Mini Review

HORMONE
RESEARCH IN
PÆDIATRICS

Horm Res Paediatr 2018;89:341–351
DOI: 10.1159/000481660

Received: July 24, 2017
Accepted: September 20, 2017
Published online: June 6, 2018

# Adrenal Crises in Children: Perspectives and Research Directions

R. Louise Rushworth[a] David J. Torpy[b] Constantine A. Stratakis[c]
Henrik Falhammar[d–f]

[a]School of Medicine, Sydney, The University of Notre Dame, Darlinghurst, NSW, Australia; [b]Endocrine and Metabolic Unit, Royal Adelaide Hospital and University of Adelaide, Adelaide, SA, Australia; [c]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA; [d]Department of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital, Stockholm, Sweden; [e]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; [f]Menzies School of Health Research and Royal Darwin Hospital, Tiwi, NT, Australia

**Keywords**
Adrenal insufficiency · Congenital adrenal hyperplasia · Adrenal crisis · Hypopituitarism · Primary adrenal insufficiency · Secondary adrenal insufficiency · Epidemiology · Glucocorticoid

**Abstract**
Adrenal crises (AC) are life-threatening physiological disturbances that occur at a rate of 5–10/100 patient years in patients with adrenal insufficiency (AI). Despite their seriousness, there is a paucity of information on the epidemiology of AC events in the paediatric population specifically, as most investigations have focused on AI and ACs in adults. Improved surveillance of AC-related morbidity and mortality should improve the delineation of AC risk overall and among different subgroups of paediatric patients with AI. Valid incidence measures are essential for this purpose and also for the evaluation of interventions aimed at reducing adverse health outcomes from ACs. However, the absence of an agreed AC definition limits the potential benefit of research and surveillance in this area. While approaches to the treatment and prevention of ACs have much in common across the lifespan, there are important differences between children and adults with regards to the physiological, psychological, and social milieu in which these events occur. Education is considered to be an essential element of AC prevention but studies have shown that ACs occur even among well-educated patients, suggesting that new strategies may be needed. In this review, we examine the current knowledge regarding AC events in children with AI; assess the existing definitions of an AC and offer a new definition for use in research and the clinic; and suggest areas for further investigation that are aimed at reducing the incidence and health impact of ACs in the paediatric age group.



## Introduction

An adrenal crisis (AC) is an acute, life-threatening episode of adrenal insufficiency (AI). These events cause considerable morbidity and occasional mortality in both children [1–6] and adults with chronic AI [7–12]. While the precise incidence of ACs in childhood is unknown, estimates from data in mainly adult populations indicate



E-Mail karger@karger.com
www.karger.com/hrp

R. Louise Rushworth
School of Medicine, Sydney, The University of Notre Dame, Australia
160 Oxford St
Darlinghurst, NSW 2010 (Australia)
E-Mail louise.rushworth@nd.edu.au

an approximate frequency of 5–10 ACs/100 patient years (PY) [13–15]. Despite efforts to reduce their incidence, ACs continue to occur among patients of all ages with well-managed AI [13–16].

All children with AI are at risk of an AC during periods of physiological stress, frequently an intercurrent illness. When exposed to a stressor, parents must escalate the dose of glucocorticoid by "stress dosing" and, when necessary, use parenteral hydrocortisone. Other strategies, such as the use of MedicAlert and informing childcare providers and schools about AI/AC, are also regarded as essential elements in AC prevention [2, 13, 15]. Although these interventions are necessary and almost certainly lifesaving, education of parents and children about AC prevention does not appear to be sufficiently effective [16]. Indeed, prevention of ACs remains a cause of considerable anxiety for some parents.

Progress towards AC event minimization is hampered by the relative scarcity of data on the epidemiology of these events in childhood. Prevention has been studied more extensively in adults and, although there are a number of differences between adults and children with AI, some impediments to AC event reduction are shared between the age groups. These include the absence of a universally agreed AC definition, an inability to fully understand variations in AC susceptibility, and the apparent failure of current prevention strategies to reduce the incidence of ACs in treated AI [13, 15]. The aim of this review is to further the progress of AC prevention in childhood by examining the epidemiology of ACs in children, offering a new AC definition for use in paediatric practice, identifying approaches to improve existing AC prevention strategies, and suggesting areas for targeted research efforts in the future.

## AC Incidence, Morbidity, and Mortality

In the general population, the incidence of ACs in treated AI is approximately 5–10 events/100 PY. These episodes are more common in primary AI (PAI) than secondary AI (SAI) and are associated with a mortality rate of 0.5/100 PY [3, 4, 13, 14, 17, 18]. However, with the exception of one study [3], these estimates were derived from adult populations or incorporated episodes that occurred during childhood as part of the lifetime experience of ACs in adults, but did not examine the incidence of ACs in children specifically. As a consequence, the applicability of these incidence estimations to paediatric patients is uncertain.

In the single study that considered ACs in children with treated AI exclusively, the incidence of these events was estimated to be 6.5 ACs/100 PY [3]. However, this measurement was derived from children with congenital adrenal hyperplasia (CAH) only and may not be transferrable to other forms of AI in childhood. The incidence of AC episodes has also been examined in children exposed to inhaled corticosteroid therapy for asthma [19–21]. Although rare, ACs have been shown to occur in this context, affecting 13% of children with symptomatic adrenal suppression due to inhaled corticosteroid therapy treatment in one Canadian study [21].

Apart from measures of incidence, there is little information on the distribution of the AC-related health burden in different subgroups of paediatric patients with treated AI. One recent study examined hospitalizations in all children with a principal diagnosis of an AC, reporting that admissions were higher among females than males in the age group 1–4 years but that males aged 5–14 years had higher rates than females [22]. Another study analyzed episodes of hospitalization in CAH and found that AC admissions diminished with increasing age through the childhood years [23], a result that is consistent with the evidence from previous cohort studies involving CAH patients [3, 4]. In addition, it has been reported that some CAH children appear to have a propensity to develop ACs, experiencing multiple AC events, while others can be observed for years without an episode [3]. This pattern has also been found in adults with other types of AI [13, 15, 17].

