ADRENAL HYPOFUNCTION: GUIDELINES FOR INVESTIGATION

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Director responsible for implementation:	Dr Edmund Lamb
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Version Control Schedule

Version	Date	Author	Status	Comment
1.0	12-2013	Mrs Ruth Lapworth Dr Susan Vickery		Archived
2.0	May 2017	Mr C Rowe/Dr S Stock		Archived
3.0	Sept 2018	Mr C Rowe/Dr S Stock		Added citalopram as a drug that may interfere with the short synacthen test and HPA axis overall - reference has been added in appropriate section of document. Page 13 ref 10.

Contents

Section		Page
1	Policy Summary	4
2	Introduction	4
3	Purpose and Scope	4
4	Definitions	4
5	Duties	4
6	Adrenal hypofunction: guidelines for investigation	5
7	Short synacthen test	6
8	Adrenocorticotrophic hormone (ACTH): guidelines for requesting in suspected adrenal hypofunction	8
9	Monitoring patients on replacement steroid therapy	9
10	Assessment of adrenal reserve: management of steroid withdrawal	10
11	Depot (1 mg) synacthen test	11
12	Key Stakeholders, Consultation, Approval and Ratification Process	12
13	Review and Revision Arrangements	12
14	Dissemination and Implementation	12
15	Document Control including Archiving Arrangements	12
16	Monitoring Compliance	12
17	References	12
18	Associated Documentation	12
	Appendices	
	Appendix A: Equality Impact Assessment	13
	Appendix B: Author's Checklist of Content	16
	Appendix C: Plan for Dissemination of Policies	17

1 Policy Summary

This policy gives guidance on the investigation of suspected adrenal hypofunction.

2 Introduction

Adrenal hypofunction typically occurs due to adrenal failure but may be secondary. Typical symptoms including hyponatraemia, hypotension, hypoglycaemia and increased susceptibility to infection result from the deficiency of cortisol and in some cases mineralocorticoids. Adrenal hypofunction can present as a chronic condition or acutely (Addisonian crisis) and responds to steroid replacement therapy.

In primary adrenal failure the adrenal gland has impaired secretory function with intact hypothalamic and pituitary reserve. In secondary adrenal failure there is impaired stimulation of the adrenals as a result of disruption to adrenocorticotrophic hormone (ACTH) secretion. In long-standing secondary failure the adrenals may also demonstrate an impaired response to stimulation.

There is evidence that use of acute and chronic opioid therapy can cause significant secondary adrenal insufficiency. The insufficiency is usually reversible after discontinuation of opioid therapy. These patients may demonstrate a supressed basal cortisol and ACTH and a blunted cortisol response to synacthen.

3 Purpose and Scope

This policy outlines the clinical investigation required to confirm or exclude a diagnosis of adrenal hypofunction. It may be used for patients both within the Trust and in primary care and the community.

4 Definitions

ACTH: adrenocorticotrophic hormone
HPA axis: hypothalamic-pituitary-adrenal axis
Synacthen: synthetic ACTH (Tetracosactide)

5 Duties

All staff involved in the investigation of adrenal hypofunction, whether clinical or laboratory, must adhere to this policy.

6 Adrenal hypofunction: guidelines for investigation

Please state on the request form all relevant clinical details and that adrenal hypofunction is suspected.

A. TO ESTABLISH THE DIAGNOSIS

(i) Measurement of serum cortisol

A blood sample (gold topped tube) must be collected between 08:00 and 10:00. Ensure the patient is not receiving steroids.

Measurement of random serum cortisol concentrations are of limited value for assessment of HPA axis unless an Addisonian crisis is suspected.

Interpretation

A serum cortisol concentration >480 nmol/L excludes adrenal hypofunction assuming the patient is not receiving steroids (including HRT and hormonal contraceptives).

A random cortisol concentration <50 nmol/L may be consistent with Addison's disease. Suggest refer to an endocrinologist.

(ii) Short synacthen test

A short synacthen test is indicated if there is clinical suspicion of adrenal hypofunction and the early morning serum cortisol concentration is <480 nmol/L. This test is carried out as described in section 7.

B. DIFFERENTIAL DIAGNOSIS OF ADRENAL HYPOFUNCTION

In cases where secondary adrenal hypofunction is suspected or an inadequate/equivocal response to the short synacthen test is obtained measurement of ACTH is indicated (see section 8). For secondary adrenal hypofunction, measurement of pituitary hormones including prolactin, thyroid function tests, FSH, LH and IGF-1 may also be indicated.

