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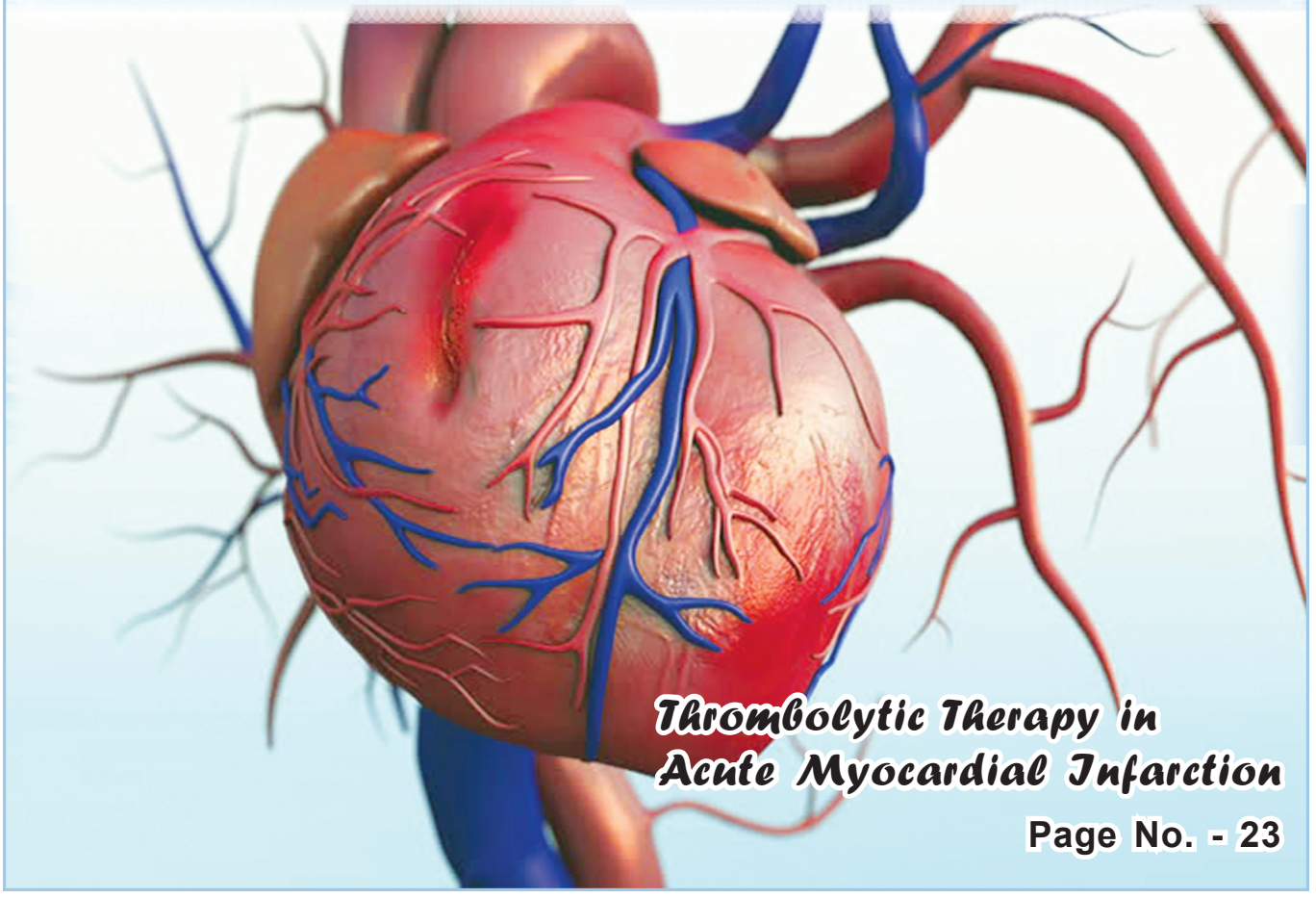

