Meet the Expert
HANDOUT

These sessions are interactive. Seats are limited and will therefore be allocated on a “first-come, first-served” basis.

Statements on any potential conflict of interest will be shown by the speaker at the beginning of their session.

Opinions and recommendations made by the presenters are not those of ESPE.

Meet the Expert Session
1:1 – 1:2

'Holistic approach to the individual with DSD'

Martine Cools (Gent, Belgium)

Session 1:1: Thursday 19 September at 14:45 - 15:45hrs in Hall B

Session 1:2: Friday 20 September at 08:30 - 09:30hrs in F1

Holistic approach to the individual with DSD

Martine Cools

Department of Pediatrics, Pediatric Endocrinology Service, Ghent University Hospital & Ghent University, Belgium

In this session, two cases will be presented. For case 1, contemporary diagnostic work-up of DSD will be discussed as well as principles of gonadal management. For case 2, we will highlight how to approach atypical genitalia and touch upon the debate of genital surgery, and we will investigate how outcomes can be further improved in the future.

Case 1 is a 2-year old 46,XY boy adopted from Asia who has atypical genitalia. Diagnostic investigations include hormonal analyses and molecular genetic tests. Various protocols for stimulation of testicular testosterone production in childhood circulate, each with their own advantages and limitations (1). AMH is useful in discriminating between gonadal developmental defects and testicular hormone problems. For steroid measurements, mass spectrometry-based methods are gradually replacing immuno-assays, however, both techniques will continue to co-exist in the near future (2). Apart from specific situations where clinical or hormonal features may directly suggest a specific genetically determined condition (eg congenital adrenal hyperplasia (CAH) or androgen insensitivity syndrome (AIS)), whole exome sequencing and analysis of a large panel of DSD-related genes (and candidates) is the most straightforward approach nowadays (3). Updated lists of (candidate) DSD genes can be found at (4, 5). With proper diagnostic work-up, a conclusive molecular genetic diagnosis can be reached in about 50%, but in unresolved cases, the diagnostic process should at least give insight in the type of DSD (gonadal development problem versus hormonal problem) and should be the starting point for establishing a gonadal management plan (6).

DSD patients who have a Y chromosome have an increased risk for malignant germ cell tumors. The risk is high (estimated at 30% or even up to 60% for *WT1* mutations) in cases where gonadal development is incomplete or otherwise disturbed, which is clinically often characterized by low serum AMH, presence of a (hemi)uterus and a pathogenic mutation in one of the genes involved in the gonadal differentiation pathway. The functional capacity of such gonads with regard to hormone production and fertility is mostly limited. In view of the high tumor risk, early gonadal biopsy with expert evaluation is advised to exclude the presence of *in situ* malignant or even preneoplastic lesions, especially in abdominally located gonads. Such gonads should be removed in cases where germ cell neoplasia *in situ* or gonadoblastoma is found, or should be brought into a stable scrotal position in all other cases, in order to facilitate follow-up by (self-)palpation and ultrasound. (Repeat) gonadal biopsy at the end of puberty is indicated for all dysgenetic gonads. In DSD conditions that result from testosterone biosynthesis disorders or androgen resistance, tumor risk is much lower, given their complete testicular differentiation. In such cases, gonadal management is

also guided by other factors such as production of (desired) hormones and their clinical effects and patient preferences (7-11).

In case 2, a newborn diagnosed with CAH is presented. Often a DSD is suspected prenatally nowadays, based on discordance of the fetal phenotype with the results of a NIPT test. Ideally the couple is referred to the DSD team already at this early stage to explain the situation, discuss possible diagnoses and prepare them for the first days, that are often very difficult for parents in view of uncertainty regarding the diagnosis and sex of rearing. An excellent information booklet, called “the first days” is available at www.dsdfamilies.org , and has been translated in many languages. Training of (para)medical staff at the neonatology and maternity departments is crucial in order to provide optimal support for parents, as positive (or negative) experiences in this vulnerable period often have lifelong effects.

The external genitalia score (EGS), a modified version of the external masculinization score (EMS), allows an objective description of the external genitalia along the phenotypic spectrum, uses a gender-neutral vocabulary and can be easily used for registration purposes. Reference values have been established for infants up to the age of 24 months, and also for pre- and dysmature babies. An EGS value below the 10th percentile for age, pregnancy duration or birth weight is proposed as a criterion for referral to a DSD expert team. Measuring the EGS does not require any technical instrument and can be performed in a primary care setting and by caregivers who do not regularly deal with atypical genitalia (Van der Straaten et al, in press).

All current guidelines propose female sex assignment in 46,XX children who have CAH, with the possible exception of severely virilised children initially raised male and who are diagnosed late. Reasons for this approach include preservation of fertility and the observation that gender dysphoria and gender change is rare in 46,XX CAH. However, recent data suggest poor psychosexual outcome and suboptimal surgical results, most notably in women who have no residual 21-OHase activity, i.e. who have a so-called nul mutation (12, 13). This, in combination with criticism against early genital surgery high on the activist and political agenda nowadays, puts forward the option of male sex assignment in severely virilised 46,XX CAH children as a valuable alternative. However, this approach also has important and irreversible consequences on the longer term, such as short final height and the need for oophorectomy and hysterectomy to avoid gynecomastia and urethroragia respectively (14). Personal experience has shown that genital virilisation becomes far less apparent in mild to moderately virilised (Prader II-III) CAH children in the first months and after instauration of appropriate hormonal treatment, rendering the question of early genital surgery completely irrelevant in such cases. More severe virilisation does not regress, however, parental acceptance and understanding of this complex situation seems to be much better than ever anticipated. With adequate support we experience that most parents can deal surprisingly well with unoperated Prader IV-V genital virilisation of their

daughter, at least in the first years of life. In line with this approach, initial contacts are with the teams' pediatric endocrinologist and psychologist only and a first contact with the surgeon is postponed until at least three months after the diagnostic phase.

Long-term outcome data will need to confirm this and other observations and the appropriateness of the new management tendencies, as well as their beneficial and eventual negative effects. This requires standardised longitudinal data collection across centers and at various ages. To facilitate this, guidelines have been proposed very recently by the COST (European Cooperation in Science and Technology) Action "DSDnet", to be found at (Flück CF et al, Eur J Endocrinol 2019, in press), which will also be incorporated in the international i-dsd and i-CAH registries. Further advances and refinements will be made possible through advanced international collaborations and networks such as the European Reference Network for Rare Endocrine Conditions (Rare EndoERN).

References

1. Ahmed SF, Keir L, McNeilly J, Galloway P, O'Toole S, Wallace AM. The concordance between serum anti-Mullerian hormone and testosterone concentrations depends on duration of hCG stimulation in boys undergoing investigation of gonadal function. Clin Endocrinol (Oxf). 2010;72(6):814-9.

