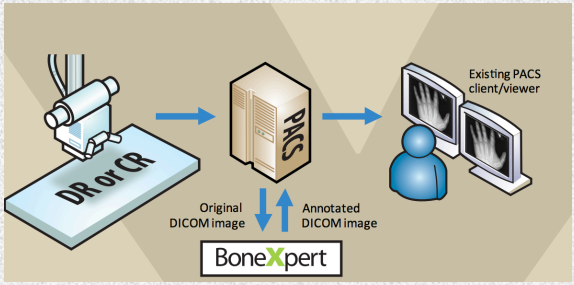
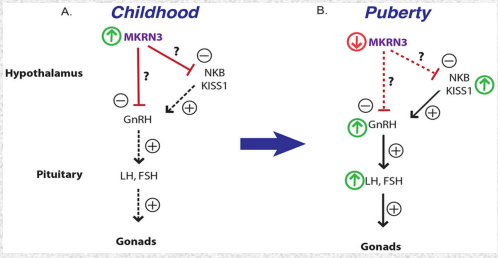
GROW India

Growth & Obesity Workforce

Advances in Pediatric Endocrinology





Editor

Anurag Bajpai

Advances in Pediatric Endocrinology

Editor
Anurag Bajpai

GROW Society Publications

GROW India

Growth & Obesity Workforce

GROW Society

Regency Hospital Limited, A2 Sarvodaya Nagar Kanpur, UP, 208001

Website- www.grow-india.org, Email grow_india@yahoo.com

From the Editors Desk

Last couple of decades has witnessed tremendous advances in Pediatric Endocrinology. Marvellous developments have taken place in the field of pathophysiology, genetics, diagnostics and treatment. No where else is the change more evident then in Type 1 DM where from a desperate situation of multiple painful injections and horrendous glycemic fluctuations we are heading towards a bionic pancreas in the near future. The pace with which these developments are unfolding is unnerving. Though this book we peek into some of these fascinating developments in the field of growth hormone, turner syndrome, PCOS, disorder of sexual development, calcium and vitamin D, bone health, diabetes in children and pubertal disorders. Special care has been taken to focus on newer tools relevant in managing children with endocrine disorders like DEXA, bioimpedance, Bone Xpert, CGMS, insulin pumps and bionic pancreas. We hope that the book would stimulate further exploration in this exciting field of Pediatric Endocrinology.

The rapid progress in Pediatric Endocrinology is only matched by the fascinating growth of Pediatric Endocrinologists in our country. From just a handful Pediatric Endocrinologists a decade ago we have witnessed an exponential rise in the number of trained paediatric endocrinologists in the country. The young pediatric endocrinologists with there hard work and dedication form the core of this effort and deserve a huge round of applause. The time has come for Pediatric Endocrinology to rise from the sidelines of Pediatrics and Endocrinology in the country and spread it's message to far and wide in the country.

Happy reading,

Anurag Bajpai, MD, FRACP, SCE,
Pediatric & Adolescent Endocrinologist,
Regency Center for Diabetes, Endocrinology & Research,
Fortis Memorial Research Institute, Gurgaon
Secretary, Indian Society of Pediatric & Adolescent Endocrinology,
Founding secretary, GROW Society (Growth & Obesity Taskforce)

Contributors

Professor P Raghupathy,	Head, Department of Pediatric Endocrinolgy, Indira Gandhi Institute of Child health, Bengaluru
Professor PSN Menon	Head, Department of Pediatrics, Jaber Al-Ahmed Armed Forces Hospital, Salamiya, Kuwait
Dr Subrata Dey	Pediatric Endocrinolgist, Apollo Glenegales Hospital, Kolkotta
Dr Anuradha Khadilkar	Pediatrician and Deputy Director, Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, Pune
Dr Smita Koppikar	Pediatric Endocrinolgist, MITR Hospital Mumbai
Dr Anurag Bajpai	Pediatric Endocrinolgist, Regency Center for Diabetes, Endocrinology & Research, Kanpur & Fortis Memorial Research Institute, Gurgaon
Dr Yuthika Sharma Bajpai	Pediatric & Adolescent Gyncecologist, Reproductive Medicine Specialist, In Charge Regency IVF, Kanpur
Dr Meena Mohan	Pediatric Endocrinolgist, Masonic Hospital, Coimbatore
Dr Anjana Hulse	Pediatric Endocrinolgist, Apollo Hospital, Bengaluru
Dr Rakesh Kumar	Additional Professor, Department of Pediatrics, PGIMER, Chandigarh
Dr Vijaya Sarathi	Assistant Professor, Department of Endocrinology, Vydehi Medical College, Bangaluru
Dr Hemchand KP	Pediatric Endocrinolgist, Mehta Children's Hospital, Chennai
Dr Reena R	DNB Trainee, Mehta Children's Hospital, Chennai

Table of contents

Section I- Year in review

1.1 Growth Hormone

Hemchand K P, Reena R

The literature pertaining to growth hormone published in 2015-2017 was reviewed and newer aspects are presented in the write-up.

