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CAPE News

Newsletter of The Indian Society for Pediatric and Adolescent Endocrinology (ISPAE)

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From the Editorial Board

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Editorial board

Dear Esteemed ISPAE members,

Wishes for a enjoyable festive season. It is a great pleasure to connect with all of you through this interesting September 2021 issue of CAPE News based on the theme "Thyroid disorders". We have presented interesting articles, guidelines, case reports, journal scan and other aspects pertaining to the thyroid. Hope you have a good reading experience. Feedback is welcome at editor.capenews@gmail.com. The next theme, for the December issue is "Diabetes".

Thank You and Regards,
Team CAPE News

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Office Bearers' Message

Dear ISPAE members,

Greetings from Team ISPAE 2021-22!

At the outset, we thank each and every member of ISPAE for your kind appreciation, received as personal feedback, and through social media and emails. It has been a big boost to our morale and helps us to do better. We also warmly welcome all the new members to the ISPAE family, which now stands at a strength of 650 members.

Preparations are in full swing for the seventh biennial meeting of ISPAE. More than 100 abstracts have been received and candidates have been selected for the Fellows' School. In view of the unpredictable nature of the COVID pandemic, the ISPAE 2021 Organizing Committee has had to take the tough decision of converting the main meeting into a virtual one with a revised schedule. We wish the Organizing Team all the success for ISPAE 2021.

The first issue of the official journal of ISPAE, "Journal of Pediatric Endocrinology and Diabetes" (JPED) is ready; the team led by Drs PSN Menon and Rakesh Kumar is taking great efforts to maintain high quality publishing standards for the journal.

We have successfully started training of the first batch of diabetes educators under the ISPAE Diabetes Education And Learning (IDEAL) program. This has been possible in a very short time due to the contributions of faculty across India. The process of having a common pediatric endocrine training program is also progressing well with the efforts of the committee led by Dr P Raghupathy.

We would request all of you to continue contributing regularly to our monthly meeting ISPAE ACES meeting, informing your activities to the CAPE news editor, encouraging young pediatricians and postgraduates to become ISPAE members and participate in our academic meetings!

Best Wishes,
Drs Shaila Bhattacharyya, Ganesh Jevalikar, Rakesh Kumar,
Team ISPAE 2021-22

Dr Shaila Bhattacharyya
President
ISPAE 2020-21

Dr Ganesh Jevalikar
Secretary cum Treasurer
ISPAE 2020-21

Dr Rakesh Kumar
Joint Secretary
ISPAE 2020-21

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A very warm welcome to all new members

1. Anuja Agarwala, Senior Dietician, Department of Pediatrics, AIIMS, New Delhi

2. Manjunath H Dodamani, Sr Resident (DM Endocrinology Trainee), KEM, Mumbai

3. Rohit Barnabas, Sr Resident (DM Endocrinology Trainee), KEM, Mumbai

4. Uthara Elsa Mathew, Sr Resident, DM Endocrinology, AIIMS, New Delhi

5. Tejaswi Venkatesh, Sr Resident, DM Endocrinology, AIIMS, New Delhi

6. Kiran Kumar Golla, Sr Resident, DM Endocrinology, AIIMS, New Delhi

7. Rachna Mohan Keshwani, Bai Jerbai Wadia Hospital for Children, Mumbai

8. Tejasvi Seshadri, Fellow in Pediatric Endocrinology, IGICH, Bangalore

9. Debaditya Das, Post Doctoral Trainee in Endocrinology DM program, IPGMER, Kolkata

10. Meenakshi BR, Asst Professor of Pediatrics, Kaher JN Medical College & Dr Prabhakar Kore Hospital, Belgaum

11. Amulya Yalamanchi, Sr Resident, Sri Ramachandra IHER, Porur, Chennai

12. Krishna Mori, Sri Ramachandra Medical College, Porur, Chennai

13. Supreeth Chandrasekar, Sr Resident, Dept of Endocrinology, IMS, BHU, Varanasi

14. Shuchy Chugh, Diabetes Education Specialist, Novo Nordisk India Private Ltd,. Bangalore

15. Shruti Sajjan, DM (Endocrinology), SGPGI, Lucknow

16. Pinky Meena, PDCC Fellow, SGPGI, Lucknow

17. Vaibhav Singhal, DM (Endocrinology), SGPGI, Lucknow

18. Kaustav Nayek, Professor & HOD Pediatrics, Burdwan MC & Hospital, Kantapukur, Bardhaman, West Bengal

19. Avani Hegde, Asst Professor, Dr Chandramma Dayananda Sagar IMER, Bengaluru

20. Mounica Reddy, Consultant Pediatrician, Rainbow Children's Hospitals, Bengaluru

21. Kaushal Sheth, Yashoda Hospital, Secunderabad

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Guidelines: Thyroid Disorders

Dr Pragya Mangla, Assistant Professor, Dept. of Endocrinology
University College of Medical Sciences and GTB Hospital, Delhi

a) Consensus- Graves' disease in children
b) Initial evaluation and management of children with thyroid nodules and
c) Papillary Thyroid Cancer- management guidelines

a) Consensus - Graves' disease in children

Léger J, Oliver I, Rodrigue D, Lambert AS, Coutant R. Graves' disease in children. Ann Endocrinol (Paris). 2018 Dec;79(6):647-655.
Rivkees SA. Pediatric Graves' disease: management in the post-propylthiouracil era. Int J Pediatr Endocrinol 2014;2014: 10

Hyperthyroidism is a rare and severe disease in children, and is primarily linked to Graves' disease (GD) (99% of cases). The disease can occur at any age, with a peak in prevalence during adolescence.

Diagnosis of Graves' disease:

- The diagnosis of GD in children is based on detecting suppressed serum TSH concentrations and the presence of anti-TSH receptor antibodies (TRAbs). Thyroid scintigraphy is not required for the diagnosis of GD unless there is a nodule.
- In the absence of TRAbs, the possibility of genetically inherited hyperthyroidism like activating germline or somatic mutations of the TSH receptor gene, McCune Albright Syndrome, resistance to thyroid hormones due to mutation of the beta receptor gene, etc. must be considered.
- Other causes like Hashitoxicosis, de Quervain's subacute thyroiditis, iodine-induced hyperthyroidism, as a side effect of cervical radiotherapy, thyrotoxicosis factitia and pituitary adenoma secreting TSH, false hyperthyroidism as a result of measurement errors in children receiving biotin: though rare, should also be considered.

Drug therapy for Graves' disease:

- Drug therapy is the primary line of treatment for children and consists of imidazole, carbimazole or methimazole (MMZ), with an initial dosage of 0.4-0.8 mg/kg/day (0.3- 0.6 mg/kg/day for MMZ) depending on the initial severity, up to a maximum of 30 mg. It is usually administered as 1-2 doses/day.
- Monitoring of drug tolerance and thyroid profile is usually required after 2 weeks, 4 weeks, and every month thereafter, until normalization of TSH. Because TSH levels may take months to normalize, they should not be used to guide changes in the dose of the medication in the early phases of treatment. When normal thyroid function is achieved (normal T4 and T3 levels), the dose should be decreased by 30-50% to the minimum effective dose (usually 5-15 mg/day); clinical and biological monitoring (only TSH) can take place on a quarterly basis after this.

- For adrenergic symptoms like tachycardia, additional treatment with beta-blockers (atenolol, or propranolol), during the first 2-4 weeks of treatment with antithyroid agents (ATD) may be proposed until normalization of the thyroid hormones.
- Propylthiouracil is contraindicated in children with GD. "Block and replace" strategy is not recommended.
- Before starting treatment, it may be useful to perform a baseline CBC to assess the degree of neutropenia caused by hyperthyroidism. An emergency CBC should be performed if symptoms include fever or sore throat. If neutrophil counts are <1000/mm^3, synthetic ATD should be discontinued or decreased; they may be permanently contraindicated in severe (<500/mm^3) and persistent neutropenia. Otherwise, treatment may be resumed.
- Transaminase levels should be measured before initiating treatment. In cases of jaundice, digestive disorders or pruritus, measuring liver enzymes (AST, ALT), total and conjugated bilirubin and alkaline phosphatases is indicated.
- Systematic monitoring of CBC and LFT is not indicated.
- Other minor and transient side effects are urticaria, arthralgia and rashes, not requiring discontinuation of treatment.
- The remission rate following 2 years of treatment is around 30% in children. The initial course of treatment might need to be given for 3-6 years. Early age, large goiter size, the initial severity of the disease, non-Caucasian ethnicity, and insufficient compliance with treatment, are associated with poor remission. Adolescence, presence of other autoimmune diseases, and prolonged treatment period (>2 yr) are associated with increased rate of remission in GD.

Radical treatment:

- Indications for radical treatment can arise in cases of: a) contraindication to ATDs; b) poorly controlled hyperthyroidism due to lack of compliance; c) relapse despite prolonged medical treatment; d) a request made by the family and child for personal reasons.
- Secondary hypothyroidism induced by radical treatment will require lifelong, monitored and well-coordinated treatment with levothyroxine. This should be fully explained to the patient and the family beforehand.
- Surgery is the radical method of treatment in children < 5 years of age, or in cases of very large (>80 gm), nodular, or compressive goiters. Surgery is also required if thyrotoxicosis is severe and accompanied by neurological symptoms, if the patient is suffering from severe thyroid eye disease, or where conventional iodine treatment is contraindicated.
- Total thyroidectomy is preferred over partial or subtotal thyroidectomy as the risk of recurrence is estimated to be 10–15%. The patient must be euthyroid at the time of surgery; Lugol's Iodine (orally daily for 10 days prior to the surgery) will help by limiting the vascularization of the thyroid.
- When radical treatment is indicated and the goiter is not too large (<80 grams), ^{131}I treatment may be discussed after 5 years of age (but more often after puberty).
- The objective of treatment with radioactive iodine (RAI) is to use an ablative dose to achieve hypothyroidism (never euthyroidism), given the risk of secondary thyroid cancer.
- A fixed dose of no more than 10-15 mCi should be given. For children between 5-10 years, the total dose should be limited to <10 mCi.

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- ATDs should be stopped seven days before RAI administration to permit adequate uptake of RAI by the thyroid. It usually takes 6-12 weeks for the patient to become biochemically euthyroid or hypothyroid. If hyperthyroidism persists, a second dose can be given after 6 months.

b) Initial evaluation and management of children with thyroid nodules and Papillary Thyroid Cancer- management guidelines

Francis GL, Waguespack SG, Bauer AJ, et al; Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015;25(7):716–759. & Pediatrics. 2018; 142(6):e20183063

Nodules diagnosed in children (⩽ 18 years) carry a greater risk of malignancy compared to those in adults. Children with papillary thyroid cancer (PTC) are more likely to have regional lymph node involvement, extrathyroidal extension, and pulmonary metastasis. Despite extensive disease at clinical presentation, children have much less long-term cause-specific mortality, more favorable progression-free survival with persistent differentiated thyroid cancer (DTC) and persistent but stable disease with continued decline in thyroglobulin (Tg) levels following ^{131}I therapy in cases of pulmonary metastases, as compared to adults.

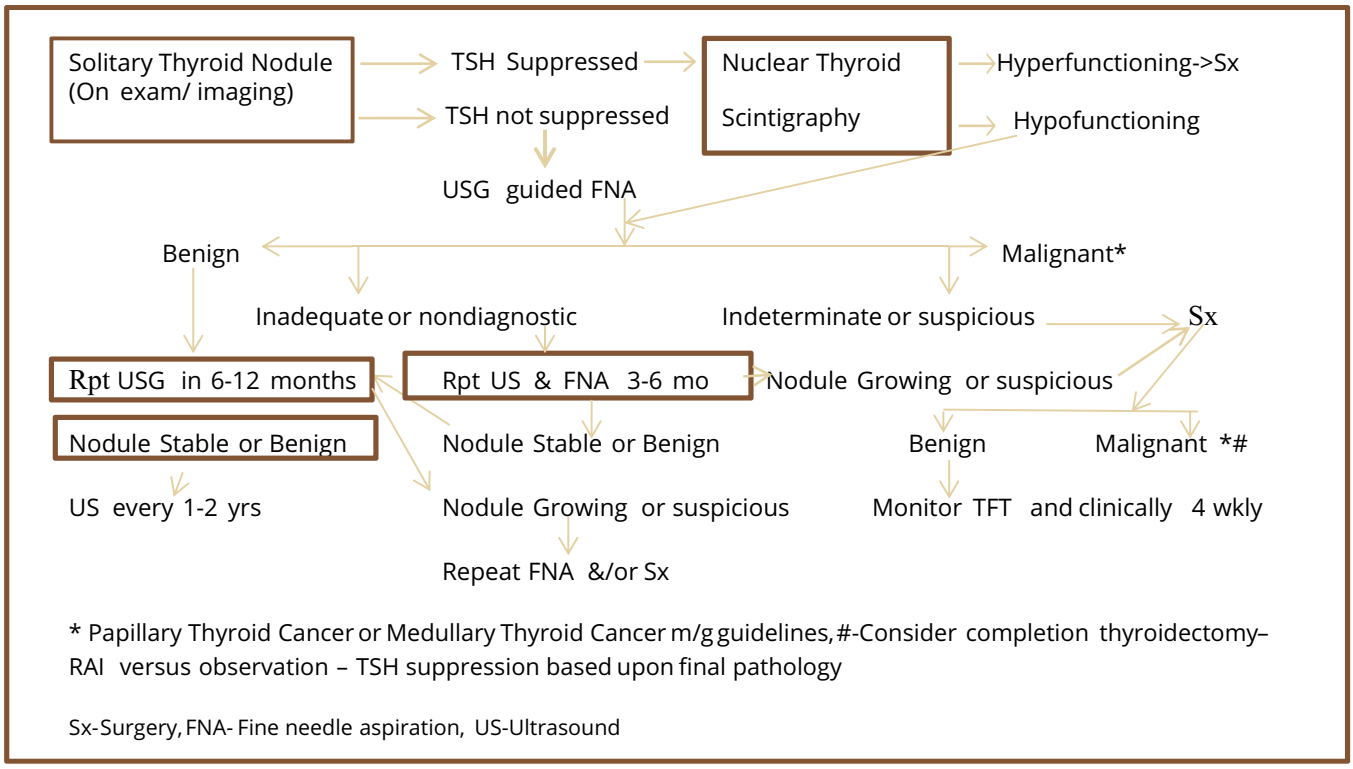

Fig.1: Management of Pediatric Thyroid Nodule. Modified from Francis GL, Waguespack SG, Bauer AJ, et al; Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015;25(7):716–759.

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Children at high risk for thyroid neoplasm:

- An annual physical examination is recommended in children at high risk for thyroid neoplasia. Additional imaging should be pursued if palpable nodules, thyroid asymmetry, and/or abnormal cervical lymphadenopathy are found on examination.

