1. Introduction

The congenital dyserythropoietic anemias (CDAs) are a heterogeneous group of hereditary disorders characterized by congenital anemia due to ineffective erythropoiesis. Patients usually present with anemia, jaundice, cholelithiasis and splenomegaly, and may develop secondary hemochromatosis. Anisopoikilocytosis and basophilic stippling are commonly observed in the peripheral blood (PB) smear. The working classification initially proposed by Heimpel and Wendt is still used in clinical practice (CDA I, II, and III; Table 1)[1]. However, there are families that fulfill the general definition of the CDAs but do not conform to any of the 3 classical types (CDA variants; Table 2) [1].

2. Pathophysiology

Anemia in CDAs is mainly caused by ineffective erythropoiesis. Erythroid precursors have a qualitative defect which leads early cell death, maturation arrest or intramedulary destruction. Non-erythroid hematopoietic cell lineages are morphologically normal. The genes mutated in the majority of patients with CDA I and II have been previously described (*CDAN1* and *SEC23B*, respectively), whereas the CDA III gene (*KIF23*) was only recently identified. Additional genetic defects such as *KLF1* and *GATA-1* have been described in CDA variants. Because of these advances, the diagnosis can be confirmed by molecular testing in an increasing number of patients[2), 3)].

3. Clinical and laboratory findings

Symptoms of patients with CDAs can be highly variable, and mild cases may remain undetected. Clinical appearance and basic laboratory data are similar between CDA type I and II with some exceptions. Most patients have only mild or moderate anemia and do not require medical intervention. Cholelithiasis, splenomegaly and iron overload are the most prevalent complications of CDA types I and II. Of those, secondary hemochromatosis is the most important long-term complication and can lead to organ damage if not recognized and appropriately treated. Iron overload is not limited to patients receiving frequent transfusion, because the highly ineffective erythropoiesis results in decreased hepcidin levels, and thus increased iron absorption.

Dyserythropoietic anemia could be suspected in the presence of symptoms and signs of increased hemoglobin (Hb) turnover, such as mild jaundice, and low or absent haptoglobin, as in hemolytic anemias, with a reticulocytosis that does not correspond to the degree of anemia. Erythrocytes are generally macrocytic but may be normocytic during childhood. PB smear shows anisopoikilocytosis with basophilic stippling of cells and late erythroblasts. The bone marrow (BM) is always hypercellular exclusively due to a pronounced increase of erythroblasts. Morphological characteristics are distinct according to different type of CDAs. Extramedullary hematopoiesis presenting as paravertebral bulks may be observed in all types of CDAs.

4. Classification (Tables 1 & 2)

CDA type I

CDA type I is inherited as an autosomal recessive disease[4]. So far, more than 150 patients have been described mainly in Western Europeans, people from the Middle East, Indians and Japanese. Diagnosis may be made rarely in utero but also at any time between the neonatal period and late adulthood; in most patients the diagnosis is made during childhood and adolescence.

Most cases show lifelong anemia with hemoglobin concentration between 7 and 11 g/dl. Red blood transfusions are often required for newborns and infants but are only occasionally necessary later in life. The anemia is usually macrocytic with MCVs between 100 and 120 fl. Physical abnormalities are more frequently observed than those in CDA type II. These patients show skeletal malformations, particularly syndactylism of hands and feet. Light microscopy of the bone marrow (BM) demonstrates erythroid hyperplasia with abnormal precursors showing a megaloblastic appearance. There are also occasional tri- and tetranucleate cells. The morphological hallmark in the BM is the presence of internuclear chromatin bridges between some nearly completely separated erythroblasts. Electron microscopy (EM) of BM shows a characteristic heterochromatin pattern, which is abnormally electron dense with a spongy appearance that has been described as "Swiss cheese like".

The gene responsible for CDA type I, *CDAN1*, is localized to chromosome 15q15.1-3, spans 28 exons, and encodes a 134-kDa ubiquitously expressed protein (codanin-1) [5]. The *CDAN1* gene is mutated in 88% of CDA type I patients and more than 30 unique mutations have been

identified so far. Genotype-phenotype correlations could not be established. No patients have been found to be homozygous for a null-type mutation, suggesting that the complete absence of functional codanin-1 may be lethal. Although codanin-1 has still not been well characterized, it seems to be related to chromosome structure and it must be involved in mitotic process.

CDA type II

CDA type II is the most frequent form of CDAs and is reported to be approximately 3 times more frequent than CDA type I[2]. The severity of anemia varies from mild to severe, however, diagnosis of CDA type II is usually made later in life compared with type I because the symptoms can be milder[2]. About 10% of patients require red cell transfusion in infancy and childhood but rarely thereafter. Splenomegaly and cholelithiasis are common.

Hemoglobin in patients with CDA type II is generally between 8 and 11 g/dL with a normal MCV. Erythrocytes are usually normocytic with moderate to marked anisopoikilocytosis, anisochromasia, basophilic stippling cells and a few circulating erythroblasts. The BM is hypercellular with erythroid hyperplasia with 10% to 35% of binucleate and rarely multinucleate late polychromatic erythroblasts. CDA type II patients have a positive HAM test[6].

