Hereditary Hemolytic Anemia in Children

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Hereditary hemolytic anemias (HHAs) refer a diverse group of inherited disorders characterized by shortened red blood cell (RBC) lifespan due to intrinsic defects involving the RBC cell membrane, cytoskeleton, hemoglobin, or metabolic enzymes. Among these, hereditary membranopathies—including hereditary spherocytosis (HS), hereditary elliptocytosis (HE), hereditary xerocytosis (HX), and overhydrated stomatocytosis (OHS), etc.—form a major subset and caused by mutations affecting membrane structural integrity or cation transport, leading to impaired deformability and altered hydration. Clinical severity varies widely, ranging from compensated hemolysis to severe transfusion-dependent anemia, with common presentations including jaundice, reticulocytosis, gallstones, or neonatal hyperbilirubinemia. Hemoglobinopathies are major subset which usually predominant in Southeast Asia, Africa, US, and Europe, but very rare in Korea, and caused by mutations involving globin synthesis, which eventually lead to defective or absent globin. α- and β-thalassemia, and sickle cell disease are the major entity of the hemoglobinopathies. Enzymopathies caused by defects in major metabolic enzymes which involve ATP synthesis in RBCs. Major enzymes are known as pyruvate kinase, gucose-6-phosphate dehydrogenase, hexokinase, enolase, pyrimidine 5-nucleotidase, trisosphosphate isomerase, etc.

Accurate diagnosis is essential for appropriate management, as therapeutic responses differ significantly among HHA subtypes. Initial evaluation starts with confirming hemolysis and excluding immune-mediated or microangiopathic processes. Further diagnostic process integrates RBC indices, reticulocyte response, and peripheral smear morphology, supplemented by specialized assays. The eosin-5-maleimide (EMA) binding test and osmotic fragility studies are valuable for detecting membrane loss in HS, while osmotic gradient ektacytometry provides a comprehensive assessment of cellular deformability, surface area–to–volume ratio, and hydration status, enabling differentiation among HS, HE, HX, and OHS. When phenotypic evaluation is limited—such as in recently transfused patients—next-generation sequencing (NGS) panels allow precise identification of pathogenic variants underlying membranopathies, enzymopathies, and congenital dyserythropoietic anemias, substantially improving diagnostic accuracy.

Management strategies depend on the specific diagnosis. Splenectomy, though effective for HS and select cases of HE, provides little benefit and carries significant risk in HX and OHS, where it is contraindicated. Partial splenectomy may offer a balanced approach for young children with severe, splenectomy-responsive HHAs, aiming to reduce hemolysis while preserving immune function, but the result of partial splenectomy is controversial. As genetic insights refine diagnostic pathways and targeted therapies emerge, individualized management remains central to optimizing outcomes in HHA.