

Endocrinology Research Review

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Issue 27 - 2015

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Abbreviations used in this issue:

Ca = carbohydrate antigen;
GH(D) = growth hormone (deficiency);
(F)PTC = (familial) papillary thyroid carcinoma;
MTC = medullary thyroid cancer;
NFPA = non-functioning pituitary adenoma;
PTMC = papillary thyroid microcarcinoma.

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Welcome to the 27th issue of Endocrinology Research Review.

Highlights of this Review include two studies with positive findings for growth hormone therapy. A nationwide registry study from Denmark found that subjects with childhood-onset growth hormone deficiency who received growth hormone replacement had lower mortality rates than those who did not. And in a retrospective Dutch analysis there was no evidence of an association between use of growth hormone therapy and tumour progression in adults with non-functioning pituitary adenomas. We also report on a study which examines the cost efficacy of non-surgical management for incidental papillary thyroid microcarcinoma and present the findings of an investigation into the relationship between serum carbohydrate antigen 19.9 and mortality in patients with advanced medullary thyroid cancer.

We hope you find the selection for this month's edition useful in your practice, and we look forward to receiving your comments or feedback.

Kind Regards,

Professor Duncan Topliss

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Frequency of genetic defects in combined pituitary hormone deficiency: a systematic review and analysis of a multicentre Italian cohort

Authors: De Rienzo F et al.

Summary: These Italian researchers investigated the frequency of mutations in 5 genes encoding transcription factors (*PROP1*, *POU1F1*, *HESX1*, *LHX3* and *LHX4*) in adult and paediatric patients with combined pituitary hormonal deficiency (CPHD). Comparisons were made between mutation rates observed in a cohort of Italian CPHD patients (n = 144), and those calculated from a systematic literature review of studies (n = 21) in which ≥ 10 patients were screened. In the Italian cohort the global mutation frequency was 2.9 and 12.5% in sporadic and familial disease respectively. This compared to respective values of 11.2 and 63% which were calculated for the literature cohort. The most commonly mutated gene was *PROP1*; found in 6.7% of sporadic cases and 48.5% of familial cases of CPHD.

Comment: This study summarises the current European experience of CPHD, a rare disorder with a genetic basis that is characterised by the impaired production of GH and one or more other pituitary hormones. Currently reported associated genes include *PROP1*, *POU1F1*, (previously named *PIT1*), *HESX1*, *LHX3*, *LHX4*, *OTX2*, *GLI2* and *SOX3*. Mutations of these transcription factor genes cause a wide range of pituitary phenotypes, from severe CPHD to isolated GH deficiency. Mutations within 'early transcription factors' may lead to extrapituitary phenotypic manifestations, including hypopituitarism with craniofacial defects such as septo-optic dysplasia (*HESX1*) or holoprosencephaly (*GLI2*). *LHX3* and *LHX4* mutations are associated with Chiari malformation, corpus callosum hypoplasia, hearing impairment and skeletal abnormalities. *PROP1* and *POU1F1* are 'later-acting transcription factors' and mutations of these genes are responsible for a pituitary-specific phenotype that is characterised by multiple hormone deficiencies without relevant extrapituitary findings. Genetic screening has failed to detect mutations within any of these genes in many patients with CPHD, but the majority of tested patients in some CPHD cohorts carried mutations that primarily affected *PROP1*. The hormonal phenotype in patients with *PROP1* mutations is characterised by deficiencies of GH, TSH, PRL, and gonadotropins, and an extremely variable phenotype within and between families in the severity of hormone deficiency, age of onset, adrenal function and height at diagnosis. The anterior pituitary is often hypoplastic on MRI.

Reference: *Clin Endocrinol (Oxf)*. 2015;Jul 6 [Epub ahead of print]

[Abstract](#)

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Clinical outcomes in patients with nonfunctioning pituitary adenomas managed conservatively

Authors: Sam AH et al.

Summary: These authors conducted a retrospective analysis in order to examine the natural history of non-functioning pituitary adenomas in patients who underwent conservative management. Subjects comprised patients with pituitary adenomas without evidence of hormonal hypersecretion who presented at a single centre between 1986 and 2009 and underwent conservative management (n = 66). Mean follow-up under conservative management was 4.3 (range 1 to 14.7) years. The proportion of patients with macroadenomas was 71%, and of these, 40% of tumours were stable or decreased in size. The respective proportion for patients with microadenomas was 21%. Enlarging macroadenomas grew at a median rate of 1.0 mm/year compared to 0.4 mm/year for microadenomas ($p < 0.01$). The proportion of patients with pituitary hormone deficiencies in ≥ 1 axis was 68 vs. 42% for those with macro- and microadenomas respectively.

