Incidence of Vitamin B12 Deficiency in Patients with Hypothyroidism

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ABSTRACT

BACKGROUND

Hypothyroidism is a common endocrine disorder which affects 11 % of the adult population in western countries. Hypothyroidism can cause a wide variety of anaemic disorders. Patients with both hypothyroidism and Vitamin B12 deficiency also have similar symptoms. Thus, this study was conducted to evaluate the relationship between the two and also hypothyroidism due to autoimmune cause.

METHODS

This was a descriptive study of 50 newly detected hypothyroid patients from Rajarajeswari Medical College evaluated for vitamin B12 deficiency. The study was conducted between January 10th 2019 to July 21st 2019. Lab parameters analysed included haemoglobin, thyroid function test (TFT), vitamin B12 levels and anti-thyroid peroxidase (anti-TPO) antibody levels.

RESULTS

Of the 50 hypothyroid patients evaluated, 23 were males and 27 were females between the age of 18 to 70 years. Anti TPO antibodies were present in 24 patients (48 %) out of 50, out of which 17 (70 %) patients had vitamin B12 deficiency. Out of 50 hypothyroid patients, 26 patients (52 %) had vitamin B12 deficiency. Thus hypothyroidism and autoimmune thyroid disease was associated with Vitamin B12 deficiency which was statistically significant.

CONCLUSIONS

Patients with hypothyroidism were studied for the incidence of deficiency of vitamin B12. It was found that 26 of 50 (52 %) patients had low B 12 levels. Incidence in females (54 %) was more than in males (46 %). Our study showed association between hypothyroidism and vitamin B12 deficiency and also autoimmune thyroid disease.

KEYWORDS

Hypothyroidism, Autoimmune Thyroid Disease, Vitamin B12 Deficiency

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BACKGROUND

Vitamin B12 (B12) also known as cobalamin[1] has a chemically complex structure. It is the largest of all vitamins. At the centre of a corrin ring, it contains an atom of cobalt and is the only active substance in the body. In the mitochondria it exists in 2-deoxyadenosyl (ado) form which is the cofactor for the enzyme L–methyl malonyl coenzyme-A (CoA) mutase. Methyl cobalamin which is the cofactor of methionine synthase is the other major cobalamin occurring naturally. Purine and pyrimidines synthesis requires methionine synthase. The reaction in which methyl group of methyl tetrahydrofolate is transferred to homocysteine to form tetrahydrofolate and methionine. Megaloblastic anaemia develops due to interruption of this reaction.

Transcobalamin II is the active transport protein for vitamin B12. The endogenous forms consist of cobalamin and holotranscobalamin. The reduced state is treated with cyanocobalamin.

Vitamin B12 is synthesised solely by anaerobic microorganisms. The food of animal origin is the only source available for humans which includes fish, meat, poultry, dairy and eggs. There are no naturally occurring active forms of vitamin B12 from plant sources. It is also available in the supplements and fortified foods in crystalline form.[2] The bioavailability of vitamin B12 depends on individual's gastrointestinal absorption capacity. The supplements contain cyano form, which is also found in trace amounts in food. Deficiency results from reduced consumption, reduced absorption, autoimmune states or genetic disorders.

Cobalamin absorption consists of two mechanisms, active and passive. Passive mechanism occurs via the buccal, duodenal and ileal mucosa but is inefficient. The active mechanism is the normal physiologic mechanism, occurs through ileum and is mediated by the intrinsic factor (IF). Hydrochloric acid which is produced by the gastric mucosa is required to separate the vitamin B12 which is bound to the protein. This released cobalamin binds to R protein and reaches duodenum where R protein gets separated. Intrinsic factor binds to the free cobalamin and is absorbed by distal ileum. Vitamin B12 is secreted in bile which via the ileal receptors gets reabsorbed into enterohepatic circulation. This process requires intrinsic factor. Intrinsic factor deficiency leads to pernicious anaemia. About 0.1 % gets excreted per day. Excess vitamin B12 gets excreted in urine.

