Pediatric Hereditary Spherocytosis —
Symptoms and Treatment

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Hereditary Spherocytosis (Minkowski-Chauffard syndrome) is one of the most common chronic hemolytic anemias worldwide, non-race dependent, yet most frequently encountered in the Caucasian population. The hallmark of this disorder is the changed shape of the red blood cells called spherocytes. Because of its morphological defect, red blood cells' life is shorter than usual resulting in RBCs hemolysis. Clinical presentation of hereditary spherocytosis is diverse, ranging from subclinical cases with mild symptoms, but can also present with severe symptoms.

Epidemiology of Pediatric Hereditary Spherocytosis

The northern European Caucasian was the main population this disease was linked to. Approximately 1 in 2000-5000 Caucasians in Europe and America have hereditary spherocytosis. The inheritance pattern is autosomal dominant, one that is responsible for three-quarters of all cases, but the disease can occur due to the spontaneous mutation, even the possibility or autosomal recessive fashion is relevant.
The resent researchers have demonstrated that numerous red blood cell membrane proteins abnormalities can lead to the development of the clinical presentation of HS. The most frequently encountered membrane protein defect recognized as the underlying molecular lesion is ankyrin 1, than spectrin and protein band 3. In the chromosomes 1, 8, 14, 15 and 17, some of the hereditary spherocytosis gene defects are identified.

**Normal Physiology of Pediatric Hereditary Spherocytosis**

A red blood cell or erythrocyte is an up to 8 microns wide blood element that, apart from being part of circulating blood, needs to be able to pass through the capillary network and the spleen. The essential facts when concentrating on erythrocyte’s path are the diameters of the capillaries and the red pulp’s endothelial passages being 3 and 1 micron wide.

The diameter of these spaces indicates that erythrocyte should be able to deform without the breaking of fragmenting and reshaping afterward.

The components that are responsible for the deformability of the red blood cells are as follows:

- **SA/V ratio**: The proportion of the area of the outer surface of erythrocyte divided by the volume of the erythrocyte – this is the indicator of erythrocyte’s geometry.
- **MHCH**: Mean corpuscular hemoglobin concentration as the parameter of the viscosity of the erythrocyte.
- The degree of the deformability and stability of the erythrocyte’s membrane, which is dependent on bending and elastic shear modulus, as well as on yield stress.

The membrane of the erythrocyte is a complex combination of proteins between double lipid layers that are positioned on the outer surface of the erythrocyte. The membrane itself has multiple penetrating proteins, as well as other cell’s membrane in order to be able to fulfill its biological functions.

However, three features are specifically needed for the erythrocyte’s membrane:

1. Non-covalent bonds between approximately ten billions of both protein and lipid molecules are making continuous thin plasma membrane of the cell. These bonds allow a stable 3D configuration that makes the necessary transformation of the erythrocytes possible.
2. Asymmetry of the distribution of the protein and lipid molecules, both inside a particular layer and throughout the membrane itself, allows the fluid structure of the plasma membrane itself.
3. The dual nature of the plasma membrane itself is demonstrated when considering both the barrier and the guarding function and, at the same time, the transporter function of the Trans membrane molecular passages for the intra-extracellular passing of the nutrients and signals.
Pathophysiology of Pediatric Hereditary Spherocytosis

In the hereditary spherocytosis, the **main issue is the defect of the plasma cell membrane** that leads to the loss of the adequate degree of deformability as the result of the membrane surface area loss.

**Several red blood cells membrane proteins defects are found to be the source of the problem**, the main ones are ankyrin-1, and band-3 and spectrum defects. It was found that multiple mutations in the genes responsible for the encoding of the above-named proteins are the primary reason for the hereditary spherocytosis spectrum to appear.

Morphologically unstable erythrocytes that cannot undergo the required transformation and break inside the narrowest place of the path, namely the epithelial slits of the spleen’s red pulp, are the reason for the hemolysis in affected individuals.

The **hemolysis of the affected spherocytes leads to the increase of the bilirubin** (the unconjugated type) as the main degradation product of the erythrocyte and the decrease in the red blood count. The elevated bilirubin levels present as kernicterus in neonates.

