Paradigm on Chronic Constipation: Pathophysiology, Diagnostic, and Recent Therapy

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ABSTRACT

Chronic constipation is a medical gastrointestinal problem which can degrade patient's quality of life. So far, the shifting pathophysiologic mechanism to colonic neuropathology has not been supported by diagnostic facility and therapy. Target therapy for chronic constipation related to enteric nervous system is still limited to study. Currently, the discovery of neurotrophin-3 has not shown any significant development needed in daily clinical practice. Until now study related to endoscopic full-thickness biopsy has not been done in human and waiting for its applications in daily practice. Targeted therapy for chronic constipation which is related to enteric nervous system is still limited to study. The discovery of neurotrophin-3, although currently on clinical trial phase II, still not showing any significant contribution in daily clinical practice.

New pathophysiologic mechanism shifting the 'idiopathic' paradigm or 'functional' to colonic neuropathology has not been met with diagnostic modalities and therapy based on this knowledge. Study regarding endoscopic full-thickness biopsy to help revealing this novel mechanism has not been done in human. Henceforth, until now applied studies pertinent to this subject are longing in order for enteric neuron etiology can be firmly established Thus, in the future, translational study is demandingly needed for a firm establishment of diagnostic and therapeutic modalities to its currently evolving pathophysiology.

Keywords: *chronic constipation, colon, enteric nervous system, neurotophin-3*

ABSTRAK

Konstipasi kronis adalah masalah gastrointestinal yang dapat menurunkan kualitas hidup pasien secara bermakna. Sampai saat ini, pergeseran patofisiologi menjadi neuropatologi kolon belum didukung sarana dan prasarana diagnostik dan terapi yang memadai. Target terapi konstipasi kronis yang berhubungan dengan persarafan enterik masih terbatas di ranah penelitian. Baru-baru ini, penemuan neurotrophin-3 belum menunjukkan perkembangan signifikan yang dibutuhkan untuk praktek klinis sehari-hari.

Mekanisme patofisiologis saat ini menunjukkan pergeseran paradigma dari idiopatik atau fungsional menuju neuropatologi kolon yang belum bersesuaian dengan modalitas diagnostik dan terapi yang tersedia. Studi menggunakan biopsi usus untuk membantu membuktikan adanya mekanisme patologis ini belum dilakukan pada manusia. Oleh karena itu masih banyak penelitian terkait topik ini perlu dilakukan untuk membangun landasan dasar patofisiologi yang kokoh akan adanya etiopatologi neuron enterik. Untuk kedepannya, penelitian translasional dibutuhkan untuk meningkatkan modalitas diagnostik dan terapeutik berdasarkan patofisiologi ini.

Kata kunci: *konstipasi kronis, kolon, persarafan enterik, neurotophin-3*

INTRODUCTION

Constipation is a medical gastrointestinal problem experienced virtually by everyone.[1] Tack et al, stated that most people will experience constipation at least once in their lifetime.[2] It is estimated that 2–27% of world population experienced constipation depends on the definition being used. Based on self-reporting, the prevalence of constipation is around 12%.[2] Around 10–20% population report one or more symptoms of constipation.[3] The prevalence of constipation vary geographically.[4-6] Constipation is a common complaint found in our daily practice. It can lower the quality of life of the patient.[6,7] Diagnosis and treatment that is established sometimes is not appropriate due to the attending physician's lack of knowledge in when to consider a case as constipation. Data gathering regarding the incidence of constipation is sometimes ambiguous, between patient's report (subjective) and the diagnosis based on Rome III criteria.[8]

Less satisfactory knowledge regarding the pathophysiology of chronic constipation is another problem in treating the patients. Up to now, chronic constipation not caused by mechanical etiology (e.g. colorectal tumor, stricture, anal fissure, intussusceptions) is considered solely as a functional or idiopathic problem without considering it as a wider entity, comprising problems in enteric nervous system. This causes the constipation experienced by the patient not further analyzed in daily clinical practice. In a literature study by Bassotti et al, it was stated that enteric glial cell (EGC) constantly played role in constipation.[9] They also firmly stated that the paradigm constipation as idiopathic problems has to be discarded, and chronic constipation has to be considered as neurogliophatic problem (glial nervous system). That statement further should be an input in therapeutic choice in chronic constipation in the future.