An increased risk of mortality in patients with AI has been documented in predominantly adult populations and some of these deaths were attributed to ACs [5, 7–11]. In the paediatric age group, reports have documented sporadic fatalities from ACs and, although these are clearly important and the deaths should be largely preventable, they do not enable determination of mortality rates [24–27]. One study, however, examined mortality in children with CAH, finding a threefold increase in the standardized mortality rate (SMR) [5]. This study also identified that the SMR increase was particularly pronounced in the age group 1–4 years (SMR 18.3), and was higher in females and those from the Indian subcontinental ethnic group [5]. An increased mortality rate in children receiving growth hormone (GH), some of which was attributable to ACs (possibly related to the known suppression of 11-beta-hydroxysteroid dehydrogenase type 1 [11BHSD1] by GH) [28] has also been reported, but the non-specificity of the studies' denominator populations precludes determination of a SAI-specific AC mortality rate [29–31]. In

addition, it has been documented that some patients in all age groups present with an AC, which may be fatal, before an AI diagnosis is confirmed, but the extent to which this occurs has not been determined [24, 25, 27, 31–36]. It is, however, reassuring to note that deaths among children in hospital due to an AC were found to be very uncommon (<1%) in a recent Australian study [23].

### Clinical Factors and Physiology

There is no universally agreed definition of an AC in paediatrics, although there is general agreement about the causative pathophysiological mechanisms underpinning the development of an AC and its indicative symptoms and signs. These include hypotension, abdominal pain and vomiting, a reduced level of consciousness, weakness, and lethargy [1, 2, 13, 15]. A number of biochemical abnormalities, including hyponatraemia, hyperkalaemia (in PAI) and, occasionally, hypercalcaemia may also be found [13, 15, 37].

Hypoglycaemia is a frequent finding in children with an AC [13, 38]. This may be associated with seizures, which are particularly dangerous and may lead to long-term neurological sequelae and even death [38]. Both hypoglycaemia and haemodynamic disturbance may be more pronounced in the context of acute AI in congenital conditions, such as CAH, than in other forms of PAI, due to problems with adrenomedullary development and epinephrine production [2, 39, 40], where the degree of adrenomedullary dysfunction correlates with the severity of the enzyme impairment [2, 39, 40]. Hyperkalaemia may also be severe and associated with life-threatening cardiac arrhythmias.

Hyponatraemia is a particular problem in infants and young children with PAI due to immaturity of the function of the renal tubules [2]. Indeed, younger patients with CAH can present with profound hyponatraemia, which requires careful management of fluid balance to restore electrolyte levels to normal. Hyponatraemia is also found in SAI, despite preservation of aldosterone secretion, due to impaired free water clearance occurring in association with glucocorticoid deficiency. Comorbid diabetes insipidus is thought to potentiate the problems of hypovolaemia and electrolyte disturbances that are associated with an AC in SAI, although the degree to which this increases a patient's AC risk is unknown and worthy of further study.

The protocols for AC management are well established and consist of parenteral administration of hydrocortisone at high doses (50–100 mg/m$^2$ body surface area stat followed by 50–100 mg/m$^2$/day divided q6h) and fluid resuscitation (0.9% saline 20 mL/kg, repeated up to a total of 60 mL/kg) for shock. These doses are based on consensus opinion rather than trial evidence, as are the recommended fluid resuscitation regimens [37]. However, it is known that hydrocortisone doses in this range will produce cortisol concentrations within the maximal physiological rather than immunosuppressive level and this suggests that these doses will be sufficient [41]. Moreover, these recommendations are supported by clinical experience from the successful treatment of patients in AC [41]. In addition, in situations where there are severe electrolyte abnormalities, specific treatments may be required. Similarly, hypoglycaemia requires urgent management with intravenous dextrose.

### Definition of an AC in Paediatrics

The pursuit of improved health outcomes in patients with AI is hindered by the absence of an agreed definition of an AC. This diminishes the potential impact of AC-related research and delays progress towards AC prevention in all age groups [13, 15]. Although much of the discussion regarding the definition of an AC in the literature has focused on problems defining ACs in adults [13, 15], the same issues apply in children. Arguably, the development of a definition of an AC in the paediatric context may be more complex, given the changes in physiology that occur over the childhood years. This is very relevant to research but is also important clinically, as without a clear definition, children who are at particular risk of significant morbidity and even mortality through repeated episodes of AC may not be identified.

Several definitions of an AC have been used in previous studies [5, 15, 16, 42]. Of these, projects that have analysed aggregated datasets have identified ACs by the presence of coded diagnoses [43]. According to the International Statistical Classification of Diseases and Related problems (ICD-10-CM), the rubric E27.2 – "Addisonian or adrenal crisis" (approximate synonym of severe adrenal insufficiency) denotes the diagnosis of an AC [43]. The absence of symptom and sign information in this definition means that the occurrence of the code E27.2 in a dataset represents a range of individual definitions of an AC applied by multiple doctors in various clinical settings. This situation is made more complex in CAH, as patients who experience a "salt-wasting crisis" may be coded as having CAH using the rubric E25.0 "Congenital

**Table 1.** Definitions of adrenal crisis in paediatric patients

| First author [Ref.], year | Definition | | Additional details |
|---|---|---|---|
| Todd [19], 2002 | At least one of the following symptoms or signs: lethargy, nausea or vomiting, diarrhoea, hypotension, abdominal pain, unexplained hypoglycaemia, convulsion<br>In addition to the above, an indication of insufficient HPA axis function | | |
| Goldbloom [21], 2016 | An acute critical illness out of proportion in severity to the current illness and manifested by any of the following: hypotension/shock, decreased level of consciousness/lethargy, unexplained hypoglycaemia or hyponatraemia, seizure, death | *Or* | Symptomatic[1] adrenal insufficiency with supportive biochemical evidence |
| Odenwald [3], 2016 | Dehydration, hypotension, salt-wasting (hyponatremia and hyperkalaemia), hypoglycaemia, or altered mental status | | Adrenal crises may present with weakness, vomiting, abdominal pain, or confusion and may cause shock, coma, and death if untreated |
| Park [1], 2016 | Characteristic features of hypoglycaemia, hypotension, collapse, and coma | | |
| Hsieh [44], 2011 | Hypotension, salt-craving, hyperpigmentation, weight loss, and nausea/vomiting/abdominal pain | | |

[1] Signs/symptoms could include anorexia, weakness, fatigue, lethargy, fever, gastrointestinal symptoms (nausea, vomiting, constipation, diarrhoea, abdominal pain), morning headache, hypoglycaemia, myalgia, arthralgia, psychiatric symptoms and growth failure.

adrenogenital disorders associated with enzyme deficiency" (applicable to: CAH, 21-hydroxylase deficiency, salt-losing CAH) which is also used to denote patients admitted for management of milder illness related to CAH, potentially affecting AC estimations in this subgroup. While this is particularly problematic in CAH due to its use of disease-specific terminology, it is also possible that similar approaches to coding may be used in the other subtypes of AI.

