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Pediatric Endocrinology Nursing Society Department

Understanding tertiary adrenal insufficiency☆,☆☆

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Glucocorticoids are used for a variety of conditions, but can have undesirable consequences if not managed correctly. Long term or high dose use of glucocorticoids can put the individual at risk of adrenal insufficiency, and more awareness is needed to aid adrenal recovery to ensure patient safety.

The adrenal glands

The two adrenal glands each sit on top of the kidneys. They begin developing at six weeks gestation (Vasudevan & Brandt, 2018) and become fully functioning when an infant is about six months of age. By this time, the different layers have formed: the adrenal medulla (the middle section) which secretes catecholamines, and also the adrenal cortex: the outer layer. The cortex is then split into three further layers, from the outside in:

- The Zona Glomerulosa (ZG) constitutes about 10% of the cortex, and produces aldosterone after being activated by the renin angiotensin axis.
- The Zona Fasciculata (ZF) makes up around 80% of the cortex and produces cortisol.
- The Zona Reticularis (ZR) makes up 10% and produces androgens (sex steroids) (Vasudevan & Brandt, 2018)

Cortisol

Cortisol is our body's natural steroid. Nearly all cells in the body have receptors for cortisol, resulting in various responses. It is controlled by three areas: the hypothalamus in the brain, which releases corticotropin releasing hormone (CRH), which then stimulates the pituitary gland – which sits just below the hypothalamus – to secrete adrenocorticotropin hormone (ACTH). ACTH then acts on the cortex of the adrenal glands to release cortisol. This is known as the hypothalamo-pituitary-adrenal (HPA) axis (Figure 1.1).

The main function of the HPA axis focuses on the body reacting to stress, initially mediated by the sympathetic nervous system with the release of adrenaline and noradrenaline. Once these hormones are released, in a 'fight or flight' situation, CRH is released, resulting in the cascade of hormone release in the HPA axis (Sheng et al., 2020). Cortisol acts on many tissues, focusing on energy stores, vasoconstriction, blood pressure regulation, metabolism, blood glucose regulation, and regulating the stress response, and is vital for homeostasis. Once cortisol is released, through a negative feedback loop, it inhibits the further release of CRH, and thus also ACTH. A stress response alters the body's homeostasis (Acconcia & Marino, 2016): this could be cold, heat, trauma, or anything perceived to be a 'stressor'. If the body is unable to produce cortisol, it is life threatening, and the cortisol needs to be replaced with synthetic glucocorticoids.

Primary Adrenal Insufficiency (PAI)

With PAI (Figure 1.2), affected individuals cannot produce cortisol and also sometimes aldosterone (Kirkgoz & Guran, 2018). The most common cause of PAI in children is congenital adrenal hyperplasia (CAH) resulting in hyperplastic, or enlarged, adrenal glands, resulting in impaired hormone production, and this inability to function will lead to increased levels of ACTH from the pituitary gland. The main function of ACTH is to stimulate the production of cortisol, but the affected adrenal gland results in no cortisol being released, resulting in no feedback to the hypothalamus to stop releasing CRH, and therefore more ACTH being released from the pituitary gland (Park et al., 2016).

Secondary Adrenal Insufficiency (SAI)

SAI (see Figure 1.3) is evident when the pituitary gland is not secreting enough or no ACTH, resulting in no cortisol secretion from the adrenal glands, thus interrupting the HPA axis negative feedback mechanism. As the adrenal gland is not the 'cause', aldosterone production is not affected. SAI is seen in children with congenital or acquired hypopituitarism, brain tumours in the hypothalamo-pituitary region, head trauma, or pituitary irradiation (Arlt & Allolio, 2003).

Tertiary Adrenal Insufficiency (TAI)

TAI is probably the most common type of adrenal insufficiency (Nowotny et al., 2021), focusing on the hypothalamus (Fig. 1.4). The most common cause is exposure to long term / high dose exogenous glucocorticoid therapy, resulting in an extended HPA axis suppression. Glucocorticoids entering the systemic circulation, which have survived the first pass metabolism in the liver, impact the negative feedback mechanism of the HPA axis.

☆ The Pediatric Endocrinology Nursing Society (PENS) is committed to the development and advancement of nurses in the art and science of pediatric endocrinology nursing and to improve the care of all children with endocrine disorders through the education of the pediatric healthcare community. To aid in achieving that goal, the purpose of the PENS department is to provide up-to-date reviews of topics relevant to the PENS membership and to the general readership of the Journal of Pediatric Nursing.