Inheritance of CDA type II is autosomal recessive. SEC23B, which was originally mapped to chromosome 20p11.23, was identified as the gene responsible for CDA type II[7]. This gene encodes the cytoplasmic COPII component SEC23B, which is involved in the secretory pathway of eukaryotic cells. This pathway is critical for membrane homeostasis, localization of proteins within cells and secretion of extracellular factors.

CDA type III

CDA Type III is the rarest among the 3 types. Both familial and sporadic cases have been reported. The largest is a five-generation family living in Northern Sweden, which contains more than 30 cases inherited in an autosomal dominant manner[8]. Few sporadic cases have also been described with possible autosomal recessive inheritance.

In contrast to CDA type I and II, anemia in patients with familial CDA Type III is milder and iron overload seems not to be clinically significant. In the Swedish family, there is an increased tendency to develop monoclonal gammopathy and multiple myeloma. BM morphology is

characterized by erythroid hyperplasia and giant multinucleated erythroblasts.

The gene causing CDA type III in a Swedish family has been previously mapped to a region on chromosome 15q23 and a mutation in the *KIF23* gene was identified by array-based sequence capture to be associated with the autosomal dominant form of CDA type III[9].

CDA variants

Several forms of CDAs do not fulfill classical BM morphologic or biochemical criteria. Based on light microscopy and EM of BM, those cases are classified into 4 additional CDA groups (IV-VII), each one including relatively few patients[2), 3)]. Nevertheless, there were still descriptions of patients not belonging to any of the groups. Indeed, in recent years additional genetic defects associated with CDA phenotypes have been identified. They include mutations in erythroid transcription factor genes (*GATA-1* and *KLF1*) and mutations in other genes where CDA is part of a broader clinical syndrome (such as mevalonate kinase gene in mevalonate kinase deficiency).

5. Diagnosis

When the clinical picture is suggestive and the findings in PB and BM light microscopy are compatible with one of the classical I to III types (Table 3), the next diagnostic step should be to sequence the appropriate gene (Figure 1). The identification of the mutated genes involved in the majority of CDA patients improved the diagnostic possibilities. Whenever clinical and hematologic findings are generally compatible with CDAs despite the absence of specific microscopic features of CDA I to III, a variant CDA should be considered. In these selected cases, mutations in *KLF1* and *GATA-1* should be explored. It must be noted that most CDA patients have only mild or moderate anemia, especially in adult cases. Since some cases may be misdiagnosed with other disorders such as congenital hemolytic anemia, other conditions presenting dyserythropoiesis should be differentiated (Table 4).

6. Therapeutic approaches

Treatment for CDAs is mostly supportive and targeted to prevent the consequences of anemia and iron overload. Decision-making depends on age, CDA type, severity of expression and comorbidity. Most CDA patients have only mild or moderate anemia and do not require medical

intervention. About 50% and 10% of neonates with CDA type I and CDA type II, respectively, need at least one erythrocyte transfusion, and some remain transfusion-dependent in the following years. In most adolescents and adults, the need for transfusions is limited to aplastic crises, pregnancy, severe infections or major operations[2), 3)].

Although iron overload is not dependent on transfusions, transfusions worsen hemochromatosis. Therefore, ferritin levels should be controlled at least annually, even in patients with light or moderate anemia. For the moment, management of iron over-load should follow the guidelines for thalassemia.

Splenectomy leads to a moderate but sustained increase in Hb concentration and decrease in serum bilirubin levels, but it does not prevent further iron loading.

With regard to the distinct erythroid hyperplasia, vitamin B12 and folic acid supplements are frequently used, although without any evidence of efficacy. Use of erythropoietin formulations also appear to be ineffective. Interferon-alpha seems to be effective in improving the chronic anemia and splenomegaly in CDA type I, but whether this shows efficacy in other types of CDAs remains uncertain.

Allogeneic bone marrow transplantation from an HLA-identical sibling has been reported to be successful in very severe cases that were transfusion-dependent. This treatment can abolish transfusion dependency, thus preventing progression of tissue damage related to iron overload. The result should be both longer life expectancy and better quality of life.

7. Conclusions

Recent identification of causative genes could help reclassify these disorders. Variant forms are very rare and this has compromised further molecular studies. Linkage studies had previously been the main tool to clarify the genetics of Mendelian disorders; however, extremely rare disorders or sporadic cases caused by de novo variants are not appropriate for this type of study design. Exome sequencing is now becoming more cost-effective due to the recent advances in high-throughput sequence technologies that have offered new opportunities for research into Mendelian disorders. The use of these new technologies will lead to the identification of new causative genes in CDA variants in the near future.

