mutations are also found to be associated with CIPO. CIPO features have also been detected in patients with hereditary degenerative smooth muscle (a familial visceral myopathy) and hereditary enteric nervous system diseases (familial neuropathies); but the incriminating genes have not yet been detected.[3,7,8] Some congenital forms of CIPO are SOX10/Waardenburg-Shah syndrome (autosomal dominant); ACTG2/Megacystis–microcolon–intestinal hypoperistalsis syndrome (autosomal dominant); SGOL1/Chronic atrial and intestinal dysrhythmia syndrome, POLG/Alpers' disease (autosomal recessive); TYMP, POLG/Mitochondrial neurogastrointestinal encephalomyopathy (autosomal recessive); 8q23-q24: A new chromosomal localization related to CIPO, plus Xq28: Filamin A and L1CAM genes (X-linked recessive), etc.[3] Acquired cases of CIPO are more commonly detected in adults, and are often found secondary to a wide variety of such diseases as connective tissue diseases, malignancy, or systemic neurological, endocrine disorders etc. These primary diseases and disorders interfere with intestinal motility through a variety of the following mechanisms: 1. autonomic neuropthies (as in stroke, encephalitis, calcified basal ganglia, orthostatic hypotension, diabetes mellitus); 2. intestinal wall neuropathies [as in paraneoplastic syndromes, viral infections, iatrogenic (by anthraquinones), diabetes mellitus, Hirschsprung's disease, Chagas' disease, Von Recklinghausen's disease]; 3. intestinal wall myopathies (as in myotonic dystrophy, progressive systemic sclerosis); 4. mixed involvement of enteric neuropathies and intestinal wall myopathies (as in scleroderma, dermatomyositis, amyloidosis, Ehlers–Danlos syndrome, jejunal diverticulosis, radiation enteritis); and 5. unknown mechanisms (hypothyroidism, hypoparathyroidism, pheochromocytoma, such drugs as clonidine, phenothiazines, antidepressants, antiparkinsonians, antineoplastics, bronchodilators). Such neurological diseases as Parkinson's disease and such metabolic diseases as diabetes mellitus affect intestinal motility function through the parasympathetic with or without involvement of the sympathetic nervous system. Paraneoplastic syndromes may result in inflammatory or immune infiltrates of submucosal and myenteric ganglionic neurons by cellular infiltrates and circulating antineuronal antibodies, resulting in intestinal motility disorders.[9-11] Progressive systemic sclerosis or Myotonic dystrophy principally affects the enteric myocytes. Collagenopathies, autoimmune disorders, radiation enteritis and jejunal diverticulosis can affect enteric neurons and myocytes and the ICCs (interstitial cells of Cajal), terminating in a combined neuro-myopathy. Many different such neurotropic viruses as cytomegalovirus, and Epstein–Barr virus, herpesviruses, polyomaviruses (JCV: John Cunningham virus) may act in the pathogenesis of CIPO. Several diseases associated with CIPO in adults include Congenital megacolon (Hirshsprung's disease), MNGIE (Mitochondrial neurogastrointestinalencephalomyopathy), Muscular dystrophies ( Duchenne, Myotonic), Autonomic disorders/dysfunctions, Autonomic disorders/dysfunctions, Multisystem atrophy, Amyloidosis, Celiac disease, SLE (Systemic lupus erithematosus), Anti-syntetase syndrome (myositis, dematomyositis), SS (Systemic sclerosis), Borrelia

burgdorferi (Lyme disease), Strongyloidesstercoralis, Tripanosomacruzi (Chagas disease), Small cell lung carcinoma and other cancers (paraneoplastic), Primary Sporadic autoimmune/inflammatory CIPO, genetic CIPO etc.[4]

## Pathology

The CIPO is featured by abnormalities of gut anatomical components, and degeneration or inflammation of the ENS with or without enteric myopathy. Secondary CIPO is said to result from a well-identified disease affecting the enteric muscles, neurons and the ICCs (interstitial cell of Cajal) that accounts for about 50% of the causes in adult patients. The idiopathic variety of CIPO is defined when neither a primary nor secondary cause is detected, that accounts for the maximal cases of childhood CIPO cases. Both congenital and acquired CIPO may have three histological features: myopathies, neuropathies, and mesenchymopathies. Multiple pathologies may be present in the same patient at a time. (A): Intestinal neuropathies include neurodegeneration and dysplasia of the enteric nervous system. Such neurodegenerative disorders as neuronal intranuclear inclusion disease are featured by gradual and progressive degeneration and disappearance of ganglion cells, resulting in a gradual decline in neurons. In addition to CIPO symptoms, these patients may have other such symptoms as ataxia of neurological abnormalities.[3,12,13] Aganglionosis in Hirschsprung's disease, diffuse intestinal ganglioneuromatosis, intestinal hypoganglionosis, and neurogenic intestinal dysplasia that involve abnormalities in intestinal nerve distribution, development, and quantity causing principally dysplastic disorders of the ENS (enteric nervous system), lead to CIPO. Such other diseases as intestinal ganglionitis may show features of CIPO. (B): intestinal myopathies (affecting the supernumerary intestinal muscle coat), diffuse abnormalities in muscle layering can also cause CIPO. Malformed regions of the intestinal muscularis propria having broad smooth muscle fascicles are found to be disposed obliquely or perpendicularly. Smooth muscles get degenerated and lost, ultimately replaced by fibrous connective tissue in degenerative leiomyopathy; CIPO symptoms thence develop gradually. Such other adverse stimuli as inflammation of the gut wall, or by drugs or ischemia, and immune disorders may cause CIPO in gut myopathies .(C): Mesenchymopathies principally cause abnormalities of the ICC (interstitial cells of Cajal) and tendinous collagenous tissues of the muscularis propria.[3]

## Clinical features

Its features may be present antenatally in about 20% cases, and during the first month of life in about 50%–70% cases. Clinically 80% patients may have features during infancy, and the rest 20% may have sporadic onset during the first two decades of life. The median age of symptom onset is about 17 years in adults.

