A Case of Atransferrinemia and 35 Cases of Hypotransferrinemia as Detected by Radioassay of Total Iron-binding Capacity of the Serum

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Total iron-binding capacity (TIBC) of the serum was determined in 600 patients by the radioassay method devised by Saito. Fifty-four $\mu\text{g}/\text{dl}$ of TIBC, which is as low as that of previously reported cases of congenital atransferrinemia, was found in a patient with marked hypoproteinemia probably due to protein losing enteropathy as shown by a high plasma RISA disappearance rate of 41 percent per day. The patient was diagnosed as having secondary atransferrinemia on the bases of hematological findings, iron metabolism and other tests. Thirty-five of 600 patients whose serum TIBC levels were determined by radioassay had low TIBC level below $200 \mu\text{g}/\text{dl}$. Twenty-one of the 35 (60%) had blood diseases, 13 (37%) had malignancies and 7 (20%) had diseases of digestive organs. TIBC was markedly increased in iron deficiency anemia, while it was normal or decreased in other diseases. TIBC radioassay is a simple, highly accurate and efficient method of measuring transferrin.

Key Words: Transferrin, Serum iron, Unsaturated iron-binding capacity of serum (UIBC), Protein losing enteropathy (PLE), Hypoproteinemia, Plasma RISA clearance, Radioiron utilization, Storage iron deposition, Mechanism of iron absorption, In vitro saturation assay.

Five cases of congenital atransferrinemia have been reported so far. Besides, there are 4 reports on secondary atransferrinemia and suspected atransferrinemia.

To make diagnosis of atransferrinemia, immunoassay of transferrin (Tf) or measurement of both serum iron (SI) and unsaturated iron-binding capacity (UIBC) is essential. One of the authors, Saito, devised the method of TIBC radioassay¹⁰⁻¹²⁾, and Res-O-mat TIBC kit based on the method

is now commercially available. Recently the authors performed determination of serum TIBC on 600 patients using the TIBC kits and found 35 patients with TIBC levels below $200 \mu\text{g}/\text{dl}$, one of them had extremely low serum Tf level.

MATERIALS AND METHODS

TIBC and UIBC were measured by using Res-O-mat TIBC and UIBC kits produced by Dai-ichi Radioisotope Laboratory, Ltd., Japan. The amount of Tf in mg/dl was obtained by dividing TIBC value in $\mu\text{g}/\text{dl}$ by 1.3. At the same time Tf was determined by using Behringwerke's Immunodiffusion Platten.

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TIBC was determined on 600 different sera which had been sent to the Radioisotope Laboratory of Nagoya University Hospital for the determination of UIBC. Plasmas or sera obtained from healthy students of Nagoya University School of Medicine were used as normal controls.

Case Report

M.N., 24-year-old Japanese girl, was admitted to Nagoya University Hospital with suspected protein losing enteropathy on September 9, 1974.

Family history was not contributory. Past history was unremarkable except for passing 2 to 3 loose stools daily since she was a pupil of an elementary school.

In July of 1970, she developed edema on upper and lower limbs, general fatigue and fever of about 39°C of 4 days' duration. Proteinuria and decreased plasma protein level were also noted. The edema disappeared after diuretic therapy. She was admitted to Kariya Toyota Hospital with a diagnosis of nephrotic syndrome on July 20, 1970 and was discharged in May of 1971, since physical and laboratory findings were normalized. In July of 1973, edema and hypoproteinemia reoccurred. She was treated as inpatient at Anjo Kosei Hospital from August 22 to 27 inclusive. In May of 1974, she developed edema which increased steadily thereafter. In July, she was admitted to Anjo Kosei Hospital with generalized edema, cough, pleural effusion, marked hypoproteinemia and elevated ESR. By kidney biopsy performed on July 31, a pathologic diagnosis of membranous glomerulonephritis was made, while urinary protein was negative. Then she was moved to Nagoya University Hospital for further study.

Physical findings at admission: The patient was rather small but normally developed girl. Height was 148 cm and body weight 44 kg. BT 36°9'C. Pulse was 88 per minute and was regular. BP was 108/64 mmHg. Her conjunctiva appeared anemic and striae cutis distensae were noted on abdominal wall. There was a mild edema

on legs. Laboratory data were listed in Table 1. Marked hypoproteinemia with hypalbuminemia, increased α_2 -globulin level, hypocalcemia, hyperlipemia and severe hypotransferrinemia were the outstanding features. High T₃RU and somewhat low thyroxin level were noted, indicating depletion of thyroxin binding protein.

