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Conditions and Diseases that Cause Vitamin B_{12} Deficiency: Form Metabolism to Diseases

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Introduction

Although vitamin B_{12} (cobalamin) was isolated almost 60 years ago, its metabolism remains incompletely defined. In practice, cobalamin metabolism is complex and requires many processes and steps, any one of which, if not present, may lead to vitamin B_{12} deficiency [1,2]. The Figure 1 describes through a synthetic view the different stages of vitamin B_{12} metabolism used in clinical practice and the corresponding etiologies of cobalamin deficiency [3,4].

For the Practitioner, it should be noted that the clinical manifestations of vitamin B_{12} deficiency are very numerous, polymorphic, sometimes frustrating, of chronic evolution, or on the contrary severe, of acute revelation (Table 1) [3,4]. The present review summarizes the current knowledge on vitamin B_{12} metabolism and metabolic pathways in a clinical perspective, with a focus on the etiologies of cobalamin deficiency, especially in adult.

Vitamin B_{12} ingestion and related disorders.

Vitamin B_{12} sources and dietary recommendations.

Vitamin B_{12} is produced exclusively by microbial synthesis in the digestive tract of animals. Therefore, animal products are the main sources of cobalamin in the human diet, in particular organ meats (liver, kidney) [2-4]. Other good sources are fish, eggs and dairy products. In foods, hydroxo - methyl- and 5-deoxyadenosyl-cobalamins are the main cobalamins present. A typical Western diet contributes 3–30 µg of cobalamin per day. The Food and Nutrition Board of the US Institute of Medicine recommends dietary allowance (RAD) of 2.4 µg per day for adults and 2.6 to 2.8 µg per day during pregnancy [5]. The RDA did not distinguish between adults and elderly people though it is questionable whether an intake of 2.4 µg per day can maintain cobalamin status in elderly people with often poor nutrition (malnutrition, in quality and quantity), malabsorption or maldigestion.

Malnutrition, Vegetarianism and Veganism

Vitamin B_{12} deficiency caused by limited intake of vitamin dietary sources (which requires any animal product intake) is rare, even exceptional, in general population [6,7]. Malnutrition of cobalamin concerns especially vegans and more rarely vegetarians not supplemented by pharmacological vitamin intakes. These nutritional practices, particularly veganism this is currently fashionable in industrialized countries to purge the body and mind, especially among working people in their early 30s and in "up to date" people.

Dietary causes of cobalamin deficiency are common in elderly people who are already malnourished, such as elderly frailty patients in psychiatric hospitals [6] or those living in institutions who may consume inadequate amounts of vitamin B_{12} containing foods. However, an inadequate intake is not the only explanation for the common cobalamin deficiency in elderly population. Food-cobalamin malabsorption is a significant participating factor in elderly people [6]. Studies focusing on elderly people, particularly those who are in institutions or who are sick and malnourished have suggested a vitamin B_{12} deficiency prevalence of 30–40% (defined as low vitamin B_{12} blood level) [6,8]. In this setting, the Framingham study demonstrated a prevalence of 12% among elderly people living in the community [9]. Using stringent definition (presence of clinical and/or biological signs of cobalamin deficiency), we found that vitamin B_{12} deficiency had a prevalence of 5% in a group of patients (mean age of the patient: 72 years) followed or hospitalized in a tertiary reference hospital in France [3].

In practice, the diagnosis of malnutrition, vegetarianism or veganism is based on patient interview and a comprehensive dietary survey (at least 1 week).

Food-Cobalamin Digestion

Physiology of cobalamin absorption

Dietary cobalamin, which is bound to proteins in food, is released in the acidic environment of the stomach where it is rapidly complexed to the binding protein and transporter haptocorrin (HC), also referred to as the R-binder or trans cobalamin I (Figure 1) [1,10]. About 80% of circulating vitamin B_{12} are bound to HC and serum cobalamin levels show positive correlation to serum HC concentrations.

Although some unexplained low serum cobalamin concentrations were reported to be caused by mild to severe HC deficiencies, these abnormalities were not accompanied by clinical manifestations of cobalamin deficiency [11,12].

