Review Article

Clinical evaluation of hyperferritinemia with or without iron overload

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Abstract: Serum ferritin is a good biomarker; when it is low, it suggests iron deficiency, but in the case of hyperferritinemia it is not necessarily an index of iron overload. As a non-iron overload condition, physicians encounter mildly increased serum ferritin commonly associated with viral or bacterial infectious diseases, and autoinflammatory diseases like systemic juvenile idiopathic arthritis (sJIA) or adult-onset Still's disease (AOSD). When these diseases develop into severe forms like hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS), serum ferritin levels rise steeply to a marked increase. HLH develops as various hereditary forms or a secondary form while MAS is secondary. Precise diagnosis of hereditary HLH requires genetic study. On the other hand, hyperferritinemia is an index of iron overload in hemochromatosis and other iron-overloading anemias. The correct diagnosis of hemochromatosis (types 1–4) and various iron-overloading anemias could be made by genetic study. Metabolic hyperferritinemia is a mixed type with or without iron overload, which is mostly noted in middle-aged men, associated with non-alcoholic fatty liver disease (NAFLD) or dysmetabolic iron overload syndrome (DIOS). Rare hereditary hyperferritinemia without iron overload, currently described in 3 types, needs to be kept in mind for differential diagnosis. One representative type is Hereditary Hyperferritinemia-Cataract Syndrome (HHCS). Precise cause(s) of hyperferritinemia, if unexplained, require thorough examinations with the use of genetic study which may lead to the discovery of rare disease(s). In this review, the major causes of hyperferritinemia, the elevated ranges of serum ferritin, the glycosylation status of serum ferritin in each category, and the gene panel useful for differential diagnosis are discussed. This review is hoped to be useful for differentiating hyperferritinemia in daily clinical practice.

Keywords: Ferritin; hyperferritinemia; iron overload; hemophagocytic lymphohistiocytosis (HLH); metabolic syndrome

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Introduction

In clinical practice, physicians order serum ferritin assay as a useful biomarker in cases of iron deficiency anemia (low serum ferritin) or iron overload (high serum ferritin). Besides iron overload, high serum ferritin is caused by a non-iron overload condition, such as viral [Epstein Barr virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, etc.] or bacterial infectious diseases (sepsis) or inflammatory diseases (Still's disease, juvenile acute arthritis, etc.), in which serum ferritin levels are employed to evaluate disease activity/severity. Most strikingly, when such conditions progress to hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS), a marked increase in serum ferritin develops. In addition, it is not infrequently that metabolic patients with hyperferritinemia are referred to hematologists

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who are not familiar with metabolic cases. Although the incidence is very low, physicians need to be aware of Hereditary Hyperferritinemia-Cataract Syndrome (HHCS) and other hereditary hyperferritinemia. In this review, differential diagnosis of various causes of hyperferritinemia with or without iron overload, characteristics of serum ferritin, and management have been overviewed.

Characteristics of serum ferritin

Iron homeostasis and ferritin

Hyperferritinemia is largely related to disturbed iron homeostasis. Iron homeostasis relies on the amount of iron absorbed by the intestine and its release from storage sites and is also dependent on the amount of iron used for erythropoiesis. In iron metabolism, many molecules are involved such as divalent metal-ion transporter 1 (DMT1), HFE, hepcidin, ferroportin 1, transferrin, ceruloplasmin, transferrin receptor, hemojuvelin, etc. of which hepcidin plays the main regulator (1). Decreased hepcidin synthesis or disrupted hepcidin binding to ferroportin causes iron overload and hyperferritinemia. Within the cells where iron is transferred, iron regulatory proteins (IRPs) bind to the iron-responsive element (IRE). The IRE/IRP interaction and hepcidin are coordinated with the fluctuation of the cellular iron level (2). There is also a link between iron and copper metabolism. Ceruloplasmin, which contains greater than 95% of the copper found in plasma, is also a player in iron metabolism as ferroxidase that oxidizes toxic ferrous iron (Fe2+) to its nontoxic ferric form (Fe3+), which is then taken up by transferrin. Thus, in daily practice, abnormal serum values of ferritin, hepcidin, transferrin, and ceruloplasmin are noted in diseases of disturbed iron homeostasis. Hyperferritinemia occurs in various pathological conditions with or without iron overload (3,4). Ferritin, with a molecular weight of approximately 500 kDa, is the major iron-storage glycoprotein found in all tissues. It is comprised of 24 subunits containing H-chain (heavy or heart, 21 kDa), and L-chain (light or liver, 19 kDa) polypeptide chains encoded by two different genes; H- and L-ferritin (*FTH* and *FTL*) genes located on chromosomes 11q and 19q (5,6). Thus, ferritin molecules are heteropolymers of H- and L-ferritin and do not function as homopolymers. In terms of intracellular localization of ferritin subunits, L-ferritin is predominantly found in the cytosol, while H-ferritin is mainly found in the nucleus. Ferritin polymers rich in L-ferritin play more of a storage function, whereas those rich in H-ferritin may have functions beyond iron storage (6). Ferritin synthesis is regulated by cytokines [tumor necrosis factor (TNF)-alpha and interleukin-1 alpha] at various levels (transcriptional, post-transcriptional, translational) during development, cellular differentiation, proliferation, and inflammation (7-9). Serum ferritin comprises mostly L-ferritin subunits (5,6). Also, ferritin resides in glycosylated and non-glycosylated forms (6,10,11). From the clinical point of view, an assay of serum ferritin is essential, and the glycosylation status of ferritin could be useful for the differential diagnosis of hyperferritinemia, though the glycosylation status remains a research test and is not routinely utilized in clinical practice.

