



ORIGINAL RESEARCH PAPER

Pathology

PERNICIOUS ANEMIA AN UPDATED REVIEW

KEY WORDS: Pernicious anemia, cobalamin deficiency

Dr. Atul Khajuria*

Ph.D. Professor & H.O.D. Medical Laboratory Technology NIMS College Of Paramedical Technology. *Corresponding Author

Mr. Raju

Ph.D. MLT(Pathology) Scholar, M.Sc. MLT (Pathology) Gold Medalist Medical Laboratory Technology NIMS College Of Paramedical Technology.

ABSTRACT

Pernicious anemia (PA) is megaloblastic anemia ensuing from a deficiency of cobalamin (vitamin B12), which in flip is brought on via a lack of intrinsic Factor (IF). Intrinsic Factor is a glycoprotein that binds cobalamin and thereby permits its absorption in the terminal ileum. Pernicious anemia is frequently described as an autoimmune sickness due to the findings of gastric autoantibodies directed towards each Intrinsic Factor and parietal cells and the accelerated frequency of different autoimmune illnesses considered in sufferers with pernicious anemia. This recreation evaluations the medical presentation, etiology, pathophysiology, clinical feature and therapy of pernicious anemia.

INTRODUCTION

Pernicious anemia (PA) is megaloblastic anemia that consequences from a deficiency in cobalamin (vitamin B12) due to a deficit of intrinsic factor (IF). Intrinsic factor is a glycoprotein that binds cobalamin and therefore allows its absorption at the terminal ileum. The disorder is regularly described as an autoimmune disease due to the findings of gastric autoantibodies directed towards each IF and parietal cells. Pernicious anemia additionally correlates with different autoimmune illnesses and as nicely as genetic illnesses [1] Pernicious anemia (PA) is the most frequent purpose of nutrition B12 deficiency. Vitamin B12 deficiency has many causes; the time period "pernicious anemia" applies solely to the circumstance related with persistent atrophic gastritis. A latest populace survey printed that 1.9 percentage of people extra than 60 years ancient have undiagnosed pernicious anemia. [2] Earlier research recommended that pernicious anemia is restrained to Northern Europeans. [2] However, subsequent research have suggested the sickness in black and Latin-American subjects, with an earlier age of onset in black women. [1,3] Although the disease is silent till the give up stage, the underlying gastric lesion can be expected many years earlier than anemia develops.

ETIOLOGY

Research has recognized two etiologies for pernicious anemia:

Autoimmune

Autoimmune gastritis is characterised with the aid of the destruction of gastric parietal cells and the ensuing lack of the glycoprotein intrinsic thing secreted via these cells. The antibodies recognized with autoimmunity are intrinsic factor antibodies (IFA) and parietal cell antibodies (PCA).

Parietal cell antibodies work towards the parietal cell proton pump ATPase. The predominant aims of parietal cell antibodies are the alpha and beta proton pump subunits. Research has decided that parietal cell antibodies are immunoglobulins from the M, G, and A isotypes, which function towards each subunits. [4]

Intrinsic component antibodies are immunoglobulin G isotype, and they can be both kind 1 and kind 2 antibodies. Type 1 conducts towards the cobalamin binding site. Type two acts towards the ileal mucosa receptor. [5]

Other autoimmune ailments encompass pernicious anemia, which can be related with autoimmune diseases, such as kind 1 diabetes (3% to 4%), vitiligo (2% to 8%), and autoimmune thyroid sickness (3% to 32%). This affiliation has led to research exposing that HLA alleles may also be associated to

autoimmune gastritis. HLA-DRB1/03 and HLA-DRB1/04 alleles may additionally predispose to autoimmune gastritis. [6][1]

Genetic

Researchers have additionally recognized congenital and juvenile types of pernicious anemia, which are idea to observe an autosomal recessive inheritance pattern.

Other reasons of cobalamin deficiency include:

- Vegetarian die
- Damage of gastric mucosa
- Insufficient pancreatic enzymes (ZES, persistent pancreatitis)
- Tapeworm infestation
- Bacterial overgrowth
- Defects in the ileal mucosa main to terrible uptake of cobalamin

PATHOPHYSIOLOGY

There are two kinds of autoantibodies recognized in pernicious anemia: intrinsic factor antibodies (IFA) and parietal cell antibodies (PCA).

Parietal cell antibodies behavior their undertaking in opposition to the parietal cell proton pump ATPase. Autoimmunity starts with the activation of gastric dendritic cells, which in flip set off CD4+ T cell lymphocytes in perigastric lymph nodes. These precipitated CD4+ T cells to perceive the proton pump ATPase, which leads to their immune destruction. [7] The mechanism by means of which the dendritic cells turn out to be activated is now not known. Some lookup research advise H. pylori contamination as a trigger. The research recommend molecular mimicry and immune cross-reactivity between the proton pump ATPase and the H. pylori organisms. [8][9] The anti parietal antibodies are current in the majority of sufferers with pernicious anemia.