Comment: This study provides further evidence that conservative management with regular surveillance is safe and effective in patients with clinically non-functioning pituitary macroadenomas without evidence of optic chiasm compression. In this study, where growth occurred, the time to detection was 1.4 years with a macroadenoma, and 1.5 years with a microadenoma. Interestingly, although 33 of the 47 macroadenomas abutted the optic chiasm and 73% of these grew, only 24% developed a visual field defect. One developed a visual field defect after 14.7 years of observation. The standard surveillance for structural and hormonal functional change with not more than yearly MRI scanning (less frequent if apparently stable) in the absence of new symptoms or signs is supported, but indefinitely long-term follow-up is required.

Reference: *Clin Endocrinol (Oxf)*. 2015;Jul 21 [Epub ahead of print] [Abstract](#)

Tumor recurrence or regrowth in adults with nonfunctioning pituitary adenomas using GH replacement therapy

Authors: van Varsseveld NC et al.

Summary: This retrospective analysis of data from the Dutch National Registry of Growth Hormone Treatment in Adults examined the risk of tumour progression in patients with non-functioning pituitary adenomas (NFPAs) who were treated with GH. Selected subjects (n = 783) had NFPA, severe GH deficiency and had received ≥ 30 days of GH therapy between 1998 and 2009. Tumour progression (including recurrence after complete remission and regrowth of residual tumour) was observed in 12.1% of subjects at a median of 2.2 (0.1 to 14.9) years. Risk of tumour progression was decreased by prior radiotherapy vs. no radiotherapy (HR 0.16; 95% CI 0.09, 0.26) and, in subjects with available data (n = 577), was increased by the presence of residual tumour at baseline vs. no residual tumour (HR 4.5; 2.4, 8.2). No evidence of an association between GH therapy and tumour progression was observed.

Comment: The main conclusion the authors draw from their follow-up study of NFPA over a median of 5.2 years, is that GH treatment does not increase tumour recurrence, although they have no control group of untreated patients. The basis for their conclusion is that the overall rate of recurrence is only 12.1%, occurring at a mean of 2.2 years (range up to 14.9 years), lower than in other published series. Cox proportional hazard analysis in patients with available baseline imaging data, and after adjustment for age and gender, showed that patients with residual tumour at baseline had an increased risk of developing tumour progression compared with patients without residual tumour (HR 3.7; 95% CI 2.0–6.8; $p < 0.001$). Radiotherapy reduced the risk (HR 0.16; 4.8 vs. 20.1%). The study supports previous published findings.

Reference: *J Clin Endocrinol Metab*. 2015;100(8):3132-9 [Abstract](#)

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Growth hormone replacement does not increase mortality in patients with childhood-onset growth hormone deficiency

Authors: Berglund A et al.

Summary: This nationwide, population-based registry study investigated the effects of GH replacement on mortality in subjects with childhood onset of growth hormone deficiency (CO GHD). Subjects with CO GHD (n = 494) were age- and gender-matched with 100 controls from the general population. Subjects with CO GHD had increased mortality rates compared with controls; HR 7.51 (95% CI 6.06, 9.31). However subjects with CO GHD who received GH replacement had a lower risk of mortality (HR 0.27; 0.17, 0.43) and malignancy-associated mortality (HR 0.14; 0.07, 0.28) compared to those who did not. This association remained in the adjusted analysis for both total mortality (HR 0.56; 0.32, 0.96) and malignancy-associated mortality (HR 0.33; 0.16, 0.69).

Comment: This is a study using Danish national data on CO GHD (n = 494) derived from all GHD patient diagnoses in Denmark between 1980 and 1999 (n = 1,823), with the cause of death known up to the end of 2012, giving an overall follow-up period of 20 years. Although the HR for mortality was high for CO GHD in comparison with the general population, there was no adverse effect of GH treatment, indeed a beneficial effect was found. The excess mortality was associated with the underlying diagnosis, e.g. craniopharyngioma and malignancy, with no increase for idiopathic GHD. It is reassuring that malignancy-associated mortality was decreased and no increase in cerebrovascular mortality was found with GH treatment.