Cobalamin continues its route in the gastrointestinal track and dissociates from HC under the action of pancreatic proteases, followed by its association in the intestine with the intrinsic factor (also known as the S-binder) which is essential for ideal absorption of cobalamin (Figure 1) [1,10]. The intestinal absorption of cobalamin into the enterocytes takes place in the terminal ileum via intrinsic factor receptor cubing. The amount of acid secretion in the gastrointestinal tract plays a critical role in binding of cobalamin to its transporting proteins.

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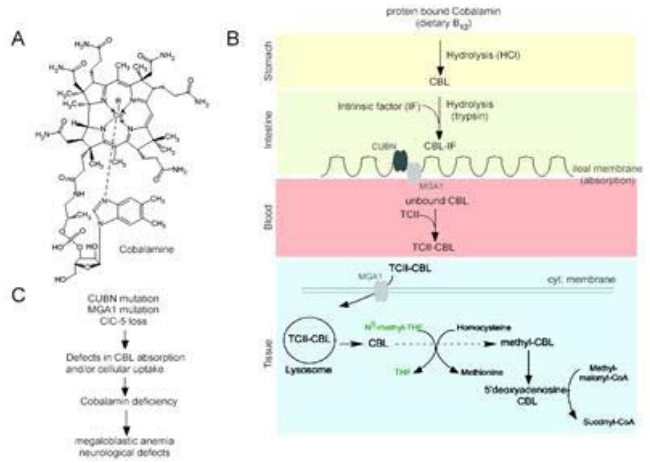

Figure 1: (A); Structure of vitamin B_{12}, (B); Various steps of vitamin B_{12} (cobalamin [cbl]) metabolism.

Indeed, homozygous nonsense and missense mutations in the gene encoding the gastric intrinsic factor GIF were reported to cause hereditary juvenile cobalamin deficiency [13]. This metabolism step is also implicated in the physiopathology of the so called Bireme's disease (see the next section) [1].

Food-cobalamin malabsorption

Food-cobalamin malabsorption (FCM) is a syndrome characterized by the inability of the body to release cobalamin from food or intestinal transport proteins ("maldigestion"), particularly in the presence of hypochlorohydria (Figure 1) [14,15]. Ralph Carmel first characterizes FCM in cases of subtle cobalamin deficiencies [15]. In our experience, this syndrome accounted for 60 to 70% of cases of mild to severe vitamin B_{12} deficiency in elderly patients [16]. The principal characteristics of this syndrome are listed in Table 2. FCM is caused primarily by atrophic gastritis [14]. Other factors that contribute to FCM are: chronic infection with Helicobacter pylori and intestinal microbial proliferation, situations in which cobalamin deficiency can be corrected by antibiotic treatment [14,17]; long-term ingestion of anti-acid agents such as H_2-receptor antagonists and proton-pump inhibitors (e.g., omeprazole, pantoprazole, esomeprazole, etc.), particularly among patients with Zollinger-Ellison syndrome (gastronome) [18], and long term intake of biguanides (metformin) [19,20]. In addition, other FCM inducers include: chronic alcoholism, especially in malnourished patients; surgery or gastric reconstruction (e.g., bypass surgery for obesity, partial gastrectomy for benign gastric tumor or malignant gastric tumors, etc.); partial exocrine pancreatic failure (e.g., chronic alcohol intake, cystic fibrosis, etc.); and rarely Soren's syndrome and systemic sclerosis or HIV [14].

It is to note that in case of FCM, patients can absorb "unbound" cobalamin through intrinsic factor or passive diffusion mechanisms [10,14]. Thus the recognition of the syndrome permits new developments of oral cobalamin therapy using free crystalized cobalamin that is readily absorbed [21]. In practice, the diagnosis of FCM is to date based on the exclusion of the main others causes of vitamin B_{12} deficiency, in connection with the fact that the Schilling's test is no longer currently available [4]. Health care providers need to be aware of FCM, since it is easy to treat and treatment can prevent serious late consequences of vitamin B_{12} deficiency.

Vitamin B_{12} Absorption

Physiology

Absorption depends mainly on intrinsic factor (IF), which is secreted by the gastric mucosa. IF binds cobalamin forming a complex that is absorbed by the terminal ileum (Figure 1) [1,10]. This mechanism is responsible for at least 60% absorption on oral cobalamin [1]. This complex is located at the apical side of brush-border membranes (BBMs) of polarized epithelia, such as the intestinal apical BBM.

