The Turkish Journal of Pediatrics
Volume 20 / Nos. 1-2 / Jan.-April 1978 / pp. 44 – 50

Familial Selective Vitamin B_{12} Malabsorption in Three Families

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In 1960, Imerslund and Gräsbeck et al.[1,2] independently described the familial occurrence of megaloblastic anemia in children due to an isolated defect of vitamin B_{12} absorption; proteinuria was also found in the affected children. Since then many cases of selective vitamin B_{12} malabsorption with proteinuria have been reported from different countries by several workers.[3,4] This is the first report, however, of this syndrome, diagnosed at Hacettepe Children's Hospital in five Turkish children from three different families, in Turkey.

Case Reports

Case 1: Y.A., a five year old boy, was brought to the Hacettepe Children's Hospital in December, 1972, with a complaint of edema on the eyelids and feet which had started a week prior to examination. On physical examination, the patient was found to be pale his height and weight were below the third percentile for his age. There was edema on the eyelids and feet. A systolic murmur of grade II/VI was heard over the precordium. The liver was palpable 4 cm below the costal margin.

Laboratory Data: His hemoglobin level was 3.4 g/dl. the hematocrit 11 %, and the reticulocyte count 0.2 %. The peripheral smear showed macrocytosis with platelets present in a good number. The bone marrow revealed megaloblastic changes in the normoblasts as well as in the myeloid cells. The values for serum folic acid (SFA)[5], serum iron (SI),[6] and serum total iron binding capacity[7] (STIBC) are shown in

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Table I. The Schilling test showed the presence of vitamin B_{12} malabsorption which was not corrected by the addition of Intrinsic Factor (IF) (double bind technique) (Table II). The other intestinal absorption tests gave normal results. SGOT, SGPT, alkaline phosphatase (Alk. phos.), CCF, blood urea nitrogen (BUN) and albumin were normal. Urine analysis revealed 2+ proteinuria. The anemia responded to parenteral vitamin B_{12} therapy, however, the proteinuria persisted.

Family Studies: The physical and laboratory examinations of the parents and three siblings showed no abnormalities. However, megaloblastic anemia and proteinuria were discovered in his one year old sister whose clinical summary is given below.

Case 2: H.A., the 12 month old sister of Case 1, was brought to the hospital in May, 1973, because of fever and dyspnea which had begun two days previously. Physical examination showed her to be pale. Scattered crepitant rales were heard over the chest fields. The liver was palpable 4 cm and the spleen 2 cm. below their respective the costal margins

Laboratory Data : Her Hb was 7.4 g/dl, with a Hct of 22 %, WBC count 10,000/mm^3, and a reticulocyte count 0.1 %. The peripheral smear showed macrocytosis, and megaloblastic changes were observed in the bone marrow smear. SFA, SI and STIBC levels are shown in Table I. Radiologic examination of the chest revealed bronchopneumonic infiltration and changes in the costae, suggesting the presence of rickets. Proteinuria was present. The patient's abnormal hematological values responded to parenteral vitamin B_{12} therapy, but the patient died of supervening sepsis two weeks after admission to the hospital.

Case 3: Z.G., a five year old girl, was admitted to the Hacettepe Children's Hospital in November, 1973, because of pallor and easy fatigability for more than two years, and edema on the feet and eyelids which was first noted two weeks prior to admission. Physical examination revealed a pale girl whose height and weight were below the third percentile (101 cm and 12.5 kg, respectively). The eyelids and feet were edematous. A systolic murmur of grade II/IV was heard over the precordial area. The liver was palpable 2 cm below the costal margin.