2. Kulle A, Krone N, Holterhus PM, Schuler G, Greaves RF, Juul A, et al. Steroid hormone analysis in diagnosis and treatment of DSD: position paper of EU COST Action BM 1303 'DSDnet'. Eur J Endocrinol. 2017;176(5):P1-P9.

3. Audi L, Ahmed SF, Krone N, Cools M, McElreavey K, Holterhus PM, et al. GENETICS IN ENDOCRINOLOGY: Approaches to molecular genetic diagnosis in the management of differences/disorders of sex development (DSD): position paper of EU COST Action BM 1303 "DSDnet". Eur J Endocrinol. 2018.

4. Cools M, Nordenström A, Robeva R, Hall J, Westerveld P, Flück C, et al. Caring for individuals with a difference of sex development (DSD): a Consensus Statement. Nature Reviews Endocrinology. 2018;14(7):415-29.

5. Baetens D, Verdin H, De Baere E, Cools M. Update on the genetics of differences of sex development (DSD). Best practice & research. 2019:101271.

6. Baetens D, Mladenov W, Delle Chiaie B, Menten B, Desloovere A, Iotova V, et al. Extensive clinical, hormonal and genetic screening in a large consecutive series of 46,XY neonates and infants with atypical sexual development. Orphanet journal of rare diseases. 2014;9(1):209.

7. van der Zwan YG, Biermann K, Wolffenbuttel KP, Cools M, Looijenga LH. Gonadal maldevelopment as risk factor for germ cell cancer: towards a clinical decision model. Eur Urol. 2015;67(4):692-701.

8. Cools M, Drop SL, Wolffenbuttel KP, Oosterhuis JW, Looijenga LH. Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. Endocr Rev. 2006;27(5):468-84.

9. Cools M, Looijenga LH, Wolffenbuttel KP, T'Sjoen G. Managing the risk of germ cell tumourigenesis in disorders of sex development patients. Endocrine development. 2014;27:185-96.

10. Cools M, Wolffenbuttel KP, Drop SL, Oosterhuis JW, Looijenga LH. Gonadal development and tumor formation at the crossroads of male and female sex determination. Sex Dev. 2011;5(4):167-80.

11. Tack LJW, Maris E, Looijenga LHJ, Hannema SE, Audi L, Kohler B, et al. Management of Gonads in Adults with Androgen Insensitivity: An International Survey. Hormone research in paediatrics. 2018:1-11.

12. Nordenstrom A. Adult women with 21-hydroxylase deficient congenital adrenal hyperplasia, surgical and psychological aspects. Curr Opin Pediatr. 2011;23(4):436-42.

13. Nordenstrom A, Frisen L, Falhammar H, Filipsson H, Holmdahl G, Janson PO, et al. Sexual function and surgical outcome in women with congenital adrenal hyperplasia due to CYP21A2 deficiency: clinical perspective and the patients' perception. J Clin Endocrinol Metab. 2010;95(8):3633-40.

14. de Jesus LE, Costa EC, Dekermacher S. Gender dysphoria and XX congenital adrenal hyperplasia: how frequent is it? Is male-sex rearing a good idea? J Pediatr Surg. 2019.

Meet the Expert Session
2:1 – 2:2

'The interpretation of abnormal thyroid function tests in children and adolescents'

Carla Moran (Cambridge, United Kingdom)

Session 2:1: Thursday 19 September at 14:45 - 15:45hrs in Hall C

Session 2:2: Saturday 21 September at 08:00 - 09:00hrs in E1

****NO HANDOUT HAS BEEN PROVIDED FOR THIS SESSION****

Meet the Expert Session
3:1 – 3:2

'Turner syndrome - Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International - Turner Syndrome Meeting'

Claus Højbjerg Gravholt (Aarhus, Denmark)

Session 3:1: Thursday 19 September at 17:00 - 18:00hrs in Hall B

Session 3:2: Saturday 21 September at 08:00 - 09:00hrs in Hall B

New international guidelines on Turner Syndrome – MTE handout

Turner Syndrome (TS) is a sex chromosomal abnormality in females, characterized by complete or partly lack of one X chromosome, providing a 45,X karyotype or a mosaic form. It is present in about 25-50 per 100,000 females and can involve multiple organs through all stages of life, necessitating a multidisciplinary approach to care. Recent advances cover all specialty fields involved in the care of girls and women with TS. Recently a new international guideline has been published, based on an international effort with emphasis on 1) diagnostic and genetic issues, 2) growth and development during childhood and adolescence, 3) congenital and acquired cardiovascular disease, 4) transition and adult care, and 5) other comorbidities and neurocognitive issues.

The genetic basis for TS is still unknown, but new data are emerging, pointing towards a much more complicated pattern that previously thought, with involvement of numerous genes both on the X chromosome, but also residing elsewhere in the genome. Likewise, an altered global methylation profile and RNA expression could be involved, all pointing towards changes in the proteome (Figure 1, Gravholt et al, Nat Rev Endocrinol, 2019).

Short stature, ovarian dysgenesis, infertility, and cardiovascular malformations are classic traits in TS, but the phenotypical spectrum is wide. TS is diagnosed at all ages, from intrauterine life, through childhood and adolescence into adult life, with a median age of 15 years.

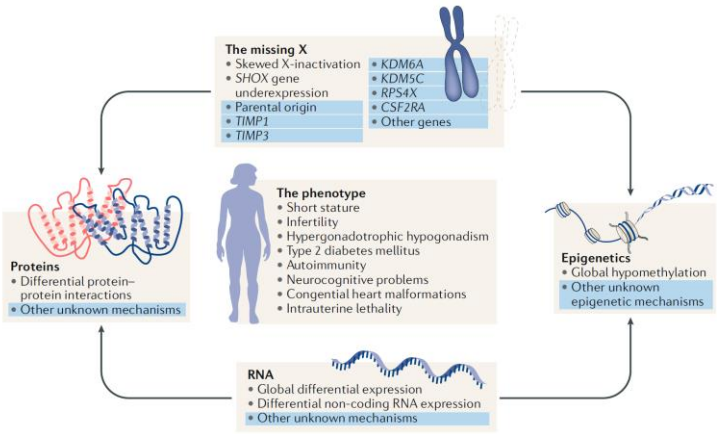


Fig. 1 | **The phenotype and current genomic understanding of Turner syndrome.** The figure depicts the current understanding of the genomics of Turner syndrome, incorporating recent genomic results. In addition, disorders that characterize the phenotype of Turner syndrome are listed. Arrows depict possible, but not proven, pathways. Genes and mechanisms with a possible, but not proven, involvement in the pathogenesis of Turner syndrome are highlighted in blue.