Source and characteristics of serum ferritin

There are two probable mechanisms as the source of increased serum ferritin; one is that it arises from damaged cells, representing a marker of cellular damage (12,13). Increased ferritin release from the injured cells may occur due to chronic viral hepatitis, metabolic hepatic steatosis (see metabolic hyperferritinemia), etc. (13). On the other hand, increased ferritin synthesis can be noted most strikingly in cases of infectious/inflammatory hyperferritinemia, which is caused by a rapid release along the augmented synthesis, not by leakage from damaged cells (14). In a mouse model, ferritin is secreted as an acute reactant from cells such as splenic macrophages, hepatocytes, Kupffer cells, and proximal tubular renal cells where ferritin is rapidly synthesized under the effect of cytokines (15). Thus, serum ferritin as a well-known acute-phase reactant reflects the degree of acute and chronic infectious/inflammatory diseases (16). In hemochromatosis and inherited iron overloading anemias, increased ferritin synthesis was also suggested (13). Among the cases of hereditary hyperferritinemia, in HHCS cases, it is due to constitutive L-ferritin production (17). In *FTL* gene mutation cases, an abnormal ferritin secretion is hypothesized but not confirmed (18). In cases of *STAB1* gene mutation cases, the mechanism remains to be clarified (19). Serum ferritin is glycosylated (normally ~50%), but there are two pathological conditions, with low glycosylated (20–42%), or hyperglycosylated (>90%) as discussed later.

Definition of hyperferritinemia

Normal values of serum ferritin differ from laboratory to laboratory. We use 5–157 ng/mL as normal ranges in our laboratory. Kowdley *et al.* employed >1.5 × upper

Table 1 Differential diagnosis of various hyperferritinemia

Diseases	Causes	Hyperferritinemia**	Iron overload
Infectious disease/autoimmune disease-triggered	No HLH/MAS	Mild to moderate	No
	HLH*/MAS	Marked	
Hereditary hyperferritinemia	HHCS	Mild to moderate	No
	FTL gene mutation	Mild to marked	
	STAB1 gene mutation	Mild to moderate	
Metabolic syndrome	NAFLD	Mild	Mixed
	DIOS	Mild to moderate	
Hemochromatosis	HFE/non-HFE	Mild to moderate	Yes
Inherited iron overloading anemia	DHS1	Mild to marked	Yes
	PKD		
	XLAS		
	CDA		
	SCD		
	Thalassemia		
Other rare disorders causing iron overload	Aceruloplasminemia	Mild to moderate	Yes
	Atransferrinemia		
	DMT1 deficiency		

Inherited iron overloading anemia is caused by hemolysis, ineffective erythropoiesis inhibiting hepcidin synthesis, and increasing iron absorption and release in the blood. In severe anemic cases, transfusion-related iron overload is also responsible. *, there are two types of HLH; primary (inherited; see *Table 2*) and secondary; **, increase of ferritin: mild increase (>1.5 × ULN–500 ng/mL), moderate increase (>500–3,000 ng/mL) and marked increase (3,000–>100,000 ng/mL). HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; HHCS, Hereditary hyperferritinemia due to cataract syndrome; *FTL* gene, L-ferritin gene; STAB1, encoding stabilin 1 protein; NAFLD, non-alcoholic fatty liver disease; DIOS, dysmetabolic iron overload syndrome; DHS1, dehydrated hereditary stomatocytosis 1; PKD, pyruvate kinase deficiency; XLAS, X-linked sideroblastic anemia; CDA, congenital dyserythropoietic anemia; SCD, sickle cell disease; DMT1, divalent metal-ion transporter 1.