In Japan, 12 cases of CDAs were reviewed in 2008. Since it is likely that mild cases or adult

cases might be overlooked, enlightening to neonatologist and adult hematologist who may have the opportunity to see CDAs patients might be needed. In the future, central diagnostic system consisting of morphological review and genetic analysis will facilitate correct diagnosis and understanding epidemiology in Japan.

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Table 1 "Classical" subtypes of CDAs

CDA type	I	II	III
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal dominant
Mutated gene (Chromosome)	*CDAN1* (15q15.1-3)	*SEC23B* (20p11.2)	*KIF23* (15q23)
Anemia	Mild – moderate (Macrocytic)	Mild – Severe (Normocytic or macrocytic)	Mild - moderate (Macrocytic)
BM morphology (light microscopy)	Abnormal chromatin structure, Chromatin bridges Binucleated erythroblasts (2-5%),	Bi- or multi nucleated erythroblasts (10-35%)	Giant multinucleated erythroblasts (10-40%)
BM morphology (electron microscopy)	Spongy "Swiss cheese" appearance of heterochromatin	Peripheral double membranes	Clefts in heterochromatin
Ham test	Negative	Positive	Negative

Table 2. Comparison of characteristic features of different types of CDA[2)]

CDA type	I	II	III	IV	Variants
Inheritance	AR	AR	AD	AD	AR or XR
Case reported	-150	-370	3 families	< 20	> 20
Morphology	Abnormal chromatin structure, chromatin bridges	Bi- or multi-nuclearity of mature erythroblasts	Giant multi-nucleated erythroblasts	Multi-nucleated erythroblasts	CDA I-like CDA II-like Others
Mutated gene	*CDAN1*	*SEC23B*	*KIF23*	*KLF1*	*Unknown/ GATA1*
Chromosome	15q15.1-3	20q11.2	15q21-25	19p13.2	Unknown/Xp11.23
Associated dysmorphology	Skeleton, others	Variable, rare	B cells, retina	Variable	CNS, thrombocytopenia
Therapy	INF-alpha iron depletion	Splenectomy, iron depletion	Unknown	Unknown	Unknown

Table 3. Findings suggestive of CDA

a.	Evidence or past history of jaundice
b.	Ineffective erythropoiesis（erythroid hyperplasia in the BM and reticulocytopenia in the PB）
c.	Morphological abnormalities in the circulating erythrocytes（anisopoikilocytosis and basophilic stippling）
d.	Morphological abnormalities in the BM（chromatin bridges、multi-nucleated erythroblasts）
e.	Macrocytic anemia
f.	Transfusion requirement
g.	Splenomegaly
h.	Family history of chronic anemia of unknown etiology
i.	Skeletal abnormalities
j.	Anemia of unknown etiology

Table 4. Differential diagnosis

- Congenital disorders
  - Thalassemia
  - Unstable hemoglobin disease
  - Hereditary spherocytosis
  - Pyruvate kinase deficiency
  - Inherited bone marrow failure syndrome
- Acquired disorders
  - Vitamin B12 deficiency
  - Folate deficiency
  - Iron-deficiency anemia
  - Myelodysplastic syndrome
  - Excessive alcohol consumption
  - Acute myeloid leukemia
  - Aplastic aneimia
  - Parvovirus B19 infection
  - HIV infection
  - Malaria
  - Liver diseases
  - Post-chemotherapeutic change
  - Post-transplantation change

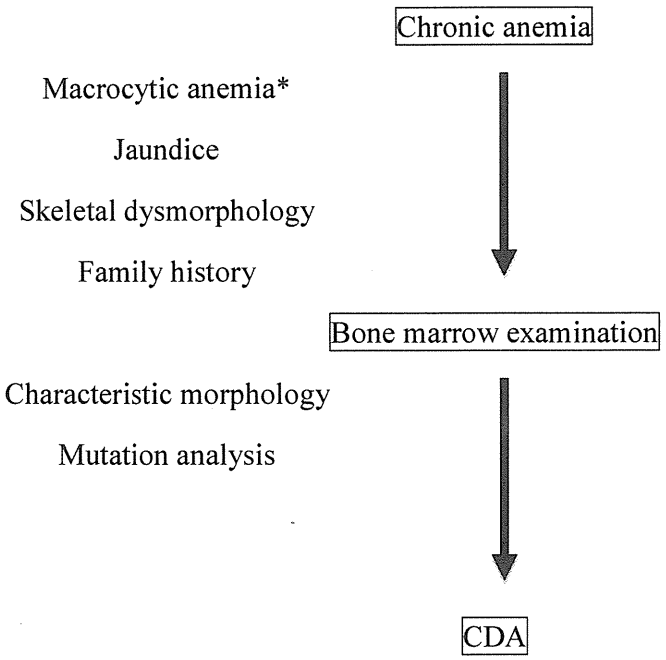

Figure 1. Diagnostic approach for CDAs

*It must be noted that most CDA patients have only mild or moderate anemia, especially in adult cases, and anemia may be normocytic during childhood.

Ⅴ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

◎は、本研究によることが明記されている論文
○は、本研究に関連する論文

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