C. PATIENTS RECEIVING STEROID REPLACEMENT THERAPY

Measuring cortisol concentration in patients receiving steroids may be of value to ensure optimal replacement (see section 9). Careful assessment of adrenal reserve is required in those patients in whom steroids may be withdrawn and the procedures in section 10 should be followed.

7 Short synacthen test

Indications for test

A short synacthen test is performed for the diagnosis/exclusion of adrenal hypofunction (including Addisonian crisis). Indications include hyponatraemia, hypotension, hypoglycaemia, uraemia and/or a 09:00 cortisol concentration <480 nmol/L in a patient where there is a high clinical suspicion of adrenal insufficiency.

Contraindications

Hydrocortisone and fludrocortisone interfere with this test. If safe, steroid therapy should be discontinued the evening prior to performing the short synacthen test. Steroid therapy can be recommenced immediately after the short synacthen test has been performed. (If a patient is on long-term steroid therapy consider a depot (1 mg) synacthen test.) The short synacthen test gives unreliable results in the two weeks following pituitary surgery. Synacthen is contraindicated in patients with a history of atopic allergy such as asthma, eczema and hayfever.

Patient preparation

There are no dietary restrictions for this test. Patients should not be receiving steroid therapy (see above).

Side effects

There are rare reports of hypersensitivity to synacthen.

Procedure

- Ideally the test should be undertaken **before** commencement of steroid therapy.
- For adults obtain 250 µg/mL synacthen (Tetracosactide) from pharmacy.
- For children see Specialist Paediatric Biochemical Investigations protocol (BIO NO 399). This is available on Q Pulse and within the healthcare professionals zone of Trustnet.
- Ideally perform test at 09:00.
- Take blood sample (gold tube) for serum cortisol at 09:00 (time 0). Write **actual time** on both the sample and form.
- Inject 250 microgram synacthen i.m. or i.v. as a single dose.
- Take second blood sample (gold tube) for serum cortisol **exactly 30 minutes post** synacthen injection. Please write **actual time** on both the sample and form.
- Send **both blood samples together** to the laboratory with the request form for a short synacthen test.
- It is not necessary to collect a sample at 60 minutes post synacthen administration. Samples collected at this time point have no diagnostic value.

Interpretation

Assuming the patient is not on steroids (including HRT and oral contraceptives), a serum cortisol concentration 30 minutes postsynacthen administration > 480 nmol/L is an adequate response and excludes primary adrenal hypofunction. A normal response does not exclude secondary (pituitary) adrenal hypofunction.

An equivocal response, a serum cortisol concentration 30 minutes postsynacthen administration between 450 and 480 nmol/L, may require further assessment of adrenal reserve after discussion with a consultant endocrinologist

An inadequate response, a serum cortisol concentration <450 nmol/L 30 minutes postsynacthen, suggests adrenal insufficiency. Further investigation may include measurement of ACTH and cortisol in paired samples taken at 09:00.

Patients who have been receiving long-term steroid replacement may also demonstrate an inadequate response to synacthen.

Patients on opioid therapy and citalopram may demonstrate an inadequate response to synacthen due to the effect of the drugs on the HPA axis.

If secondary adrenal hypofunction is suspected refer to a consultant endocrinologist.

Please contact the Duty Biochemist (01233 616287 or ext 723 6287) prior to requesting ACTH. Samples for ACTH cannot be collected in primary care, as must arrive in the laboratory within 15 minutes of collection.

8 Adrenocorticotrophic hormone (ACTH): guidelines for requesting in suspected adrenal hypofunction

Indications for test:

Adrenocorticotrophic hormone (ACTH) measurement is required for the differential diagnosis of adrenal hypofunction in patients who have demonstrated an inadequate response to synacthen.

Patient preparation:

Avoid stress.

Procedure:

- It is essential to contact the Duty Biochemist (01233 616287 or ext 723 6287) prior to collecting blood for ACTH. Blood for ACTH measurement must not be collected in primary care.
- Collect the blood samples between 08:00 and 10:00.
- Take a 4 mL blood sample into an EDTA tube (purple tube) for plasma ACTH and a paired 4 mL blood sample (gold tube) for serum cortisol.
- Clearly state on both the request form and sample tubes the actual time the blood was collected.
- Send both blood samples with a request form for ACTH and cortisol to the laboratory immediately. Plasma for ACTH must be separated from the red blood cells and frozen within 15 minutes of venepuncture.
- Samples that are haemolysed or not separated within 15 minutes are unsuitable for analysis.
- ACTH measurement is performed at a referral laboratory.
- Requests will be vetted by the Duty Biochemist before despatch.
- The turnaround time for the result is 2-3 weeks.