Course in the Hospital: Despite severe hypoproteinemia, edema was successfully treated with 40-80 mg of furosemide daily, but recurred soon after the drug was withdrawn. On September 30, she had a brief episode of shock followed by marked tachycardia and tachypnea lasting for several days. In December, she developed leg edema, ascites, fever and cough of several days' duration.

Plasma protein level remained low and rarely rose above 4 g/dl. Striking hypercatabolic hypoproteinemia, as shown by a rapid RISA disappearance (Figure 1), strongly suggested the existence of protein losing enteropathy (PLE), for urinary pro-

Fig. 1. Plasma RISA disappearance curve.

Table 1. Laboratory data.

	1974	1975			
	Sept	Oct	Dec	Feb	Apr
Total protein (6.8-8.2)g/dl	3.6	3.2	3.7	4.1	5.5
Albumin %	24.8	28.3	22.5	25.3	38.7
α -1 globulin "	6.7	5.0	5.4	6.1	6.5
α -2 "	44.9	43.4	35.1	38.4	21.5
β - "	10.1		10.8	13.1	10.8
γ - "	13.5	23.3	26.2	17.1	22.5
GOT (15-36)U	64	48	29	26	24
GPT (9-31)U	32	33	18	18	18
Cholesterol (116-228)mg/dl	349	348	236	314	178
Alkaline phosphatase (3.2-10.5)	55.8	6.4	4.3	5.2	5.6
LDH (130-286)	370	130	160	120	
Cholinesterase (0.76-1.30) PH	0.52	0.45		0.81	0.75
Bilirubin, total (0.17-0.98)mg/dl	0.3	0.2	0.3	0.3	0.4
direct (0 -0.2) "	0.2	0.1	0.1	0.2	0.2
TTT (0-4)U	9	4	5	2	3
BUN (8.0-18.5)mg/dl	9.8	7.2	9.8	11.5	11.1
Na (135-144) mEq/l	133	137	133	136	132
K (3.2-4.9) "	4.3	4.5	4.9	5.1	4.6
Cl (95-185) "	106	109	105	103	100
Ca (4.2-4.9) "	3.5	4.0	3.1	3.8	4.0
Amylase (40-135) Caraway unit	58	60	46	51	
WBC /cmm	7,500	7,000	6,300	10,000	8,900
RBC 10^6 /cmm	3.77	4.52	3.64	4.13	4.13
Hb g/dl	10.8	13.5	10.5	12.5	11.2
Hematocrit %	34	40.7	31.0	35.4	34.2
Platelets 10^5 /cmm	2.9	2.16		2.85	
Reticulocytes %		0.3			
ESR 1 hour mm	125	124	108	106	
2 " "	136	140	116	118	
Triglyceride (43-168)mg/dl	1,558	1,542		1,780	446
β -lipoprotein (380-800) "	1,100	862		840	365
Phospholipid (155-270) "	493	381		413	217
FFA (0.2-0.6) mEq/l	0.65	0.19	0.11	0.15	
TIBC (356 $\pm$ 39) μ g/dl	54	81	77		
UIEC (251 $\pm$ 49) "	25	51	42		
SI (105 $\pm$ 25) "	29	30	35		
Prothrombin time (control 12.0)		10.6			
Thrombo test (70-130)%/11.7sec over		100	26.7 seconds		
Fibrinogen (200-400)mg/dl		688			
D-xylose excretion test (4-8)g		6.0			
Glucose tolerance test		normal curve			
T ₂ resin uptake (25-35)%		38.1			
Thyroxin (5-14) μ g/dl		4.6			
RISA half time (14 <) days		1.7			
fractional catabolic rate (5 >)%/day		41			
131-I-triolein absorption					
blood counting (13 <)%		30.8			
stool (2 >)"		1.3			
Schilling test 24hr urine (8.0 <)%		16.6			
Fe absorption (with 4mg of carrier in the form of FeSO ₄ (Japanese female by whole body counting) 33%, when retics = 0.3% 28 $\pm$ 8%)					
Desferal test (1000mg desferrioxamine i.m. injection) 1.2mg Fe/day (1 <)					
Ferrokinetics					
PID T1/2 = 27min (60-120)					
PIT = 0.49mg/kg/day (0.4-0.9)					
%RCU = 91% (85-100)					
RCV = 724ml					
PV = 1550ml					
BV = 2274ml					
Erythroid marrow distribution :					
Larger over the abdomen and chest than pelvic region at 5 and 24 hours					
Radioiron deposition in the liver by transverse linear scan :					
Increased at 5, 24 and 10 days					
Radioiron deposition in the spleen by transverse linear scan :					
Increased slightly at 10 days					
Intestinal blood loss by stool counting : 0.2-1.1ml/day (normal)					
(reabsorption is neglected)					
Mean red cell life span with 59-Fe = 51days					

