Clinical Endocrinology (2012) 77, 357–362 doi: 10.1111/j.1365-2265.2012.04376.x

ORIGINAL ARTICLE

Cortisol response to synacthen stimulation is attenuated following abusive head trauma

Natasha L. Heather*, José G. B. Derraik*, Christine Brennan*, Craig Jefferies†, Paul L. Hofman*, Patrick Kelly†, Rhys G. Jones‡, Deborah L. Rowe*,§ and Wayne S. Cutfield*

*Liggins Institute, University of Auckland, †Starship Children's Hospital, Auckland District Health Board, ‡Te Kupenga Hauora Māori, School of Population Health, University of Auckland, and §School of Nursing, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

Summary

Background Child abuse and other early-life environmental stressors are known to affect the hypothalamic–pituitary–adrenal axis. We sought to compare synacthen-stimulated cortisol responses in children who suffered inflicted or accidental traumatic brain injury (TBI).

Methods Children with a history of early-childhood TBI were recruited from the Starship Children's Hospital database (Auckland, New Zealand, 1992–2010). All underwent a low-dose $ACTH_{1–24}$ (synacthen 1 μg IV) test, and serum cortisol response was compared between inflicted (TBI_I) and accidental (TBI_A) groups.

Results We assessed 64 children with TBI_I and 134 with TBI_A. Boys were more likely than girls to suffer accidental ($P < 0{\cdot}001$), but not inflicted TBI. TBI_I children displayed a 14% reduction in peak stimulated cortisol in comparison with the TBI_A group ($P < 0{\cdot}001$), as well as reduced cortisol responses at + 30 ($P < 0{\cdot}01$) and + 60 min ($P < 0{\cdot}001$). Importantly, these differences were not associated with severity of injury. The odds ratio of TBI_I children having a mother who suffered domestic violence during pregnancy was 6·2 times that of the TBI_A group ($P < 0{\cdot}001$). However, reported domestic violence during pregnancy or placement of child in foster care did not appear to affect cortisol responses.

Conclusion Synacthen-stimulated cortisol response is attenuated following inflicted TBI in early childhood. This may reflect chronic exposure to environmental stress as opposed to pituitary injury or early-life programming.

(Received 18 November 2012; returned for revision 08 December 2012; finally revised 21 February 2012; accepted 21 February 2012)

Correspondence: Wayne S. Cutfield, Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand. Tel.: +64 9 923 5118; Fax: +64 9 373 8763; E-mail: w.cutfield@auckland.ac.nz

Introduction

Family violence (including child abuse) is pervasive, underreported and a cause of long-term morbidity in most societies.[1] A well-recognized consequence of violence during infancy is abusive head trauma (the 'shaken baby syndrome'), which in New Zealand is conservatively estimated to affect 15–25 per 100 000 infants per year.[2] Childhood abuse is associated with a high prevalence of depression in adult life, possibly via programming of the hypothalamic–pituitary–adrenal (HPA) axis.[3]

The HPA axis function can be assessed using a variety of methods. These include assessment of unstimulated cortisol, such as baseline levels (i.e. 8 am serum measurement) and circadian cortisol rhythms (i.e. salivary levels). Other methods assess the cortisol secretory reserve, using provocative stimulation (e.g. CRH, insulin, and $ACTH_{1–24}$). The low-dose $ACTH_{1–24}$ (synacthen 1 μg IV) test is regarded as a gold standard method for the assessment of baseline and stimulated adrenal function in children and adults.[4,5] Although it has been suggested that gender differences in spontaneous cortisol levels emerge during puberty,[6,7] the data regarding the relative influence of age, gender, pubertal status, and body mass index (BMI) are conflicting.[8–10]

Nonetheless, several studies have demonstrated that childhood abuse can lead to HPA dysfunction that may persist for years. For example, adults who were abused during childhood display decreased cortisol feedback sensitivity[11] and increased pituitary sensitivity to corticotropin-releasing factor (CRF).[12] Morning salivary cortisol is decreased both amongst children in foster care[13] and those raised in neglectful institutions.[14] HPA axis challenge studies in children who have suffered abuse have been very small and report apparently contradictory results, such as a variably increased or decreased ACTH response to a CRF challenge.[15,16]

We aimed to describe the long-term impact on the HPA axis associated with inflicted traumatic brain injury (TBI), which is one objective measure of abuse in early childhood. For this purpose, we adopted a low-dose synacthen test to compare basal and stimulated serum cortisol responses between children who suffered inflicted or accidental TBI in early childhood.

