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1. Introduction

Sideroblastic anemia is characterized by anemia with the emergence of ringed sideroblasts in the bone marrow. There are two forms of sideroblastic anemia, *i.e.*, congenital sideroblastic anemia (CSA) and acquired sideroblastic anemia. Most of acquired sideroblastic anemia cases were observed in myelodysplastic syndrome (MDS), and occasionally associated with alcoholism or certain drugs. On the other hand, CSAs are very uncommon genetic disorders. To date, mutations of genes involved in heme biosynthesis, Fe-S cluster biogenesis, or the biology of mitochondria have been reported in CSA. Impaired function of these genes is speculated to result in disutilization of iron, leading to accumulation of iron in mitochondria. In 1945, Coorey initially reported X-linked form of microcytic/hypochromic anemia. In the next year, Rundles and Falls reported 2 pedigrees including the initial pedigree. Thus, the disease was called as Rundles and Falls syndrome [1]. Later, it has been demonstrated that the disease was caused by mutation of erythroid-specific 5-aminolevulinate synthase (*ALAS2*), the first enzyme of heme synthesis in erythroid cells [2]. Whereas the most common form of CSA is caused by the mutation of *ALAS2*, other causative genes have been reported, such as genes involved in Fe-S cluster biogenesis/transport, mitochondrial transporter, mitochondrial DNA, mitochondrial tRNA (Table 1). However, there is still significant number of "genetically undefined" CSA cases. CSAs also occur as a part of several genetic syndromes associated with abnormalities in various non-hematopoietic organ systems (*e.g.*, manifested by ataxia, mitochondrial myopathy, diabetes mellitus, exocrine pancreatic insufficiency), depending on the genes mutated. In such syndromic CSAs, the anemia may be mild and of secondary importance or severe. Whereas no specific therapy has been available for most of syndromic CSAs, some cases could respond to the treatment, as represented by XLSA due to *ALAS2* mutation. Therefore, it is important to make a precise diagnosis for all CSA cases based on genetic analysis for CSA.

	Inheritance	Chromosome	Gene	Mutation type	Treatment
XLSA	X-linked	Xp11.21	ALAS2	M, N	Pyridoxine
XLSA/A	X-linked	Xp13.3	ABCB7	M	-
SA/GLRX5	AR	14q32.13	GLRX5	M, S	?
SA/SLC25A38	AR	3p22.1	SLC25A38	M, N, S	?
PMPS	Maternal*	Mitochondria	Mitochondrial	D	-
TRMA	AR	1q24.2	SLC19A2	M, N	Thiamine
MLASA/PUS1	AR	12q24.33	PUS1	M, N	-
MLASA/YARS2	AR	12p11.21	YARS2	M	-

Abbreviations: M, Missense; N, Nonsense; S, Splicing; D, Deletion;
XLSA, X-linked sideroblastic anemia; XLSA/A, X-linked sideroblastic anemia with ataxia;
PMPS, Pearson Marrow Pancreas Syndrome; TRMA, Thiamine-responsive megaloblastic anemia;
MLASA, Mitochondrial myopathy and sideroblastic anemia.
* Sporadic cases are also reported.

Table 1. Genetic features of congenital sideroblastic anemia

2. Diagnosis

1) Definition

Anemia characterized by the emergence of ringed sideroblasts in the bone marrow

2) Diagnostic criteria

Ringed sideroblasts, > 15% of nucleated erythroid cells (FAB classification)

Increased serum ferritin, unsaturated iron binding capacity (UIBC)

Above 2 criteria plus confirmation of mutations of causative gene (*i.e. ALAS2*)

Presence of family history strongly suggest CSA

Most prevalent type (XLSA) is characterized by microcytic/hypochromic anemia in a boy

Definition of ringed sideroblasts (revised WHO classification):

10 or more granules in a perinuclear position, surrounding the nucleus or encompassing at least one third of the nuclear circumference.

3) Flowchart for diagnosis

CSA is initially suspected by the emergence of ringed sideroblasts in the bone marrow, yo ung onset and the presence of family history, and subsequently need to be confirmed by genetic analysis. If the family history is not obvious, genetic analysis should be conducted

based on non-hematopoietic cells (*i.e.* oral mucosa) to assess the presence of germ-line mutation. Among CSAs, XLSA is the most frequently observed. Thus, if the case is young male and responds to vitamin B6 therapy, genetic analysis is strongly recommended. In XLSA cases, it is possible to analyze the enzymatic activity of mutated ALAS2 protein.