**Signs and Symptoms of Pediatric Hereditary Spherocytosis**

The signs and symptoms of the hereditary spherocytosis are solely the results of the spleen destroying abnormal erythrocytes-spherocytes. The **amount of the spherocytes in the circulating blood is the one determining the course of the disease**, either in acute or chronic form.

**Acute form**

It is presented as the episode of anemia, jaundice, followed by the various degrees of:

- Paleness
- Fatigue
- Hypoxia
- Tachycardia
- Exercise intolerance

**Chronic form**

The disease itself can manifest in various age groups starting with the neonate period, next is the presentation of the disease being in the children of four to five years up to adult individuals.

Some children remain asymptomatic.

A chronic form of the disease manifests as severe anemia, with pallor, jaundice, fatigue, and exercise intolerance (symptoms of anemia).

Severe cases may be marked by the expansion of (but to a lesser extent to thalassemia major):
- Diploë of the skull.
- Medullary region of other bones.
- After infancy, splenomegaly may occur, followed by hypersplenism with decreased WBC count and platelets, resulting in pancytopenia.
- Gallbladder sludge can accumulate following an elevated level of unconjugated bilirubin as the result of the spherocytes degradation.
- Abdominal pain or cramps as the result of either splenomegaly or gallbladder pigmented, stones can occur in these patients.
- Because of the high RBC turnover and heightened erythroid marrow activity, children are susceptible to an aplastic crisis as a result of parvovirus infection and hypoplastic crisis as a result of other infections.

Diagnosis of Pediatric Hereditary Spherocytosis

**Hemoglobin:** The hemoglobin level is usually 6-10 g/dL, but it can be in the normal range.

**Mean corpuscular volume (MCV):** Is normal level.

**MHCH:** Is typically elevated in the hereditary form.

**Evidence of hemolysis**
- Increased reticulocyte counts, due to an elevated need for the red blood cells.
- Indirect hyperbilirubinemia.
- Decreased haptoglobin.
- Presence of gall stones on abdominal U/S.

**Peripheral blood smear**
- The simplest test to demonstrate spherocytosis is the peripheral blood smear.
- **Affected red blood cells will present without the central pale spot** that the healthy erythrocytes possess, and will be smaller.
- Finding itself is not seen only in hereditary form, it is common for all types of the spherocytosis.

**Osmotic fragility test**
- The gold standard test for defining the hereditary spherocytosis has been the osmotic fragility test.
- The test itself is conducted as the spherocytes will burst inside the less concentrated liquid which will cause the regular erythrocytes to rupture.
- Even though this test is essential for confirming the diagnosis, one-quarter of all cases are missed when it is used.

Diagnosis of hereditary spherocytosis in neonates

The **anemia rarely manifests in the first seven days of a baby's life.** The peripheral blood smear may not show spherocytes as they are not frequently seen. Splenomegaly is rarely present in neonates. The reticular count is infrequently elevated.

The **most consistent findings are pathological MHCH and MCV parameters.**

The essential information regarding neonates is acquired from future parents regarding their history of the hereditary spherocytosis.
One of the proposed algorithms for the HS positive parents’ neonate management is that the MCHC/MCV ratio should be determined. Based on the cut off value of 0.36, the following paths are proposed:

1. If the value is higher than 0.36, the likelihood of autosomal dominant hereditary spherocytosis is considered.
2. If the value is lower than 36, spherocytes are looked for in the peripheral blood smear, and, if found, autosomal dominant form is considered. The smear without detected spherocytes doesn’t exclude the possibility of HS.

The probable autosomal dominant form of HS demands the following tests and hematology consultation.

Although the genetic basis for the development of hereditary spherocytosis has been well researched and documented, genetic tests are not routinely conducted due to the possibilities of simpler tests for confirming the diagnosis.

However, the DNA based method for the detection of the plasma membrane protein’s defects is an applicable one. Single strand rapid screening for confirming mutations in recognized regions of HS-associated genes is available.