Reference: *Clin Endocrinol (Oxf)*. 2015;Jul 4 [Epub ahead of print] [Abstract](#)

Crooke's changes in Cushing's syndrome depends on degree of hypercortisolism and individual susceptibility

Authors: Oldfield EH et al.

Summary: These researchers utilised data from a prospective computer database and a retrospective chart review in order to examine the prevalence of, and clinical characteristics associated with, Crooke's changes in pituitary corticotrophs. Subjects were 213 consecutive patients undergoing pituitary surgery at a single centre who had a preoperative diagnosis of Cushing's disease. Crooke's changes, identified by histopathological analysis of normal pituitary tissue associated with the surgical specimen, were observed in 74% of the total cohort and 81% (144/177) of subjects with ACTH-staining tumours. Increased frequency of Crooke's changes was observed in subjects with ACTH-staining tumours and 24-h urinary free cortisol $\geq 4 \times$ ULN vs. those with lower cortisol levels; 91 vs. 74% ($p = 0.008$).

Comment: Crookes' changes, replacement of the cytoplasmic granules of the basophilic cells of the anterior pituitary with homogeneous hyaline material in patients with Cushing's syndrome (CS), was first described in 1935. Crooke's change is associated with both endogenous and iatrogenic excess glucocorticoid exposure. Corticotroph cells characteristically have perinuclear bundles of cytokeratin filaments. With glucocorticoid excess, corticotroph cells accumulate cytokeratin filaments in the cytoplasm in an annular or concentric fashion with displacement of the secretory granules to either the periphery of the cell or around the nucleus. This is a Crooke's cell and is the morphologic manifestation of functional corticotroph suppression. The frequency of Crooke's changes and its basis are still poorly described. In this study, in patients thought to have Cushing's disease, the likelihood of not finding a tumour in patients with no Crooke's changes (38%) was substantially higher than in patients with Crooke's changes (10%). The presence of Crooke's changes is a clear indication of the presence of CS, although the absence of Crooke's changes does not exclude it.

Reference: *J Clin Endocrinol Metab*. 2015;100(8):3165-71 [Abstract](#)

Clinicopathological features and prognosis of familial papillary thyroid carcinoma

Authors: Cao J et al.

Summary: This matched-case comparative study investigated the clinicopathological features and prognosis of familial papillary thyroid carcinoma (FPTC). Subjects, 372 patients with FPTC, were matched for age, gender, tumour/node/metastasis stage and length of follow-up with 372 controls who had a diagnosis of sporadic PTC. Between-group differences included a higher frequency of tumour multicentricity, bilateral growth and concomitant nodular goitre in those with familial disease ($p < 0.05$). Subjects with papillary thyroid microcarcinoma and a family history of PTC had an increased risk of recurrence which remained significant in multivariate analysis.

Comment: In this study FPTC was defined as one or more first-degree relatives with PTC. 89% had just 2 family members affected (including the proband) and 11% had 3 affected family members. 4.54% of PTCs were deemed to be FPTC (372/8,195). Whether FPTC was defined at diagnosis of the proband or if there was a further time period for diagnosis of FPTC is unclear but FPTC and sporadic PTC were determined similarly. 58% of the FPTC and 61% of the sporadic PTC were microcancers. The recurrence rates difference was 7.3% for FPTC versus 1.3%, but only one death occurred across the whole study group over a mean follow-up of 35 months and a longest follow-up of 108 months. It is unclear, due to the rarity of major progressive and fatal disease, if the observed differences in bilaterality, multicentricity, and recurrence rates, are clinically important. As the authors comment, the genetic inheritance of FPTC remains unknown, and the causative genes predisposing to FPTC have not been yet identified. Although a number of susceptibility genes for familial non-medullary thyroid cancer have been identified, viz. *MNG1* (chromosome 14q31), *TCO* (chromosome 19p132), *fPTC/PRN* (chromosome 1q21), *NMTC1* (chromosome 2q21), *FTE* (chromosome 8p23.1-p22), *FOXE1* (chromosome 9q22.33), *NKX2-1* (chromosome 14q13.3), *DICER1* (chromosome 14q32) and *SRGAP1* (chromosome 12q14), and the role of different miRNAs and the effect of telomeres and telomerases in genetic predisposition have also been investigated, the susceptibility genes have not been validated by subsequent studies. Currently therefore genetic testing for FPTC is not available.

