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Iron Profiles and Serum Vitamin B12 Levels

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Abstract:

Vitamin B12 and iron are essential micronutrients required for normal hematological function, neurological development, and cellular metabolism in children. Deficiencies in these nutrients are common worldwide, particularly in developing countries, due to nutritional and socioeconomic factors. Vitamin B12 deficiency is a major cause of macrocytic anemia and neurological impairment, while iron deficiency remains the most prevalent nutritional deficiency associated with anemia and impaired cognitive development. Endocrine disorders such as thyroid dysfunction and type 1 diabetes mellitus may further influence vitamin B12 and iron metabolism through autoimmune mechanisms, malabsorption, and altered physiological regulation. Early identification and assessment of serum vitamin B12 levels and iron profiles in pediatric populations are crucial to prevent long-term complications, including irreversible neurodevelopmental damage and hematological abnormalities.

Keywords: Vitamin B12, Iron deficiency, Iron profile, Pediatric patients, Anemia, Endocrine disorders, Thyroid dysfunction, Type 1 diabetes mellitus, Micronutrient deficiency, Neurodevelopment

Introduction:

Cobalamin, often known as vitamin B12, is a water-soluble vitamin founding in foods including dairy, eggs, and red meat. The synthesis of nucleic acids and proteins, in addition to the metabolism of carbohydrates and lipids, mitochondrial processes, erythroid serial development, and myelination of nerve fibers, are all significantly influenced by vitamin B12. A glycoprotein called intrinsic factor, produced by parietal cells in the stomach, is necessary to B12 absorption in the terminal ileum. After absorption, B12 is utilized as a cofactor by enzymes
that create DNA, fatty acids, and myelin. **(1)**

While vitamin B12 deficiency's the most common cause is malabsorption in developed countries, inadequate dietary intake of vitamin B12 is due to socioeconomic reasons in developing countries. Today, due to changes in lifestyle and eating habits, it has become a global problem and has become a common problem in children and young adults. Since vitamin B12 is important to cellular division and growth, its deficiency or prolonged borderline deficiencies can have adverse effects on physical growth and development of the nervous system in children. **(2)**

Vitamin B12 deficiency mostly causes anemia in children and complete recovery is observed with treatment. However, since vitamin B12 has an important role in the development of the nervous system, its long-term deficiency is known to cause permanent neurological damage. Briefly, Vitamin B12 deficiency is a common cause of macrocytic anemia and has been associated with a number of neuropsychiatric disorders. For this reason, early detection and early treatment of deficiency is extremely important especially for children in rapid growth periods such as infancy and adolescence. (**3)**

As B12 deficiency is a preventable cause of neurological morbidity, it becomes critical to determine the prevalence of B12 deficiency and to reveal the risk factors, especially in children in developing countries.

Especially determining risky periods according to gender and age groups and taking measures accordingly will eliminate the negative effects of deficiency in children. **(2)**

Pathophysiology of vitamin B12 deficiency

In healthy patients, dietary vitamin B12 binds to a protein called R-factor, which is secreted from salivary glands. Once the complex arrives at the small intestine, B12 is cleaved from R-factor by pancreatic enzymes, allowing it to bind to a glycoprotein called intrinsic factor, which is secreted by gastric parietal cells. The newly formed complex of B12 and intrinsic factor can then bind to receptors on the ileum, which allows for absorption of B12. Once absorbed, B12 is involved in metabolic pathways important in both neurologic and hematologic functions. If B12 cannot be absorbed, regardless of the etiology, many impairments may occur. **(4)**

Vitamin B12 is a cofactor for the enzyme methionine synthase, which is used in the conversion of homocysteine to methionine. As a byproduct of this reaction, methyltetrahydrofuran (methyl-THF) is converted to THF, which is converted to intermediates used in the synthesis of pyrimidine bases of deoxyribonucleic acid (DNA). In B12 deficiency, homocysteine cannot be converted to methionine, and thus, methyl-THF cannot be converted to THF. As a result, homocysteine levels accumulate, and pyrimidine bases cannot be formed, slowing down DNA synthesis and can cause megaloblastic anemia. The anemia then leads to symptoms such as fatigue and pallor that are commonly seen in patients with B12 deficiency. The impaired DNA synthesis causes problems for other rapidly proliferating cell lines, such as polymorphonuclear leukocytes (PMNs). Thus, B12 deficiency characteristically results in the formation of hypersegmented neutrophils. **(4)**

