CASE REPORT

Imerslund-Grasbeck Syndrome: Association with Diabetes Mellitus

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A 14 year male adolescent born of 2nd degree consanguineous marriage presented with asymptomatic proteinuria and severe anemia. He had leucopenia, anisopoikilocytosis, megaloblastic erythropoiesis, megakaryocytes with low serum B_{12} level. His younger sibling was similarly affected. This combination suggested Imerslund-Grasbeck syndrome. The hemoglobin levels improved with injection of vitamin B_{12} but proteinuria persisted. During follow-up, he developed ketoacidosis due to insulin dependent diabetes mellitus. This rare combination has not been reported in the Indian literature.

Key words: *Imerslund-Grasbeck syndrome, Diabetes mellitus, Vitamin B_{12}.*

Imerslund-Grasbeck syndrome (IGS) is a rare autosomal recessive disease characterized by vitamin B_{12} (cobalamine) deficiency due to selective malabsoprtion of this vitamin resulting in megaloblastic anemia appearing in later childhood. The anemia responds well to parenteral vitamin B_{12} therapy. This syndrome is frequently accompanied by proteinuria and sometimes neurological symptoms(1). Associated genitourinary tract abnormalities(2), dolichocephaly(3), beta-thalassemia trait(4) and diabetes mellitus(5) have been reported. We present a case of IGS with diabetes mellitus.

CASE REPORT

A 11-year old boy, first born to second degree consanguineous parents was referred for persistent asymptomatic proteinuria since one year. There was no hematuria, oliguria, skin rash, joint pain or swelling. At the age of 2 years, during a diarrheal illness, he had periorbital puffiness, severe anemia, hyper-pigmen-tation of the hands and 2+ proteinuria. With vitamin B_{12} injection and oral medications, he had improved.

On examination, his growth and development were normal and his weight was 36 kg. He did not have anemia or pedal edema. He had hyperpigmentation of the skin over the dorsum of the fingers and toes. Blood pressure was normal. Cardiovascular and respiratory system were clinically normal and he had no ascites or organomegaly. Investigations showed protienuria of 2+ by dipstick. Blood counts and peripheral smear was normal, hemoglobin was 11.5 g/dL. Renal function tests were normal. Serum proteins and cholesterol was normal. 24-hours urine protein excretion was 294 mg/day. Ultrasonogram of the abdomen was normal. Serum ANA was negative. Renal biopsy was reported as minimal lesion nephropathy by light microscopy and immunofluorescence showed no immune deposits. Enalapril and losartan potassium were given for renoprotective and antiproteinuric effects.

He remained asymptomatic for 3 years but had persistent non-nephrotic proteinuria with normal hematological values. His weight increased to 44 kg. At 14 years, he was hospitalized for fever with vomiting. On this occasion, he had severe anemia,

facial puffiness and loss of weight to 37 kg (25th percentile). His height was 158 cm (50th percentile)(6). There was no neurological deficit, optic atrophy, or hearing defect. Blood pressure was normal. Investigations revealed severe anemia with leucopenia and thrombocytopenia; hemoglobin was 4.9 g/dL. There were macrocytes, hypersegmented neutrophils and anisopoikilocytosis in the peripheral smear. Bone marrow revealed megaloblastic erythropoiesis with occasional megakaryocytes. Serum LDH levels were elevated. In view of megaloblastic anemia, persistent proteinuria and absence of chronic diarrhea, parasitic infestations or obvious nutritional deficiency, the possibility of IGS was considered and serum vitamin B_{12} levels were estimated. This was low (vitamin B_{12} 97 [211-911 pg/mL]). Injection of vitamin B_{12} was given with advice for follow-up B_{12} injections. At follow-up, his general condition was good with an increase in weight to 39 kg. Hemoglobin increased to 11.9g/dL. Three months later, he was admitted for severe diabetic ketoacidosis (fasting urine sugar4+, fasting plasma glucose 421 mg/dL, post prandial plasma glucose 590 mg/dL). With human insulin and four monthly injections of Vitamin B_{12} he remained asymptomatic with a weight gain to 42 kg.

His ten years old younger sibling, who was asymptomatic but for hyperpigmentation of the dorsum of the fingers, was administered 2 monthly injection of B_{12} by his pediatrician in view of the elder sibling's diagnosis. The hemogram done subsequently was normal with non-nephrotic proteinuria. His vitamin B_{12} level was normal (444 [211-911 pg/mL]) and glucose tolerance test was normal. We plan to stop vitamin B_{12} injections for him and recheck his serum B_{12} values after 6 months.

DISCUSSION

In the absence of history of exposure to nitrous oxide, vegetarian diet, parasitic infestation or chronic gastroenterstinal malabsorption syndromes, the cause of macrocytic and megaloblastic anemia is likely to be due to an inherited disorder of folate or vitamin B_{12}. In clinical practice, diagnosis can be nearly reached by observing the response to treatment with oral dose of folate or injection vitamin B_{12}. The response in this child favours the diagnosis of a B_{12} deficiency state. The presence of proteinuria favors the diagnosis of IGS, which is present in about 70% of the patients(7).

Imerslund-Grasbeck syndrome was first described in Finland and Norway where the prevalence is about 1:200,000. The clinical features include megaloblastic anemia, failure to thrive, recurrent infections, neurological manifestations and asympto-matic proteinuria which is neither glomerular nor tubular with no signs of kidney disease(8). These symptoms may manifest at any time between 1 to 15 years of age with the mean age being 3.5 years.

The selective malabsorption of vitamin B_{12} and proteinuria involves a mutation in one of two genes, cubulin (CUBN) on chromosome 10 or amnionless (AMN) on chromosome 14. Both proteins are components of the ileal enterocyte receptor for the vitamin B12 intrinsic factor complex and the receptor mediating the tubular reabsorption of protein from urine(9). Life long treatment with injection B_{12} leads to complete recovery. Proteinuria persists with normal renal function. Schroder, *et al*.(5), reported two siblings with IGS and in one of them type 1 diabetes mellitus (DM) preceded the diagnosis of IGS by 7 years(5). Our child developed DM with ketoacidosis later on. This presentation is because of the rare association and unexplainable common etiological factor.

Contributors: MS was looking after the child and MVK, SR and BRN supervised the work. MS and MVK prepared the manuscript. BRN reviewed it. BRN will act as the guarantor of the manuscript.

Funding: None.

Competing interests: None stated.

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