4) Differential diagnosis

It is important to exclude acquired sideroblastic anemia (below)
Drug (Anti-tuberculosis), Toxicity (Lead poisoning), Alcohol, Myelodysplastic syndrome

Generally, acquired sideroblastic anemia could be distinguished based on the age of onset and the absence of family history [3]. However, it is occasionally difficult to distinguish wit h the hereditary cases. Acquired sideroblastic anemia due to alcohol and drug should be s uspected based on life history and present illness. Drug-induced sideroblastic anemia is typ ically caused by the inhibition of vitamin B6, which acts as coenzyme for ALAS2. The inhib ition of vitamin B6 by certain drug can led to decreased ALAS2 enzymatic activity and ons et of sideroblastic anemia. Isoniazid is one of the major causative drugs to interfere with vi tamin B6 metabolism. If multi-lineage dysplasia or chromosomal abnormality is also observ ed in addition to the emergence of ringed sideroblasts, the case could be diagnosed as m yelodysplastic syndrome. On the other hand, if the case only shows anemia without chrom osomal abnormality, and responds to vitamin B6 supplementation, genetic analysis should be conducted.

3. Epidemiology

4) Incidence

Because of its rarity, the detailed and comprehensive epidemiological data for CSA has not been available. Regarding most frequent form CSA (XLSA), 94 pedigrees and 57 mutation s have been reported (Table 2). According to a relatively large cohort in the USA (n = 83), mutations of *ALAS2*, *SLC25A38*, mitochondria DNA, and *PUS1* were identified in 37, 15, 2.5, and 2.5%, respectively [4]. On the other hand, Japan Public Health Center-based pro spective study for "Establishment of diagnostic criteria and therapeutic approach for conge nital sideroblastic anemia" has reported that genetically identified cases were exclusively X LSA, whereas no mutation was observed for *SLC25A38*、*PUS1*、*ABCB7*、*GLRX5*、*SLC19 A2* (Tables 3, 4) [5].

2) Prognosis

Because of its rarity, the detailed data for prognosis of CSA has not been available.

Ex.	substitution		No. of pedigree		Ex.	substitution	No. of pedigree	Ex.	substitution		No. of pedigree	
4	L107P		1		6	S251P	1	9	R452	C	9 (2)	20
5	M154I		1		7	D263N	2			G	1	
	K156E		1			C276W	1			S	2	
	D159	N	1	2		I289T	1			H	8 (2)	
		Y	1			G291S	1		R458H		1	
	T161A		1			K299Q	1		I476N		1	
	F165L		2			V301A	1	10	Y506-fs		1	
	R170	S	1	8	8	P339L	1		T508S		1	
		C	2 (1)			D351R	1		R517	C	1	2
		L	3 (2)			R375C	1			G	1	
		H	2			T388S	1		P520L		3	
	A172T		1		9	C395Y	1		H524D		1	
	D190V		1			G398D	1	11	K535del		1	
	Y199H		1			R411 C	6 (2) 10		R559H		1	
	R204	Q	1	2		R411 H	4		R560H		2	
		stop	1			G416D	1		V562A		1	
6	R218H		1			M426V	1		M567I		1	
	R227C		1			R436W	1		S568G		2 (1)	
	E242K		1			R448Q	3		R572H		2	