Interpretation:

ACTH concentration will be appropriately elevated relative to the serum cortisol concentration in primary adrenal hypofunction.

ACTH concentration will be inappropriately low relative to the serum cortisol concentration in secondary (pituitary) or tertiary (hypothalamic) adrenal hypofunction.

9 Monitoring patients on replacement steroid therapy

Indications

Measurement of serum cortisol concentration may be useful in patients receiving hydrocortisone steroid therapy who are under the care of an endocrinologist. This is only indicated in patients where the replacement steroid is hydrocortisone. Day curves to assess adequacy of glucocorticoid replacement are not generally indicated and should only be undertaken in patients under the care of an endocrinologist.

Patient Preparation

Continue to take hydrocortisone as usual throughout the test.

Procedure

The following procedure is recommended unless otherwise agreed with consultant endocrinologist

- Take blood sample (gold tube) for serum cortisol at 09:00. Please write **actual time** on both the sample and form. (NB morning hydrocortisone dose to be taken at the normal time).
- Take second blood sample (gold tube) for serum cortisol at 12:30 hour prior to the lunchtime dose, unless otherwise agreed with consultant endocrinologist. Please write **actual times** on both the sample and form.
- Take final blood sample (gold tube) for serum cortisol at 17:30 hour prior to the evening dose, unless otherwise agreed with consultant endocrinologist. Please write **actual times** on both the sample and form.
- Please send each blood sample to the laboratory within 4 hours of venepuncture along with the request form.

Interpretation

Assessment of adequacy of hydrocortisone replacement, based on the above serum cortisol measurements, is made by a consultant endocrinologist.

10 Assessment of adrenal reserve: Management of steroid withdrawal

Indications

Patients who are receiving a prednisolone dose <5 mg per day and are being considered for withdrawal may require assessment of adrenal reserve. Adrenal insufficiency is common in patients who are having long-term steroids slowly withdrawn.

Contraindications

All corticosteroid preparations, except dexamethasone, cross-react with cortisol assays.

Procedure

- Omit the morning dose of corticosteroid.
- Take blood sample (gold tube) for serum cortisol at 09:00.

Interpretation

See section 6 for the interpretation of serum cortisol concentration.

If an equivocal serum cortisol concentration is obtained a short synacthen test (see section 7) may be performed (NB again omitting morning dose of corticosteroid on day of short synacthen test).

NB If cortisol is measured in patients who have taken prednisolone or hydrocortisone at the time of testing falsely high cortisol concentrations will be obtained.

11 Depot (1 mg) synacthen test

Indications for test

Depot (1 mg) synacthen tests are generally not recommended but may be undertaken in a small number of patients if specifically requested by a consultant endocrinologist. If a patient has been on long-term steroid therapy and adrenal hypofunction is suspected suggest discuss with consultant endocrinologist.

12 Key Stakeholders, Consultation, Approval and Ratification Process

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this policy.

Consultation has been through e-mail and face-to-face communication between clinical biochemistry staff and Trust consultant endocrinologists Dr C Williams, Dr M Flynn and Dr S Joseph. Correspondence is held on the shared-drive.

13 Review and Revision Arrangements

Three years from implementation date, by author.

14 Dissemination and Implementation

Dissemination to relevant staff within Pathology via Q Pulse. Dissemination to users of the service via documentation hosted in the healthcare professionals zone of Trustnet.

15 Document Control including Archiving Arrangements

Archive of this document will be through QPulse.

16 Monitoring Compliance

Within the Trust, compliance with this policy must rest with the requesting Divisions with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry.

17 References

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10. Pariante, C.M., Papadopoulos, A.S., Poon, L., Cleare, A.J., Checkley, S.A., English, J., Kerwin, R.W. and Lightman, S., 2004. Four days of citalopram increase suppression of cortisol secretion by prednisolone in healthy volunteers. *Psychopharmacology*, *177*(1-2), pp.200-206.

18 Associated Documentation

Not applicable

Appendix A - Equality Impact Assessment

Equality and Human Rights Impact Analysis (EHRIA)

Part One – Screening Tool

Name of the policy, strategy, function or methodology:	Adrenal hypofunction: guidelines for investigation

Details of person completing the EHRIA	
Name	Mr Ceri Rowe
Job Title	Senior Clinical Scientist
Department/Specialty	Pathology/Clinical Biochemistry
Telephone Number	723 6287

1. Identify the policy, strategy, function or methodology aims

What are the main aims, purpose and outcomes of the policy, strategy, function or methodology?
To ensure appropriate investigation of suspected adrenal hypofunction across the health service in East Kent.
Does it relate to our role as a service provider and/or an employer?
Service provider.