- Several risk factors are associated with the development of thyroid nodules in children, including iodine deficiency, prior radiation exposure (including radiotherapy treated childhood cancer survivors), a history of antecedent thyroid disease, and children with several genetic syndromes like APC-associated polyposis, the Carney complex, DICER1 syndrome, PTEN hamartoma tumor syndrome and Werner syndrome. Cases of DTC have also been reported in Beckwith–Wiedemann syndrome, familial paraganglioma syndromes, Li–Fraumeni Syndrome, McCune–Albright syndrome, and Peutz–Jeghers syndrome.

- Patients at increased risk of developing familial DTC should be referred to centers of excellence so that appropriate evaluation, follow-up, genetic counseling, and/or treatment can be undertaken without subjecting patients and families to unwarranted and aggressive therapy.

Optimal evaluation of children with thyroid nodules:

- 'The evaluation and treatment of thyroid nodules in children (Fig. 1) should be the same as in adults, with the exceptions that (a) US features such as hypoechogenicity, irregular margins, increased intranodular blood flow, presence of microcalcifications and abnormal cervical lymph nodes are more common in malignant lesions. Thus US features and clinical context should be used rather than size alone to identify nodules that warrant FNA, (b) all FNA in children should be performed under US guidance, (c) preoperative FNA of a hyperfunctioning nodule in a child is not warranted as long as the lesion is removed, (d) a diffusely infiltrative form of PTC may occur in children and should be considered in a clinically suspicious gland (microlithiasis or palpable cervical lymph nodes), (e) surgery (lobectomy plus isthmusectomy) is favored over repeat FNA for most nodules with indeterminate cytology.

- A positive mutational test might help as it is highly associated with malignancy.

Management of benign thyroid nodules:

- Guidelines do not recommend for or against the routine use of LT4 therapy for children with benign thyroid nodules. In patients with compressive symptoms or a history of radiation exposure the benefits of LT4 therapy may be more apparent.

- Benign lesions should be followed by serial US and undergo repeat FNA if suspicious features develop or the lesion continues to grow. Lobectomy may be performed in patients with compressive symptoms and cosmetic concerns or according to patient/ parent preference and should be considered in all apparently benign solid thyroid nodules > 4 cm, those lesions demonstrating significant growth, or in the presence of other clinical concerns for malignancy.

- For pediatric patients with a suppressed TSH associated with a thyroid nodule, thyroid scintigraphy should be pursued. Increased uptake within the nodule is consistent with autonomous nodular function. Surgical resection, most commonly lobectomy, is the recommended approach for most autonomous nodules in children and adolescents as up to one third of these patients may be found to have a DTC.

c) Papillary Thyroid Cancer - Management guidelines

Preoperative Evaluation:

- A comprehensive neck US to examine all regions of the neck is required in order to optimize the preoperative surgical plan. FNA of suspicious lateral neck lymph nodes is recommended. Anatomic imaging by MRI or CT with contrast should be considered in patients with large or fixed thyroid masses, vocal cord paralysis, or bulky metastatic lymphadenopathy as US might be less sensitive.
- If iodinated contrast agents are used, further evaluation and treatment with RAI may need to be delayed for 2–3 months until total body iodine burden decreases.
- Routine chest CT is not recommended for patients with minimal neck disease because pulmonary metastases are likely to be identified when the child is subsequently staged with a stimulated Tg and diagnostic whole-body scan (DxWBS).
- Thyroid nuclear scintigraphy for the evaluation of newly diagnosed PTC should only be pursued if the patient presents with a suppressed TSH.

Recommended surgical approach:

- For the majority of children, total thyroidectomy (TT) is recommended due to high incidence of bilateral and multifocal disease. Central neck dissection (CND) is recommended for children with malignant cytology and clinical evidence of gross extrathyroidal invasion and/ or locoregional metastasis on preoperative staging or intraoperative findings.
- Lateral neck dissection should be performed on patients with preoperative cytologic evidence of metastases to the lateral neck. Measurement of Tg in the FNA washout can be considered if the cytological diagnosis is equivocal.

Complications of Surgery:

- Pediatric thyroid surgery should ideally be performed by an experienced high-volume surgeon as this is associated with lower complications rates, decreased hospital stay, and lower cost.
- Transient or permanent hypoparathyroidism is the most common endocrine complication. The early incorporation of calcium and calcitriol in patients at high risk for hypocalcemia may decrease the risks of symptomatic hypocalcemia. Postoperative iPTH level of <10–15 pg/mL is associated with an increased risk of clinically significant hypocalcemia.
- Surgery specific, non–endocrine-related complications include recurrent laryngeal nerve damage, spinal accessory nerve injury, and Horner syndrome.

Tumor classification system for Pediatric PTC:

- Children with PTC should be stratified into risk levels (ATA Pediatric Low-, Intermediate-, or High-Risk) based on clinical presentation, tumor size, and evidence of regional invasion and metastasis, using the AJCC TNM classification system.
- Patients found to have disease confined to the thyroid gland, as well as incidental evidence of minimal, microscopic disease confined to lymph nodes in the central neck (level VI), fall into the **ATA Pediatric Low-Risk level**. Also **incidentally discovered PTC** on histological examination of thyroid tissue resected for other benign diseases such as Graves' disease, autonomous nodule (s), or multinodular goiter should be managed as ATA Pediatric Low-Risk PTC.
- The presence of extensive, extrathyroidal invasion or metastasis defines patients at greater risk for persistent regional or distant metastasis. Patients with these features are categorized within the **ATA Pediatric Intermediate- or High-Risk levels.**

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- Pediatric patients are considered to have stage II disease if distant metastases are identified (M1); otherwise, all pediatric patients are considered to have stage I disease.

Postoperative staging:

- Postoperative staging is usually performed within 12 weeks after surgery (Fig. 2) and allows for stratification of patients who may or may not benefit from further therapy, to include additional surgery or ^{131}I therapy. ATA Pediatric Low-Risk patients may be initially assessed and followed with a TSH-suppressed Tg alone. In contrast, a TSH-stimulated Tg and a DxWBS is typically recommended to assess for evidence of persistent disease in ATA Pediatric Intermediate- and High-Risk patients. Additional imaging, to include neck US and/ or hybrid imaging using SPECT/CT, may be used. Whenever possible, ^{123}I (preferable) or lowest possible activity of ^{131}I should be used for the DxWBS.

^{131}I therapy:

- ^{131}I is indicated for treatment of iodine-avid persistent locoregional or nodal disease that cannot be resected, as well as known or presumed iodine-avid distant metastases.
- In order to facilitate ^{131}I uptake by residual iodine-avid cancer, the TSH level should be > 30 mIU/L. This can be achieved in almost all children by withdrawing LT4 for ⩾14 days, else rhTSH may be considered.
- A post-treatment WBS is recommended for all children 4–7 days after ^{131}I therapy. Acute and long-term side effects of ^{131}I therapy should be anticipated and properly managed.

Surveillance and Follow-Up of PTC in Children

- Tg serves as a sensitive tumor marker in the evaluation, treatment, and long-term follow-up of DTC in children, even in children not previously treated with ^{131}I.
- An undetectable TSH-stimulated Tg (with negative TgAb) identifies patients in remission with a very high probability to remain completely free of disease during follow-up.

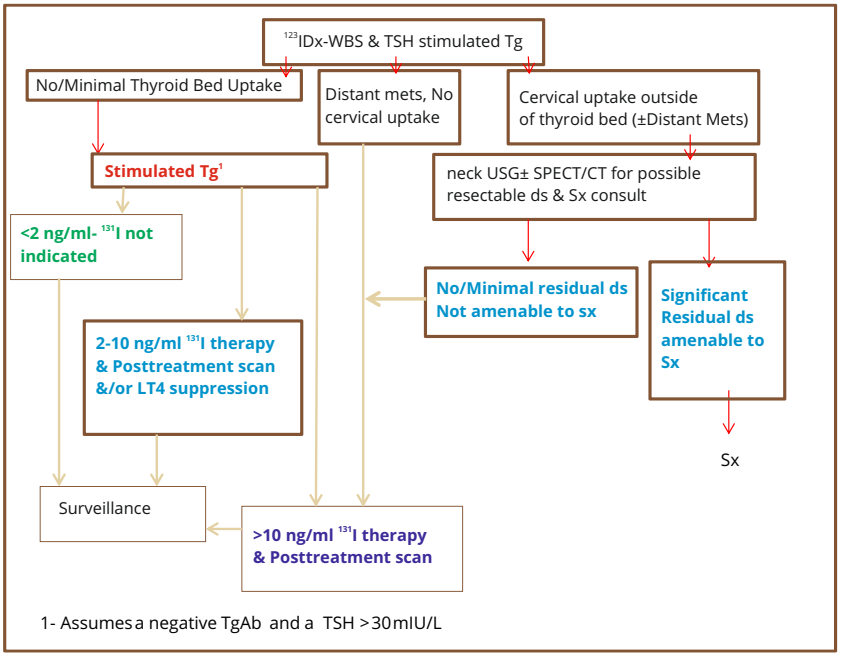

Fig. 2: Postoperative staging of Pediatric Thyroid cancer. Modified from Francis GL, Waguespack SG, Bauer AJ, et al; Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015;25(7):716–759.

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- Detection of a low-level TSH-stimulated Tg (<10 ng/mL) in a patient who has undergone surgery and therapeutic ^{131}I may indicate persistent disease.
- Increasing or frankly elevated levels of TSH-stimulated Tg (>10 ng/mL) warrant further evaluation to localize disease and requires decision as to whether additional surgery and/ or ^{131}I therapy or continued observation would be beneficial.
- Neck US should be performed periodically. Follow-up beyond 5 years should be individualized based on recurrence risk.

Goals and Potential Risks of TSH Suppression Therapy:

- In children with no evidence of disease, the TSH can be normalized to the low-normal range after an appropriate period of surveillance. Potential risks can be similar to Graves' disease but might not be fully applicable in children with DTC (table 1).

Table 1: Goals of TSH Suppression Therapy

ATA Pediatric risk level	Low	Intermediate	High
Goal of TSH suppression	0.5-1.0 mIU/L	0.1-0.5 mIU/L	<0.1 mIU/L

Detailed algorithm for residual/ recurrent disease as well as distant metastasis in pediatric patients is given in the Guidelines.

Mini Review

Newborn screening for congenital hypothyroidism: Some basic technical concepts

Dr Siddhnath Sudhanshu, Assistant Professor Pediatric Endocrinology
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Congenital hypothyroidism (CH) is the most common cause of preventable mental retardation. The incidence of primary CH in India has been found to be higher than the worldwide reported incidence obtained from various nation-wide newborn screening (NBS) programs [1-3]. This, coupled with the high birth rate in India, poses the risk of adding a significantly high number of mentally compromised infants and children to our population every year, if NBS for CH is not practiced appropriately. NBS is the most effective way to detect and treat an infant with CH before it becomes too late. Unfortunately, there is no national NBS program in India at present. Healthcare providers (HCP) who are aware of the vital importance of NBS for CH, provide this as per their own settings and facilities. But given the immense diversity of the healthcare facilities across India, every setting has its own challenges and opportunities. NBS guidelines for CH which are adapted to acknowledge the diverse healthcare settings in India are available, and can be of immense help and guidance for HCP in India who wish to provide this service [4].

Understanding the basics of key technical aspects of NBS is essential for the HCP to be able to adapt to and perform NBS for CH appropriately in all kinds of healthcare settings.

The first step is to choose the ideal screening test which should have high sensitivity and specificity and should be cost-effective. Primary TSH-based NBS for CH has been adopted in most parts of the world [5-7]. Although a T4-based screen is more sensitive to detect central hypothyroidism, mass NBS is not targeted to detect this rare disorder.

The biochemical assay used to measure TSH depends on the type of sample obtained for the screening test. For a dried blood spot (DBS) sample on a filter paper sent to a centralized NBS laboratory, an immuno-fluorescence or colorimetric neonatal-TSH kit assay (e.g., Perkin Elmer® or Biorad®) is used; while for a serum sample sent to a routine laboratory, an ELISA or chemiluminescence TSH-assay is employed.

The TSH value can be expressed in both whole-blood units as well as serum units. If it is a serum sample analyzed in a routine laboratory, then the measured TSH will be expressed in serum units only. For a filter paper DBS sample analyzed in a centralized NBS laboratory, the TSH is measured primarily in whole-blood units, but can be reported in derived serum units as well (by multiplying the whole-blood units value by 2.2; to adjust for the hematocrit) if the machine is preset to report TSH in serum units. Since the serum units value of TSH is 2.2 times the whole blood units value, this becomes absolutely essential to mention and acknowledge the reporting units of the measured TSH value clearly and uniformly. For the sake of uniformity and clarity, the guidelines and recommendations on NBS for CH have expressed all the cut-off values of TSH in serum units [4]. So, for DBS samples, we must always be careful to check the reporting units of TSH first, before analyzing it against the cut-off values.

Sample collection is the most crucial aspect of any screening program. Understanding of the basics of sample collection for NBS for CH is vital as an inappropriate sample would fail the very purpose of the NBS. Various terminologies are used regarding the NBS sample for CH (cord blood sample vs. heel-prick sample vs. filter paper sample vs. serum sample etc.), which can be confusing. It is important to note that the samples are primarily just two types: cord blood and postnatal. A cord blood sample is taken at the time of birth; ideally the postnatal sample is taken after 48-72 hours of birth, in order to avoid the neonatal TSH surge which may result in false positive screen reports and also a high recall rate for confirmatory venous sample for TSH and T4 [8]. Cord blood and postnatal sampling have their own advantages and disadvantages, but for all practical purposes, either of them can be sent for NBS: the same TSH cut-off values have been recommended for both. Cord blood sampling is very useful in centers with early-discharge policy [4, 9, 10].

Whether the NBS sample is transported to the laboratory as filter paper DBS or as serum, depends on the existing clinical settings and the laboratory facilities. Where a centralized NBS laboratory facility is available, the sample has to be sent as a filter paper DBS. A postnatal filter paper DBS sample can be collected very conveniently using heel-prick method. Care is essential to use the appropriate technique to ensure a good DBS. Even if the cord blood sample is collected, it can also be sent to the centralized NBS laboratory as a filter paper DBS sample by laying the collected cord blood sample immediately onto a filter paper and allowing it to dry-up. Where centralized NBS laboratory facility is not available, the NBS sample has to be sent to the routine laboratory as serum. A cord blood serum sample can be conveniently and directly sent, but to collect a postnatal sample, venipuncture of the

neonate is necessary. So in the absence of a centralized NBS facility, it is safer and more convenient to collect the cord blood serum sample for NBS, because issues of poor acceptance and poor compliance can crop up with postnatal venipuncture. The majority of HCP in our country would not have access to a centralized NBS laboratory, nor is it necessary: close and effective co-ordination between the gynecologists and the pediatricians of the concerned center would ensure universal NBS.