Table 2. Amino acid substitution of ALAS2 in patients with XLSA

Case number	Age at diag	Gender	Position of ALAS2 mutation	*SF3B1* mutation	Hb at onset (g/dl)	MCV at onset (fl)	Increment of Hb by Vit B6 treatment (g/dl)	In vitro enzymatic activity of mutant protein*	
								w/o PLP	with PLP
1	0	M	R170C	N/D	4.8	52.5	1.7	64.1%	72.5% **
2	20	M	R411C	N/D	4.8	52.5	5.2	11.9%	25.1% [ref 19]
3	68	M	R452C	-	6.0	67.3	No effect	99.9%	94.0% [ref 21]
4	17	M	D190V	N/D	8.9	66.9	No effect	98.6%	98.5% [ref 20]
5	36	M	R452C	-	7.4	70.0	No effect	99.9%	94.0% [ref 21]
6	36	M	M567I	N/D	6.5	64.4	3.4	38.1%	25.2% [ref 21]
7	14	M	V562A	-	8.1	61.2	4.7	150.6%	116.9% [ref 21]
8	31	M	R170L	-	4.1	50.8	8.1	31.1%	60.8% **
9	3	M	R452C	-	5.4	54.4	2.9	11.9%	25.1% [ref 19]
10	62	M	R170L	N/D	8.0	73.9	No effect	31.1%	60.8% **

*% of WT, ** present study

Table 3. XLSA identified in Japanese population, based on study for "Establishment of di agnostic criteria and therapeutic approach for congenital sideroblastic anemia"

Case number	Age at diag (y.o)	Gender	Family history	Gene mutation							Hb (g/dl)	MCV (fl)	Response to Vit B6
				ALAS2	*SLC 25A38*	*GLRX5*	*ABCB7*	*SLC 19A2*	*PUS1*	*SF3B1*			
11	14	M	-	Ex11 dup.	-	-	-	-	-	-	7.1	60.0	-
12	19	M	-	intron 1	-	-	-	-	-	-	7.8	73.9	-
13	4	M	-	Intron 1	-	-	-	-	-	-	6.6	73.6	-
14	0	M	+	Intron 1	-	-	-	-	-	-	3.9	65.0	-
15	20	M	+	Intron 1	-	-	-	-	-	-	7.6	82.0	+
16	0	M	-	-	-	-	-	-	-	-	6.8	88.1	N/D*
17	32	M	-	N/D	N/D	N/D	N/D	N/D	N/D	N/D	11.2	69	+
18	36	M	-	N/D	N/D	N/D	N/D	N/D	N/D	N/D	10.8	67.3	+
19	18	F	+	-	-	-	-	-	-	-	9.3	96.2	+

N/D: not done, *Vit B6 was not administered due to PMPS

Table 4. CSA (other than XLSA) identified in Japanese population, based on study for "Establishment of diagnostic criteria and therapeutic approach for congenital sideroblastic anemia"

4. Pathophysiology

Several genes with distinct function have been reported to be involved in the pathogenesis of CSA. As abnormal accumulation of intramitochondrial iron is one of the peculiar characteristics of this disease, a great deal of attention has been focused on alterations in genes related to intramitochondrial heme-iron metabolism, including 1) heme biosynthesis, 2) mitochondrial protein synthesis, and 3) iron-sulfur [Fe-S] cluster metabolism.

In erythroid cells, heme biosynthesis is initiated by the condensation of glycine and succinyl CoA to form aminolevulinic acid (ALA), which is catalyzed by ALAS2. Thus, mutation of ALAS2 results in the defect of heme biosynthesis, which subsequently could cause iron utilization. *SLC25A38* encodes an erythroid-specific protein of the inner mitochondrial membrane, and has been predicted to be involved in mitochondrial import of glycine [6]. Thus, similar to XLSA, the *SLC25A38* mutation could lead to the defect of heme biosynthesis and cause CSA. On the other hand, mutations for *SLC19A2*, which encodes the high-affinity thiamine transporter, causes mitochondrial iron overload [7]. Although it is not clear how mutations of *SLC19A2* contribute to sideroblast formation, it has been speculated that the impairment of thiamine-dependent generation of succinyl-CoA, which is required for heme synthesis, is the cause of the ringed sideroblast abnormality [7]. However, in CSA cases with *SLC19A2* mutation, serum protoporphyrin concentration did not decrease and the anemia is macrocytic. Thus, further examinations are r

equired to reveal if the CSA of *SLC19A2* mutation could result from the defect of heme biosy nthesis, similar to XLSA.