Treatment with growth hormone (GH) during childhood and adolescence allows a considerable gain in adult height. SHOX deficiency explains some of the phenotypic characteristics in TS, principally short stature. Puberty has to be induced in most cases, and female sex hormone replacement therapy should continue during adult years.

In most countries it seems that the transition period from pediatric to adult care is especially vulnerable and the proper framework for transition has not been established.

TS is associated with an increased morbidity due to an increased occurrence of type 1 and 2 diabetes, thyroid disorders, autoimmune diseases, osteoporosis, fractures, ischemic heart disease and aortic dissection as well as congenital heart disease such as coarctation of the aorta, abnormal anatomy of the coronary arteries, and bicuspid aortic valve. Women with TS suffer from premature ovarian failure and subsequent estrogen deficiency. Hence, they share a similar comorbidity pattern as postmenopausal women, just occurring at a younger age. Mortality is threefold higher in TS women than in the female background population.

Spontaneous pubertal development is seen in women with TS, but menarche is present in few (6-9%) 45,X women, of whom about one third continue to have regular menstrual bleedings (2-3%). In contrast, 20-40% of women with mosaic TS and no structural abnormalities of the second X, present with spontaneous menarche, but the great majority proceed to premature ovarian failure. Although rare, natural pregnancies occur in TS women. According to TS guidelines, hormone replacement therapy (HRT) should be initiated in TS women with primary or secondary amenorrhea, preferably starting between 11 and 12 years of age, continuing until the normal age of natural menopause. HRT is necessary to induce puberty, to maintain secondary sex characteristics, and to facilitate uterine growth, appropriate peak bone mass, and possibly neurocognitive function, and it improves the metabolic profile via a positive influence on body composition. However, empiric data on the long-term effects of HRT in women with TS is limited, especially concerning the impact on endocrine conditions, cardiovascular diseases and mortality. Some have raised concerns that HRT in TS women may induce the development of deep venous thrombosis and pulmonary embolism. The proper dose of HRT with female sex steroids has not been established, and, likewise, benefits and/or drawbacks from HRT have not been thoroughly evaluated. Likewise, no framework is in place for continuous follow-up during adult years in many countries. Recent data from the Netherlands and Denmark show that a sizable proportion (13-15%) of females with TS do not receive proper HRT, despite guideline recommendations. New long term data on HRT underscores the importance of securing optimal treatment (Figure 2, Gravholt et al, Nat Rev Endocrinol, 2019).

During the transition period many young females opt out of longitudinal follow-up, probably because they feel well and cannot clearly see the need for continued medical surveillance, which has to be thoroughly and well explained to patients.

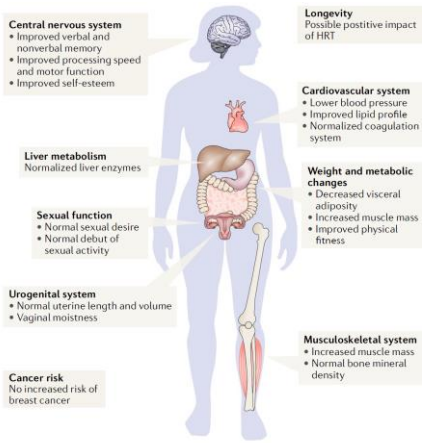
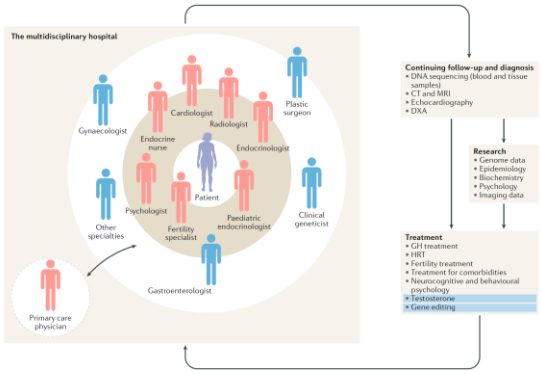


Fig. 2 | **The beneficial effects of hormone replacement therapy in Turner syndrome.** The figure depicts putative beneficial effects of appropriate female sex hormone replacement therapy (HRT) in Turner syndrome. Not all these effects have been thoroughly proved in Turner syndrome.

Morbidity and mortality is quite elevated and many conditions need to be vigorously and routinely checked for and diagnosed as early as possible in order to prevent long-term health consequences. Congenital and acquired heart related morbidity remain the leading cause of death in TS and much of this morbidity can be prevented. In addition, osteoporosis, diabetes, both type 1 and 2, hypothyroidism, obesity and a host of other endocrinological diseases and conditions are seen more frequently in Turner syndrome in the long term. Prevention, intervention and proper treatment is only just being recognized. Hypertension is frequent and can be a forerunner of cardiovascular disease.

Multidisciplinary clinics are recommended in all countries (Figure 3, Gravholt et al, Nat Rev Endocrinol, 2019), with the patient with TS being at the center of attention. We advocate for the creation international collaboration to increase the number of participants in future trials involving TS individuals.



Meet the Expert Session
4:1 – 4:2

'Klinefelter syndrome - when should testosterone be started'

Julia Rohayem (Münster, Germany)

Session 4:1: Thursday 19 September at 17:00 - 18:00hrs in Hall C

Session 4:2: Saturday 21 September at 08:00 - 09:00hrs in E2

****NO HANDOUT HAS BEEN PROVIDED FOR THIS SESSION****

Meet the Expert Session
5:1 – 5:2

'Managing endocrinopathies in McCune-Albright Syndrome'

Daniele Tessaris (Torino, Italy)

Session 5:1: Friday 20 September at 08:30 - 09:30hrs in E1

Session 5:2: Saturday 21 September at 08:00 - 09:00hrs in Hall C

Managing endocrinopathies in McCune-Albright Syndrome

Ovarian system [1, 6, 7]