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GENERAL

Methylcobalamin in Diabetic Neuropathy

SANJAY AGRAWAL, NITA SHARMA DAS

Introduction

Insulin is a hormone secreted from pancreatic β- cells to utilize glucose (the smaller unit of edible carbohydrate) and provides energy to every body cells for perform cellular functioning. Diabetes is a condition in which blood glucose level is significantly higher (hyperglycemia) than the normal range. Impaired functioning of insulin is primarily responsible for this disease development.[1] Chronic and progressive diabetic condition impairs overall physiological condition by damaging blood vessels, heart, kidney, nerves and eyes. The involved pathophysiology of diabetes mainly develops either due to impaired pancreatic β- cells functioning leads to insufficient insulin synthesis or body unable to utilize produced insulin properly. According to WHO estimation, globally four hundred twenty two million adults have diabetes in 2014. This value is almost four times greater than the estimated diabetes incidence in 1980.[2] Type1 and type 2 and gestational diabetes are three broad categorization of diabetes. Among these three types, gestational diabetes is not a prolonged condition, as it develops during pregnancy and after child birth, blood glucose level become normalized. However, sometimes gestational diabetes an indication of type 2 diabetes, which may develop in future. Type 1 diabetes is an auto-immune disorder, in which body's own immune system destroys pancreatic β- cells and insulin synthesis is reduced. Type 1 diabetes is a inherited condition and can occur at any age.[1] The exact etiology of type 1 diabetes is unknown.[3] Type 2 diabetes usually develops in middle aged people and is the most common form. The hyperglycemic condition in type 2 diabetes can develop either due to insufficient insulin synthesis, or body unable to utilize insulin properly. Both insulin insufficiency and insulin resistance along with hyperglycemia are characteristic features of type 2 diabetes.[4]

One of the most common complications of diabetes is diabetic neuropathy. Diabetic neuropathy is a peripheral nervous system dysfunction associated with diabetes. Broadly diabetic neuropathy is classified into two groups - symmetric and asymmetric diabetic neuropathy. Beside this, diabetic polyneuropathy is one of the clinical classification of symmetric diabetic neuropathy.[5] Metformin is widely used anti-diabetic medicine, which accumulates in the body. Prolonged consumption of this medicine leads to vitamin B12 deficiency and considered as one of the most common cause of Diabetic neuropathy.[6]

Vitamin B12 is a water soluble vitamin and has significant role in blood cells production, DNA synthesis and normal functioning of nerves. Vitamin B 12 analogs is participating in different essential metabolic functioning, including fatty acids production, DNA synthesis and its regulation and production of energy.[7] The deficiency of vitamin B12 causes different diseases like pernicious anemia, neurological damage etc.[8] Different dietary nutrients contain vitamin B12 analogs, but except Methylcobalamin, none of the vitamin B12 analogs are readily absorbable in the intestine. In addition, Methylcobalamin is an active form and directly increases the bioavailability of vitamin B12. Healthcare experts expect systemic or oral administration of Methylcobalamin supplementation can provide better treatment opportunity in nervous system related conditions.[7]

In this article we broadly discuss why we should concern about diabetic neuropathy at very early stage and role of Methylcobalamin in the control and treatment of the diabetic neuropathy.

Prevalence and Difficulties of Diabetic Neuropathy

Almost 60 percent of diabetic patients suffering from diabetic neuropathy[9] and face several associated disabilities, including foot ulceration, gait disturbance, leg amputation, and fall-related injury.[6] Diabetic neuropathy affected patients have five times greater risk of falling. The consequences of this, leads to difficulty to move of the injured joint, restricted mobility, evasion of daily activity, hospitalization and mortality. These consequences not only provide physical harm, but also negatively affect patient's psychology, as patient may have behavioral issues like patient is too afraid to go outside or even move inside the house alone, due to fear of falls. It is noticeable that

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most of the diabetic neuropathy patients face problem in balance impairment at the median lateral plane during upright or downright of the staircase and one of the major risks of fall down. Gait disturbance or balancing problem associated with diabetic neuropathy is associated with sensory and motor nerve dysfunctionalities which cause lack of sensation during motion and coordination difficulty during movement. Postural hypotention is also another contributory factor for falling. Diabetic neuropathy also has higher risk to burn during cooking or other activities due to lack of sensory nerve perception. Sometimes delayed wound healing and infection of the injured area may require amputation. Therefore, diabetic neuropathy hampers patient's quality of life. Researchers also assumed that cardiac autonomic neuropathy and renal failure in diabetic patients also have a correlation with diabetic neuropathy and albuminuria.[9]

Besides the above mentioned problems, almost 10 percent diabetic neuropathy patients often faced persistent pain symptom. The characteristic features of the painful diabetic neuropathy include severe, unmovable, impulsive or spontaneous pain, which mainly worsens at night. Patients complain burning sensation, pin pricking like symptoms. The nature of the pain includes shooting, cramping, jabbing, sharp aching and tingling sensation with feeling of cold. Depending upon the affected nerve fibers, the symptoms may vary, like small fibers neuropathy leads to paresthesia, along with pain symptoms, which may be associated with insulin therapy.