CIPO presentations depend on age of onset, site and extent of the affected segment of gastro-intestinal tract. It can affect any segment of the GI tract. Oesophageal motility problems are found in about 70% of CIPO patients.

All CIPO patients present with such nonspecific exacerbating and remitting symptoms as non-colicky, persistent abdominal pain and abdominal distension/intestinal dilatation (80%), nausea (75%) and vomiting (40-50%), constipation (40%) and diarrhea (20-30%). The pain is most commonly situated in the umbilical or upper abdominal regions and then subsequently may spread all over the abdomen. The onset of CIPO is most commonly insidious, may have first acute GI symptoms that may get subsequently significantly worsened;or, may be lasting for several hours. Or, the symptoms may simulate a sub-acute intestinal obstruction. Or, the patients may remain asymptomatic in between acute episodes, or may simulate persistent GI obstruction. Thus, there may occur unpredictable acute, sub-acute or intermittent exaggerations at variable frequency and severity, with no detectable cause, that can vary over a wide spectrum. Viral or bacterial infections, sepsis, malnutrition, psychic stress can trigger these symptoms. In severe CIPO cases, the patients may develop intestinal failure. In addition, intestinal dilatation and inadequate transit result in SIBO (Small Intestinal Bacterial Overgrowth) in about 30% of cases, inducing mucosal damage, malabsorption, diarrhea, steatorrhea, vitamin deficiencies, weight loss and small gut damage etc. If SIBO is treated with antibacterials, intractable constipation may develop. Oral intake of food usually deteriorates symptoms. Malnutrition is frequently seen as a recurrent event. The extra-intestinal involvement can cause bladder and ureteral dilatation associated with a microcolon, a phenotype referred to as Megacystis Microcolon Intestinal Hypoperistalsis syndrome (MMIHS). MMIHS starts antenatally, and can be diagnosed by ultrasonography prenatally in about 59% CIPO patients. Other extra-intestinal manifestation may be depression during the prolonged course of CIPO, having unsatisfactory treatment. In old age, secondary CIPO is usual, presenting with the features of the primary diseases. For example, MNGIE (Mitochondrial neurogastrointestinal encephalopathy) disease involves multiple parts of the body, especially the GI system (simulating intestinal obstruction) and the nervous system (in the form of also progressive external ophthalmoplegia, ptosis, and peripheral polyneuropathy etc.) in the elderly. The features of MNGIE may develop at anytime from infancy to adulthood, but they most commonly start by the age of 20. All these often lead to a poor QOL (Quality Of Life) and substantial morbidity and mortality.[3,14-16]

Owing to the non-specific features of CIPO, even if the diagnosis of CIPO can be made clinically, there is every possibility to confuse CIPO with other such ailments that have similar features as functional constipation, cyclic vomiting syndrome, hypothyroidism, gastroparesis, and drug reactions etc.

## Diagnosis

As there is no unique diagnostic tool for CIPO patients, correct diagnosis is more frequently made at an advanced stage of the disease. The median interval is about 8 years between symptom onset and diagnosis,when the patients give of a long history of recurring attacks of nausea, vomiting and abdominal distention, associated with variable radiological evidences of gut obstruction (dilatation with air-fluid levels).

The initial step to arrive at diagnosis is the cautious exclusion of mechanical occlusion. Abdominal MRI (magnetic resonance

imaging) or CT (computed tomography) scan is required to exclude obstrucive agent/s. Endoscopic evaluation of the site of "pseudo-obstruction" distal to the dilated gut segment is required to exclude atresia, stenosis, obstructive membrane/s. Such drugs that jeopardize GI motility as anticholinergics, ganglionic blockers, opioids, tricyclic antidepressants, clonidine, and phenothiazines are to be stopped as these induce bad effects in CIPO.

The early concrete diagnosis of CIPO is often very difficult, because: 1. The diagnosis depends on clinical experiences, as it doesn't have any biomarkers; 2. Clinically it mimics intestinal mechanical sub-occlusive crisis, and may have such clinical complexities as by the presence of comorbidities (e.g., urinary bladder abnormalities or any of its syndromic forms); 3. The mechanism of broad heterogeneous spectrum that results in CIPO and related clinical features are additional causes of difficulties in diagnosis. Thus the diagnosis of CIPO may only be made following multiple explorations to obviate mechanical intestinal obstruction. It may need to have final diagnosis on an average of about 8 years or more delay, and 88% patients may be submitted to three non-therapeutic operative procedures.[3,17,18]

CT and plain abdominal x-rays exhibit features of non-specific small gut obstruction. Traditional contrast imaging study using barium can eliminate mechanical obstruction, but there remain the risks of contrast retention and development of fecal stones, causing exaggeration of obstruction. HRCT and MRI can eliminate the need of traditional barium studies. In addition to delineating obstruction, HRCT can give such additional information as bands and adhesions. Cine-MRI can identify subtle contractile gut motility disorders.