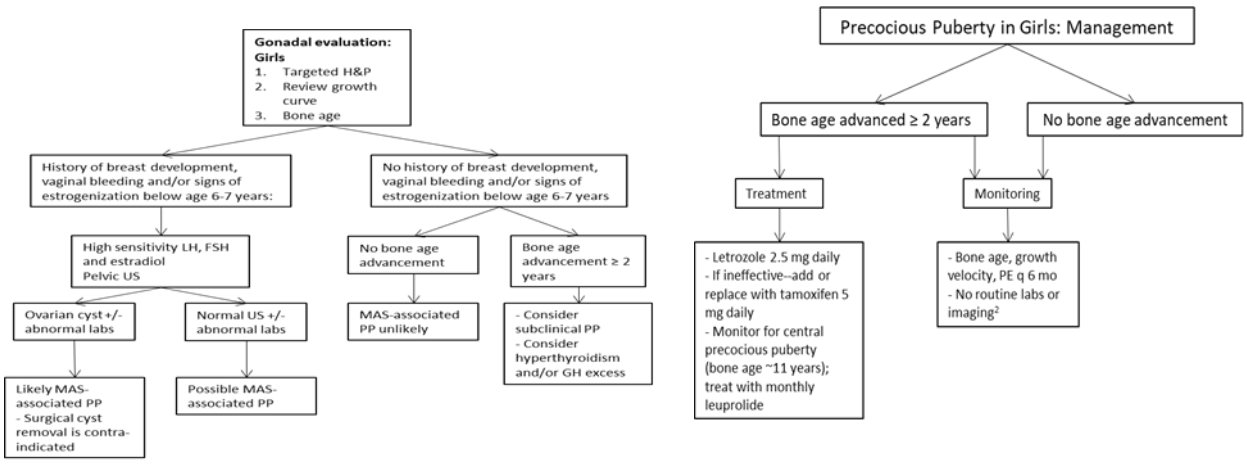
Clinical history and physical examination including history of breast development, vaginal bleeding and/or signs of estrogenization (e.g. below age 8 years), ovarian cysts and irregular menses as defined as menstrual cycles that are shorter than 21 days or longer than 35 days).

All children should have a review of their growth curve for linear growth and a standardised bone age examination. If symptomatic, girls should have a random blood FSH, LH, estradiol and pelvic ultrasound.

In general, ovarian surgery for cysts should be avoided, as disease is usually bilateral. Ovariectomy should only be performed when there is a risk of torsion and after expert consensus. Patients should be informed that the risk of torsion is small.

Treatment for precocious puberty is indicated if bone age is advanced and there is frequent bleeding. Treatment goals in MAS-associated PP are to prevent disabling short stature in adulthood, and to mitigate psychosocial consequences of early sexual development. First line therapy is letrozole, with tamoxifen or fulvestrant as second line or adjuvants. Patients should be monitored for central puberty and the need to add a gonadotropin-releasing hormone analogue (GnRHa), e.g. leuprolide.

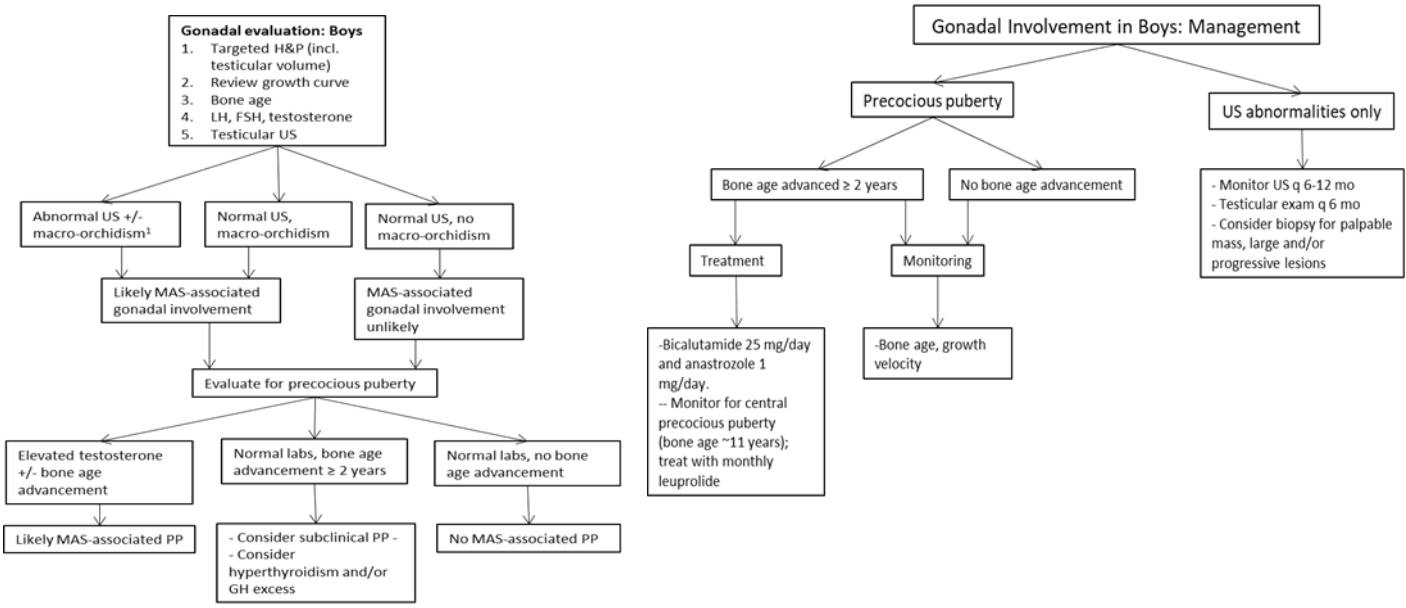
Adult women should be monitored for dysfunctional uterine bleeding because hyperestrogenism can persist also during adult age. For contraception and HRT it may be prudent to avoid additional estrogenic compounds to avoid a possible increase in the risk for breast cancer.



Testicular system [2, 6, 7]

Clinical history including history of pubertal development, and physical examination including Tanner staging including testicular volume. All males should have a testicular ultrasound at baseline. If symptomatic, boys should have measurements of FSH, LH and free testosterone.

In general, surgery should be avoided: ultrasonography of testes follow-up is indicated for *microlithiasis* or other lesions, considering biopsy for rapid changing size or structure. Treatment for precocious puberty is indicated in case of an associated elevated serum testosterone and/or bone age advancement and/or pubertal behavior with psychological discomfort. Combination of testosterone receptor blocker and aromatase inhibitor are needed (for example combination of bicalutamide and anastrazole) as well as monitoring for central precious puberty, in which case GnRHa may need to be added.



Thyroid system [3, 6, 7]

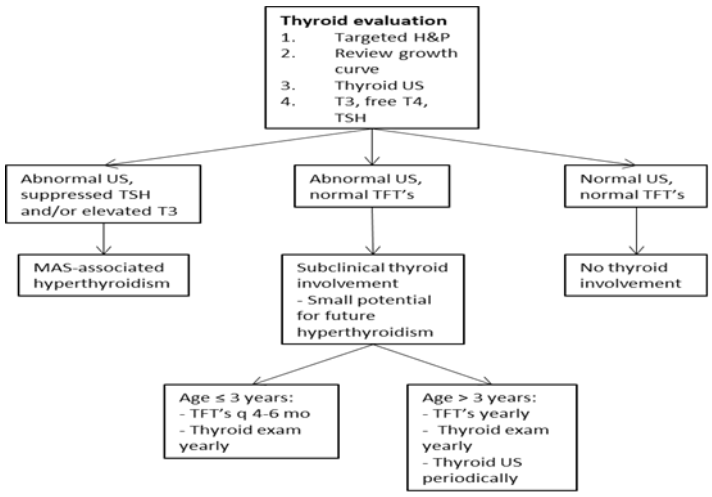
Clinical history and physical examination, measurement of TSH, free T4 , free T3 and thyroid ultrasound. Of note, in FD/MAS, hyperthyroidism is a T3 driven disease due to increased deiodinase activity so that measurement of T3/T4 ratios is helpful, with a ratio of > 20 being indicative of disease.

