Aplastic Anaemia in Children

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Introduction

Aplastic anaemia is a life threatening blood disorder that affects a large number of children each year in India. Exposure to toxic agents like benzene, radiation and viruses like hepatitis A have been implicated in its aetiology. The incidence in developing countries is far higher compared to developed countries. Investigating a child with pancytopenia is more complex than that of an adult as numerous inherited bone marrow failures can also present with aplastic anaemia without any obvious somatic features. Precise aetiological diagnosis is therefore mandatory in children before embarking on any therapy.

Initial Evaluation of a Child with Cytopenia

Children with aplastic anaemia can present initially with a single cell line failure before the onset of pancytopenia. Anaemia results in failure to thrive, respiratory distress and cardiac failure. Leucopenia can present with recurrent fever, mouth ulcers and gingivitis. Thrombocytopenia presents with skin petechiae and mucosal bleeds. A thorough history regarding the time of onset, the presenting symptoms and family history of similar illness, or early sibling deaths would point to an inherited bone marrow failure syndrome. Clinical examination to look for dysmorphism including short stature, hyperpigmentation, ear anomalies and radial ray defects involving the hands would help point to a genetic aetiology.

Lab diagnosis of a child with cytopenia involves a reticulocyte count at the outset. If reticulocyte count is low, a bone marrow aspiration and biopsy is indicated to help confirm the diagnosis of aplastic anaemia. Hepatitis serology, HIV serology, antinuclear antibody assay, screening for paroxysmal nocturnal haemoglobinuria with CD55/59 assay by flow cytometry are baseline investigations. A possible genetic aetiology can be ruled out by a peripheral blood stress cytogenetics with Mitomycin C. A positive screening confirms the diagnosis of Fanconi anaemia and these children need to be treated as per protocol for Fanconi anaemia. Telomere length to rule out subtle forms of Dyskeratosis congenita is also mandatory for any child with newly diagnosed aplastic anaemia. Echocardiogram to rule out associated heart defects and ultrasonogram to diagnose a horse shoe kidney are required if Fanconi anaemia is suspected. All evaluation should be done with speed as infections and bleeding would compromise management and result in early mortality. HLA typing from the peripheral blood to type HLA antigens A, B, C, DRB1 and DQB1 is to be done on the child and any siblings available to identify a matched family donor at the earliest.

Supportive Care

Optimal supportive care must be provided during evaluation for a child with aplastic anaemia. Packed red cells screened and negative for HIV, Hepatitis B and C and is leucocyte filtered and irradiated can be transfused at 10-15 ml/kg if haemoglobin is less than 8 gm. It is best to avoid donations from close family members. All fevers must be treated with broad spectrum antibiotics after culture. Neutropenic children do not manifest all the symptoms of infections. Early imaging like CT chest for minimal cough is indicated to rule out a fungal and prompt institution of antifungal antibiotics will prevent early mortality. Platelet transfusion is indicated for bleeding diathesis or if count is less than 10,000. The children must be taken care of in a clean environment to avoid infections. Adequate care must be taken to keep mucous membranes of the mouth and perianal region free of infections with good hygiene. A low bacterial neutropenic diet which consists of simple well cooked foods with minimum spice and oil is recommended. Soft cheese,
canned foods and fresh salads and fruits are not recommended. Pasteurised milk and curd can be consumed. The child should be referred early to a higher centre where all facilities including those for haematopoietic stem cell transplantation exists.

**Definitive Therapy**

Acquired aplastic anaemia can be treated with either haematopoietic stem cell transplantation or immunosuppressive therapy. Matched sibling donor transplant offers over a 90% chance of cure and is the first choice. Immunosuppressive therapy with antithymocyte globulin and cyclosporine offers about 70% chance of cure especially if treatment has started within 2 months of diagnosis. All inherited bone marrow failure syndromes need to be treated only with haematopoietic stem cell transplantation with modifications specific to the underlying defect.

**Haematopoietic Stem Cell Transplantation**

If an HLA matched donor has been identified, the sibling donor needs to also undergo mandatory testing for Fanconi anaemia or other forms of IBMFS if suspected as they can be completely asymptomatic at the time of diagnosis. Conditioning chemotherapy for transplantation is minimal with combinations of fludarabine and cyclophosphamide or antithymocyte globulin. Bone marrow harvest done from the sibling donor is the stem cell of choice for aplastic anaemia as it avoids the risk of graft versus host disease. One to one nursing in a HEPA filtered room is recommended to prevent bacterial infections and fungal infections like Invasive Aspergillosis. Graft versus host disease prophylaxis needs to be continued for 6 months to 1 year to ensure that there are no late complications.