limit of normal (ULN; >300 ng/mL in women and >450 ng/mL in men) as a definition of hyperferritinemia in metabolic diseases (20). If this definition is adapted for our laboratory >236 ng/mL could be hyperferritinemia regardless of males or females. On the other hand, diagnostic criteria for HLH and MAS employed ≥500 and >684 ng/mL, respectively, as hyperferritinemia (21,22). Hyperferritinemia could be classified from mild (>1.5 × ULN–500 ng/mL), moderate (500–3,000 ng/mL), and markedly high (3,000–>100,000 ng/mL). Thus, as defining hyperferritinemia, strict cut-off values such as >1.5 × UNL are employed for mild~moderate increase while a cut-off of ≥500–684 ng/mL could be employed for a disease showing markedly high serum ferritin.

Differentiation of hyperferritinemia with or without iron overload

As mentioned above, hyperferritinemia does not necessarily mean iron overload. To differentiate if hyperferritinemia is associated with or without iron overload, serum iron concentration as well as transferrin saturation (TSAT; calculated as serum iron/total iron binding capacity × 100), are good indicators for this purpose. In addition, magnetic resonance imaging (MRI) of the liver is useful, because whenever iron overload is present, the liver is the main organ involved. For directly assessing the liver iron content (LIC), liver biopsy was previously employed as the standard procedure but is less used than before because the high level of precision of T2* measurement by dedicated MRI now allows a non-invasive and efficient procedure for measurement of iron concentration in the liver and other organs (23,24).

Major causes of hyperferritinemia

Major causes of hyperferritinemia and their characteristics are shown as an algorithm in *Table 1* and *Figure 1*, and the

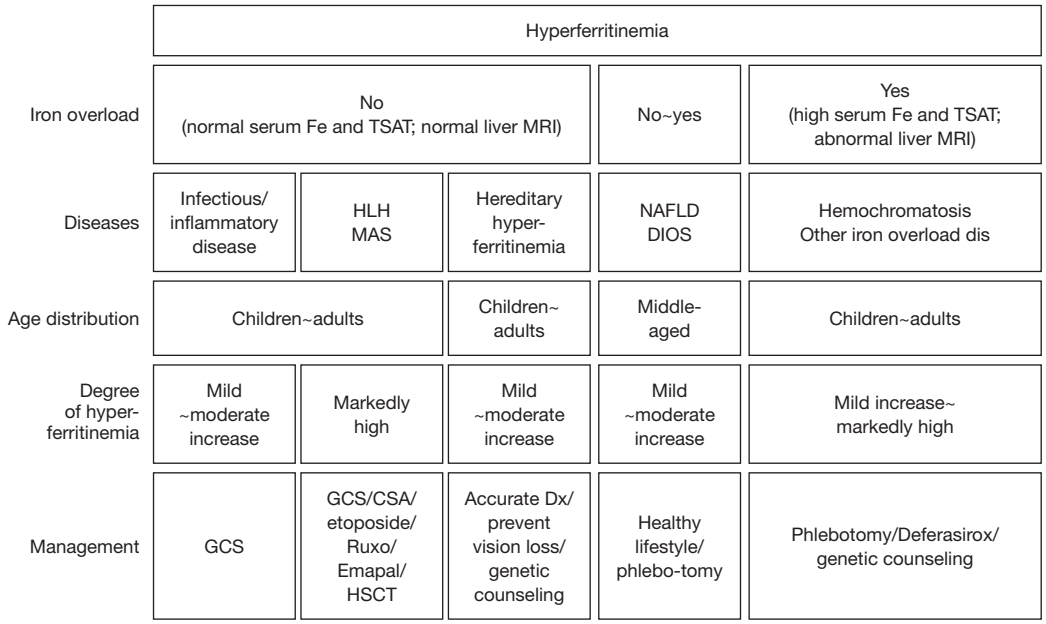

Figure 1 Algorithm of hyperferritinemia with or without iron overload. TSAT, transferrin saturation; MRI, magnetic resonance imaging; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; NAFLD, non-alcoholic fatty liver disease; DIOS, dysmetabolic iron overload syndrome; GCS, glucocorticoids; CSA, cyclosporine A; Ruxo, ruxolitinib; Emapal, emapalumab; HSCT, hematopoietic stem cell transplantation; Dx, diagnosis.

degree of serum ferritin levels are comparatively illustrated in *Figure 2*. Hyperferritinemia-related gene panels due to inherited disorders (25,26) are listed in *Table 2*. Below, each hyperferritinemic disease is overviewed in the order of non-iron overload, mixed type (with or without iron overload), and iron overload.