Vitamin B12 is also used as a cofactor for the enzyme methylmalonyl-CoA mutase, which converts methylmalonyl-CoA to succinyl-CoA. In patients with B12 deficiency, methylmalonic acid (MMA) levels will accumulate, as it cannot be converted to succinyl-CoA. A hypothesis states that elevated levels of MMA, along with elevated levels of homocysteine, contribute to myelin damage, accounting for the neurologic deficits, such as neuropathy and ataxia, seen in these patients. The damage to the myelin results in a condition known as subacute combined degeneration of the spinal cord (SCDSC). This condition affects various parts of the spinal cord, including the dorsal columns, the lateral corticospinal tracts, and the spinocerebellar tracts, resulting in a loss of proprioception, ataxia, the development of peripheral neuropathy, and dementia. **(5)**

Complications

Complications of the condition can be diverse and serious. Anemia may lead to heart failure if left untreated, while progressive neurological involvement can result in severe and disabling deficits. Patients also face an increased risk of developing gastric cancer, making long-term monitoring essential. In addition, the autoimmune nature of the disease predisposes individuals to other autoimmune disorders such as type 1 diabetes, myasthenia gravis, Hashimoto's disease, and rheumatoid arthritis. **(6)**

Iron Homeostasis and the Clinical Significance of Iron Deficiency in Early Childhood

Iron is an essential nutrient for the development of the fetus, infant, and child. The body's iron content is dependent on its intake and absorption with nutrition. The homeostasis of this nutrient is determined by the balance between its uptake and release from the cells where it is stored and recycled. Iron is released into the circulation, where it is carried by the plasma protein transferrin, into the duodenum by enterocytes that absorb dietary iron, and by macrophages which recycle senescent erythrocytes and liver reserves. **(7)**

If iron levels in the body are inadequate, its intestinal absorption is enhanced in case of excess, it is stored in the enterocytes as ferritin and the liver, spleen, and bone marrow as hemosiderin. The release of free iron ions in the plasma, essential for the maintenance of its homeostasis, is mediated by ferroportin, whose expression is subordinated to the activity of hepcidin. **(8)**

