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Hereditary Spherocytosis (Spherocytic Anemia)

Guideline

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Hereditary Spherocytosis (Spherocytic Anemia)

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1 Definition and Basic Information

Hereditary spherocytosis is a heterogeneous group of diseases affecting the red blood cells (erythrocytes). Their common features are structural membrane defects which result in an impairment of erythrocytic deformability. The highly variable clinical manifestations of the disease depend on the various mutations of genes encoding membrane proteins, their various functional consequences, and the respective mode of inheritance.

The disease was first described in the second half of the nineteenth century. In 1900 Oskar Minkowski published his observations on familial clusters [1]. Hereditary spherocytosis belongs to the congenital hemolytic anemias, named after the microscopic aspect of spherocytes in a blood smear.

1.1 Prevalence

Prevalence in Germany is estimated to amount to approx. 1:2000 - 2500 [2]. Hereditary spherocytosis is by far the most common congenital hemolytic anemia in persons of northern or central European descent.

1.2 Cause

The common cause of the various forms of hereditary spherocytosis are membrane defects. These defects decrease the deformability of the erythrocytes and accelerate their degradation in the spleen. The genes encoding the membrane proteins ankyrin, band 3, and spectrin are most frequently affected [3]. Modifications of the genes encoding protein 4.2, the RH complex and cases with hitherto undefined defects are less frequent [4]. The disease follows an autosomal-dominant trait in about 70 percent of all persons affected, whereas autosomal-recessive inheritance prevails in only 15 percent. Other patients acquire the disease on account of new mutations. Table 1 shows a classification based on molecular features [3- 6].

Table 1: Molecular Classification of Hereditary Spherocytosis

Type	Defect	Frequency[1]	Inheritance[2]	Proteins	Course[3]	OMIM[4]
1	Ankyrin-1	USA & Europe: 40 - 65%	autos. dom., autos. rec.,	Ankyrin-1 and Spectrin	Mostly moderate; seldom mild or severe	#182900

Type	Defect	Frequency[1]	Inheritance[2]	Proteins	Course[3]	OMIM[4]
		Japan: 5 - 10%				
2	β Spectrin	15 - 30%	autos. dom.,	β Spectrin	Mild to moderate	#182870
3	α Spectrin	< 5%	autos. rec.	α Spectrin	Mostly severe	#270970
4	Band 3	20 - 35%	autos. dom.	Band 3	Mild to moderate; very seldom severe recessive form	#109270
5	Protein 4.2	USA & Europe: < 5% Japan: 45 - 50%	autos. rec.	Protein 4.2	Mild to moderate	#612690

Legend:
*[1] Frequency - relative frequency in central Europe; [2] autos. - autosomal, dom. - dominant, rec. - recessive; [3] course - see Table 2; [4] OMIM - Online Mendelian Inheritance in Man [5]; *adapted after Perrotta et al., [4]*

2 Clinical Presentation

2.1 Symptoms

The clinical spectrum of hereditary spherocytosis ranges from severe forms requiring transfusions in early childhood to asymptomatic patients with incidental diagnosis by laboratory analysis or other indication. Characteristic features and typical complications are compiled in Table 2 and 3.

Table 2: Characteristic Features in Cases of Hereditary Spherocytosis

Symptom	Comment
Anemia	Coombs negative
Icterus	Indirect bilirubin increased in most patients
Splenomegaly	Variable extent
Family history	Mostly positive

Table 3: Typical Complications in Case of Hereditary Spherocytosis

Symptom	Comment
Cholelithiasis	Consequence of chronic hemolysis
Aplastic crisis	Most common after initial infection with Parvovirus B19
Hemolytic crisis	After intercurrent infections
Megaloblastic crisis	In case of folic acid deficiency

Hemolytic crises reoccur particularly in the context of intercurrent infections. The course is mostly mild in young adults, and blood transfusion will not be necessary. The aplastic crisis mostly occurs only once. It might result in a strong decrease of the hemoglobin concentration, making a blood transfusion necessary.

Of seldom occurrence are cardiovascular complications, extramedullary hematopoiesis, or secondary hemochromatosis [4].

In patients with a mild form of the disease - who did not undergo splenectomy - the condition of chronically enhanced hemolysis might also lead to extramedullary hematopoiesis with the clinical picture of intrathoracic, paravertebral tumors subsequent to a progression over decades. Varicose ulcers might appear in elderly patients. Whether the association between hereditary spherocytosis and spinocerebellar ataxia, rare cases of which have been reported, relies on the same genetic defect has not been elucidated yet.