Methods

Study population

Starship Children's Hospital is the only hospital in New Zealand with a dedicated paediatric intensive care unit, as well as being the regional neurosurgical paediatric centre for the Auckland region. Admissions after accidental or inflicted TBI were identified from both the Hospital's Trauma (2000–2010) and Child Protection (1992–2010) databases. Cases were eligible if structural TBI had occurred within the first 5 years of life and more than 12 months previously. Structural TBI was defined as the presence of skull fracture, intracranial haemorrhage (extradural, subdural, subarachnoid or intraventricular) or cerebral injury (contusion, infarct, oedema or diffuse axonal injury) reported on computerized tomography or magnetic resonance imaging scan. Exclusion criteria were death during or after admission, residence outside of New Zealand, age under 3 years at assessment or pituitary dysfunction that predated TBI.

From the group of eligible subjects, children were recruited for a detailed follow-up assessment,[17] and were further separated into those who suffered an accidental (TBI_A) or inflicted (TBI_I) traumatic brain injury. TBI_I children had to meet the following additional criteria: injuries incompatible with the history,[18] careful evaluation by a multidisciplinary child protection team and notification to the statutory authorities.

Measured parameters

Injury data were obtained from hospital records, including age at injury, cause of injury, neuro-imaging reports and intensive care admission. Anatomical head injury severity was assessed according to the Abbreviated Injury Scale (AIS). AIS scores are based on CT or MRI scans,[19] and injuries are ranked on a 'threat to life' scale ranging from 1 to 6 (1–mild, 2–moderate, 3–serious, 4–severe, 5–critical and 6–not survivable).[19]

Ethnicity was recorded by self-report using a priority system, such that if multiple ethnicities were selected, the subject was assigned to a single ethnicity, following a hierarchical classification of Māori, Pacific Islander, Other and then European.[20] Those participants described as 'Other' were of ethnicities not otherwise stated (e.g. Indian, South-East Asian, African and Middle Eastern).

Guardianship was confirmed prior to assessment, and we recorded whether the subject was currently living with one or two biological parents, or in foster care. In addition, the accompanying guardian or birth mother was interviewed regarding domestic (interparental) violence during pregnancy, specifically, whether the mother had been physically hurt by her partner during this time.

Geo-coded deprivation scores were derived from current address using the New Zealand Index of Deprivation 2006 (NZDep2006).[21] This index is based on household census data reflecting nine aspects of material and social deprivation to divide New Zealand into tenths (scored 1–10) by residential address. Scores of 1 represent the least deprived areas and 10 the most deprived. Scores are derived from units covering a small area, each reflecting approximately 90 people.

Clinical assessments were performed at the Maurice & Agnes Paykel Clinical Research Unit, at the Liggins Institute, University of Auckland. Height was measured to the nearest 0·1 cm using a Harpender stadiometer. Height standard deviation scores (SDS) were derived from Tanner/Whitehouse reference data,[22] and weight and BMI SDS according to British 1990 standards.[23] Parental heights were whenever possible measured at the time of assessment or otherwise reported by a caregiver and used to calculate mid-parental height. Pubertal staging was assessed by a physician or a trained research nurse. Puberty was defined as Tanner stage 2 breast development in girls and testicular volume > 3 ml in boys as per Tanner and Whitehouse.[24,25]

Laboratory assessments

Low-dose (1 μg) synacthen (synthetic $ACTH_{1–24}$; Novartis, Basle, Switzerland) tests were commenced between 08:00 and 10:00 am, when an intravenous cannula was inserted into an antecubital vein using topical anaesthetic. After a 15-min period of rest, blood samples were drawn for the measurement of baseline cortisol, free thyroxine (T4), free triiodothyronine (T3) and thyroid-stimulating hormone (TSH) concentrations. A low-dose (1 μg) synacthen bolus was then given intravenously, and blood samples drawn at + 30 and + 60 min for cortisol measurement. Whole blood samples were stored in EDTA tubes at ambient temperature for up to 2 h and then centrifuged at 2400 *g* for 5 min.