Intrinsic factor antibodies are immunoglobulin G isotype, and they can be both kind 1 or kind two antibodies. Type 1 operates towards the cobalamin binding site, whereas kind two directs its pastime in opposition to the ileal mucosa receptor. [3] B12 and intrinsic factor bind to receptors on the ileum, which permits for absorption. Vitamin B12, as soon as absorbed, is a cofactor for the enzyme methionine synthase, which takes section in the conversion of homocysteine to methionine. If this technique can't manifest due to pernicious anemia, homocysteine ranges accumulate, and pyrimidine bases can't form, which interferes with DNA synthesis and motives megaloblastic anemia. Vitamin B12 is additionally a cofactor for the enzyme methylmalonyl-CoA mutase, which

converts methylmalonyl-CoA to succinyl-CoA. In sufferers with pernicious anemia, methylmalonic acid (MMA) tiers accumulate. Elevated ranges of MMA and homocysteine make a contribution to myelin damage, which reasons neurologic deficits, such as neuropathy and ataxia.[10] When there is cobalamin deficiency, sufferers can increase extreme neurological impairment, together with peripheral neuropathy, psychosis, or leukoencephalopathy.

Common dietary supply of cobalamin consists of milk and meat. Because the physique stores of cobalamin are limited, strict adherence to a vegetarian weight loss plan can lead to pernicious anemia.

It is vital to word that the coexistence of iron deficiency anemia is additionally frequent because, in the absence of acid, the dietary ferric iron can't be absorbed from the stomach. Finally, sufferers with pernicious anemia might also additionally have thyroid ailment and are susceptible to gastric cancers.

CLINICAL FEATURE

The scientific presentation of pernicious anemia is multifarious and insidious in onset. Symptoms can also consist of fatigue, pallor, paresthesia, incontinence, psychosis, and generalized weakness. The analysis is tricky secondary to the confined availability of diagnostic tools. Treatment goals at the repletion of therapeutic doses of nutrition B12 both via intramuscular injections or oral supplementation. When the ailment stays undiagnosed and untreated for an extended period, it might also lead to neurological problems and even deadly anemia.

LABORATORY DIAGNOSIS

Hematologic Examination

In hooked up megaloblastic anemia, examination of the peripheral blood exhibits macrocytosis with hypersegmented polymorphonuclear leukocytes, anemia, leukopenia, and thrombocytopenia or pancytopenia. Examination of bone marrow reveals megaloblasts and massive myeloid precursors ("giant metamyelocytes"). Examination of the marrow is not indicated if the prognosis is unequivocal. Vitamin B12 deficiency as the reason of megaloblastic anemia is installed by using a low serum nutrition B12 concentration and regular serum folate concentration. A Schilling check will verify that the nutrition B12 deficiency is the end result of intestinal malabsorption due to intrinsic-factor deficiency. In sufferers with pernicious anemia, urinary excretion of orally administered vitamin B12 is low, and it will increase if vitamin B12 is administered with intrinsic factor. A simpler check is size of serum holotranscobalamin II, the circulating protein that provides vitamin B12 to cells. In sufferers with diet B12 deficiency, serum concentrations of holotranscobalamin II fall earlier than these of diet B12.[13]

Serologic Examination

Serum antibodies to gastric parietal cells can be detected via oblique immunofluorescence with unfixed, air-dried, frozen sections of mouse belly in which the antibodies stain parietal cells. Mouse stomachs are preferable to rat stomachs due to the fact the latter may also provide false positive heterophile reactions.[14] These autoantibodies are located in about ninety percent of sufferers with pernicious anemia however additionally in about 30 percentage of nonanemic first-degree spouse and children of patients with pernicious anemia and in sufferers with autoimmune endocrinopathies. In ordinary subjects there is an age-related extend in the occurrence of parietal-cell autoantibodies, from 2.5 percentage in the third decade to 9.6 percentage in the eighth decade.[15] The explanations for the seronegative outcomes in 10 percent of sufferers with pernicious anemia include faulty diagnosis, whole binding of antibody to antigen so that none is circulating at the time of measurement,

disappearance of antibody due to the fact of disappearance of the antigen, or failure of production of the antibody.

MANAGEMENT

Patients usually obtain an intramuscular injection of a thousand mcg B12 each day or each different day at some stage in the first week of treatment. The subsequent month, they get hold of injections each and every week, due to this fact observed through month-to-month injections. The choice to intramuscular injection B12 is high-dose oral B12. A thousand to 2000 mcg/day has been tested to be effective, even though pointers are to usually use the parenteral route in extreme neurological manifestations. Approved sublingual and intranasal formulations of B12 are additionally available.[1][11] Oral dosage is advocated for sufferers unable to take IM injections, however cobalamin ranges need to be measured regularly to make sure absorption. Finally, oral remedy is now not endorsed for sufferers with CNS symptoms.

Monitoring

The earliest signal of remedy response is an expand in reticulocyte count, generally inside three days of treatment. Following adjustments in the minimize of biochemical markers such as MMA and plasma homocysteine tiers have been determined in the first 5 days of treatment. Sustained normalization of serum cobalamin generally happens following two weeks of therapy.[12] The macrocytosis correction takes location in the course of the first month of treatment. A medical interview need to be regarded each and every 12 months to screen for new symptoms. These may additionally encompass epigastric pain, dysphagia, iron deficiency, and/or others that can require gastroscopic investigation.