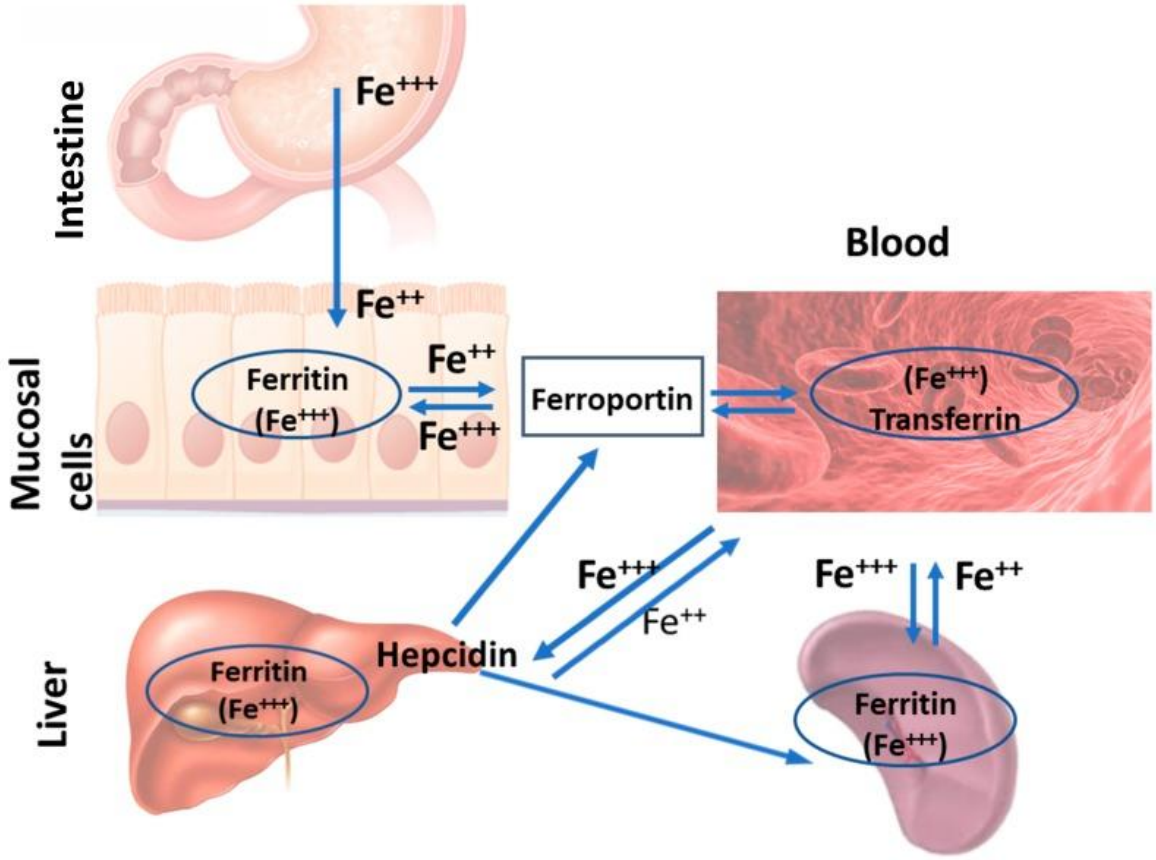


Figure (1) The main tissues involved in the regulation of systemic iron metabolism. **(9)**

Iron deficiency is one of the most common single-nutrient deficiencies in both developing and developed countries, peaks in prevalence between 1 and 3 years of age and is associated with poor long-term neurodevelopment which may be irreversible. In a report on the diagnosis and prevention of iron deficiency in children under 3 years of age, the American Academy of Pediatrics (AAP) recommends universal screening for anaemia, with measurement of haemoglobin (Hb) concentration and consideration of additional tests to assess iron status, specifically serum ferritin (SF) and C-reactive protein (CRP). Although there are no established decision limits derived from clinical studies of outcomes, the AAP recommends a cut-off value for Hb of <110 g/L and for SF of <12 µg/L. The AAP describes other indicators of iron status including mean corpuscular volume, iron and transferrin. Few studies have examined the reference intervals for laboratory tests of iron status in young children; sample sizes have been small and age partitions wide. **(10)**

Effect of endocrine disorders on vitamin B12 status

- **Association with Thyroid Disorders**

Thyroid function is regulated by various nutrients, primarily iodine and selenium. Iodine is an essential micronutrient required for thyroid hormone synthesis, whereas selenium is a cofactor of thyroid enzymes. Certain vitamins also play moderating roles in thyroid function, such as vitamins A, E, D and B. Previous studies have reported vitamin deficiencies in patients with TD. Regarding the B complex vitamins, B12 is one of the most important as it is indispensable to several biochemical processes. In fact, Vitamin B12, or cobalamin, plays a central role in hematopoiesis and is a component of enzymes, such as methylmalonyl-coenzyme. Although the causes of vitamin B12 deficiency in patients with TD may be multifactorial, they would be predominantly related to the comorbidity of other autoimmune disorders and dietary habits. **(1)**

The intrinsic factor of Castle is a mucoprotein essential for the absorption of vitamin B12 at the distal ileum that is synthesized and secreted by the parietal cells of the stomach. Therefore, these cells play a key role in pathologies associated with vitamin B12 deficiency, such as pernicious anemia (PA) and autoimmune atrophic

gastritis (AAG). Thus, the detection of anti-parietal cell antibodies (APCA) has emerged as a means for screening these pathologies. **(11)**

Vitamin B12 deficiency is closely linked to thyroid disorders, particularly in individuals with subclinical or overt hypothyroidism. The prevalence of deficiency tends to be higher in thyroid disease than in the general population, although the exact frequency may vary depending on definitions and testing methods. **(12)**