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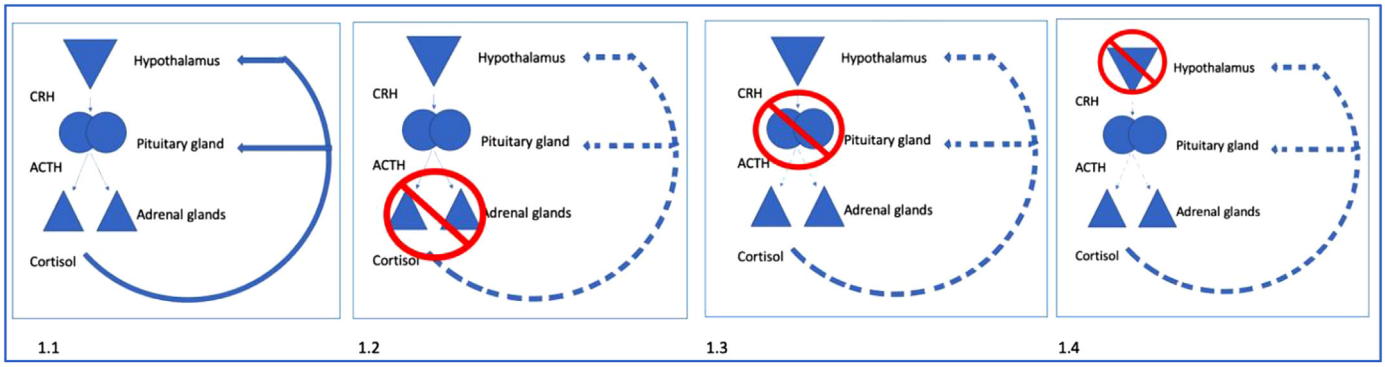

Fig. 1. The Hypothalamo Pituitary Adrenal Axis
1.1: Normal adrenal physiology
1.2 Primary Adrenal Insufficiency
1.3 Secondary Adrenal Insufficiency
1.4 Tertiary Adrenal Insuffiency
Adapted *from The Lancet, 361(9372), Arlt, W., & Allolio, B, Adrenal insufficiency, 1881-1893, 2003, Copyright 2003 with permission from Elsevier.*

There is a negative impact on the neurons in the hypothalamus that secrete CRH, and also the corticotroph cells in the pituitary gland. Therefore, there is a 'knock on effect' on the reduction of cortisol being produced in the adrenal glands. This reduced adrenal function from long term exposure will result in the adrenal glands atrophying (Prete & Bancos, 2021). Once the glucocorticoid therapy is discontinued, the HPA axis recovers, with ACTH and CRH recovering first, and then ultimately cortisol production. However, this can stay suppressed in long term glucocorticoid therapy. Stopping the glucocorticoid treatment abruptly, or rapid tapering / weaning of the medications can be life threatening, and so it may take weeks, or months until normal adrenal function is resumed (Akahoshi & Hasegawa, 2020).

Glucocorticoids are used in the management of many paediatric conditions, including inflammatory disorders such as asthma, autoimmune diseases (Becker, 2013), acute lymphoblastic leukaemia (Hull & Wedrychowicz, 2022), or exacerbations in inflammatory bowel disease (Bruscoli et al., 2021). Treatment for longer than two weeks can lead to a degree of adrenal suppression (Ahmet et al., 2021), but multiple short courses should also be considered risky. After only one month of corticosteroid treatment, adrenal glands can take up to a few months to recover, so longer courses can be at higher risk of clinical management.

Weaning of the glucocorticoids is essential once the initial need for the glucocorticoids is reduced, although there is no standardized protocol for tapering. Temporary replacement with oral hydrocortisone may be needed in equivalent physiological doses, due its shorter duration of action, allowing the HPA axis to recover (Pelewicz & Miskiewicz, 2021). However, poorly managed TAI will result in patients with signs and symptoms of adrenal insufficiency, such as fatigue, nausea, headaches or muscle wasting, to shock and hypotension, such as in an adrenal crisis (Bowden et al., 2019)

Multidisciplinary Team Liaison

Health care professionals managing children on long term / high dose glucocorticoid treatment are advised to liaise with their paediatric endocrine colleagues in order to correctly diagnose and therefore manage the steroid induced adrenal insufficiency. A 0800 / 0900 serum sample for cortisol levels can initiate the diagnostic process (Pelewicz & Miskiewicz, 2021), with further dynamic testing of the HPA axis advised, such as the insulin tolerance test (ITT) or ACTH stimulation test (Younes & Younes, 2017), although synacthen testing is common practice (Ahmet et al., 2021).

Conclusion

This review has briefly highlighted the importance of recognising the risk of glucocorticoid induced adrenal insufficiency in children treated with long term glucocorticoids. Liaison with paediatric endocrine teams is paramount in order to safely manage children, whilst recognising that there are yet no standardized protocols for safe management. The paediatric endocrine nurse can educate paediatric colleagues working in other specialities regarding adrenal insufficiency, and the importance of emergency and sick day management.

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