This article focus on reviewing chronic constipation seen from the latest pathophysiology, diagnosis based on international clinical criteria (Rome III) and national consensus from Indonesian Society of Gastroenterology (ISG),[6] and choice of therapy based on the latest evidence. It is aimed that this article can ignite research,especially translational research, particularly regarding the relationship between chronic constipation and diagnostic method as well as novel therapeutic choice, thus the treatment of chronic constipation will be more optimum in the future.

PATHOPHYSIOLOGY: A REVIEW ON THE ROLE OF ENTERIC NERVOUS SYSTEM

According to Rome III criteria, chronic constipation is defined as constipation that has persisted for more than 3 months, with onset of six months before the diagnosis is established.[6,8,10] Chronic constipation can be caused by several factors that might be mechanic, metabolic, neuropathic, myopathic and idiopathic (functional).[10] The mechanical cause can easily be detected through colonoscopy with findings such as tumor, colon stricture, anal fissure and intussusceptions. Metabolic cause such as: hypothyroidism, diabetes mellitus, hypercalcaemia, hypokalemia, and uremia might need further testing band etiologic diagnosis is established based on hypothesis.

Enteric nervous system dysfunction has never been considered as etiology of chronic constipation in daily clinical practice.[9] In the conditions in which no mechanical and metabolic etiology can be identified, the etiologic diagnosis will be averted to functional or idiopathic. Just like irritable bowel syndrome (IBS) which symptom is predominated by constipation, other possible causes of chronic functional constipation will not be further considered. Thus the diagnosis and therapy administered will be the same in every condition without further evaluation.

Recently, advance research has found the organic cause of various alimentary tract abnormalities that is previously considered as functional. Although the role of functional and psychosomatic cannot be undermined in these disorders, these organic findings in cases such as inflammatory bowel syndrome (IBS) and esophageal achalasia have shifted the paradigm in the field of gastroenterology and provide novel and more holistic therapeutic consideration in treating these diseases. Combination between functional and organic therapy as well as surgery has become the best choice in various gastrointestinal abnormalities.

Chronic constipation is one of the gastrointestinal problems with such shifting paradigm. During the 90-s chronic constipation without mechanical cause has always been considered as functional or often considered as metabolic problem, however, studies from the last twenty years has proven that there is involvement of neurologic mechanism. Bassottiet al, summarized the evidence of nervous system (ENS) involvementas well as neurochemical imbalance in the colon.[9] Additionally, other researchers also found the decreasing amount of intra ganglionic neuro filament, hypoganglionism in myenteric plexus and decreasing amount of interstitial cells of Cajal

(ICC) in constipation cases, although there are still disagreements between the available studies.

The complex pathophysiology of constipation is aided by the availability of colonic specimens from various types of constipation that is obtained through surgery or endoscopy.[9,11] From those various specimens it is known that there are several ENS abnormality in all type of chronic constipations. From various types of constipations, slow transit constipation (STC) is one of the most scrutinized constipation because of its persistent nature to various medical treatments and often requires surgical treatment. In STC is known that there is a decreasing number of enteric neuron and ICC that is important for colonic motility.[9] In another Basotti's writing, it is stated that neuropathologic abnormality is not limited to colon but also in terminal ileum and this condition also cause chronic constipation.[12]

ENS abnormality has been proven in many studies as the etiology of chronic functional constipation.[9] Further investigation showed that decreasing number of neuron was only found in sub mucosal plexus, while EGC lost could be found in the sub mucosal and myenteric plexus. The role of ICC apparently remained controversial, as Bassotti stated in his other report.[13] The role of ICC and EGC was significant in constipation cases caused by colonic diverticular disease.[9,14] Based on these studies, it could be concluded that the role of ENS differed in various causes of constipation. However, we could firmly state that ENS played important role in all chronic functional constipation cases.