All samples should have careful and correct recording of the identification of the newborn and contact details, which are essential for prompt communication with the parents in screen-positive cases needing recall for collecting sample for repeat or confirmatory testing.

To conclude, every newborn must be screened for CH. Either the cord blood or the postnatal sample can be collected for a primary TSH-based screening, and sent either as a filter paper DBS or serum sample for further processing. The reporting unit of TSH value must be checked for DBS samples to decide the cut-off values provided in the Guidelines. Finally, it is everyone's responsibility to keep spreading awareness regarding NBS for CH among HCP, to maximize the number of newborns screened.

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Non Thyroidal Illess Syndrome

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Non thyroidal illness syndrome (NTIS) or Sick Euthyroid syndrome is a common entity. Due to the acute stress of illness, there is a shift of energy expenditure with alterations in catabolism and anabolism (1). In pediatric patients, it has been described mostly in critically ill patients with septic shock (2-4), oncological problems (5, 6), cardiac surgery (7, 8) or diabetic ketoacidosis. It is also seen in situations like anorexia nervosa.

Thyroid function tests in NTIS

Illness Severity	Free T3	Free T4	Reverse T3	TSH
Mild	↓	Normal	↑	Normal
Moderate	↓ ↓	N, ↑ ↓	↑ ↑	N, ↓
Severe	↓ ↓ ↓	↓	↑	↓ ↓
Recovery	↓	↓	↑	↑

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Pathogenesis of NTIS

Changes at level of		Mechanism	Pathophysiology
CENTER	**Hypothalamus**	TRH expression is suppressed	Increased D2 activity leads to increased T3 at pituitary level cytokine-induced increase in D1 expression in the pituitary.
	Iatrogenic	TSH release is suppressed	Glucocorticoids reduce TSH release Carbamazepine, oxcarbemazepine and valproic acid, may alter pituitary responsiveness to TRH
PERIPHERY	**Peripheral hormone availability**	Conversion of T4 to biologically inactive rT3	D3 expression induced in the liver and skeletal muscle
	Thyroid gland	Down regulationof T4 and T3 secretion	Cytokines suppresses thyroglobulin expression and secretion

Impact of NTIS on outcome of a patient

Literature shows that lower serum T4 level and a lower T3/rT3 ratio were independently associated with prolonged stay in the PICU. However, in neonates the results are conflicting (9); the association between TSH and clinical outcome is less clear.

Implications of NTIS

The association between the severity of NTIS and worsening of clinical outcomes has been established, but it is unclear whether NTIS is beneficial or harmful (10). Recent studies suggest the acute, peripheral inactivation of thyroid hormone may be beneficial, while the slower, central decrease of TSH and thence suppression of thyroid hormones, appears harmful, so the possibility of intervention at this point may be explored.

Need for intervention

In pediatric patients, treatment with T3 in critically ill children has been attempted only in children undergoing cardiac bypass surgery (11). In the majority of these trials, treatment with T3 has no impact on length of PICU stay or myocardial activity. The multicenter TRICC (Triiodothyronine Supplementation in Infants and Children Undergoing Cardiopulmonary Bypass) RCT in critically ill children younger than 2 years has shown no effect of T3 infusion on time to endotracheal extubation, but suggested a potential benefit in children younger than 5 months (11). As of now, there is no evidence or studies conducted in children other than cardiac surgeries with regard to T3 treatment, and since excessive levels of T3 can be harmful, no recommendations can be made. Treatment with T4 with RCT has been studied in adults only (12) and has shown no benefits.

Conclusion

NTIS is a common entity in the pediatric population; despite definite progress in its understanding, the pathophysiology is still not completely understood. As of now, it seems best to closely monitor children with individualized repeat thyroid function testing. No recommendations can be made for treatment with T3 or T4.

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A review on preventive approaches through diet to thyroid peroxidase

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The most common autoimmune endocrine diseases are autoimmune thyroid disorders (ATDs), characterized by autoantibodies directed against thyroperoxidase (TPO), thyrotropin receptor antibodies (TRAb), and thyroglobulin (Tg). Thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) are the two most common antibodies in serum, found among distinct populations. Further, TPOAb is a membrane-bound protein available in the thyroid gland that aids in thyroid hormone production catalysis in the apical membrane of follicular cells (1). Immunity factors are essential in this regard because they can produce abnormal antigen presentation due to cell death, virus or tumor invasion, or viral cell damage (e.g., Yersinia enterocolitica). Inheritance of specific Human leukocyte antigens (HLA), T-cell receptor (TCR), or other antigen presentation protein genes, abnormal T or B cells, or clonal deletion failure can all lead to self-reactive cells. Another pathophysiologic event is a typical immune system maturation failure, which causes fetal T and B cells to autoreact (2).

Vegetables of the *Brassicaceae* family like turnips, cauliflower are said to be rich in indole glucosinolate. Data from animal studies postulate that this compound metabolizes into thiocynate that inhibits Na/iodide symporter and blocks thyroid hormone synthesis. Also, goitrogens like isoflavone have been found in soy products that inhibits thyroid hormone synthesis. There is lack of pediatric data on impact of restriction of *Brassicaceae* vegetables and soy milk on goiter size in children.

Thyroid disruptors are synthetic chemicals and bioactive compounds that may interfere with specific aspect of thyroid hormone metabolism. The common examples include: dietary factors (polyunsaturated fatty acids, pepper, fish oil, coffee, cinnamon, grapes); pesticides used in vegetable cultivation and compounds like bisphenol A and phthalates used in food storage (3). Most of them are based on animal studies and not on pediatric data. The relationship between these disruptors and pediatric autoimmune thyroid disease is not clear.

Authors	Key maneuver	Key observation
Mitra Nourbaksh et al (4)	Authors measured Selenium, selenoprotein P (SPP), Glutathione peroxidase (GPX) in children and adolescents with Hashimoto's thyroiditis, hypothyroidism and controls.	The levels of selenium, SPP and GPX in cases and controls were not significantly different. Authors did not observe any correlation between GPX or SPP and antithyroid peroxidase or anti-thyroglobulin antibodies.
A C Medin et al (5)	Authors studied 1722 subjects, ages 4-, 9-, and 13-y from Norway.	3-36% subjects, especially adolescent girls, were at risk of suboptimal intake of iodine. Milk, milk products, fish, cheese and shellfish were sources of iodine rather than supplements.
Hydrovitz JD (6)	Described a case of goiter in a 4 mo infant on soya bean milk feeding.	The goiter regressed in a week of substitution of soy milk with whole milk.
S Palaniappan et al (7)	Authors studied 43 children with AITD and 43 children with simple goiter.	A higher urine iodine excretion was observed in subjects with AITD vs. those with simple goiter. There was a positive correlation between antithyroid peroxidase antibody and urine iodine excretion.

Key message:

The relationship between dietary factors and thyroid autoimmunity in the pediatric and adolescent age group is unclear. There is a need for more prospective studies to understand this relationship. However, one should ensure that growing children receive their recommended daily allowance of iodine to prevent iodine deficiency, especially in the adolescent age group. Also, gluten restriction should be advised in those with associated celiac disease.

Dietary factors and role of thyroid disruptors in pediatric autoimmune thyroid disease are exciting areas of potential research in the future.

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CASE REPORTS :
Van Wyk-Grumbach syndrome (VWGS)

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Introduction:
Van Wyk and Grumbach first described an unusual clinical spectrum of hypothyroidism, isosexual precocious puberty and ovarian mass, which is now termed VWGS [1]. VWGS presents as precocious menarche, breast development, galactorrhea, delayed bone age, and multicystic ovaries in combination with long-standing primary hypothyroidism [1]. The authors report an interesting case of VWGS they encountered.

Case report
A 5.2 year old girl (figure-1) was referred to the Endocrine Clinic with concerns of bleeding per vagina and poor height gain. She was the second born child to non-consanguineous parents, with normal height. There was no history of hypothyroidism in the family. Her height was 82.5 cm (height SD score - 5.3), weight 10.14 kg (weight SD score - 3.8) and BMI was 14.8 kg/m^2 (BMI Z-score of +0.3). The upper segment: lower segment ratio was 1.4:1. Sexual maturity rating was Tanner B1, PH1 with menarche. Baseline investigations revealed bone age of 3y, anemia (hemoglobin 5.3gm/dL), normal renal functions, LH 0.31 mIU/L (N:0.7-0.9 mIU/L), FSH 9.1 mIU/L (N: 0.23-2.6 mIU/L), estradiol 26.2 pg/mL (N: <22 pg/mL); TSH > 500 µIU/mL, low free T4: 0.07 ng/dL (N: 0.96-1.77 ng/dL): consistent with primary hypothyroidism. Ultrasound revealed bulky uterus (59x47x25 mm) and enlarged right ovary (75x45 mm) with ovarian cysts. Antithyroid peroxidase antibody and antithyroglobulin antibody could not be tested owing to logistic reasons.

Discussion:
Precocious puberty may be a rare presentation of untreated hypothyroidism, while delayed puberty is the norm [2]. A presentation of premature menarche with short stature and delayed bone age, absence of breast development and lack of axillary and pubic hair differentiates this condition from other causes of pubertal precocity which would have advanced height and bone age, with thelarche and pubarche [3]. The isosexual precocious puberty in VWGS is always incomplete [4]. The etiology of hypothyroidism in VWGS is often lymphocytic thyroiditis, though it also has been reported in association with unrecognized congenital hypothyroidism [5]. The gonadotropins and TSH are glycoproteins which share the same α-subunit, though the β-subunit is specific to each hormone. Anasti *et al.* have demonstrated the interaction of recombinant TSH with FSH receptor to stimulate adenylate cyclase activity and shown that recombinant TSH acted as a competitive inhibitor of FSH [6]. Therefore, extremely high levels of TSH act through the FSH receptors ("specificity spillover") to induce FSH-like effects on the gonads, causing multicystic ovaries, uterine enlargement with bleeding and breast enlargement [7,8]. Sella turcica enlargement may be occasionally seen and is attributable to thyrotroph hyperplasia. These changes are reversed with thyroxin replacement. The final height prognosis may be poor because there may not be enough time for complete catch-up growth.

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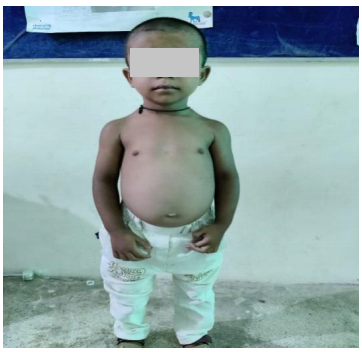
Key message:
Incomplete sexual precocity with delayed bone age and stunting should direct alert a clinician to a possibility of Van Wyk Grumbach syndrome.



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Levothyroxine Absorption Test

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The mainstay of therapy for hypothyroidism is levothyroxine (LT4). The typical dose of LT4 required for adults is 1.5-1.6 mcg/kg/day. Some patients remain hypothyroid even after titrating to high doses of the medication. There are several possible explanations for higher than typical levothyroxine requirements, including decreased gut absorption, increased metabolism and non-adherence.

Non-adherence is one of the main causes of uncontrolled hypothyroidism. Levothyroxine absorption takes place primarily in the jejunum and ileum of the small intestine. Approximately 80% of an orally administered dose is absorbed in the fasting state and reaches peak concentration in 2 hours after oral administration.

Case Report
A 19 year 2 month old female, a known case of congenital hypothyroidism, was on treatment since childhood. She presented 4 months late for follow up, with history of increased tiredness and hairfall. Her weight was 58.8 kg, height 153 cm, BMI 25.12 kg/m^2 (overweight range). She had dry skin and delayed relaxation of reflexes. She was on oral Thyronorm in the dose of 2.9 mcg/kg/day.

Her TSH level was 76.95 mcIU/mL (normal 0.4-4.3mcIU/mL) and free T4 0.45 ng/dl (normal 0.6-2.0 ng/dL). The patient was questioned about the method and timing of taking the tablets. The mother confirmed that she herself gives the tablets regularly and that no doses were missed. Compliance was reinforced, medication was continued at the same dose and the thyroid function tested after 1 month. TSH was 79.33 mcIU/mL and FT4 0.62 ng/dL. After repeated probing and questioning, the patient gave the history of taking generic thyroxine tablet from a local pharmacy for the past 3 months due to non-availability of Tab Thyronorm. The LT4 absorption test was planned with Tab Eltroxin (different brand) to rule out true malabsorption.

We used the short levothyroxine absorption test over 4 hours and measured FT4 as it changes quickly and helps predict absorption of an orally administered dose of LT4. The patient was advised to come in the overnight fasting state without taking the morning dose of medication, and was not allowed to eat anything during the test. The basal sample was taken at 8 am for FT4 and TSH. A supervised dose of LT4 (10 mcg/kg i.e. 600 mcg) of tablet Eltroxin was given and observed until she swallowed it. Blood was collected hourly for 4h for FT4 measurement. The baseline FT4 level at 0 min was 0.719 ng/dL and TSH was 76.33 mcIU/mL. After administration of Eltroxin, the FT4 was 1.9 ng/dL, 1.96 ng/dL, 1.94 ng/dL and 1.95 ng/dL at 1h, 2h, 3h and 4h, respectively. We observed that the peak concentration was more than 2.5 times the basal level, thereby ruling out true malabsorption in our patient. She was advised to continue Tab Eltroxin 150 mcg daily on empty stomach. The thyroid functions were repeated after 1 month with TSH 7.470 mcIU/mL and FT4 1.070 ng/dL.

The LT4 absorption test can help distinguishing malabsorption from pseudo-malabsorption. Benvenga et al. reported that FT4 rises linearly in the first 60–90 min before plateauing out. The absorption peak of LT4 is more than 70%, occurring at about 2h in euthyroid subjects, and 3h in those with untreated primary hypothyroidism. Approximately 62–82% of orally administered LT4 is absorbed within the first 3h of intake after an overnight fast. Intestinal absorption can be impaired by several drugs including sucralfate, calcium carbonate and ferrous sulfate. Drugs such as carbamazepine, phenytoin and phenobarbital increase the metabolism of levothyroxine leading to higher dose requirement.

Patients in the pseudo-malabsorption group are heterogeneous and may vary from grossly non-adherent (hence biochemically and possibly clinically presenting like treatment naive hypothyroidism) to infrequently non-adherent (hence presenting as biochemically mildly hypothyroidism). Here, an LT4 absorption test can help differentiate true malabsorption from non-adherent patients.
An increment of FT4 at 3h of > 0.40 ng/dL in an LT4 absorption test had a sensitivity of 97% and specificity of 80% to rule out true malabsorption. Patients with elevated TSH on an otherwise adequate dose of LT4 can be reliably diagnosed to be non-adherent to treatment with the LT4 absorption test.