Growth charts

The growth chart committee constituted by Indian academy of Paediatrics came out with the current recommendation on optimal use of growth charts in Indian children. They recommend – usage of IAP modified WHO charts in children < 5 years and combined WHO-IAP charts in children > 5 years. The key points in the new charts include:

1. Availability of the 3rd percentile to diagnose short stature in modified WHO and new IAP combined charts
2. To replace the old 85th and 95th percentile to define overweight and obesity with the new definitions of – 23rd and 27th adult equivalent of adult BMI
3. The target height range should be considered as ± 6cm above and below the target height at 18 years

Unusual presentations of GHD

- Gilliland T et al (1) describe a pediatric case of **NASH (No alcoholic steatohepatitis) secondary to panhypopituitarism** from craniopharyngioma - Pubertal dosed GH therapy led to rapid and complete resolution of hepatic steatosis. High-dose GH replacement should be considered in pediatric patients with GH deficiency and recurrent NASH.
- Four children **with cerebral palsy (2)** who were born before 29 weeks gestation who were referred to an endocrinology unit, three for delayed puberty and one for short stature, in whom investigations identified MPHD. MRI scans showed an ectopic posterior pituitary gland. Endocrine evaluation of children with CP when warranted must be performed.
- A child with eye maldevelopment secondary to **OTX-2 mutation** and ectopic posterior pituitary and GHD is described by Lonero A et al (3).
- Jivani N et al (4) report a case of **Shwachman-Diamond syndrome** (bone marrow failure syndrome with pancreatic dysfunction) presenting with hypoglycemia and micropenis in the newborn period and was diagnosed with congenital hypopituitarism.
- Quintos JB et al(5) describe 8 cases with **Kearns sayre syndrome** with growth hormone deficiency treated with Growth hormone. The authors

observed that mean improvement in height was from -3.9 to -2.9 SDS in patients with KSS and two patients did not show growth improvement. **Children with KSS may respond to GH** depending upon the severity of GHD and severity of underlying mitochondrial dysfunction.

- Hodax JK et al (6) report a child who underwent 14 hour fasting evaluation for hypoglycemia and found to have low growth hormone levels, confirmed on provocative testing and had hypoplastic pituitary on MRI. A genetic sequencing (done due to clinical features)showed hemizygous variant c. 721A>G (p1241V) in the X-linked Phosphorylase kinase gene, a causative gene for GSD IX. The authors report **- two unrelated conditions – GSD IX and GHD** resulting in deranged metabolic adaptation to fasting leading to severe hypoglycemia.
- Ludwig et al(7) report the fifth case of **Central Precocious Puberty in a genetically-confirmed Prader Willi Syndrome** male. Combined therapy with GnRHa and rhGH may be beneficial in this rare condition of precocious pubertal development in PWS.
- Stagi S et al (8) suggest evaluating the growth hormone axis in children with **6q24.2-q25.2 deletions** and growth failure.

Diagnosis of GHD

- Clonidine Stimulation tests on 250 consecutive (9) subjects in a single center were evaluated with respect to the peak time of the CST. Peak GH occurred typically at 30, 60, and 90 minutes (91.6% of tests, versus 60% expected) (P<.001). Removal of the 120-minute sample affected the final result in 0.4% of evaluations. **Can clonidine stimulation test be terminated at 90 minutes from stimulation?**
- In a retrospective study in 372 (10) subjects who underwent evaluation of GH secretion – an Receiver Operating Curve analysis was used to evaluate the optimal GH cut-offs and the diagnostic accuracy of provocative tests (74 patients with organic GHD and 298 controls). The optimal GH cut-off for arginine resulted 6.5µg/L, 5.1µg/L for ITT and 6.8µg/L for clonidine proving that the cut-off limits which discriminate between normal and GHD are lower than those commonly employed.
- An analysis of 75 EPP patients (11) with short stature and reduced growth velocity was done. Normal GH response was observed in 15 of 75 (20%) patients - There was a trend to more frequent multiple hormone deficiency and lower height in nonresponsive when compared with responsive patients. Thus, Normal GH values after stimulation tests do not exclude EPP-associated GH deficiency.
- A study on 69 children (12) with IGHD, 29 ISS children and 66 controls observed that mean pituitary volumes were 230.8 (±89.6); 286.8 (±108.2); 343.7 (±145.9) (p<0.001), respectively. The authors noted a normal

increase in PV with age in the ISS patients and controls, but a minimal increase in the IGHD patients. This speculates a possibility of pituitary volumes on MRI scan having a diagnostic role in the evaluation of GHD.