Classification of Pediatric Hereditary Spherocytosis

The hereditary spherocytosis can be divided into three groups based on severity:

**Mild**
- The disease has an autosomal dominant transfer.
- Hemoglobin level is normal.
- Reticulocytes are below 6%.
- Bilirubin level is between 17 and 34.2 micromole per liter.
- Some spherocytes in the peripheral blood smear.
- Splenectomy is rarely done.
- Transfusion is rare.

**Moderate**
- The disease has autosomal dominant transfer, but can be encountered as spontaneous mutation.
- Hemoglobin level is between 60 and 80 g/l.
- Reticulocytes are above 6%.
- Bilirubin level is up to 51 micromole per liter.
- Spherocytes in the peripheral blood smear.
- Splenectomy is done due to the decreased physical ability, but may be needed in patients older than 5 years.
- Transfusions are done up to two times in the infant period.
- SDA PAGE shows ankyrin -1, band-3 and protein 4 positive results.

**Severe**
- The disease has autosomal recessive transfer.
- Hemoglobin level is below 60 g/l.
- Reticulocytes are higher than 10 5
- The bilirubin level is higher than 51 micromoles per liter.
- Microspherocytes and poikilocytosis in the peripheral blood smear.
- Splenectomy is done at the age two to three.
- Transfusions are frequently done.
- SDA PAGE positive for ankyrin 1 and band 3.

Complications of Pediatric Hereditary Spherocytosis

Common complications of hereditary spherocytosis include:

Cholelithiasis

The condition is stored in the gallbladder forming sludge and calculi due to excessive unconjugated bilirubin. This results in the following:

- Abdominal pain.
- Potential complications of gallbladder stones, such as cholecystitis.
- Potential carcinoma of the gallbladder.
- Gallbladder small bowel obstruction (more frequently).

Hemolytic episodes

Rapid onset of anemia happens due to an acute viral infection that is followed by the hyperplasia of the reticuloendothelial system, prolonged serious illness or other unusual strain.

Aplastic crises

It is a rare event which usually happens after a parvovirus B19 infection.

Following the viral attack on the red blood cells precursors in bone marrow, the intermittent red blood cells aplasia develops, leading to the drop of the reticulocyte count below 1%, as well as the drop of the hemoglobin level below 60 g/l.

The episode itself should last for up to ten days and resolve completely.

The parvovirus B19 post infectious immunity should be permanent once the crisis has resolved.

Differential Diagnosis of Pediatric Hereditary Spherocytosis

A differential diagnosis is made regarding disorders that produce anemia.

- Acute oxidant injury – the spherocytes may develop, although not likely.
- Microangiopathic, macroangiopathic and immune hemolytic anemias.
- Hemolytic transfusion reactions.
- Hereditary pyropoikilocytosis.
- Zinc toxicity.
- Various causes of poisoning.
- Severe low phosphate blood levels.
For neonate cases of ABO incompatibility.

Management of Pediatric Hereditary Spherocytosis

Splenectomy

The intervention cures almost all the cases of the hereditary spherocytosis due to the elimination of the main spherocytes fragmentation place; therefore, recovering the reticulocyte count and the bilirubin levels to normal values thus preventing the usual complication of HS.

The intervention itself should be postponed up to the age of six to nine if the clinical course of the disease allows it.

Regardless of the severity of the clinical presentation of hereditary spherocytosis, splenectomy should not be done if the patient is younger than three, even in the setting of frequent transfusions needed to cope with the disease.

Mode of surgery: Laparoscopic intervention is the gold standard if there are no contraindications.

Long-term immunization: The immunization against Neisseria meningitides, Pneumococci and Haemophilus should be done in advance.

Complications of surgery: The operation has its own complications that include:

- Bleeding.
- Pancreatitis as early complications.
- Post-splenectomy encapsulated bacteria and parasitic infections (late severe complication).

Folate therapy

Folate therapy should be considered in moderate and severe cases, although the benefit of the therapy is not precisely defined.

References


https://ghr.nlm.nih.gov/condition/hereditary-spherocytosis#inheritance

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