Central Precocious Puberty Complicating Congenital Adrenal Hyperplasia: North Indian Experience

Sir,

Increased androgen production often leads to peripheral precocious puberty (PPP) in congenital adrenal hyperplasia (CAH). The chronic hyperandrogenemia may activate hypothalamic-pituitary axis and cause central precocious puberty (CPP) with advancement of bone age (BA) that compromises stature. Short stature is indeed common in adults with CAH in less developed countries. Gonadotropin-releasing hormone analogs (GnRHa) reduce the rate of linear growth and BA advancement and are considered an effective adjunct to steroids in the treatment of CPP complicating CAH. However, data on GnRHa use are scarce from resource poor settings.

Of the 55 patients diagnosed as precocious puberty (PP), five (four girls and one boy) treated as CPP complicating CAH between 2007 and 2016 were retrospectively reviewed. Four had simple virilizing CAH whereas one had classic salt-wasting form. The diagnosis of CPP was based on either basal serum LH of ≥ 0.3 IU/L or peak stimulated LH ≥5.0 IU/L. The presenting features were premature breast or pubic hair development in girls and testicular enlargement in boy. The mean chronological age (CA) at onset of PP and at start of treatment was 3.6 ± 0.74 years (range 2.7–4.3 years) and 4.7 ± 1.2 years (range 3.5–6.5 years), respectively. All had an advanced BA (mean 8.0 ± 2.4 years, range 6–12 years) at diagnosis. The mean BA advancement at diagnosis and at 3 years of treatment was 3.2 ± 1.3 years (range 2.4–5.5 years) and 2.0 ± 0.35 years (range 1.5–2.5 years), respectively; the slowing of BA advancement was statistically insignificant (P-value 0.08). Four underwent GnRH stimulation test. The mean baseline and stimulated peak LH values were 0.4 ± 0.55 IU/L (range 0.1–1.23 IU/L) and 5.6 ± 0.52 IU/L (range 5.0–6.2 IU/L), respectively. All children received oral hydrocortisone (8–15 mg/m²) and fludrocortisone. Depot leuprolide (initiated at 3.75 mg per month or 11.25 mg 3 monthly) was titrated according to LH values in follow-up. All children were followed up at 6 monthly intervals for at least 3 years. The mean height velocity (HV) and the mean unstimulated serum LH concentrations before and during 1st, 2nd, and 3rd years of therapy were 8.2 ± 0.5, 6.9 ± 1.7, 7.7 ± 1.0, and 7.6 ± 1.7 cm, and 1.4 ± 2.4, 0.21 ± 0.1, 1.4 ± 2.3, and 0.41 ± 0.1 IU/L, respectively. The improvement in mean predicted adult height (PAH) from the start to completion of 3 years of therapy was statistically significant (142.2 ± 6.3 cm vs 150.4 ± 4.2 cm, P value 0.04). Regression in testicular size and breast size was observed. The mean duration of follow up was 4.2 ± 1.6 years.

GnRHa therapy suppresses gonadotropin levels, stabilizes secondary sexual characteristics, and decreases rate of linear growth and BA maturation. These effects were observed in our patients also. However, the treatment outcomes appear to be different as compared to patients treated in the developed countries. Although our patients showed slowing down of BA advancement, the HV did not decrease significantly after GnRHa therapy in contrast with data from developed countries. Additionally, the improvement in PAH barely reached statistical significance after 3 years of therapy.

The lack of significant benefits of GnRHa therapy can be attributed to several factors peculiar to our setup such as delays in diagnosis of CAH due to lack of newborn screening, poor metabolic control, and late presentations with CPP. The mean delay in seeking treatment exceeded 1 year in our patients that probably caused significant BA advancement. It is well-known that BA at initiation of GnRHa therapy is the most important factor that affects HV. Delays in diagnosis and initiation of GnRHa therapy adversely affect height outcomes in CAH complicated by CPP in resource-limited setups.

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Conflicts of interest
There are no conflicts of interest.

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Letters to the Editor

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Sir,

In a patient of diabetes with nonketotic hyperglycemia (NKH), high signal intensity lesions on T1-weighted magnetic resonance imaging (MRI) confined to basal ganglia and contra lateral chorea is a unique syndrome often termed as diabetic striatopathy.

We present the details of an elderly person who was unsuccessfully treated for his movement disorder for many weeks before a proper diagnosis was made.

A 64-year-old male, not a known case of diabetes, with a past history of poorly controlled hypertension, noticed sudden onset of choreo-ballistic movements of the right upper and lower extremities for the past 3 months. These involuntary movements were present even during sleep. He was seen by a local physician and was put on trihexiphenidyl tablets with minimal improvement in symptoms. At present patient was admitted with history of osmotic symptoms for few weeks, investigations revealed random blood glucose of 490 mg/dL. On examination, he had an unstable gait, hypotonia in right upper and lower limbs. He had uncontrollable involuntary chorea like movements more in his right lower than upper limb. His muscle power was normal and systemic examination was unremarkable.

Investigations revealed initial plasma glucose of 490 mg/dL, with HbA1c of 14.4%, serum sodium was 130 meq/L, and calculated serum osmolality was 290 mosm/kg. Serum ketones were negative and the venous blood gas analysis was normal. Serum creatinine was 1.2 mg/dL and the liver enzymes were normal. A review of non-contrast computed tomography (CT) of brain done 3 months back which was reported as normal, revealed subtle hyperdensity in the basal ganglia region. MRI brain showed T1 hyperintensity in the head of left caudate nucleus and putamen with T2 hypointensity in the same areas. With this clinical presentation, NKH and MRI findings, a diagnosis of diabetic striatopathy was made. His diabetes was managed with insulin and he was put on low dose of haloperidol (0.25 mg twice daily) to control his involuntary movements. Within 5 days of admission, he showed marked improvement in symptoms and choroid form movements disappeared during his sleep. The patient is doing well and under follow up with a plan to repeat MRI brain after 3 months.

Hemichorea-hemiballismus, as a manifestation of NKH, is a rarely described entity, typically seen in elderly Asian women with type 2 diabetes, though very rarely it has also been reported in type 1 diabetes, those with diabetic ketoacidosis and in children. It is characterized by high signal on T1-weighted MRI, which is likely due to accumulation of lipid-laden macrophages, confined to the striatum. Most accepted pathophysiological mechanism in diabetic striatopathy involves hyperviscosity leading to local tissue hypoperfusion, depletion of gamma-Aminobutyric acid, and accumulation of manganese-containing gemistocytes in the basal ganglia which typically appear as T1 hyperintense lesions.

In a large meta-analysis of 53 cases, two-third of Chorea Associated with Nonketotic Hyperglycemia (Diabetic Striatopathy) in an Elderly Male

Figure 1: Magnetic resonance imaging brain showing T1 hyper-intensity in the basal ganglion region (arrows)