Research projects using other methods, including surveys or cohort studies using samples of patients [5, 16, 42, 44], usually define ACs according to preset study criteria, which may or may not be detailed in the text. Some studies, for example, have identified acute episodes of AI-related illness as ACs (or "salt-wasting crises") or "urgent hospitalizations" [16, 42], while others have given more detailed descriptions (Table 1). While each definition may suit the particular purposes of a study, substantial differences between definitions impede synthesis of data on the incidence of ACs in AI and its subtypes.

Previously, we have addressed the definition of AC in adults [15]. In that review, we recommended that hypotension (either absolute or relative) was a necessary feature of an AC, and that this must be accompanied by a clear resolution of symptoms following the administration of intravenous glucocorticoids [15]. We suggest that this definition may be generally applicable to older children and adolescents but in younger children and infants, in particular, hypotension may not be detected in the context of an AC, lowering the sensitivity of this criterion (increasing the number of false negatives) for an AC diagnosis. Other signs indicative of haemodynamic compromise, such as delayed capillary return and sinus tachycardia, may be present but these do not necessarily have the sensitivity and specificity to contribute to a robust definition of an AC in this age group.

Given these considerations, we suggest that an AC in children should be defined as an acute deterioration in health that is associated with haemodynamic disturbance (hypotension/sinus tachycardia relative to age-related normal levels/or delayed central capillary refill time [>3 s]) or a marked abnormality in at least one electrolyte (hyponatraemia, hyperkalaemia) or hypoglycaemia, which cannot be attributable to another illness (Table 2). Unlike the

**Table 2.** New definition of an adrenal crisis in paediatric patients

| |
|---|
| **Text** |
| An acute deterioration in health that is associated with acute haemodynamic disturbance (hypotension or sinus tachycardia relative to age-related normal levels) or a marked abnormality in one or more electrolytes (hyponatraemia, hyperkalaemia) or hypoglycaemia that is not attributable to another illness, the features of which show significant resolution following parenteral glucocorticoid administration |
| **Added details** |
| Frequent concomitant features include acute abdominal symptoms, altered levels of consciousness/obtundation; nausea/vomiting; abdominal pain; poor feeding (in infants); pyrexia<br>Consideration of the effects of incidental illness as causes of the major features, in particular shock, improves the specificity of diagnosis |

previous definitions used in paediatrics, the second essential component of this definition is that a clear resolution of the major features of the episode is observed following the administration of parenteral (most often intravenous) hydrocortisone (Table 2). In addition, we suggest that patients with CAH fitting the above criteria be classified as having an AC (E27.2), with CAH recorded as a comorbid (underlying) diagnosis, and that the term "salt-wasting crisis" be avoided.

Where patients have symptoms of AI but without the severe physiological manifestations of an AC, the diagnostic term "symptomatic AI" is recommended [15]. These patients with AI are unwell but are not suffering an AC and are often admitted to hospital for treatment of milder symptoms, such as postural dizziness, nausea and abdominal discomfort or lassitude and poor feeding in younger patients [15]. These children may have a principal diagnosis of AI and there may often be a concurrent illness, frequently a viral infection [23].

## Risk Factors

Although all patients with AI are at risk of developing an AC when exposed to a physiological stressor, such as an illness or injury, the propensity to develop an AC does not appear to be uniform across all children with AI or even between children within the specific AI subtypes [2, 3, 16]. It has been shown in a number of studies that AC events are more common in younger children with CAH than among older children and adolescents [4, 23, 45]. Moreover, in children with CAH, there is evidence documenting an increased risk of hospitalization among those with the more severe salt-wasting phenotypes (as measured by the dose of fludrocortisone) [45]. Disparities between the sexes in AC incidence have also been found and these have been shown to vary by age [22]. These may be due to differences in the distribution of underlying subtypes of AI between the sexes, such as an increased incidence of acquired hypopituitarism from acquired brain injury in males [46, 47]. Alternatively, they may be due to physiological differences between males and females that are related to age [39] or possibly differences in the dosages of glucocorticoid replacement therapy between the sex and age groups, particularly in children with CAH. These variations are important but largely unexplained and are, therefore, worthy of further investigation.

Even within different subtypes of AI, the risk of experiencing an AC episode is not equally distributed among patients [3, 14–16, 48]. Patients with type 1 diabetes mellitus and PAI, for example, have an increased AC incidence relative to other AI patients [48]. Evidence also suggests that there are subgroups of patients in both the adult and paediatric age groups who have an increased propensity for ACs, having multiple episodes, while other patients may not have any events over an extended period of time [3, 14, 16, 48]. The characteristics of these patients at particular AC risk are not well defined and the reasons for this variability are uncertain and merit further research.

Psychosocial factors may also modify the baseline AC risk, particularly during adolescence when patients move away from parental oversight of their treatment towards self-management [49, 50]. Problems relating to compliance with routine glucocorticoid replacement, encompassing missed and late doses of replacement therapies, and failure to implement stress protocols appropriately may also increase the risk of an AC [16]. Moreover, alterations in cortisol pharmacokinetics, which cause an increased clearance and distribution volume but without any change in the cortisol half-life that have been demonstrated during the pubertal period, further complicate management in this age group [51]. It is also possible that variations in 11BHSD1 function determined by genetic or other factors contribute to the development of an AC under certain conditions, such as for example treatment with GH [28]. The development of a more nuanced understanding of AC incidence in relation to social, demographic, physiological, genetic, and compliance factors may assist in identifying at-risk patients with greater accuracy, potentially leading to a reduction in AC incidence in this age group.

