Literature Review

Congenital Dyserythropoietic Anemia

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Abbreviations: **CDA** – Congenital Dyserythropoietic Anemia, **CDAN1** – Codanin 1, **CDA-I** – Congenital Dyserythropoiesis Anemia-Type I, **CDA-II** – Congenital Dyserythropoiesis Anemia-Type II, **XLTDA** – X-linked recessive hematologic disorder, **DNA** – Deoxyribonucleic Acid, **GATA1 – GATA** Binding Protein 1, **LPIN2** – Lipin 2, **VUS** – Variant of Uncertain Significance, **NGS** – Next Generations Sequencing, **CBC** – Complete Blood Count, **G-6PD** – Glucose-6 Phosphate Dehydrogenase, **NSAID** – Non-steroidal anti-inflammatory drugs, **RBC** – Red Blood Cells.

Abstract

Congenital dyserythropoietic anemia (CDA) is a rare inherited hematological disorder characterized by impaired erythroblast maturation, leading to anemia. An overview of CDA with an emphasis on its molecular underpinnings, clinical characteristics and manifestations are provided in this article.

Mutations in crucial genes for erythroid differentiation, which affect nuclear morphology and hemoglobin production, are part of the physiopathology of CDA. Jaundice, hepatosplenomegaly and anemia are a few examples of the clinical symptoms. Genetic test and bone marrow analysis are used for diagnosis.

1. Introduction

Congenital dyserythropoietic anemia (CDA) is one of a heterogenous group of inherited anemias characterized by ineffective erythropoiesis[1]. Consequently, this disorder affects the evolution of erythrocytes. This illness is one of numerous varieties of anemia, a condition marked by a deficiency in red blood cells. Due to this deficiency, the blood is unable to provide enough oxygen to the body's tissues[2].

2. Pathogenic mechanism

Based on their unique structure, clinical and hereditary characteristics, CDA's are divided into three primary kinds (I, II, III), as well as transcription factor-related CDA's and CDA variants.

CDA-I is caused by bi-allelic mutations in either *CDAN1* or *C15orf41* and other 56 causative mutations that has been discovered[3].

It is probable that both of the proteins that these two genes expression will play crucial roles in DNA repair and/or chromatin reassembly after DNA replication.

The *C15orf41* protein is predominantly localized either to the cytosol or to the nucleus. This implies that this protein has a dual role inside these two subcellular domains[4].

3. Clinical manifestations

Majeed syndrome is an extremely rare autosomal recessive ailment that is characterized by decreasing in erythrocyte color and in size than normal with dyserythropoiesis, inflammatory dermatosis and persistent recurrent multifocal osteomyelitis.

The causative gene is *LPIN2*, which encodes a phosphatidate phosphatase, important in lipid metabolism[5].

As for other types of hereditary anemias, the classical diagnostic workflow for CDA includes different lines of examination, which start from the analysis of family and personal history, move on to biochemical and structural evaluation and end with genetic testing.

The next following items are clinical manifestations for CDA[6]:

- Typically manifesting in childhood, chronic moderate congenital anemia (red cells with nonspecific abnormalities, basophilic stippling, sporadic normoblasts).
- Given the extent of anemia and the presence of increased count of erythroid precursor cells in the bone marrow, the reticulocyte response in inadequate.
- Granulopoiesis and thrombopoiesis in a normal state.
- Moderate jaundice that is persistent or sporadic.
- Splenomegaly.
- Hemosiderosis is caused by high rate of plasma iron turnover and a poor rate of erythrocyte iron utilization (ineffective erythropoiesis).
- Shortened red cell survival time.
- Hemosiderosis from progressive iron overload.
- Marrow that generally distinguishes between the three forms of CDA due to aberrant erythroid morphology.

4. Clinical results

The results show that treating CDA-I patients holistically and cooperatively produces the greatest outcomes. This is in contrast to the careful treatment of iron excess and the use of interferon alpha.

The study of iron metabolism in CDA-II has made the most strides in our understanding of CDA's. It has been shown that the erythroblast-produced hormone erythroferrone mediates hepatic iron overload by specifically blocking the production of hepcidin.

CDA-III is the most unique of these three classical CDA forms[7].

A set of clinically diverse disorders with bleeding propensity, minor to major type of anemia and abnormal large platelets with over granulated platelets make up XLTDA. Severe bleeding and/or blood transfusion dependency occur at the clinically most severe end of the spectrum and last a lifetime. Dysfunctional red blood cell development and impaired megakaryopoiesis and characteristics of the bone marrow with ageing.