A classification of hereditary spherocytosis based on clinical severity grades is shown in Table 4 [2, 7-10].

Table 4: Clinical Classification of Hereditary Spherocytosis*

	Carrier	Mild	Moderate	Severe	Very Severe
Patients (%)[1]		25 – 30	60 - 70	10	3 – 5
Hemoglobin (g/L)	Normal	11 – 15	8 - 11	6 - 8	< 6
Reticulocytes (%)	1 – 4	< 6	≥ 6	> 10	> 10
Bilirubin (mg / dL)	< 1	1 – 2	≥ 2	≥ 2 - 3	≥ 3
Peripheral blood smear	Normal, occasional single spherocytes	Single spherocytes	Spherocytes identifiable	Spherocytes identifiable	Microspherocytes Poikilocytosis
Transfusion requirement	None	0 – 1	0 - 2	≥ 3	Regularly

Legend:
*[1] relative frequency (%); [2] osmotic fragility; *adapted after Perrotta et al., [4]*

2.2 Asymptomatic Persons with Conspicuous Laboratory Parameters

A special group are carriers of the genetic abnormality without clinical symptoms and without a positive family history, in whom incidentally conspicuous laboratory parameters were found. Laboratory findings indicative of hereditary spherocytosis are summarized in Table 5 [9]:

Table 5: Laboratory Values Indicative of Hereditary Spherocytosis

Parameters	Comments
•MCHC above normal range (35 or 36g/dl)*	The combination of MCHC exceeding normal range and RDW > 15% has a high specificity; however, RDW values are only rarely increased in abortive, mild cases
•Reticulocyte count increased	May appear intermittently
•Spherocytes	Isolated
•LDH increased •Indirect bilirubin increased	Rare

Parameters	Comments
•Haptoglobin decreased	Occasionally normal in asymptomatic persons
•Increase of hyperchromatic, hyperdense erythrocytes	
•Slight increase of osmotic fragility	In particularly sensitive tests (AGLT)

Legend:
** see Chapter 2.3 for a comprehensive discussion of the parameter MCHC*

A combination of several parameters is needed to confirm the tentative diagnosis of a genetic predisposition. If no spherocytes are detected, if the erythrocyte indices remain unchanged, and if the reticulocytes are within normal range, hereditary spherocytosis cannot be ruled out, but it is unlikely that such person will ever show any symptoms. The differentiation between a clinically asymptomatic predisposition and a mild form of spherocytosis can be difficult. Mild forms may occasionally exacerbate due to splenomegaly of a different etiology (e.g. lymphomas) or due to viral infections (EBV, parvovirus).

2.3 MCHC as an Indicator of RBC Membrane Disease

The elevated MCHC (mean cellular hemoglobin concentration) value is of special relevance to identifying spherocytosis patients. It reports the concentration of hemoglobin in terms of hemoglobin per 100ml erythrocytes.

Increased MCHC values may be found in the following situations:

- Hemoglobin value is determined too high due to any kind of plasma turbidity
- RBC count is determined too low, e.g. in case of coagulated blood samples
- High cold agglutinin titers
- Hereditary RBC membrane disorders such as spherocytosis and variants, e.g. xerocytosis
- Hemoglobin CC anomaly
- Homozygous sickle-cell disease (occasional)
- Hemochromatosis patients with massive iron overload [11], also depending on the genotype

3 Diagnosis

3.1 Diagnostics in Cases of Suspected Hereditary Spherocytosis

Meticulous medical history and physical examination provide the basis of rational diagnostics. Further diagnostic steps to be taken in adults are shown in Table 6 and 7 and as an algorithm presented in Figure 1.

Table 6: Basic Diagnostics in Cases of Suspected Hereditary Spherocytosis

Parameter	Specification	Evaluation (as diagnostic criterion)
Family History	• Autosomal dominant or recessive	Facultative
Splenomegaly	• Physical examination • Sonography	Facultative
Differential blood cell count, automated cell counter	• Anemia • MCHC[1] > 35 g/dl • Anisocytosis (RDW[2])	Facultative Facultative Facultative
Differential blood cell count, microscopy	• Spherocytes • Anisocytosis	Variable[3, 4] Facultative
Enhanced hemolysis	• Reticulocytes normal or increased • Increase of indirect bilirubin • Increased LDH[5] • Haptoglobin not detectable	At least 2 parameters obligatory
Coombs Test	• Negative	Obligatory