Treatment-related factors may also modify AC risk overall or within patient subgroups. In adults, there have been suggestions that the trend towards provision of lower dose, short-acting glucocorticoid replacement therapy may be associated with an increased risk of AC in treated AI, and that geographic variations in AC incidence may be related to underlying treatment differences [52, 53]. This phenomenon has not been fully investigated in the paediatric population but doing so may be of benefit.

### Precipitating Factors

A range of factors can precipitate an AC, but the most commonly occurring of these is an infection [13, 15, 17, 54]. The majority of infections in children are viral, which is in contrast to the predominance of bacterial infections in adults [23, 54, 55]. Viral infections, particularly in younger children, are often associated with fever and anorexia, with or without vomiting, which can reduce a patient's ability to take oral replacement therapy.

In both adults [15] and children, an infection is a particularly potent AC precipitant. This is because immunomodulation is partly controlled by cortisol and, in an environment of insufficient circulating cortisol, excess proinflammatory cytokines in the circulation can lead to the development of uncontrolled inflammation, vasodilatation, impaired cardiac function, and shock [15, 56, 57]. The absence of the facilitating role of cortisol on catecholamine action on the cardiovascular system, leads to amplification of these effects [58]. Gastroenteritis is a common infective AC precipitant, and is particularly hazardous in AI, especially in very young children, because vomiting and diarrhoea interfere with absorption of oral glucocorticoids, in addition to causing dehydration and electrolyte abnormalities [13, 15, 17].

A number of other factors may act as precipitants of an AC in children. These can include the abrupt withdrawal of glucocorticoid therapy, including inhaled corticosteroid therapy, which may be deliberate or inadvertent. Failure to provide appropriate glucocorticoid cover for a surgical procedure is another preventable cause of an AC in treated AI, a phenomenon that has been documented in case reports on adult patients [17, 59]. Delays in providing stress doses of glucocorticoid have also been suggested as a cause of poor outcomes in AI [13, 16], and death in this context has been reported [7, 26].

### Prevention

The cornerstone of AC prevention is the institution of a protocol of escalating doses of glucocorticoid ("stress dosing") in the event of an intercurrent illness or injury, when the requirement for cortisol is greater than that in the circulation [1, 6, 13, 15]. All parents and older children should be educated about the need for stress dosing. In addition, patients and their families should be given written instructions about AC prevention and management for themselves, for their childcare centre or school, and for healthcare staff.

Despite the implementation of these strategies, there is evidence to indicate that education of patients is not sufficient to avert some episodes of AC [13, 14, 16], and that even well-educated patients and parents can have difficulties applying the schedule of escalating glucocorticoid doses, sometimes with fatal outcomes [5, 7]. While oral stress dosing is often administered, transferring to intramuscular glucocorticoids when oral therapy is unable to be taken or absorbed, or has not been effective in relieving symptoms of acute AI, is difficult for many patients and their families [16]. One potential solution to this problem that has been investigated in adults is the subcutaneous administration of hydrocortisone [60, 61]. Studies have demonstrated that hydrocortisone given subcutaneously is absorbed within a suitable time frame for management of an acute episode in adults who are not obese and are not in active shock, and that this form of administration is regarded by many patients as a more acceptable option than intramuscular injection [60, 61]. Although its use in the paediatric age group has not been investigated, it may be of benefit to some paediatric patients, should its safety and efficacy be demonstrated. Alternatively, rectal hydrocortisone suppositories may be used in illness episodes where there is no diarrhoea, and many parents regard this as being preferable to giving an intramuscular injection [62, 63]. In addition, the identification of children at risk of repeated episodes of AC manifest by hypoglycaemia as the main or only feature of the AC may prevent the development of adverse neurological sequelae or even mortality from hypoglycaemic seizures [13]. In clinical practice, the provision of glucometers for home use and glucagon for injection has been used for this purpose.

AC prevention and management is a source of anxiety for patients and their families. This may be reflected in unnecessary presentations for medical care or, alternatively, it may result in failure to take appropriate action in situations where oral stress dosing or administration of parenteral glucocorticoid is required [7, 16]. It is also of

concern to note that a proportion of all ACs appear not to be preventable [13, 16], evolving so rapidly that stress dosing is not effective [13, 64]. In addition, some ACs have no obvious precipitant [13, 16, 17].

### Epidemiological Considerations

In children, AI is a rare disorder and AC events are even more rare. While this situation presents a number of challenges, it does not obviate the need to pursue improved health outcomes for patients with all forms of AI. Indeed, monitoring AC incidence on a population basis is necessary for ongoing evaluation of the welfare of patients, as small changes in health outcomes for rare illnesses are unlikely to be detected in a clinical setting.

Surveillance of population-based data on AI and AC can provide information on trends in underlying disease or changes in outcomes (morbidity or mortality) over time and between patient subgroups. These may provide evidence of the health effects of modifications to treatment or other unrelated factors, such as the unexpected health consequences of disruptions to the supply of medications [52, 53, 65]. Accurate measures of incidence, however, need to be based on consistently applied AC and AI definitions. Potential indicators for surveillance purposes may include the incidence of underlying diseases, AC event rates or, alternatively, a calculated indicator such as an AC/AI ratio, which may act as a more sensitive indicator of health outcomes [15].

Disease registers or aggregated databases, such as hospital admission datasets, are possible sources of AC/AI surveillance data. Regional (state or national) disease-specific registers are particularly useful, as these allow for aggregation of data across geographic areas and time, thereby increasing the study population when the sample size for individual regions, years, or rare subtypes of AI may be too small for a meaningful analysis. However, morbidity data have some limitations, including the likelihood of measurement error due to the potential misclassification of cases of AC as AI (false negatives) or of less severe episodes of an AI-related illness as AC (false positives). Routinely collected mortality data are another potential source of information on the occurrence of AC-related mortality in children, but these may be affected by unreliability in the identification of AI/AC as a cause of death [7].