Pearson marrow-pancreas syndrome (PMPS) is a rare syndromic disorder, presenting with si deroblastic anemia, accompanied by metabolic acidosis, ataxia, and endocrine pancreas dysfun ction [8]. The disease is usually fatal, and patients die during infancy [8]. The mechanism of ri nged sideroblast formation in PMPS remains unclear. It has been speculated that the defect o f mitochondrial respiratory function by mitochondrial DNA mutation/deletion may deteriorate cyto chrome c (complex IV) function, which functions to keep iron in the reduced (Fe^{2+}) state. As ir on should be in the reduced state (Fe^{2+}) when incorporated into PPIX by FECH in the final st ep of heme synthesis, the mitochondrial DNA defect may result in insufficient iron utilization in mitochondria. On the other hand, the association of CSA with defective mitochondrial protein expression can be seen most directly by the mitochondrial myopathy with lactic acidosis and e ded sideroblasts (MLASA) phenotype, which results from mutations in genes encoding pseudou ridine synthase 1 (*PUS1*), which functions in pseudouridine modification of tRNAs. Whereas it has been assumed that the *PUS1* mutation may lead to aberrant translation, the molecular me chanism of how the mutation directly affect iron metabolism remains unknown [9]. Nevertheles s, insufficient iron utilization would cause iron overload, leading to the emergence of ringed sid eroblasts as well as the onset of anemia by inducing apoptosis [10].

ABCB7 and GLRX5 (*Glutaredoxin5*) are both involved in iron-sulfur [Fe-S] cluster metabolism [11,12]. Whereas ABCB7 transports the [Fe-S] cluster to the cytosol, GLRX5 is involved in th e [Fe-S] cluster biogenesis. Thus, it has been speculated that the mutations for ABCB7 and G LRX5 deteriorate efficient iron utilization in mitochondria by presumably distinct mechanisms. D ecreased level of [Fe-S] by the *GLRX5* mutation cluster in the iron-regulatory protein 1 (IRP1) blocked ALAS2 translation by binding to the iron-responsive element (IRE) located in the 5'-u ntranslated region of ALAS2 mRNA, whereas similar effect was not observed in by *ABCB7* mu tation.

5. Clinical and laboratory features

2) Anemia

Patients present mild to moderate anemia depending on the genes mutated. Even among the same causative gene, anemia severity could be different based on the position of mut ation.

2) Hemochromatosis

Severity of hemochromatosis could be different depending on the genes mutated as well as the total amount of transfused red blood cells. With the presence of *HFE* gene mutatio n, the hemochromatosis could be rapidly progressive. But the frequency of the *HFE* mutati on is relatively low in Japanese population.

3) Other complications

In case of CSA other than *ALAS2* or *SLC25A38* mutation, systemic symptoms, such as at axia, metabolic acidosis, exocrine pancreatic dysfunction, insulin dependent diabetes mellitus, neurologic symptoms, could be observed.

4) Characteristics of each CSA type

XLSA: Microcytic/hypochromic anemia and systemic iron overload are observed. In most XL SA cases, missense mutations of ALAS2 may alter the structure of ALAS2 protein, which decrease the binding affinity between ALAS2 and vitamin B6. Thus, administration of pyrid oxal 5'-phosphate (PLP, vitamin B6) is effective for the majority of XLSA cases.

CSA due to *GLRX5* mutation: By a consequence of decreased [Fe-S] cluster biosynthesis, iron overload in mitochondria is observed, though the proportion of singed sideroblasts ma y not obviously high. In addition, moderate anemia, hematosplenomegary and systemic iro n overload could be observed.

XLSA with ataxia (XLSA/A): XLSA/A patients present with anemia with motor delay and evi dence of spinocerebellar dysfunction, including early onset (< 1 year old) ataxia associated with severe cerebellar hypoplasia. Ataxia is not progressive or could be slowly deteriorati ng. Anemia is typically mild and microcytic/hypochromic, which do not respond to PLP the rapy. The disease is caused by the mutation of mitochondrial transporter ABCB7.

CSA due to *SLC25A38* mutation: *SLC25A38* encodes an erythroid-specific protein of the in ner mitochondrial membrane, and has been predicted to be involved in mitochondrial impo rt of glycine. The disease is the second most common, and the pattern of inheritance is a utosomal recessive. Most cases show severe microcytic/hypochromic anemia and systemic iron overload, resembling XLSA. Thus, if ALAS2 mutation is not detected in patients with above XLSA-like symptoms, genetic analysis for SLC25A38 should be conducted.

