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ADVANCES IN MECHANISMS, DIAGNOSIS, AND TREATMENT OF PERNICIOUS ANEMIA

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Abstract:

In 1849 Addison elucidate an entity with conditions such as pallor appearance, weakness, and consistently decline heath. Thereafter multiple advances have brought the clue of this issue that PA is characterized through the impaired absorption of cobalamin. It is an eminent cause of cobalamin deficiency globally. This review mainly focused on the current understanding of the disorder it's a neurological, hematological, and biochemical presentation with emphasis on diagnosis, treatment, and monitoring strategies. We hereby, review the diagnostic approach by deeming the present performance and constraint with current diagnostic tools used to find out the cobalamin status and identification of autoimmune chronic atrophic gastritis. Lifelong treatment is necessary for the patient of PA along with the cobalamin replacement treatment. The enteral and parenteral supplements used for the current treatment of PA by comparing with efficacy and tolerability.

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INTRODUCTION:

In 1849 Addison elucidates this disorder during the study of many cases of a syndrome that has pallor appearance, weakness, and consistently declines heath. Finally in 1860, flint find a clue of this issue associated with poor food absorption cause the atrophic gastric mucosa and the existence anemia was found. So, this progressive disease named as pernicious anemia.[4] The worldwide, disorder Pernicious anemia (PA) is an autoimmune disease leading atrophy of gastric mucosa which includes fundus of the stomach and produced hematological and neurological complications.[1] It affects the intrinsic factor indispensable for the absorption of vitamin B_{12} which ultimately impose an adverse effect on erythropoiesis and myelin synthesis, this is because of a reduction in numbers of parietal cells. Therefore, earlier detection of PA is necessary as it is progressive from mild to chronic inflammation of stomach body leads to advance stages correlated with cobalamin deficiency. The coexistence of PA patient's with other autoimmune disorder because autoimmune nature of disease gradually preceded and produced the autoantibodies against intrinsic factors. Recent epidemiological studies supported that treatments of PA are straightforward while the diagnosis is challenging.[2] The globally accurate evidence for the prevalence of vitamin B_{12} deficiency is insufficient, mainly because of variation in diagnosis methods and different aspects of variable use in an epidemiological survey. In the U.S.A estimated 151 per 100,000/year prevalence of PA was documented.[3] The disease frequency rate was highest for females and European ancestry folk. The treatment and recognition of PA is a lengthy and critical process because of its lethal outcomes. This review paper is about the critical review of updates of PA problems which approached the diagnosis, and current treatment approaches.

Diagnosis

- Pernicious anemia has some confirmation through the clinical, hematological, biochemically, and serologically associated with characterization. The featuring of PA entitle is based on below points
  - i. Hb <13 gr/dL for male and <12 gr/dL for female
  - ii. The low cobalamin blood level
  - iii. Laboratory test for Atrophic gastritis
  - iv. Positive intrinsic factor antibodies
  - v. Indication of myelopathy, neuropathy and cognitive dysfunction

Out of these criteria, everyone has methods to investigate for diagnosis and single-use might be associated with risk. It is found that accurate diagnosis of laboratory tests are affected by specific co-occurrence of health issues testing cut off selection, and aberrant con-founders.[14] It is a guileful showoff clinically. People aged greater than sixty years are typically effected by Pernicious anemia. Moreover, round about 50% of people less than sixty years are also found. Affected people don't always have specific conditions joined but some have to be with such as unable to focus mentally and tiredness. Anemic people may suffer from neurologic threats or may have some autoimmune health issues.

- **Neurological manifestation:** Pernicious Anemia's patients have a link to neurological disorder because of cobalamin deficit led to demyelination or destruction of the myelin sheath. In case of no treatment given, this condition may worsen to degeneration of axon and neural cell death.[11] Initially aberrant feeling known to have like tingling and numbness but later on becomes posterior cord syndrome with its hints. Diagnosis of 1-2% cases are mostly don't have a divergence of autonomic reflexes and lapse of memory. More or less than 12 % cases existing with the aberrant motor. Furthermore, nonexistence of anemia may also have developed neurologic signs.[10]

- **Hematologic abnormalities:** Shortfall of cobalamin influences the hematopoiesis, and it is the utmost pre-eminent red blood cells (RBCs) parentage.[12] The alterations in RBCs consequences from abortive inclusion of nucleosides in polychromatic nucleated cells of bone marrow in the course of synthesis stage of the cell cycle (Yoshida *et al*., 1968). The insufficient erythropoietic parentage characterization occurred by the presence of immature erythroid pioneer which is proceeding of damage deoxyribonucleic acid formation and its result of repairment. In a later stages these cells are unable to differentiate eventually falls to the apoptotic process.[13]

- **Intrinsic factor antibodies (IFA) and parietal cell antibodies (PCA)**: The specificity of IFA and PCA was check-in patients with PA through the anti-intrinsic test and anti-parietal cell bodies test. A sampling of patient's performed before the cobalamine supplementation therapy because it may give a false indication of positive results. The sensitivity of these tests is round but 40-60% which can be enhanced up to 80% with disease duration. The PA symptoms in the patient with proper diagnosis and therapy decline within the year of treatment.