Studies on ENS in chronic constipation still continue in various publications. However, not many researchers give attention to colonic neuropathology and its role in chronic constipation. Thus, opinions and findings only come from few researchers; among them is Bassotti who has published plenty of literature studies and reports in this field. In several of his publications, Bassotti stressed on the role of EGC in the incidence of chronic constipation.[9,12-14]

EGC represented the population of enteric ganglionic cells with the ratio of four to one compared to neuron. EGC itself has special mechanical function in colonic motility, participating in neurotransmission, promoting communication between synapses in enteric neuron, keeping homeostasis function of enteric neuron, keeping the immunity function and playing role in colonic inflammation process. Loss of EGC might decrease the motility and prolong the colonic transit. The role of EGC is very vital that several literatures consider EGC as pacemaker of colonic motility.

Loss of EGC plays role in the incidence of degeneration of enteric neuron population. Thus, based on Bassotti hypothesis, idiopathic phenomenon is not idiopathic but excessive apoptotic process of enteric neuron that causes chronic constipation in a patient. Many causes of this increasing apoptosis need to be studied further. Thus cellular, molecular, or pharmacological intervention can be done to the patient. Up to now, infections, inflammation, aging and xenobiotic are considered as the most important cause of apoptosis in cell's life. Whether these causes also apply in the enteric neuron, still need to be studied further.

Bassotti et al, also tried to show the role of infection and colonic normal flora in the apoptosis of enteric neuron.[9] In studies done by Sechi et al, it was stated that there was role of *Mycobacterium avium* and expression of prion in enteric neuron cell.[15] Chronic infection cause destruction and increase of apoptosis in those cells. Other studies showed the role of colonic normal flora in ENS plasticity.[16] Other factors suspected to play role is aging, a factor seen in daily clinical practice where plenty of geriatric populations experience chronic constipation, inappropriate use of laxative and chromosomal abnormality (genetic etiology).[9,17] The relationship between aging process with chronic constipation has been proven by several researchers and has been published in various scientific papers.[17-19] The relationship between normal colonic flora with ENS is the scientific basis why probiotic is used as therapy in chronic constipation.[20,21]

From several recent studies, it has been known that the chronic and excessive use of laxative can initiate heavy inertia in the colon. This inertia might decrease the amount and volume of ICC and ENS.[22] This can lead to chronic constipation that is hard to treat with various medical treatments. In the future, this can be proven with preclinical studies (and later clinical trial) using per-endoscopic colonic biopsy with special technique (full-thickness biopsy).[9,11]

Several studies are still being conducted to find the cause of increasing apoptosis of enteric neuron.[9,16] However, its relationship with chronic clinical constipation has not been totally proven. The bench to bedside evidences is still minimum to study constipation as a whole. Various studies only partly reveal information and facts, although every information is very important to conclude cellular theory regarding chronic constipation as a whole. For clinician in general, the relationship between cellular process, clinical symptoms, and (later) its utilization

in diagnostic method and treatment is of paramount importance as it might improve the medical service in patients with chronic constipation.

DIAGNOSIS: FROM CONVENTIONAL TO PROBABILITY IN THE FUTURE

There are two aspects need to be reviewed regarding diagnosis of chronic constipation. Those are diagnostic criteria and infrastructure required to investigate the etiology. The Rome criteria have been used for a long time to establish the diagnosis of constipation. The term chronic is used if the constipation has occurred for 3 month and its onset started six months before the diagnosis has been established. Currently the Rome criteria that is employed is Rome III, released in 2006.[10] Below is the Rome III criteria being used to establish the diagnosis of constipation.