3 - 4 % of the general population have vitamin B12 deficiency. The reduced state is very rare in kids and adolescents. Vitamin B12 helps in central nervous system myelination, synthesis of nucleic acids and erythropoiesis. A sufficient contribution of B12 is necessary to support the functions.[3] Malabsorption and reduced consumption through diet are not the uncommon reasons for reduced state of B12, which is usually seen in the elderly.[4] Strict vegetarians are prone to B12 deficiency and can meet their requirements from supplements and fortified foods. Vegetarian pregnant and lactating women are at high risk of deficiency and require adequate intake of vitamin B12 supplements. Undernutrition is common among the elderly due to physical capacity, illnesses and inflammation of gastric mucosa. Malabsorption usually occurs due to inability to break free B12 which is present bound to protein. Bariatric surgery patients are at increased risk of developing vitamin B12 deficiency and also require lifelong supplementation through diet.

H. pylori infection, chronic inflammation of gastric mucosa and long-term antacid therapy leads to malabsorption as they adversely affect gastric acid and pepsin secretion.

The reduction in the availability of functional gastric mucosa and reduced secretion of intrinsic factor lead to vitamin B12 deficiency. Chronic inflammation of gastric mucosa leading to atrophic changes leading to reduce IF, diminished HCl production resulting in pernicious anaemia. It is an autoimmune disorder which contains anti intrinsic factor antibodies and anti-gastric parietal cell antibodies.[5] It is the end stage of an auto immune gastritis which results in loss of intrinsic factor. Vitamin B 12 deficiency can also occur due to reduced ileal uptake due to diseases such as Crohn's, chronic inflammatory conditions. Drugs such as proton pump inhibitors, metformin, nitrous oxide anaesthesia, epileptic medications and colchicine lead to vitamin B 12 deficiency.

Symptoms and signs of vitamin B 12 takes several years to manifest. B12 deficiency leads to haematological, neurological, cardiovascular and psychiatric manifestations. Clinical features include fatigue, pallor, dementia, peripheral neuropathy, ataxia and loss of proprioception. Clinical signs of B 12 deficiency may be subtle and missed if not detected by a laboratory evaluation of vitamin B 12. B 12 induced nerve damage may cause peripheral neuropathy.

Evaluation in suspected cases is done with complete blood count with a peripheral smear, serum vitamin B 12 levels and folate levels. Other tests include methylmalonic acid (MMA) and homocysteine levels. Treatment involves repletion with B 12.

Hypothyroidism is defined as abnormally low activity of the thyroid gland, resulting in retardation of growth and mental development in children and adults. It is divided into primary and secondary according to level of endocrine dysfunction. It also has congenital and acquired types depending on the time of onset of the disease. Depending on the severity, it is divided into mild, subclinical and overt types. The main thyroid hormones are Thyroxine (T4) and Triiodothyronine (T3). T4 is produced only from thyroid gland, whereas T3 is produced from thyroid and peripheral deiodination of T4. Hormones of thyroid gland help in production of erythroid colonies. This occurs with the help of erythropoietin. Underactive thyroid leads to anaemia. Hypothyroidism can cause a variety of anaemic disorders.[6]

The underactive thyroid leading to reduced synthesis and production of thyroid hormones is known as primary hypothyroidism. 50 % of the cases are of autoimmune aetiology.

Autoimmune thyroid diseases (AITD) encompass a group of disorders characterised by antibodies against thyroid gland such as Hashimoto's thyroiditis and Graves' disease. AITD occurs more commonly in women between the ages of 40 to 60. There is infiltration of lymphocytes and also distinct antibodies circulate in hypothyroidism due to autoimmunity. Presence of thyroid autoantibodies in serum is necessary for

the diagnosis of AITD. The main autoantigens of thyroid are thyroperoxidase (TPO), thyroglobulin and thyroid stimulating hormone receptor (TSH-R). 95 % of cases have increased anti TPO antibodies and 60 % have anti thyroglobulin antibodies.

Patients with AITD may also present as hyperthyroid or even euthyroid 50 - 75 %.[7] 26 - 51 % have hypothyroidism which is subclinical and 6 - 11 % have overt hypothyroidism. Environmental and genetic factors lead to autoimmunity induced thyroid disease. Infectious agents may also predispose to development of autoimmune thyroid disease. Iodine deficiency also predisposes to autoimmune thyroid disease. Genetic factors constituting 70 %, include major histocompatibility gene (*HLA*), immune regulator genes (*CTLA 4, PTPN22, FOXP3, CD25, CD40, FRCL3*) and thyroid specific genes. Environmental causes constituting for 30 % include alcohol, stress, smoking, iodine, Vitamin D deficiency, pregnancy, drugs, bacterial and viral infections.

