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Cyclic Neutropenia

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Introduction

Neutrophils play a vital role in our immune defenses by ingesting, killing, and digesting invading microorganisms. Failure to carry out this role results in immunodeficiency, which manifests itself in the form of recurrent infections.[1] Common causes of neutropenia include autoimmune diseases, drug reactions, chemotherapy, and hereditary disorders.[2] Cyclic neutropenia is a very rare hematological condition and is characterized by regular fluctuations in blood neutrophil counts, leading to periodic neutropenia with a 21-day turnover frequency.[2][3] It is now considered an autosomal dominant disease caused by ELANE gene mutations.[4] The symptoms and clinical manifestation of cyclic neutropenia may range from mild to severe, depending on the degree and duration of neutropenia. The absolute neutrophil count can drop to zero, and these extremely low counts may last for up to three to five days.[5]

Etiology

Recent research in the field of molecular biology has permitted the discovery of the underlying genetic basis for many inherited diseases.[5] Genetic sequencing in patients with cyclic neutropenia has highlighted mutations at locus 19q13 in the gene for neutrophil elastase. This gene is now referred to as ELANE, and the mutations are consistently found to be present in all patients suffering from cyclic neutropenia but not in their unaffected family members. Some authorities refer to this condition as ELANE associated neutropenia.[5][6]

Epidemiology

Cyclic neutropenia is an autosomal dominant disease, so it affects males and females in equal proportions and is familial in some.[4] Although the disorder is often discovered in young children, the condition lasts throughout the lifetime of the patient.[7] There have also been reports of cases where patients presented with acquired cyclic neutropenia, and the disease onset was later in life.[8]

Pathophysiology

Neutrophils play a pivotal role in the immune defense of the body. Once the neutrophil count is below 1 x 10^9/L, the patient becomes susceptible to recurrent infections.[1] The exact pathophysiological basis of cyclic neutropenia remains unknown, but several studies in the 1950s by Page and Good concluded that the interrupted cell production by the bone marrow may be the main underlying cause of cyclic neutropenia.[9] Subsequent studies also showed that there are cyclic fluctuations in all blood cells. This suggests that the intrinsic defect leading to the disorder is in the hematopoietic stem cells.[10]

Histopathology

Cyclic neutropenia presents with a periodically decreased number of neutrophils in the bone marrow and circulation during an attack.[2] The absolute neutrophil count is usually <.2 x 10^9/L.[11] Acquired cyclic neutropenia in adults may show a clonal proliferation of large granular lymphocytes.[3]

History and Physical

Patients with cyclic neutropenia usually have a periodic decrease in absolute neutrophil count (often <.2 x10^9/L), and present with a clinical syndrome characterized by recurrent fever, oral mucosal ulcers, and respiratory infections.[11] Opportunistic infections appear during a reduction in absolute neutrophil count and manifest clinically as fever, oral ulcers, gingivitis, tonsillitis, pharyngitis, dermatological infections, and swollen lymph nodes.[12][13][14] Patients also exhibit periodontitis with alveolar bone loss during childhood. It has been observed that the systemic symptoms of cyclic neutropenia such as recurrent fevers diminish after adolescence, but even adult patients continue to experience oral ulcers, gingivitis, periodontitis, and other infections.[15] Infections usually respond well to antibiotics. Severe infections are very rare. However, long-term follow-up of patients showed that the life-threatening complications encountered were the occurrence of spontaneous peritonitis, segmental bowel necrosis, and septicemia.[8]

Evaluation

Diagnosis and evaluation of cyclic neutropenia are based on clinical symptoms, duration, history of hereditary inheritance, white cell counts, immune function, bone marrow alterations, and weekly differential leukocyte count (DLC). Investigations such as complete blood count, bone marrow biopsy, histopathological studies, tumoral markers, levels of cytokines (granulocyte-colony stimulating factor), chest x-ray, diagnostic ultrasound, and CT scan should be done to rule out other immunodeficiency disorders. DNA studies can be carried out as a confirmatory test for most genetic disorders, including cyclic neutropenia.[1]

Treatment / Management

The mainstay of treatment and management includes regular monitoring of blood counts, prevention and control of infections through judicious use of antibiotics, oral and dental care, and patient education. Alternate-day corticosteroid regimes have been used successfully to treat recurrent signs and symptoms.[8][12] Most children suffering from severe congenital neutropenia require the long-term administration of granulocyte-colony stimulating factor (G-CSF).[16][17]. G-CSF is now considered a remarkably safe and efficacious treatment for preventing infections and to improve the quality of life in patients suffering from cyclic neutropenia.[18] A recent study has suggested that the combination therapy of G-CSF and high-dose immunoglobulin might be an effective treatment for cyclic neutropenia.[19] Hematopoietic stem cell transplantation (HSCT) is still the ultimate radical treatment, which can permanently correct cyclic neutropenia and is the best long term option for patients who do not respond to G-CSF treatment.[17]

Differential Diagnosis

- Cyclic neutropenia may have a similar presentation to several causes of recurrent fever, such as recurrent tonsillitis, infectious diseases, juvenile idiopathic arthritis, Behçet's disease, and familial Mediterranean fever syndrome.[20]

Rare disorders with a presentation similar to cyclic neutropenia are as follows:

- Marshall syndrome (MS) is a recurrent fever syndrome characterized by fever at 3-8 weeks intervals, cervical adenopathy, pharyngitis, and aphthous ulcers. MS is a diagnosis of exclusion.[20]
- PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, and adenitis) is a non-hereditary autoinflammatory disease, presenting with recurrent fevers lasting for 3 to 6 days duration, accompanied by aphthous ulcers, pharyngitis, tonsillitis, and cervical lymphadenitis.[21]

Prognosis

The clinical course of cyclic neutropenia is usually benign compared with other conditions with neutropenia.[8] The systemic symptoms of cyclic neutropenia such as recurrent fevers usually diminish after adolescence but even adult

patients continue to experience oral ulcers, gingivitis, periodontitis, and other infections.[15] Many patients exhibit periodontitis with alveolar bone loss, during childhood.

Complications

Studies show that serious long term complications such as septicemia, spontaneous peritonitis, and segmental bowel necrosis may occur in some patients suffering from cyclic neutropenia.[8]

Deterrence and Patient Education

Patient education about careful oral and dental care and the judicious use of antibiotics are the mainstays of management for cyclic neutropenia. The importance of oral hygiene and regular monthly dental visits should be explained to the patient.[22]

Enhancing Healthcare Team Outcomes

Cyclic neutropenia is a distinctive disorder of unknown etiology, characterized by regularly cycling episodes of neutropenia, which occur about every three weeks.[8] Cyclic neutropenia frequently poses a diagnostic dilemma. These patients may exhibit non-specific signs and symptoms such as recurrent fever, oral ulcers, and infections. The cause of recurrent fever may be due to a myriad of diagnoses including, recurrent tonsillitis, infectious diseases, juvenile idiopathic arthritis, Behçet's disease, and familial mediterranean fever syndrome. The physical exam may reveal the fever, aphthous ulcers, and periodontitis, but the cause is difficult to know without proper diagnostic studies. Over the past few years, hematologists, immunologists, and geneticists have collaborated to bring about the discovery of the genetic and biochemical basis of cyclic neutropenia.[23] While the hematologist is almost always involved in the care of patients with cyclic neutropenia, it is important to consult with an interprofessional team of specialists that include an immunologist, geneticist, radiologist, and dentist. A collaboration of the team, interprofessional communication, care coordination, regular patient follow up visits, including lab tests, periodic dental cleaning, and judicious use of antibiotics are recommended to improve patient outcomes.[24]

Questions

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