Hypereosinophilic Syndrome

See the separate, general article on Eosinophilia.

Introduction

Hypereosinophilic syndrome (HES) is currently defined as a blood eosinophil count $>1.5 \times 10^9/L$ (for more than six months) and associated organ damage in the absence of secondary causes; it is categorised under the idiopathic group of eosinophilias. However, changes to this definition have been proposed based on recent studies identifying specific cellular and molecular disease phenotypes. This may have clinical and therapeutic significance.\[1\]

Due to the increasing availability of treatments, for example, it is unlikely that a patient would be left without therapy for six months whilst organ damage occurred. Furthermore, individuals with eosinophilia-related complications (eg, eosinophilic pneumonia) have been discovered who do not meet the criteria of an eosinophil level $>1.5 \times 10^9/L$. Finally, a secondary cause has been identified in some patients (eg, Fip1-like-1 (FIP1L1)/platelet-derived growth factor receptor alpha (PDGFRA)-associated HES).\[2\] Despite these advances the molecular pathogenesis remains unknown in most cases.\[1\]

The most up-to-date consensus definition was published by the Year 2011 Working Conference on Eosinophil Disorders and Syndromes, as follows:\[3\]

- Criteria for peripheral blood hypereosinophilia ($>0.5-1.5 \times 10^9/L$) fulfilled; and
- Organ damage and/or dysfunction attributable to tissue hypereosinophilia; and
- Exclusion of other disorders or conditions as major reason for organ damage.

Epidemiology\[4\]

- HES is rare in adults and tends to be under-diagnosed. It is even rarer in children.\[5\] There are no formal patient registers and lack of published data makes estimates of prevalence difficult.
- HES can present anywhere from the age of 20 to 50 years.
- HES has a preponderance in males (4:9:1).

History and examination

HES can only be diagnosed once secondary causes and clonal eosinophilias have been ruled out.\[6\] Document all medications, including herbal remedies and over-the-counter medicines and any recent travel. A full and thorough examination is needed, as the list of potential organs involved and the pathologies in each system are numerous.

Diagnosis

The diagnosis of HES is not always straightforward - eg, differentiating between idiopathic eosinophilia with organ involvement and eosinophilia associated with a systemic vasculitis. In order to diagnose HES, clonal eosinophilia, ie neoplastic proliferation of eosinophils, also needs to be excluded. This can be seen in a number of myeloid malignancies or as an eosinophilic leukaemia. Exclusion of clonal eosinophilia will usually require investigations similar to any suspected bone marrow (BM) neoplasia - eg, peripheral blood smear, BM examination and cytogenetic studies.

If all these tests are negative then idiopathic eosinophilia is the likely diagnosis - the most important subcategory of which is HES.
Presentation

The history and examination needs to be very thorough due to the multisystem nature of HES.

- Generalised symptoms - fatigue, aches and pains, fever, night sweats and pruritus.
- Diarrhoea is common, as are abdominal pain and nausea.
- Other symptoms depend on which organ is involved and extent of involvement; for example:
  - Cardiac - chest pain and breathlessness.
  - Respiratory - shortness of breath, and dry cough.
  - Alcohol intolerance with abdominal pain, flushing, and nausea.

Organ involvement in HES

This can be manifold and the following are some examples:

- Blood - thrombocytopenia, hypercoagulability.
- Cardiac - cardiomyopathy, valve abnormalities, pericardial effusion, thromboembolic disease.
- Respiratory - pneumonitis, pulmonary emboli, pleural effusion and eosinophilic infiltrates.
- Skin - dermatitis, urticaria, papular rashes.
- Ear, nose and throat - sinusitis.
- Central nervous system - acute cerebrovascular event and peripheral neuropathy.
- Gastrointestinal tract - tract inflammation, infarction of the gut secondary to emboli, splenomegaly, ascites, hepatitis, pancreatitis.
- Neurological - acute cerebrovascular accident, confusion, ataxia, peripheral neuropathy.
- Eyes - episcleritis, retinal thrombi.

Investigations

- FBC - eosinophils >1.5 x 10^9/L (0.5 x 10^9/L under the new definition); neutrophilia and anaemia are also common. Platelet counts can be high or low.
- Peripheral smear - eosinophils may have cytoplasmic vacuolisation and nuclear hypersegmentation and there may also be nucleated erythrocytes.
- ESR - usually raised.
- U&E and LFTs may both be abnormal.
- 12-lead ECG - may show conduction defects or inverted T waves.
- CXR - look for pleural effusions.

Further tests should be tailored towards the presenting symptoms and signs - eg, echocardiogram, further lung imaging, biopsy of endocardium, skin or BM.

An algorithm has been developed to assist in the differentiation between clonal eosinophilia, haematological malignancies and idiopathic eosinophilia. This involves peripheral blood screening for genetic abnormalities, BM cytogenetics, peripheral blood lymphocyte phenotyping and T-cell receptor gene rearrangement studies.

Management

- The rarity of HES means there are no evidence-based guidelines on management. Management is aimed at reducing tissue and blood eosinophils and monitoring and restricting organ damage - eg, regular echocardiographic and serum troponin monitoring.
- Corticosteroids are first-line - eg, prednisolone with hydroxyurea or interferon alpha as second-line agents. If these also fail, or the monoclonal antibodies, such as mepolizumab (not licensed yet) and alemtuzumab, may be useful.
- Allogeneic hematopoietic cell transplant may be a treatment option in refractory HES.

Other generic measures may include anticoagulants, and symptomatic relief agents - eg, histamines and opiates. Other treatment will depend upon the organs involved - eg, diuretics in cardiac failure.
**Prognosis in hypereosinophilic syndrome**

- Good prognostic factors include response to prednisolone and lack of systemic symptoms.
- Poor prognosis is associated with anaemia, thrombocytopenia and organ involvement at time of presentation.
- The five-year survival rate is 80% with congestive heart failure being the most common cause of death.
- Leukaemic change is a risk in prolonged disease.

**Further reading & references**


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