CLINICAL STUDY

Adrenal crisis in treated Addison's disease: a predictable but under-managed event

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Abstract

Context: Adrenal crisis is a life-threatening event that occurs regularly in Addison's patients receiving standard replacement therapy. Patient reports suggest that it is an underestimated and under-managed event.

Objective: To assess the frequency of adrenal crisis in diagnosed patients and to understand the factors contributing to the risks of adrenal crisis.

Design: We conducted a postal survey of Addison's patients in four countries, UK ($n=485$), Canada ($n=148$), Australia ($n=123$) and New Zealand ($n=85$) in 2003, asking about patients' experiences of adrenal crisis and their demographic characteristics. In 2006, a shorter follow-up survey was conducted in the UK ($n=261$).

Method: The frequency and causes of adrenal crisis were compared across both surveys. Demographic data from the 2003 survey were analysed to establish the main variables associated with an elevated risk of crisis.

Results: Around 8% of diagnosed cases can be expected to need hospital treatment for adrenal crisis annually. Exposure to gastric infection is the single most important factor predicting the likelihood of adrenal crisis. Concomitant diabetes and/or asthma increase the frequency of adrenal crises reported by patients.

Conclusion: The endocrinologist has a responsibility to ensure that Addison's patients have adequate access to life-saving emergency injection materials and repeated, practical training sessions in how to use them, while the general practitioner plays a vital role as in arranging prompt emergency admissions.

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Introduction

Adrenal crisis is a life-threatening event that occurs regularly in Addison's patients receiving standard replacement therapy. Until the 1950s, adrenal crisis was the main cause of death for patients with chronic adrenal insufficiency. Patients could be adequately stabilised, employing deoxycorticosterone implants, from 1939 onwards. But they did not have immediate access to high-dose glucocorticoid medication in the event of illness or injury, and so frequently died a sudden and painful death. In 1953, leading UK endocrinologists reported to a Royal Society of Medicine symposium that many of their patients had died within 2 years of diagnosis and none had lived for more than 13 years – until the 1952 advent of the first synthetic glucocorticoid, cortisone, which could be injected *in extremis*. As Dr Leonard Simpson told his audience, cortisone had minimised the dangers and terrors of Addisonian crisis (1).

In the 21st century, adrenal crisis is still a recognised cause of death in undiagnosed or under-treated adrenal disease (2–7). It is, however, a largely preventable

outcome and reported deaths from adrenal crisis among diagnosed Addison's patients are now thankfully rare (8–12). Despite this, the 21st century preference for conservative replacement doses of hydrocortisone (13) means that patients today are at greater risk of adrenal crisis than was the case from 1952 onwards, because they have less of a 'cushion' of excess circulating cortisol to protect them in the event of infection or injury. A standard replacement dose today would be 20 mg, where doses of 30 mg and upwards were commonplace even 10 years ago. This dosage reduction was an important and necessary development, preventing secondary complications of glucocorticoid excess such as type 2 diabetes and osteoporosis. However, it has led to the situation where adrenal crisis is an underestimated and under-managed event.

Patient education about the prevention and treatment of adrenal emergency is an essential responsibility for all medical practitioners caring for the Addison's patient. The general practitioner (GP)'s role in treating everyday infections and providing after-hours on-call services means that they typically hold a first-line

responsibility for the prevention and treatment of adrenal crisis. Endocrinologists may find they have not been informed of their patient's adrenal crises and hence may tend to underestimate the likelihood of this life-threatening event.

Subject and methods

In 2003 and again in 2006, we conducted postal surveys of UK Addison's Disease Self-Help Group members about their experiences of adrenal crisis. The 2003 questionnaire was a reply-paid omnibus questionnaire that included comprehensive demographic information, information about daily medication dosages, timing, height and weight, other medical conditions and the nature of the patient's contacts with their GP and endocrinologist. The 2006 questionnaire was a short questionnaire (return postage not provided) that asked only about experiences of adrenal crisis, with no demographic information requested.

The shorter 2006 questionnaire received replies from 261 members of the UK Addison's support group. The 2003 survey was distributed to members of the Canadian, Australian and New Zealand Addison's support groups, in addition to the UK. A total of 485 members of the UK group responded in 2003, along with 148 patients in Canada, 123 in Australia and 85 in New Zealand. Respondents to the 2003 survey were asked to identify the cause of their adrenal failure; those who self-identified with intact mineralocorticoid function (pituitary failure due to pituitary tumour, Cushing's, Sheehan's syndrome, isolated ACTH deficiency or adrenal suppression due to steroid usage) were excluded from this analysis. All patients who self-identified with primary adrenal insufficiency were included in the analysis ($n=841$), including a small number whose adrenal failure was due to surgical removal of the adrenal glands ($n=18$), congenital adrenal hyperplasia ($n=6$), haemorrhage ($n=3$) or adrenoleukodystrophy ($n=2$). Some respondents left their answers to selected questions blank, so that the number of responses to questions about emergency experiences in 2003 ($n=767$) was slightly lower than the total number of survey respondents ($n=841$).