Alternatively, detailed data can be collected on patient outcomes by analysis of data on a sample of patients (often from a hospital or a clinic) in a cohort study. These are usually retrospective in design and can provide detailed information on AC events, clinical management, risk factors, and precipitants. However, the retrospective nature of these designs means that much of the data collected is not contemporaneous and may be affected by measurement error. This is particularly the case when patient or parent reports of AC events are used as outcome measures, unless these are validated through a review of medical records [15]. Also, studies utilising samples from a circumscribed group of patients, such as from a tertiary hospital clinic [16], may be affected by selection bias and have limited generalizability.

Record linkage studies are particularly useful in the context of AC/AI research, as they can provide unbiased longitudinal data on individual patients. These may use information from screening programs, hospital morbidity data, or data from specific disease registries or clinic samples, providing there are patient identifiers (such as date of birth) that are common to all datasets. In countries that operate a newborn screening program for CAH or have a national disease register, data can be linked to morbidity and mortality datasets and analyzed progressively, providing information on a wide range of outcomes [7, 66–69]. These can also be combined with other data sources, such as stored pharmaceutical prescription data, which can act as proxies for underlying diagnoses or even act as indices of severity [45].

Data analyses that examine patterns of incidence or other outcomes in subgroups, based on age, sex, type of AI, are also of value. Stratification assists in identifying whether changes in incidence are widespread or confined to certain subgroups. This approach can also address the potential confounding effects of physiological differences or other factors that are associated with age and sex [22].

### Future Research Directions

Progress in AC prevention in children has been hindered by the absence of a coordinated approach to research into AI/AC. Given the rarity of AC events in this age group, development of collaborative research projects across groups and internationally may be particularly beneficial. Use of aggregated population-based datasets can enable the determination of incidence and AC risk across all forms of AI, as well as within AI subtypes. While such data are important for surveillance, we suggest that there also should be greater emphasis placed on the development of research programs aimed at identifying factors that increase or ameliorate AC risk in the paediatric

population specifically. It is especially important that a prospective, observational study of AC/AI presentations in children with established chronic PAI or SAI be conducted. Within this framework, a comprehensive investigation into variations in the propensity to develop an AC between different children with AI may uncover other factors that influence the risk of AC. Together with a documentation of the social and psychological factors in affected children, a more precise investigation into the pathophysiology of AC events could be undertaken by the measurement of cortisol, electrolytes, catecholamine, and inflammatory cytokine levels. Such examination would enhance the understanding of AC events in this age group.

There are many other issues relating to AC physiology in children that are not yet understood. A more comprehensive understanding of the physiological response to infection is a necessary element in achieving progress. As has been described previously [15], augmentation of the delivery of cortisol to inflamed tissue is believed to be as a result of a combination of inflammatory cytokine induced HPA axis activation, in combination with rapid cleavage of corticosteroid-binding globulin (CBG) by tissue elastases [70]. An increase in the secretion of cortisol and a diminution in CBG production occur early in this process [71]. The consequent depletion of circulating CBG may contribute to an insufficient supply of cortisol to inflamed tissues, leading to increased tissue damage, as cellular processes become overwhelmed by unrestrained activation of NF-κB [70]. However, as has been noted previously [15], the relative contribution of these processes to AC initiation has not been assessed and research to ascertain the levels of cytokine, CBG, circulating hydrocortisone, and catecholamine levels at the time of AC presentation, along with relevant inflammatory markers is required. Likewise, the relative contribution of 11BHSD1's conversion of the inactive cortisone to cortisol to the development of ACs in children (and adults) is unknown: 11BHSD1 is very sensitive to GH and other hormonal and non-hormonal factors and as much as one-third of the circulating active cortisol may be derived at times from cortisone. It is possible that genetic variants and environmental factors affecting 11BHSD1 function have a significant effect on the incidence of ACs [28, 72].

Cortisol is involved in catalyzing the conversion of adrenomedullary noradrenaline to adrenaline via the phenylethanolamine N-methyltransferase enzyme, the levels of which are known to be low in AI [73]. Moreover, as a minimal level of cortisol is required for adrenomedullary organogenesis, the effect of the loss of this conversion may be more severe in congenital forms of AI, such as CAH [39, 40]. The tendency to vascular collapse in AI may also be a result of insufficient levels of circulating adrenaline, although the relative role of both adrenaline and noradrenaline in the commencement and progression of an AC is uncertain. It is also not known whether an AC event occurs in the context of a complete or relative deficiency of circulating glucocorticoid, where relative deficiency implies that the level of circulating glucocorticoid is lower than the concentration that is required for the degree of physiological stress imposed by an illness. These matters are of great importance and the pursuit of AC prevention would be enhanced by further research in this area.

The cellular pathophysiology of ACs is likely to be complex and diverse, in that both the severity and duration of glucocorticoid deficiency are likely to influence the derangement of cellular pathways, as does the underlying cause of the AC, such as infection, which may lead to greater cellular consequence from unrestrained NF-κB activity. Other cellular pathways, such as formation of cortisol from the inactive cortisone (mediated by 11BHSD1 as detailed above), expression of the GR and its interaction with chaperone proteins and transcription factors, as well as transport of cortisol to the cell surface by CBG and through the cell membrane, may also play a role in the genesis or compensation for the clinical state of glucocorticoid deficiency, although these have not been specifically studied in states approximating AC, to date.

The interrelationship between AI and glucose metabolism is another important area of investigation, particularly in children. Previous research has demonstrated that morning glucose levels are lower in adult AI patients [39, 74, 75], and that occult nocturnal hypoglycaemia can occur among adults with AI [76, 77]. As we have described previously [15], the underlying mechanism for this is likely to involve reduced nocturnal gluconeogenesis during an overnight fast, a process that is partially dependent on glucocorticoids. Sympathoneural responses may become impaired in AI patients with recurrent nocturnal hypoglycaemia and this may increase the predilection to, or severity of, AC events. While this research was conducted in adult patients, it is likely that it is also a feature in the paediatric population. For this reason, it would be valuable to assess the frequency of hypoglycaemic events in those children who experience frequent ACs, as one important element of an investigation into the factors underlying some patients' apparent predisposition to ACs. As recurrent hypoglycaemia can be a problem in some

children, further efforts are needed to identify effective preventive and management strategies to address this serious complication.