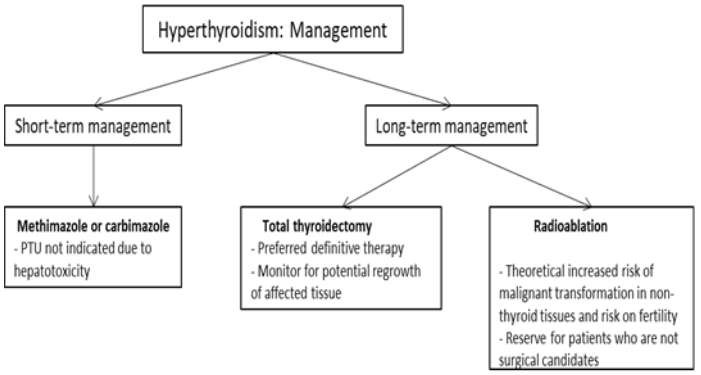
The onset of thyroid disease ranged from 1 to 20 years, a strict monitoring of thyroid function is recommended every 6 months. Satisfactory treatment can be obtained and maintained with antithyroid drugs: methimazole or carbimazole are recommended.

Long-term monitoring with an abnormal US and normal thyroid function tests (TFTs), is also necessary. In case lesions are found, follow-up of patients with FD/MAS-related thyroid disease should be performed according to current guidelines: MAS-associated thyroid disease is correlated with a slight increased risk of thyroid cancer.

Surgery should be considered in cases with clinically significant nodules, compression symptoms, or poorly controlled thyrotoxicosis for which the correct approach might be total thyroidectomy to avoid recurrences. In evaluating radioactive iodine therapy in

hyperthyroidism consider risk on fertility, and of malignancy already increased in MAS patients.





Pituitary system [4, 6, 7]

Clinical history and physical examination including height measurement and comparison with mid-parental height, growth velocity and head circumference SDS. Evaluation of growth velocity may be confounded by bone disease and/or additional endocrinopathies.

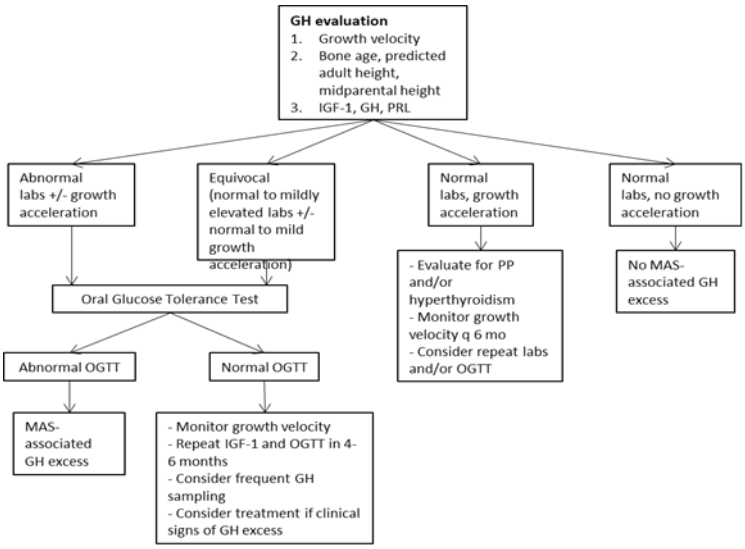
Basal hormonal screening in all patients: random blood test for IGF-1, growth hormone (GH) and prolactin measurements. If there is a laboratory abnormality and/or clinical suspicious of GH-excess, the recommendation is to investigate by e a glucose tolerance test and/or overnight growth hormone sampling to confirm the diagnosis. In GH excess pituitary MRI is recommended to detect pituitary adenomas or altered enhancement, although a normal pituitary MRI does not rule out the possibility of GH excess.

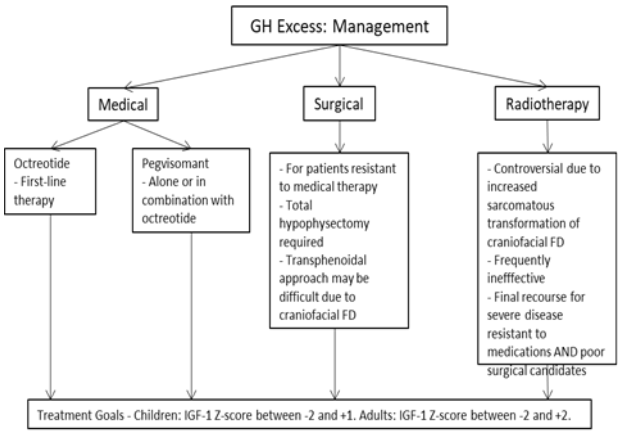
The majority of patients with MAS-associated GH excess will have prolactin co-secretion.

GH excess in MAS is reported to be associated with possible vision loss, macrocephaly, increased postoperative regrowth after craniofacial surgery and other comorbidities.

Medical therapy is the preferred first-line treatment: options include (alone or in combination) octreotide and the growth hormone receptor antagonist pegvisomant. The treatment goals are to achieve an IGF-1 Z-score between − 2 and + 1.

Pituitary surgery as total hypophysectomy is second-line treatment that should be reserved for MAS patients with intractable disease not responsive to pharmacotherapy, it is usually complicated for fibrous dysplasia. Radiotherapy given the risk of sarcomatous transformation and hypopituitarism should be reserved to extremely severe GH excess resistant to pharmacotherapy and in patients not candidates for surgery, as third-line treatment.