- Body composition was studied in children with moderate and severe GHD and normal children (13). Children with severe GHD is associated with significant impairment of body composition suggesting its utility as a diagnostic tool.

Mode of Administration and Dosing

- ***LB03002 (depot long acting preparation of LG sciences)(14) -*** GH is incorporated into sodium hyaluronate and dispersed in an oil base of medium chain triglycerides. Dose is 0.5 mg/kg/week - given as once a week. The pros and cons of the same versus daily injections of GH are as follows:

Similar to daily injections	Different from daily injections
Similar increment in height in first and second year; similar bone maturation and IGF and IGFBP3 profiles and normal sugar metabolism.	More local injection site minor reactions and higher antibody positivity (37.4%)at least once (versus 4.6% in daily group).

- Lipid estimation was performed in 51 children on GH (SGA or GHD) after 52 weeks of GH. Post treatment reductions in LDL and CRP was observed. Children with GHD or born SGA may benefit from **GH by growth acceleration and reduction of cardiovascular long-term risks** (15).
- A multicentre, randomized, clinical trial 104 children (90 boys) to receive GH at 33 or 66 ug/kg/day during puberty was performed. Children who received a higher GH dose had higher IGF-1 levels and had better increment in height SD scores. The attempt to mimic normal physiology by giving a **higher GH dose during puberty was associated with both an increase in IGF-I and a dose-dependent gain in height(SDS)** (16).

Compliance to GH Therapy

Why do families discontinue GH therapy? - Observational study of the Australian GH Program (17) comparing Completed Treatment (CT), Early Cessation (EC) and Non-Response (NR) groups over 23 years pertaining to various aspects studied. 51.9% of patients were EC, 40.7% CT and 7.4% NR. Early Cessation was observed at very high rates and appears, generally, to be a little-recognised but frequent problem in GH therapy. Poor

treatment compliance is likely a major causal factor in EC. Suggested solutions include: long acting GH formulations or individualized treatment plan.

Adverse Effects of Growth Hormone

- All cancer survivors referred to the transition unit in Turin (18) for 12 years diagnosed as GHD in childhood (as a result of cancer therapy) included and followed up. The cumulative incidence of Second neoplasms was similar in GH-treated and -untreated patients (8 SNs out of 26 GH-treated and 6 out of 23 GH-untreated patients; p = 0.331). Thus, **GH replacement therapy did not seem to increase the risk of Second neoplasms**.
- A study done comparing 28 and 36 children receiving supraphysiological dose and physiological dose of **GH did not reveal any adverse impact on CIMT** (carotid intima media thickness (a surrogate marker of cardiometabolic risk)) (19).
- Comparison of lipid profile and CIMT (Carotid Intima Media Thickness) in 40 GHD children and controls was done. Cases underwent CIMT assessment prior to and after 1 year of GH therapy. GHD is associated with increased atherosclerotic risk in children. An **improved lipid profile and CIMT were detected after 1 year of GH** replacement therapy (20).
- 99 children with GHD were followed up for 6 years annually – underwent OGTT to calculate HOMA-IR, insulinogenic index and oral disposition index. Although HOMA-S remained unchanged, an increase in IGI and ODI was observed, becoming significant after 6 years of treatment. There seems to be a **positive influence of GH treatment on the β-cell secretory capacity** in children with **GH deficiency (21).**
- 104 children with **Turner syndrome** were followed up for 7 years annually – underwent OGTT to calculate HOMA-IR, insulinogenic index and oral disposition index. No significant changes were observed in term of HOMA-S, IGI or ODI. There is **no negative influence of GH treatment on insulin sensitivity** and on beta cell secretory capacity in girls with TS (22).
- Long-term safety data on 13834 GH treated patients with short stature analysed (1998-2013). 61.0% of patients were classified as low-risk, 33.9% intermediate-risk, and 5.1% high-risk. Three hundred and two AEs were reported in 261 (1.9%) patients during a treatment duration of 3.9 (2.8) years. The authors **confirm a favorable overall safety profile in accordance with other pediatric observational studies**. No association between GH dose and incidence of AEs during GH therapy was noted (23).
- A mortality model of the Swedish general population born between 1973 and 2010, using continuous-hazard functions adjusting for birth characteristics, sex, age intervals, and calendar year to estimate

standardized mortality ratio (SMR) was developed and applied to assess expected deaths in Swedish rhGH-treated patients with idiopathic isolated GH deficiency (IGHD), idiopathic short stature (ISS) or born small for gestational age (SGA). Compared with the general Swedish population, the ratio of observed/expected deaths (21/21.99) was not increased in childhood rhGH-treated IGHD, ISS, and SGA patients when applying an advanced sex-specific mortality model adjusting for birth characteristics (24).