Social and psychological factors, in addition to problems with access to health services, are also important features in the occurrence of some AC events and, therefore, in the pursuit of AC event reduction. Problems in these areas may be a factor in isolated AC events, but they may have a greater influence on the phenomenon of recurrent AC episodes in some children. Impediments to the use of stress dosing and especially to any failure on the part of parents or caregivers to move from oral stress dosing to parenteral therapy also need further investigation. Providing the safety and efficacy of subcutaneous administration of hydrocortisone can be established in the paediatric population, the effectiveness of this mode of administration of hydrocortisone by parents and caregivers at home should be assessed as its use may be of benefit to patients. Where treatments are evolving, such as the introduction of modified release preparations of hydrocortisone, these need assessment in paediatric populations specifically.

## Conclusions

AC events cause significant morbidity and mortality in childhood, but the paucity of available information on the epidemiology of AC in the paediatric age group specifically makes progress towards reducing the impact of these adverse outcomes more difficult. The absence of a universally agreed definition of an AC impedes synthesis of the extant research in this area, to the potential detriment of progress. Although there are significant commonalities in the risk factors and preventive strategies between adults and children, the level of transferability of research findings from adults to paediatric practice is not known. Opportunities to implement targeted research programs, particularly towards identifying children at increased risk of recurrent events, may offer the possibility of a reduction in the health impact of ACs in this age group and elucidation of the molecular pathophysiology of AC. Surveillance and monitoring of AC episodes in treated AI increase the likelihood of early detection of the adverse effects of treatment changes or changes in underlying incidence of AI that may not be apparent in the clinical setting. Improvements in evidence-based AC prevention strategies must remain a priority.


## Acknowledgements

Professor Falhammar was supported by grants from the Magn. Bergvalls Foundation, Karolinska Institutet, and Stockholm County Council.


## Disclosure Statement

The authors have no conflicts of interest to disclose.

## References


1 Park J, Didi M, Blair J. The diagnosis and treatment of adrenal insufficiency during childhood and adolescence. Arch Dis Child. 2016 Sep;101(9):860–5.

2 Webb EA, Krone N. Current and novel approaches to children and young people with congenital adrenal hyperplasia and adrenal insufficiency. Best Pract Res Clin Endocrinol Metab. 2015 Jun;29(3):449–68.

3 Odenwald B, Nennstiel-Ratzel U, Dörr HG, Schmidt H, Wildner M, Bonfig W. Children with classic congenital adrenal hyperplasia experience salt loss and hypoglycemia: evaluation of adrenal crises during the first 6 years of life. Eur J Endocrinol. 2016 Feb;174(2):177–86.

4 Reisch N, Willige M, Kohn D, Schwarz HP, Allolio B, Reincke M et al. Frequency and causes of adrenal crises over lifetime in patients with 21-hydroxylase deficiency. Eur J Endocrinol. 2012 Jul;167(1):35–42.

5 Swerdlow AJ, Higgins CD, Brook CG, Dunger DB, Hindmarsh PC, Price DA et al. Mortality in patients with congenital adrenal hyperplasia: a cohort study. J Pediatr. 1998 Oct;133(4):516–20.

6 Shulman DI, Palmert MR, Kemp SF; Lawson Wilkins Drug and Therapeutics Committee. Adrenal insufficiency: still a cause of morbidity and death in childhood. Pediatrics. 2007 Feb;119(2):e484–94.

7 Erichsen MM, Løvås K, Fougner KJ, Svartberg J, Hauge ER, Bollerslev J et al. Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. Eur J Endocrinol. 2009 Feb;160(2):233–7.

8 Falhammar H, Frisén L, Norrby C, Hirschberg AL, Almqvist C, Nordenskjöld A et al. Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2014 Dec;99(12):E2715–21.

9 Burman P, Mattsson AF, Johannsson G, Höybye C, Holmer H, Dahlqvist P et al. Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. J Clin Endocrinol Metab. 2013 Apr;98(4):1466–75.

10 Bergthorsdottir R, Leonsson-Zachrisson M, Odén A, Johannsson G. Premature mortality in patients with Addison's disease: a population-based study. J Clin Endocrinol Metab. 2006 Dec;91(12):4849–53.

11 Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS et al; West Midlands Prospective Hypopituitary Study Group. Association between premature mortality and hypopituitarism. Lancet. 2001 Feb;357(9254):425–31.