Adrenal system [5, 6, 7]

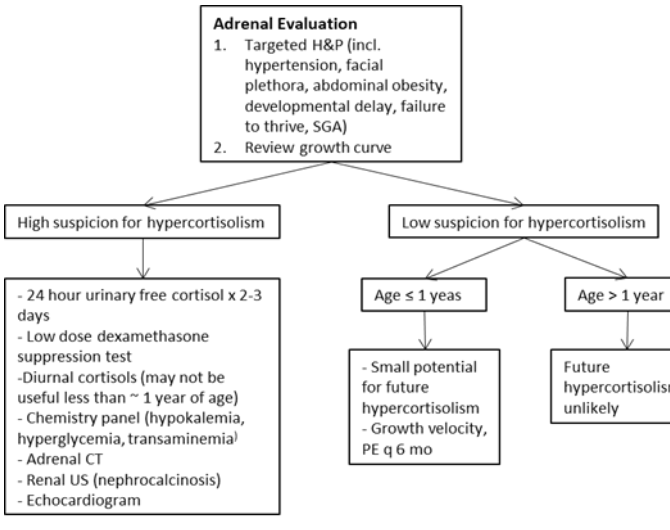
Hypercortisolism in unlikely after the first year of life and in major cases spontaneously resolve. Clinical history and physical examination should be performed, to include a history of infantile illness, developmental delay, poor linear growth with excessive weight gain.

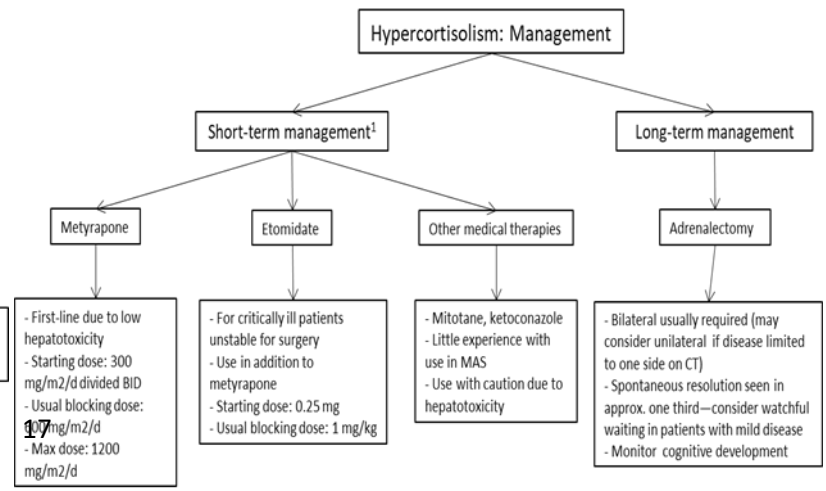
In case of clinical suspicion of current hypercortisolism, 24-h urinary free cortisol, low dose dexamethasone suppression test, diurnal cortisol and adrenal CT should be performed.

Liver disease is highly correlated with MAS-associated hypercortisolism. Prognosis of hypercortisolism is negatively correlated with the presence of heart disease.

Metyrapone is the preferred first-line agent with etomidate for critically ill patients. Other options include mitotane and ketoconazole. Ketoconazole should be used with caution as it is frequently associated with hepatic toxicity. Unilateral/bilateral adrenalectomy should be considered in persistent cases.

Assessment of adrenal insufficiency is recommended after resolution of hypercortisolism and increased risk for neurodevelopmental delays should be considered.





References

1. Long-term outcomes of letrozole treatment for precocious puberty in girls with McCune-Albright syndrome. Estrada A, Boyce AM, Brillante BA, Guthrie LC, Gafni RI, Collins MT. Eur J Endocrinol. 2016 Nov;175:477-483.

2. Combined treatment with bicalutamide and anastrozole in a young boy with peripheral precocious puberty due to McCune-Albright Syndrome. Tessaris D, Matarazzo P, Mussa A, Tuli G, Verna F, Fiore L, Lala R.Endocr J. 2012;59:111-7.

3. Thyroid abnormalities in children and adolescents with McCune-Albright syndrome. Tessaris D, Corrias A, Matarazzo P, De Sanctis L, Wasniewska M, Messina MF, Vigone MC, Lala R. Horm Res Paediatr. 2012;78:151-7.

4. Growth hormone-Insulin-like growth factor 1 axis hyperactivity on bone fibrous dysplasia in McCune-Albright Syndrome. Tessaris D, Boyce AM, Zacharin M, Matarazzo P, Lala R, De Sanctis L, Collins MT. Clin Endocrinol (Oxf). 2018;89(1):56-64.

5. Cushing syndrome in the McCune-Albright syndrome. Brown RJ, Kelly MH, Collins MT.J Clin Endocrinol Metab. 2010;95:1508-15.

6. Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium. Javaid MK, Boyce A, Appelman-Dijkstra N, Ong J, Defabianis P, Offiah A, Arunde P, Shaw N, Pos VD, Underhil A, Portero D, Heral L, Heegaard AM, Masi L, Monsell F, Stanton R, Dijkstra PDS, Brandi ML, Chapurlat R, Hamdy NAT, Collins MT. Orphanet J Rare Dis. 2019;14:139.

7. Fibrous Dysplasia/McCune-Albright Syndrome. Boyce AM, Florenzano P, de Castro LF, Collins MT. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews®[Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. 2015 Feb 26 [updated 2019 Jun 27].

Meet the Expert Session
6:1 – 6:2

'Management of Diabetic Ketoacidosis'

Zdenek Sumnik (Prague, Czech Republic)

Session 6:1: Friday 20 September at 08:30 - 09:30hrs in Hall B

Session 6:2: Saturday 21 September at 14:00 - 15:00hrs in Hall B

****NO HANDOUT HAS BEEN PROVIDED FOR THIS SESSION****

Meet the Expert Session
7:1 – 7:2

'Management of Graves disease'

Tim Cheetham (Newcastle, United Kingdom) and Claire Wood (Newcastle, United Kingdom)

Session 7:1: Friday 20 September at 08:30 - 09:30hrs in E2

Session 7:2: Saturday 21 September at 14:00 - 15:00hrs in E2

Management of Graves' disease.

Dr Tim Cheetham, University Reader and Consultant in Paediatric Endocrinology, Newcastle University c/o Department of Paediatric Endocrinology, Great North Children's Hospital, Royal Victoria Infirmary, Newcastle Upon Tyne, NE1 4LP.

Tim.Cheetham@nuth.nhs.uk

Dr Claire Wood, Academic Clinical Lecturer, Newcastle University and Department of Paediatric Endocrinology, Great North Children's Hospital, Royal Victoria Infirmary, Newcastle Upon Tyne, NE1 4LP.

Claire.Wood@Newcastle.ac.uk

Background – Graves' disease as a cause of thyrotoxicosis

Graves' disease is the most common cause of thyrotoxicosis. The biochemical hallmark of thyrotoxicosis is a suppressed thyroid hormone stimulating hormone (TSH) level with raised thyroid hormone concentrations (free T3 and / or free T4). Most (>98%) young patients found to be thyrotoxic beyond the neonatal period will have one of the following conditions.

