Current Practice

Adrenal insufficiency

Navoda Atapattu[1]

Sri Lanka Journal of Child Health, 2013; **42**: 90-94

(Key words: Adrenal insufficiency; children; treatment)

Introduction

The adrenal gland is made up of two distinct embryological cell lines, the cortex derived from mesenchymal cells and the medulla from neuroectodermal cells. The adrenal cortex consists of three concentric zones, the outer zona glomerulosa secreting the mineralocorticoid aldosterone, the intermediate zona fasciculata secreting cortisol and the inner zona reticularis secreting androgens. Chromaffin cells in the adrenal medulla produce catecholamines.

Primary adrenal insufficiency

Primary adrenal insufficiency results when the adrenal gland itself becomes dysfunctional. The commonest cause of primary adrenal insufficiency is autoimmune destruction of the adrenal cortex[1]. Autoimmune destruction of the adrenal gland could occur as an isolated event or as part of an autoimmune polyglandular syndrome. The aetiology of primary adrenal insufficiency is given in table 1.

Table 1: ***Aetiology of primary adrenal insufficiency***

Adrenal destruction	Adrenal hypoplasia	Impaired steroidogenesis
Autoimmune • Isolated • Autoimmune polyglandular syndrome (APS) type 1 • APS type 2 Adrenoleukodystrophy (ALD) Infections Haemorrhage Metastatic Drugs • Ketoconazole Metabolic • Amyloidosis • Wolman syndrome • Zellweger syndrome	SF 1 mutation DAX 1 mutation Xp21 contiguous gene deletion IMAGe syndrome ACTH receptor defect Familial glucocorticoid deficiency Triple-A syndrome	Cholesterol biosynthetic defect Smith-Lemli-Opitz syndrome Abetalipoproteinaemia Steroid biosynthetic defect Congenital adrenal hyperplasia (CAH) P450 oxidoreductase deficiency Steroidogenic acute regulatory (StAR) protein mutations

Autoimmune polyglandular syndrome type 1

Autoimmune polyglandular syndrome type 1 (APS-1) is a rare recessively inherited disease. There are 3 cardinal features viz. mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency. The first manifestation is mucocutaneous candidiasis during infancy or early childhood usually before 5 years. Hypoparathyroidism develops before 10 years and adrenal insufficiency before 15 years[2]. There are minor manifestations which may appear before any of the three cardinal manifestations. This variable presentation makes the diagnosis challenging. There should be two out of the three cardinal manifestations to define APS-1. Any child presenting with one of the three cardinal features should be evaluated for the other cardinal and minor manifestations (table 2)

[1]*Acting Consultant Paediatric Endocrinologist Lady Ridgeway Hospital for Children, Colombo*

Table 2

Hyper gonadotropic hypogonadism
Autoimmune thyroid disease
Type 1 diabetes mellitus
Pituitary defects
Pernicious anaemia
Malabsorption
Cholelithiasis
Chronic active hepatitis
Vitiligo
Alopecia
Urticarial-like erythema with fever
Nail dystrophy
Dental enamel hypoplasia
Tympanic membrane calcification
Keratoconjunctivitis
Hyposplenism/asplenia

Adrenal insufficiency could present as late as 20 years of age. Therefore, it is necessary that a patient coming with an autoimmune condition should have close follow up. Any clinical evidence of cortisol deficiency should be confirmed by the synacthen test.

Autoimmune polyglandular syndrome type 2

The presence of primary adrenocortical insufficiency with either autoimmune thyroid disease or type 1diabetes in the same individual is defined as autoimmune polyglandular syndrome type 2 **(**APS-2). Addison disease + thyroid disease is known as Schmidt syndrome.

Addison disease + type 1diabetes is known as Carpenter syndrome.

Addison disease is present in all patients. Only 19 % of the patients have all three components[3]. Compared to APS1, minor manifestations are rare.

Adrenoleukodystrophy (ALD)

Neurological symptoms are the earliest manifestations. Symptoms of adrenal insufficiency appear after symptoms of white matter disease but 20% of the patients had adrenal insufficiency before neurological signs. In adrenomyeloneuropathy adrenal insufficiency may appear 10-15 years later[4].

Triple A (Allgrove) syndrome

This is an autosomal dominant disorder consisting of Addison disease, achalasia of the cardia and alacrima. Adrenal insufficiency is rarely the presenting symptom. Clinical presentation is quite variable. Sensorineural deafness, progressive neurological impairment, peripheral or cranial neuropathies and autonomic dysfunctions are other associated manifestations. Usually these patients present with achalasia or failure to thrive.

Familial glucocorticoid deficiency

There are two types. Patients present with hypoglycaemia due to cortisol deficiency. Marked elevation of adrenocorticotrophic hormone (ACTH) seen in this condition causes hyperpigmentation which does not resolve with cortisol replacement therapy[4].Tall stature is seen in patients with type 2 disease and they present later.