GI manometry can efficiently assess and evaluate the intensity and the coordination or non-coordination of GI tract contraction, as an important diagnostic tool. Oesophageal manometry can detect abnormal pressure that occurs in about 50% cases. Evaluating gastro-duodenal, jejunal, ileal and colonic pressures is also helpful. Sometimes, there may be no relation amongst the findings of GI manometry and the pathological variants of CIPO, or there may have no correlation amongst the manometric patterns and the variants and the severity of symptoms. Still GI manometry is now being widely used to diagnose CIPO, in centers where this facility is available. An abnormal GI manometry, if clinical and radiological features of dilated gut supports is almost confirmatory for CIPO diagnosis.[3,19]

GI endoscopy is often helpful to diagnose mechanical obstruction (as by SOLs-Space Occupying Lesions and stenosis/strictures in the GI tract). Colonoscopy has an additional therapeutic value in GI decompression. Potential risky capsule endoscopy can give more information. The capsule endoscopy is not now routinely recommended for diagnosis of CIPO.

Genetic investigations are required for quick and correct diagnosis and screening of genetic diseases (e.g. POLG/Alpers' disease, TYMP mutation, SOX10/Waardenburg–Shah syndrome, ACTG2/MMIHS,SGOL1/CAID, andPOLG/MNGIE) linked with CIPO.

Histopathological interpretation of the nerves and muscle coats of gut wall relating to CIPO is often very difficult. Discernible abnormalities despite thorough microscopic examinations of full-thickness gut biopsies are not commonly seen in children with CIPO. Thus the full-thickness biopsies of the small intestine, colon and gastric antrum have enormous limitations, and are not routinely practiced.

Thence the diagnosis of CIPO is to be made principally on clinical grounds, as well as on findings of extensive small gut dilatation and multiple gas-fluid levels, imaging and manometry investigations, along with exclusion of mechanical obstruction.[20,21]

As CIPO is regarded as the most severe phenotypic expression of gut dysmotility, it must be differentiated from such other GI disease processes as enteric dysmotility where intestinal motility is also seriously jeopardized.Thus the principal way of diagnosis of CIPO relies on the radiological finding of chronically dilated small or large gut, contrariwise the diagnosis of intestinal dysmotility depends on the finding of small gut dysmotility as evidenced by small-gut manometry or by other such reliable ways as wireless motility capsule (sometimes) or cine-MRI. These two clinical processes must be identified clearly and separately, because CIPO possesses a very poorer prognosis with the variable possibilities of underlying associated disease processes. CIPO is also quite different from acute intestinal pseudo-obstruction (Ogilvie syndrome, where the neuromuscular architecture of the intestinal wall is found preserved (i.e., intact), but having a temporary and reversible dysequilibrium between excitatory and inhibitory neurotransmitters that causes acute dilation of the colon with or without involving the small gut.

Once the diagnosis of CIPO has been done, the next step is to consider whether it is associated with diseases having defined treatment and prognosis. A cautious history taking and elaborate physical examination, including neurological assessment and evaluation, are essential to identify these diseases and to avoid the unnecessary diagnostic investigations. It is to be kept in mind that this CIPO may be the initial presentation of these previously undiagnosed diseases.[4,22,23] Some diagnostic tests and investigations in adult CIPO include anorectal manometry, extramucosal rectal biopsy for Hirschsprung's disease (Congenital megacolon), serum CPK, LDH, lactate, brain MRI, TYMP, POLG genes for mitochondrial neurogastrointestinal encephalomyopathy, CPK, DMPK, CNBP, DMD genes for Muscular dystrophies (Myotonic, Duchenne), autonomic function tests; anti-gAChR for Autonomic dysfunctions and CIPO, autonomic function tests for multisystem atrophy and CIPO, Autonomic function tests and Congo Red on gastric, rectal, or skin fat biopsies, APOA1, FGA, LYZ genes for amyloidosis and CIPO, immunoglobulin A, anti-transglutaminase antibodies for Celiac disease and CIPO, ANA for Systemic lupus erythematosus and CIPO, CPK. Anti -PL-7, anti-EJ antibodies for antisynthetase syndrome (myositis, dermatomyositis) and CIPO, Capillaroscopy, SCL70 antibodies for Systemic sclerosis and CIPO, Anti-Borrelia antibodies for Borrelia burgdorferi (Lyme disease), Anti-Strongyloides antibodies for Strongyloides stercoralis, Anti-Trypanosoma

cruzi antibodies for Trypanosoma cruzi (Chagas disease), Anti-Hu antibodies for Paraneoplastic CIPO, Anti-Hu antibodies, anti-GAD antibodies, ASMA, anti-gAChR, Full-thickness biopsies for sporadic autoimmune inflammatory CIPO, Sequencing for ACTG2, FLNA, SGO1, RAD21, MYLH, MYH11 for genetic CIPO, etc.[4]

Sporadic CIPO may be a manifestation of an abnormal autoimmune response directed against gut neurons or muscles, even if there is no pre-existing autoimmune, infective, or paraneoplastic disease. Then detection of these antibodies (e.g., anti-Hu, anti-gAChR, anti-GAD, anti-smooth muscle), albeit nonspecific, is required for diagnosis.