Results

Eight percent per annum frequency of adrenal crisis

In 2006, eight percent of all members of the UK Addison's Disease Self-Help Group reported that they had needed hospital treatment with injected hydrocortisone and/or i.v. fluids within the past 12 months (74 out of a membership of 982 or over one-quarter of those who returned the questionnaire). This number has been interpreted conservatively, as a proportion of

the total membership, on the grounds that individuals who had not experienced adrenal crisis in the previous 12 months had less motivation to return the questionnaire. Moreover, an 8% annual frequency of adrenal emergency is broadly consistent with other analyses of primary hypoadrenalism patients (14–17). In two analyses of German adrenal insufficiency patients, Arlt & Alolio (2003) and Hahner *et al.* (2008) found rates of adrenal crisis around 6 per 100 patient years among primary adrenal insufficiency patients (15, 16). Their analyses were based on hospital records and hence offer clinical verification of the state of adrenal crisis, which this current research does not. However, hospital records are unable to capture episodes of crisis occurring away from home, whereas the patient reports analysed in this research do include such episodes.

Vomiting and/or diarrhoea the main causes of adrenal emergency

Respondents were asked to identify all factors that had led to adrenal crisis needing an emergency response, using both a tick box set of prompts and open comment response options. Vomiting and/or diarrhoea triggered more adrenal crises than other factors and were responsible for more than half of all adrenal crises. This survey records self-reporting by patients; therefore, it is possible that in some instances, these episodes of vomiting and diarrhoea were major signs of adrenal crisis triggered by other, unknown factors, such as asymptomatic infection. Nevertheless, for the medical practitioner, the implication is the same: any episode of vomiting and/or diarrhoea should be regarded as potentially life-threatening for steroid-dependent patients if only due to delayed gastric absorption during intercurrent illness.

Flu-like illness and associated major infections were the next most important risk factors (17% in 2003). Surgical procedures carried out with insufficient steroid cover (6%) consistently caused more adrenal emergencies than accidental injury (4%) (Fig. 1). Other causes included urinary tract/chest infections, septicaemia, heart attack, migraine, allergic reactions and severe diabetic hypoglycaemia. In 2006, dehydration outstripped winter influenza as a cause of adrenal emergencies in the UK, possibly reflecting milder flu strains that season and an unusually hot summer. Influenza and other infections were responsible for fewer adrenal crises in the UK in 2003 than in Canada, Australia or New Zealand, possibly reflecting higher rates of vaccination.

These findings suggest that there is scope for medical practitioners to better support their adrenal insufficiency patients in prevention and treatment of winter influenza and summer dehydration. For example, it would be useful to encourage all patients to obtain a flu vaccine and to adjust their mineralocorticoid replacement (fludrocortisone medication) to

Figure 1 Factors leading to unplanned emergency hydrocortisone injection in the 767 respondents to the International Addison's Survey 2003 (UK, Canada, New Zealand, Australia).

compensate for the greater fluid loss in hot weather. Moreover, it appears that some medical practitioners are making insufficient provision for the need of steroid-dependent patients during surgical procedures, or else are withdrawing additional steroid cover too soon during the post-surgical recovery period.

Exposure to infection, diabetes, premature ovarian failure and asthma increase the risks of adrenal emergency

Some patients appear to be highly unstable compared with others. In 2003, we analysed the frequency of adrenal crises reported by all patients ($n=817$) against their years of post-diagnosis life. Although a handful of patients had lived for more than 50 years post-diagnosis without needing emergency treatment, others reported multiple emergencies within a year of diagnosis (Fig. 2).

We compared the reported frequency of adrenal crisis against key demographic characteristics but could find little to explain the wide variation in the stability – or instability – of Addison's patients.

Health conditions such as type 1 and type 2 diabetes, asthma and premature ovarian failure were associated with higher rates of adrenal emergency (Fig. 3). These factors appear to be compounding, so that 82% of Addison's patients who also had diabetes plus asthma reported one or more adrenal crises, compared with

just 36% of Addison's patients with no associated conditions (confidence index Z-score = 99.9%). However, hypothyroidism or body mass index > 30 (40%) was not significantly associated with increased rate of adrenal emergency. For patients without associated health conditions, we then analysed rates of adrenal crisis by occupation (Fig. 4). Those outside the paid workforce reported significantly higher rates of adrenal crisis. Healthcare workers reported higher rates of adrenal crisis than all other occupations, although sample size constraints meant that this was not statistically significant. Nevertheless, healthcare workers' more frequent exposure to infectious illness should be considered in this context.