tein was negative on repeated urinalysis. However, UGI, BaE and X-ray examination of the small intestine by means of duodenal intubation revealed no abnormalities in gastrointestinal tract. Jejunal biopsy and absorption studies did not yield any positive results. Although occult blood in stool

was often positive, blood loss in the gut determined with radioiron was 0.2 to 1.1 ml per day, i.e., within normal range. RBC and hemoglobin level were generally within normal limit. Ferrokinetics were performed and the results are shown in Table 1, and Figure 2.

Fig. 2. Radioiron distribution along the longitudinal body axis (A) and at the height of liver and spleen (B).

From February 1, 1975 on, she suffered from persistent intractable tachycardia, cough and dyspnea. She died on April 30 in severe dyspnea. Curiously enough, serum protein level rose to 5.5 g/dl, albumin level to 2.7 g/dl and serum cholesterol level decreased to 178 mg/dl at terminal stage. Permission to perform autopsy was not obtained.

Cases of Low Serum TIBC Level

Of the 600 patients whose serum TIBC levels were determined during the last one and half years, TIBC was found lower than 200 $\mu\text{g/dl}$ in 35 patients. The underlying diseases are blood diseases such as aplastic anemia, erythroleukemia, chronic myelocytic leukemia, hereditary spherocytosis, hereditary elliptocytosis and paroxysmal nocturnal hemoglobinuria, malignancies such as erythroleukemia, chronic myelocytic leukemia, cancers and Hodgkin's disease, diseases of digestive organs such as liver diseases, and protein losing enteropathy and endocrine diseases such as hyperthyroidism and hyperparathyroidism. The details are listed in Table 2.

Table 2. Thirty five cases having TIBC value lower than 200 $\mu\text{g/dl}$.

Cases	TIBC $\mu\text{g/dl}$	
Aplastic anemia (2)	172, 186	Blood diseases
Pure red cell aplasia (1)	174	
Pancytopenia (1)	135	
Hemosiderosis (3)	143, 196, 193	
Heredit. spherocytosis (2)	169, 181	
" elliptocytosis (1)	187	
Paroxysmal nocturnal hemoglobinuria (1)	192	
Hemolytic anemia unknown etiology (2)	159, 161	
Anemia unidentified (1)	186	
Hodgkin's disease (3)	162, 181, 192	
Chronic myelocytic leukemia (1)	160	Malignancies
Erythroleukemia (3)	157, 163, 184	
Uterine cancer (3)	158, 174, 197	
Lung cancer (1)	145	
Chordoma (1)	153	
Hepatoma (1)	121	Diseases of digestive organs
Liver cirrhosis (1)	181	
Malnutrition + Diabetes mellitus (1)	136	
Protein losing enteropathy (2)	146, 176	
Hypoproteinemia (2)	54, 150	
Hyperthyroidism (1)	160	
Hyperparathyroidism (1)	193	

In contrast, marked increase in TIBC was observed only in iron deficiency anemia. TIBC tended to decrease in hemochromatosis and renal failure, as seen in Table 3.

Table 3. TIBC, UIBC and SI as determined by radioassay method.