It consists of the intrinsic factor-vitamin B_{12} receptor named cubing, a 460 kDa peripheral membrane glycoprotein, encoded by the CUBN gene which was mapped to chromosomal region 10p12.33-p13 [22], and the 48 kDa amnion less (AMN) protein encoded by the AMN gene, a gene localized on human chromosome 14 [23]. In this setting, the human mega in /gp330/LRP-2 receptor, encoded by the LRP-2 gene located on chromosome 2q24-q31 [24], may play an important role in the stability of the cubing /AMN complex [10,25-29]. It is noteworthy that the interaction of these factors is $Ca+^{2}$ dependent [26-29].

Cubing and megalin are also expressed in the apical side of proximal kidney tube and are considered responsible for cobalamin reuptake into the circulation [10].

Table 1: Main clinical features of cobalamin deficiency [2,3,6,14].

Hematological manifestations	Neuro–psychiatric manifestations	Digestive manifestations	Other manifestations
Frequent: macrocytosis, neutrophil hyperseg– mentation, aregenera– tive macrocytary anemia, medullar mega– Loblastosis (''blue spinal cord'')	Frequent: polyneuritis (especially sensitive), ataxia, Babinski's phe– nomenon (especially sensitive), ataxia, Babinski's phe– nomenon	Classic: Hunter's glossi–tis, jaundice, LDH and bilirubin elevation (''intramedullary destruction'')	Frequent: Tiredness, loss of appetite Under study: atrophy of the vaginal mucosa and the vaginal mucosa and chronic vaginal and urinary infections (especially mycosis), hypofer– tility and repeated miscarriages, venous thromboembolic dis–ease, angina (hyperhomocysteinemia)
Rare: isolated thrombo–cytopenia and neutro–penia, pancytopenia	Classic: combined sclerosis of the spinal cord Rare: isolated thrombo– cytopenia and neutro–penia, pancytopenia	Debatable: abdominal pain, dyspepsia, nausea,vomiting, diarrhea, dis–functioning	
Very rare: hemolytic anemia, thrombotic microangiopathy (pre– sence of schistocytes)	Under study: changes in the higher functions, dementia, stroke and atherosclerosis (hyper– homocysteinemia), par– kinsonian syndromes, depression, multiple sclerosis	Rare: resistant and recurring mucocuta– neous ulcers	

Table 2: Food-cobalamin malabsorption syndrome [14].

Criteria for food-cobalamin malabsorption
Low serum cobalamin (vitamin B_{12}) levels
Normal results of Schilling test using free cyanocobalamin labeled with cobalt-58 or abnormal results of derived Schilling test ‡
No anti-intrinsic factor antibodies
No dietary cobalamin deficiency
Presence of an associated conditions or agents (*e.g.*, atrophic gastritis, *Helicobacter pylori* infection, partial gastrectomy, gastric by-pass, pancreatic insufficiency (alcohol abuse), intestinal bacterial overgrowth, long term anti-acid agents (proton-pump inhibitors) or biguanides (metformin) intake

‡ Derived Schilling tests use food-bound cobalamin (e.g., egg yolk, chicken and fish proteins)

Table 3: Biermer's or Addison's disease [1,30,32].

Criteria for Biermer's disease (pernicious anemia)
Low serum cobalamin (Vitamin B_{12}) levels
Abnormal results of Schilling test using free cyanocobalamin labeled with cobalt 58 ‡
Presence of anti-intrinsic factor antibodies (sensibility of 50%, specificity >98%)
Presence of an auto-immune gastritis (especially fundal), with absence of Helicobacter pylori in the status phase of the disease
Associated conditions: auto-immune disorders (*e.g.*, Sjögren's syndrome, Hashimoto's disease, type 1 diabetes mellitus, and celiac disease)
Predisposition of gastric cancer

‡Schilling test is not used anymore in clinical practice.

Biermer's or addison's disease

In adults, vitamin B_{12} deficiency is classically caused by Biermer's also named Addison's disease, formerly known as "pernicious anemia" [30,31]. This disorder is an auto-immune disease characterized by: the destruction of the gastric mucosa, especially fundal, associated with a primarily cell-mediated auto-immune process; and the presence of various antibodies, especially anti-intrinsic factor antibodies and gastric parietal anti-cell antibodies that target the H+/K+ ATPase α and ß subunits [30,31]. Pernicious anemia has a genetic component [30].