Pearson marrow pancreas syndrome (PMPS): A patient with PMPS presents metabolic aci dosis, ataxia, exocrine pancreatic dysfunction, and typically dies during infancy. Anemia is normocytic, and often accompanied by neutropenia and thrombocytopenia. The disease is caused by the deletion of mitochondrial DNA, and is usually sporadic.

Thiamine-responsive megaloblastic anemia (TRMA): TRMA is considered as a systemic di sorder presenting insulin-dependent diabetes mellitus and sensorineural hearing loss. The disease is very rare and often diagnosed during infancy. The pattern of inheritance is auto somal recessive. Anemia is typically macrocytic, which could be responded by thiamine. T he disease is caused by the mutation of thiamine transporter *SLC19A2*.

Mitochondrial myopathy and sideroblastic anemia (MLASA): MLASA is a very rare with a utosomal recessive inheritance. The patient presents myopathy, lactic acidosis and sideobl astic anemia, caused by the mutation of *PUS1* gene.

6. Treatments

1) Drug

(A) Vitamine supplementation

Pyridoxal 5'-phosphate (PLP, vitamin B6) : A majority of XLSA cases responds to PLP treatment at a dose of 50-100mg/day. Table 2 shows mutations of ALAS2, and PLP-r esponsive mutation is highlighted by gray-shade.

Thiamine (vitamin B1) : Thiamine (25-75mg/day) is effective for a patient with TRMA. presents metabolic acidosis, ataxia, exocrine pancreatic dysfunction, and typically dies during infancy. Anemia is normocytic, and often

There is no specific drug therapy available for the rest of CSA types.

(B) Iron chelation therapy

The risk of hemochromatosis is high in transfusion dependent cases. Thus, iron chelatio n therapy is considered based on serum ferritin level or the presence/absence of target organ damage induced by systemic iron overload (i.e. heart, liver or pancreas).

2) Transfusion

Transfusion should be considered for severe anemic cases.

3) Hematopoietic stem cell transplantation (HSCT)

Three CSA cases have been treated by HSCT [13]. In all cases, the treatment was considered effective, with noticeable hematopoietic recovery. However, as it is probable that the candidate CSA cases for HSCT would often be accompanied by hemochromatosis, it is important to consider the HSCT protocol, such as conditioning regimen.

7. Perspectives

It is important to conduct genetic analysis for all CSA cases, as some cases could be treated by specific therapy such as vitamin B6. However, due to its rarity, it is necessary to establis h a genetic analysis center for CSA, which would yield the detailed and comprehensive epide miological data for CSA in Japan. In the future, it would be also important to detect the causati ve genes for yet genetically undefined CSA cases, by establishing gene analysis systems espe cially based on next generation sequencer.

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Congenital Dyserythropoietic Anemia
診療の参照ガイド

Congenital Dyserythropoietic Anemia 診療の参照ガイド
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Congenital Dyserythropoietic Anemia の効果的診断法の確立と
治療ガイドラインの作成に関する研究班

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1. 緒言

Congenital dyserythropoietic anemia (CDA) は、1966年にCrookstonらによって提唱された、成熟障害による赤芽球系無効造血を呈する先天性疾患群で、慢性貧血、黄疸、胆石、脾腫および続発性ヘモクロマトーシスを来す。赤血球系の障害は赤芽球系前駆細胞レベルから生じ、形態異常は多染性および正染性赤芽球レベルで著明である。1968年にHeimpelとWendtが形態異常に基づいてこれらの疾患群をI型からIII型の３病型に分類した（表１）[1]。今でもこの分類が広く用いられているが、CDAが疑われながらこの3病型に該当しない亜型も散見される（表２）。

2. 病態生理と臨床症状、検査所見

CDAの貧血の主因は、赤血球の成熟障害と骨髄内溶血による無効造血である。原則として顆粒球系、リンパ球系および血小板系に異常はみられないが、亜型の中には血小板減少を合併するものもある（表２）。