Pernicious Anemia Presenting with Vague Symptoms or with No Anemia

PA patients maybe with multiple imprecise symptoms such as mood swings, depression, sleep disorder, fatigue, frustration, and impatience it creates difficulty in the establishment of a diagnosis. According to a survey conducted by Anemia society in unity kingdom, at initial stage 40% diagnosis were wrong and approximately 5 to 10 years required to reach the correct diagnosis of 14 -22% patients because of many reasons.[22] The literature review showed that diagnosis of PA may be delayed up to 91 months and patients may developed irreversible peripheral neuropathy due to delayed diagnosis.[23]

Treatment

The lifelong therapy is required with cobalamin supplementation to bring the malnourished body of vitamin B_{12} to a normal state. In case of treatment interruption, the deficits symptoms start appearing again within a short time possibly 6 months while most of them included neurologic manifestations. However, in U.S.A. 1,000 mcg dose of intravascular Intramuscular cyanocobalamin has recommended in PA treatment.[6] The changes in dose prescription of regimen depend on the follow up plans that vary from days to weeks, weekly to monthly, and then lifelong. In a clinical trial on 70 patients, results were effective to restore the normal serum cobalamin when recommended high oral dose replacement with 500 – 1,000 mcg. This oral replacement evaluation for dose 1,000 mcg proved to better over lower loss probably to temporary poor compliance. The evidence for oral supplementation to observe the lifelong effects are insufficient due to lack of studies.[5] The outcomes of multiple comparison studies based on clinical trials or review's efficacy of oral cobalamin supplementation to intravascular dose offer the significant equivalent efficacious response to restoring all parameters including biochemical and hematological with the reduction in clinical symptoms.[7] On the other hand, sublingual replacement of vitamin B_{12} studied in limited numbers of patients, eventually this route have equally substantial effect to the oral route to retrieve the cobalamin serum level. In PA treatment above mentioned dosages are non-toxic. The strict monitoring of the patient's necessary for the desire response.[8]

Monitoring strategy

In a case study of 30 patients, the rise in reticulocyte count was measured during the first three days of treatment while within 5 days of treatment a subsequent reduction in methylmalonic acid (MMA) serum level and plasma homocysteine the level was observed. The documented oral and intravascular doses both proved to maintain the normal cobalamin serum level after the 2 weeks of therapy.[9] In a few patients clinical relapse had found, such patients exhibit the more sensitive interaction of MMA and homocysteine with cobalamin deficiency. At least 3 months required to bring correction of macrocytosis while normality of hemoglobin might take more time and severity of disease symptoms determined the response of neurological impairment.[10]

DISCUSSION:

- The patients with PA may suffer from more complications such as anemia, neuropsychiatric impairment, and osteoporosis.[17]
- The patient with PA is at greater risk of gastric cancer. Therefore, frequent diagnosis and cobalamin supplementation are mandatory for patients of Pernicious anemia. The prevalence of PA is not exactly known due to its non-specific symptoms and comparatively hard to diagnose.[15]
- The prevalence rate depends upon the many factors including age, diagnostic tool, and countries. However, a comprehensive study evaluates the overall 1.9% prevalence of PA while for black women, it's about 4.3%. According to the present study, its incidence was 0.7%, women and older adults are at greater risk to develop cobalamin deficiency.[16]
- The clinical identifications of PA are imprecise and nonspecific. There are diseases that can cause anemia and it is a very common recommendation of iron without any investigational study. Hereby, PA can easily be neglected, and its diagnosis becomes a challenge for clinicians.[18] The most crucial feature to approach the correct diagnosis of PA is clinical suspicion along with the confirmative laboratory tests. Mostly, endoscopy provides valuable results for atrophic body gastritis and tests to check the serum cobalamin level, MMA, and pepsinogen are not accurately measured.[20] In 90% patients shows positive response to anti-parietal cell bodies can lead to a diagnosis of PA. The anti-intrinsic factor test is more specific but its testing sensitivity is less than 60%. Thus, the PA diagnosis is complex and under-diagnosis is common.[19]

CONCLUSION:

Pernicious anemia (PA) is an autoimmune disease leading atrophy of gastric mucosa which includes fundus of the stomach and produced hematological and neurological complications. Despite safe and worthwhile therapy is at hand, PA consistently in trouble related to medical issues due to numbers of problems including automated diagnostic methods, comparability of cobalamin deficiency with bone

marrow morphology which makes the diagnosis more challenging and difficult. Therefore, critical caution is needed throughout the clinical examination to make sure the exact diagnosis of PA. Diagnosis of PA may take longer and delay in diagnosis may occur for several months due to vague symptoms, clinical identification, and sensitivity of PA with MMA, IFA, and PCA. Few patients with PA gives a tough time in diagnosis such patients required a challenging therapy with adequate supplements of cobalamin.

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