Hyperferritinemia in infectious/ inflammatory diseases

This condition is noted from young children to the elderly. Causes of hyperferritinemia are due to acute ferritin synthesis under the cytokine effect. The cellular response by cytokines to viral and bacterial infections, or inflammatory diseases like pediatric systemic lupus erythematosus (SLE), systemic juvenile idiopathic arthritis (sJIA), or adult-onset Still's disease (AOSD) stimulates the expression of ferritin genes (16,27-30). High serum ferritin levels have been described in viral infectious conditions, such as Epstein-Barr virus (EBV) (31-33) and SARS-CoV-2 infections, etc. (34-36). Particularly, during the recent pandemic of SARS-CoV-2 infection, data on coronavirus disease 2019 (COVID-19)-triggered hyperferritinemia has been accumulated (34-36), in which the serum ferritin levels in severe COVID-19 patients were significantly increased compared with the levels in non-severe patients (34). Even in sepsis, a high level of serum ferritin was an independent prognostic marker for the prediction of mortality (37,38). In infectious/inflammatory diseases, serum ferritin, as one of the key acute-phase reactants, is employed to evaluate disease activity/severity if the disease develops into HLH or MAS. For the diagnosis of HLH/MAS, physicians carefully must refer to the diagnostic criteria of HLH (21) or MAS (22,39). It is well-recognized that the laboratory abnormalities in HLH and MAS overlap. Actual serum levels of ferritin were; in EBV-infectious mononucleosis >1,650 ng/mL (33), 2,430 ng/mL (31), and 1,901 ng/mL (32). In patients with COVID-19, serum ferritin values were median (ranges) of 1,024 (434–1,821) ng/mL, and a median of 501.9 ng/mL in the survivor group *vs.* 1,722 ng/mL in the non-survivor group (35). In patients with sepsis, serum ferritin values were median (ranges) of 542 (244–1,125) ng/mL (38), and a median of 430 ng/mL in the survivor group *vs.* 892 ng/mL in the non-survivor group (37). In the management of these cases, glucocorticoids (GCS) or cyclosporine A (CSA) are mostly effective (27). For cases of COVID-19 with severe systemic hyperinflammation, the Janus kinase 1/2 inhibitor ruxolitinib has been employed (40).

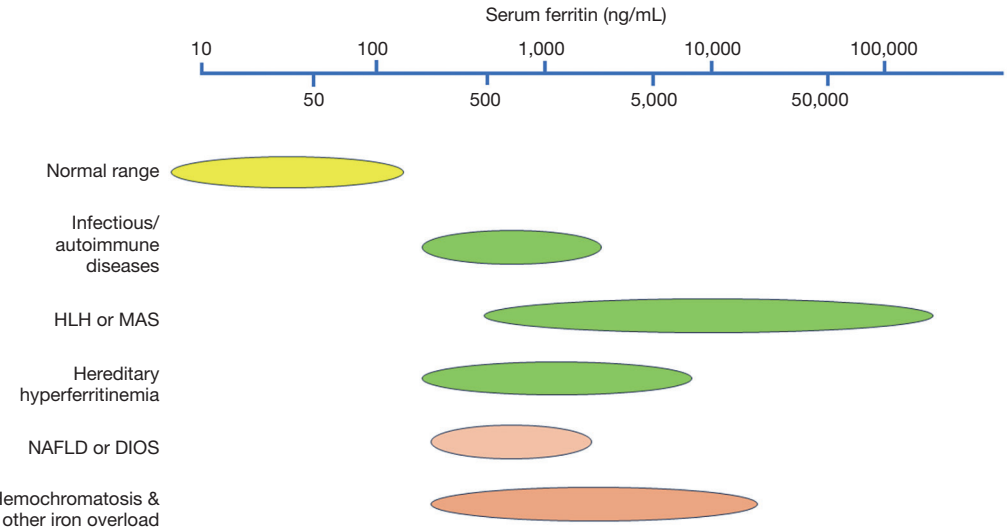

Figure 2 Comparative serum ferritin levels (on log scale) in various hyperferritinemia. Normal range is in yellow-, non-iron overload in green-, and iron overload in orange-colored. HLH, hemophagocytic lymphohistiocytosis, MAS, macrophage activation syndrome; NAFLD, non-alcoholic fatty liver disease; DIOS, dysmetabolic iron overload syndrome.