12 Bensing S, Brandt L, Tabaroj F, Sjöberg O, Nilsson B, Ekbom A et al. Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. Clin Endocrinol (Oxf). 2008 Nov;69(5):697–704.
13 Allolio B. Extensive expertise in endocrinology. Adrenal crisis. Eur J Endocrinol. 2015 Mar;172(3):R115–24.
14 Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. J Clin Endocrinol Metab. 2015 Feb;100(2):407–16.
15 Rushworth RL, Torpy DJ, Falhammar H. Adrenal crises: perspectives and research directions. Endocrine. 2017 Feb;55(2):336–45.
16 Leblicq C, Rottembourg D, Deladoëy J, Van Vliet G, Deal C. Are guidelines for glucocorticoid coverage in adrenal insufficiency currently followed? J Pediatr. 2011 Mar;158(3):492–498.e1.
17 Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. Eur J Endocrinol. 2010 Mar;162(3):597–602.
18 Smans LC, Van der Valk ES, Hermus AR, Zelissen PM. Incidence of adrenal crisis in patients with adrenal insufficiency. Clin Endocrinol (Oxf). 2016 Jan;84(1):17–22.
19 Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. Arch Dis Child. 2002 Dec;87(6):457–61.
20 Zöllner EW, Lombard CJ, Galal U, Hough FS, Irusen EM, Weinberg E. Hypothalamic-pituitary-adrenal axis suppression in asthmatic school children. Pediatrics. 2012 Dec;130(6):e1512–9.
21 Goldbloom EB, Mokashi A, Cummings EA, Abish S, Benseler SM, Huynh HQ et al. Symptomatic adrenal suppression among children in Canada. Arch Dis Child. 2017 Apr;102(4):338–9.
22 Rushworth RL, Chrisp GL, Dean B, Falhammar H, Torpy DJ. Hospitalisation in children with adrenal insufficiency and hypopituitarism: is there a differential burden between boys and girls and between age groups? Horm Res Paediatr. 2017;88(5):339–46.
23 Rushworth RL, Falhammar H, Munns CF, Maguire AM, Torpy DJ. Hospital Admission Patterns in Children with CAH: Admission Rates and Adrenal Crises Decline with Age. Int J Endocrinol. 2016;2016:5748264.
24 Walker C, Butt W. A case of cardiovascular collapse due to adrenal insufficiency. Aust Paediatr J. 1988 Jun;24(3):197–8.
25 Donaldson MD, Morrison C, Lees C, McNeill E, Howatson AG, Paton JY et al. Fatal and near-fatal encephalopathy with hyponatraemia in two siblings with fluticasone-induced adrenal suppression. Acta Paediatr. 2007 May;96(5):769–72.
26 Brodsky MC, Conte FA, Taylor D, Hoyt CS, Mrak RE. Sudden death in septo-optic dysplasia. Report of 5 cases. Arch Ophthalmol. 1997 Jan;115(1):66–70.
27 http://www.coronerscourt.wa.gov.au/inquest14/07.
28 Stratakis CA. Cortisol and growth hormone: clinical implications of a complex, dynamic relationship. Pediatr Endocrinol Rev. 2006 Apr;3 Suppl 2:333–8.
29 Buchanan CR, Preece MA, Milner RD. Mortality, neoplasia, and Creutzfeldt-Jakob disease in patients treated with human pituitary growth hormone in the United Kingdom. BMJ. 1991 Apr;302(6780):824–8.
30 Taback SP, Dean HJ; The Canadian Growth Hormone Advisory Committee. Mortality in Canadian children with growth hormone (GH) deficiency receiving GH therapy 1967-1992. J Clin Endocrinol Metab. 1996 May;81(5):1693–6.
31 Stochholm K, Gravholt CH, Laursen T, Laurberg P, Andersen M, Kristensen LO et al. Mortality and GH deficiency: a nationwide study. Eur J Endocrinol. 2007 Jul;157(1):9–18.
32 Fischer JE, Stallmach T, Fanconi S. Adrenal crisis presenting as hypoglycemic coma. Intensive Care Med. 2000 Jan;26(1):105–8.
33 Papierska L, Rabijewski M. Delay in diagnosis of adrenal insufficiency is a frequent cause of adrenal crisis. Int J Endocrinol. 2013;2013:482370.
34 Kovács J, Votava F, Heinze G, Sólyom J, Lebl J, Pribilincová Z et al; Middle European Workshop on Paediatric Endocrinology-Congenital Adrenal Hyperplasia Study Group. Lessons from 30 years of clinical diagnosis and treatment of congenital adrenal hyperplasia in five middle European countries. J Clin Endocrinol Metab. 2001 Jul;86(7):2958–64.
35 Gidlöf S, Falhammar H, Thilén A, von Döbeln U, Ritzén M, Wedell A et al. One hundred years of congenital adrenal hyperplasia in Sweden: a retrospective, population-based cohort study. Lancet Diabetes Endocrinol. 2013 Sep;1(1):35–42.
36 Simm PJ, McDonnell CM, Zacharin MR. Primary adrenal insufficiency in childhood and adolescence: advances in diagnosis and management. J Paediatr Child Health. 2004 Nov;40(11):596–9.
37 Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364–89.
38 DeVile CJ, Stanhope R. Hydrocortisone replacement therapy in children and adolescents with hypopituitarism. Clin Endocrinol (Oxf). 1997 Jul;47(1):37–41.
39 Charmandari E, Eisenhofer G, Mehlinger SL, Carlson A, Wesley R, Keil MF et al. Adrenomedullary function may predict phenotype and genotype in classic 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2002 Jul;87(7):3031–7.
40 Falhammar H, Filipsson Nyström H, Wedell A, Thorén M. Cardiovascular risk, metabolic profile, and body composition in adult males with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Eur J Endocrinol. 2011 Feb;164(2):285–93.
41 Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. Am J Respir Crit Care Med. 2003 Feb;167(4):512–20.
42 Khalid JM, Oerton JM, Dezateux C, Hindmarsh PC, Kelnar CJ, Knowles RL. Incidence and clinical features of congenital adrenal hyperplasia in Great Britain. Arch Dis Child. 2012 Feb;97(2):101–6.
43 National Centre for Classification in Health. International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM). 5th Edition. Sydney, Australia: Australian Classification of Health Interventions (ACHI), Australian Coding Standards (ACS), National Centre for Classification in Health; 2006.
44 Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood. J Clin Endocrinol Metab. 2011 Jun;96(6):E925–8.
45 Yang M, White PC. Risk factors for hospitalization of children with congenital adrenal hyperplasia. Clin Endocrinol (Oxf). 2017 May;86(5):669–73.
46 L Wilson M, Tenovuo O, Mattila VM, Gisler M, Celedonia KL, Impinen A et al. Pediatric TBI in Finland: an examination of hospital discharges (1998-2012). Eur J Paediatr Neurol. 2017 Mar;21(2):374–81.
47 Richmond E, Rogol AD. Traumatic brain injury: endocrine consequences in children and adults. Endocrine. 2014 Feb;45(1):3–8.
48 Meyer G, Badenhoop K, Linder R. Addison's disease with polyglandular autoimmunity carries a more than 2·5-fold risk for adrenal crises: german Health insurance data 2010-2013. Clin Endocrinol (Oxf). 2016 Sep;85(3):347–53.
49 Di Bartolo P, Nicolucci A, Cherubini V, Iafusco D, Scardapane M, Rossi MC. Young patients with type 1 diabetes poorly controlled and poorly compliant with self-monitoring of blood glucose: can technology help? Results of the i-NewTrend randomized clinical trial. Acta Diabetol. 2017 Apr;54(4):393–402.
50 Lass N, Reinehr T. Low Treatment Adherence in Pubertal Children Treated with Thyroxin or Growth Hormone. Horm Res Paediatr. 2015;84(4):240–7.
51 Charmandari E, Hindmarsh PC, Johnston A, Brook CG. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: alterations in cortisol pharmacokinetics at puberty. J Clin Endocrinol Metab. 2001 Jun;86(6):2701–8.