Legend:
[1] MCHC - mean corpuscular hemoglobin concentration; [2] RDW- size distribution of the RBC in automated differential blood cell counts; [3] only recognizable in immaculate blood smears; [4] the microscopic picture may be uncharacteristic in adults, only few spherocytes might be identifiable in mild forms, or none at all, whereas polychromasia and anisocytosis are almost invariably observed; [5] LDH – lactate dehydrogenase;

Table 7: Extended Diagnostics in Cases of Suspected Hereditary Spherocytosis

Parameter	Specification
Osmotic fragility	Acidified Glycerol Lysis Time (AGLT)
Flow cytometry	Binding of eosin-5-maleimide
Membrane analysis	SDS PAGE
Gen analysis	Sequencing of candidate genes: linkage analysis

There is no single test that identifies all forms of hereditary spherocytosis. For this reason it is recommended to combine two test procedures. A recent study with 150 patients even achieved a sensitivity of 100 percent by combination of AGLT and EMA test [12]. An examination of osmotic resistance with hypotonic salt solutions has a distinctly lower sensitivity than AGLT and EMA test.

Acidified Glycerol Lysis Time (AGLT)

The acidified glycerol lysis time (AGLT) is a highly specific method for measuring hemolysi. The sensitivity of the test ranges between 80 and 95% [13]. It has to be performed within hours after blood sampling or by using samples which have been dispatched by courier (samples must be chilled depending on the season!).

Flow Cytometry (EMA Test)

The method of flow cytometry (EMA test) was introduced in 2000 [14]. It is based on the binding of the fluorescent dye eosin-5-maleimide to erythrocytes. Binding is decreased in patients with hereditary spherocytosis as compared to healthy persons. The sensitivity of the tests amounts to 90 - 95%, its specificity is at 95 - 99%. The result will be valid only if the measurement proceeds within a maximum dwell time of 48 hours between blood sampling and test performance. Even lower fluorescence binding than in hereditary spherocytosis is observed hereditary pyropoikilocytosis, whereas binding is increased in cases of stomatocytosis [15].

Ektacytometry

An exact determination of osmotic fragility (and thus a differentiation between spherocytosis and macrocytic stomatocytosis) is possible by means of osmotic-gradient ektacytometry. However, this method is currently available only in Zurich (Laboratory of Dr. J. Goede, Hematology Clinic, University Hospital Zurich, Rämistrasse 100, 8091 CH Zurich: Tel.: +41 (0)44 255 95 97; Fax: +41 (0)44 255 89 68) and in Paris, Hospital Kremlin Bicêtre.

As the test can only be performed with fresh blood samples taken at the site of analysis, ektacytometry remains reserved to few exceptional cases in which the diagnosis cannot be obtained otherwise.

Membrane Analysis

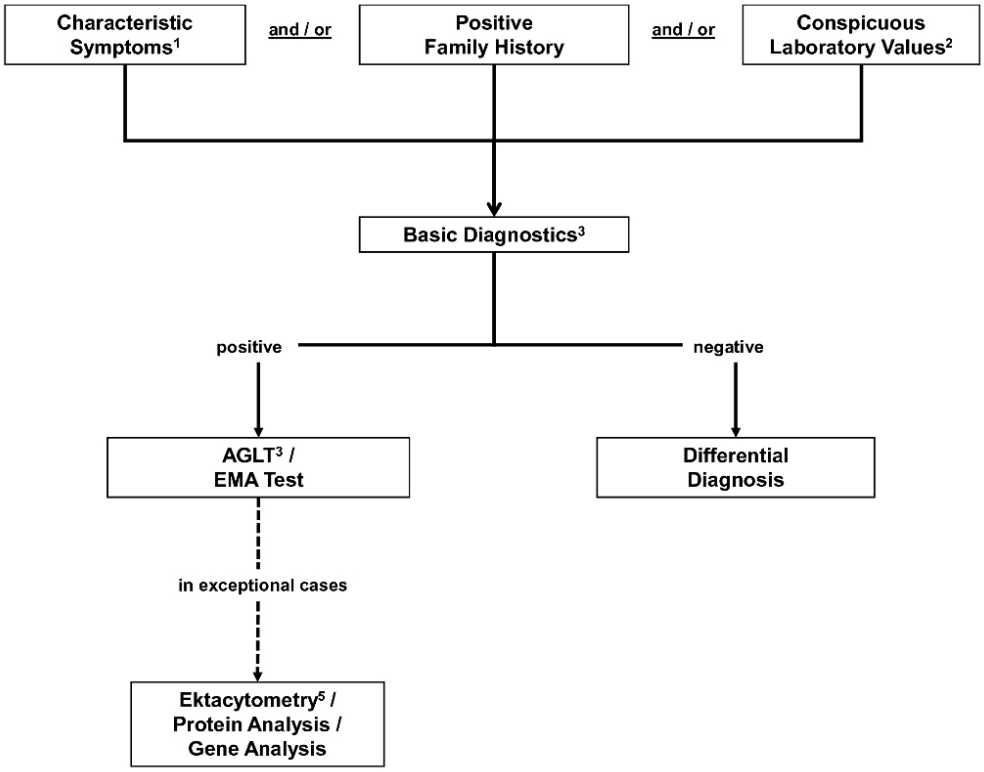
Biochemical analysis by means of gel electrophoresis can be applied as a quantitative method to prove a decrease in the number of membrane proteins, and qualitatively to identify the particular proteins affected. Only seldom do these methods contribute to diagnostics.