Table 2 Gene panel for the differential diagnosis of hyperferritinemia*

Primary HLH and related	Hemochromatosis	Hereditary hyperferritinemia	Inherited iron-overloading anemias	
FRF1	*HFE*	*IRE region of FLT*	*PIEZO1*	*CP*
UNC13D	*HAMP*	*FLT*	*PKLR*	*TF*
STX11	*TFR2*	*STAB1*	*ALAS2*	*DMT1 (SCL11A2)*
STXB2	*SLC40A1*		*CDAN1*	**TMPRSS6*
LYST			*KLF1*	
RAB27A			*SEC23B*	
ADTB3A			*Thalassemia gene*	
SH2D1A			*SCA beta-globin gene*	
XIAP				

*, based on the references (25) and (26); **, *TMPRSS6* gene mutation is responsible for IRIDA, which needs to be differentiated from iron-overloading microcytic anemias. HLH, hemophagocytic lymphohistiocytosis.

Hyperferritinemia in HLH, or MAS

HLH or MAS develops from the above infectious/inflammatory diseases, which fulfill the diagnostic criteria of either HLH or MAS and occur in young children to the elderly. HLH is classified as primary (hereditary) and secondary (21,25), while MAS is secondary under inflammatory diseases, as mentioned above. Historically, when we first noted significantly higher levels of serum ferritin in cases of hemophagocytic syndrome in the mid-1980s (41), on a literature survey such high values were only known in cases of Lysinuric Protein Intolerance (LPI), a metabolic disease (42), which was later clarified caused by HLH. To date, significant amounts of data on this type of hyperferritinemia have been accumulated and a marked increase of serum ferritin is well recognized in HLH (43-45) and MAS associated with pediatric sJIA or with SLE (22, 29,39). Hyperferritinemia in this category indicates the activation of the monocyte-macrophage system, which is a crucial part of the inflammatory cytokine storm. In

the differentiation of hyperferritinemia between HLH or MAS and hemochromatosis, it was once proposed that evaluating clinical characteristics, serum triglycerides, and blood counts was the only reliable and rapid way to distinguish the two conditions (46). However, more recently, Ishihara *et al.* proposed that glycosylated ferritin could be an improved differential marker between these two hyperferritinemia (47). A low percentage (<20%) of glycosylated ferritin has been reported as a marker of HLH or MAS (48-50). As above mentioned, the highly elevated serum ferritin in HLH or MAS cases is due to a rapidly increased synthesis under the effect of cytokines such as TNF-alpha (8). Thus, markedly high serum ferritin in HLH or MAS is not normally (~50%) glycosylated. Actual serum ferritin levels of HLH reported were; a maximum value ranging from 1,140 to 68,600 ng/mL (43), and in hospitalized cases, on admission from 757 to 63,919 ng/mL, and a maximum from 994 to 189,721 ng/mL (44). In MAS cases, serum ferritin values were; median (ranges) of 7,838 (360–150,099) ng/mL in sJIA-MAS, and 4,158 (1,300–15,456) ng/mL in SLE-MAS (29). These data indicate that serum ferritin values in HLH or MAS are much higher, compared to mild to moderate increases in other diseases showing hyperferritinemia (*Figure 2*). As management, most HLH and MAS cases could be controlled with GCS and CSA with/without etoposide (27). HLH-94 or HLH-2004 regimen (dexamethasone/CSA/etoposide) has most commonly and globally been employed to date (21,51). More recently, ruxolitinib (52-54) and emapalumab (a fully human anti-IFNγ monoclonal antibody) (55-58) have proven to be effective in the control of disease activity. However, hereditary HLH requires hematopoietic stem cell transplantation (59).