For CIPO diagnosis, full thickness biopsies of gut are not usually required and recommended. Histopathologic confirmation of inflammatory gut neuropathy or myopathy is mandatory before administration of long-term immunotherapies with indefinite unpredictable efficacy and potentially dangerous adverse effects. But full thickness gut biopsies are recommended in suspected CIPO cases if all other diagnostic workups are negative.[4,24]

Genetic mutations causing changes in muscle, neural, or mesenchymal anatomy and physiology, are more commonly identified in pediatric than in adult CIPO patients. Some genes involved in CIPO and other associated phenotypes identified in humans include ACTG2: Actin gamma 2 (smooth muscle) located at 2p13.1 in Megacystis-microcolon-intestinal hypoperistalsis syndrome 5 (autosomal dominant), RAD21: Cohesin complexes contain SCC1 located at 8q24.11 in visceral myopathy 1 (autosomal dominant, Mungan syndrome (autosomal recessive), Cornelia de Lange syndrome 4 (autosomal dominant), FG syndrome 2 (X-linked), Cardiac valvular dysplasia (X-linked), Congenital short bowel syndrome (X-linked recessive), Frontometaphyseal dysplasia 1 (X-linked recessive), Periventricular heterotopia type 1 (X-linked dominant), Neuronal intestinal pseudo-obstruction (X-linked recessive), FLNA: Filamin A located at Xq28 in Melnick-Needles syndrome (X-linked dominant), Otopalatodigital syndrome, types I and II (X-linked dominant), Terminal osseous dysplasia (X-linked dominant), TYMP: Thymidine phosphorylase located at 22q13.33 in Mitochondrial DNA depletion syndrome 1 (MNGIE type, autosomal recessive), POLG Mitochondrial DNA polymerase gamma located at 15q26.1 in Mitochondrial DNA depletion syndrome 4A (Alpers type, autosomal recessive), Mitochondrial DNA depletion syndrome 4B (MNGIE type, autosomal recessive), Mitochondrial recessive ataxia syndrome (SANDO and SCAE, autosomal recessive), Progressive external ophthalmoplegia (autosomal dominant/autosomal recessive), SGO1: Shugoshin 1 located at 3p24.3 in Chronic atrial and intestinal dysrhythmia (autosomal recessive), MYLK: Myosin light chain kinase located at 3q21.1 in Aortic aneurysm, familial thoracic 7 (autosomal dominant), Megacystis-microcolon-intestinal hypoperistalsis syndrome 1 (autosimal recessive), MYH11: Myosin heavy-chain (smooth muscle) located at 16p13.11 in Aortic aneurysm, familial thoracic 4 (autosomal dominant), Megacystis-microcolon-intestinal hypoperistalsis syndrome 2 (autosomal recessive), Visceral myopathy 2 (autosomal dominant), etc.[4,25]

## Treatment of CIPO

CIPO patients need to be managed by MDA (multidisciplinary approach) with MDT (multidisciplinary team), that entails nutritionists, gastroenterologists, psychotherapists, and general surgeons, geneticists, and occasionally experienced transplant surgeons. Most of the CIPO patients, accounting to about 89%, (in contrast to a small group of about 11%) have progressively worsening symptoms, who need careful medical treatment and nutritional support, with a view to relieving distressing symptoms, enhancing GI motility, revamping nutritional states, and sustenance of the stable internal environment (milieu interior). Multivitamins and micronutrients are to be supplemented to prevent vitamin and trace elements deficiencies. Monitoring for prevention of metabolic bone diseases is also required. Intestinal motility and tone stimulant drugs may be useful only in a small group of patients. No surgery has yet been proved to be curative for CIPO. Surgery is required only in selected cases for symptomatic relief by decompression, and to provide enteral feeding. In the worst cases, patients may become dependent upon artificial nutrition via parenteral nutrition, or may choose to have an intestinal transplant. It is noteworthy that the overall results of CIPO treatment are not that much satisfactory, and as the disease follows a prolonged course, the patients are highly susceptible to depression and other psychic ailments. Thus, chronically debilitating CIPO patients often need psychological and/or psychiatric counseling, and treatment. In severe cases, patients' QOL is seriously compromised. Genetic counseling is required in cases of genetic CIPO to provide psychological support. Specific gene therapies for genetic CIPOs are not yet available, but ongoing research is there for it.[3,4,26,27]

Initial considerations (general measures and initial treatment: Dietary, analgesics, antiemetics and prokinetics etc.)
Initial treatment of CIPO consists of dietary adjustment, analgesic, antiemetic and prokinetic drugs when indicated. Patients having incessant symptoms, pharmacotherapy with analgesics, anti-emetics and prokinetic drugs is often necessitated. Early nutritional intervention is essential, especially for patients with recurrent vomiting or inadequate oral intake. The CIPO patients are encouraged to take small and soft frequent meals, according to his or her tolerance. Small meals made by liquids or homogenized (simplified uniform blended mixture) standard foods are better accepted than solid foods. CIPO patients often need supplemented nutritional support. Hyper-caloric liquid preparations should be given to CIPO patients suffering from low calorie intake. Enteral nutrition is ideal in CIPO patients with neuropathy/neuropathies and in patients where there is localized motility disorder in the duodenum and/or stomach. Parenteral nutrition may be required by patients where there are severe motility disorder/disorders, most commonly in myopathic CIPO. A single pharmacological agent is not usually effective to relieve distressing symptoms. And, thence several tools are required. In some cases, CIPO may only be managed with symptomatic treatment aimed at reducing symptom severity, preventing unnecessary operative procedures, and improving the nutritional status of the patients by ensuring sufficient calorie intake orally, promoting gut motility and managing

SIBO. Chronic visceral pain is due to inhibition of GI peristalsis that needs treatment by low-dose tricyclic antidepressants and gabapentin as analgesic agents, and not by opioids. In cases of progressive disease, about 25% of patients may sequentially increase their tolerance to analgesic medications, when pain specialists and psychotherapists can help a lot. Such drugs as neostigmine and pyridostigmine can reduce intestinal dilatation, and prucalopride (serotonin receptor agonist) can improve gut peristalsis. Colonoscope may be used to decompress an overtly distended colon immediately. Ostomies (like percutaneous endoscopic gastrostomy or jejunostomy) are often safe and effective to treat symptomatic segmental gut distention and to provide enteral nutrition.[3,4,28,29]

**Nutritional assessment and support**

About 65% to 70% CIPO patients have inadequate nutritional intake, who may present with remarkable weight loss. Thence, rigid nutritional assessment and evaluation for identifying, selecting and providing appropriate nutritional supports are essential and mandatory to revamp patients' QOL and long-term prognosis.