52 Rushworth RL, Torpy DJ. Adrenal Insufficiency in Australia: Is it Possible that the Use of Lower Dose, Short-Acting Glucocorticoids has Increased the Risk of Adrenal Crises? Horm Metab Res. 2015 Jun;47(6):427–32.
53 Rushworth RL, Torpy DJ. Modern hydrocortisone replacement regimens in adrenal insufficiency patients may increase the risk of adrenal crisis. Horm Metab Res. 2015 Aug; 47(9):637–42.
54 Smans LC, Souverein PC, Leufkens HG, Hoepelman AI, Zelissen PM. Increased use of antimicrobial agents and hospital admission for infections in patients with primary adrenal insufficiency: a cohort study. Eur J Endocrinol. 2013 Mar;168(4):609–14.
55 Rushworth RL, Torpy DJ. A descriptive study of adrenal crises in adults with adrenal insufficiency: increased risk with age and in those with bacterial infections. BMC Endocr Disord. 2014 Oct;14(1):79.
56 Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve–an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev. 2000 Dec;52(4):595–638.
57 Elenkov IJ, Iezzoni DG, Daly A, Harris AG, Chrousos GP. Cytokine dysregulation, inflammation and well-being. Neuroimmunomodulation. 2005;12(5):255–69.
58 Yang S, Zhang L. Glucocorticoids and vascular reactivity. Curr Vasc Pharmacol. 2004 Jan; 2(1):1–12.
59 Salem M, Tainsh RE Jr, Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg. 1994 Apr; 219(4):416–25.
60 Hahner S, Burger-Stritt S, Allolio B. Subcutaneous hydrocortisone administration for emergency use in adrenal insufficiency. Eur J Endocrinol. 2013 Jun;169(2):147–54.
61 Rushworth RL, Bischoff C, Torpy DJ. Preventing adrenal crises: home-administered subcutaneous hydrocortisone is an option. Intern Med J. 2017 Feb;47(2):231–2.
62 Ní Chróinín M, Fallon M, Kenny D, Moriarty S, Hoey H, Costigan C. Rectal hydrocortisone during vomiting in children with adrenal insufficiency. J Pediatr Endocrinol Metab. 2003 Oct–Nov;16(8):1101–4.
63 De Vroede M, Beukering R, Spit M, Jansen M. Rectal hydrocortisone during stress in patients with adrenal insufficiency. Arch Dis Child. 1998 Jun;78(6):544–7.
64 Aso K, Izawa M, Higuchi A, Kotoh S, Hasegawa Y. Stress doses of glucocorticoids cannot prevent progression of all adrenal crises. Clin Pediatr Endocrinol. 2009;18(1):23–7.
65 Rushworth RL, Slobodian P, Torpy DJ. Interruptions to supply of high-dose hydrocortisone tablets and the incidence of adrenal crises. Clin Endocrinol (Oxf). 2015 Dec;83(6): 999–1000.
66 Strandqvist A, Falhammar H, Lichtenstein P, Hirschberg AL, Wedell A, Norrby C et al. Suboptimal psychosocial outcomes in patients with congenital adrenal hyperplasia: epidemiological studies in a nonbiased national cohort in Sweden. J Clin Endocrinol Metab. 2014 Apr;99(4):1425–32.
67 Falhammar H, Frisén L, Hirschberg AL, Norrby C, Almqvist C, Nordenskjöld A et al. Increased Cardiovascular and Metabolic Morbidity in Patients With 21-Hydroxylase Deficiency: A Swedish Population-Based National Cohort Study. J Clin Endocrinol Metab. 2015 Sep;100(9):3520–8.
68 Engberg H, Butwicka A, Nordenström A, Hirschberg AL, Falhammar H, Lichtenstein P et al. Congenital adrenal hyperplasia and risk for psychiatric disorders in girls and women born between 1915 and 2010: A total population study. Psychoneuroendocrinology. 2015 Oct;60:195–205.
69 Ohlsson Gotby A, Nordenström A, Falhammar H, Nordenskjöld A, Linden Hirschberg A, Frisén L et al. Congenital Adrenal Hyperplasia, Polycystic Ovary Syndrome and criminal behavior: A Swedish population based study. Psychiatry Res. 2015 Oct;229(3):953–9.
70 Nenke MA, Rankin W, Chapman MJ, Stevens NE, Diener KR, Hayball JD et al. Depletion of high-affinity corticosteroid-binding globulin corresponds to illness severity in sepsis and septic shock; clinical implications. Clin Endocrinol (Oxf). 2015 Jun;82(6):801–7.
71 Meyer EJ, Nenke MA, Rankin W, Lewis JG, Torpy DJ. Corticosteroid-binding globulin: a review of basic and clinical advances. Horm Metab Res. 2016 Jun;48(6):359–71.
72 Seckl JR, Walker BR. Minireview: 11beta-hydroxysteroid dehydrogenase type 1- a tissue-specific amplifier of glucocorticoid action. Endocrinology. 2001 Apr;142(4):1371–6.
73 Betito K, Diorio J, Meaney MJ, Boksa P. Adrenal phenylethanolamine N-methyltransferase induction in relation to glucocorticoid receptor dynamics: evidence that acute exposure to high cortisol levels is sufficient to induce the enzyme. J Neurochem. 1992 May; 58(5):1853–62.
74 Falhammar H, Filipsson H, Holmdahl G, Janson PO, Nordenskjöld A, Hagenfeldt K et al. Metabolic profile and body composition in adult women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2007 Jan;92(1):110–6.
75 Falhammar H, Filipsson H, Holmdahl G, Janson PO, Nordenskjöld A, Hagenfeldt K et al. Increased liver enzymes in adult women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Endocr J. 2009;56(4): 601–8.
76 Meyer G, Hackemann A, Reusch J, Badenhoop K. Nocturnal hypoglycemia identified by a continuous glucose monitoring system in patients with primary adrenal insufficiency (Addison's Disease). Diabetes Technol Ther. 2012 May;14(5):386–8.
77 Petersen KS, Rushworth RL, Clifton PM, Torpy DJ. Recurrent nocturnal hypoglycaemia as a cause of morning fatigue in treated Addison's disease–favourable response to dietary management: a case report. BMC Endocr Disord. 2015 Oct;15(1):61.