An unusual case of massive hepatosplenomegaly

Sir,

Gaucher disease (GD), a rare genetic disorder but commonest amongst the lysosomal storage disorders, has even few reporting in resource limited countries like India, the largest series being a study of 07 cases from the Malabar coastal region of Kerala amongst Mappila Muslims.\(^1\)

A 25-year-old Hindu lady, (product of a non-consanguineous marriage and no previous medical/family history), presented with easy fatigability, early satiety, gum bleeds with minor trauma and secondary amenorrhea of one year duration. Examination revealed pallor and massive hepatosplenomegaly (liver span 20 cm and palpable spleen size of 19 cm) \[Figure 1\]. She had pancytopenia with low corrected reticulocyte count, microcytic hypochromic picture with features of hemolysis on peripheral blood smear. Serum bilirubin, serum LDH, serum transaminases and alkaline phosphatase were raised. Lipid profile revealed low levels of total cholesterol, Low density lipoproteins (LDL) and High density lipoproteins (HDL) with hypertrygliceridemia. Workup for malaria, kala-azar and thalessemia were negative. Bone marrow studies revealed Gaucher cells \[Figure 2\]. Skeletal survey revealed generalized osteopenia skull and typical Ehrlenmeyer flask deformity \[Figure 3\].

Deficiency of glucosylceramidebeta glucosidase (in peripheral leucocytes) was detected (value \(<0.37\text{nmol/hr/mg}\) versus normal values \(>4\text{nmol/hr/mg}\)).

On basis of age, mode of presentation and evidence on bone marrow with enzyme deficiency, a diagnosis of GD Type I was made. Patient was managed splenectomy and enzyme replacement (part of clinical trial).

GD (autosomal recessive disorder) results from mutation of the Gaucher gene on chromosome 1q21 that codes for the lysosomal enzyme glucosylceramidebeta glucosidase, which catalyses the metabolism of the glucocerebroside (glucosylceramide) resulting in the accumulation of glucosylceramide in the cells of macrophage-monocyte system leading to enlargement of different visceral organs.\(^2\)

GD has 03 phenotypic variants depending on the age of onset, age of death, hepatosplenomegaly, neurological deficit, ethnicity, other organ involvement and mutation analysis. Accordingly it is classified as type I, II and III.

Type I (adult onset, non-neuronopathic type) has variability in signs, symptoms, severity, and progression even among siblings with the same genotype. The anemia is both hypoproliferative as well as due to increased peripheral destruction. Congestive and infiltrative hepatomegaly results in raised transaminases. Hypocholesterolemia in GD is due to an abnormal clearance of cholesterol by LDL macrophages.\(^3\) In addition to the skeletal features seen in our patient, other manifestations are bone pains,
pathologic fractures, and avascular necrosis of the long bones.

Type II and III are associated with onset at infancy and early childhood, neurological involvement and with higher mortality and shorter life expectancy.

The detection of insufficient enzyme activity in peripheral leucocytes (gold standard)/cultured skin fibroblasts or other nucleated cells is required for the diagnosis of GD. Where not available, demonstration of Gaucher cells in bone marrow is sufficient for the diagnosis.

ERT (started in early 1990s) and substrate reduction therapy (SRT) form the backbone of management. The drugs available are placenta derived beta glucocerebrosidase (Alglucerase), recombinant Imiglucerase and now Velaglucerase alfa (gene-activated human fibroblast cell line).[4]

Indications for ERT and targets for follow up have been developed by consensus of international experts.[5]

Advances in the management of orphan disorders like GD continue to be hindered by high cost and rarity of the disease. This case is unusual because of lack of consanguinity or family history. Differential diagnosis of storage disorders should always be considered while dealing with patients with massive hepatosplenomegaly.

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A difficult to treat case of Cushing’s syndrome

Sir,

An 18-year-old girl presented in 1998 with clinical, biochemical, hormonal and radiological evaluation consistent with Cushing’s disease. She underwent trans-sphenoidal resection for pituitary microadenoma. Serum cortisol level on third post-operative day remained elevated. She was re-evaluated in June 2001 and underwent bilateral adrenalectomy in May 2002. She had marked improvement in her symptoms and was on steroid replacement. In March 2003 her symptoms re-appeared and glycemic control deteriorated. She has already stopped steroid replacement. Her basal cortisol done twice was elevated (32 and 38 µg/dl) with raised ACTH levels (98.7 pg/ml). MRI of pituitary showed a focal hypodense lesion and CT adrenal showed hyperplasia of right adrenal remnant [Figure 1]. She underwent host of imaging studies to find missed ectopic ACTH secreting tumor, but were negative. She was advised second trans-sphenoidal surgery for which she refused. She was started on tab ketoconazole, which she took intermittently. Her cortisol levels done every year, remained elevated. Gamma knife instrument was installed in this hospital in 2007. In 2010, we persuaded her to undergo gamma-knife surgery, which she refused. However, on repeated persuasion she agreed, and underwent it in September 2011. After surgery her symptoms gradually improved. In July 2012, she reported with persistent anorexia, vomiting, extreme asthenia with weight loss of about 20 kg. Examination revealed hypotension and investigations showed hyponatremia Na-129 meq/l, hyperkalemia K-6.0 meq/l and hypoglycemia. Her insulin requirement had come down by 50% with no need for anti-hypertensive, and her cortisol was 2.6 µg/dl. Finally she had developed adrenal insufficiency with possible permanent cure of Cushing’s disease.

This case highlights agony of patient and treating physician. She had first failed pituitary surgery indicated by persistent hypercortisolemia. She had recurrence even after bilateral adrenal surgery. Recurrence after adrenalectomy may be due either to regrowth of adrenal cells in the surgical bed or growth of adrenal rest tissue. Unsuccessful adrenalectomy is usually the consequence of failure to excise hyperplastic adrenal tissue extending around the right adrenal vein. At this stage, a missed or occult ectopic-ACTH secreting tumor was suspected. Common causes of such slow growing tumor are thoracic carcinoid (36-49%), small cell carcinoma of lung (18-37%) and others (15-44%) like pancreatic carcinoid, pheochromocytoma and medullary thyroid carcinoma. Her imaging studies for ectopic-ACTH secreting tumor were negative. Facilities for inferior petrosal sinus sampling were not available at this hospital at that time. Options at this stage were second TSS, remnant adrenalectomy, radiotherapy or medical therapy. Success rate of second TSS varies between 30 to 70% and predictors of success are correct diagnosis, initial incomplete TSS and residual tumor on CT/MRI. However, in absence of biochemical evidence such focal defects in the pituitary gland on CT/MRI...