Laboratory Data: At admission, the Hb was 4.39 g/dl the Hct 12 %, WBC of 11,600/mm^3 and reticulocyte count 0.4 %. Examination of the peripheral smear revealed macrocytosis with platelet clumps present. A megaloblastic erythroid hyperplasia was noted in the bone marrow smear. The values for SFA, SI, and STIBC are shown in Table I. The gastric juice pH was 1. The Schilling test showed severe vitamin B_{12} malabsorption which was not improved by the ad-

TABLE I

HEMATOLOGICAL VALUES OF THE PATIENTS

Case No.	Age/years	Sex	Hb g/dl	Hct %	Ret %	Bone marrow	SFA ng/dl	SI ug/dl	STIBC ug/dl
I. YA	5	M	3.46	12	0.2	MC	8.6	70	297
7 days a.t.*			5.0	15	2.6				
3 years a.t.			14.2	42	0.2				
II. HA (sister of case I)	1	F	7.4	22	0.1	MC	18	118	200
10 days a.t.			8.7	25	4.0				
III. ZG	5	F	4.39	12	0.4	MC	10	200	387
10 days a.t.			6.62	22	5.8				
4 years a.t.	9		12.77	38	0.4				
IV. MD	4	F	10	30	0.4	MC	8.4	171	212
7 days a.t.			11.1	32	5.4				
3 years a.t.	7		13	38	0.2				
V. KD (brother of case IV)	2	M	9.1	21	0.2	MC	—	—	—

*a.t. = after therapy
MC = Megaloblastic changes

dition of IF (double bind technique) (Table II). Absorption studies of the gastrointestinal system indicated no other abnormalities. SGOT, SGPT, Alk. Phos., and bilirubin tests were all normal. Albumin, calcium, phosphorus, BUN, and creatinine were all within normal limits. The urine examination showed 2+ proteinuria and leukocyte clumps. E. coli grew out in three consecutive urine cultures, after which he was treated for three weeks with the appropriate antibiotics. After the infection cleared, an intravenous pyelogram (IVP) was performed but no abnormality was found. A closed needle biopsy of the left kidney demonstrated protein-like material detected by hematoxiline-eosine staining in the tubuli.

The megaloblastic anemia responded to vitamin B_{12} therapy and the patient has been receiving 1000 µg of B_{12} yearly to maintain her hematologic status at normal levels.

Family Studies: The parents were cousins; they had no living children except for the patient. A total of 10 children had died of undetermined illnesses between the ages of 6 months and 4 years without any medical attention. Physical examination of the parents revealed no abnormalities. The hematological examination of the mother indicated the presence of iron deficiency anemia. (The Hb was 8 g/dl, SI 32 µg/dl, and STIBC 304 µg/dl). This anemia responded to oral iron therapy. Proteinuria was present in both parents. The Schilling tests were normal. The results of HLA typing of the patient and her mother are shown in Table II.

TABLE II

SPECIFIC LABORATORY DATA

Case No.	Schilling Test (% of total excreted in 24 hrs). B_{12} alone	B_{12} + IF	Urine Examination Proteinuria	HLA Groups
I. YA	0.8	0.6	++	A_3A_9
Mother	—	—	negative	$A_3A_9CW_4$
Father	—	—	negative	—
5 years a.t.*	—	—	+	
II. HA (sister of case I)	—	—	++	—
III. ZG	0.5	0.2	++	$A_2A_{10}BW_{35}$
Mother	24	34	+	—
Father	13.5	22.5	+	$A_9B_5A_{10}BW_{35}$
5 years a.t.				
IV. MD	2.4	0.9	+	$A_9B_{18}BW_{35}$
Father	—	—	+	$A_9B_{18}BW_{35}$
V. KD (brother of case IV)	—	—	+	$A_9B_{18}BW_{35}$

* a.t. = after therapy

Case 4 and Case 5: M.D., a four year old girl, was referred to the Hacettepe Children's Hospital in March, 1975, for the evaluation of the anemia which had started a year previously; she had been given a blood transfusion a week prior to her referral to hospital. Her physical examination revealed an undernourished child whose height and weight were below the tenth percentile. Bilateral microphthalmia and enophthalmia were observed. The fundoscopic examination of the eyes revealed changes compatible with a diagnosis of tapeto-retinal dystrophy.