Subclinical hypothyroidism refers to biochemical evidence of thyroid hormone deficiency in patients who have few or no apparent clinical features. Levothyroxine is recommended if patient wishes to conceive or when thyroid levels are above 10 m IU / L. Subclinical hypothyroidism is a risk factor for cardiovascular disease. Overt hypothyroidism may have presented as subclinical previously. They have many serious outcomes like dyslipidaemia, high risk of developing myocardial infarction, neurological consequences and infertility issues.

Patients with hypothyroidism mainly present with fatigue, dry skin, cold intolerance, impaired memory, weight gain, constipation, hair loss, voice hoarseness, facial periorbital oedema and bradycardia. Neurological manifestations include depression, psychosis, ataxia, seizures and coma.

Autoimmune disorders are frequently related to other disorders of autoimmunity.[8] Hence patients with AITD may also have other autoimmune disorders such as pernicious anaemia and / or atrophic gastritis. Primary hypothyroidism and pernicious anaemia are often related, up to 12 % association is present between the two. The association between hypothyroidism and B12 deficiency in the absence of AITD has not been evaluated in detail and may vary according to dietary habits across population groups.[9]

Patients with both hypothyroidism and vitamin B12 deficiency also have similar symptoms such as fatigue, dementia, weakness, memory loss, depression, lethargy and tingling. Thus, vitamin B12 deficiency may be ignored in hypothyroidism. Macrocytosis occurs commonly in patients having underactive thyroid. The relationship between TSH and B 12 vitamin is not studied in detail. Due to inadequate intake, sluggish bowel motility, bacterial overgrowth, vitamin B12 deficiency can occur in hypothyroidism. Hypothyroid patients on thyroid hormone replacement therapy may not fully recover at times due to vitamin B12 deficiency.

Thus, the present study was done to know the incidence of deficiency of vitamin B12 in hypothyroid patients.

METHODS

Inclusion Criteria

Patients between the ages of 18 to 70 years of either sex.
Patients who gave voluntary informed consent.
Patients newly detected with hypothyroidism (T3 = < 0.69 sng / mL, T4 = < 5.0 mcg / dL, TSH = > 5.0 µIU / mL).

Exclusion Criteria

Patients with genetic disorders of thyroid.
Patients with obesity
History of gastric or ileal resection.
Use of metformin and gastric acid inhibitors were noted.
Vegetarian patients were excluded.
Pregnant ladies were excluded
Patients with diabetes mellitus were excluded
Patients with chronic kidney disease, coronary artery disease, cerebrovascular diseases were excluded.
Patients with previous history of underactive thyroid on medication were also excluded.
Consent not provided by the patients to take part in the study

Lab Parameters

Haemoglobin (Hb) levels, vitamin B12 levels, anti-thyroid antibodies and thyroid function tests (TSH). Patients having TSH from 5.0 – 10 µIU / mL were considered to have subclinical hypothyroidism. Patients with TSH more than 10 µIU / mL and T3 and T4 levels less than cut off value were considered to have overt hypothyroidism. Haemoglobin by Coulter counter. Radioimmunoassay (RIA) on a gamma counter was used for B 12 level estimation, 201 to 899 pg / mL was the normal range. The haemagglutination method was used for antibodies of thyroid. Anti TPO antibody < 34 IU / mL is considered negative. Hb levels: males = 13 – 16 = normal, < 13 is considered low; females = 12 - 14 = normal, < 12 is considered low.

Statistical Analysis

The collected data was analysed using descriptive and inferential statistics. In descriptive statistics, results were expressed as mean ± standard deviation, for categorical data, percentage was calculated. In inferential statistics, analysis of data was done by chi-square and Fisher's exact test. If P-value < 0.05 was considered statistically significant.

RESULTS

Of the 50 hypothyroid patients evaluated, 23 (46 %) were males and 27 (54 %) were females. Age of patients was from 20 to 70 years. The mean age was 45 ± 12.8 years (52.7 ± 11.4 for males and 42.8 ± 14.1 years for females). 22 out of 50 had overt hypothyroidism (44 %) and 28 had subclinical hypothyroidism (56 %).