Hereditary hyperferritinemia: HHCS and others

Hereditary hyperferritinemia is extremely rare and has been reported without iron overload in otherwise healthy individuals. There are three types of hereditary hyperferritinemia reported. One type is HHCS which is an autosomal dominant inheritance disease characterized by congenital bilateral cataracts associated with high serum ferritin levels. In HHCS, hyperferritinemic children aged 7–9 years can be diagnosed with a positive family history of early onset cataracts, who have no tissue iron overload or inflammation (17,60,61). The cause of hyperferritinemia in HHCS is the dysregulation of the IRE/IRP system due to mutations in the IRE stem-loop, i.e., the gene mutations are detected in *IRE* in the 5' untranslated region of the L ferritin mRNA, and L-ferritin synthesis is constitutively upregulated (62) which is responsible for the increase of serum low glycosylated (20–40%) serum ferritin (17,62). L-ferritin aggregates accumulate preferentially in the lens, provoking bilateral cataracts since childhood (63). The second type of hereditary hyperferritinemia is caused by a novel heterozygous p.Thr30Ile mutation in the NH2 terminus of L-ferritin subunit ("A" alpha helix) identified by sequencing analysis of the ferritin light chain (*FTL*) gene. This mutation is hypothesized to increase the efficacy of L-ferritin secretion into sera due to the increased hydrophobicity of the N terminal (18). Kannengiesser *et al.* identified this mutation in 25 family cases and 66 isolated cases, aged from 8 to 83 years (18). Similarly, two novel missense L-ferritin variants; p.Gln26Ile and p.Ala27Val. were also reported (64). These cases were 45- and 75-year-old. In this *FTL* gene mutated cases, hyperglycosylated (>90%) ferritin is characteristic (18,64). As another genetic cause of hereditary hyperferritinemia, ten subjects from seven families due to bi-allelic *STAB1* (encoding stabilin-1) mutations were described, suggesting an important role of stabilin-1 in the regulation of serum ferritin levels (19). Actual serum ferritin values reported in HHCS were; from 366 to 1,890 ng/mL (60), from 239 to 1,290 ng/mL (61), from 919 to 1,143 ng/mL (17), and from 653 to 1,796 ng/mL (63). Serum ferritin values in the disease of *FTL* gene mutations were; from 400 to 6,000 ng/mL (18) and from 618 to 1,200 ng/mL (64), and in the *STAB1* mutation disease were; median (ranges) 1,970 ng/mL (365–4,654) ng/mL (19). In the management of hereditary hyperferritinemia, accurate diagnosis is essential to avoid unnecessary treatment and to prevent early vision loss in HHCS. In addition, genetic counseling is required for other family members who are at risk (65).

Metabolic hyperferritinemia with or without iron overload:

It is well known that mild hyperferritinemia is observed in one-third of patients with non-alcoholic fatty liver disease (NAFLD) (66-69) or patients of dysmetabolic iron overload syndrome (DIOS), which is also termed Dysmetabolic Hepatic Iron Overload (DHIO) (70-73). These patients exhibit mildly elevated serum ferritin associated with high serum alanine aminotransferase due to liver steatosis and high fasting insulin C-peptide due to insulin resistance. The diagnosis of metabolic hyperferritinemia is mainly made in middle-aged males, associated with mostly low to normal

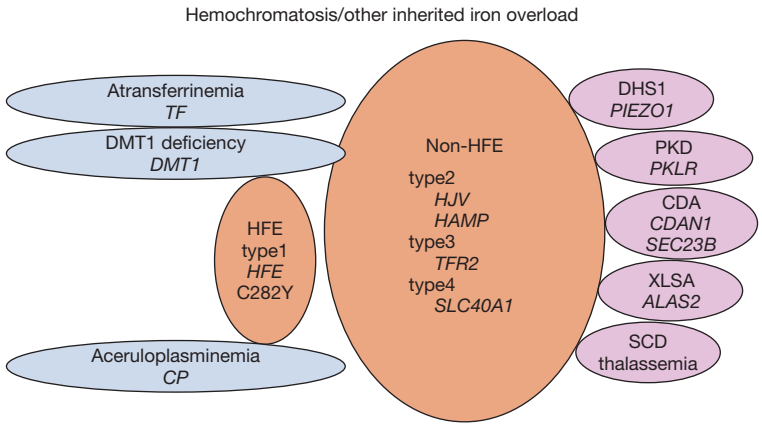

Figure 3 Schematic illustration of hemochromatosis (dark brown colored; HFE and non-HFE) and other iron-overloading anemias (light pink colored) causing iron overload. Extremely rare microcytic anemias showing iron overload (gray colored) are also included. Hemochromatosis comprises of HFE (type 1) and non-HFE (types 2–4). Responding gene mutations for each disease are shown in italic. For CDA, gene mutation for type 1 and type 2 alone is shown. For SCD/thalassemia, responsible genes are not shown because of limited space. DMT1, divalent metal-ion transporter 1; DHS1, dehydrated hereditary stomatocytosis type 1; PKD, pyruvate kinase deficiency; CDA, congenital dyserythropoietic anemia (type 2 CDA is most common); XLSA, X-linked sideroblastic anemia; SCD, sickle cell disease.