Classification of Diabetic Neuropathy

Broadly painful diabetic neuropathy is classified as Acute sensory type neuropathy and chronic sensorimotor neuropathy. Acute diabetic neuropathy pain usually occurs in hyperglycemic condition and after normalization of glucose level in blood the condition becomes less. Neuropathic cachexia is an outcome of acute diabetic neuropathy pain, which mainly occurs in male patients and affected individuals have sudden weight loss and depression. Whereas, chronic diabetic neuropathy pain is a classic painful diabetic neuropathy, which may last for several months to year and often leads to with tolerance or drug addiction. Gradual reduction of nerve fibers density is remarkable in diabetic neuropathy.[5, 10]

Causes of Diabetic Neuropathy

Hyperglycemia or uncontrolled diabetic condition is a primary cause of diabetic neuropathy. But obesity, hypertension, hyperlipidemia, alcohol consumption and cigarette smoking are also associated with diabetic neuropathy.[10]

Pathophysiology of Diabetic Neuropathy

Hyperglycemic condition in diabetes due to poor blood glucose management alters different metabolic pathways. The result of this leads to intracellular protein glycation enhancement, the higher concentration of glucose in nerve and vascular tissue, vasoconstriction and increased thickening of the basement membrane of the blood vessels. Both intracellular protein glycation enhancement and higher concentration of glucose in nerve and vascular tissue damage nerve tissues by increasing oxidative stress, as reactive oxygen species (ROS) triggers the synthesis of advanced glycation end products. In addition, impaired blood supply to nerve tissues due to vasoconstriction and increased thickening of the basement membrane, damages nerves.[10] Different therapeutic and life style managements are recommended for treating diabetic neuropathy, but none of these can completely cure this problem. [11]

Correlation of Vitamin B12 Deficiency and Diabetic Neuropathy

It has been found that elderly patients have more risk to develop diabetic neuropathy due to age related loss of nerve functioning.[12] But the compromised metabolic condition with increasing of age also causes vitamin B12 deficiency. It is estimated that 30 percent diabetic patient above 40 years aged diagnosed with vitamin B12 deficiency induced neuropathy.[13] But apart from age factor, Metformin, the anti-diabetic medicine also a leading cause of vitamin B12 deficiency in diabetic patients and risk increasing factor for developing Diabetic Neuropathy in any age group. World health organization already recommended screening for B12 deficiency in diabetic population, as early detection is treatable and restored Vitamin B12 level may prevent Vitamin B12 deficiency related diabetic neuropathy.[14]

Metformin is an oral hypoglycemic agent and most frequently recommended anti-diabetic agent. Globally almost 120 million diabetic patients regularly consume Metformin. several study report suggested prolonged use of Metformin is the leading cause of vitamin B12 deficiency, as dosage and duration of Metformin therapy inversely affect serum vitamin B12 level. It is expected that Metformin may reduce calcium dependent vitamin 12 absorption, especially in type

2 diabetic patients.[13] Because Metformin competes with calcium for binding to receptors present in the mucosal cell membrane. Thus, unavailability of calcium due to presence of Metformin in the gut wall leads to decrease absorption and bioavailability of Vitamin B12, as Vitamin B12 absorption is a calcium dependent process.[15] A cross-sectional study result also concluded that prolonged Metformin treatment with co-administration of acid blocker increase the risk of vitamin B12 deficiency. Experts also suggested that Vitamin B12 supplementation with Metformin therapy can prevent vitamin B12 deficiency in diabetic patients.[13]

Methylcobalamin and Its Role in Diabetic Neuropathy

Vitamin B12 is alternatively known as cobalamin; cyanocobalamin, methylcobalamin, hydroxy-cobalamin, and adenosylcobalamin are analogs of vitamin B12.[7] Our body is unable to use Vitamin B12 and therefore Vitamin B12 analogs are taking primary role in different metabolic functioning of the body. They are important contributors in fatty acid synthesis, DNA production and also take part in energy production and regulation. Among the four vitamin B12 analogs, Methylcobalamin is an active and readily absorbable in the body. In protien methylation cycle, Methylcobalamin is a coenzyme of methionine synthase and takes part in methionine formation.[7]