**Nutritional assessment and evaluation**

A systematic and rigid nutritional assessment and evaluation of CIPO patients should be undertaken by experienced nutritionist/nutritionists. Macro measurements such as BW (body weight), BMI (body mass index), and eating patterns, and such laboratory investigations as serum prealbumin, albumin, C-reactive protein, lymphocyte count, and sometimes serum calcium, iron, vitamin B12, thiamine, Vitamin D, and niacinamide, folic acid, fat-soluble vitamins are to be done. However, the laboratory findings need to be corrected, as there may be insufficient intake and/or absorption obstacles or malabsorption in some patients.

**Nutritional support**

Dietary advice and support: Patients and their care givers should get nutritional education, and create his or her individualized diet plans with the help of nutritionist/nutritionists. Truly speaking, oral intake is the most desired route, and small, frequent meals (e.g., five to six times daily) are the most fruitful ways of nutritional support. The best and the most ideal diet is a liquid preparation having protein and high fat. High fiber containing diets should have restrictions, or even excluded. Serum levels of lipo-phobic water-soluble vitamins, minerals, and electrolytes should be regularly and routinely monitored, and supplemented when required. If bacterial overgrowth occurs, the serum levels of lipo-philic hydrophobic vitamins and vitamin B12 should be investigated. When required, all fundamental diets and medium-chain triglyceride-rich dietary supplements are to be provided.[4,30]

**Enteral nutrition**

Enteral nutrition is indicated if oral feeding cannot satisfy the needs. Non-elemental standard enteral nutrition can usually meet the needs of most CIPO patients. NGTs (nasogastric tubes) or GTs (gastrostomy tubes) are used here for sustained small-dose feeding, when required. A NJ (Nasojejunostomy) or a jejunostomy tube is warranted when there is gastroparesis. Continuous, low-dose, or periodic feeding is more easily suitable when compared with one-time high-dose alimentation. Parenteral nutrition: Different grades of parenteral nutritional support are sometimes given to about 60%–80% CIPO patients, and about 20 % CIPO patients may be managed with home parenteral nutrition. At least one third CIPO affected children needs parenteral nutrition (total or partial) for adequate energy intake. If CIPO patients exclusively need TPN (total parenteral nutrition), total energy intake is estimated by about 25 kcal/kg/-day, and about 30% of total parenteral calorie should come from lipids, along with 1.0–1.5 g/kg/day of protein and the remaining calories being from glucose. It has been observed that parenteral nutrition can successfully maintain patients' BW (body weight), relieving CIPO symptoms, with acceptable survival rates. But about 90% of deaths of CIPO patients may be linked to parenteral nutrition-related complications. The mortality of CIPO affected children may range from about 4.7% to 15.29%. Metabolic bone disease, electrolyte imbalances, dehydration, and intestinal failure-associated liver disease are some metabolic complications of parenteral nutrition. Catheter-related sepsis is not uncommon. Catheter breaks, catheter occlusions, catheter dislocation, thrombosis, especially DVT (deep vein thrombosis), SVC (superior vena cava) syndrome, and air embolism are also seen. Thence, maximizing maximal oral intake in CIPO patients is advised to minimize or evade the untoward complications of the parenteral nutrition.[4,31,32]

**Gut motility, ENS, IES and Neurotransmitters, gut microbiota therapy:**

There is yet no evidence to recommend GI motility drugs. Still, some prokinetic drugs are prescribed that can entrust improvement in GI motility disorders. Erythromycin ((a macrolide antibiotic) may promote gastric motility. Octreotide (a nonspecific somatostatin analogue acting on receptors 2 and 5 subtypes) and amoxicillin-clavulanic acid may promote intestinal motility. These (erythromycin and octreotide) are useful prokinetic agents that can induce antrum-duodenal phase III of the migrating motor complex, resulting in acceleration of the small gut transit. In adults, intravenous neostigmine 8 mg/d, and oral pyridostigmine 20 mg/d as acetylcholinesterase inhibitors (AChEIs) have been used to revamp gastrointestinal motility, even in cases refractory to standard treatment, as these drugs can improve at least some symptoms of CIPO. Prucalopride (a 5-HT4 receptor agonist) can induce prokinetic effect in increasing gastric emptying and small gut transit. Long-term use of metoclopramide can cause tardive dyskinesia, and thus should be avoided. Value of domperidone in CIPO patients has not yet been documented clearly.[4,33]