Cases	TIBC $\mu\text{g/dl}$	UIBC $\mu\text{g/dl}$	SI (TIBC-UIBC)
Normal male (48)	316 $\pm$ 31	207 $\pm$ 44	109 $\pm$ 30
range	258 - 368	132 - 270	55 - 179
Normal female (17)	356 $\pm$ 39	251 $\pm$ 49	105 $\pm$ 25
range	296 - 442	160 - 360	71 - 162
Polycythemia vera (16)	309 $\pm$ 60	242 $\pm$ 77	67 $\pm$ 38
Hemochromatosis (15)	262 $\pm$ 45	62 $\pm$ 55	199 $\pm$ 37
Aplastic anemia (17)	284 $\pm$ 61	70 $\pm$ 56	214 $\pm$ 55
Renal failure (7)	254 $\pm$ 41	161 $\pm$ 49	93 $\pm$ 39
Iron deficiency anemia (54)	418 $\pm$ 41	389 $\pm$ 41	31 $\pm$ 15

DISCUSSION

A case of hypoproteinemia associated with marked Tf deficiency: The TIBC level of the case was as low as that of congenital atransferrinemia reported so far. In previously reported cases, the relation of "TIBC ($\mu\text{g/dl}$) = Tf (mg/dl) $\times$ 1.3 is not seen; Tf values were 3 to 9 mg/dl and TIBC were 24 to 50 $\mu\text{g/dl}$. Either overestimation of TIBC or inaccuracy of Tf measurement may account for such a marked discrepancy. TIBC value by radio-

assay and Tf value by immunoassay correlated well^{9,12}. Variation of Tf values measured by using Behringwerke's Partigen Transferrin Immunodiffusion Platten can be significant¹², for very small amount of serum is used for immunoassay. The low Tf value as measured by immunoassay might be caused by the alteration of Tf itself. It should be noted that TIBC radioassay is accurate, highly reproducible and free of possible iron contamination as experienced in colorimetry. Radioassay is an excellent and indispensable method for measuring TIBC and Tf as confirmed by others¹³⁻¹⁶.

Rapid disappearance of intravenously administered RISA in this case cannot simply be attributed to increased protein loss in the gut. Two factors should be taken into account, i.e., increased degradation and loss of protein. Measurement of plasma disappearance rate of ¹³¹I-Tf, detection of lymph in intestinal tract and measurement of ¹³¹I-PVP in stool were scheduled but not performed. Diagnosis of plasma protein loss in the gut is made by counting ¹³¹I-PVP in stool, however, actual amount of loss of protein cannot be estimated. ⁵¹Cr-albumin is not superior to ¹³¹I-PVP, because the release of ⁵¹Cr and resultant short life are prominent. The test for PLE by using ⁶⁷Cu-ceruloplasmin is considered to be most reliable, but it was not available for us. In this case, extremely low plasma protein level was observed in association with a very rapid plasma RISA disappearance rate of 41% per day, the highest ever experienced here. However, Yoshino et al.¹⁷ reported a plasma RISA disappearance rate of 60% per day in PLE.

The results of absorption studies on vitamin B₁₂, ⁵⁹Fe and ¹³¹I-triolein were all normal or above normal in this patient. Her nutritional state had been well maintained until persistent dyspnea developed. Hypoproteinemia due to a failure to synthesize protein, as seen in malabsorption syndrome or liver cirrhosis, can be ruled out from rapid RISA disappearance rate and laboratory data. Although profound hypo-

proteinemia, hypoalbuminemia, hyperlipemia and kidney biopsy finding were compatible with nephrotic syndrome, absence of urinary protein will exclude the possibility of kidney disease as a cause of plasma protein depletion. Thus intestinal protein loss is the most likely mechanism of hypoproteinemia in this case, but its etiology remains unknown.

Although short red cell survival was noticed in this case, it is not necessarily assumed that deficient Tf is somewhat related to hemolysis, for anemia due to iron deficiency or other cause is usually accompanied by a certain degree of hemolysis. Brief febrile episodes occasionally took place during the course. Inflammation may be a cause of hemolysis and sometimes it may cause a decrease of Tf¹⁸. However, it seems unlikely that such a significant decrease of Tf level in this patient is caused by inflammation. Mean red cell life span (RCLS) of the case measured with ⁵⁹Fe was as short as that in the case reported by Sakata et al³. Although radioiron loss in stool was normal, occult blood in stool was often positive in this case. Furthermore, RCLS obtained by using ⁵⁹Fe tends to be shorter than that determined by ³²P-DFP¹⁹. In view of these facts, actual RCLS in this case may be a little longer.