Reference: *Clin Endocrinol (Oxf)*. 2015;Jul 20 [Epub ahead of print] [Abstract](#)

A cost-effectiveness comparison between early surgery and non-surgical approach for incidental papillary thyroid microcarcinoma

Authors: Lang BH & Wong CK

Summary: These authors conducted a cost-effectiveness analysis comparing two strategies, an early surgical approach vs. a non-surgical approach, for managing incidental papillary thyroid microcarcinoma (PTMC). The model was based on a hypothetical 40-year old female patient with a diagnosis of unifocal, intra-thyroidal PTMC (9mm) for whom either management strategy would be deemed appropriate. Data pertaining to outcomes and treatment costs were obtained from the literature. At a threshold for cost-effectiveness of US\$50,000 per quality-adjusted life year (QUALY) the non-surgical intervention was cost-effective; the additional cost associated with this approach was US\$682.54 for a gain of 0.260 QUALY. The non-surgical approach was cost-saving at ≤ 16 years from diagnosis, and cost effective after that. Cost efficacy was not altered by factors including patient age, complications or rate of PTMC progression.

Comment: As the authors state, a conservative, non-surgical, approach to papillary microcarcinoma is becoming an acceptable treatment option. The clinical consequences of such a strategy still requires prospective study i.e. for efficacy and safety, and another potential criticism is its cost-effectiveness given the long-term surveillance that would be required. Specific costs will vary widely across jurisdictions according to differences in health care systems so that such an analysis may not be exactly applicable in any particular country. This analysis however does provide useful information indicating that non-surgical management may well be cost-effective in the long-term with improved quality of life.

Reference: *Eur J Endocrinol*. 2015;173(3):367-75 [Abstract](#)

Radiation safety precautions in ¹³¹I therapy of Graves' disease based on actual biokinetic measurements

Authors: Liu B et al.

Summary: This prospective study was conducted in order to enable the formulation of radiation precautions for patients with Graves' disease undergoing ¹³¹I therapy. Pre- and post-therapy biokinetic measurements were carried out in a cohort of 72 consecutive patients with Graves' disease. Significant inter-patient variability in ¹³¹I biokinetics was observed. For the thyroid, the mean peaking ¹³¹I uptake (± 1 SD) was 68% ($\pm 19\%$), range 18 to 89%. For the rest of the body the mean effective ¹³¹I half-life was 5.1 (± 0.9) hours, range 3.5 to 7.2. Following ¹³¹I administration the mean measured initial dose rate at 1.0 m was 0.039 (± 0.003) $\mu\text{Sv h}^{-1} \text{MBq}^{-1}$ (range 0.017 to 0.055). The actual 0.3:1.0 m initial dose rate was between 2.9 and 7.1, whereas the projected ratio (using inverse square law approximation) was 11.1.

Comment: This study demonstrates wide variation in potential exposure of others to radiation after ¹³¹I for Graves' hyperthyroidism, using a 1 mSv dose limit. The practicality of measuring patient-specific iodine biokinetics to provide individual advice on limiting radiation dose seems problematic. In Australia dosimetry calculation using tracer doses of iodine to measure uptake at 4 and 24 hours is no longer available, although presumably dosimetry could still be done using the therapy dose. It seems very unlikely nuclear medicine departments would be keen to do this routinely given the extra workload this would impose. Importantly, the measurements in this study show it is permissible on the day of administration for the patient to use public transport for 10 hours after a 370 MBq dose (10 mCi) and for 6 h after a 555 MBq dose (15 mCi). Furthermore, the results indicate that no precautions are needed to protect non-pregnant adult family members that do not sleep next to the patient over the range of administered activities of 185–1110 MBq of ¹³¹I (5–30 mCi). For 370 MBq (10 mCi) there is no required restriction for contact with a pregnant woman for 6h/day at 1m, and a 3-day restriction for contact with a member of the public for 8h/day at 1m. Overall, it would be useful if the advice to patients from nuclear medicine departments in Australia could be uniformised according to objective standards and these data should assist this aim.

Reference: *J Clin Endocrinol Metab.* 2015;100(8):2934-41
[Abstract](#)

Thyroid status, cardiac function, and mortality in patients with idiopathic dilated cardiomyopathy

Authors: Wang W et al.