Gut motility is a coordinated function among the CNS (central nervous system) that implicates an interplay among the 600 million neurons of the ENS (enteric nervous system), the gut smooth muscle cell contractile function, the pacemaker interstitial cells of Cajal (ICCs) and the afferent and efferent nerve fibers. Six hundred million neurons of the ENS within gut wall are connected by microcircuits, along with the interneurons and the IPANs (intrinsic primary afferent neurons), that are capable of initiating reflexes. There is always a well integrated interaction between the CNS and the ENS, as the CNS (brain and spinal cord) interacts with autonomic activities of the GI tract and vice versa. The ENS intimately controls the peristalsis of

the gut. Any interruption or damage to any of the pathways or machineries interferes with the gut motility resulting in motility disorders. The ENS works in association with the IES (intestinal endocrine system). The IES is located in the wall of GI tract. The IES consists of EECs (enteric enterochromaffin cells or enteroendocrine cells) located in the enteric mucosa including the crypts and villi. These EECs elaborate bioactive chemical messengers (local hormones) to control variable intestinal such physiological activities as motility and monitoring the gut ecosystems. The ENS & IES jointly controls the GI motility, through secretions of such neurotransmitters as acetylcholine, serotonin (5-HT) and dopamine. These neurotransmitters have varied roles in signal detection, behavior and conditions, e.g., learning, memory and attention. Acetylcholine is the principal neurotransmitter of peripheral neurons, and it principally causes contraction of smooth muscles, increases secretions, dilates blood vessels and slows heart rate. Dopamine is a precursor of such catecholamines as norepinephrine (NE)/noradrenaline and epinephrine/adrenaline. The neurotransmitter dopamine affects human behavior. Norepinephrine is associated with excitation, vigilance, cognition, memory, learning and attention. Bacteria can produce catecholamines, and respond to them. The growth rate of Escherichia coli O157:H7 (EHEC) is augmented in presence of dopamine, norepinephrine. Norepinephrine increases its motility, biofilm development and virulence. Moreover, Norepinephrine, probably owing to iron acquisition augments the growth rate of Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Shigella sonnei and Enterobacter cloacae.[4,5,34]

Serotonin controls several physiological processes that include peristalsis, GI excretion, secretion, vasoconstriction, respiration, neurological function and behavior. The gut microbiota controls the functions and anatomy of the ENS through serotonin release and the activation of its 5-HT4 receptor. Drugs that interfere with the acetylcholine, 5-HT (serotonin) and GABA mediators support the significance of these neurotransmitters in CIPO pathology. E.g., cisapride (a serotonin agonist) and a 5-HT3 antagonist, having prokinetic activities, get attached to the serotonin receptors in the gut nerve plexus, causing acetylcholine release and the gut muscle contractions, leading to augmented post-prandial duodenal contractions in these patients. But, though tegaserod (a serotonin agonist) and cisapride are good prokinetc agents, they are banned because of causation of fatal arrhythmias by them. Moreover, highly selective 5-hydroxytryptamine-4-receptor agonist prucalopride ( having no cardiotoxicity), provides good enterokinetic actions, expediting liberation of acetylcholine, causing stimulation of cholinergic neurotransmission, speeding up gastric, small gut and colonic transit.[4, 35, 36]

Here gut microbes may influence gene expression, synthesis and/or function of these neurotransmitter chemicals. The enterochromaffin cells (ECs) are a subset of EECs (Enteroendocrine cells). They release the amine serotonin (5-hydroxytryptamine) when stimulated by mechanical, chemical or neural means. This serotonin acts when bound to specific serotonin receptors (e.g., 5-HT4), thus causing reflexes for increased peristalsis and transit. Majority of the endogenous 5-HT is produced by EECs of the GI mucosa through the enzymatic action of the enzyme tryptophan hydroxylase-1. A very small amount of serotonin is produced in the ENS through the action of the Tryptophan hydroxylase 2 (TPH2). Serotonin is a pleiotropic amine that is known for its interactions with many gut functions, that means single locus is going to affect two or more distinct phenotypic traits. Conventional functions of serotonin in the gut include its intrinsic reflexes that causes excitation of gut propulsive and segmentation motility, epithelial/endocrine secretions, and vasodilations. Within the gut, serotonin also asserts non-conventional actions that involve serving as a pro-inflammatory signaling molecule, and as a trophic agent promotes the growth and sustenance of the neurons and the interstitial cells of Cajal. The serotonin synthesis is influenced by 1. variations in luminal glucose levels, 2. increases in luminal short-chain fatty acids (SCFAs) of bacterial origin, 3. neuro-modulating agents of the CNS and/or the ENS. The most current classification of serotonin receptors (serotonergic), as suggested by IUPHAR (International Union of Basic and Clinical Pharmacology) in 1998 include: 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6 and 5-HT7. Out of these, the 5-HT3 and the 5-HT4 are principally found in the GI tract. They are able to improve peristalsis and provoke cholecystokinin release. On basis of successful treatments with serotonin antagonists, it is presumed that the gut dysmotility might have linkage with serotonergic pathway malfunction. The intestine is thought affect the development of the ENS and CNS and such pathologies as NDDs (neurodegenerative diseases), CVAs (cerebrovascular accidents) and behavioral, neuroimmune-mediated disorders or motility disorders. This "gut−brain axis" includes the pathways dictated by the the immune system, the vagus nerve or the variation of neuroactive microbial composition. Altered GABA (an inhibitory neurotransmitter of the CNS) levels are associated with plenty of disorders involving the CNS, host behavior, pain, sleep, ENS, gastric emptying, acid secretion, gut motility.[3-5]

**Treatment of SIBO and FMT**

**Antibacterial medication**

The most common complication of long standing gut dilatation is SIBO (Small Intestinal Bacterial Overgrowth). Here the Colony-Forming Units indicative of bacterial concentrations are commonly more than 103 to 105 CFU/mL. Such oral antibacterial treatments, as amoxicillin-clavulanic acid (625 mg, thrice daily), ciprofloxacin (500 mg, twice daily), doxycycline (100 mg, twice daily), metronidazole (250 mg, thrice daily), neomycin (500 mg, twice daily), rifaximin (550 mg, twice daily), and tetracycline (250 mg, 6 hourly) for 7 to 10 days every month are usually effective, switching over to another one/ones each month for 5-6 months.