Mutations in GATA1, a X-linked gene (the X-linked gene it describes features or traits that are impacted by genes on the X chromosome) that codes for a DNA-binding protein with two zinc bonds and a transactivation domain, lead to XLTDA. GATA1 has a necessary role in evolution and sustention of both erythroid and megakaryocytic lineages. Considering the X-linked patrimony, males are primarily impacted, and the severity and specificity of the phenotype depends on the imbalance in GATA1 function[8].

We can discuss the difference between patients with transfusion-dependent anemia (TD) and the patients with non-transfusion-dependent anemia (NTD).

For the TD patients, the principal steps to reach molecular diagnosis of these conditions are: NGS-based genetic testing (pathogenic variants in CDA related genes, VUS in CDA related genes, pathogenic variants or VUS in genes related to other anemias) and single/multiple gene testing.

NGS-based hereditary testing speak to an enormous parallel sequencing technology

that gives ultra-high throughput and speed. This innovation is used to decide the arrange of nucleotides in whole genomes or focused on locales regions of DNA or RNA[9].

For the NTD patients, by testing CBC investigation and particular tests.

Table 1. Investigations and particular tests for each type of CDA.

CDA type	Investigations that need to be done
CDA-I	Examination of skeletal mutations.
CDA-II	Examination of bone marrow; Investigation of 3-hypoglycosylation by sodium dodecyl sulphate polyacrylamide gel electrophoresis.

5. Complications

The main CDA problems associated with chronic hemolytic anemia (lower number of erythrocytes due to hemolysis) include iron excess, edema in an

unborn or newborn baby, aplastic crisis, hyperbilirubinemia, gallstones and enlarged spleen. A common problem with CDA's is iron overload[10].

In correlation with what has been said above, there are some complications and modern therapeutic elucidations.

Table 2. Current therapeutic solutions in CDA problems and complications.

CDA manifestation	Complications	Current therapeutic solutions
Iron overload[11]	Liver damage; Liver cirrhosis; Injury to the islet cells of the pancreas; Diabetes; Hypothyroidism; Hypogonadism.	Reduction therapy; Blood transfusion; Iron chelation therapy;
Hydrops fetalis[12]	Fluid around the heart and lungs; Severe low blood sugar; Lungs development issues (underdeveloped); Severe anemia.	Fetal blood transfusion; Early caesarean delivery; Giving blood to the baby while still in the womb.
Aplastic anemia[13]	Bleeding; Infections.	Ticlopidine; NSAID; Immunosuppressive therapy using: eltrombopag; horse/rabbit anti-thymocyte globuline, cyclosporine A.
Hyperbilirubinemia[14]	Brain and spinal cord injuries.	Intravenous immunoglobulin; Exchange transfusion; Cholestyramine.
Enlarged spleen[15]	Splenic rupture; Cytopenias; Low number of RBC, leukocytes and platelets.	Antibiotics; Splenectomy; Blood transfusions; Exchange transfusions.
Gallstones[16]	Acute cholecystitis; Jaundice; Infection of the bile ducts; Acute pancreatitis.	Ursodiol link and chenodiol link; Cholecystectomy.

The mechanism of hepatic iron excess has been studied recently, primarily for CDA-II. Hepcidin's expression was previously shown to be reduced, and other erythroid regulators, such as growth/ differentiation factor 15, have been suggested as pathological suppressors of hepcidin expression[17].

The differential diagnosis incorporates other haemolytic anemias, such as: congenital spherocytic anemia, paroxysmal nighttime hemoglobinuria, chronic non-spherocytic haemolytic anemia due to G-6PD insufficiency, autoimmune haemolytic anemia and anemias with ineffectual erythropoiesis like thalassemia and myelodysplastic disorders.

Inherent spherocytic anemia – the foremost common misdiagnosis – is effortlessly recognized by the nonattendance of anisopoikilocytosis (variation of shape and size of red blood cells) and the higher rate of reticulocytes, in advance of more particular tests, such as osmotic delicacy and protein electrophoresis[18].

6. Conclusions

The morphological characteristics of CDA erythroblasts point to their delayed maturation into adult erythrocytes. Even though a number of CDA associated genes have been recognized, it is frequently unclear how their modified functions contribute to erythroblast multinuclearity. Nevertheless, research on the pathogenic mechanisms underlying CDA's continues to yield new findings that are helpful for the clinical management of these patients as well as the investigation of novel therapeutic approaches.

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