TSAT (22–45%) and with various metabolic abnormalities, such as increased body mass index with android fat distribution, elevated blood pressure, dyslipidemia, abnormal glucose metabolism, steatohepatitis (66). Though iron overload is not noted in all cases, DIOS cases mostly show mild hepatic iron excess in MRI studies which needs to be differentiated from ferroportin disease (74). In cases where phlebotomy was employed, normalized liver dysfunction and insulin resistance associated with decreased ferritin levels could be obtained (67,68). However, its pathophysiology and the degree to which it reflects tissue iron overload remain unclear. In NAFLD or DIOS, serum or urinary hepcidin levels are higher, indicating that synthesis of this hormone is not impaired, which thus is not responsive to iron storage (75,76). One hypothesis is that iron accumulation in metabolic diseases is due to the inhibition of iron mobilization from hepatocytes and Kupffer cells (66,67,69). Accordingly, the pathogenesis of hyperferritinemia in these cases seems to differ from that in hemochromatosis, in which serum or urinary hepcidin is impaired. Nevertheless, the increased production of hepcidin in patients with NAFLD or with DIOS is not yet fully understood (70). More recently, metabolic hyperferritinemia is classified as Stage 1 (normal iron stores, serum ferritin <550 ng/mL), Stage 2 (increased iron stores, serum ferritin 550–1,000 ng/mL), and Stage 3 (DIOS; very increased iron stores, serum ferritin >1,000 ng/mL) (77). Actual serum ferritin values reported in the NAFLD were; from 366 to 1,080 ng/mL (66), from 283 to 2,190 ng/mL (68), and a case of DIOS showed 2,210 ng/mL (74). As management, because high serum ferritin and hepatic iron stores are associated with the risk of several liver diseases, type 2 diabetes mellitus, and cardiovascular damage, a healthy lifestyle, such as a balanced diet low in processed foods, regular exercise, and limited alcohol consumption, and the pharmacological control of cardiovascular risk factors are recommended (77). In addition, phlebotomy can be employed for cases with iron overload (67,68).

Hyperferritinemia in hemochromatosis

Hemochromatosis was previously classified as primary (hereditary) and secondary (78,79). However, more recently, hemochromatosis has been defined as a non-anemic group of inherited disorders that cause iron overload due to failed regulation of hepcidin (26,80,81). Patients with iron overload including hemochromatosis show high serum Fe levels, TSAT, and abnormal images [computed tomography (CT), MRI] of the liver (23,24,26,80-82). Clinically, patients with iron overload initially may be asymptomatic, but if progressed it presents with hepatic dysfunction, endocrine abnormalities like diabetes mellitus or hypogonadism, heart failure, CNS diseases, and other organ problems. Precise diagnosis of hemochromatosis, and other iron-overloading anemias may require genetic studies (26,82) (*Table 2*, *Figure 3*). In Japan, of 1,109 iron overload cases analyzed, the

number of hemochromatosis was very limited, and the remaining 1,033 cases (93.1%) were transfusion-related (82). Hemochromatosis could have an autosomal recessive inheritance (HFE type 1 as well as non-HFE types 2 to 4) (80). In Caucasians, type 1 could be the major type, where *HFE* homozygous (C282Y) gene mutation is the most common in whites (83,84). On the other hand, in other ethnic groups, non-HFE types may be prevalent (85). Non-HFE-types consist of mutations in the four main genes: hemojuvelin (*HJV*, type 2A juvenile hemochromatosis), hepcidin (*HAMP*, type 2B juvenile hemochromatosis), transferrin receptor 2 (*TFR2*, type 3 hemochromatosis), and type 4 hemochromatosis (*SLC40A1*, previous type 4B) (85-89). Gene mutations of *SLC40A1* encoding ferroportin-the unique cellular iron exporter, whose function is controlled by hepcidin, cause two types of iron overload disease. One is ferroportin disease associated with mild iron overload, which is due to "loss of function" mutations causing iron retention in reticuloendothelial cells and hyperferritinemia with normal TSAT (previous type 4A). The other is type 4 hemochromatosis, caused by "gain of function" mutations associated with severe iron overload, showing resistance to hepcidin-mediated ferroportin degradation (26). Currently, ferroportin disease is no more included in hemochromatosis. Actual serum ferritin values in hemochromatosis were; from 200 to 1,000 ng/mL in type 1 (84), 2,222–16,000 ng/mL in 4 cases of type 2A (85,88), 3,000 and 5,696 ng/mL in two cases of type 2B (85,89), from 1,057 to 10,191 ng/mL in 5 cases of type 3 (85), and 7,980 ng/mL (85), >1,650 and 10,175 ng/mL (87) in 3 cases of type 4 hemochromatosis. As management, periodic phlebotomy, and oral chelating agent deferasirox are optionally employed. It is recommended that serum ferritin needs to be reduced to 50–100 ng/mL (90). In addition, genetic counseling is required for any patients with hemochromatosis.