The key administration precept is the significance of pursuits follow-up. Patients with underlying reasons like continual pancreatitis, bacterial overgrowth, or tapeworm will require extra treatments. Blood transfusions are no longer required in most patients. With treatment, the signs and symptoms of coronary heart failure resolve, however some sufferers may additionally require concomitant diuretic therapy.

PROGNOSIS

Prognosis is variable, and most pernicious anemia sufferers have a refined development that can take 20 to 30 years, or even more, to turn out to be clinically significant. Even with a noticeably benign prognosis, pernicious anemia can have deadly penalties if left undiagnosed. These penalties can be secondary to extreme anemia and its complications, neurological compromise, and susceptibility to all sorts of gastric tumors. Delayed remedy may also no longer continually reverse neurological deficits. In addition, if the anemia is severe, it may also lead to coronary heart failure.

CONCLUSIONS

Pernicious anemia is the stop stage of kind a chronic atrophic (autoimmune) gastritis. The gastritis mean in the damage of parietal cells in the fundus and body part of the stomach. The loss of these cells is associated with the failure of intrinsic-factor production and outcomes in diet B12 deficiency and megaloblastic anemia. An autoimmune groundwork for the gastritis is supported by means of the presence of mononuclear-cell infiltration into the gastric mucosa with loss of parietal and zymogenic cells, autoantibodies to parietal cells and intrinsic factor, regeneration of parietal and zymogenic cells after remedy with corticosteroids or immunosuppressive drugs, familial predisposition, and affiliation with autoimmune endocrinopathies and antireceptor autoimmune diseases.

The identification of gastric H1/K1-ATPase as the goal of parietal-cell autoantibodies was once a major breakthrough in our appreciation of the molecular and immunologic

groundwork of autoimmune gastritis. The immunologic mechanisms that permit the initiation and development of the T-cell response to this enzyme, main to autoimmune gastritis, stay to be established.

REFERENCE

1. Lahner E, Annibale B, Pernicious anemia: new insights from a gastroenterological point of view. *World journal of gastroenterology*. 2009 Nov 7
2. Carmel R. Prevalence of undiagnosed pernicious anemia in the elderly. *Arch Intern Med* 1996;156:1097-100.
3. Nutritional folate deficiency. In: Chanarin I. *The megaloblastic anaemias*. 2nd ed. Oxford, England: Blackwell Scientific, 1979:457-65.
4. Callaghan JM, Khan MA, Alderuccio F, van Driel IR, Gleeson PA, Toh BH, Alpha and beta subunits of the gastric H⁺/K⁺-ATPase are concordantly targeted by parietal cell autoantibodies associated with autoimmune gastritis. *Autoimmunity*. 1993
5. Conn DA. Detection of type I and type II antibodies to intrinsic factor. *Medical laboratory sciences*. 1986 Apr
6. Fernando MM, Stevens CR, Walsh EC, De Jager PL, Goyette P, Plenge RM, Vyse TJ, Rioux JD. Defining the role of the MHC in autoimmunity: a review and pooled analysis. *PLoS genetics*. 2008 Apr 25;
7. Toh BH, Sentry JW, Alderuccio F. The causative H⁺/K⁺ ATPase antigen in the pathogenesis of autoimmune gastritis. *Immunology today*. 2000 Jul;
8. Chmiela M, Gonciarz W. Molecular mimicry in *Helicobacter pylori* infections. *World journal of gastroenterology*. 2017 Jun 14;
9. Uibo R, Vorobjova T, K, Kisand K, Kivik T. Association of *Helicobacter pylori* and gastric autoimmunity: a population-based study. *FEMS immunology and medical microbiology*. 1995 Mar;
10. Ankar A, Kumar A. Vitamin B12 Deficiency (Cobalamin) 2018 Jan;
11. Andres E, Serraj K. Optimal management of pernicious anemia. *Journal of blood medicine*. 2012
12. Nazarenko GI, Kolenkin SM, Lugovskaia SA, Mikolauskas VP. [Significance of parameters of automated reticulocyte analysis in diagnosis and evaluation of treatment outcome in B12-deficient anemia]. *Klinicheskaia laboratornaia diagnostika*. 2004 May;
13. Herbert V. Vitamin B-12. In: Ziegler EE, Filer LJ Jr, eds. *Present knowledge in nutrition*. 7th ed. Washington, D. C.: ILSI Press, 1996:191-205.
14. Muller HK, McGiven AR, Nairn RC. Immunofluorescent staining of rat gastric parietal cells by human antibody unrelated to pernicious anaemia. *J Clin Pathol* 1971;24:13-4.
15. Strickland RG, Hooper B. The parietal cell heteroantibody in human sera: prevalence in a normal population and relationship to parietal cell autoantibody. *Pathology* 1972;4:259-63.