The mechanisms behind this association are multifactorial. In autoimmune thyroid disease, the coexistence of other autoimmune conditions such as autoimmune atrophic gastritis, pernicious anemia, and celiac disease plays a major role. Beyond autoimmunity, factors like dietary insufficiency, disturbances in gut microbiota, bacterial overgrowth, and impaired intestinal motility—especially in hypothyroidism—can further compromise B12 absorption. Aging also increases the risk, as both thyroid dysfunction and vitamin B12 deficiency are more common in older adults. **(13)**

Anti-parietal cell antibodies (APCA) are frequently detected in thyroid disease and serve as an important marker for autoimmune atrophic gastritis and pernicious anemia, both of which hinder vitamin B12 absorption. These antibodies are particularly relevant in conditions such as Hashimoto's thyroiditis and Graves' disease, where their presence may indicate a greater risk of anemia due to intrinsic factor loss and parietal cell destruction. **(14)**

Given the hematological and neurological consequences of deficiency, assessing vitamin B12 status is clinically important in patients with thyroid disorders. Although not yet a routine part of thyroid disease management, nutritional evaluation can help identify and address deficiencies early, improving overall outcomes. **(14)**

- **Association with type 1 diabetes**

Autoimmune gastritis and pernicious anemia are common autoimmune disorders, being present in up to 2% of the general population. In patients with type 1 diabetes, the prevalence is increased up to 3 to 5-fold. Presence of parietal cell antibodies (PCA) and antibodies to intrinsic factor have been demonstrated in these patients. These factors could contribute to the occurrence of B12 deficiency in these patients. In addition, the dietary habits which vary from one population to another could also contribute to the deficiency. Association of vitamin B12 deficiency in type 1 diabetic patients has been demonstrated in previous studies. **(15)**

Type 1 diabetes is frequently managed in primary care, where physicians must not only address glycemic control but also identify associated comorbidities, including vitamin B12 deficiency. This condition often goes unnoticed because its symptoms may present late and can mimic diabetic peripheral neuropathy, making accurate diagnosis essential. Correctly identifying vitamin B12 deficiency is important since replacement therapy can reverse neurological manifestations that might otherwise be misattributed to hyperglycemia. **(16)**

The reported prevalence of low vitamin B12 in type 1 diabetes varies depending on the diagnostic cut-off values used, and the absence of a gold standard test further complicates evaluation. Serum B12 measurement remains the most commonly used method, despite limitations in sensitivity and specificity compared to additional biomarkers such as methylmalonic acid or holotranscobalamin, which may be costly or unavailable in many settings. **(17)**

In younger patients, vitamin B12 deficiency cannot be explained by age-related risk factors and is often independent of diabetes duration, metabolic control, or gender. Since these patients are typically not on medications such as metformin, other contributors—including nutritional patterns—must be considered. Dietary variation between populations highlights the need for further evaluation of dietary intake, particularly in regions where data remain limited. **(18)**

Clinical signs of Vitamin B12 deficiency in children with T1DM

In children, vitamin B_{12} deficiency often presents with neurologic symptoms that may occur even in the absence of anemia. These can include developmental delay or regression, hypotonia, tremors, ataxia or gait abnormalities, convulsions, paresthesias (tingling sensations), vision blurring, and fatigue or concentration

difficulty. In reported pediatric cases, neurological deficits often improve within weeks after B_{12} supplementation, although recovery may be incomplete if the deficiency was prolonged or severe. **(19)**

Hematological signs classically include macrocytic anemia with hypersegmented neutrophils and other features of megaloblastic hematopoiesis. However, in children and in mild deficiency states, hematologic abnormalities may be subtle or even absent, making reliance solely on blood counts risky. **(20)**

In diabetic patients more broadly, fatigue, weakness, memory disturbances, and peripheral neuropathy are among the clinical features associated with B_{12} deficiency. Because T1DM itself can cause neuropathy, overlapping symptoms may mask or delay recognition of the B_{12} deficiency contribution. **(21)**