The GI tract is the largest area of colonization by microbes in the human body. These gut microbes powerfully influence gut homeostasis and diseases including CIPO. Gut constitutes a second genome to regulate human health and disease. With over one hundred trillion of microbial cells in symbiotic relationship with the host (and the gut), they modulates GI physiology, nutrition and immune function, metabolism, thus affecting the overall health and diseases of the human body. GI microbial composition, metabolic activity and diversity get changed in such GI disorders as IBD (inflammatory bowel disease), CD

(celiac disease), IBS (irritable bowel syndrome), CIPO, weight loss and overweight etc. Exacerbations of CIPO are detected following bacterial or viral infections, psychic stresses or malnutrition -all these being assumed to be related to intestinal microbes. Moreover, SIBO is invariably seen in gut dilatation and slow peristaltic movement of CIPO patients. A changed gut flora can lead to gut epithelial barrier malfunctions, immune disorders, and dysmotility. FMT (Fecal Microbial Transplant) is now used as diagnostic and therapeutic tools, where fecal material from a healthy subject is administered to dysbiotic patients to restore gut microbiota. After about eight weeks of FMT, a symptomatic relief from pain and bloating is being seen in CIPO patients.[4,32]

An important vital aspect of CIPO management is to treat and inhibit SIBO principally by antibiotics. GI fermentation can be halted or lessened by provision of a diet low in lactose and fiber, and courses of antimicrobials to control microbial overgrowth. The most commonly used antimicrobials are those that are either not absorbed or very poorly absorbed ones, e.g., rifaximin and aminoglycosides (e.g., neomycin, and streptomycin), as well as metronidazole, doxycycline, and norfloxacin, amoxicillin clavulanate, etc. Fluoroquinolones (e.g., ciprofloxacin), nitroimidazole antimicrobials (e.g., metronidazole), amoxicillin-clavulanate and tetracyclines (e.g., doxycycline) etc., are the agents most often employed to improve distressing abdominal pain and distension. However, the most current approved agent is rifaximin (a semisythetic rifamycin based nonsystemic broad spectrum gut sterilizer), that causes non-traditional effects on the gut microbes in addition to its bactericidal and bacteriostatic activity, resulting in reduced microbial resistance than the previously used traditional agents. Rifaximin causes a positive modulation of intestinal microbes, that favors the beneficial bacterial growth without hampering overall microbial composition. Rifaximin revamps SIBO-related symptoms and the breath test findings. Finally, not of least significane, FMT has currently been suggested as a new therapeutic option. FMT is being found to cause substantial improvement in relieving pain and bloating symptoms plus curing of SIBO in about 71% of patients by two weeks.[3, 4, 22]
Fecal bacterial transplantation (FBT) /Fecal Microbiota Transplant (FMT) / Fecal transplantation/Bacteriotherapy.

It is collecting feces (stool/poop), from healthy donors and transferring them into a patient's GI tract, either by colonoscopy, endoscopy, sigmoidoscopy, or enema etc, both in children and adults. The procedure can control Clostridium difficile infection called (CDI) by adding healthy bacteria into the recipient's intestines. This restores healthy bacteria (normal gut flora) in the lower intestine, restoring the balance of the gut microbiome, that aids in controlling C. difficile infection, and even preventing its re-infection. It is found to be more effective than antibacterials for controlling and preventing C. difficile. Thence, it may be regarded as a super-antibacterial or super-antibiotic therapy. C. difficile infection (CDI) can cause serious lethal bacterial infection/superinfection (pseudomembranous colitis) in the colon. FMT substantially alleviates patients' abdominal pain and distention, increasing the tolerance for enteral nutrition, and preventing and treating SIBO, emphasizing as a new direction in CIPO treatment. [4,5]

## Surgery for CIPO

Excepting for some selected cases, surgery should be avoided, as surgery increases adhesions and can lessen the absorbent surface area of the gut, and it is quite unsuccessful to resolve the pathology. Nutritional support needs to be ensured without delay in undernourished and malnourished patients and in those who are losing weight and not getting sufficient nutrition with only oral food. Enteral nutrition is the initial step of choice. Initially naso-enteric feeding is attempted before a permanent enteric feeding tube placement. An optimal composition and rate of the formula are determined. If small gut function is severely jeopardized, parenteral nutrition need to be instituted. In selected cases, intestinal transplantation may be performed, when 5-year mortality rate is about 30%.[4,5,36]

**Treatment of acute intestinal obstruction**
It is highly important to assess, evaluate and sustain the stability of the milieu interior. Surgical intervention needs to be minimized, since surgery can interfere with gut motility, and even causing gut failure. However, CIPO patients associated with Hirschsprung's colonic aganglionosis as are at risk of developing colonic volvulus needs timely surgical treatment.[3, 5]

**Gastrointestinal decompression**
Enemas (by polyethylene glycol, glycerin), NG (nasogastric) aspiration, SI (small intestinal) tube aspiration, alimentary endoscopies, and intended operative fistulation are optional decompressive treatment strategies. Colonoscopic decompression is found successful in the preoperative treatment of CIPO affected pregnant women. Percutaneous endoscopic gastrojejunostomy can completely relieve pressure, and can cause abdominal pain relief. It is also used for good nutritional support in CIPO patients. Still, there is some controversy as regards to the timing of decompression by enterostomies in CIPO patients.[3, 33]