Genetic Analysis

Molecular genetic diagnostics identifies the genetic defect specific to the patient and/or the family [3, 5]. These diagnostics remain reserved to special cases on account of the numerous target genes showing heterogeneity of possible mutations and the considerable costs arising therefrom.

All diagnostic methods produce false-positive and/or false-negative results. As a rule, the diagnosis of patients without a positive family history should therefore not just rely on one single method only (e.g. only osmotic resistance, only EMA, only biochemical membrane diagnostics). For screening purposes at least two different methods should be applied, preferentially the EMA test and AGLT. The specificity and sensitivity of future diagnostic tests will have to be compared with these two laboratory procedures.

Figure 1: Diagnostic Algorithm in Case of Suspected Hereditary Spherocytosis



Legend:
[1] characteristic symptoms – anemia, icterus, splenomegaly , hemolytic or aplastic crisis subsequent to viral infection;
[2] conspicuous laboratory findings – MCHC > 35 and RDW > 15 %; reticulocyte count increased, hemolysis parameters positive;
[3] Basic diagnostics – physical examination; differential blood cell count with microscopical differentiation of erythrocytes, Reticulocytes, LDH, bilirubin, haptoglobin, Coombs test;
[4] AGLT – Acidified glycerol lysis time, test to determine osmotic fragility, EMA – eosin-5-maleimide, dye-coupling flow cytometry test;
[5] Ektacytometry – see Chapter 3.1.

3.2 Differential Diagnosis

Differential diagnostics of adult patients with hyperregenerative, normochromic anemia and spherocytes can be classified into congenital and acquired disorders:

Congenital

Hereditary elliptocytosis: The findings in basic diagnostics are quite identical to those belonging to hereditary spherocytosis, however, the osmotic fragility of the RBC will be mostly increased if the course of the disease is moderately severe to severe. Crucial is the microscopical analysis of the blood smear. The same applies to spherocytic elliptocytosis, in which spherocytes are found next to the elliptocytes.

Hereditary pyropoikilocytosis: The pathophysiological basis is homozygosity of spectrin anomalies with a positive family history of hereditary elliptocytosis. Flow cytometry (EMA Test) reveals significantly decreased binding rate of the dye similar to Herediary Spherocytosis. Crucial is the morphological examination of blood smears and, contrary to other membrane-dependent diseases, a pronounced decrease of MCV values below 70fl.

Hereditary defects of the cation permeability of the RBC membrane: Differential diagnostics are summarized in Table 8 [16].

Table 8: Hereditary Defects of RBC Membrane Cation Permeability*

	Stomatocytosis with Cellular Hyperhydration	**Cryohydrocytosis**	**Familial Pseudohyperkalemia**	**Xerocytosis**
Hemolysis	**Moderate to severe**	**Mild to moderate**	**Mild to normal**	**Mild to moderate**
MCV (80 - 100 fl)	110 – 150	90 – 105	82 - 104	84 - 122
MCHC (32 - 36 g/dl)	24 – 30	34 – 38	33 - 39	34 - 38
RBC K+ and Na+ (95-110 mmol/L RBC)	110 – 140	75 – 105	87-109	75-99
Osmotic fragility	Highly increased	Normal to slightly increased	Slightly reduced	Reduced
Intrauterine ascites	No	No	No	Low to Hydrops
Response to splenectomy	Good	Poor	Splenectomy not required	Poor

Legend:
**modified after [16]; MCV – mean corpuscular volume; MCHC – mean corpuscular hemoglobin concentration ;*

Hereditary stomatocytosis: Blood smears are crucial in case of this very rare disease. Differentiation is important as splenectomy is often ineffective and hampered with an increased risk of thromboembolic complications. Storage of blood samples from patients with Hereditary stomatocytosis over 2 hours at 4°C usually leads to an increase of serum potassium and MCV increase, whereas MCHC normalizes.