Hematological abnormalities related to endocrine disorders

- **Association with Thyroid Dysfunction**

Thyroid gland modulate the metabolism, differentiation, and proliferation of almost every cell in the body including red blood cell (RBC), platelet and white blood cell (WBC) synthesis. Previous finding indicated that thyroid dysfunction affects normal blood cell production resulting in hematological abnormality. The pathophysiology of thyroid dysfunction in hematological abnormalities has not been well stated, though some literature try to elaborate. Even if the mechanism is not well mentioned, hematological abnormalities such as anemia, leukocytopenia, leukocytosis, thrombocytopenia, and thrombocytosis are common findings in thyroid dysfunction patients, which can also be justified by the presence normal hematological values in individuals with functional thyroid hormone (euthyroidism). **(22)**

In terms of WBC and platelet, hypothyroid patients have a slightly reduced total WBC count, neutropenia, and thrombocytopenia. Furthermore, hyperthyroid patients have raised, normal, or slightly lowered total WBC count, with a relative decrease in neutrophils and an increase in eosinophils and mononuclear cells. Nonetheless, studies found hyperplasia in all myeloid cell lines in hyperthyroidism and hypoplasia in hypothyroidism. With regard to lymphocytes, T_3 has been shown to be a prerequisite for normal B-cell production in the bone marrow through its regulation of pro-B-cell proliferation. **(23)**

Worldwide anemia was the most prevalent hematological abnormality among thyroid dysfunction patients, particularly in Ethiopia prevalence rate of 66.5% was indicated in thyroid dysfunction patients. Particularly in Ethiopia the prevalence of anemia among hypothyroidism was 57.5 but in hyperthyroidism it was 53.3. The type of anemia was different between the findings, that could be normochromic-normocytic, microcytic-hypochromic or macrocytic normochromic anemia. Moreover, the associations between thyroid hormone levels with WBC and platelet, is inconsistent. In spite of showing the association between thyroid disorder and hematological abnormality, there was variability between reported studies. In addition, only a limited studies have been done in Ethiopia on the alteration of hematological abnormalities in thyroid dysfunction patients. Furthermore, previous studies did not thoroughly assess the associated factors. In this context, studying the extent of hematological abnormalities and associated factors among thyroid dysfunction patients will add a significant value to patients, the community and the scientific society. **(22)**

- **Hematological Abnormalities in Type 1 Diabetes Mellitus**

Type 1 diabetes mellitus (T1DM) is frequently associated with a spectrum of hematological abnormalities that extend beyond glycemic disturbances. Anemia is a common finding, affecting nearly one-third of individuals, while leukocytosis is even more prevalent, occurring in a majority of patients. Within white blood cell alterations, neutrophilia and lymphocytosis are frequently observed, reflecting the inflammatory and immune-mediated nature of T1DM. **(24)**

Platelet abnormalities, although less frequent, may manifest as either thrombocytosis or thrombocytopenia. These alterations are not random; their magnitude appears to correlate with factors such as male sex and longer disease duration. Red blood cell parameters, including hemoglobin concentration and hematocrit, are consistently reduced compared with non-diabetic populations, and red cell indices are often altered as well. Such hematologic changes may contribute to systemic complications of diabetes, particularly those related to oxygen transport, immune function, and vascular health. **(25)**

- **Hematological Abnormalities in Adrenal Dysfunction**

The hematological manifestations of adrenal dysfunction are less well characterized compared with diabetes and thyroid disease, but available evidence suggests that adrenal insufficiency can exert subtle influences on hematopoiesis. Cortisol plays a key role in modulating immune and inflammatory responses, and its deficiency may contribute to mild leukopenia and relative eosinophilia, which are sometimes observed in patients with adrenal insufficiency. **(26)**

Unlike the consistent association between thyroid dysfunction and anemia, the hematologic changes in adrenal disorders are often less pronounced and may vary depending on the underlying etiology, disease severity, and coexistence of other systemic disorders. In conditions where adrenal insufficiency coexists with chronic illnesses, such as thalassemia or autoimmune polyendocrine syndromes, hematological abnormalities may be overshadowed by the primary disease process. While routine blood counts in adrenal dysfunction may appear within reference ranges, subclinical changes in immune cell distribution and bone marrow activity highlight the modulatory role of adrenal hormones in hematopoiesis. **(27)**

