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IMERSLUND-GRÄSBECK SYNDROME AND GENERALIZED MALABSORPTION*

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Although megaloblastic anemia due to Vit-B_{12} deficiency is not common in childhood, every form of megaloblastic anemia caused by Vit-B_{12} deficiency has been described. The Imerslund-Gräsbeck syndrome is the familial occurrence of megaloblastic anemia in children caused by an isolated defect of Vit-B_{12} absorption together with benign proteinuria[1,2]. In this syndrome, anemia generally becomes prominent during the first two years of life. Among the published cases, generalized malabsorption and growth retardation together with the Imerslund-Gräsbeck syndrome have been described in only one case[3]. It is on account of the rarity of the clinical occurrence of the Imerslund-Gräsbeck syndrome with generalized malabsorption that we wished to present this case.

Case Report

A three-year-old girl was admitted to the Hacettepe Children's Hospital with the complaints of increasing pallor and growth retardation since six months of age. Frequent bronchitis, watery stools and mouth ulcers were also noted. The parents were first cousins, and they had previously had two children who died at 1 and 1.5 years of age having had clinical findings similar to those of the patient.

Physical examination revealed a pale girl whose height (81 cm) and weight (9.2 kg) were below the third percentile. With the exception of the palpable liver (3 cm below the costal margin) and a systolic murmur in the precordium, other physical findings were within normal limits as were the results of a neurological examination.

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A laboratory examination of the patient showed pancytopenia (Table I). An increasing mean corpuscular volume of erythrocytes (110 μ^3), mild reticulocytosis (4%) and megaloblastic changes were detected by bone marrow needle aspiration. Gastrointestinal system studies showed generalized malabsorption (Table II); however, no parasite was found on stool examination. Proteinuria (1 +) was detected by urine analysis, but urine culture, intravenous pyelogram, creatinine clearance and urinary amino acid excretion by chromotography did not disclose any abnormality. Further, the sweat chloride of the patient (29 mEq/L), the results of the immune electrophoresis, delayed hypersensitivity skin tests, E rosette formation and blastic transformation of lymphocytes were all within normal limits. The serum folic acid level[4] was found to be 8.5 μg/L (normal 7-25 μg/L), and the serum iron[5] and iron binding capacities[6] were 290 μg/dl and 320 μg/dl, respectively. There was no hematological response following parenteral folic acid treatment. The serum Vit-B_{12}* level was found to be 30 ng/L (normal 200-1000 ng/L), and the Schilling test showed the condition of Vit-B_{12} malabsorption which was not corrected by the addition of an intrinsic factor (by double bound technique urinary excretion was 2.5% and 3%, respectively). Following 1000 μg intramuscular Vit-B_{12} treatment, the reticulocyte count rose to 17% within four days, and the hemoglobin level reached 6.5 g/dl in 15 days. After 1000 μg Vit-B_{12} had been given parenterally every three months for two years, the patient was evaluated again. In the physical and laboratory examination hematologic findings were normal as was growth, and there was no longer malabsorption; proteinuria persisted and the Schilling test still showed abnormalities. Hematologic findings and urinalysis of the parents were found to be within normal limits. The two living siblings (3.5 and 7 years old) could not be examined, but no history relating to the syndrome was obtained.

Discussion

When, at 3 years of age, the patient was admitted to the hospital with the complaints of increasing pallor and growth retardation since 6 months of age, megaloblastic anemia was diagnosed by means of bone marrow needle aspiration. As the level of serum folic acid was normal in the patient and as there was no improvement in the hematologic findings following folic acid treatment whereas there was following Vit-B_{12} treatment, it has been accepted that the cause of the megaloblastic anemia in our patient was Vit-B_{12} deficiency. The Schilling test showed the presence of Vit-B_{12} malabsorption, which was not corrected by the addition of the intrinsic factor. The existence of Vit-B_{12} malabsorption together with benign proteinuria confirms the diagnosis of the Imerslund-Gräsbeck syndrome. The facts of this case support the autosomal recessive inheritance theory associated with this syndrome:

* Vitamin B_{12} radioassay kit (Amersham, Buckinghamshire, England)

inter-marriage in the family and siblings with similar clinical findings who had died at an early age. The correction of the malabsorption and growth retardation after the patient was given parenteral Vit-B_{12} treatment point to the fact that the findings were the result of Vit-B_{12} deficiency.

TABLE I

Hematologic Findings of the Patient

	At time of diagnosis	Following 2 years Vit-B_{12} therapy
Hemoglobin (g/dl)	2.8	12
White blood cell count/mm^3	3331	6200
Platelet count/mm^3	92,000	280,000
Bone marrow aspiration	Megaloblastic changes	Normal

TABLE II

Development Status and Gastrointestinal Findings of the Patient

	At time of diagnosis	Following 2 years Vit-B_{12} therapy
Patient weight	9.2 kg	18.8 kg
Patient height	81 cm	102cm
Gastric acidity	pH: 6	
Glucose tolerance test	Flat curve	Normal
Xylose excretion (20%)*	4.2%	30%
Serum Vit-A (30-65 μg/dl)*	23 μg/dl	46.5 μg/dl
Serum carotene (0.91-2.3 μg/ml)*	0.16 μg/ml	1.8 μg/ml
Serum Vit-E (0.2-1 mg/dl)*	0.2 mg/dl	0.7 mg/dl
Serum total protein (6-8 g/dl)*	5.6 g/dl	7.8 g/dl
Serum calcium (9-11.5 mg/dl)*	7.5 mg/dl	10.4 mg/dl
Small bowel x-ray	No abnormality	

* Normal values of our laboratories.

In our patient and her two siblings who had died, frequent bouts of diarrhea and bronchitis were prominent complaints. Although the secretory immunoglobulin A level could not be determined, sweat chloride, quantitative immunoglobulin levels, and cellular immunity were found to be normal.

Malabsorption and growth retardation may be postulated by the malabsorption due to intestinal mucosal changes in Vit-B_{12} deficiency[7,8]. However, the relation of mucosal changes to clinical findings has not been fully explained. Although many patients present mucosal alterations, the clinical reflection of these changes has been witnessed in only a few patients.

The fact that these findings are encountered only in a few cases of Vit-B_{12} deficiency suggests that, in these rare cases, the underlying defect is reinforced by Vit-B_{12} deficiency.

Summary

A three-year-old patient with familial vitamin B_{12} malabsorption, or Imerslund-Gräsbeck syndrome, and growth retardation, was examined. Gastrointestinal studies showed that the patient had generalized malabsorption in addition to that of vitamin B_{12}. The hematological findings, malabsorption and growth retardation of the patient returned to normal after vitamin B_{12} treatment. It is thought that the findings are the results of vitamin B_{12} deficiency. The combination of the Imerslund-Gräsbeck syndrome and generalized malabsorption suggest that an underlying defect is reinforced by vitamin B_{12} deficiency in these rare cases.

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