A striking contrast to simple iron deficiency anemia was that the saturation rate (%Sat) was above the normal range in this case. In general, there is a positive relationship between plasma iron disappearance rate ($PID\ T\frac{1}{2}$) and level of SI. On the other hand, $PID\ T\frac{1}{2}$ was short and SI was also low in this patient as in the case of iron deficiency anemia. In most cases of hemolytic anemia, $PID\ T\frac{1}{2}$ is shortened while SI and %Sat are increased.

Generally speaking, increased body iron stores is one of the factors decreasing %RCU. All cases of previously reported congenital atransferrinemia¹⁻⁵ had been transfused with blood, but our case received no blood transfusion. For this reason, perhaps,

decrease in %RCU was not observed in this case despite the decrease of Tf. In cases of congenital atransferrinemia, it is not clear whether the same quantity of iron was deposited as that supplied by transfused blood, or larger quantity of iron than that given by blood transfusion was deposited owing to the development of hemochromatosis. In this case, ^{59}Fe appeared as a peak of early incorporation in the erythroid marrow within 6 minutes after injection and its distribution pattern 6 to 24 hours thereafter was similar to that of iron deficiency anemia except for the occurrence of a peak over the abdomen as shown in Figure 2A. Radioiron distribution pattern differs from iron deficiency anemia in that some of radioiron deposition was actually observed as shown in Figure 2B. If the patient had received a large amount of blood, the amount of radioiron deposition would have been much larger. Radioiron was deposited in the liver in this case unlike the radioiron turnover as observed in patient with hemochromatosis, or in patient with extramedullary hematopoiesis. In view of radioiron deposition in the liver and hemolysis as indicated by short RCLS, it is not likely that %RCU of the patient is 91%. Perhaps %RCU might have been overestimated. Of the previously reported cases of atransferrinemia, those in whom iron metabolism was thoroughly studied are listed in Table 4. As seen in the Table, iron absorption is enhanced in all cases. The reason why iron absorption is markedly enhanced in spite of increased iron storage and low UIBC is not known. As far as

atransferrinemia is concerned, UIBC does not seem to play an important role in iron absorption. As mentioned above, many similarities and some differences were observed between this and previously reported cases of atransferrinemia¹⁻⁸⁾, and iron deficiency anemia. On the basis of hematological findings, especially of ferrokinetic study mentioned above, this case can be called atransferrinemia.

Cases having TIBC level below 200 $\mu\text{g}/\text{dl}$: It is well known that in normal subjects UIBC level is around 200 $\mu\text{g}/\text{dl}$. Therefore, subjects having TIBC level lower than 200 $\mu\text{g}/\text{dl}$ are unusual. We set up a tentative standard and found 35 cases whose TIBC was lower than 200 $\mu\text{g}/\text{dl}$. Twenty-one of the 35 cases had blood diseases, 11 of which were of non neoplastic nature. Thirteen cases of the 35 had malignant diseases. Seven cases of the 35 had diseases of digestive organs, including 2 cases of PLE. None of patients with kidney diseases had decreased TIBC level. Majority of patients with hypotransferrinemia had blood diseases in our series. Kozuru^{9,20)} reported that the decrease of TIBC was frequently found in tumors, nephrosis and PLE. Considering the factors influencing Tf level, hypotransferrinemia may frequently be found in diseases of blood, digestive organs and kidneys and in malignant tumors.

If TIBC radioassay is adopted as routine laboratory procedure, atransferrinemia will be more frequently detected.

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Table 4. Iron metabolism in congenital and acquired atransferrinemia.

Reported by	Heilmeyer 1965	Heilmeyer 1961	Sakata 1969	Gouya 1970	Walbaum 1971	Saito present case
Diagnosis	Pyo-nephrosis	Cong. atransferrinemia	"	"	"	PLE?
Transferrin mg/dl	18.5	4.4	9	3	-	37-71
TIBC $\mu\text{g}/\text{dl}$	24	33	50	46	33	54-91
SI "	21	9	14-118	12	14	25-35
PIF mg/kg/day	-	1.63	0.73	-	-	0.49
PID T _{1/2} min.	21	5	42	25	5	27
RCU % 52 at 7 days	10	53	55	12	91	
Fe absorption %	87	30	-	39	30	33

Due to insufficiency of data, the cases of Cap²⁾, Hitzig²¹⁾, Oliva⁸⁾ and Riegel⁶⁾ are not listed in this table.

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