Table 1. Rome III criteria for the diagnosis of constipation[10]

Has to fulfill two of the following symptoms:
Straining during at least 25% of defecations
Lumpy or hard stools in at least 25% of defecations
Sensation of incomplete evacuation for at least 25% of defecations
Sensation of anorectalobstruction/blockage for at least 25% of defecations
Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
Fewer than three defecations per week
Loose stools are rarely present without the use of laxatives
Insufficient criteria for irritable bowel syndrome
Recurrent stomach-ache or uncomfortable feeling for at least three days in a month, related to two or more of these acute symptoms:
Relieve with defecation
Onset associated with a change in frequency of stool
Onset associated with a change in form (appearance) of stool

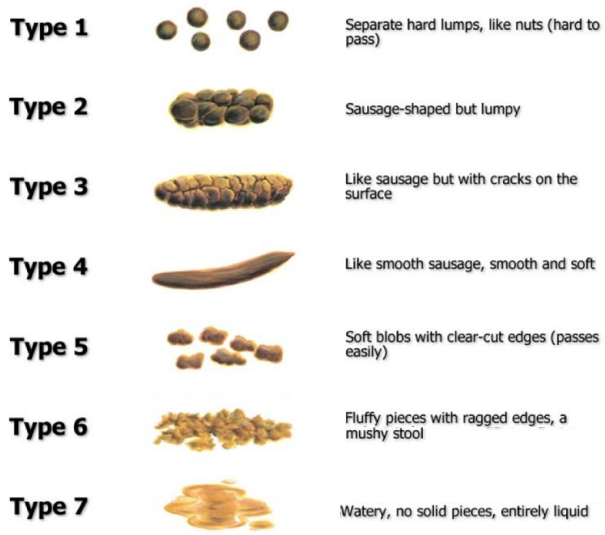

Figure 1. Bristol stool chart[29]

All points in Rome III criteria are the result from patients' complaints which means the data comes from patient's memory recall. Although these criteria also put recall bias into consideration, incorrect memory recall might still happen during patients' interview. It is not easy to remember 25% of defecations experience.

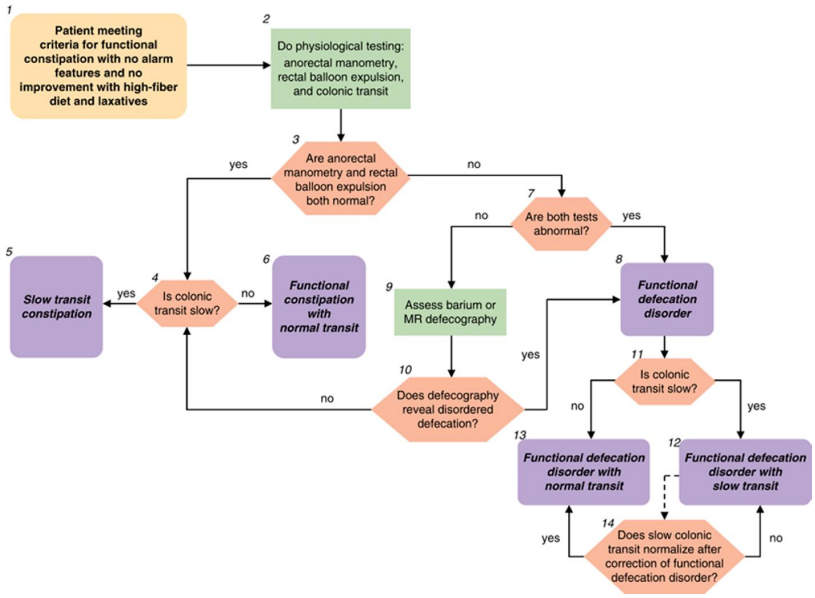

Figure 2. Diagnostic guide for chronic constipation[23]

This criterion is often used to diagnose functional or idiopathic constipation. For more specific diagnosis of constipation, for example due to mechanical cause, normally other symptoms,such as stomachache, blood stool or vomiting occur . On the other hand, in cases of constipation due to metabolic causes, metabolic abnormality such as diabetes, hypothiroid, uremia and electrolit imbalance has to occur first. Drug induced constipation need to be suspected if during interview long-term use of drugs is found.