- Autoimmune thyroid disease with hyperthyroidism (Graves' disease)
- Autoimmune thyroid disease without hyperthyroidism (Hashitoxicosis)
- Toxic adenoma – (single hot nodule)
- Toxic multinodular goitre
- McCune Albright syndrome
- Familial non-autoimmune autosomal dominant hyperthyroidism
- Thyroxine ingestion
- Linked to medication administration eg Amiodarone

Autoimmune thyroid disease can be viewed as a spectrum with more persistent hyperthyroidism in association with raised thyroid receptor antibodies (TRAb) at one end of the continuum (Graves' disease) and patients with more transient discharge of excess thyroid hormone in association with thyroid peroxidase antibodies (TPO) - often referred to as Hashitoxicosis – at the other. Patients with Graves' often have TPO and can become hypothyroid in the longer term because of associated thyroid tissue destruction. The focus of the remainder of this text will be on Graves' disease.

Graves' disease

In Graves' hyperthyroidism excess thyroid hormone generation is the consequence of pathogenic antibodies (TRAb - sometimes also referred to as thyroid binding inhibitory immunoglobullin or TBII) stimulating the thyroid gland through the cell-surface TSH-receptor

(TSHR). Antibodies are produced from plasma cells that reside in the thyroid and adjacent lymphoid tissues. In some instances only free T3 concentrations are raised but TSH concentrations are always suppressed. Increasingly autoimmune thyroid disease including Graves' is recognised after bone marrow transplantation or treatment with immune modulators such as Alemtuzumab. In these situations, the balance between autoreactive T cells and T regulatory cells is disrupted, resulting in autoimmunity that was not present pre-intervention.

Graves' disease in the young versus adults

Managing Graves' disease remains a challenge for the young person, their family, paediatrician and the managing health care team because:

- The child or adolescent with Graves' tends to have more severe disease
- The young person is more likely to develop adverse effects when treated with ATD
- The young person is more likely to relapse when ATD is stopped after 1.5 to 3 years of therapy (20 to 25% versus 40 to 50%).
- The young person will require thyroid hormone replacement for longer following definitive therapy with surgery or radio-iodine.
- The young person may be at greater longer term risk of neoplasia in tissues outside the thyroid gland following RI therapy.
- There are many key life events to negotiate at this time.

Incidence

Hyperthyroidism affects 2% of women and 0.2% of men. The incidence of acquired thyrotoxicosis in the UK and Ireland is 0.9 per 100,000 <15 years olds (95% CI: 0.8-1.1). There is a suggestion in some parts of the world that the incidence may be rising.

Presentation

Patients with Graves' disease can present to a range of subspecialists such as gastroenterologists (with diarrhoea or weight-loss) cardiologists (with tachycardia or palpitations), psychologists or psychiatrists (with mood alteration or anxiety) or opthalmologists (with eye discomfort or proptosis). Symptoms may have been present for months or years before an endocrinologist is consulted. There are patients who seem to tolerate thyroid hormone excess remarkably well and not all report weight loss. Thyroid hormone excess can have a profound impact on eductional performance and learning.

Initial management

Patients with mild symptoms and a diagnosis of Graves' disease on the basis of the presence of TRAb can be commenced on anti-thyroid drug (ATD). Patients with more profound symptoms can be commenced on a beta blocker as well such as atenolol 25 to 50mg once daily or propranolol 20mg tds (in the case of a teenager) until they are euthyroid. In many

(relatively) well patients, there is an argument for only starting ATD once the result of the TRAb assay confirms a diagnosis of Graves' (available after a matter of days in many units) with the patient managed symptomatically – for example with a beta blocker - in the interim.

Thyroid storm

Very occasionally patients with Graves' disease can present with a thyroid storm or crisis with symptoms and signs that can include:

- tachycardia,
- heart failure,
- hyperthermia,
- extreme anxiety
- gastrointestinal upset

This may be a consequence of infection or surgery in someone with undiagnosed or poorly controlled Graves' disease or very occasionally following RI therapy.

A euthyroid state can be reached more rapidly by administering:

- Iodine (eg potassium iodide solution)
- Glucocorticoid
- Carbimazole
- Beta blocker

Carbimazole and iodine are used to block thyroid hormone synthesis and secretion; beta blockers, glucocorticoids, and iodine containing preparations inhibit the peripheral conversion of the biologically inactive prohormone thyroxine (T4) to active triiodothyronine (T3) whilst beta blockers attenuate the peripheral adrenergic actions of thyroid hormone. Management is best undertaken on a high-dependency unit.

Treatment options

The key treatment modalities used in Graves' disease are ATD, surgery and radio-iodine. Many young people with Graves' hyperthyroidism become adults taking long-term thyroid hormone replacement because of the low remission rate following a 2 to 4 to 6 year course of ATD. Whilst thyroid hormone replacement with thyroxine is relatively straight-forwards, longer-term quality of life might not always be the same as it is in those individuals without thyroid dysfunction.

Anti-thyroid drug

The first line treatment for the young person with Graves' is Methimazole or Carbimazole. This need only be given once daily. The drug propylthiouracil should only be used in exceptional circumstances because of the risk of liver failure. Carbimazole therapy is associated with a range of side-effects that occur in up to 25% of people and can also cause

liver dysfunction. Relatively common side-effects include rashes and headache but the key side effect of note is the development of neutropaenia. If patients on Carbimazole develop a sore throat or fever, then they should stop Carbimazole straightaway and only recommence this when they are known to have a normal neutrophil count. Patients should be provided with a written card reminding them about what to do when unwell. In the case of neutropaenia the cell count will typically increase when ATD is stopped although Graves' per se and inter-current illness can also be associated with a low neutrophil count and so ATD administration is not always the underlying mechanism. A full blood count and liver function should be checked before ATD is commenced.

Anti-thyroid drug regimen

There are two principle approaches to administering ATD. One approach involves administering a larger 'blocking' dose of ATD (around 0.5 to 0.75mg/kg carbimazole a once daily dose) that abolishes endogenous thyroid hormone release. Thyroxine is then added in a 'replacement' dose. This is commonly referred to as 'block and replace' therapy or BR for short. The other approach is to administer a dose of ATD that reduces endogenous thyroid hormone production to normal. This is called 'dose titration' or DT. Patients can be commenced on 0.25 – 0.5mg/kg carbimazole daily with the dose weaned as thyroid hormone concentrations move down to within the age-related biochemical reference range. The advantage of DT is that the lower ATD dose is less likely to be associated with adverse events. Advocates of the BR strategy feel that it is easier to establish a euthyroid state which can be particularly advantageous at certain times of life. Patients managed with either approach can have a suppressed TSH for a while even when thyroid hormone concentrations have normalised. The growing child on ATD should be seen every 3 to 4 months in clinic although during the initial phase more frequent monitoring is needed.