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"Lurking Behind the Mask": Papillary thyroid carcinoma in a case of autonomously functioning thyroid nodule- A rare presentation

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Introduction:

Thyroid nodule is a discrete lesion in the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma.[1] Thyroid nodules can be caused by many disorders: benign (colloid nodule, Hashimoto's thyroiditis, simple or hemorrhagic cyst, follicular adenoma and subacute thyroiditis) and malignant (papillary cancer, follicular cancer, hurthle cell cancer, anaplastic cancer, medullary cancer, thyroid lymphoma and metastases). [2] Hot/ autonomously functioning thyroid nodules (AFTN) are benign monoclonal tumors which produce T3 and T4 and concentrate radioiodine on thyroid uptake scan. [3] Hot nodules can present as a single nodule or as toxic multinodular goiters. [3]

Case report:

A 10-year-old girl was brought to the Endocrine Clinic with complaints of tremors of the hand for 2 years, for which she was receiving treatment by a neurologist; neck swelling for 1.5 years; weight loss in spite of a good appetite; palpitations associated with anxiety; fatigue in the evenings; disturbed sleep; and passage of formed stools 4-5 times a day. Her scholastic performance was good. She had no history of dysphagia, hoarseness of voice or prior exposure to radiation. She was born at term to non-consanguineous parents through IVF conception, with a birth weight of 4.2 kg. Her post-natal period was uneventful. Her mother had gestational diabetes mellitus; there was no family history of malignancy or thyroid disorder.

On examination, she appeared emaciated, had a staring look, and tremors of the hands. Her weight was 30.9 kg (25th- 50th centile), height 154.5 cm (97th centile cf. mid-parental height of 161.9cm, which is 50th-75th centile) and BMI 12.9 kg/m2 (3rd centile). She had a goiter of 5cm×10cm on the left side, and no lymphadenopathy (Figure-1). Her TT4 was 8.6mcg/dl, T3 3.2 ng/dl, TSH 0.01 mIU/l, anti-microsomal and anti-thyroglobulin levels were normal. Ultrasonography of the thyroid showed a large heterogenous lesion in the left lobe (Figure-2). Radionuclide thyroid scan was suggestive of an autonomous functioning nodule of the left lobe of the thyroid (Figure-3). FNAC of the nodule showed features of adenomatous hyperplasia. She was started on carbimazole (0.5mg/kg/day) and propranolol. On follow up 4 months later, her weight had increased to 41.8 kg (75th -90th centile) and her symptoms had reduced, but the thyroid nodule had increased in size. Hence a hemithyroidectomy was performed; the histopathology report of classical type of papillary carcinoma was unanticipated as the earlier FNAC was reported normal. The tumor was unifocal with focal capsular invasion and occasional lymphovascular emboli. The isthmus was free of tumor.

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As the histopathology confirmed papillary thyroid carcinoma, she underwent a total thyroidectomy subsequently with central neck dissection. Her postoperative period was uneventful. She underwent radioactive thyroid ablation and was started on oral levothyroxine supplementation.

Discussion:

Palpable thyroid nodules are less common in children than adults but sonographic and/or pathological abnormalities are common (0.2–5% of children, 13% of adolescents).[4] AFTNs have been reported in 5-7.5% of pediatric patients presenting with thyroid nodules. [5] The possibility of malignancy is the major concern in a patient presenting with a thyroid nodule. Cold thyroid nodules are thought to have a higher risk for malignancy compared to AFTN: in pediatric patients, malignancy is present in an average of 26.4% of with cold nodules, [6] and 0-29% in AFTN. [7]

According to the American Thyroid Association, in pediatric patients with an AFTN, a thyroid uptake scan should be done for evaluation; surgical resection is the recommended treatment. Surgery may be deferred if asymptomatic. FNA biopsy is recommended for nodules > 1 cm, with suspicious features on USG neck. A recently published systemic review comparing malignancy rates in hot vs. cold nodules found much lower rates of 3.8-46% in hot nodules, compared to 5-100% in cold nodules, but not as low as expected previously. This metanalysis casts a doubt on the widely adopted recommendation mentioned above, to skip cytologic evaluation of hot nodules assuming a very low malignancy risk. [8] The current case report and recently published systematic review [8] emphasize re-evaluation of malignancy risk in hot nodules. The presence of hyperthyroidism in association with a hyperfunctioning thyroid nodule does not rule out thyroid cancer; all nodules warrant careful evaluation, even in the absence of cervical lymph node invasion.

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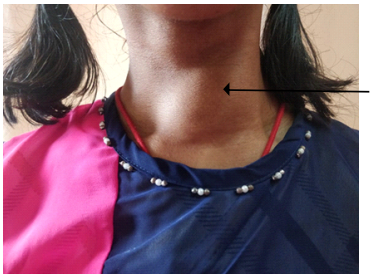

Figure 1:
Left sided swelling in the front of neck showing 10 cm x 5 cm with smooth surface, no palpable lymph nodes in the neck

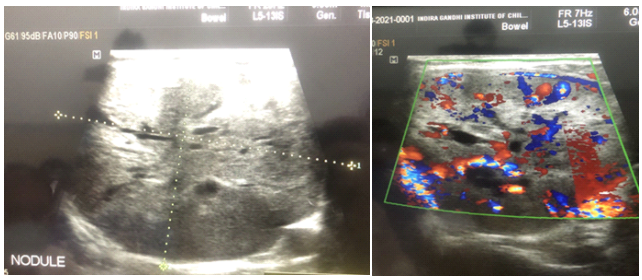

Figure 2:
Ultrasonography of the thyroid showed a large solid heterogenous lesion in the left lobe of the thyroid

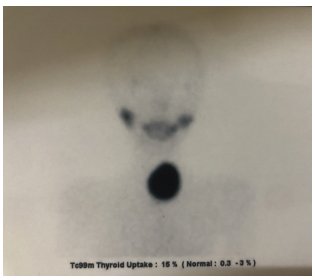

Figure 3:
Radionuclide thyroid scan was suggestive of an autonomous functioning nodule of the left lobe of the thyroid

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Primary Hypothyroidism : Post Levothyroxine Partial Empty Sella Syndrome

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Primary hypothyroidism is a common endocrine disorder in children. Pituitary hormone alterations have been documented in treated primary hypothyroidism patients. An empty sella is a reported association in some of these patients. We report a 9 year-old girl with primary hypothyroidism, in whom empty sella with hypopituitarism were identified on follow up.

Case report:
A 9.8 year old girl presented with weight gain, easy fatiguability, intermittent headaches, puffiness of face and short stature. She was the first child born to 3rd degree consanguineous parents with a history of primary hypothyroidism in two maternal aunts. Her auxology included height 111 cm (below 3rd percentile), weight 24.1 kg, body mass index 19.6 kg/m^2 (in overweight range). Physical examination revealed stage 1b goiter, normal blood pressure, Tanner stage B3, PH1. Hormonal evaluation revealed primary hypothyroidism: the child was initiated on oral thyroxine supplementation at a dose of 75 mcg/day. Biochemical testing was performed periodically, and biochemical euthyroidism was maintained (TSH maintained below 3mIU/L).

Reassessment after 6 months revealed height gain of 2 cm and reduction in BMI by 3.1 kg/m^2, with good improvement in clinical symptomatology. In view of subnormal growth velocity, the child underwent further assessment. IGF-1 was found to be below 3rd percentile for age; MRI brain and sella revealed a small sized pituitary gland with flattening of the anterior pituitary along the floor of sella, which was filled with CSF, suggestive of partial empty sella syndrome. The child was established to have growth hormone (GH) deficiency, while other pituitary hormones tested were normal. Parents were advised GH therapy, which was not possible owing to logistic considerations.

Primary hypothyroidism is characterized by increased TSH secretion, with varying degrees of hyperplasia of the pituitary thyrotrophs.[1] The authors have encountered ten adults with primary hypothyroidism who developed empty sella syndrome. In this report, we describe a pediatric patient with classical goitrous hypothyroidism who had good clinical and biochemical improvement but limited catch up growth due to concomitant GH deficiency, and was found to have empty sella. Pituitary enlargement due to primary hypothyroidism is usually reversible with thyroxine therapy.[2] Very few patients with primary hypothyroidism develop an empty sella: it can be speculated that this occurs only in patients with an abnormal diaphragma sella.[3,4] One should also consider other common possibilities for incomplete catch up including poor compliance and comorbidities like celiac disease and other autoimmune disorders.

Key message: Children with primary hypothyroidism who have incomplete catch up after thyroxine replacement should be evaluated for sellar abnormalities after ruling out common causes like poor compliance and associated autoimmune disorders.

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Pedendoscan

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Farghaly HS, Metwalley KA, Raafat DM, Algowhary M, Said GM: Epicardial Fat Thickness in Children with Subclinical Hypothyroidism and Its Relationship to Subclinical Atherosclerosis: A Pilot Study. Horm Res Paediatr 2019;92:99-105.

The thyroid hormones are essential for the smooth functioning of the cardiovascular system. The visceral fat of the heart, also known as the epicardial adipose tissue, is a new marker which indicates the cardiometabolic health because it is in close proximity to the myocardium and coronary arteries. The authors proposed to evaluate the relation of epicardial fat thickness (EFT) in children with subclinical hypothyroidism (SH) and the future risk of atherosclerosis.
They studied 32 children with SH, matched with the same number of controls. All the participants underwent a thorough anthropometric assessment and measurement of fasting lipids, glucose, insulin, homeostasis model assessment for insulin resistance, highly sensitive-CRP, TSH, FT4, FT3 and antithyroid autoantibodies. EFT was measured by 2D ECHO; carotid intima-media thickness and brachial artery flow-mediated dilation (FMD) responses were measured by non-invasive ultrasound. Compared to controls, patients had higher atherogenic index (AI) and hs-CRP ($p = 0.001$ for each). The patients also had significantly higher EFT ($p = 0.001$) and significantly lower FMD response ($p = 0.001$). In multivariate analysis, EFT values were significantly correlated with TSH (OR 1.2; 95% CI 1.04–1.34; $p = 0.01$), hs-CRP (OR 1.1; 95% CI 1.09–1.14; $p = 0.001$, AI (OR 1.6; 95% CI 1.17–2.03; $p = 0.001$), and FMD response (OR 2.4; 95% CI 1.14–2.53; $p = 0.01$). **The authors concluded that EFT is higher in children with SH compared with controls and associated with lower FMD responses. 2D ECHO could be used to recognise and identify those individuals with SH who are at a higher risk of atherosclerosis.**

Naafs JC, Vendrig LM, Limpens J, van der Lee HJ, Duijnhoven RG, Marchal JP, van Trotsenburg AS, Zwaveling-Soonawala N. Cognitive outcome in congenital central hypothyroidism: a systematic review with meta-analysis of individual patient data. Eur J Endocrinol. 2020 Mar;182(3):351-361.

Systematic review with individual patient data (IPD) meta-analysis was done to provide an overview of cognitive and motor outcome, and quality of life (QoL) in patients with congenital central hypothyroidism (CCH). OVID MEDLINE, EMBASE and PsycInfo were searched from their inception to 11th June 2019. All patients with CCH, either isolated, or with multiple pituitary hormone deficiency (MPHD), were included. Full-scale intelligence quotient (FSIQ) and motor outcome were the primary outcomes measured; a secondary outcome was the assessment of QoL. Following data-extraction, one-stage IPD meta-analysis was performed, fitting a linear mixed model with FSIQ as dependent variable. Random intercepts were fitted for each study. Six studies measuring FSIQ were eligible for meta-analysis, consisting of 30 CCH patients (20 males; 27 MPHD patients).

FSIQ range was wide (64–123). Mean weighted FSIQ was 97 (95% CI: 88–105). 27% had a FSIQ below 85 (⩾1 SD below norm score), and 10% below 70 (⩾2 SD below norm score). There was no significant association between FSIQ and sex or age. Age at treatment initiation was available from three studies only, thus affecting the interpretation of this parameter. To add to this, motor outcome and QoL were each studied in only one study and therefore no quantitative analyses could be performed for these outcomes. **The authors concluded that due to a wide range in FSIQ scores, the results should be interpreted with caution, more so because the analysis included MPHD patients predominantly, and age at treatment initiation was unknown for the majority of patients.**

Ito S, Fujiwara SI, Murahashi R, Nakashima H, Matsuoka S, Ikeda T, Kawaguchi SI, Toda Y, Ban T, Nagayama T, Umino K, Minakata D, Morita K, Nakano H, Yamasaki R, Ashizawa M, Yamamoto C, Hatano K, Sato K, Oh I, Ohmine K, Kanda Y. Clinical association between thyroid disease and immune thrombocytopenia. Ann Hematol. 2021 Feb;100(2):345-352.

Immune thrombocytopenia (ITP) can coexist with any autoimmune disorder including autoimmune thyroid disease. Here, the authors retrospectively reviewed 248 patients presenting between 2000 and 2019 with new onset ITP for whom thyroid function data at diagnosis was available. 74/248 patients had thyroid disease: 36 with overt thyroid disease (13 Graves' disease: GD, and 23 Hashimoto's thyroiditis: HT), and 38 with subclinical thyroid disease (3 hyperthyroidism and 35 hypothyroidism). ITP and thyroid disease were concurrently diagnosed in 54 patients. There was a female sex predominance and positivity for ANA seen in patients with thyroid disease. Platelet-associated immunoglobulin G levels in patients with GD were higher than those in patients with HT. Thrombopoietin-receptor agonist was administered more frequently in patients with thyroid disease. The cumulative incidences of thrombosis, bleeding and overall survival did not differ between patients with and without thyroid disease; nor were the platelet counts different in the two groups. Treatment for thyroid disease in 22 patients improved thrombocytopenia in 21 patients, especially in 4 patients who were not treated for ITP. **This study demonstrated that not only is thyroid disease commonly found in patients with ITP, but also treatment of the thyroid disease may improve thrombocytopenia.**

Vuong HG, Chung DGB, Ngo LM, Bui TQ, Hassell L, Jung CK, Kakudo K, Bychkov A. The Use of the Bethesda System for Reporting Thyroid Cytopathology in Pediatric Thyroid Nodules: A Meta-Analysis. Thyroid. 2021 Aug;31(8):1203-1211.

This meta-analysis investigated the use of Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) in pediatric thyroid nodules. Relevant articles were searched in PubMed and Web of Science. Meta-analysis of proportion and its 95% confidence interval (CI) were calculated utilizing the random-effect model along with subgroup analyses and meta-regression to explore the other heterogenous sources. Egger's regression test and funnel plot visualization were used to scrutinize publication bias.17 articles comprising of 3687 pediatric thyroid nodules were analyzed. TBSRTC outputs, including frequency and risk of malignancy (ROM), for the majority of categories were not statistically different from recently published studies on adult patients. The resection rate (RR) in the pediatric group was significantly higher in most of the categories compared to the adult data: benign, 23.2% [CI = 18.6–27.9] vs. 13.0% [CI = 9.5–16.5]; atypia of undetermined significance/follicular lesion of undetermined significance, 62.6% [CI = 50.3–74.9] vs. 36.2% [CI = 29.9–42.5]; follicular neoplasm/suspicious for follicular neoplasm, 84.3% [CI = 75.2–93.4] vs. 60.5% [CI = 54.5–66.5]; and suspicious for malignancy, 93.8% [CI = 90.1–97.6] vs. 69.7% [CI = 64.0–75.5].