Adrenal hypoplasia congenital (AHC)

Usually males are affected. Mutations of the *DAX-1* gene on chromosome Xp21is implicated in this condition. Fetal adrenal zone is not developed and it is vacuolated. Neonates present with salt losing crisis. These patients will not go through puberty. Deletions of the *DAX-1*gene may also involve adjacent genes, causing glycerol kinase deficiency, Duchene muscular dystrophy and mental retardation[5].

Congenital adrenal hyperplasia (CAH)

Congenital adrenal hyperplasia (CAH) is a recessively inherited group of disorders. Reported incidence is 1:10,000- 1: 15,000[6]. Classic salt losing form presents with salt losing crisis in the early neonatal period. Girls will have ambiguous genitalia and consequently come to medical attention early. However, boys can go unnoticed, giving an increased risk of neonatal deaths. When a neonate presents with unexplained dehydration or shock it would be lifesaving to treat as adrenal insufficiency after taking baseline blood for electrolytes and if possible serum cortisol. When blood sampling is impossible at the acute stage, treating with hydrocortisone will not hamper the diagnosis of CAH. Once the patient is stabilized a detailed history will lead to the diagnosis of CAH when pigmentation, vomiting, poor feeding, ambiguous genitalia are elicited in the history. When the diagnosis is more in favour of CAH, fludrocortisone and salt supplements should be commenced. It is necessary to send blood for confirmatory tests at the earliest opportunity. 17-hydroxyprogesterone, dehydroepiandrostenedione, testosterone and cortisol are the available tests in this country. Renin, aldosterone levels, urinary steroid profile, and genetic tests will give the complete diagnosis but their absence has not precluded the management of these children. Management and follow up of a patient with CAH is a topic on its own and will not be discussed here.

Congenital lipoid adrenal hyperplasia (StAR protein mutation)

Congenital lipoid adrenal hyperplasia is a rare autosomal recessive disorder, characterized by absent or diminished adrenal and gonadal steroid hormone synthesis[7]. Affected children present with adrenal

insufficiency in early infancy due to a failure of glucocorticoid and mineralocorticoid biosynthesis. 46, XY babies appear phenotypically female due to impaired testicular androgen secretion. There are non-classic forms of this condition which may present late with adrenal insufficiency with normal male genitalia[8].

Secondary Adrenal Insufficiency

Any impairment in ACTH production or release can cause secondary adrenal insufficiency. Secondary adrenal insufficiency does not affect mineralocorticoid release but glucocorticoid and androgen release.

Aetiology of secondary adrenal insufficiency

- Hypothalamic causes
- ACTH deficiency
- Long term steroid therapy
- Disorders of proopiomelanocortin (POMC)

Hypothalamic causes

Secondary adrenal insufficiency occurs due to tumours, after surgery or radiotherapy in the hypothalamo-pituitary region. 25% of the patients with craniopharyngioma have adrenal insufficiency[9]. However, adrenal insufficiency is a rare presentation of a tumour.

ACTH deficiency

ACTH deficiency may occur as a part of multiple pituitary hormone deficiency (MPHD) or as an isolated ACTH insufficiency. MPHD results from disorders of transcription factors involved in hypothalamo–pituitary development (e.g. HESX1, LHX4, SOX3). Most common genetic cause is PROP1 mutation. It may appear years after the diagnosis of growth hormone, thyroid hormone deficiency. Isolated ACTH deficiency results from mutation in TPIT. It is a rare recessively inherited condition. Isolated ACTH deficiency can be associated with memory defects and hair abnormalities as part of triple H syndrome[10].

Long term steroid therapy

Long term steroids suppress POMC gene transcription, ACTH and corticotrophin releasing hormone (CRH) synthesis and storage. Vigilance is required following removal of long term steroids even nasal sprays or eye drops. Recovery of the axis takes a variable duration of time based on the duration of therapy, potency of the steroid used and also the age of the child[11].

Disorders of POMC

Defects in POMC synthesis and processing can cause ACTH deficiency. It is a rare recessively inherited condition which is associated with red hair, obesity, and pale skin[12].

Diagnosis of adrenal insufficiency

Patients can present with anorexia, nausea, vomiting, loss of appetite, chronic fatigue, weight loss, weakness and a lack of energy, recurring abdominal pain, increased skin pigmentation mainly in gums, knuckles, elbows, knees and salt craving. Latter 2 symptoms are not seen in secondary adrenal insufficiency. Patient with febrile illness, surgery, trauma can present with adrenal crisis. A neonate may have hypoglycaemia, and or jaundice with secondary adrenal insufficiency. Evidence of ambiguous genitalia will indicate possibility of congenital adrenal hyperplasia. Appropriate history and examination are of paramount importance to arrive at a diagnosis. Hyponatraemia with hyperkalaemia may be seen when patient presents with adrenal crisis with or without hypoglycaemia. Plasma cortisol level <5ug/dl in the morning will confirm the diagnosis of adrenal insufficiency. If the diagnosis is unclear, short synacthen test is indicated. Test protocols and interpretations may differ in different centres.