Serum cortisol was measured using the Roche cortisol competitive electrochemiluminescence immunoassay (ECLIA), on a Roche E170 analyser (Indianapolis, IN, USA). Intrabatch coefficient of variation (CV) was <2·0% for values between 129 and 866 nmol/l. Interbatch CV was 5·2% at 63 nmol/l, 2·9% at 474 nmol/l and 3·0% at 852 nmol/l. Free T3 and free T4 were measured using the Roche FT4 and FT3 competitive ECLIAs on a Roche E170 analyser. Intrabatch CV for T3 was <3·5% for values between 2·8 and 22 pmol/l and for T4 < 2·0% for values between nine and 41 pmol/l. Interbatch CV for T3 was 6·2% at 4·0 pmol/l, 3·2% at 12 pmol/l and 3·3% at 22 pmol/l; for T4 were 3·4% at 13·7 pmol/l, 3·9% at 36 pmol/l and 5·7% at 89 pmol/l. TSH was measured using the Roche TSH sandwich ECLIA, on a Roche E170 analyser. Intrabatch CV was <3·0% for values between 0·04 and 9·3 IU/l, while interbatch CV was 2·2% at 0·5 IU/l, 2·6% at 6·2 IU/l and 2·7% at 36 IU/l.

Ethics

Ethics approval for this study was provided by the hospital (Auckland District Health Board) and regional (Northern X) ethics committees. Written informed consent was obtained from guardians of all participants.

Statistical analysis

Baseline demographic data were compared using one-way ANOVA. Binary logistic regressions and chi-square tests were used

to compare the relative frequencies of ethnic groups between the TBI database and study cohort, as well as the incidences of admission with TBI_A and TBI_I amongst ethnic groups in relation to age-matched New Zealand Census population data. Auxological and hormonal data were analysed using linear mixed models. Where hormone data were the responses, group (TBI_I *vs* TBI_A), ethnicity and gender were included as factors, while age at assessment, BMI SDS, NZDep2006 and AIS as covariates. Note that 'time of testing' was also included as a co-variate in the models, as it was found to significantly impact most hormonal measurements. Further, the model was subsequently run also with the addition of 'violence during pregnancy' and 'placement in foster care' separately as factors. For auxology, the variable of interest was the response; group, gender, pubertal status and ethnicity were factors; while age at assessment and mid-parental height were included as covariates.

Statistical analyses were carried out in SAS v.9.2 (SAS Institute, Cary, NC, USA) and Minitab (Minitab v.15; Pennsylvania State University, PN, USA). The Johnson transformation was adopted as required to stabilize the variance. All data are expressed as mean ± standard error of the mean (SEM).

Results

This study identified 770 TBI admissions of children under 5 years of age. A total of 156 children had no structural TBI, 42 were deceased, and an additional 127 were excluded owing to either young age or geographical distance from the testing centre. A total of 175 could not be contacted, and 270 were invited to participate. Sixty-seven declined participation, and five others were excluded because secure venous access could not be obtained. As a result, 198 participants were studied: 64 TBI_I and 134 TBI_A.

Children in the follow-up cohort were slightly younger at the time of TBI than those in the database ($P = 0{\cdot}053$) and suffered comparatively more severe injuries as illustrated by longer stay in hospital ($P < 0{\cdot}001$), greater frequency of admissions to the ICU ($P = 0{\cdot}003$) as well as a greater number of subjects with severe AIS ($P < 0{\cdot}001$). The ethnic distribution within our cohort was representative of the database, as the proportion of Māori and Europeans in our cohort (33·3% and 37·4%, respectively) was nearly identical to that in the overall dataset (32·3% and 37·7%, respectively; $P = 0{\cdot}82$).

We studied more boys (116) than girls (82), reflecting a similar ratio to the overall TBI database ($P = 0{\cdot}20$), as boys were more likely than girls to suffer accidental ($P < 0{\cdot}001$) but not inflicted TBI (Table 1). Primary causes of accidental TBI were falls ($n = 71$), road traffic accidents ($n = 41$) and other events ($n = 22$). There was no difference in socio-economic status between the TBI_I and TBI_A groups.