In national concencus, it states the role of Rome III criteria in diagnosing constipation. As alarm sign and symptoms, we have to be aware of the existence of hematoschezia, abdominal mass, familial history of IBD and colonic cancer, weight loss, anorexia, persistent vomiting and anemia. The consensus also states several physical examination associated with constipation, such as: (1) vital signs and nutritional status; (2) complete abdominal examination to evaluate presence of abdominal mass, abdominal distension, signs of acute abdomen, and bowel sounds; (3) digital rectal examination to assess the condition of sphincter ani, existence of hemorrhoid, rectal prolapses.[6]

Stool evaluation is important in estimating the colon transit time. The evaluation tool that is commonly employed is bristol stool chart that shows several fecal consistencies. The following picture shows bristol stool chart. Patients are asked which of these stools is his within the last one week.

After data collection through thorough history taking and physical examination, especially when alarm signs and symptoms present, additional testing might be done. Some additional tests were including laboratory examination (peripheral blood examination, electrolyte, blood glucose level, thyroid function test and fecal analysis), imaging (plain abdominal X-ray, barium enema and CT colonography), colonoscopy, colorectal physiologic test, colonic transit test, anorectalmanometry, defecography and balon expulsion test.[6,8,10] Although quite advanced, tests mentioned above can only evaluate fecal transit time in the colon and cannot surely establish the etiologic diagnosis of functional chronic constipation.

The combination of history taking (including the Rome III criteria), physical examination, and conventional supportive test allow clinicians to diagnose chronic constipation as well as its etiology. Supportive test to assess the colon physiology and transit time might direct the physician to diagnose functional constipation as slow transit constipation or normal transit constipation.[23] The chart below, created by American College of Gastroenterology (ACG), guides the diagnosis of chronic constipation.

Regarding the shift of paradigm from functional and idiopathic etiology to enteric nervous system etiology, we are expecting other diagnostic method which can be used. However, methods that are superior to colonoscopy in finding the etiology of constipation have not been available in many research and literature study. Absent of tumor, polyp or intussusceptions will only guide the diagnosis to functional or idiopathic constipation. Physiology test and colorectal transit time will only differ the colon transit time (whether it's normal or slow). Apparently, we need to do further research to prove nervous system inflammation, as well as other various process occurring at the cellular or molecular levelto prove the role of ENS and neuron apoptosis as the cause of chronic constipation.

One of the few studies succeeded in analyzing neuropathology in the colon is study by Neunlist et al.[24] This study, for the first time, demonstrated the endoscopic full-thickness biopsy (eFTB) in pigs to see the amount of myenteric plexus and neuromuscular transmission in the pig's colon with immunohystochemistry stain. The ability to see the colonic nervous system that consists of myenteric plexus, muscular proper, ganglion and myenteric neuron as a whole give hope for clinical trial to find out the role of ENS in every case of chronic constipation.[24]

Two years after Neunlist et al published their work, Fritscher-Ravens et alfound that feasibility, safety, as well as wound recovery in eFTB technique is excellent in pigs' colon (with sample of 30 pigs, more than sample used by Neunlist of 6 pigs) thus Neunlist hope of applying this method in human comes closer to manifest.[25] The investigation for enteric nervous system etiology in constipation cases is hoped to be followed by findings in target therapy for constipation with enteric nervous system etiology.[9]

THERAPY: IMPLICATION TO PARADIGM SHIFT

As we have already known, the therapies for chronic constipation consist of various pharmacologic and non-pharmacologic treatments. In non-pharmacologic treatment, patients are advised to change their lifestyle, educations are given to increase fiber and fluid intake (30-50 cc/KgBW/day for normal person), increase the consumption of probiotic (*Bifidobacteria animalislactis* DN-173, for example Activia^{R}), increase physical activity, avoid holding stool and routinely defecate.[6]