In this context, pernicious anemia is associated with other immunologic diseases such as Soren's syndrome, Hashimoto's disease, type 1 diabetes mellitus, and celiac disease [30,32]. In our experience, Biermer's disease accounted for 30 to 40% of cases of cobalamin deficiency in adults, and more than 60% in severe vitamin B_{12} deficiencies [4]. In this later situation, hematological (e.g. macrocytic anemia) or psycho-neurological manifestations (e.g. medullar combined sclerosis) are commonly observed [32].

In practice, the diagnosis of Biermer's or Addison's disease is based on the presence of intrinsic factor antibodies in serum (specificity > 98% and sensitivity around 50%) or biopsy-proven autoimmune atrophic gastritis (Table 3) [1,30]. The presence of Helicobacter pylori infection in gastric biopsies is an exclusion factor.

It is important to note that of Biermer's disease require a long term gastric follow-up (upper-endoscopy with biopsies, every year in case of gastric lesions or every 2 to 5 years in the absence of detectable lesion), because this disorder favors the emergence of various cancers of the stomach [1,4].

Cobalamin malabsorption

Since the 1980s, the prevalence of vitamin B_{12} malabsorption declined, owing mainly to the decreasing frequency of gastrectomy (due to the provision of antacid drugs) and terminal small intestine surgical resection [4,10].

However, several disorders commonly seen in gastroenterology practice might, to date, be associated with cobalamin malabsorption [10]. These disorders include: exocrine pancreas' function deficiency following chronic pancreatitis (usually alcoholic), lymphomas or tuberculosis (of the intestine), celiac disease, Crohn's disease, Whipple's disease, and uncommon celiac disease [4].

In practice, the diagnosis is based on patient interview (personal surgical history), a full clinical examination and digestive explorations in doubt.

Genetic Disorders of Cobalamin Malabsorption

In this setting, the Imerslund-Gräsbeck syndrome or megaloblastic anemia due to selective cobalamin malabsorption with proteinuria is a vitamin B_{12} deficiency leading to megaloblastic anemia in childhood and is corrected by parenteral administration of vitamin B_{12} [10,34-38]. This pathology is mainly localized in Finland, Norway and the Mediterranean Muslim countries. The disease was described around 1960 simultaneously by Olga Imerslund, a Norwegian pediatrician and Ralph Gräsbeck, a Finnish physician-biochemist [33]. Other manifestations of the disease include stature-weight loss, frequent infections and neurological signs. Proteinuria without kidney damage is present in half of the patients. Abnormalities of the urinary tract are sometimes observed.

Mutations in CUBN were reported to cause hereditary megaloblastic anemia 1 (MGA1), a rare autosomal recessive disorder affecting human subjects with neurological symptoms and juvenile megaloblastic anemia [34-36]. Two principal mutations were identified in Finnish patients (FM), a 3916C→T missense mutation named FM1 changing a highly conserved proline to leucine (P1297L) in CUB domain 8, suggesting that this proline is functionally crucial in cubilin, and one point mutation (FM2) in the intron interrupting CUB domain 6 responsible for in-frame insertions producing truncated cubilin [10,35]. Other mutations were also uncovered but were subsequently identified as polymorphisms after their detection in normal individuals in the general population. The cubilin P1297L mutation associated with hereditary MGA1 was reported to cause impaired recognition of the cobalamin-IF complex by cubilin [36]. Moreover, mutation in AMN was reported in recessive hereditary MGA1 [10,36] and hence was demonstrated to be crucial for a functional cobalamin-IF receptor [10]. This study demonstrated that homozygous mutations affecting exons 1-4 of the human AMN gene translated into selective malabsorption of vitamin B_{12}, a phenotype associated with hereditary MGA1. Another study reported AMN

Table 4: Definitions of cobalamin (Vitamin B_{12}) deficiency [3,4,6,10,14].

Serum cobalamin levels <150 pmol/l and clinical features and/or hematological anomalies related to cobalamin deficiency.
Serum cobalamin levels <150 pmol/l (<200 pg/ml) on two separate occasions.
Serum cobalamin levels <150 pmol/l and total serum homocysteine levels >13 mmol/l or methyl–malonic acid levels >0.4 mmol/l (in the absence of kidney failure or atheroma and of Methylene Tetra Hydro Folate Reductase (MTHFR) deficiency and in the absence of folate and vitamin B_6 deficiencies).
Low serum holotranscobalamin levels <35 pmol/l.