Widely accepted short synacthen test protocol

- Serum cortisol is sent at 0 minute
- Synthetic ACTH is given intravenously
  < 6 months: 62.5µg
  6 - 24 months: 125µg
  >24 months: 250µg
- Serum cortisol is sent at 30 and 60 minutes.
- Interpretation: 30 minute cortisol level >550nmol/l or >200nmol/l over base line value is considered normal.

Based on the underlying aetiology additional appropriate investigations are needed.

Management of adrenal crisis

- Correct dehydration and salt loss with intravenous normal saline
- Correct hypoglycaemia with intravenous dextrose saline solution.
- 10% glucose: 5 ml/kg. Bolus if hypoglycaemic
- Followed by infusion: 5% glucose + 0.9% sodium chloride
- Intravenous hydrocortisone 100 mg/m^2 bolus, then 100 mg/m^2/day (in 4 divided doses)
- Treatment of hyperkalaemia
- Monitor electrolytes, glucose
- Later add fludrocortisone if hyponatraemia or hypokalaemia is noted.

Long term management of adrenal insufficiency

- Hydrocortisone 8-10mg/m^2/day in three divided doses
- Fludrocortisone 0.05-0.15mg/day (only with primary adrenal failure)
- Stress dose of hydrocortisone with fever, surgery, trauma (advice to take 2-3 times of the usual requirement)
- Advice on early medical attention with vomiting, diarrhoea
- Monitor adequacy of treatment clinically
    - Under treatment will cause weakness, morning hypoglycaemia, pigmentation
    - Over treatment will result in cushingoid features
- Monitor growth and blood pressure
- Medic alert to wear
- It is important to remember that the underlying cause needs to be evaluated and managed appropriately.

Adrenal insufficiency is a life threatening condition. Management protocols should be in place in every medical institute in order to prevent life limited consequences.

References

1. Perry R, Kecha O, Paquette J et al. Primary adrenal insufficiency in children: twenty year experience at the Sainte-Justine Hospital, Montreal. *Journal of Clinical Endocrinology & Metabolism* 2005; **90** (6):3243-50. http://dx.doi.org/10.1210/jc.2004-0016

2. Betterle C, Greggio NA, Volpato M. Clinical review 93: autoimmune polyglandular syndrome type I. *Journal of Clinical Endocrinology & Metabolism* 1998; **83**:1049–55. http://dx.doi.org/10.1210/jc.2004-0016

3. Betterle C, Dal Pra C, Mantero F et al. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens and their applicability in diagnosis and disease prediction. Endocrine Reviews 2002; 23: 327–64. http://dx.doi.org/10.1210/er.23.3.327

4. Sperling MA. Paediatric Endocrinology 3rd ed. Chapter 12: The Adrenal cortex and its disorders. Philadelphia: Saunders Elsevier; 2008.

5. Lin L, Gu W-X, Ozisik G *et al*. Analysis of DAX1 (*NR0B1*) and steroidogenic factor-1 (SF1/Ad4BP, *NR5A1*) in children and adults with primary adrenal failure: Ten years' experience. *Journal of Clinical Endocrinology & Metabolism* 2006; **91**: 3048–54. http://dx.doi.org/10.1210/jc.2006-0603

6. Krone N, Arlt W. Genetics of congenital adrenal hyperplasia. *Best Practice & Research Clinical Endocrinology & Metabolism* 2009; **23**:181–92. http://dx.doi.org/10.1016/j.beem.2008.10.014

7. Miller WL, Strauss JF 3rd. Molecular pathology and mechanism of action of the steroidogenic acute regulatory protein, StAR. *Journal of Steroid Biochemistry & Molecular Biology* 1999; **69**:131–41. http://dx.doi.org/10.1016/S0960-0760(98)00153-8

8. Baker BY, Lin L, Kim CJ et al. Non-classic congenital lipoid adrenal hyperplasia: a new disorder of the steroidogenic acute regulatory protein with very late presentation and normal male genitalia. *Journal of Clinical Endocrinology & Metabolism* 2006; **91**:4781–5. http://dx.doi.org/10.1210/jc.2006-1565

9. DeVille CJ, Grant DB, Hayward RD, et al. Growth and endocrine sequelae of craniopharyngioma. *Archives of Disease in Childhood* 1996; **75**:108-14. http://dx.doi.org/10.1136/adc.75.2.108

10. Farooqi IS, Jones MK, Evans M et al. Triple H syndrome: a novel autoimmune endocrinopathy characterized by dysfunction of the hippocampus, hair follicle, and hypothalamic-pituitary adrenal axis. *Journal of Clinical Endocrinology & Metabolism* 2000; **85**(8):2644-8. http://dx.doi.org/10.1210/jc.85.8.2644

11. Graber AL, Ney RL, Nicholson WE et al. Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids *Journal of Clinical Endocrinology & Metabolism* 1965; **25**:11–16. http://dx.doi.org/10.1210/jcem-25-1-11

12. Krude H, Biebermann H, Luck W, et al. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nature Genetics* 1998; **19**:155–7. http://dx.doi.org/10.1038/509