Based on the age-matched New Zealand Census population data, Māori children in the Auckland region were over-represented in the TBI database and were 2·7 times more likely to suffer TBI than Europeans (95% CI: 1·3–5·7; $P < 0{\cdot}001$). Further, the odds ratio of a Māori child suffering inflicted TBI or having a parent who reported domestic violence during pregnancy was 5·7× (95% CI: 3·1–10·5; $P < 0{\cdot}001$) and 3·5× (95% CI: 1·3–9·6; $P = 0{\cdot}015$) those of Europeans, respectively. Although Māori children were significantly more socio-economically disadvantaged than Europeans (NZDep2006 6·7 ± 0·4 *vs* 5·3 ± 0·4, $P < 0{\cdot}006$), differences in the incidence of violence remained even after SES was controlled for in the analyses.

Although both TBI_I and TBI_A groups were assessed at similar ages, children who suffered TBI_I were younger at the time of injury ($P < 0{\cdot}001$; Table 1). The likelihood of intensive care admission was similar in both groups (Table 1). Structural head injuries (AIS) were more severe amongst TBI_I children ($P < 0{\cdot}001$), whose odds ratio of suffering subdural haemorrhage was over 10 times that of TBI_A children (95% CI: 4·9–21·1; $P < 0{\cdot}001$) (Table 1). Importantly, the majority of TBI_I cases had radiological evidence of recurrent subdural haemorrhage

Table 1. Demographics and auxology of children who suffered inflicted and accidental traumatic brain injury (TBI)

	Inflicted TBI	Accidental TBI	*P*-value
Demographics			
n	64	134	
Gender	34 M, 30 F	82 M, 52 F	0·29†
Ethnicity			
European	17 (27%)	59 (44%)	0·020
Māori	29 (45%)	37 (28%)	0·016
Pacific Islander	14 (22%)	27 (20%)	0·85
Other	4 (6%)	11 (8%)	0·78
NZDep 2006	6·94 ± 0·39	6·28 ± 0·28	0·15
Interparental violence during pregnancy*	40%	10%	<0·001
Living in foster care	52%	0%	<0·001
Auxology			
Age at assessment (years)	8·7 ± 0·5	8·1 ± 0·2	0·52
Pubertal status			
Tanner 1	65%	81%	0·030
Tanner 2–3	16%	16%	0·99
Tanner 4–5	19%	3%	<0·001
Height SDS	0·72 ± 0·15	0·87 ± 0·12	0·24
Weight SDS	0·82 ± 0·17	0·87 ± 0·12	0·016
BMI SDS	0·78 ± 0·16	0·97 ± 0·11	0·006
TBI parameters			
Age at injury (years)	0·9 ± 0·1	2·1 ± 0·1	<0·001
AIS severe–critical (AIS 4–5)	52 (81%)	70 (52%)	<0·001
Subdural haemorrhage	52 (81%)	40 (30%)	<0·001
Intensive care unit admission	27 (42%)	51 (38%)	0·64
Evidence of recurrent subdural haemorrhage	34 (53%)	0	<0·001

Where applicable, data are mean ± SEM. AIS, Abbreviated Injury Scale, ranging 1 (mild) to 6 (not survivable); BMI, body mass index; NZDep2006, socio-economic index scored 1–10, where 1 indicates the least and 10 the greatest deprivation; SDS, standard deviation scores; TBI, traumatic brain injury.

*$n = 55$ for children with inflicted and 72 with accidental TBI.

†*P*-values for the assessment of a sex ratio different from 1:1 were $P = 0{\cdot}62$ amongst Inflicted and $P < 0{\cdot}001$ amongst Accidental TBI groups.

and thus repeated episodes of injury, which was not observed in any TBI_A subject (Table 1).