**Small gut/multi-visceral transplantation**
Small gut transplantation for CIPO constitues about 9% of all small gut transplantations. The survival rates of small gut transplantation is not unsatisfactory. Moreover, the infection and opportunistic complication rates are almost similar in CIPO and non-CIPO small gut transplantation. It is now accepted that for CIPO patients with small gut failure and for potential lethal complications of TPN, small gut transplantation is a better treatment option that can revamp long-term survival and prognosis. If other organs for transplantation are involved, such multi-visceral transplantation as stomach–duodenum–pancreas–small intestine transplantation, or combined liver and intestine transplantation is advised. As, this type of operation is very difficult and much traumatic, and needs more complicated postoperative management, this sort of treatment is approved only in experienced transplantation team in designated centers.[3, 34]

**Specific treatment for autoimmune inflammatory CIPO**
IV methylprednisolone or immunoglobulins needs to be used as the first-line treatment followed by azathioprine, cyclosporine, or rituximab as second-line treatments in patients with autoimmune/inflammatory CIPO. Immunosuppressive agents can

inhibit the inflammatory and immune reactions in the myenteric ganglion or neuromuscular tract, thus may be used in neuropathic/myopathic CIPO. However, owing to absence of evidence-based data, this type of treatment nedds to be employed cautiously.[4,35]

**Treatment of secondary CIPO**

Like all other diseases, treatment needs essentially to be addressed to the underlying aetiology and pathogenesis. E.g., enzyme replacement ttherapy can relieve GI features of x-linked genetic CIPO subjects of Anderson–Fabry disease (a group of lysosomal storage diseases). Thus, the main and specific treatment is directed to the underlying pathology.That is the primary disease of the secondary CIPO needs to be actively addressed and treated. Several such diseases as Hirschsprung's disease, mitochondrial neuro-gastro-intestinal encephalomyopathy (MNGIE), or some paraneoplastic syndromes have been found to be associated with CIPO. In these situations, the management and prognosis are clearly and strongly linked with those of the associated primary disease processes. In the rest cases, CIPO seems "primary" or "idiopathic," but two subgroups as found among these "primary" or "idiopathic," are: (a). Sporadic autoimmune inflammatory CIPO that results from a sporadic abnormal autoimmune inflammatory response in neural or muscular structures of the gut, and, (b). Genetic CIPO where an inherited or de novo mutation causes the faulty functions of the gut muscle, neural, or any other cell. The early diagnosis of these two subgroups of primary CIPO is very much essential, because autoimmune inflammatory CIPOs are expected to get benefitted from immunosuppressive therapy, and genetic CIPOs are expected to get benefitted from a more elaborate exact explanation of the causative pathogenesis, genetic counseling, and expectedly, in coming days from gene therapy.[3,4,25]

**Allogeneic hematopoietic stem cell transplantation**

This allogeneic hematopoietic stem cell transplantation treatment causes substantial improvement of CIPO symptoms having prolonged mitochondrial neurogastrointestinal encephalomyopathy, but it is not effective in patients of CIPO with intestinal failure.[4,34]

## Prognosis

Despite its rareness, CIPO is a serious health issue, because of severe and almost permanent impairment of QOL and many of the sufferers need lifelong parenteral nutrition and, in serious cases, intestinal transplantation. There are often a delayed diagnosis and a high mortality for these patients. The long-term prognosis of CIPO patients is not good. Small gut myopathies, esophageal implication, insufficient response to nutritional therapy, intestinal malrotation, urinary retention , and gut motor instability during fasting are poor prognostic indicators. About 10%–25% CIPO affected children may die before attainment of adulthood. Oral feeding and parenteral nutrition in combination can expectedly revamp survival rates. Successful oral feeding per se is an independent and isolated indictor of long-term survival.[11,21]

## Conclusion

Though CIPO is an uncommon clinical syndrome affecting especially the small gut function featured by abnormal gut motility and peristalsis, simulating intestinal obstruction, it is essential to exclude a mechanical gut obstruction. The incidence of misdiagnosis is rampant, despite meticulous inquiry into the history and cautious physical examinations. Clinician's lack of judgement is an important cause of high incidence of misdiagnosis. Once the organic etiology is excluded, the probability of CIPO should be contemplated. The principal stages for diagnosis of CIPO include (1) identification of primary causative diseases to provide benefit from specific treatment; (2) detection of sporadic inflammatory CIPOs to provide benefit from immunosuppressive treatment; and (3) detection of genetic CIPOs to provide benefit from genetic counseling and, expectedly, in the future from gene therapy. Greater vigilance and awareness, avoidance unwanted surgeries, and full thickness biopsies at an early and potentially curable stage of the disease are advised. Now, it is well known that the symbiotic and mutualistic composition of gut microbes has a significant role in the pathogenesis of gut motility disorders. Despite much research-work, there are limited data regarding gut microbes, ENS, IES and ECCs in CIPO patients. Aberrations in neurotransmitter signaling pathways, that are integrated by change of gut microbes or their products, are strongly thought to cause gut motility disorders in CIPO patients. Further studies aiming at evaluating any probable interaction between gut microbes and factors linked to intestinal motility can help physicians to better realization of the CIPO pathology, explaining the CIPO microbial biomarkers, as well as innovating new therapeutic aims, and revamping the management and treatment strategies for these patients.[3,4,33]

## Recommendations

More and more researches are recommended to evaluate the diagnostic field, with special attention to the indications for full thickness gut biopsies for idiopathic CIPOs. Genetic tests would definitely be worthwhile for better characterization of the motor disorders in cases of genetic CIPOs. Genetic tests can unfold a vista to have new tools for earlier diagnosis and to provide targeted genetic therapy for this rare heterogeneous clinical syndrome.[5]

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