ACTH deficiency in patients with suspected hypopituitarism: Choosing the right diagnostic test

The pituitary gland is a pea-sized gland located at the base of the brain. Often termed the “master-gland”, it secretes hormones which control growth, metabolism and fertility. Hypopituitarism is a clinical syndrome of deficiencies in one or more pituitary hormones, of which adrenocorticotrophic hormone (ACTH) deficiency resulting in adrenal failure is the most serious and life-threatening feature.

ACTH deficiency may manifest as acute crisis with hypotension, hypoglycemia and hyponatremia. In other cases its presentation may be indolent in nature. The most common cause of ACTH deficiency is suppression of its secretion by chronic high levels of exogenous glucocorticoids (e.g. oral, topical). Other causes include tumors (including pituitary tumours, craniopharyngiomas), pituitary surgery, cranial radiation, traumatic brain injury and subarachnoid haemorrhage.

Secretion of ACTH by the anterior pituitary is stimulated by corticotropin releasing factor (CRF), a hormone secreted by the hypothalamus. ACTH then acts on the adrenal gland cortex to stimulate the production of cortisol. These processes are under negative feedback; ACTH inhibits CRH release, and cortisol inhibits the release of ACTH and CRH, thereby keeping cortisol levels in relative equilibrium. This concept of negative feedback is integral to endocrinology and underlies the basis for dynamic testing in hypopituitarism.

The “ideal test” for ACTH deficiency is one which is convenient, non-expensive, without side-effects while having a high degree of reproducibility and diagnostic sensitivity and specificity. Morning cortisol may be helpful if it is clearly low or clearly healthy; however often it neither and further dynamic testing is required to establish the diagnosis. Stimulation testing is done when hormone deficiency is suspected, and is designed to assess the capacity for synthesis and secretion of the hormone under study. In the case of ACTH deficiency hypoglycemia and glucagon can be used to stimulate ACTH secretion (insulin tolerance test and glucagon stimulation test, respectively). Plasma cortisol (ie. the target homone) is measured as a surrogate for ACTH secretion. The insulin tolerance test is viewed by many as the “gold standard” for assessment of the hypothalamic-pituitary-adrenal axis. However, it is labour intensive and can be unpleasant for patients and requires medical experience and supervision. Because the test involves inducing hypoglycemia it is contraindicated in patients with cardiovasulcular disease or seizure disorder. The glucagon stimulation test is equally time-consuming, and can be associated with nausea in some patients. It has a false positive (fail) rate of up to 8% so confirmation of ACTH deficiency with a second test may be required depending on the clinical picture. Both tests have an advantage that they assess growth hormone secretory reserve also.

Synthetic corticotrophin can also be used (short synacthen test) but this stimulates cortisol secretion at the level of the adrenal gland rather than stimulating ACTH. Therefore, if ACTH

deficiency is of recent onset, for example post-pituitary surgery or traumatic brain injury, the adrenal gland may not yet have atrophied and may mount a (false) normal response to ACTH stimulation. However, this test is relatively simple and well tolerated, and can reliably exclude clinically significant ACTH deficiency where ITT is contraindicated, if performed six weeks after the onset of pituitary injury. The cut-off for normality has been shown to be assay dependent, and therefore should be determined in each unit based on responses in healthy controls.

The choice of test used to diagnose ACTH deficiency should be individualized for each patient, and the results interpreted within the clinical context and with understanding of potential pitfalls of the test used. Borderline results are often difficult to interpret and should be clarified by an alternative test.

A Garrahy, A Agha
Division of Endocrinology, Beaumont Hospital, Dublin, Ireland

Publication

How should we interrogate the hypothalamic-pituitary-adrenal axis in patients with suspected hypopituitarism?
Garrahy A, Agha A
BMC Endocr Disord. 2016 Jun 17