Haemoglobin values were noted in all patients. Overall 69.5 % of the males had Hb < 14 g / dL while 48.1 % females had Hb < 12 g / dL. Underactive thyroid patients with vitamin B12 deficiency were found to have an elevated incidence of anaemia when compared to the other group in males and females and more in males.

Anti TPO antibodies were present in 24 patients (48 %) out of 50, out of which 17 (70 %) patients had vitamin B 12 deficiency. 26 out of 50 (52 %) had B12 levels < 200 pg / mL (normal 200 – 900 pg / mL).

		Frequency	Percentage (%)
Vitamin B12	< 200	26	52
	> 200	24	48

Table 1. Incidence of Vitamin B12 Deficiency

		Frequency	Percentage (%)
Anti-TPO	Normal	26	52
	Positive	24	48

Table 2. Incidence of Autoimmune Thyroid Disease

		Frequency	Percentage (%)
Hypothyroidism	Overt hypothyroidism	28	56
	Subclinical hypothyroidism	22	44

Table 3. Distribution of Patients with Hypothyroidism

Thyroid	B12		Total
	< 200	≥ 200	
Sub	16	12	**28**
Overt	10	12	**22**
Total	**26**	**24**	**50**

Table 4. Association of Hypothyroidism with Vitamin B12 Deficiency

Out of 50 hypothyroid patients, 26 patients (52 %) had vitamin B12 deficiency thus hypothyroidism was not associated with vitamin B12 deficiency which was statistically not significant. (Using Fisher's exact probability test P-value = 0.674326)

Anti TPO	B12		Total
	< 200	≥ 200	
Positive	17	7	**24**
Negative	9	17	**26**
Total	**26**	**24**	**50**

Table 5. Association of Autoimmune Thyroid Disease with Vitamin B12 Deficiency

Out of 50 hypothyroid patients, 24 patients (48 %) had positive anti TPO antibody levels out of which 17 patients (70 %) had vitamin B12 deficiency. Thus autoimmune thyroid disease was associated with vitamin B12 deficiency which was statistically significant. (Using Fisher's exact probability test P-value = 0.02)

DISCUSSION

Pernicious anaemia is a rare autoimmune condition in which patient is unable to absorb vitamin B12. The vitamin was first secluded in 1948 and was used in the treatment of pernicious anaemia.[9] The vitamin B12 deficiency has been described in up to 16 - 20 % in a few population groups.[9] The present study evaluated the incidence of B12 deficiency in hypothyroid state, including autoimmune thyroid disease. We calculated the incidence of deficiency of vitamin B12 in patients with hypothyroidism and found 26 out of 50 (52 %) patients showed reduced levels of vitamin B12.

Incidence in males was 46 % and females was 54 %. Hypothyroidism affects females more than men. The incidence of clinical hypothyroidism is 0.5 % - 1.9 % in women and < 1 % in men and of subclinical hypothyroidism, 3 - 13.6 % in women and 0.7 - 5.7 % in men. Females are more prone to vitamin B12 deficiency due to reduced dietary intake, menstrual loss, pregnancy and lactation. Vitamin B12 is a particularly important vitamin for women of child bearing age and for older people.

Age of patients was from 20 to 70 years. The mean age was 45 ± 12.8 years (52.7 ± 11.4 for males and 42.8 ± 14.1 years for females). 22 had overt hypothyroidism (44 %) and 28 had subclinical hypothyroidism (56 %). Older women had higher incidence of disorders of thyroid especially underactive thyroid. The complaints and clinical features of thyroid dysfunction are very common and alike to the process of ageing. This makes it necessary for the use of upgraded methods for diagnosis of thyroid dysfunction in aged population.

Gastric hypochlorhydria and malabsorption of vitamin B12 is caused by H2 receptor antagonists and proton pump inhibitors. Untreated *Helicobacter pylori* infection also leads to vitamin B12 deficiency.