A clinical trial conducted with Type 2 diabetic patients concluded that supplementation of vitamin B12 along with folic acid and vitamin B6 can delay the onset of diabetes. [16] Both systemic and oral administration of Methylcobalamin can increase the bioavailability of the Vitamin B12.[8] Healthcare experts expect that this benefit of Methylcobalamin can be therapeutically successful to treat or prevent nervous system related conditions.[7]

How Methylcobalamin acts Against Diabetic Neuropathy?

The basic pathophysiology of diabetic neuropathy is associated with nerve damage and the result of this leads to impaired nerve conduction. Apart from controlling hyperglycemia and life style management, one of the primary therapeutic approach is in diabetic neuropathy management is nerve regeneration and improved nerve conduction.[5,6]

The possible mechanism of action of Methylcobalamin is obtained from different in vitro, in vivo, pre-clinical and clinical studies, which support Methylcobalamin can alter pathophysiology of the diabetic neuropathy:

- Animal study data showed that Methylcobalamin in a high dose effective to regenerate motor nerve fibers and also to improve nerve conduction. Thus, high dose of Methylcobalamin treatment will be able to alter pathophysiology of the diabetic neuropathy.[17]
- Methylcobalamin also inhibits discharge of ectopic nerve impulsions from injured primary sensory neurons.[7]
- Methylcobalamin also able to repair the oxidative stress-induced nerve cell damage and impaired protein kinase C nerve signaling pathway.[18]
- Sufficient dose of Methylcobalamin increases methylation and activates Akt ERK1/2 and AKT signals. Increased activation of Akt ERK1/2 and AKT signals cause nerve regeneration and functional recovery.[19]
- Methylcobalamin increases protein synthesis by up-regulation of gene transcription.[20]
- Clinical trial data suggest treatment with Methylcobalamin can improve the symptoms of diabetic neuropathy; possibly through regeneration of motor nerve fibers and gradually also improve nerve conduction.[17]

Methycobalamin acts as an analgesic in Painful Diabetic Neuropathy

Pain management is another therapeutic challenge in painful diabetic neuropathy. The intensity of pain and other symptoms of Diabetic neuropathy can vary from patient to patient. Analgesics, NSAIDs (non–steroidal anti–inflammatory drugs), antidepressants, and anticonvulsants are different classes of medication used for the purpose of Neuropathic pain management . But most of the commonly used drugs increase the side effect burden. For example, opioid analgesics, non–steroidal anti–inflammatory drugs may provide addictive effect and other drugs like duloxetine cause withdrawal symptoms.[5]

Vitamin B12 has analgesic property, as it increase the effectiveness and availability of noradrenaline and 5-hydroxytryptamine at the site of pain, which inhibits nociceptive system.[21] Methylcobalamin as an analog of vitamin B12 assists the regeneration of nerves and has inhibitory effect against ectopic spontaneous discharges. But apart from these, following evidences support that Methylcobalamin can assist to reduce Diabetic neuropathy related pain symptom.

- Methycobalamin is effective in improving Diabetic neuropathy related pain, burning sensation, paraesthesia and heaviness of the limb. Different clinical trial reports showed Methycobalamin alone or in combination with others has potent analgesic effect and effectively reduces Diabetic neuropathy pain symptom and other associated symptoms.[7]
- Oral dose of Methycobalamin and pregabalin combination therapy for two weeks treatment can reduce a significant pain score. This combination is also well tolerated by patient.[22] It has been also noticed that nerve conduction also improved in Diabetic neuropathy patients during different Methycobalamin trial period.[21]
- Epalrestat is an aldose reductase inhibitor and used in treatment of Diabetic neuropathy. Clinical study showed combination therapy of Epalrestat and Methycobalamin is better than Epalrestat alone in the treatment of Diabetic neuropathy.[23]
- Electrophysiologic techniques applied to measure the symptomatic relief of the patients who underevent different therapeutic approaches to control the diabetic neuropathy. A clinical trial finding support that pure Methylcobalamin intervention in diabetic neuropathy patient improves the electrophysiologic results, which indicates symptoms get better.[24]