貧血は基本的に大球性貧血であるが小児期には正球性貧血を呈することもある。貧血の程度は軽症から重症まで様々であるが、輸血などの介入を要さない例も多く、小児期に輸血依存であっても徐々に貧血の改善がみられる例もある。特に思春期以降は重症感染症や妊娠、大手術などの機会を除き輸血が必要になることは少ないようである[2]。また、サラセミアなど他の赤血球疾患を合併することがあり、その場合、貧血は重症となり得る[2]。溶血性貧血と異なり網赤血球数は正常ないし軽度増加にとどまることが多い。末梢血塗抹標本では赤血球の大小不同、奇形赤血球、多染性、好塩基性斑点などがみられる。骨髄では赤芽球の著明な増加がみられ、各病型ごとにそれぞれ特徴的な所見を有する（表１，2)。検査所見の特徴として黄疸（間接型ビリルビンの上昇)、脾腫、ハプトグロビンの低下などが挙げられる。輸血されなくても鉄過剰状態のため血清鉄の上昇も特徴的所見であり、続発性ヘモクロマトーシスを来たす危険が高い。

3. CDA の分類（表１、表２）

Ｉ型はクロマチン架橋などクロマチン構造の異常が特徴的である。中東や北アフリカの遊牧民であるベドウイン族に多く、常染色体劣性の遺伝形式をとる[3]。通常はMCVが100-120fLの大球性貧血を呈し、生涯にわたり輸血不要の軽症例から出生直後からの輸血依存例まで貧血の程度は様々である。一部の症例では合指などの骨格系異常の合併が報告される。骨髄は巨赤芽球変化に加え、細胞分裂が不完全に終わった１対の赤芽球の核同士が細いクロマチンにて架橋されていることが特徴的である。責任遺伝子として15番染色体上に座位するCDAN1が同定された[4]。CDAN1の機能については明らかでない点が多いが、細胞分裂過程におけるクロマチン形成に関与すると考えられている。

II型も常染色体劣性遺伝で、南イタリアを中心に300例以上の報告がある[5, 6]。CDAの中でもっとも高頻度でI型の3倍もの症例が報告されている[2]。貧血の重症度は様々ではあるが、一般に軽症例が多くしばしば成人期に診断される。正球性を呈することが多く、骨髄でもI型のような巨赤芽球変化が目立たない一方で、多核赤芽球の存在が特徴的である。CDAの中でII型だけがHam試験陽性となる[7]。2009年に責任遺伝子として20番染色体上に座位するSEC23Bが同定された[8]。SEC23Bの変異により小胞体からゴルジ体への新規合成蛋白の輸送が障害されるものと考えられている。

III型はスウェーデンの家系の報告より[1]、15番染色体上に責任遺伝子が座位するものと推測されているが症例数が極めて少ないこともあり同定には至っていない。骨髄で10核以上にもなる多核の巨大赤芽球がみられることが特徴である[9]。

I, II, IIIのいずれの病型にもあてはまらないCDAは亜型とされ、これまでにIV型からVII型までが報告されている[10]。IV型はII型ないしIII型と同様に多核赤芽球を特徴とする骨髄所見を呈するがHam試験は陰性である。2010年にIV型の責任遺伝子として19番染色体上に座位するKLF1が同定された[11]。KLF1は赤芽球造血に重要な転写因子である。さらに、CDA with prominent erythroblastosis after splenectomy, CDA with intraerythrocytic inclusions, CDA with thrombocytopeniaなどが亜型に含まれる。興味深いことにDown症候群の一過性骨髄異常増殖症の原因であるGATA-1遺伝子の異常がCDA with thrombocytopeniaで認められている[2]。

4. 予後

長期予後に関して、ドイツのCDA Registryからの報告がある。19家系21例（診断時年齢 0.1-45歳, 中央値 17.3歳）を最長37年間追跡したもので、12例が輸血をされ、うち5例は４歳までに複数回の輸血を施行されたが、４歳以後は輸血不要となっていた。全例でヘモクロマトーシスを認め、９例が除鉄療法を受けた。５例が死亡しており（死亡時年令 31-57歳)、死因は心疾患と肝疾患の合併が３例、耳の扁平上皮癌が１例、摘脾後敗血症が１例であった[12]。

2006年に多賀らが行った全国調査で確認されたCDAの12例のうち5例が死亡しており（死亡時年令 ８ヶ月-15歳)、１例は肝硬変であったが、他はCDAと直接関連しない死因だった[13]。