2. Assess the likely impact on human rights and equality

Use this table to check if the policy, strategy, function or methodology:

- could have a negative impact on human rights or on any of the equality groups, or
- could have a positive impact on human rights, contribute to promoting equality, equal opportunities or improve relations.

It is not necessary to complete each box, nor to mark whether it is positive or negative, although you can do this if you find it helpful.

	Protected Characteristic								
	Race	**Sex**	**Disability**	**Sexual Orientation**	**Religion or belief**	**Age**	**Gender reassignment**	**Marriage & Civil Partnership**	**Pregnancy & Maternity**
Could this policy, procedure, project or service affect this group differently from others? **YES/NO**									
Could this policy, procedure, project or service promote equal opportunities for this group? **YES/NO**									
Right to life *e.g. decisions about life-saving treatment, deaths through negligence in hospital*									
Right not to be tortured or treated in an inhuman or degrading way *e.g. dignity in care, abuse or neglect of older people or people with learning disabilities.*									
Right to respect for private and family life e.g. *respecting lgb relationships, confidentiality*									
Right to freedom of thought, conscience and religion *e.g. respect for cultural and religious requirements*									
Right to freedom of expression *e.g. access to appropriate communication aids*									
Right to freedom of assembly and association *e.g., right to representation, to socialise in care settings*									
Right to education *e.g. access to basic knowledge of hygiene and sanitation*									
Right to liberty e.g. informal detention of patients who do not have capacity									

3. How does it impact on people's human rights and equality?

Using the table above, explain anticipated impacts. If a full EHRIA is recommended, you can summarise the impacts - it is not necessary to set these out in detail,

Could people's human rights be impacted negatively? Could the policy, strategy, function or methodology result in inequality or discrimination?
No
Could this policy, strategy, function or methodology result in positive impacts on people's human rights or equality? Could it present opportunities to promote equality?
No

4. Recommendations

Is a full EHRIA recommended? If not, give reasons
No. The policy has equal impact.

5. Publication of EHRIA

Give details of where Screening Tool or the full EHRIA will be published and when this will take place
With document.

Details of person completing the EHRIA	
Name	Mr Ceri Rowe, Senior Clinical Scientist

Signed …… Date: ……

Approval and sign-off	Name
Head of Department/Director	Dr Edmund Lamb, Head of Service Clinical Biochemistry

Signed …… Date: ……

	Name
Trust Board approval and sign-off	not applicable

Signed …… Date: ……

Appendix B – Author's Checklist of compliance with the Policy for the Development and Management of Organisation Wide Policies and Other Procedural Documents

POLICY:

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

	Requirement:	Compliant Yes/No/ Unsure	Comments
1.	**Style and format**	Yes	
2.	**An explanation of any terms used in documents developed**	Yes	
3.	**Consultation process**	Yes	
4.	**Ratification process**	Yes	
5.	**Review arrangements**	Yes	
6.	**Control of documents, including archiving arrangements**	Yes	
7.	**Associated documents**	n/a	
8.	**Supporting references**	Yes	
9.	**Relevant NHSLA criterion specific requirements**	n/a	
10.	**Any other requirements of external bodies**	n/a	
11.	**The process for monitoring compliance with NHSLA and any other external and/or internal requirements**	n/a	

Appendix C – Plan for Dissemination of Policies

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

Acknowledgement: University Hospitals of Leicester NHS Trust (Amended)

Title of document:	Adrenal hypofunction: guidelines for investigation		
Version Number:	2.0		
Approval Date:	01-2014	**Dissemination lead:**	Mr Ceri Rowe
Previous document already being used?	Yes		
If yes, in what format (paper / electronic) and where (e.g. Directorate / Trust wide)?	Electronic version hosted on Q pulse (document management system within pathology) and within the healthcare professionals zone of Trustnet		
Proposed instructions regarding previous document:	This guideline will replace version		

To be disseminated to:	**How will it be disseminated, who will do it and when?**	**Format (i.e. paper or electronic)**	**Comments:**
Trust clinical staff	Trustnet	electronic	
Primary care	Trustnet	electronic	
Clinical Biochemistry staff	Q Pulse	electronic	

Author's Dissemination Record - to be used once document is approved – to be kept with the master document

Date document forwarded to be put on the Trust's central register / in SharePoint:		**Date document put on Directorate register (if appropriate) / on Directorate webpage (if applicable)**	

Disseminated to: (either directly or via meetings, etc.)	**By Whom?**	**Format (i.e. paper or electronic)**	**Date Disseminated:**