Effect of endocrine disorders on iron levels

Endocrine disorders such as Type 1 Diabetes Mellitus (T1DM), hypothyroidism, and adrenal dysfunction have significant effects on iron metabolism and iron status. In children with T1DM, disturbances in iron levels are increasingly recognized. Studies have reported that while absolute iron deficiency occurs in a small proportion of these patients, functional iron deficiency is far more prevalent, affecting nearly half of children in some cohorts. Functional iron deficiency reflects impaired iron utilization despite adequate or borderline stores, and this imbalance can contribute to anemia in a subset of patients. **(28)**

Furthermore, serum iron levels in children and adolescents with T1DM have been shown to correlate inversely with HbA1c, indicating that lower iron availability is linked to poorer glycemic control. This relationship also has clinical implications for the interpretation of HbA1c, as iron deficiency may artificially elevate HbA1c values independent of glucose status. In adults with long-standing T1DM, decreased serum iron and ferritin have been associated with reduced quality of life and an increased risk of depressive symptoms, further highlighting the systemic consequences of altered iron status in this condition. **(29)**

In hypothyroidism, abnormalities in iron metabolism are common and may occur even in the subclinical stage of the disease. Patients often demonstrate reduced hemoglobin, lower ferritin levels, and abnormal red cell indices, with a notable prevalence of iron deficiency anemia. Overt hypothyroidism typically presents with more marked changes, including low serum iron and ferritin, decreased transferrin saturation, and elevated total iron binding capacity (TIBC). These alterations can be explained by both decreased gastrointestinal absorption of iron and impaired mobilization of stored iron. **(30)**

In contrast, the relationship between adrenal dysfunction and iron status is less clearly defined, though some associations have been described. Data from populations with chronic hemoglobinopathies, such as sickle cell disease and β-thalassemia, suggest that iron overload can impair adrenal function. In these conditions, high serum ferritin levels correlate negatively with basal cortisol concentrations, indicating that excess iron may disrupt adrenal hormone production. While these findings relate primarily to secondary adrenal insufficiency due to iron overload, they underscore the sensitivity of adrenal tissue to changes in iron homeostasis. Evidence for adrenal insufficiency leading to direct alterations in iron metabolism in otherwise typical endocrine patients is limited, and further research is needed to clarify this relationship. **(31)**

Overall, the interplay between endocrine disorders and iron status is multifaceted. T1DM primarily predisposes patients to functional iron deficiency with potential effects on anemia and glycemic markers; hypothyroidism exerts strong regulatory effects on iron metabolism via hepcidin and absorption pathways, often leading to iron deficiency anemia; and adrenal dysfunction appears to be influenced by iron overload states, though its role in iron deficiency remains less well characterized. These findings highlight the importance of monitoring iron status in patients with endocrine disorders, as alterations in iron metabolism can both complicate disease management and exacerbate systemic morbidity. **(32)**

Assessment of Serum Iron and Vitamin B12 in Pediatric Patients

Assessment of serum iron and vitamin B12 in pediatric patients is an important component of evaluating nutritional status and identifying deficiencies that may impact growth, development, and overall health. Both micronutrients show wide biological variability during childhood, with reference ranges differing significantly by age. Serum vitamin B12 levels are highest during infancy and gradually decline into adolescence, while serum iron and ferritin values also vary with age and sex. This age-dependent variation underscores the importance of using pediatric-specific reference intervals rather than adult cut-offs to avoid misclassification of deficiency. **(33)**

For iron assessment, the most commonly used parameters include serum ferritin, serum iron, total iron binding capacity (TIBC), and transferrin saturation. Serum ferritin reflects iron stores and is considered the most specific marker for deficiency, though it is also an acute-phase reactant and may be falsely elevated during inflammation or infection. To improve diagnostic accuracy, ferritin is often measured alongside markers of inflammation such as C-reactive protein (CRP). Reduced serum iron combined with elevated TIBC and low transferrin saturation further supports the diagnosis of iron deficiency. Age-specific cut-offs are recommended, with the World Health Organization defining ferritin levels <12 μg/L in children under five years and <15 μg/L in older children as indicative of deficiency, though higher thresholds are suggested when inflammation is present. **(34)**