The above analysis projected the use TBSRTC to make clinical decisions for pediatric patients with thyroid nodules. Pediatric patients with benign and indeterminate thyroid nodules had a higher RR than adult counterparts, but ROM of these categories in adults and children was not statistically different, suggesting a potential risk of overtreatment in pediatric patients. However, there is still room for determining the best modalities of treatment and additional tools for risk stratification before we stratify patient management.

Rochmah N, Faizi M, Dewanti C, Suryawan A. Pediatric Quality of Life in Congenital Hypothyroidism: an Indonesian Study. Int J Thyroidol 2020;13:150-154.

Improper treatment of hypothyroidism can affect the cognition and the quality of living. In this cross-sectional study, the authors analysed the correlation between age at first treatment, length of treatment, initial levothyroxine (LT4) dose, and serum levels of free thyroxine (fT4), TSH and pediatric quality of life in patients with congenital hypothyroidism (CH). 41 children (17 girls) with CH who consumed LT4 for at least 3 months during March 2019-December 2019 were studied. The quality of life was assessed from parents' reports using the Pediatric Quality of Life Inventory (PedsQL) generic scale. The mean PedsQL scores in physical and psychosocial functioning were 78.12 (68.75-100) and 233.30 (215-251.67), respectively. Age at first treatment was correlated with physical functioning ($r=-0.501$, $p<0.05$) and psychosocial functioning ($r=-0.440$, $p<0.05$). The initial LT4 dose was negatively correlated with physical functioning ($r=-0.568$, $p<0.05$) and psychosocial functioning ($r=-0.482$, $p<0.05$), but the length of treatment correlated positively with physical functioning ($r=0.776$, $p<0.05$) and psychosocial functioning ($r= -0.852$, $p<0.05$). The serum fT4 and TSH levels were not correlated with quality of life in children with CH ($p>0.05$). **The researchers concluded that the age at first treatment, initial dose of LT4, and length of treatment correlated with quality of life in children with CH.**

Song A, Kim SJ, Kim MS, et al. Long-Term Antithyroid Drug Treatment of Graves' Disease in Children and Adolescents: A 20-Year Single-Center Experience. Front Endocrinol (Lausanne). 2021;12:687834. Published 2021 Jun 14.

Although Graves' disease is the most common form of hyperthyroidism in children, there are some controversies regarding the best mode of treatment and the factors predicting remission or relapse. This retrospective study highlights the clinical profile of 195 children and adolescents with GD treated at a single tertiary institution in Korea (January 2000 to October 2020). The diagnosis of GD was based on clinical features, high thyroxine (FT4), suppressed TSH, and a positive titer of thyrotropin receptor antibodies. Remission was defined as maintenance of euthyroid status for more than six months after discontinuing antithyroid drug (ATD). The mean age at diagnosis was 12.9 ± 3.2 years; 162 patients (83.1%) were female. Among all 195 patients, five underwent thyroidectomy and three underwent radioactive iodine therapy. The mean duration of follow-up and ATD treatment were 5.9 ± 3.8 years and 4.7 ± 3.4 years, respectively. The cumulative remission rates were 3.3%, 19.6%, 34.1%, 43.5%, and 50.6% within 1, 3, 5, 7, and 10 years of starting ATD, respectively. FT4 level at diagnosis ($P = 0.001$) was a predicting factor for remission [HR, 0.717 (95% CI, 0.591 –0.870), $P = 0.001$]. Methimazole (MMI)-related adverse events (AEs) occurred in 11.3% of patients, the most common of which were rash and hematologic abnormalities. Of a total of 26 AEs, 19 (73.1%) occurred within the first month of taking MMI. **The authors concluded that long-term MMI is a useful treatment option before definitive treatment in children and adolescents with GD.**

Zirilli, G., Salzano, G., Corica, D. et al. Thyrotropin serum levels and coexistence with Hashimoto's thyroiditis as predictors of malignancy in children with thyroid nodules. Ital J Pediatr 45, 96 (2019).

Pediatric thyroid cancer (PTC), although rare, has a good prognosis. Thyroid nodules in children, have a greater risk of malignancy, especially those with peculiar clinical and ultrasonographic risk factors. This commentary aims at addressing the possibility of nodular Hashimoto's thyroiditis (HT) and serum TSH levels predisposing to thyroid cancer in the future. According to the available pediatric literature on the relationships between these risk factors and phenotypical expression of Thyroid Cancer (TC) in children, it is possible to conclude that: a) It is not completely clarified if HT per se predisposes to malignancy, or if it represents an incidental histologic finding in cases with TC, or if it may be the result of an immune response against tumoral cells. b) It is unclear whether phenotypic expression of TC is related to HT itself and not the levels of TSH. c) Persistently elevated TSH levels play an independent role as predictors of the likelihood of TC, especially in children. d) Patients with nodular HT and subclinical hypothyroidism need to be treated with Levothyroxine in order to prevent the development of both TC and severe thyroid dysfunction.

Kyrgios I, Giza S, Kotanidou EP, Kleisarchaki A, Tsinopoulou VR, Papadopoulou A, Markantonatou AM, Kanellidou E, Giannakou A, Galli-Tsinopoulou A. l-selenomethionine supplementation in children and adolescents with autoimmune thyroiditis: A randomized double-blind placebo-controlled clinical trial. J Clin Pharm Ther. 2019 Feb;44(1):102-108

As we all know, selenium (Se) administration has been suggested in adults with autoimmune thyroiditis (AT), however there is paucity of data in children and adolescents about this. The researchers proposed to evaluate whether the administration of high dose organic Se (200 μg daily as l-selenomethionine) would have any effect on the antithyroid antibody titres in children and adolescents with AT. 71 children and adolescents, with a mean age of 11.3 ± 0.3 years (range 4.5-17.8), diagnosed with AT (antibodies against thyroid peroxidase[anti-TPO] and/or thyroglobulin [anti-Tg] ⩾ 60 IU/mL, euthyroidism or treated hypothyroidism and goiter on ultrasonography) were randomized to receive 200 μg l-selenomethionine or placebo daily for 6 months. Serum fT4, TSH, anti-TPO and anti-Tg levels were measured, and a thyroid gland US was performed at the beginning of the study and 6 months post-intervention. There was a significantly higher reduction in anti-Tg levels Se group compared to the placebo group (Δ: −70.9 ± 22.1 vs −6.7 ± 60.6 IU/mL, P = 0.021). However, the anti-TPO levels, although low in the Se group, were not significantly lower compared to the control group (Δ: −116.2 ± 68.4 vs +262.8 ± 255.5 IU/mL, P = 0.219). No significant difference in thyroid gland volume was observed between the two study groups (P > 0.05). **This original study suggests the probability of organic Se supplementation helping to reduce anti-Tg levels in children with AT, although larger trials are needed.**

Pitts L, McCormick W, Mick GJ. Congenital Hypothyroidism: 8-Year Experience Using 2 Newborn Screens in Alabama. Horm Res Paediatr. 2019;91(5):319-328.

New-born screening (NBS) protocols for congenital hypothyroidism (CH) are variable, either using TSH alone or TSH with T4, and single or 2-screen. The authors conducted an 8 year retrospective study to note the 3 year clinical outcome of infants diagnosed with CH and screen-positive CH using a 2-screen protocol that measures both TSH and T4 on all samples. The records of 168 patients with CH who were detected by first (NBS1): 139 (83%), or second (NBS2): 29 (17%) in Alabama (2009–2016) were collated. Clinical follow-up established the final diagnoses in 146 patients, including a subset of 72 patients with eutopic glands.

Screening T4 concentrations were 45% reduced in NBS2 compared to NBS1 (p = 0.0002). Thyroid dysgenesis was present in 55% of NBS1 patients while all in NBS2 were eutopic. Follow-up of 146 patients confirmed permanent CH in 92 NBS1 patients (75%) and 5 of NBS2 (20%). Hispanic infants were detected by NBS1 only: 93% had permanent CH. In patients with eutopic, permanent CH, dyshormonogenesis was confirmed in 23% of NBS1 patients and 40% of NBS2. One case of central CH was detected by each screen. This study was the first 2-screen study to incorporate thyroid ultrasound. **The authors concluded that the 2-screen approach helps in identifying clinically significant permanent thyroid dysfunction, including dyshormonogenesis and central hypothyroidism, because 4 of 5 second-screen infants with permanent CH had no risk factors for CH; these infants would otherwise not have been detected.**

Drug Review

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Use of Levothyroxine/ Liothyronine Combinations in Treating Hypothyroidism

Thyroinine (T3) is the active form of thyroid hormone which is responsible for the metabolic actions. The use of levothyroxine (LT4) in treatment of hypothyroidism is based on the premise of its conversion into T3 in adequate amounts by the enzyme deiodinase, thus normalizing the raised TSH levels, to achieve pituitary euthyroidism. However, animal studies have shown residual lag in normalization of T3 levels at the tissue level even when adequate thyroxine (T4) and TSH levels have been achieved. Thyroidectomised animals achieved normal tissue T3 and T4 levels when they were supplemented with liothyronine (Lt3).

Studies on hypothyroid adults in clinical settings have shown higher rates of patient dissatisfaction and lag in resolution of clinical symptoms with LT4 alone. A combination therapy of LT3 + LT4 has been used in such adults under research settings. Adult studies are yet to ascertain the suitability in those with low serum levels of T3 or as measured by magnitude of change in serum T3 on LT4 monotherapy. There is limited literature available on use of the combination therapy in childhood. Those with substantially low endogenous thyroid hormone secretion, like severe congenital hypothyroidism (CH) and primary hypothyroidism with myxedema may perhaps do better with the LT4 + LT3 combination.

The drug is usually substituted for LT4 in a ratio of 1:3 (LT3:LT4), known as *pharmacological equivalence* even though the physiological concentration of T3:T4 in-vivo is 1: 14. The usual dose used in adult studies varies between 3.25-10 ug per day in two to three divided doses in combination with LT4. The levels of T3 peak after administration, reaching maximum concentration in 1.8-2.4h, with a half-life of 22-22.9h. The dosing of LT3 is therefore advisable three times a day instead of a daily dose. A few clinical trials have used a twice a day dosing regimen for ease of administration.

A study in children with CH and central resistance to T4 showed better reduction in mean TSH, lower odds of raised TSH >5 or >10 mIU/L, and T4 elevation with the use of combination therapy of LT3 (variable dose 2.5-10 ug/day) and LT4. This combination achieved biochemical euthyroidism in this subgroup, though the potential benefit of normalizing TSH was unexplored. Liothyronine has also been used in successful and faster restoration of thyroid hormones in myxedema. However, the pediatric experience is limited at present.

The following may be potential issues with use of combination therapy in children:

a. The non-availability of LT3 in Indian settings is a limitation, with concern of added cost.
b. The interpretation of TSH on LT3 preparations is difficult.
c. Patients on LT3 would need monitoring of total T3 (preferable) and fT3. These measurements may be difficult and inaccurate unless performed using tandem-mass spectrometry. fT3 levels show higher pulsatility than fT4, which may be difficult to interpret in the absence of age-wise reference values. The measurement is also subject to variations in dosing (frequency, dose, time of day) and calorie deprivation (which affects total T3 levels).
d. The influence of LT4 + LT3 combination therapy on cancer incidence is still unknown in adults. A prolonged use of this agent in childhood may have higher safety concerns.
e. The effect of genetic variations like Thr92Ala polymorphism of the type 2 deiodinase is associated with decreased T3 delivery to the tissues. Such findings may play a role as genetic determinants of eligibility for the combination therapy in the future

To conclude, at present there is insufficient evidence to recommend the use of combination therapy of LT4 + LT3 for hypothyroidism in childhood. More robust scientific evidence is required before the agent can be recommended for use in those with poorer and/or slower response to Lt4.

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History Corner – George Redmayne Murray and Myxedema

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George Redmayne Murray (1865–1939) was born on 20 June 1865 at Newcastle, the eldest son of William Murray (a physician) and Frances Mary. He studied at Eton College and Trinity College, Cambridge, graduating in 1886, completing MB in 1889, and MD in 1896. Aiming at a career in experimental medicine, he visited medical clinics in Berlin and Paris 1889-1890, returning to Newcastle in 1891. He worked as a pathologist in the Hospital for Sick Children, and was lecturer in bacteriology and comparative pathology in the University of Durham College of Medicine.

Murray devised an effective treatment for myxedema by the injection of an extract of sheep thyroid. This was the first successful hormone replacement therapy. It removed the doubts towards organotherapy in Britain. In February 1891, he showed a patient with myxoedema at a meeting of the Northumberland and Durham Medical Society in Newcastle, and suggested that '*it would be worthwhile to try the hypodermic injection of an emulsion or extract of the thyroid gland of the sheep*'. He obtained permission from the patient, and at the October meeting, he showed her greatly improved after six months' treatment. These findings were published in the British Medical Journal in 1891, as were further cases in 1892. The effectiveness of the treatment was rapidly confirmed. Hector WG Mackenzie and EL Fox separately introduced oral treatment in 1892, and Murray's first patient was then treated with oral thyroid extracts for many years.

Murray married Annie Katharine in 1892. They had three sons, two of whom were killed in the First World War, and a daughter.

Murray was appointed Heath Professor of Comparative Pathology at Durham in 1893, and physician to the Royal Victoria Infirmary at Newcastle in 1898. In 1908 he was appointed Professor of Systematic Medicine at Manchester University, which carried with it the post of physician to the Manchester Royal Infirmary. He did not return to experimental medicine, occupying himself in teaching, medical practice, and university administration. He retired in 1925 from active work, because of increasing angina, and died at his home in Cheshire, in 1939.

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Biochemistry Corner

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Case Presentation

An 8-day old male baby delivered by normal vaginal delivery came with a report of newborn screening by dried blood spot (DBS) on whole blood of TSH 12 mIU/L. The parents were reassured that it was nothing to worry about as the TSH was < 20mIU/L, but they consulted a pediatric endocrinologist, concerned that the level was more than the normal range. The pediatric endocrinologist converted the DBS result of TSH 12 mIU/L on whole blood unit to serum unit by correcting for hematocrit, by multiplying by 2.2, so the TSH value was interpreted as 26.4. The baby was advised venous T4 and TSH sample. The result showed T4 of 24 µg/dL and TSH of 5.9 mIU/L, suggestive of hyperthyroidism. However, before advising other tests, a FT4 test was done from same sample: it was 1.75 ng/dL, which is normal for the baby's age. There was no history of Grave's disease in the mother; but history of hyperthyroidism found in the father being treated with antithyroid drugs, which he had stopped as he had no symptoms. His father and his elder brother also showed thyroid hormone results similar to those of the neonate. His thyroid binding globulin (TBG) level was within the normal range. On the basis of these findings, he was suspected to have familial dysalbuminemic hyperthyroxinemia (FDH). Therefore, all report of TSH and FT4 were considered normal and he was advised that no treatment was needed.