Other iron overloading anemias

Other inherited iron-loading anemias are characterized by ineffective erythropoiesis and hepcidin suppression (91). This group of anemias includes some forms of hemolytic anemias such as dehydrated stomatocytosis 1 (DHS1) (92-94) and pyruvate kinase deficiency (PKD) (95,96), congenital dyserythropoietic anemias (CDAs; classified into the 3 major types-I, II, III and the transcription factor-related CDAs (97), congenital sideroblastic anemias like X-linked sideroblastic anemia (XLSA) (98), thalassemia and sickle cell disease (SCD) (*Figure 3*). These anemias are mostly normocytic ~ macrocytic, but in β-thalassemia minor it is microcytic. Also, in severe anemic cases, acquired transfusion-related iron overload occurs (13,78,79). One of the underestimated types of iron overload is DHS1 (92-94), which needs to be emphasized as a cause of non-transfusion-dependent iron overload. Iron overload in DSH1 (99-101) could be explained by chronic hemolysis, but the findings that PIEZO1 activation induced Ca^{2+} influx and suppression of HAMP expression causing low hepcidin indicate a link between PIEZO1 and iron metabolism (93). In these anemias, serum ferritin may be already high on non-transfusion status and become even higher after transfusions (102). In addition, extremely rare types of inherited microcytic anemias showing iron overload include congenital aceluroplasminemia (ACP), congenital atransferrinemia (ATF), and DMT1 deficiency (26,103-105) (*Figure 3*). ACP is characteristic of the brain, and other organ damages due to the accumulation of iron but with low serum Fe, normal TSAT, and microcytic anemia (103). ATF and DMT1 deficiency are characterized by iron-deficient erythropoiesis, severe microcytic anemia with high TSAT associated with decreased serum levels of transferrin and iron, and parenchymal iron overload due to secondary hepcidin suppression (26,104). Of these cases, ACP and ferroportin disease may belong to the diseases due to inefficient iron export from storage cells, while ATF and MDT1 deficiency to the diseases due to defects of iron delivery to maturing erythroblasts or erythroblast iron handling (26). These inherited microcytic anemias need to be differentiated from thalassemias and iron-refractory iron deficiency anemia (IRIDA) (106). Actual serum ferritin values were; from 815 to 5,141 ng/mL in DHS1 (99,101), median (ranges) of 228 (58–3,160) ng/mL in non-transfused patients with PKD (96), from 890 to 1,493 ng/mL in XLAS (98), 916±507 ng/mL in cases of post-transfusion CDA type I (107), 1,996 ng/mL in a case of CDA type II (108). If transfused cases were included; from 300 to >2,500 ng/mL in cases of SCD (109), and median (ranges) of 1,960 (44–21,828) ng/mL in the combined cases of SCD, thalassemia, and other congenital anemias (110). Serum ferritin values in ACP were; from 855 to 1,140 ng/mL (85,111), in ATF were; from 250 to 837 ng/mL (104), and from 58 to 305 ng/mL in DMT1 deficiency (105). Management policy for these disorders is similar to that in hemochromatosis.

Conclusions

From the clinical point of view, various conditions of

hyperferritinemia with or without iron overload have been overviewed. Physicians most frequently encounter patients with hyperferritinemia due to infectious/inflammatory causes: Especially, HLH and MAS as the most severe forms in which markedly high serum ferritin (>3,000 ng/mL) is caused by rapid synthesis and release into sera under the cytokine effect. On the other hand, hemochromatosis and inherited iron-loading anemias represent hyperferritinemia associated with iron overload. In these diseases, serum ferritin is mild to moderately elevated and becomes significantly higher after transfusions. It is not infrequent that middle-aged adult patients with metabolic hyperferritinemia are referred to hematologists as unknown hyperferritinemia. Rare hereditary hyperferritinemia such as HHCS is known to be without iron overload and shows mild to moderate hyperferritinemia. Since mild to moderately elevated serum ferritin is most frequently noted with various conditions (*Figure 2*), careful differentiation is required from clinical information and with the use of serum Fe, TSAT, and imaging studies. From a future perspective, assays of hepcidin and glycosylated ferritin status should be available in daily practice. In addition, target gene sequencing analysis is encouraged to be applied broadly for unexplained hyperferritinemia, especially for inherited disorders using a gene panel as listed in *Table 2*.

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Footnote

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