GH In Non GHD Indications

Linear growth (height, sitting height, and leg length) was prospectively investigated in a cohort of 322 pediatric Kidney transplant recipients, with a mean follow-up of 4.9 years. In children born SGA, growth outcome after Kidney transplant is significantly more impaired and affected by different clinical parameters compared with non-SGA patients (25).

SGA

- The efficacy of GH treatment (1 mg/sqmday) in short SGA children on Adult height was studied. Longitudinal GH trial in 170 children observed that - children with greater spontaneous catch-up growth after birth show a lower total height gain SDS during GH. Height SDS declines from mid-puberty, due to a marked early deceleration of growth velocity (26).
- Vandersteen M et al studied the body composition, blood pressure, and lipid profile during GH treatment, either with or without 2 years of additional GnRHa. 107 children short SGA received GH; 64 received additional GnRHa. Authors conclude: Combined GH/GnRHa treatment has no long-term negative effects on metabolic health compared to only GH (27).

Russel Silver Syndrome

Twenty nine children with RSS and 171 non RSS born SGA were compared on their metabolic parameters during GH and 2 years post GH therapy (Lean body mass, Fat mass% and insulin sensitivity). GH-treated SRS patients have a similar metabolic health and safety profile as non-SRS subjects born SGA, both during and until 2 years after GH-stoppage (28).

Miscellaneous

Concentrations of total IGF-I and total IGF-II and auxology at birth was studied in IUGR, SGA and AGA babies. Low IGF-I cord blood concentrations in hypotrophic neonates after IUGR might not only result from low birthweight per se, but also reflect prenatal placental environment. Alterations of the IGF axis could be in the causal pathway of IUGR and thus constitute a potential surrogate marker for IUGR in the assessment of foetal programming (29).

References:

1. Gilliland T, Dufour S, Shulman GI, Petersen KF, Emre SH. Resolution of Non alcoholic Steatohepatitis after GHtherapy in paediatric liver transplant with panhypopituitarism. Pediatr Transplant. 2016 Dec;20(8):1157-1163.
2. Uday S, Shaw N, Krone R, Kirk J. Hypopituitarism in children with cerebral palsy. Arch Dis Child. 2016 Oct 27.
3. Lonero A, Delvecchio M, Primignani P, Caputo R, Bargiacchi S. A novel OTX-2 gene frameshift mutation in a child with microphthalmia, ectopic pituitary and GHD. J Pediatr Endocrinol Metab. 2016 May 1;29(5):603-5.
4. Jivani N, Torrado-Jule C, Vaiselbuh S, Romanos-Sirakis E. A unique case of Shwachman Diamond Syndrome presenting with congenital hypopituitarism. J Pediatr Endocrinol Metab. 2016 Nov 1;29(11):1325-1327
5. Quintos JB, Hodax JK, Gonzales-Ellis BA, Phornphutkul C, Wajnrajch MP et al. Efficacy of Growth Hormone therapy in Kearns Sayre Syndrome: the KIGS experience. J Pediatr Endocrinol Metab. 2016 Nov 1;29(11): 1319-1324
6. Hodax JK, Uysal S, Quintos JB, Phornphutkul C. Glycogen storage disease type IX and growth hormone deficiency presenting as severe ketotic hypoglycemia. J Pediatr Endocrinol Metab. 2017 Feb 1;30(2):247-251
7. Ludwig NG, Radaeli RF, Silva MM, Romero CM. A boy with PWS: unmasking of precocious puberty during GH therapy. Arch Endocrinol Metab. 2016 Nov-Dec;60(6):596-600.
8. Stagi S, Lapi E, Pantaleo M, Carella M, Petracca A, et al. A new case of de novo 6q24 deletion on paternal chromosome 6 with GHD. BMC Med Genet. 2015 Aug 23;16:69.
9. Gillis D, Magiel E, Terespolsky N, Naugolny L, Strich D. Clonidine stimulation test for GH deficiency – a new look at sampling. Endocr Pract. 2016 Mar;22(3):338-42
10. Guzzetti C, Ibba A, Pilia S, Beltrami N, Di Iorgi N Cut-off limits of the peak GH response to stimulation tests for the diagnosis of GH deficiency in children and adolescents: study in patients with organic GHD. Eur J Endocrinol. 2016 Jul;175(1):41-7
11. Kochi C1, Scuderi CG, Barros L, Ribeiro L, Amadei G et al. High Frequency of Normal Response during GH Stimulation Tests in Patients with Ectopic Posterior Pituitary Gland: A Source of False-Negative Diagnosis of Pituitary Insufficiency. Horm Res Paediatr. 2016;85(2):119-24.
12. Kessler M, Tenner M, Frey M, Noto R. et al. Pituitary volume in children with GHD, ISS and controls. J Pediatr Endocrinol Metab. 2016 Oct 1;29(10): 1195-1200.
13. Matusik P, Klesiewicz M, Klos K, Stasiulewicz M· Baseline body composition in pre pubertal short stature children with moderate and severe GH deficiency. Int J Endocrinol. 2016;
14. Khadilkar V, Radjuk KA, Bolshova E, Khadgawat R, El Kholy M. 24 month use of once weekly GH LB03002, in pre pubertal children with GH deficiency. J Clin Endocrinol Metab. 2014 Jan;99(1):126-32.
15. Krebs A, Kratzin T, Doerfer J, Winkler K, Wurm M et al. Decrease of small dense LDL and lipoprotein associated phospholipase A2 due to GH therapy