Analysis

If the TSH measured from a DBS is expressed in whole blood units, serum units may be derived by multiplying the whole blood units value by 2.2 (to adjust for the hematocrit). The expression of serum or whole blood units for TSH results should be clearly specified and uniform. (1). Several genetic abnormalities of the iodothyronine-binding serum proteins have been described and are manifest at birth. These include complete TBG deficiency, partial TBG deficiency, TBG excess, transthyretin (TTR) (prealbumin) variants, and FDH. Total T4 may be high/ low, but fT4 is normal and the patients are therefore euthyroid. Sometimes, these abnormalities are picked up by screening programs which measure total T4. An elevated total T4 is at least 10-fold more likely to be due to TBG excess or FDH than due to Graves' disease or transplacental passage of TSH receptor antibody (TRAB) (2). Clinicians interpreting a total T4 report at any age, should be aware of abnormalities in albumin and TBG, which

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FT4, instead of total T4, is measured by an ever-increasing number of clinical laboratories but, depending on the assay method, fT4 can also be spuriously elevated in FDH. Hence the clinician must consider the clinical context and the serum TSH to avoid an erroneous diagnosis of hyperthyroidism (3).

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Patient corner

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Isaac Asimov

Isaac Asimov, the well-known America writer, was born in Russia in 1920, and grew up in America. He wrote or edited more than 500 works in science-fiction, and stated the "three laws of robotics". His famous contributions include the Foundation trilogy: Foundation (1951), *Foundation and Empire* (1952), and *Second Foundation* (1953); a collection of stories on robots compiled as *I, Robot* (1950) and *The Bicentennial Man* (1972).

At age 52 years, he developed a visible lump in the neck, which was diagnosed as papillary thyroid cancer. He underwent a hemithyroidectomy successfully and received replacement thyroid hormones, surviving more than 20 years after the thyroid surgery. He died at age 72 years of renal failure and cardiovascular disease.

Apart from science fiction, Isaac Asimov also wrote humor and limericks. One of his quotes reads- *"If my doctor told me I had only six minutes to live, I wouldn't brood. I'd type a little faster"*. He remains an inspiration for students and young scientists. He will always be remembered for his futuristic and rationalistic views which questioned pseudoscientific beliefs. "*In life, unlike chess, the game continues after checkmate*." — Isaac Asimov

Gail Devers

Gail Devers was an American born (1966) athlete from California. At the young age of 22, she developed features of hyperthyroidism which were unnoticed. She qualified for the 1988 Olympics' 100m hurdles but was eliminated from the semi-finals due to her health condition. It was later that she was diagnosed with Graves' disease, which was treated with radioactive iodine and thyroid hormone replacement. She developed pedal edema and skin blisters during her treatment with RAIU.

She recovered from her illness; valiantly returned to win a silver medal at the 1992 World Championships, and went on to win three Olympic gold medals subsequently. She held the record for the fastest time at 60 m hurdles at 7.86 seconds at the age of 40 years in 2007. She is a 13-time USA indoor and outdoor 100m hurdles champion; and a two-time winner of the Excellence in Sports Performance Yearly (ESPY) for Women's Track & Field athlete of the year.

Her perseverance and journey have been filmed in the 1996 television movie, "Run for the Dream: The Gail Devers Story". She was elected into the National Track and Field Hall of Fame in 2011, and in the US Olympic Hall of Fame in 2012. Her book "Gail Devers My Life in Story: Stronger" was released in 2015.

As she writes, *"Every accomplishment starts with the decision to try"*.

Inspirational Patient story

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In 2005, an apparently well, girl child was born to non-consanguineous parents at term gestation. Just like any normal day in the labor ward of an unassuming private medical college hospital, the first-time parents were elated and distributed sweets to everyone. However, the hospital had just started the newborn screening (NBS) program for congenital hypothyroidism (CH) using filter paper test. Doctors informed the parents about the benefits of doing an NBS; fortunately, the parents agreed to do the test. On day 3 of life, the heel prick sample for NBS for CH was sent. The report came in 2 weeks, as it could not be processed in-house due to logistic reasons. TSH by NBS was > 100 µIU/mL. Immediately the parents were informed telephonically and called back. A confirmatory venous sample for TSH, TT4, and TT3 was sent and was found to have elevated TSH and low TT4 and TT3. There was no family history of hypothyroidism. The baby was immediately started on thyroxine supplementation, and biochemical monitoring done once in 3-4 months as per guidelines at that time. She was growing well and attaining normal developmental milestones.

At age 5 years, "Trial off therapy" was done, and imaging done after stopping thyroxine. US and ^{99}Tc scan of the neck showed absent thyroid shadow and uptake respectively. Parents were explained about agenesis, and need for lifelong thyroxine replacement. She was admitted in a CBSE school, has been academically competitive, always scored the highest marks in her class; and was also a part of the school volleyball team for a few years. She attained menarche at age 12y, and has regular menstrual cycles. Currently, she is 16 years old, 158 cm, studying in 10th standard, and preparing robustly for her exams. Throughout the years, the family has always been rigorously compliant about replacement and testing, never missing a single consultation. ***Let's give a thumbs-up for the child and the family in being very compliant with the therapy, proving that CH patients can achieve academically as well as in sports activities.*** NBS for CH is a very simple procedure, requires a little blood and small sum of money. Treatment of CH is simple and not expensive. On the other hand, missing the diagnosis has devastating lifelong consequences. All practitioners should be aware about NBS and every newborn must be screened for CH.

Newborn screening for hypothyroidism: Spreading Awareness

Dr Sirisha Kusuma B, Consultant Pediatric Endocrinologist
Rainbow Children's Hospital, Hyderabad

Congenital hypothyroidism (CH) is the most common cause of preventable intellectual disability. As per the latest ICMR data, the overall prevalence of CH in India is 1 in 722 births, and if babies with transient hypothyroidism are excluded, the prevalence is 1:1130[1]. If identified and treated within 2-4 weeks of life, these infants will have normal intellect.

However, as the majority are asymptomatic in early life, less than a third get diagnosed before 3 months.

Initiated in 1970s, newborn screening (NBS) for CH has become the standard of care in most developed countries, in addition to screening for many other metabolic diseases in the same dried blood spot (DBS). As of 2015 in Asia: China, Thailand, and Malaysia have functional, government-sponsored NBS with 85-95% coverage[2]. In 2013, the Rashtriya Bal Swasthya Karyakram (RBSK) program of the Ministry of Health and Family Welfare, India, incorporated CH as an optional health condition to be screened for. RBSK has provisions for early identification and treatment of metabolic defects (in DBS by heel prick) like CH, Congenital Adrenal Hyperplasia (CAH) and Glucose-6- Phosphate Dehydrogenase (G6PD). However, this is possible only if facilities for sample collection, centralized laboratory and follow-up of affected newborn are available at the state level[3]. This makes the state health ministry primarily responsible, and years later NBS materialized only in three states/Union Territories, Chandigarh (since 2007), Kerala (since 2013), and Goa (2008-2013 and again since 2018)[4].

Adding to the limitations of the public health sector, the poor coverage of NBS in the private sector is also extremely concerning. There is a need to heighten awareness among pediatricians, neonatologists, and obstetricians regarding the importance of NBS for CH, create and sustain motivation, and provide easy access to up-to-date diagnosis and treatment algorithms. The last requisite has been met by the ISPAE CH guidelines published in 2018. There is a much greater unmet need of spreading awareness among health care workers and the general public, regarding the criticality of NBS for CH, and how a small blood test performed at the crucial time can make such a huge difference.

As a step forward to achieve these goals, in 2019, with financial support from Global Pediatric Endocrinology and Diabetes (GPED) and Novo Nordisk, ISPAE invited members to develop public awareness videos. We had the opportunity to contribute by creating these videos in Hindi as well as in Telugu and Tamil, with the clear message that universal NBS for CH is a must. Now, it is time we all ISPAE members carry the torch and disseminate this message.

https://youtu.be/boYu-esSLMM
https://youtu.be/S4kGFOBFVaA
https://youtu.be/nAMfZE0r_w8

Sirisha Kusuma B
Dhivyalakshmi J

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Update: ISPAE Academic & Clinical Education Series (ACES)

Prof Mahesh Maheshwari, In-charge Pediatric Endocrinology
AIIMS, Bhopal

ISPAE's flagship academic program, Academic and Clinical Education Series (ACES), is being conducted virtually on the last Saturday of every month, as interactive meetings. The ACES series is generating a great deal of interest among postgraduate residents, fellows and pediatric endocrinologists in as well as outside India.

In June the theme was ***"Pubertal Disorders".*** Two interesting cases were discussed. NROB1 mutation presenting as adrenal insufficiency and central precocious puberty (CPP) was presented by Dr Versha Rani Rai and moderated by Dr Ahila Ayyavoo. Combined pituitary hormone deficiency (CPHD) presenting as delayed puberty was presented by Dr Saniya Gupta and moderated by Dr Nalini Shah. "Peripheral precocious puberty: Treatment options" was discussed by Dr Erica Eugster from Indiana, US, while "Delayed puberty in males: Approach and management" was discussed by Dr Romina Grinspon from CEDIE, Argentina.

In July the theme was ***"Disorder/ Differences of Sex Development".*** Two interesting cases were discussed. Dr Angad Kumar presented Ambiguous Genitalia - A Diagnostic Dilemma, moderated by Dr Vandana Jain. Dr Amulya Yalamanchi presented a rare and interesting cause of DSD, managed successfully by a multidisciplinary team, moderated by Dr Belinda George. International experts Dr S Faisal Ahmad from Glasgow talked on "XY DSD - Challenges in Diagnosis & Management" and Dr Jayant Radhakrishnan from Chicago, US, given his insights on "Contentious issues surrounding genital surgery among children with DSDs". In August the theme was "***Neonatal Diabetes and Neonatal Hypoglycemia***". Two interesting cases were discussed. Dr Karishma Bhade presented a case of Neonatal diabetes with skeletal dysplasia, moderated by Dr Anurag Bajpai. Dr Lokesh Sharma's case of Neonatal Hyperinsulinism was moderated by Dr Subrata Dey. Dr Senthil Senniappan from Liverpool, UK, given the expert talk on "Management of Neonatal hypoglycemia with a special focus on newer therapies". Dr. Radha Venkateshan from MDRF Chennai also shared her experience about genetics in neonatal diabetes and responses to diazoxide and sulphonylureas.

We are looking forward to another exciting meeting on the last Saturday every month. We encourage you to visit our YouTube channel to access some of the cases and lectures from previous meetings. The link to the YouTube channel is available at the ISPAE official website: www.ispae.org.in

ISPAE ACES series - Pubertal disorders learning pearls

Dr Pragya Mangla, Assistant Professor, Dept. of Endocrinology
University College of Medical Sciences and GTB Hospital, Delhi

1. **Case discussion: NROB1 mutation presenting as adrenal insufficiency and CPP - Dr Versha Rani Rai/ Dr Ahila Ayyavoo**
    - Adrenal hypoplasia congenita (AHC) is an X-linked condition, caused mostly by a nonsense or missense mutation in the NROB1 gene.

- It can have varied presentation of pubertal disorders: underdeveloped reproductive tissues, cryptorchidism, infertility (azoospermia); usually presents with hypo-gonadotropic hypogonadism (HH), but can have hypergonadotropic hypogonadism, peripheral precocious puberty (mainly due to Leydig cell hypoplasia) or CPP.
- Similar to DAX-1 mutation, different members of the same pedigree can present with hypogonadism, arrested puberty or precocious puberty.
- The adrenal insufficiency has a bimodal presentation: during infancy, and beyond 7 years of age.
- Babies with SGA can have chronic respiratory distress and bronchopulmonary dysplasia.
- As part of large contiguous chromosomal deletion on a segment of X chromosome, these patients can additionally have Duchenne muscular dystrophy, glycerol kinase deficiency and DAX-1 gene deletion.
- Carrier females are mostly asymptomatic.

2. Peripheral precocious puberty: Treatment options - Dr Erica Eugster

a)**McCune Albright Syndrome (MAS) -**

- In girls, PP is often diagnosed < 6y of age, with large ovarian cysts, very high serum estradiol and suppressed gonadotropins. Can present as sudden onset painless vaginal bleeding with acute breast enlargement. Surgical management for the ovarian cysts may not be warranted.
- Natural history of PP is pleomorphic with unpredictable intervals between bleeding; may have extended periods of quiescence. A subset of girls can have frequent vaginal bleeding, linear growth acceleration, advanced skeletal maturation and poor prognosis for adult height.
- In boys, autonomous testicular function with episodic testosterone elevation is seen. Leydig cell hyperplasia is also seen.
- Isolated macroorchidism and testicular microlithiasis is more common.
- Growth Hormone excess is seen in 18-20% cases – therefore, annually IGF-1 and random GH should be done.
- Only 15% of children needed medical therapy for PP over 7.6y of follow up.
- Treatment Goals: a) halting vaginal bleeding (girls) / slowing pubertal progression (boys) and b) slowing growth velocity (GV) and rate of skeletal maturation
- Tamoxifen or letrozole are the best therapeutic options as long term follow up is reassuring.
- Boys - Mostly aromatase inhibitors and androgen receptor blocker (ARB) [Anastrozole/ Letrozole + Bicalutamide, Testolactone/ Letrozole + Spironolactone] are given together. Serum testosterone increases with ARB.
- GnRH analogue to be given in both boys and girls if CPP ensues.

Girls – Drugs	Key points
1. Medroxyproges-terone Acetate	May control vaginal bleeds, but doubtful efficacy for bone age (BA) progression
2. Ketoconazole	Potential for hepatic toxicity
3. Anti-estrogens - Current standard of care	
a. Aromatase inhibitors (mainly 3rd generation)	Anastrozole found to be completely ineffective in treatment of MAS in girls. Letrozole can halt menses, slow BA advancement, and decrease growth velocity (GV), but no change in ovarian and uterine volumes
b. Fulvestrant (pure estrogen receptor blocker)	Is effective in halting bleeds and slowing GV and BA advancement, with no significant side effects.
c. Tamoxifen (selective estrogen receptor modulator)	Is effective in halting bleeds and slowing GV and BA advancement, but increases ovarian and endometrial volume.

b) Familial Male precocious puberty (FMPP)/ Testotoxicosis

- PP in boys by 2-6y of age; can have waxing and waning course of PP.
- Presentation: Secondary sexual development, growth acceleration, advanced skeletal maturation, acne and significant behavioral problems.
- Disproportionately small testicular volume compared to masculinization. Increased spermatogenesis with Leydig cell hypoplasia.
- Treatment in boys is similar to MAS. Ketoconazole can also be given, has good efficacy, but with potential for hepatic toxicity.