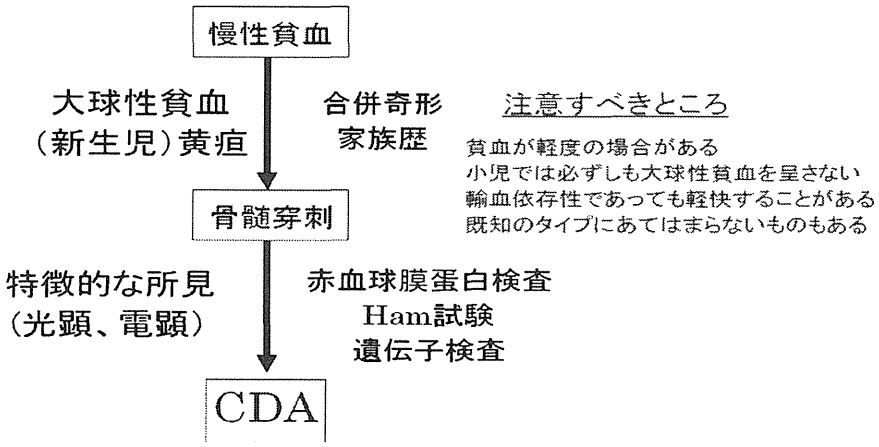
5. 診断

表3にあるような家族歴、既往歴、身体所見、検査所見が見られ、骨髄所見と他疾患の除外からCDAの可能性が

考えられる場合は、遺伝子検査を行い診断確定する。注意すべき点として、貧血は臨床上問題にならないほど軽度の場合があること、輸血依存であっても成長とともに改善することがあること、小児やサラセミア合併例では大球性貧血を呈さないことがあること、などがあげられる。また、報告されているどのタイプにも合致しない症例もみられる。

先天性溶血性貧血と診断されていた症例が後からCDAと診断されることがしばしばあり、他の先天性貧血疾患やdyserythropoiesisを伴う先天異常疾患の除外は必須である。図１には診断のフローチャートを、表3にはCDAを疑う所見、表4には主な鑑別疾患を示す。

図１　CDA診断へのフローチャート



6.　治療法、薬物療法、造血幹細胞移植

・輸血療法

多くの症例は生涯にわたり貧血を呈するが、貧血自体は軽症～中等症であることが多く、輸血が必要となることは少ない。１回でも輸血が必要となった例はI型の50%、II型の10%で、その後も輸血依存となるのはその一部のみである[2)]。

・除鉄

輸血依存でなくても鉄過剰となりうるため血清フェリチン値の定期的なモニタリングが必要である。除鉄を開始するフェリチン値のカットオフとして1000～1500μg/lが推奨されている[10)]。輸血依存があれば積極的に除鉄を考慮する。

・摘脾

CDAは赤血球寿命が短縮していることから、II型など一部の症例で有効であるといわれている。摘脾によってHbは上昇し、血清ビリルビンは減少するが、鉄過剰を防ぐことはできない。II型以外でも有効例は報告されているが、効果を予測する因子は見つかっていない。摘脾によって血小板数が増加し、Budd-Chiari症候群や門脈血栓症を来した報告があり、注意を要する。

・インターフェロン

I型でインターフェロンαの投与が有効であったとの報告があり、輸血依存の場合には考慮すべき治療法である。ただし、副作用、保険適応について留意する必要がある。II型には無効である。

・そのほかの薬物療法

赤芽球過形成に対してビタミンB12や葉酸を補充が行われる。また、ビタミンEが有効であったという報告もある。

・造血幹細胞移植（HSCT）

輸血依存性のI型、βサラセミアを合併した II型などで報告がある。多賀らの調査でも亜型の１例でHSCTが行われ輸血不要となっていた[13)]。ヘモクロマトーシスを合併していても十分な除鉄を先行させて非血縁ドナーからのHSCTを行った例の報告もあり[14)]、適当なドナーがいる輸血依存例には考慮すべきであろう。