For vitamin B12, serum cobalamin measurement is the standard test, but it lacks sensitivity and specificity for early or functional deficiency. More sensitive markers include methylmalonic acid (MMA), homocysteine, and holotranscobalamin, which can identify functional deficiency even when serum B12 levels appear normal. However, these advanced biomarkers are more costly and not widely available in routine pediatric practice, so serum B12 remains the primary test in most settings. The diagnostic threshold for deficiency varies, with serum levels <148 pmol/L (~200 pg/mL) typically considered deficient and 148–221 pmol/L considered borderline, though cut-offs must be interpreted in the context of clinical findings and age-appropriate ranges. **(35)**

Practical recommendations for pediatric practice emphasize that both iron and vitamin B12 status should be assessed in children with unexplained anemia, macrocytosis, or neurodevelopmental concerns. In suspected B12 deficiency, especially if megaloblastic anemia or neurological symptoms are present, measurement of MMA or homocysteine is useful when available. For iron deficiency, serum ferritin remains the most reliable first-line marker, provided inflammation is excluded. Screening at critical ages, such as around 12–18 months, has been suggested to allow early detection of iron deficiency. Ultimately, accurate interpretation of laboratory results requires consideration of age-specific reference intervals, clinical context, and, where possible, the combined use of multiple biomarkers to ensure reliable diagnosis of iron and vitamin B12 deficiencies in pediatric patients. **(37)**

Complications of micronutrient deficiencies

Vitamin B12 deficiency in children often presents with both hematologic and neurologic impairments. Early signs can include failure to thrive, anorexia, vomiting, pallor, and hypotonia. Neurologic patterns may show developmental delay or regression, tremors, seizures, and decreased tone. In many infants, these neurologic changes begin before overt anemia is noticeable. Prompt diagnosis and supplementation can lead to significant recovery, but if treatment is delayed, neurologic damage may become permanent. **(38)**

Hematological complications include megaloblastic anemia characterized by enlarged red blood cells and hypersegmented neutrophils, and in more severe cases pancytopenia with low counts across multiple blood cell lines. Some children may show macrocytosis, while others have subtle or mixed blood picture abnormalities depending on the severity and duration of deficiency. In addition, signs such as knuckle pigmentation, fragile hair, glossitis, and other mucocutaneous changes have been reported. Delays in neurodevelopment are a particularly serious complication. In B12 deficiency, children may lag behind peers in motor skills, language, and social milestones, and may even regress. Some recovery is often observed after treatment, but in cases of prolonged or severe deficiency, the risks of lasting impairment are higher. **(39)**

Iron deficiency, even when not yet causing full anemia, is associated with adverse effects on cognitive development and behavior. Deficits in attention, processing speed, learning ability, and general intellectual

function have been observed especially in preschool-aged children. Children may also exhibit developmental delay or lower motor skill milestones. Immune dysfunction is another important complication, as iron deficiency weakens immune responses, making children more susceptible to recurrent infections, particularly of the respiratory and gastrointestinal tracts. Physical symptoms and more overt hematologic signs include fatigue, pallor, reduced exercise tolerance, tachycardia, and, in severe cases, heart failure or other cardiovascular strains. In young children especially, iron deficiency can lead to sleep disturbances, loss of appetite, and developmental regression. In school-aged and adolescent children, symptoms may include dizziness, cold intolerance, reduced attention span, and poor growth or delayed puberty. **(40)**

Together, deficiencies in vitamin B12 and iron during childhood result in significant health complications, ranging from impaired hematological function to irreversible neurodevelopmental delays. These micronutrients are essential for cellular metabolism, red blood cell production, immune competence, and nervous system development, and their deficiency in children not only causes immediate health problems but also poses long-term risks to growth, cognition, and overall quality of life. **(41)**

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