Methylcobalamin is safe for treating diabetic neuropathy patients with renal impairment

Diabetes is a chronic condition and gradually small blood vessels present in kidney become damaged.[25] Moreover, diabetes increases the functioning load of the kidneys.[26] Chronic diabetes reduces kidney functioning.[27] These factors increase the incidence of diabetes associated kidney failure. Therefore, renal failure is quite a common complication in diabetes and most of the drugs are restricted for them. Because drug cannot be completely eliminated from the body and the accumulated drug increases the side effect-risk. Methycobalamin is a good treatment option for diabetic neuropathy patients with kidney problem. A small scale clinical trial showed intravenous administration of methycobalamin treatment potentially provides benefits in diabetic neuropathy with chronic hemodialysis patients. This study also conclude that Methycobalamin treatment is safe for patients with impaired renal functioning.[28]

Critical evaluation of Methylcobalamin efficacy in comparing with other cobalamin supplements in Diabetic Neuropathy

Cyanocobalamin, Methyl-cobalamin and Hydroxocobalamin are the three therapeutic analogues of vitamin B12. It is quite a common finding that lack of detailed knowledge about the different cobalamin substrates, general people often thought that the all the cobalamins are synonymous. But different studies showed that the efficacy of Methylcobalamin is better than other cobalamin analogs.

Hydroxocobalamin is bioactive form; but cannot be given orally and Hydroxocobalamin injections are painful.[29] A clinical review report showed that among other vitamin B 12 analogs, methylcobalamin is best to treat vitamin B12 deficiency. After oral administration of methylcobalamin, significant amount of this active component is available in the blood in comparison with cyanocobalamine.[30, 31]

Cyanocobalamin cannot produce any health benefits of vitamin B12 until it converts to Methylcobalamin. In human body, the Cyanocobalamin is initially inactive; but in mitochondria, methylmalonyl Co-A mutase converts Cyanocobalamin to Methylcobalamin by replacing its cyanide group with a methyl group. Therefore, it is clear that cyanide is released in this metabolic reaction, which can get accumulated in the body.[7] Liver and kidney are two major organs involve in cyanide elimination from the body. Rhodanese enzyme present in liver and kidney takes part in cyanide metabolism and converts it to thiocyanate, which is excreted in the urine.[32]

Both liver disease and kidney problems are associated with diabetes.[33] Therefore, total excretion of cyanide from the system is doubtful in diabetic patients. In addition, subchronic cyanide poisoning can cause neurologic lesions and provides sensory spinal ataxia, nerve deafness, bilateral optic atrophy, weakness of legs, and numbness of feet,[32] which can also aggravate diabetic neuropathy symptoms.[5] Therefore, Cyanocobalamin is not at all suitable for diabetic patients as a supplement of vitamin B12.

Cyanocobalamin containing products usually have 0.14 mg average daily dose. But in some products the amount of daily dose of Cyanocobalamin can increase up to 1 mg. It has been also analyzed that in the gastrointestinal tract, almost 2 percent of total Cyanocobalamin dose converts to cyanide.[34] Therefore, the increased dose of Cyanocobalamin has a great risk of increased cyanide concentration in the body. Usually

this risk is increased in case of kidney failure patient or smokers, though healthy people eliminate this little amount of cyanide from their system. But most of the time, people prefer to Cyanocobalamin formulation because of its lower cost.[35]

Dose of Methylcobalamin

According to Food and Nutrition Board (FNB) the Recommended Dietary Allowance (RDA) of vitamin B12 for adult is 2.4 mcg.[36] Most of the healthcare professionals recommended oral dose of co-enzyme supplements is above 1,000 µg/day.[37] But the usual prescribed oral dose of Mecobalamin is 500 mcg to 1000 mcg per day, depending upon the patient's age and symptom.[38] In case of individuals with vitamin B12 malabsorption problem can be benefitted by oral intake of Methylcobalamin with 1,500 µg/ day dose.[39]

Conclusion

All the above mentioned information supported that Methylcobalamin alone or in combination with other drugs is more promising therapeutic regimen than other vitamin B12 analogue in diabetic neuropathy treatment. In this discussion, we represent efficacy and safety profile of Methylcobalamin in diabetic neuropathy treatment based on different available preclinical and clinical study evidences. It is well known that Methylcobalamin assists in regeneration of nerve tissue, improve electrophysiological measures, inhibits ectopic nerve discharge and improves the symptoms of diabetic neuropathy. This mechanism of action may showcase the potency of Methylcobalamin to challenge different analgesics and other synthetic drugs available in the market for treating diabetic neuropathy. But more detail and long-term clinical trial will be required to establish Methylcobalamin as a prospective nutraceutical in diabetic neuropathy treatment for future generation.