7.　問題点、将来展望

これまでは臨床所見、血液・検査所見、形態学的所見、さらには他疾患の除外に基づいてCDAの診断が行われてきたことから、既存の病型に合致せず確定診断が得られない例も多かった。これまでにCDAN1、SEC23B、KLF1などの責任遺伝子が発見されており、今後はこれらの解析を用いることで診断がより正確に行われることが期待される。また、CDA自体が稀少疾患である上に、各亜型に属する症例数は極めて少ないため連鎖解析などの手法を用いた責任遺伝子の同定は困難であったが、エクソームシーケンスやディープシーケンスによって新規の責任遺伝子が発見されれば、さらなる診断精度の向上が得られるであろう。

本邦においても2006年度の多賀らの全国調査によりCDA患者が存在することが確認されたが、軽症例や自然軽快例、成人例などが見逃されて実態が十分に把握できていない可能性が高い。本疾患に遭遇する機会が多いと考えられる新生児科医や内科医などに本疾患が十分認識されていない現状を鑑みると、班研究などを中心に本疾患の啓発活動を行う必要がある。その上で、遺伝子検査も含めた中央診断を取り入れることで的確な診断と症例の把握が可能になることが期待される。

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表１　CDAの古典的3病型

	I型	II型	III型
遺伝形式	常染色体劣性	常染色体劣性	常染色体優性
責任遺伝子	15q15.1-3 CDAN1	20q11.2 SEC23B	15q21-25 不明
貧血の程度	軽度－中等度	軽度－重度	軽度－中等度
赤血球サイズ	大球性	正球性から大球性	大球性
骨髄の赤芽球像 (光顕)	巨赤芽球様変化 ２核赤芽球(2-5%), クロマチン架橋	２核－多核の赤芽球(10-40%) 異型核赤芽球	多核赤芽球 巨大赤芽球(10-40%)
骨髄の赤芽球像 (電顕)	核膜の部分欠損 核質内への細胞質や小器官の流入	細胞膜内周の二重膜構造	核膜のスポンジ様構造 核膜の亀裂や凹凸
Ham 試験	陰性	陽性	陰性
抗i抗原凝集反応	陰性	強陽性	陰性または弱陽性

表２　CDA I～IV型および亜型の比較

CDA病型	I	II	III	IV	亜型
遺伝形式	常染色体劣性	常染色体劣性	常染色体優性	常染色体優性	常染色体劣性、 または伴性
報告数	～150例	～370例	３家系	20例未満	20例以上
形態学的特徴	巨赤芽球変化 クロマチン構造異常 クロマチン架橋	多核赤芽球	巨大多核赤芽球	多核赤芽球	他の病型に準じる
責任遺伝子	CDAN1	SEC23B	不明	KLF1	不明 (一部でGATA1異常)
染色体	15q15.1-3	20q11.2	15q21-25	19p13.2	不明 (Xp11.23)
奇形徴候	骨格系異常など	まれ	B細胞、網膜	種々	中枢神経 血小板減少
治療	インターフェロンα 除鉄	摘脾 除鉄	不明	不明	不明

表3　CDAを疑う所見

a.　黄疸がある、あるいは黄疸の既往（重度あるいは遷延性新生児黄疸を含む）がある
b.　赤芽球系の無効造血（骨髄での赤芽球過形成と末梢血の網赤血球減少）
c.　末梢血での赤血球形態異常（大小不同、奇形赤血球、多染性、塩基性斑点など）
d.　骨髄での赤芽球形態異常（クロマチン架橋、多核赤芽球、巨赤芽球変化など）
e.　大球性貧血
f.　輸血歴、輸血依存性
g.　脾腫
h.　原因不明の慢性貧血の家族歴
i.　四肢、骨格奇形
j.　赤血球形態異常
k.　上記には該当しないが原因不明の貧血がある

表4　CDAと鑑別を要する疾患

先天性疾患
- サラセミア
- 不安定ヘモグロビン症
- 遺伝性球状赤血球症
- ピルビン酸キナーゼ欠損症
- 先天性骨髄異形成症候群

後天性疾患
- ビタミンB12欠乏症
- 葉酸欠乏症
- 鉄欠乏性貧血
- 骨髄異形成症候群
- 飲酒過剰
- 急性骨髄性白血病
- 再生不良性貧血
- パルボB19ウイルス感染
- AIDS
- マラリア
- 肝疾患
- 抗腫瘍剤投与後
- 骨髄移植後

Guideline for the clinical management of congenital dyserythropoietic anemias

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