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Use of mutation analysis in endocrine neoplasia syndromes

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The major benefit in the identification of gene mutations causing endocrine neoplasia syndromes has been to allow accurate and rapid diagnosis of affected family members. In particular, the focus of clinical surveillance, radiology and endocrine tests can be on only those carrying mutations.[1] It also allows testing of young individuals with apparently sporadic endocrine tumours, and many families with occult disease have been diagnosed and treated over the last 15 years.[2] Indeed, the original case description of phaeochromocytoma by Fraenkel has been shown to be due to multiple endocrine neoplasia type 2A.[3] Genetic studies have also defined new and clinically distinct endocrine neoplasia syndromes, for example: several familial paraganglioma syndromes resulting from mutations in the succinate dehydrogenase subunit genes[4-6]; multiple endocrine neoplasia type 4,[7] and hyperparathyroidism-jaw tumour syndrome.[8] As a rule, genetic testing and interpretation of the results is easier in the autosomal dominant neoplasia syndromes, where one abnormal allele is sufficient for disease. In contrast, genetic testing in inherited metabolic syndromes (for example, congenital adrenal hyperplasia) is complex and less useful. This is partly because the metabolic syndromes are often autosomal recessive conditions where both alleles are mutated and a there is a high frequency of compound heterozygosity (where each allele carries a different mutation) or whole gene deletions. Furthermore, occult disease is unusual in the autosomal recessive metabolic syndromes, where biochemical tests will identify most affected individuals, in contrast to the frequent identification of occult neoplasia in asymptomatic carriers of familial endocrine neoplasia mutations.

From the clinician's view, the first major advances were in 1993. The identification of RET proto-oncogene mutations causing multiple endocrine neoplasia type 2A and familial medullary thyroid carcinoma was reported by Ponder's group.[9] In multiple endocrine neoplasia type 2A, the mutations are usually in cysteine codons and this allows very quick diagnostic testing in families with medullary thyroid cancer, phaeochromocytoma and hyperparathyroidism. Prophylactic thyroidectomy is now routine for young children carrying a RET mutation and is effective in improving the disease-free survival. RET mutation analysis has made pentagastrin-stimulation tests for the diagnosis of MEN2A obsolete (although pentagastrin-stimulation tests may still be helpful in follow-up of patients after resection of medullary thyroid carcinoma). The von Hippel-Lindau (VHL) disease tumour suppressor gene causing haemangioblastomas, retinal angiomas, renal cell carcinomas, bilateral phaeochromocytomas and pancreatic cysts and neuroendocrine tumours was also reported in 1993 (10). Testing for VHL syndrome in families had involved brain, renal, pancreatic and adrenal scanning, biochemical testing and retinal examination. This burden has effectively been halved by mutational analysis. The identification of the role of the VHL disease protein in the cellular response to hypoxia promises much for future medical treatments.

Multiple endocrine neoplasia type 1 is a much more complex clinical and genetic disease with a wide range of clinical manifestations. Although primary hyperparathyroidism due to multiple adenomas is common, using serum calcium as a screening test in families was insensitive and non-specific. The disease is caused by mutations in the MENIN gene. Genetic testing is complex because many types of mutation may affect the gene, but is important for confirming the diagnosis in patients with unusual or limited manifestations, especially the minority without hyperparathyroidism. Genetic testing also allows the possibility of identifying early pre-symptomatic hyperparathyroidism and using treatment with the calcium-sensing receptor agonist, cinacalcet, possibly avoiding extensive and repeated parathyroid surgery.

The main disappointment for clinicians is that, in general, the link between the genetic mutation and the clinical manifestations is very loose and is not useful in predicting outcome. However, genetic studies have led to much greater

understanding of possible biological pathways to endocrine neoplasia. The hope is that this understanding may guide medical anti-tumour therapy, although the first trials of imatinib (a tyrosine kinase inhibitor, including anti-RET) in medullary thyroid carcinoma with RET activating mutations are disappointing. Another problem is how best and cost-effectively to test the many patients with familial endocrine neoplasia syndromes for tumours. Patients will need annual scans of several body parts. This represents a substantial lifetime radiation exposure if computed tomography is used. Magnetic resonance imaging is still slow, and the hope is that new magnetic imaging modalities will speed up scans without reducing diagnostic sensitivity and specificity. The finding that paragangliomas in patients with succinate dehydrogenase B subunit mutation are best identified by fluorodeoxyglucose positron emission tomography will help with the problem of imaging.[11] Such avidity for a glucose analogue potentially fits with the biology of the mutation, whereby a cellular defect in the flow sheet of Kreb's cycle respiration may lead to increased demands for glucose by alternative pathways.

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Giant leaps forward

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Introduction

A review of developments in the management of pituitary disease in the last 30 years reveals the contrasting pace of advances in treatment options between acromegaly and Cushing's disease. Both diseases have benefited from refinements in surgery and radiotherapy. The opening up of the transsphenoidal route to the fossa, the operating microscope, and more recently the endoscope, have greatly improved the results of surgery which still remains the first line of treatment. Multi-fractional, three field radiotherapy has been available for 40 years, but the accuracy afforded by computed tomography (CT) planning, and more lately superseded by magnetic resonance imaging (MRI), has reduced morbidity, while in the last decade the Gamma Knife and other forms of stereotactic radiotherapy have provided advances.

Drug treatment

The contrast in progress becomes apparent when one considers the new pharmacological agents available for acromegaly, while Cushing's syndrome is still likely to be treated with the same drugs as a generation ago, namely metyrapone, mitotane and ketoconazole. The transformation in the treatment of acromegaly can be credited to a combination of fortuitous observations and scientific endeavour. Underpinning the therapeutic advances was the 'somatomedin hypothesis' of Daughaday which postulated that the actions of growth hormone (GH) were mediated through a downstream factor initially known as somatomedin-C and latterly renamed insulin-like growth factor-1 (IGF-I), which, along with GH, can be used as a measure of disease activity.

Dopamine agonists

Prior to the introduction of bromocriptine, the first dopamine agonist, in the early 1970s, the only available medical option was oestrogen therapy which, as early as the 1930s, was shown to improve the well-being and glucose tolerance of patients with acromegaly. The paradox of the dopamine agonists is that they induce a pulse of GH secretion in normal individuals but inhibit secretion in patients with acromegaly. The recognition of the potential for treating acromegaly came from the observation of disease regression in a patient initiated on bromocriptine for Parkinson's disease. Cabergoline has become the dopamine agonist of choice because of the combination of greater efficacy and reduced side effects.