Given the low likelihood of remission following a 2 to 3 year course of ATD some clinicians recommend administering low dose ATD for many years on the basis that they may then be more likely to remit after lengthy ATD therapy and on the basis that the likelihood of neutropaenia on a low dose of ATD after the first 18 months is small.

Other treatment options

Patients who relapse and who do not want to return to ATD treatment have no option but to undergo definitive thyroid gland removal by surgery or gland destruction by radio-iodine. A small minority of patients will develop significant early side-effects of ATD and are forced in the direction of surgery or radioiodine sooner rather than later.

Surgery

The surgical treatment of Graves' disease involves total thyroidectomy and then thyroid hormone replacement. Whilst a partial thyroidectomy can result in a euthyroid state this approach is generally not recommended because of the risk of hyperthyroidism recurrence or hypothyroidism. The key consideration from a surgical perspective is to make sure that

the operation is undertaken by a so-called 'high-volume' thyroid surgeon. This individual will frequently be an adult surgeon because thyroid disease requiring surgical treatment is rare in the young. The risk of long-term hypoparathyroidism or recurrent laryngeal nerve damage will be smaller when conducted by someone performing this operation on a weekly basis. Short term hypocalcaemia is an issue in some patients because of damage to the parathyroid glands or, in the case of patients who were thyrotoxic in the weeks and months before surgery, because of osteopaenia and associated 'hungry bones'.

Patients undergoing thyroid surgery need to be euthyroid at the time of the procedure. If the young person is hyperthyroid then they can be rendered euthyroid and hence safe for surgery with potassium iodide solution. This will typically reduce FT3 levels to normal within a week because of the so-called Wolff-Chiakoff effect.

Radioiodine

Radioiodine (RI) has been used to treat Graves' disease for many years and the data on safety in adults and the young is very encouraging. There has been no discernible impact of RI therapy on fertility and no increase in thyroid cancer provided a dose that ablates the thyroid gland is used. The long-term safety data regarding malignancy out-with the thyroid is generally reassuring although there may be a small increased risk in tissues most exposed to the RI dose when it is swallowed (the stomach) and excreted (the kidney).

Patients need to stop ATD 7 days prior to RI therapy and avoid iodine-containing foods in the diet such as fish and dairy in the weeks leading up to RI therapy so that uptake is not impaired. Doses used in the adolescent range from 300 to 400 MBq. Some teams advocate dose calculation which is based on tracer uptake prior to RI therapy but there is no good evidence to suggest that this approach is better. Caution should be exercised in the case of individuals with a very large gland because a second dose of RI may be needed. Patients with significant eye disease should also be managed carefully because their eye disease can deteriorate. This deterioration can be ameliorated with glucocorticoid 'cover'.

The objective of RI therapy is to render the patient hypothyroid but thyroid status can fluctuate post RI with periods of over and underactivity in the subsequent weeks. One approach to dealing with this variability is to start the patient on BR therapy for 6 months. ATD and thyroxine can be commenced in the days after RI with the ATD stopped after 6 months on the basis that the patient will now be hypothyroid but on thyroid hormone replacement. If patients are still hyperthyroid 6 months after the first dose of RI then a second dose may be required.

Long term outcome of Graves' disease

A range of factors have been associated with an increased likelihood of remission following a course of ATD including the presence of a small goitre, modest thyroid hormone excess and relatively low TRAb titre at presentation. The minority of patients who become euthyroid after a course of ATD will usually have no detectable TRAb when the ATD is

stopped but frequently have thyroid peroxidase antibodies (TPO) that can damage the thyroid gland and result in hypothyroidism in the longer term. The natural history of Graves' disease in some patients is for them to become hypothyroid many years post presentation. ATD should not be stopped if the TRAb titre is still positive because patients will almost certainly relapse.

Thyroid eye disease

Severe thyroid eye disease is uncommon in children but can be relatively severe in the occasional patient. Patients can have a rather prominent stare at diagnosis because of excess sympathomimetic activity, an appearance that settles as a euthyroid state is restored.

Discussions with the family

The paediatrician should discuss the advantages and disadvantages of the key three treatment modalities with the patient and family. Planning should include a discussion about the timing of any trial off ATD and negotiating important educational milestones. Factors that may make relapse more likely; young age, severe disease at presentation and persistent of TRAb for example, can be highlighted by the managing team although even patients with supposed risk factors for early relapse can still surprise and enter remission. Long term lower dose DT therapy is a treatment option, in part because the risk of neutropenia after the first 18 months is likely to be very small. Patients will still need to stop ATD and have a white cell count checked if they become unwell with a sore throat or fever.

Research

In the same way that diabetologists and rheumatologists have become interested in agents that can modify the immune response, so endocrinologists are becoming interested in interventions that can ameliorate or modify the immune response in Graves' disease. Hence there are ongoing clinical trials of interventions that could potentially modify the immune response in this clinical context.

Clinical practice points

- Graves' disease is the most common causes of hyperthyrodisim in children and adolescents.
- Clinicians need to be aware of the diverse range of presenting signs and symptoms in order to facilitate timely diagnosis and management.
- The characteristic biochemical picture is that of a suppressed thyroid hormone stimulating hormone (TSH) level and raised thyroid hormones (Free T3 or Free T3 and Free T4) concentrations.
- If TRAb is present then this suggests that hyperthyroidism is unlikely to remit in the short to medium term, whereas thyroid hormone excess in the absence of TRAb antibodies is more likely to be self-limiting.

- Patients who develop significant side-effects of ATD will usually require surgery (total thyroidectomy) or radioiodine.
- Planning should include a discussion about the timing of any trial off ATD, avoiding important educational milestones.

Further Reading

Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016 Oct;26(10):1343-1421

Rivkees SA. Pediatric Graves' disease: controversies in management. Horm Res Paediatr. 2010;74(5):305-11

Peterson SJ, McAninch EA, Bianco AC. Is a Normal TSH Synonymous With "Euthyroidism" in Levothyroxine Monotherapy? J Clin Endocrinol Metab. 2016 Dec;101(12):4964-4973.

Léger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C; French Childhood Graves' Disease Study Group. Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study. J Clin Endocrinol Metab. 2012 Jan;97(1):110-9

Meet the Expert Session
8:1 – 8:2

'Management of neonatal hypoglycaemia'

Klaus Monicke (Magdeburg, Germany) and Fellow Susann Empting (Magdeburg, Germany)

Session 8:1: Friday 20 September at 08:30 - 09:30hrs in Hall C

Session 8:2: Saturday 21 September at 14:00 - 15:00hrs in Hall C

****NO HANDOUT HAS BEEN PROVIDED FOR THIS SESSION****