Laboratory Findings: Her Hb was 10 g/dl, Hct 30 %, WBC count 6600/mm^3, and reticulocyte count 0.4 %. Macrocytosis was seen in the peripheral smear and megaloblastic changes in the erythroid cells were noted in the bone marrow smear. Her hematological data is summarized in Table I. The Schilling test was performed by the double bind technique and showed witamin B_{12} malabsorption which was not correctable by the addition of IF (Table II). Other absorption tests of the gastrointestinal system were normal. Proteinuria (1+) was present; an IVP was performed and disclosed no abnormalities.

The patient's hematological status was maintained within normal limits by yearly parenteral administration of 1000 µg of vitamin B_{12} during a 3-year follow-up period, however, proteinuria persisted in the follow-up period.

Family Studies: The parents were cousins. Physical and laboratory examination of the parents and a five year old sister showed no abnormal findings except for proteinuria in the father. The parents had a son, K.D., (Case 5), in 1976, and his hematological status was evaluated every two months after nine months of age. At nine months, proteinuria was present. Slight but continuous decreases in the hemoglobin and hematocrit levels and slight but continuous macrocytosis have persisted since one year of age. His most recent hematological values are shown in Table I. The result of HLA typing of the patient and her parents are shown in Table II.

Discussion

The presence of isolated vitamin B_{12} malabsorption together with proteinuria in our patients is sufficient enough to make the diagnosis of Imerslund-Gräsbeck syndrome. Three of the five patients were brought to the hospital between 4 and 5 years of age, but, in two of them, hemoglobin levels were very low, and, in another, a blood transfusion had been given due to the anemia discovered in another institution. This suggests that the megaloblastic anemia probably had begun long before the pa-

tients were brought for medical attention. The presence of megaloblastic anemia in the 12 month old sister of Case I suggests that the anemia could start at an early age. However, the presence of a severe infection in this case might have accelerated the need for vitamin B_{12}. In the fifth case, a decrease in the hemoglobin level was first noticed around the age of one year.

The presence of intermarriage in two of the three families and the presence of affected sibling or siblings who had died at an early age in all three families supports the presence of an autosomal recessive mode of inheritance.[3]

The presence of proteinuria in some of the parents indicated that proteinuria could be detected in the heterozygote state in some cases. No pathologic changes were seen in the IVP studies of three of the patients, and the detection of protein in the tubuli was the only pathology in light microscopic examination of the kidney biopsy of one patient. This observations supports the idea that proteinuria, in most cases, is not accompanied by a kidney disease demonstrable by IVP or biopsy.[8, 9]

Pathological abnormality which is responsible for vitamin B_{12} malabsorption in this syndrome has not been well established. Normalization of the Schilling test in one patient by oral administration of vitamin B_{12} together with succus entericus taken from jejunum of another subject was reported.[4] However, such an observation has not been made by others.[4]

HLA typing in our patients showed the occurrence of BW_{35} in three, two of whom were siblings, and A_9 in two.

The distinctive eye findings of tapeto-retinal dystrophy in Case IV have not been seen in any of our cases or in any of the other 90 or so reported cases of this syndrome, so we feel that these findings are coincidental to her having Imerslund-Grabseck syndrome.

Summary

A total of five cases from three different families with selective vitamin B_{12} malabsorption and proteinuria are presented. Two cases were brought to the hospital because of anemia and heart failure and one for evaluation of the anemia. Two additional cases were detected during family studies among the siblings of two different cases. All three index cases had abnormal Schilling test , none of which were corrected by IF. The anemias responded to parenteral vitamin B_{12} therapy. In the affected siblings, megaloblastic anemia was present; a Schilling test was

not performed. All five cases and three of the parents had proteinuria without any obvious kidney abnormality. One of the cases also had tapeto-retinal dystrophy.

Acknowledgement

We would like to thank Dr. Izzet Berkel, Hacettepe Children's Hospital Department of Immunology, for his help with the HLA typings.

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