Hereditary xerocytosis (formerly also referred to as dehydrated hereditary stomatocytosis): The differential blood cell count is mostly inconspicuous, stomatocytes and echinocytes are rare (evidenced especially by phase contrast microscopy). Osmotic fragility is slightly decreased. The medical history contains frequent occurrences of intrauterine hydrops with ascites. Splenectomy is ineffective and contraindicated on account of an increased risk of thromboembolic complications.

Congenital dyserythropoetic anemia type II: Despite the fact that single spherocytes are identifiable in blood smears here as well, this type of anemia displays pronounced poikilocytosis, almost invariably associated with basophilic stippling The reticulocyte count is often normal, however not always adequately increased relative to the anemia. To achieve an unequivocal differentiation in uncertain cases it is required to demonstrate the existence of dyserthyropoiesis in a bone-marrow aspirate. The shift of band 3 in SDS PAGE may contribute to the diagnosis. The disease is confirmed by molecular genetic detection of the *SEC23B* gene mutation.

Other forms of congenital hemolytic anemia: Hereditary enzyme defects or structural defects of the hemoglobin genes cause hemolytic anemias. The microscopic differential blood cell count often guides further diagnostic procedures.

Acquired

- Autoimmune hemolytic anemia, in particular the rare forms with negative Coombs test
- Microangiopathic hemolytic anemia
- Hemolytic–uremic syndrome
- Hypophosphatemia
- (Delayed) hemolytic transfusion reaction
- Hemolysis of toxic or infectious etiology

4 Therapy

There is no causal therapy of the genetic defect. The most effective symptomatic therapy consists in splenectomy. Cholecystectomy is indicated in case of cholelithiasis [17].

4.1 Splenectomy

Splenectomy often contributes to the elimination of anemia and to the regression of increased hemolysis parameters. However, the alterations discovered in blood smears will become more distinctive than they had been previously. Splenectomy is mostly indicated in childhood, but should, if possible, not performed before school age. Splenectomy also has to be considered in adults with symptomatic disease. Splenectomy is an option for adults with extramedullary hematopoiesis. It remains an open question whether extramedullary hematopoiesis recedes afterwards.

If hemolysis persists after splenectomy the diagnosis will have to be reconsidered. Accessory spleens must be searched for and, if they exist, they must be removed. The indication for splenectomy depends on the degree of clinical severity, see Table 9 [2].

Table 9: Indications for Splenectomy

Severity Grade	Recommendation
Mild	Usually not required
Moderately severe	In case of multiple hemolytic crises In case of > 2 transfusions beyond newborn stage In case of pronounced loss of physical performance
Severe and very severe	All patients

The risk of splenectomy consists in the operation and in the life-long increased rate of severe infections, particularly due to pneumococci with a mortality of 0.1 – 0.4 % [2, 18]. The risk is reduced by a partial instead of a complete splenectomy [19, 20]. Subtotal splenectomy is recommended in patients with hereditary spherocytosis. A mild anemic condition might persist in patients with a severe variant of the disease, particularly in case of spectrin defects. Prior to and after splenectomy recommendations concerning vaccinations and/or antibiotic prophylaxis must be observed. [21, 22].

5 Monitoring of Asymptomatic Patients

There is no evidence on the efficacy of regular follow-up examinations. Differential blood cell counts should be conducted as required, particularly in case of anemic symptoms related to infections. Due to the occasional iron overload in moderately severe and severe forms it is recommended to check serum ferritin in yearly intervals. On the occasion of these checkups the levels of vitamin B_{12} and folic acid should be determined due to their increased requirement. Sonography of the bile ducts and the spleen is recommended at least every three years.

6 Family Planning

If there is a desire to have children genetic counseling which includes testing the life partner for the potential existence of an erythrocytic membranopathy is recommended.

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