Table 5: Recommendations for oral vitamin B_{12} treatment [39].

	Pernicious anaemia	Intake deficiency and food-cobalamin malabsorption
Parenteral administration (intramuscular)	**Cyanocobalamin:**	**Cyanocobalamin:**
	1,000 µg *per* day for 1 week than 1,000 µg *per* week for 1 month than 1,000 µg *per* each month, for life (1,000 to 2,000 µg *per* day for at least 1 to 3 months in case of severe neurological manifestations)	1,000 µg *per* day for 1 week than 1,000 µg *per* week for 1 month than 1,000 µg *per* each 1 or 3 months, until the cobalamin deficiency cause is corrected (1,000 µg *per* day for at least 1 to 3 months in case of severe neurological manifestations)
Oral administration	**Cyanocobalamin:**	**Cyanocobalamin:**
	1,000 µg *per* day for life*	1,000 µg *per* day for 1 month than 125 to 1,000 µg *per* day, until the cobalamin deficiency cause is corrected*

*The effect of oral cobalamin treatment in patients presenting with severe neurological manifestations has not yet been adequately documented.

deletion mutants in dogs with selective intestinal malabsorption of cobalamin associated with urinary loss of low molecular weight protein reminiscent of the human Imerslund-Gräsbeck syndrome (IGS a.k.a. MGA1) [34,35]. The authors showed that these mutations in the AMN gene abrogated AMN expression and blocked cubilin processing and targeting to the apical membrane [37]. The essential AMN-cubilin interaction was recapitulated and validated in a heterologous cell-transfection model, hence explaining the molecular basis of intestinal cobalamin malabsorption syndrome [10,38].

Of particular interest for the practitioner in this section of malabsorption is the observation that about 1 to 5% of free vitamin B_{12} (or crystalline cobalamin) is absorbed along the entire intestine by passive diffusion [10]. This absorption explains the mechanism underlying oral cobalamin treatment of vitamin B_{12} deficiencies [39]. Our working group has developed an effective oral treatment for FCM [40] and pernicious anemia [41] using crystalline cobalamin (cyanocobalamin) (Table 5). Oral cobalamin has been proposed as a way of avoiding the discomfort, inconvenience and cost of monthly injections.

Cobalamin Transport to Blood and Tissues

Physiology

After vitamin B_{12} is absorbed at the BBM-blood barrier, it dissociates from the intrinsic factor and reaches the systemic circulation where it associates with Trans cobalamin II (TCII) (Figure 1) [1,10,38]. The kidney represents an essential organ were body vitamin B_{12} stores are maintained and studies demonstrated that the kidney regulates plasma vitamin B_{12} levels by maintaining a pool of unbound cobalamin that can be released in case of vitamin B_{12} deficiency [10,42]. The insular cobalamin-TCII complex uptake is achieved through megalin (LRP2), and trans cobalamin II receptor (TCII-R)-mediated endocytosis which plays a crucial role in cobalamin homeostasis [32,43].

Following cobalamin-TCII cellular uptake, TCII undergoes lysosomal digestion, which allows cobalamin separation from TCII and its cytoplasmic transfer. It has been estimated that there is a delay ranging from 5 and 10 years between the onset of cobalamin deficiency and the appearance of clinical manifestations, due to largehepatic stores (> 1.5 mg) and the enterohepatic cycle ensuring re-absorption of the vitamin in the gastrointestinal tract [1,10]. Also the reabsorption of TCII-bound cobalamin in the proximal tubules limits the loss of B_{12} in urine.

The average vitamin B_{12} content is approximately 1.0 mg in healthy adults, with 20-30 µg found in the kidneys, heart, spleen and brain. Estimates of total vitamin B_{12} body content for adults range from 0.6 to 3.9 mg with mean values of 2-3 mg. The normal range of vitamin B_{12} plasma concentrations is 150-750 pg/ml, with peak levels achieved 8-12 hours after ingestion of a single dose of the vitamin.