Overall, men and women reported similar rates of adrenal emergency, despite the greater proportion of women with one or more associated health conditions such as premature ovarian failure. About 55% of women and 52% of men reported one or more adrenal crises since diagnosis, at an average of 12.8 years since diagnosis for women and 11.4 years for men.

Up to one-third of all emergencies occur away from home

More than two-thirds of all adrenal emergencies occurred at home, as reported in both our 2003 and 2006 surveys. Around 11% were overseas or else in

Figure 2 Number of adrenal crises as a function of time since diagnosis. International Addison's survey 2003 participants ($n=767$) answered the question 'Have you needed emergency treatment/i.v. fluids at hospital since diagnosis', which included indicating the number of these events. The graph shows the total number of crises in patients diagnosed in the last 5 years preceding the completion of the questionnaire ($n=224$) and patients diagnosed more than 50 years ago ($n=6$).

transit on an aircraft or boat, 7% were at the house of a friend or relative, 5% were at a hotel, 4% were in the countryside or playing sport, 2% were driving in their car, with 3% at work or out shopping. This geographic diversity highlights the need for Addison's patients to carry an emergency injection kit with them whenever they are away from home, and preferably to keep a spare set of injection materials in their car.

Only a few patients able to self-inject

Sixty-eight percent of respondents to the 2006 UK survey ($n=178$) had an in-date supply of injectable hydrocortisone, most of these (80%) prescribed by the GP. But only 12% of those who had experienced an adrenal crisis in the preceding 12 months gave themselves the emergency injection; a further 17%

Figure 3 Frequency of adrenal crisis in relation to associated co-morbidities. The graph shows the incidence (% of patients) of one or more adrenal crises in respondents of the 2003 International Addison's Survey in patients with at least one associated co-morbidity ($n=415$) in comparison with patients with primary adrenal insufficiency and no associated health condition ($n=315$).

Figure 4 Influence of professional occupation on the incidence of adrenal crises requiring hospital treatment. The graph illustrates the proportion of patients (%) that have experienced at least one adrenal crisis according to professional occupations, among the 2003 International Addison's Survey respondents that provided information on their occupation (n=380).

were given the injection by a partner, relative, friend or neighbour. Over two-thirds relied on medical personnel for their first-line emergency treatment (4% ambulance personnel, 23% GP/nurse, 38% hospital personnel). This finding showed a small improvement on the 2003 survey, when 6% reported that they were able to give themselves an injection, with 8% receiving an initial injection from family, friend or colleagues and 85% relying on medical personnel for their first-line emergency treatment. Patient education emphasises the importance of hospital monitoring in all instances of adrenal crisis; nevertheless, it is important for patients to stabilise their condition by an emergency i.m. injection where possible – before seeking medical help – as even a small delay can see circulatory or cardiac complications arise.

Many respondents requested further education and training in how to use their injection kit, both for themselves and their immediate family. Some commented that the speed of their first crisis had taken them by surprise, so that they were too weak to prepare the injection by the time they realised they needed it.

Discussion and conclusion: patient education is vital

In his 1953, address to the Royal Society of Medicine, Dr Leonard Simpson suggested that all Addison's patients should carry a card identifying their risk of sudden death from hypoglycaemic crisis and explaining their need for immediate steroid treatment. Despite occasional papers regretting that junior hospital doctors lack sufficient exposure to this rare condition to be confident in their management (18, 19) it was to be another 52 years before such a card became available to

Addison's patients in the UK. In 2005, the Addison's Disease Self-Help Group was able to print and distribute laminated emergency cards to its members (Fig. 5), thanks to the support of its Clinical Advisory Panel and several generous individual donations. The ADSHG also makes these emergency treatment instructions freely available on its website at www.addisons.org.uk.

The findings of our 2006 and 2003 patient surveys reinforce the need for:

- More comprehensive patient education and training in how to adjust glucocorticoid medication for illness or injury, as well as self-injection technique. Endocrine nurse involvement is likely to be a key factor in the effectiveness of this important part of patient education and training.

Figure 5 Emergency card including instructions for steroid emergency administration issued by the United Kingdom Addison's Self-Help Group (ADSHG) (www.addisons.org.uk).

- Vigilance on the part of GPs in ensuring that after-hours services are able to respond urgently to requests for assistance from Addison's patients or their relatives.
- Awareness that everyday gastric infections or influenza are potentially life-threatening for the steroid-dependent adrenal insufficiency patient, without prompt and sufficient treatment.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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