in children with GHD and SGA. J Pediatr Endocrinol Metab. 2016 Feb;29(2): 203-8
16. Lundberg E, Kriström B, Jonsson B, Albertsson-Wikland K et al. Growth Hormone dependant IGF response relates to pubertal height gain. BMC endocr Disord 2015 dec 18; 15: 84.
17. Hughes IP, Choong C, Rath S, Atkinson H, Cotterill A. Early cessation and non response are important and possibly related problems in GH therapy: an OZGROW analysis Growth Horm IGF Res. 2016 Aug;29:63-70
18. Brignardello E, Felicetti F, Castiglione A, Fortunati N, Matarazzo P et al GH replacement therapy and second neoplasms in adult survivors of childhood cancer: a retrospective study from a single institution. J Endocrinol Invest. 2015 Feb;38(2):171-6.
19. Rothermel J, Knop C, Lass N, Toschke C, Wunsch R.Carotid Intima Media thickness in children treated with GH – a follow-up study over 3 years. Horm Res Paediatr. 2017 Jan 10.
20. Binay C et al. GH therapy and the risk of atherosclerosis in GHD children. Growth Horm IGF res 2015 Dec 25(6) 294-7.
21. Baronio F, Mazzanti L, Girtler Y, Tamburrino F, Fazzi A et al. The influence of GH therapy on glucose homeostasis in children with GHD – a 6 year follow-up study.
22. Baronio F, Mazzanti L, Girtler Y, Tamburrino F, Lupi F. The influence of GH treatment on glucose homeostasis in girls with Turner syndrome: a 7 years study. J Clin Endocrinol Metab. 2016 Dec 2
23. Sävendahl L, Pournara E, Pedersen BT, Blankenstein O. Is safety of childhood GH therapy related to dose? Data from a large observational study. Eur J Endocrinol 2017 Mar 176.
24. Albertsson-Wikland K, Mårtensson A, Sävendahl L, Niklasson A. Mortality is not increased in recombinant GH treated patients when adjusting for borth characteristics. J Clin Endocrinol Metab. 2016 May;101(5):2149-59
25. Franke D, Steffens R, Thomas L et al. Kidney transplantation fails to provide adequate growth in children with chronic kidney disease born SGA. Pediatr Nephrol. 2017 Mar;32(3):511-519.
26. Renes JS, Willemsen RH, Mulder JC, Bakker-van Waarde WM, Rotteveel J. New insights into factors influencing adult height in short SGA children: results of a large multi centric study. Clin Endocrinol (Oxf). 2015 Jun;82(6): 854-61
27. Van der Steen M, Lem AJ, van der Kaay DC, Bakker-van Waarde WM. Metabolic health in short children born SGA and treated with GH and GnRHa: results of a randomised, dose response trial. J Clin Endocrinol Metab. 2015 Oct;100(10):3725-34.
28. Smeets CC, Renes JS, van der Steen M, Hokken-Koelega AC.Metabolic health and safety of GH therapy in Silver Russell syndrome. J Clin Endocrinol Metab. 2016 Dec 21.
29. Tzschoppe A, Riedel C, von Kries R, Struwe E. Differential effects of low birth weight and intrauterine growth restriction on umbilical cord IGF concentrations. Clin Endocrinol (Oxf). 2015 Nov;83(5):739-45.