Pharmacologic therapies are divided into bulk laxative (psyllium, methylcellulose), osmotic laxative (lactulose, stool softener), rectal enema (bisakodil, phosphate enema) and lubricant (CIC-2 chloride canal activator). Other pharmacologictherapies than laxative contain prokinetic agent (metocloparimde, domperidone). In patients with slow transit constipation, combination of stimulant laxative and prokinetic shows very good result, if combined with adequate non-pharmacologic therapy. These empirical therapies have to be evaluated within 2-4 weeks. If no improvement occurs, further investigation is warranted. Therapy for underlying diseases with surgery might be done in constipation with mechanical etiology. This surgery is also indicated for functional constipation resistant to various medication.[26,27]

Other than standard therapies that are often given in daily clinical practice (e.g. lactulose, bisacodyl or polyethylen glycol (PEG)), there are several drugs that has been studied within the last ten years. Linaclotide is one of the drugs that has been widely published recently. This agent is guanilatecyclase receptor agonist type C that stimulates secretion of chloride and bicarbonate through increasing cGMP.[28] Linactolide was proven to increase transit time in ascending colon, soften the stool consistency, and thus, decrease straining during defecation.[29] Linactolide has entered phase III clinical trial and is known to be useful in constipation, predominantly in IBS cases and chronic constipation.[28]

Besides linaclotide, velusetrag and tegaserod have been studied in various clinical trials and show good efficacy as chronic constipation therapy. The existence of velusetrag is to lessen the side effect of tegaserod such as cardiovascular and stroke. Both are serotonin receptor agonist, in which velusetrag is more specific to 5-HT_4 compared to tegaserode. Both are prokinetic agent to upper or lower digestive tractand can be used in patients with colon dismotility that manifest as chronic constipation.[30]

Based on latest data, apparently 'functional' paradigm shift to enteric nervous system has not yet been able to shift the conventional therapeutic choice being used in daily clinical practice. These three novel drugs for chronic constipation (mentioned above: linactolide, tegaserod and velusetrag) do not fully treat the enteric neuron apoptosis. Targeted therapy that has been mentioned several times in the pathophysiology review is still on research and development. One of the drugs is neurotrophin-3.

Neurotrophin-3 stimulates the growth and function of the enteric nervous system as well as colon transit time. In phase II clinical trial with placebo control, injection of neurotrophin-3 three times a week significantly increases the frequency of spontaneous movement in colon. This agent also improves other parameter of chronic constipation. However, as the development of this agent is not optimum, it is still not widely indicated in patients with chronic constipation.[29] Other than study by Parkman et al published in 2003, no other development regarding this drug is available. Up to now, this agent is not yet marketed or approved for chronic constipation.[31]

If the theory of normal flora related to the prevention of infection and nurture the amount and volume of enteric neuron is true, then therapy with pharmacobiotic is the direct implication of this theory. The theory itself has been used by researchers and clinicians in gastroenterology field; that the gut normal flora is very important in the wellbeing of enteric system. In various appraisals regarding latest pharmacotherapy for chronic constipation, therapy with probiotic is frequently mentioned. Normal flora proven to improve constipation by shortening colon transit time is *Bifidobacteria lactis*. Other strain, *Bifidobacteria infantis* is also proven to improve fecal profile (based on Bristol stool chart) and decrease straining during defecation.[29]

CONCLUSION

Novel pathophysiologic mechanism that shifts the 'idiopathic' paradigm or 'functional' to colonic neuropathology has not been met with diagnostic infrastructure and therapy based on this knowledge. Research regarding endoscopic full-thickness biopsy has not been done in human. Until now this still wait for application thus in the future enteric neuron etiology can be firmly established. Targeted therapy for chronic constipation that is related to enteric nervous system is still limited to research. The discovery of neurotrophin-3, although has reached clinical trial phase II, up until now has not shown any development that is significant in term of daily clinical practice. Therapy, whether its old or novel, for chronic constipation is still not based on enteric nervous system. In the future, translational research that is related to this topic has to be increased thus target based medical therapy choice is wider than before and surgery become the last modality in chronic constipation cases.

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