Part of the cobalamin serves as a cofactor for methionine synthase-mediated homocysteine catabolism into methionine and methyl tetrahydrofolate reductase (MTHFR)-mediated formation of the vitamin B_9 biologically active form, tetrahydrofolate, which is then involved in the synthesis of purines and pyrimidines (Figure 1) [10,44]. In clinical practice, several of these molecules are implicated in the definitions of vitamin B_{12} deficiency (Table 4). The other part of vitamin B_{12} is transferred to the mitochondria where it is transformed into adenosyl-B_{12}, an important cofactor in methylmalonyl-coenzyme a mutase-mediated formation of succinyl-CoA from methylmalonyl-CoA, the product of odd-chain fatty acid and some amino acid catabolism. Hence, cobalamin deficiency will cause homocysteine accumulation, increased methylmalonyl-CoA levels and decreased MTHFR activity. These changes are translated into several abnormalities including folate deficiency and subsequent inhibition of purines and pyrimidines formation essential for RNA and DNA synthesis [10,38].

Genetic Disorders of Cobalamin Transport

It is worth mentioning that TCII is responsible for the cellular uptake of B_{12} in most tissues and that TC deficiency is associated with severe megaloblastic anemia [45-48] and developmental disorders (see the review in [48]).

Impaired megalin function has not been associated with cobalamin deficiency so far; however inappropriate megalin signaling has been shown to cause deleterious effects as a consequence of cobalamin uptake inhibition in tissues. This was particularly the case where mutations in the human LRP2 gene encoding megalin were recently described to cause Donna -Barrow and facio-oculo-acoustico-renal syndromes. Patients affected with these rare autosomal recessive disorders display severe malformations with proteinuria [47].

The clinical manifestations of the metabolic abnormalities are hereditary megaloblastic anemia, neurological defects, malformations, increased cardiovascular thrombotic risk and renal disease, and methyl malonic acidemia [10,38,44]. Functional cobalamin deficiency can also be caused by defects in the intracellular processing of cobalamin such as abnormal lysosomal digestion of the TCII-cobalamin complex, and subsequent defective lysosomal release

of cobalamin, and abnormalities in intracytoplasmic cobalamin metabolism with all the consequences on biochemical reactions in which cobalamin acts as an important cofactor [10,44].

Conclusion

In this paper, we presented the main etiologies of vitamin B_{12} deficiency in relation to different steps of the cobalamin transport and metabolism. However to date, many causes of cobalamin deficiency remained unknown. These causes include mutations in genes encoding important proteins of the cobalamin transport or metabolic pathway. Moreover, many clinically diagnosed vitamin B_{12} deficiency remain unexplained and molecular tools aimed at targeting genes involved in vitamin B_{12} absorption and cellular uptake signaling pathways will pave the way for new therapeutic approaches to efficiently treat functional cobalamin deficiency.

Dietary vitamin B_{12} is absorbed in food bound to proteins and undergo acidic gastric digestion. The released cbl is attached to the R-binder haptocorrin and transported to the intestine following pancreatic proteases processing. The unbound cbl is then associated in the gut with the gastric-produced intrinsic factor (IF). This association is necessary for intestinal cbl absorption through a complex of endocytic receptors and proteins, including the endocytic receptor cubilin (CUBN) and the apical membrane protein amnion less (AMN), which is stabilized by two other proteins, namely the receptor megalin/LRP-2 and its binding protein receptor associated protein (RAP) which also binds to cubilin. After it absorption free cobalamin reaches the systemic circulation where it associates with Tran's cobalamin II (TCII) and subsequently the cbl-TCII complex is up taken in cells through it binding to megalin/LRP-2 and TCII receptor (TCII-R). Intracellularly, the complex is dissociated following lysosomal digestion. Part of cbl serves as a cofactor for the methionine synthase (MS) mediated transformation of homocysteine into methionine and for methyl-tetrahydrofolate reductase-mediated formation of tetrahydrofolate (THF) a precursor of purine and pyrimidine necessary for nucleic acid synthesis. The other fraction of cbl reaches the mitochondria where it forms adenosyl-cbl, a cofactor for the methyl-malonyl mutase-mediated catabolism of methyl-malonyl coA. (C): Mutations in genes encoding the intrinsic factor, cubilin, amnion less or Trans cobalamin II or its receptor provoke defects in cbl absorption and/or cellular uptake which translates into functional cbl deficiency and its clinical manifestations.

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