The affected patients are asymptomatic for several years as symptoms and signs of vitamin B12 deficiency takes long time to manifest. Clinical signs of vitamin B12 deficiency may be subtle and missed if not detected by laboratory evaluation of vitamin B12. B12 deficiency may also lead to peripheral nerve damage leading to neuropathy. The clinical features of vitamin B12 deficiency in elderly patients such as fatigue, weakness, lethargy, depression, dementia, loss of memory is often attributed to aging. Neuropsychiatric manifestations may be the early marker of deficiency. It is crucial to identify the correct aetiology of neuropsychiatric manifestations as simple vitamin B12 replacement may reverse the neurological symptoms.

Our study showed no association between hypothyroidism and vitamin B12 deficiency (P-value not significant) but, however, showed that autoimmune thyroid disease is more related to vitamin B12 deficiency (P-value significant) hence proving the link between the two. Vitamin B12 levels should be screened as soon as the disease is confirmed and also yearly. The screening of levels of vitamin B12 suggested for patients with autoimmune thyroid disease at the first visit and then yearly but regular screening is not necessary if the patient is antibody negative.

Patients with primary hypothyroidism are associated with pernicious anaemia. Around 1 / 3rd of them have antibodies to gastric parietal cells. Vitamin B12 deficiency can also occur in hypothyroidism due to malabsorption in the intestine, reduced motility of intestine, oedema of intestinal wall or increased growth of microorganisms.

Hypothyroid and vitamin B12 deficient patients have common symptoms. Many patients, despite being on adequate thyroxine replacement, had persistence of symptoms and subsequently were found to be B12 deficient.[9]

Amenia with or macrocytosis, tend to occur later in vitamin B12 deficiency and may be absent. Myocardial infarction is associated with increased level of homocysteine. Measurement of serum MMA and holotranscobalamin II (holo–TCII) couldn't be performed.

Long term consequences of the vitamin B12 deficiency like cognitive impairment can be prevented by early initiation of treatment.

Parental cobalamin administration in the form of cyanocobalamin and hydroxyl cobalamin is required. The vitamin B12 can be given at doses of 1g IM every day for a week. Then the dose should be continued once per week for a month and then should be taken monthly once for a year. The stores can be easily reloaded through this regime. Daily doses of 2000 micrograms of vitamin B12 has also been proved to be effective, including those with atrophic gastritis and pernicious anaemia.

Hypothyroidism and vitamin B12 deficiency often have similar symptoms such as weakness, lethargy, impaired memory, tingling and numbness. Thus, hypothyroidism may potentially mask vitamin B12 deficiency and it is important to recognise this and treat both diseases. Vitamin B12 deficiency may be ignored in hypothyroidism. Macrocytosis occurs commonly in patients having underactive thyroid.

CONCLUSIONS

We studied the incidence of reduced vitamin B 12 levels in patients with hypothyroidism due to autoimmune cause and found 26 of 50 (52 %) patients to have reduced B12 levels. Incidence in females (54 %) was more than males. (46 %) Hypothyroidism may be related to pernicious anaemia as part of the autoimmune poly glandular endocrinopathy.[10] Pernicious anaemia is found to be associated with the state of low thyroid stimulating hormone levels. The relation is up to 11 %. Our study showed association between hypothyroidism and vitamin B12 deficiency (P-value significant) and also showed that autoimmune thyroid disease is more related to vitamin B12 deficiency (P-value significant) hence proving the link between the two. The levels of vitamin B12 should be checked as soon as hypothyroidism is diagnosed and also should be done early and on yearly basis. Yearly follow-up is necessary. Other markers such as methylmalonic acid and holotranscobalamin must be assessed. Neurological conditions and other causes of vitamin B12 deficiency like diet should be assessed. Study with larger population is necessary for proper conclusion. Long term sequelae of vitamin B12 deficiency can be prevented by initiation of early therapy. Identification of correct aetiology of neuropsychiatric manifestations is crucial as simple replacement of vitamin B12 may reverse the neurological symptoms. Thus evaluation of B12 levels in primary hypothyroid patients is crucial.

Limitations

Other markers such as methylmalonic acid and holotranscobalamin were not evaluated. Neurological conditions and other causes of vitamin B12 deficiency like diet were not evaluated. The study size was small to conclude the relationship between primary hypothyroidism and vitamin B12 deficiency. Larger study size would help in providing better link between primary hypothyroidism and vitamin B12 deficiency and its relationship with autoimmune thyroid disease.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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