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ANNOUNCEMENT

We are happy to announce to our Readers that we are going to re-introduce soon the page **"Correspondence"** in our journal "The Antiseptic", in which we will publish the questions of readers with answers to the same by the specialists of respective field of medicine and surgery.

Readers are intimated that they may send their questions to the following address.

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Readers may also send their questions to us through email **admin@theantiseptic.in**

GENERAL

Types of Hepatitis

SANJAY AGRAWAL

Hepatitis B virus (HBV) is a small, circular and partially double-stranded deoxyribonucleic acid (DNA) virus in the Hepadnaviridae family. Hepatitis refers inflammation of liver cells and finally getting damage to the liver. The functions of liver include detoxifying the blood, storing vitamins and producing hormones. Hepatitis can disrupt these processes and create severe health problems throughout the human body. There are many causes. Heavy alcohol use, toxins, some medications, and certain medical conditions can also be caused hepatitis. However, hepatitis is most often caused by a virus. The liver is a vital organ that processes nutrients, filters the blood, and fights infections. When the liver is damaged, its function can be affected. The most common types of viral hepatitis are Hepatitis A, Hepatitis B and Hepatitis C. Hepatitis A can last from a few weeks to several months. Hepatitis B can range from a mild illness, lasting few weeks to a serious life long or chronic condition. Hepatitis C also can range from a mild illness, lasting few weeks, to a serious life long infection. Most people who get infected develop chronic Hepatitis C.

Hepatitis A is spread when a person ingests fecal matter even in microscopic amounts from contact with objects, food or drinks contaminated by feces or stool from an infected person.

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Hepatitis B spreads when blood, semen, or certain other body fluids from a person infected with the Hepatitis B virus even in microscopic amounts enters the body of someone who is not infected. The Hepatitis B virus can also be transmitted from birth to an infected mother; sex with an infected person; sharing equipment that has been contaminated with blood from an infected person, like tools of needles, syringes, medical equipment such as glucose monitors; sharing personal items such as toothbrushes or razors.

Hepatitis C is spread when blood from a person infected with the Hepatitis C virus even in microscopic amounts enters the body of someone who is not infected. This can happen through multiple ways of sharing equipment that has been contaminated with blood from an infected person, such as needles and syringes. There is no vaccine available for Hepatitis C. About 75 per cent to 85 per cent of people who get infected with the Hepatitis C virus develop a chronic infection; 5 per cent to 20 per cent of people with chronic Hepatitis C develop cirrhosis; and 1per cent to 5 per cent will die from cirrhosis or liver cancer, according to report.

Many people with hepatitis do not have symptoms and do not know they are infected. If symptoms occur with an acute infection, they can appear anytime from 2 weeks to 6 months after exposure. Symptoms of hepatitis can include: fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, grey coloured stools, joint pain and jaundice.

At least five viruses can cause hepatitis disease from these the three common are hepatitis viruses A, B and C. Each is caused by a different virus. All three types can be acute, lasting for 6 months or less, and types B and C can be chronic, lasting for longer. Each type has different characteristics and is transmitted in different ways, but symptoms tend to be more or less similar.

India has intermediate endemicity of Hepatitis B, with Hepatitis B surface antigen (HBsAg) prevalence between 2 per cent and 7 per cent among populations studied. The prevalence does not vary significantly by region in the country. The number of HBsAg carriers in India has been estimated to be over 40 million (4 crore). It has been estimated that, in India of the 25 million infants born every year, over one million run the lifetime risk of developing chronic HBV infection. Every year over 100,000 Indians die due to illnesses related to HBV infection, according to report.

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The rare finding of colonic interposition between the liver and the right hemidiaphragm (chilaiditi sign) may present as a syndrome with mild to severe gastrointestinal symptoms including abdominal pain, constipation, bowel obstruction, volvulus or even ischemic bowel.

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