**Immunosuppressive Therapy**

Acquired aplastic anaemia in children can be treated with immunosuppressive therapy – IST, if there are no matched family donors available for haematopoietic stem cell transplantation. Immunosuppressive regimens are designed to reduce the number of T lymphocytes that result in loss of stem cells due to immunedysregulation. IST regimes involve a combination of antithymocyte globulin, cyclosporine and steroids. Antithymocyte globulin – ATG administration in children necessitates the insertion of a central line. Horse ATG at a dose of 15 mg – 40 mg / kg / day for 5 days is the recommended protocol. The dose is rounded up to the nearest 250 mg vial to avoid wastage of medication. ATG is known to cause allergy and anaphylaxis and children need to be covered with steroids during the infusion. The child needs to be given cover with paracetamol, antihistamine and steroids all through the five day period. Cyclosporin A is added on day 6 to continue immunosuppression for 6 months to 1 year. During this time, the child will continue to require blood and platelet support and recovery can be expected by 12 weeks. Recent reports from the NIH suggest that addition of Elthrombopag results in higher remission rates with IST. All vaccines are to be avoided whilst on cyclosporine. Long term follow up is required to detect a relapse or transformation to acute myeloid leukaemia.

**Inherited bone marrow failure syndromes**

<table>
<thead>
<tr>
<th>Type</th>
<th>Defect</th>
<th>Diagnosis</th>
<th>Gene mutation</th>
<th>Peculiar features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi anaemia</td>
<td>FANC gene</td>
<td>Mitomycin C test in peripheral blood</td>
<td>Several</td>
<td>Sensitive to chemotherapy DNA repair defect. Only 20% chemotherapy doses used during transplantation</td>
</tr>
<tr>
<td>Schwachman Diamond syndrome</td>
<td>SDBS gene</td>
<td>Chromosomal analysis</td>
<td>Chromosome 7</td>
<td>Atrophic pancreas, failure to thrive</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>DKC gene</td>
<td>Chromosomal analysis - short telomere length</td>
<td>X chromosome</td>
<td>Mouth and nail changes Pulmonary toxicity during transplant</td>
</tr>
<tr>
<td>Pearson syndrome</td>
<td>Mitochondrial defect</td>
<td>Chromosomal analysis</td>
<td>Mitochondria</td>
<td>Early death in infancy</td>
</tr>
<tr>
<td>Congenital Amegakaryocytic thrombocytopenia</td>
<td>Thrombopoietin receptor defect</td>
<td>Chromosomal analysis</td>
<td>c-mpl gene mutation</td>
<td>Thrombocytopenia progressing to complete marrow failure</td>
</tr>
</tbody>
</table>

The inherited marrow failure syndromes (Table 1) need to be diagnosed accurately for management of the index child and for providing prenatal diagnosis to prevent birth of another affected child in the family. These children can be managed initially with the support of androgenic steroids – Stanazolol and Oxymethalone until definitive HSCT can be offered. All marrow suppressive medications like chloramphenicol, phenytoin, cotrimoxazole and linezolid need to be avoided in children with aplastic anaemia.

**Conclusion**

Children with aplastic anaemia have excellent outcomes if treated adequately with antibiotics, blood products and referred early. Once the genetic nature is confirmed, HSCT is the only form of cure.
HSCT if a matched sibling donor is available or immunosuppression are two choices available for children with acquired aplastic anaemia. Novel drugs like eltrombopag\(^8,9\) and transplantation techniques like haploidentical HSCT and gene therapy offer hope for the future in the management of these children.

**Key points**

1. Adequate measures to look after the child during the referral process
2. Fanconi anaemia is common in our country due to consanguinity and features of the disease including thumb anomalies, short stature must be looked for in any child or young adult with pancytopenia
3. It is good practice to store DNA in all children with aplastic anaemia for accurate genetic diagnosis
4. Children with Fanconi anaemia can be referred to a specialist centre to have their transplant as the conditioning regimens for these transplants are low intensity due to their DNA repair defect
5. Immunosuppressive therapy with ATG, cyclosporine and steroids as a combination is best instituted early to obtain optimal results

**References**