Summary: These researchers examined relationships between thyroid status and mortality in patients with idiopathic dilated cardiomyopathy. Subjects were a cohort of 572 consecutive patients (458 evaluable) with idiopathic dilated cardiomyopathy and full thyroid function profiles. Thyroid dysfunction identified amongst the cohort included subclinical hypothyroidism (n = 41), subclinical hyperthyroidism (n = 35), low T3 syndrome (n = 17) and hypothyroidism (n = 12). An increased risk of mortality was associated with hypothyroidism (HR 4.189; 95% CI 2.118, 8.283), low T3 syndrome (HR 3.147; 1.558, 6.355) and subclinical hypothyroidism (HR 2.869; 1.817, 4.532) but not subclinical hyperthyroidism. The authors suggest that, based on these results, monitoring of thyroid function should be carried out in patients with heart failure.

Comment: As the authors concede, there are significant caveats to the interpretation of these data. First the definition of thyroid dysfunction can be debated: Is low T3 syndrome really thyroid dysfunction or a non-thyroidal effect on thyroid hormone economy unrelated to thyroid dysfunction? Similarly does a TSH < 0.55 mU/L really diagnose subclinical hyperthyroidism? Does this really become overt hyperthyroidism if FT4 is high but not FT3? And does a single TSH > 4.78 mU/L diagnose hypothyroidism? What does thyroid dysfunction really mean in this context where the potential effects of thyroid hormone changes on cellular function are integrated with a range of other influences on the same genes affecting myocardial function? Without interventional data it is impossible to know if these data describe epiphenomena or treatable aspects of idiopathic dilated cardiomyopathy with heart failure but the association of 'thyroid dysfunction' and increased mortality risk should be further explored.

Reference: *J Clin Endocrinol Metab.* 2015;100(8):3210-8
[Abstract](#)

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Association of hypoglycaemia and cardiovascular risk in diabetes

This review is intended as an educational resource for health professionals. It presents a background on hypoglycaemia in patients with diabetes including burden and risk factors, then goes on to discuss evidence for the association of hypoglycaemia and cardiovascular risk and describes potential mechanisms for this association.

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Elevated level of serum carbohydrate antigen 19.9 as predictor of mortality in patients with advanced medullary thyroid cancer

Authors: Elisei R et al.

Summary: This study aimed to determine whether serum concentrations of carbohydrate antigen (Ca) 19.9 are prognostic for mortality in patients with advanced medullary thyroid cancer (MTC). Two hundred patients with MTC were recruited; 100 with advanced structural recurrent/persistent MTC and 100 with cured or biochemically affected MTC. Elevated serum concentrations of Ca 19.9 were detected in 16% of subjects with advanced MTC in comparison to nil in the control group. Subjects who had elevated Ca 19.9 also had significant increases in calcitonin and carcinoembryonic antigen vs. those with normal Ca 19.9 ($p < 0.0001$ for both comparisons). In logistic regression analysis elevated Ca 19.9 was an independent predictor of mortality (OR 3.78; $p = 0.04$).

Comment: Ca 19.9 is a tumour marker most associated with pancreatic and colorectal carcinoma. Ca 19.9 binds to the tumour surface marker Sialyl-Lewis^x. 10% of Caucasians do not express Lewis antigen so Ca 19.9 is not expressed and cannot function as a tumour marker in that group. The authors suggest Ca 19.9 is predictive of poor prognosis independent of calcitonin doubling time. This is an interesting suggestion but whether Ca 19.9 will have useful additional predictive value should await corroborative data from other MTC cohorts.

Reference: *Eur J Endocrinol.* 2015;173(3):297-304

[Abstract](#)

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Selection and review of the research has been carried out independently by Professor Duncan Topliss, MB BS Hons, MD, FRACP, FACE.

Professor Duncan Topliss is Director of the Department of Endocrinology and Diabetes at the Alfred Hospital Melbourne, Professor of Medicine in the Department of Medicine Monash University and a past-President and Life Member of the Endocrine Society of Australia. He has served on the editorial board of the Journal of Thyroid Research and Clinical Endocrinology and is a frequent reviewer for Clinical Endocrinology, Thyroid, and other endocrine journals. Professor Topliss heads the Diabetes Clinic at the Alfred Hospital, has a long-term interest in diabetes prevention and management and has been an investigator on several major international diabetes trials. He has a wide interest in clinical endocrinology including osteoporosis, pituitary and adrenal disease and endocrine hypertension and has over 25 years of experience in the management of thyroid disease and thyroid cancer. His other interests are drug regulation and safety, and he is a member of the Australian Advisory Committee on the Safety of Medicine and the Australian Advisory Committee on Pharmaceutical Medicines of the Therapeutic Goods Administration.

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