1) CPHD presenting as delayed puberty - Dr Saniya Gupta/ Dr Nalini Shah

- 20% cases of delayed puberty in girls and 10% in boys are caused by congenital/ acquired defects of the HP axis.
- For CPHD, genetic testing should be guided by hormonal deficits, extrapituitary manifestations and neuroimaging findings.
- Secondary hypothyroidism as an isolated finding is very rare. Very subtle or mild symptoms are seen, compared to primary hypothyroidism. On thyroxin treatment, TSH levels should not be more than 0.5-1 mIU/L.
- Proper thyroxin and hydrocortisone replacement should be ensured in deficient individuals before conducting GH stimulation test.
- If sampling is done after taking thyroxin dose, serum T4 can be high in 20-25% patients, compared to testing before taking the medication.
- In pituitary stalk interruption syndrome, caution should be exercised while using Gadolinium as a contrast medium for MRI in children. Taking T2-related sequences is preferable.

2) Delayed puberty in males: Approach and management - Dr Romina Grinspon

1) Constitutional delay in puberty (CDP) - In boys, 63% cases of delayed puberty are due to CDP. In 79% history of a 1st degree relative with delayed puberty is given: 1 parent - 45%, both parents - 34%.

2) Central Hypogonadism (CH) -

- CH does not lead to genital ambiguity as Leydig cell function in the 1st trimester of fetal life depends on placental HCG; in 2nd-3rd trimester, it is LH dependent.
- In prepubertal testis >75% mass is formed by Sertoli cells. Microorchidism at birth in CH is mainly caused by insufficient stimulation of Sertoli cells by FSH.
- In CH, when we treat with FSH, the AMH level increases.
- Classical triad: cryptorchidism, micropenis, microorchidism
- Associated clinical phenotype and genes in Kallman syndrome:
    - synkinesia- KAL1 (highly) b) Renal agenesis- KAL1 (possibly)
    - deafness- CHD7 (highly) d) Reversal: FGF8/FGFR1, HS6ST1 (possibly)
    - cleft lip/ palate- FGF8/FGFR1, HS6ST1, CHD7 (possibly)
    - bone anomalies (syndactyly) and dental agenesis: FGF8/FGFR1 (highly)

3) CDP vs. HH

- Consider CH if no puberty till 18y or initial puberty does not progress in next 4y.
- If basal testosterone (T) $\geqslant$ 50 ng/dl - 100% PPV for CDP, 58% NPV for CDP; if morning T $\geqslant$ 20 ng/dl - 77% entered puberty in next 12 months and 100% in 15 months.
- Basal FSH < 1.2 IU/L (IFMA) - PPV 100%, NPV 54% for HH
- Basal LH <0.4 IU/L (IRMA) - PPV 95%, NPV 60% for HH

- If Basal FSH ⩾ 1.2 IU/L, and post GnRH infusion if FSH peak <4.6 IU/L and LH peak <5.8 IU/L – CDP. If more than this (FSH and/or LH) - CDP.
- Some overlap exists in both the groups.
- In CDP- synchronic nocturnal pulsatility of gonadotropins - LH/ FSH/ T - low, AMH/ Inhibin B - High
- In CH - absence of gonadotropin pulses - LH/ FSH/ T - low, AMH/ Inhibin B – low.

ISPAE ACES series - DSD - Learning Pearls

Prof Mahesh Maheshwari, In-charge Pediatric Endocrinology
AIIMS Bhopal

1. Case discussion: Ambiguous Genitalia: Dr Angad Kumar/ Dr Vandana Jain

1. XX DSD with palpable gonads has two differential diagnoses: 1. Testicular DSD 2. Ovo - testicular DSD.
2. AMH is a marker of functional testicular tissue.
3. AMH helps in differentiation between bilateral cryptorchidism and anorchia.

Expert talk - XY DSD- Challenges in Diagnosis & Management: Dr S Faisal Ahmad

1. Genetic vs Endocrine / Sequential vs Parallel evaluation is debatable.
2. Emphasized the concept of collaboration and bench marking.
3. Establishing a rapport with patient/ parents is important.
4. External Masculanisation score plays some role in decision of rearing the child.
5. 50 % XY DSD may have a genetic diagnosis.
6. Of the boys with genetic abnormalities, 50 % had normal endocrine function.
7. 90 % XX DSD have CAH.
8. Serum testosterone, 17OHP, karyotyping, pelvic US are most common first line tests.
9. HCG stimulation test is usually a second line test. Prolonged HCG stimulation is required in some cases.
10. 46 XY DSD may be associated with adrenal dysfunction.
11. Multidisciplinary team efforts are needed to manage a DSD.
12. Evaluation during mini puberty may help in some cases especially in life threatening disorders.

2. Case Presentation: A rare & interesting cause of DSD - successful management by multidisciplinary team: Dr Amulya Yalamanchi/ Dr Belinda George

1. DSD should only be managed in centers with a local multidisciplinary committee (LMDC).
2. LMDC should have at least three specialists 1. Pediatrician 2. Pediatric Surgeon 3. Psychiatrist under the chairmanship of Dean/ Director of the institution.
3. Sex assignment should only be done after thorough evaluation and discussion with all stakeholders.
4. Cases of hypospadias with palpable gonads in XY male do not need to go to the LMDC.
5. CAH/XX/ No gonads: LMDC can assign female sex. Avoid clitoroplasty without consent of an Apex Multi-disciplinary committee (AMDC).
6. For other DSDs, involve the AMDC.

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Expert talk: Contentious issues surrounding genital surgery among children with DSDs: Dr Jayant Radhakrishnan

1. In cases of XX DSD, indication to do clitoroplasty should be individualized on a case to case basis
2. Functional effects of genital surgery
   - Cosmetic appearance
   - Sensory changes
   - Adequacy of vaginal introitus
3. A doctor should avoid making judgements and deal honestly with DSD children and their parents.

ISPAE ACES Learning Pearls - Neonatal Diabetes and Hypoglycemia

Prof Mahesh Maheshwari, In-charge Pediatric Endocrinology
AIIMS Bhopal

1. Case discussion: Neonatal Diabetes with Skeletal dysplasia: Dr Karishma Bhade (Jr Resident, Pediatrics, TNMC & BL Nair Hospital, Mumbai)/ Dr Anurag Bajpai

1. Neonatal Diabetes is defined as a rare transient or permanent genetic disorder, which usually requires Insulin therapy.
2. Wolcott Rallison syndrome is a rare autosomal recessive condition with permanent type of insulin dependent neonatal diabetes.
3. Consanguinity, skeletal deformity, liver dysfunction are highly characteristic of this syndrome.
4. Sepsis, neutropenia and hypothyroidism are other associations with WR Syndrome.
5. Genetic test is must in Neonatal Diabetes babies aged less than 6 months, 6 months to 12 months without antibody and children with syndromic facies.

2. Case Presentation: A case of congenital hyperinsulinism: Dr Lokesh Sharma (Sr Resident, SGPGI, Lucknow)/ Dr Subrata Dey

1. Hyperinsulinemia is the most common cause of persistent hypoglycemia.
2. Persistent hypoglycemia is defined as requiring glucose infusion at a rate of 12 mg/kg/min; and/ or persisting beyond 48 hours.
3. Early diagnosis and treatment may prevent irreversible brain damage in congenital hyperinsulinism
4. Collecting the critical sample for metabolic clues during hypoglycemia is important.
5. Diazoxide remains the therapy of choice in responsive patients.

Expert talk: Management of Neonatal hypoglycemia with a special focus on newer therapies: Dr Senthil Seniappan

1. Abnormal neurodevelopment is common in children with transient congenital hyperinsulinism.
2. Hydrocortisone can mask diabetes insipidus.
3. Hypertrichosis, pulmonary hypertension and heart failure are important side effects of diazoxide.
4. Somatostatin analogues are an alternative treatment in children unresponsive to diazoxide.
5. Tachyphylaxis is more common with octreotide.
6. Focal lesions are important to recognise with the help of molecular genetics and PET scanning, as they can be cured by surgery.
7. Surgical treatment of children with unresponsive diffuse CHI gives unsatisfactory outcomes.
8. Exendin scan looks more promising in diagnosing focal lesions than the current standard of care DOPA-PET scan.
9. Sirolimus (mTOR inhibitors) may cause immunosuppression.
10. Intravenous human monoclonal antibody and soluble glucagon are newer promising drugs.

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Events conducted by ISPAE members

Dr Aashima Dabas, Associate Professor, Dept of Pediatrics
MAMC, New Delhi

Online Pediatric Endocrinology CME: Dr Ankita Maheshwari: An online CME was conducted by IAP Indore on 11 July 2021: 10 am - 1 pm, especially addressing practicing pediatricians. The eminent speakers were Drs Vaman Khadilkar, Sudha Rao, M Vijaykumar, Hemchand Prasad, Prashant Patil and Ankita Maheshwari. The topics covered included basics of pediatric endocrinology, rickets, thyroid function tests, atypical genitalia, growth disorders and diabetic ketoacidosis. The meeting was attended by 150 delegates and well appreciated.

Growth & development: Pillars of pediatrics in clinical practice: Online CME: Dr Nikhil Lohiya & Dr Nirali Lohiya: A web CME was organized by AOP Nagpur to enlighten pediatricians on growth and development disorders. Drs Vaman Khadilkar, Samir Dalwai, Leena Srivastava, Hemchand Prasad, Pragya Mangla, Himanshi Dua, Hari Mangtani, Shabina Ahmed, Dinesh Saroj, Kuldeep Sukhdeve, Nirali Lohiya and Nikhil Lohiya were the faculty. The event was awarded 2 MMC credit points; it was sponsored by Novo Nordisk. 150 participants attended.

National Nutrition week celebration: Feeding Smart Right From Start: Online event: Dr Priti Phatale: An online event was conducted by the Pediatric & Adolescent Nutrition Society (PAN), and IAP Nutrition Chapter on the dIAP Platform on 3 Sept 2021: 2.30-4.30 pm. With the objective of creating awareness about obesity and its consequences, the topics discussed were: 'Nutrition Impact on Obesity': Dr Sheetal Gandhi; 'Clinical Approach to Overweight and Obese Children and Adolescents': Dr Preeti Phatale; Panel Discussion: 'Pediatric and Adolescent Nutrition': moderated by Dr Pramod Jog, panelists Drs Upendra Kinjawadekar, Samir Shah, Yashwant Gabhale and Parag Gaikwad. Attended by over 700 participants, the webinar was very informative and insightful. Many doable actions were discussed to reduce the exponential rise in childhood and adolescent obesity.

E-Gurukul: Online 3 day event: Dr Zalak Upadhyay: This online program was organized by the Academy of Pediatrics, Gujarat, with Academy of Pediatrics, Rajkot and Surat, on the E-Gurukul learning platform, under the AOP Gujarat Action plan, for postgraduates, pediatricians with special interest in endocrinology, and pediatric endocrine trainees.

This unique webinar was done in 3 parts. Part 1 was a Pediatric Endocrinology update on 13thJune 2021, attended by 1618 viewers. Part 2 was a PG clinic, including case-based discussion, on 19th June, attended by 510 viewers. A case was presented by a Pediatric Endocrine fellow; the mentor, moderator and experts made it very interactive and interesting with a detailed discussion on history, examination, approach and management. Part 3 was the second half of the Pediatric Endocrinology update on 20th June, viewed by 1080 doctors. Both updates had 4 lectures each, followed by panel discussions, delivered by stalwarts in the field, from India and abroad. The huge success of the program can be attributed to our faculty, good topics, and the quality of learning that E-Gurukul has been providing in all the Pediatric subspecialty branches. All the 3 webinars are available online on the dIAP platform.

Online meetings with children with Type 1 Diabetes and their families: Dr Meena Kumari Mohan: Two meetings were organized on virtual platforms to discuss COVID related challenges faced by affected families with healthcare providers and diabetes educators. The first meeting on 4.4.21 was to discuss the impact of COVID on day to day living, with its positive and negative effects and coping strategies.

The children and adolescents shared and exchanged their ideas. Ten families attended the meeting with good interaction.

The second meeting was organized on 6.6.21, attended by patients, family and extended family members during the lockdown. The disturbances in caring for type 1 diabetes during COVID, the challenges faced with possible solutions, impact of COVID on the eating habits, daily routine, play and exercise were discussed. The meeting was well received. Twenty five families attended: they discussed their issues with diabetes educators. All the parents interacted very well and were able to pick up cues from each other also.

Online meetings with children with Type 1 Diabetes and their families: Dr Meena Chhabra: A virtual series of monthly meetings was initiated from 15th August with the help of RSSDI Delhi Chapter to discuss challenges faced by patients and families with type 1 diabetes (T1D). Each meeting begins with experience sharing by a young person adult with several years of T1D, followed by short talks and discussions. The first meeting on 15th August declared independence from the stress of diabetes! It was moderated by Drs Meena Chhabra and Shalini Jaggi; Ms Avantika Kakkar talked about lessons learned during her 15y journey with diabetes across India, UK and Spain; Dr Rajni Sharma (AIIMS Delhi) talked about whether alternative therapies are advisable in T1D; Dr Preeti Singh (KSCH, Delhi) about conventional vs. analog insulins; Dr Anju Virmani (Max, Rainbow, Delhi) about home BG monitoring, including CGMS; Dr Bhanukiran Bhakhri (PGICH, Noida) about importance of regular reviews including A1c; Dr Aashima Dabas (MAMC, Delhi) about diet; and Dr Anil Vedwal (YDF, Delhi) about exercise including yoga, in diabetes. Over a 100 persons joined in: there was enthusiastic discussion by families on each aspect.

The 19th September was more focused on diet. Moderated by Drs Shalini Jaggi and Anju Virmani, it began with Ms Chhavi Gupta talking about leading a full life: handling T1D, celiac disease (CD), a job, and volunteer work with YDF, while planning to start making and selling gluten-free goodies suitable for T1D. Dr Bhanu discussed the importance of eating a normal diet, and Dr Preeti the way forward for special situations; Dr Meena emphasized how to take care of insulin. She also informed the group about providing poor families with T1D and CD with donated home chakkis (grinders). The families attending were motivated to get the children to earn some money before Diwali using their talents, like making cards/ candles/ food items/ jewelry, for donating to YDF. About 60 persons joined it, and interacted well; a concerned parent asked about how to handle the upcoming reopening of schools.

In keeping with parental concerns, the session on 15th October (Dusshera) aims to burn the evil of Covid and return to school, from which the children have been banished for so long! Mr Samarth will be hosting the session and talking about how he uses diabetes technology in school; Ms Monica sharing her experience with overcoming the fear of diabetes; Dr Aashima on Covid and school; and Dr Ganesh Jevalikar (Max Delhi & Gurgaon) on T1D and school.

Chakkis for children with Type 1 Diabetes and celiac disease: Dr Meena Chhabra: Families who have a child with T1D and CD and are not well off financially, find the expenses of handling both conditions very high. Dr Chhabra has been encouraging her patients with type 2 diabetes to help such children with gluten free supplies. This year, she and 2 others joined hands with YDF Delhi to donate a series of chakkis to such families, which is a more permanent solution than buying gluten free foods. The families can buy gluten free grains, wash and dry them to get rid of wheat contamination, and grind them at home. Because millets are not expensive, this makes managing CD easy. On 18th September, in a short ceremony graced by Ms Bindiya of YDF, the third chakki was presented - the family receiving it

agreed to network with nearby families with CD and allow them to also use it, thus enlarging the benefits of the donation. The next chakki will be donated by a group of middle class families who cannot afford to buy singly and are therefore pooling their donations. This is in keeping with the belief that donating food/ grain to the needy is a very pious act.

Publications by ISPAE members

Dr Deep Dutta

Dutta D, Singla R, Surana V, Sharma M. Efficacy and Safety of Letrozole in the Management of Constitutional Delay in Growth and Puberty: A Systematic Review and Meta-analysis. J Clin Res Pediatr Endocrinol. 2021 Sep 3. doi: 10.4274/jcrpe.galenos.2021.2021.0169. Epub ahead of print. PMID: 34477355

The authors report a meta-analysis on the role of letrozole in the management of CDGP, showing that letrozole was helpful in improving pubertal parameters and height outcomes. An added advantage over injectable testosterone is that letrozole is an oral preparation.

Dr Meena Kumari Mohan

SWEET Registry: Prahalad P, Schwandt A, Besancon S, Mohan M, Obermannova B, Kershaw M, et al. Hemoglobin A1c Trajectories in the First 18 Months After Diabetes Diagnosis in the SWEET Diabetes Registry. Pediatric Diabetes [Under publication]

Dr Anuradha Khadilkar

Mid upper arm circumference in obesity: Khadilkar AV, Khadilkar VV, Gondhalekar KM, Kajale NA, Karkera PH, Prasad M, et al. Nutrition. 2021 [doi:10.1016/j.nut.2021.111401]

Malnutrition is common in developing countries and likely to be seen in older children (> 5yr of age). For early identification of malnutrition, mid upper arm circumference (MUAC) has been suggested as an easy, non-invasive as well as a low-cost method. We have presented MUAC percentiles and cut- offs to screen for over- and under-nutrition in 5-17 years old Indian children and adolescents. The study was a cross-sectional, observational, multicentric study conducted in 7 Indian states (June 2018-November 2019) on healthy 5-17 years old children (n=6680). Cut-offs for MUAC Z-scores for thinness and overnutrition were defined and validated on healthy children (n=726) and in children with cancer (n=500). Cut-offs defined for thinness and for obesity were -0.7 and +1.5 Z-score respectively (corresponding to 25th and 95th percentiles of MUAC for age/height). For ease of use, rounded cut-offs for thinness were 16 and 18.5 cm from 5-9 years and 10-14 years respectively in both genders, and a cut-off of 22 cm in boys and 20 cm in girls from 15-17 years. For obesity, cut-offs of 20 and 25.5 cm from 5-9 years and 10-14 years respectively, in both genders; and 29 cm in boys and 27 cm in girls from 15-17 years are proposed. These data may also be used in children with cancer and other chronic disorders for screening malnutrition.

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Double Puzzle – Trainee's Quiz Section

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Welcome all, to yet another exciting quiz on the thyroid gland. Unjumble the words using the clues given below. Discover the phrase at the end using the numbers.

Clues

1. Pseudohypertrophy of the calf muscles in long standing hypothyroidism.
2. The gene responsible for deiodination using iodotyrosine dehalogenase of DIT and MIT to allow recycling of the iodide.
3. The important micronutrient present in deiodinases.
4. NKX2-1 mutations cause _____ syndrome?
5. This organ has Type 3 iodothyronine monodeiodinase enzymes which degrade T4 to reverse T3 and T3 to 3,3' T2.
6. The most common type of thyroid carcinoma in children.
7. The most important protein useful in outlining the management of differentiated thyroid carcinoma.
8. Hung up reflex is also called as _____ sign.
9. A syndrome of Sensorineural hearing loss and hypothyroidism.
10. An autosomal dominant disorder mostly seen in Hispanic individuals where Free T4 values are normal and total T4 values are high.
11. An X-linked syndrome of severe psychomotor retardation, extrapyramidal signs and seizures combined with mild abnormalities of thyroid function (high T3, low T4, and normal or high TSH).
12. A syndrome of severe long standing hypothyroidism leading to a increased gonadotropin secretion, triggering gonadal activity and hence precocious puberty.
13. The effect wherein excess iodine acutely inhibit organic binding of iodine and thus creates a hypothyroid state.
14. Iodide-induced hyperthyroidism (Low TSH, Low Radioactive iodine uptake).
15. An unusual and old form of exogenous thyrotoxicosis causes by consumption of bovine thyroid in ground beef preparations.
16. What is the sign called when an individual with retrosternal goiter raises his arms leading to facial congestion, respiratory distress and syncope?
17. Classification for cytopathology of thyroid nodule.
18. Large visceral hemangiomas or tumors in infants can cause _____ hypothyroidism.
19. The mutation in this gene causes toxic diffuse thyroid hyperplasia without the pathologic characteristics of autoimmune disease and can have an autosomal dominant inheritance.
20. An X-linked disorder (sometimes associated with colour blindness) resulting in the deficiency of a protein where Free T4 values are normal but Total T4 values are low.

Please send the responses of the quiz to editor.capenews@gmail.com. Successful members will be acknowledged in the next issue of capenews.

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KCHEOR EEBRD AGMNLEIESE

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11

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2

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9

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12 AVN KYW UMRHBAGC

5

13 FOFWL FHKACOIF

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15 HURBAGEMR

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Obesogenic Word Hunt

Dr Diksha Shirodkar
Asst. Professor, Pediatrics and Pediatric Endocrinologist, Yenepoya Medical College and Hospital, Yenepoya University, Mangalore, Karnataka

Search for all the words using the clues given below related to the genetics, neuroendocrine mechanisms, treatment and syndromes of obesity. The words could be arranged in a horizontal, diagonal or a vertical fashion. Look for the colored alphabets to guide you in this maze.
Good luck and Happy Word-Hunting!
Clues:

1. An afferent nerve conveying hunger signals to the Nucleus-Tractus-Solitarius
2. An orexigenic hormone/ peptide.
3. Cocaine/_____Related transcript (CART).
4. The "Reward" neurotransmitter.
5. "Fetal origin of adult disease" is synonymous with the _____Hypothesis
6. IgG2 monoclonal antibody against proprotein convertase subtilisin–kexin type 9 for reduction of LDL.
7. Name the syndrome with retinitis pigmentosa, obesity, kidney dysfunction, polydactyly, behavioural dysfunction and hypogonadism.
8. Name the syndrome with acrocephaly, soft tissue syndactyly, brachy- or agenesis mesophalangy of the hands and feet, preaxial polydactyly, congenital heart disease, mental retardation, hypogonadism, obesity and umbilical hernia.
9. Name the syndrome with intellectual disability, facial dysmorphism, microcephaly, retinal dystrophy, truncal obesity, joint laxity and intermittent neutropenia.
10. Mutation of this gene causes obesity, hypocortisolism and red hair.
11. The _____(one of the vertices of the limbic triangle) transduces fear and stress, which results in increased cortisol release from the adrenal cortex.
12. The children who have a BMI between the 85th to 95th centile on the BMI chart are _____.
13. This part of the hypothalamus is called the central processing unit, integrating the afferent signals and central stimuli for food intake and hunger.
14. This study is performed to assess the severity of obstructive-sleep apnea
15. What does "A" stand for in the abbreviation ROHHAD (a rare serious respiratory and obesity disorder)?
16. An autosomal recessive disorder characterized by progressive cone-rod dystrophy leading to blindness, sensorineural hearing loss, childhood obesity associated with hyperinsulinemia, type 2 diabetes mellitus and dilated cardiomyopathy.
17. A type of gastric-bypass bariatric surgery.
18. US-FDA approved drug for children above 12 years with obesity.
19. An anti-epileptic drug which causes weight loss.
20. A hypothesis in which favorable genes during famine or calorie deficient environment become obesogenic/diabetogenic in the modern world.

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Winners Of the Obesogenic Hunt: Congratulations!

1. ***Dr Aaradhana, Associate Professor, Dept of Pediatrics***
   UCMS & GTBH, Delhi.
2. ***Dr Tejaswini M, Fellow PICU***
   Kovai Medical Center, Coimbatore, Tamil Nadu

Answer

	Q	M	P	**C**	N	P	B	W	R	E	K	R	A	**B**	V	Z	A	C	F	**P**	
	U	C	W	H	A	K	X	E	R	V	Y	L	L	W	Q	I	L	Y	O	Y	
	T	Q	N	K	L	R	R	U	F	H	**O**	A	I	F	J	C	H	M	E	N	
	H	H	D	E	A	U	P	H	P	R	T	I	E	N	O	P	C	B	Y	**A**	
	G	F	T	C	D	I	P	E	L	E	Z	D	G	W	A	S	**A**	D	L	G	
	I	J	F	S	G	Y	T	I	N	Q	U	E	V	R	S	M	O	S	A	B	
	E	F	Y	C	Y	V	S	R	Y	T	L	M	G	**C**	P	U	T	E	J	A	
	W	H	P	Y	M	T	N	F	I	J	E	O	Z	H	O	R	G	Z	B	J	
	R	Y	S	Y	**A**	I	G	K	D	N	N	R	E	U	O	H	C	A	L	F	
	E	I	I	T	O	K	W	F	K	M	J	T	S	M	N	**B**	E	J	**V**	X	
	V	E	Y	F	S	Q	D	P	O	Z	A	N	V	U	U	A	R	N	Q	**R**	
	O	N	Q	I	V	X	N	S	W	M	A	E	U	H	K	R	P	K	I	O	
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	S	A	S	**T**	O	N	E	X	I	D	Y	L	O	C	W	T	G	T	H	E	
	F	P	G	**P**	J	Z	E	P	L	Q	K	W	R	L	O	B	Q	I	J	N	
	W	O	F	I	E	U	E	H	**A**	U	T	O	N	O	M	I	C	A	R	Y	
	O	**D**	B	D	R	I	D	A	L	E	N	G	R	F	K	E	W	N	K	U	
	G	J	O	R	W	**E**	V	O	L	O	C	U	M	A	B	D	Q	A	V	O	
	T	I	R	T	E	T	A	M	A	R	I	P	O	**T**	S	L	B	Q	N	J	

1. VAGUS	6. EVOLOCUMAB	11. AMYGDALA	16. ALSTROM
2. GHRELIN	7. BARDET BIEDL	12. OVERWEIGHT	17. ROUX EN Y
3. AMPHETAMINE	8. CARPENTER	13. VENTROMEDIAL	18. ORLISTAT
4. DOPAMINE	9. COHEN	14. POLYSOMNOGRAPHY	19. TOPIRAMATE
5. BARKER	10. POMC	15. AUTONOMIC	20. THRIFTY

ISPAE

Pediatric Endocrinology for Postgraduates (PEP) VIRTUAL

Under the auspices of the Indian Society for Pediatric & Adolescent Endocrinology (ISPAE)

Exclusively for DNB / MD Pediatrics or DCH Postgraduates

(Held once in 3 months)

22nd Oct -21 (5 – 7pm) Topics: GHD & Rickets

Time	Topic	Speaker	Time slot
5.00	Introduction	Prof Shaila Bhattacharyya, President ISPAE	2 min
5.02	PEP	Prof Raghupathy P, Patron, ISPAE	3 min
5.05	Case 1 Growth hormone deficiency	PG1 Guide 1 Coguide 1 Prof Dr PSN Menon	10 min presentation 30 min discussion
5.45	Case 2 Rickets	PG2 Guide 2 Coguide 2 Prof Rajesh Joshi	10 min presentation 30 min discussion
6.20	OSCE	Dr HemchandPrasad Growth charts (short stature)& Rickets	Interactive session Ans & Qns in chat box 20 min
6.45	How to answer Theory Questions on Short stature & Rickets topics	Dr Amarnath Kulkarni	Outline & division of marks 10 min
6.55	Vote of thanks	Dr Amarnath Kulkarni	5 min

Guide: MD or DNB examiner; Co-guide: Paediatric Endocrinologist (Optional).

Candidates ready to appear for final exam preferred. Certificate from HOD ESSENTIAL.
Instructions for Case presentation: Prepare PPT 10 – 12 slides with clear messages, clinical photos (if any), investigations and short, crisp discussion.

PEP ISPAE Virtual 3:
Topic – 1. Delayed Puberty - Turner Syndrome 2. Diabetes
21st Jan 2022: 5.00 – 7.00 pm

Note: Please share this message with all DNB / MD Paed / DCH trainees.

Dr Amarnath Kulkarni
(9490468388 / WhatsApp)
PEP Cordinator

ISPAE 2021, *Pune*

12th -13th November, 2021

Virtual conference

We are pleased to invite you to the 7th Biennial meeting of the **Indian Society for Pediatric and Adolescent Endocrinology**, scheduled on **12th and 13th November, 2021.**

The theme this year is, **"From Bedside Basics to Molecular Pediatric Endocrinology".** We welcome you to this academic feast!

To register, visit: www.ispaepune2021.com

ISPAE Members	Non-ISPAE Members	Students & accompanying person
Rs. 2,000	Rs. 2,500	Rs. 1,500

International Faculty:

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Dr. Cecilia Camacho Hubner, USA
Dr. Margaret Zacharin, Australia
Prof. Nick Bishop, UK
Dr. Nils Krone, UK
Dr. Ohad Cohen, Israel
Dr. Paul Wadwa, USA
Dr. Piemonti Lorenzo, Italy
Dr. Raja Padidela, UK
Dr. Reiko Horikawa, Japan
Dr. Senthil Senniappan, UK
Dr. Sylvia Estrada, Philippines

A galaxy of national speakers will be part of this scientific extravaganza!

Dr. Vaman Khadilkar
Chairperson, ISPAE 2021

Dr. Anuradha Khadilkar
Chairperson, Local Organizing Committee

Dr. Supriya Gupte
Secretary, ISPAE 2021

Dr. Rahul Jahagirdar
Joint Secretary, ISPAE 2021