Following adjustment for all confounding factors, baseline (0 min) cortisol concentrations were not different amongst groups ($P = 0{\cdot}27$), but TBI_I children had reduced cortisol concentrations at +30 ($P = 0{\cdot}005$) and +60 ($P < 0{\cdot}001$) min (Fig. 1). Further, TBI_I children also displayed a 14% reduction in peak stimulated cortisol ($P < 0{\cdot}001$; Fig. 1). Importantly, these differences were not associated with injury severity graded as per AIS. In addition, there were no differences amongst the TBI_I group in baseline or peak cortisol concentrations between those with evidence of pre-existing subdural haemorrhage (presumed to have suffered from previous episodes of TBI) *vs* those without it. There were no observed differences between TBI_I and TBI_A in the thyroid hormones assessed: free T3 ($6{\cdot}44 \pm 0{\cdot}10$ *vs* $6{\cdot}64 \pm 0{\cdot}07$ pmol/l; $P = 0{\cdot}49$), free T4 ($17{\cdot}44 \pm 0{\cdot}24$ *vs* $17{\cdot}05 \pm 0{\cdot}19$ pmol/l; $P = 0{\cdot}29$) and TSH ($2{\cdot}00 \pm 0{\cdot}09$ *vs* $2{\cdot}14 \pm 0{\cdot}09$ mU/l; $P = 0{\cdot}76$), respectively.

In addition, even when all other factors and covariates were accounted for, stimulated (but not baseline) cortisol concentrations were also shown to be affected by age at assessment, gender and BMI SDS. Interestingly, it was not pubertal status but age and gender that affected cortisol levels. Girls had basal cortisol concentrations that were 9·5–16·7% greater than boys at + 30 min (693 ± 15 *vs* 633 ± 10; $P < 0{\cdot}001$), +60 min (665 ± 23 *vs* 569 ± 18; $P < 0{\cdot}001$) and peak (739 ± 18 *vs* 663 ± 13; $P < 0{\cdot}0001$). Age was negatively associated with peak cortisol ($P < 0{\cdot}0001$), as well as concentrations at +30 ($P < 0{\cdot}001$) and +60 ($P = 0{\cdot}002$) min. BMI SDS was also negatively associated with cortisol response at +60 min ($P = 0{\cdot}030$), and it tended to negatively affect baseline response as well ($P = 0{\cdot}087$).

Overall, there were 17 subjects with mildly abnormal peak cortisol concentrations (<500 nmol/l), whose mean response was 435 ± 12 nmol/l. Ten of these cases occurred in the TBI_I group, so that the prevalence of an abnormal response was much greater amongst TBI_I (16%) than TBI_A (5%) children ($P = 0{\cdot}027$). All children with low stimulated cortisol levels were reviewed by endocrinologists at Starship Children's Hospital, and none required cortisol replacement.

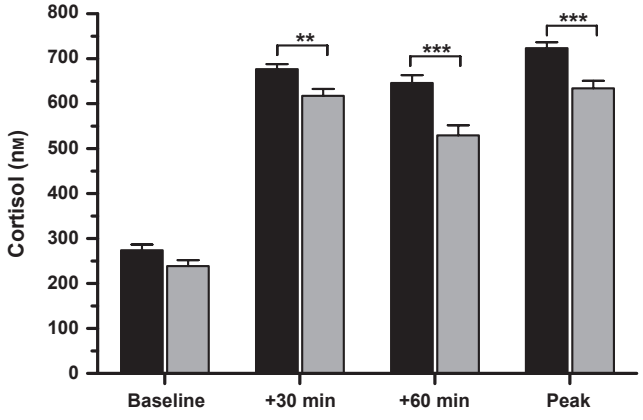

Fig. 1 Timed cortisol response following a low-dose synacthen test. Black bars represent children who suffered accidental traumatic brain injury (TBI), and grey bars those who suffered inflicted TBI. $^{**}P < 0{\cdot}01$, $^{***}P < 0{\cdot}001$ for accidental *vs* inflicted TBI.

At the time of assessment, 48% of the TBI_I group were living with at least one biological parent and 52% were in foster care. However, neither these living arrangements nor their socio-economic status (NZDep2006) had an observed effect on cortisol concentrations, either at baseline or following synacthen stimulation. 127 subjects (55 TBI_I and 72 TBI_A) provided information on interparental violence during pregnancy, which was reported to have occurred in 10% of the TBI_A and 40% of TBI_I group. The odds ratio of a TBI_I child having a mother who was a victim of domestic violence during pregnancy was 6·2 times that of the TBI_A group (95% CI: 2·4–16·0; $P < 0{\cdot}001$; Table 1). However, as observed for living arrangements, there were no effects on cortisol concentrations associated with interparental violence during gestation.

Discussion

Our study shows that the cortisol response to synacthen stimulation was 14% lower amongst children who suffered inflicted TBI. Notably, the observed differences between groups are likely to be underestimated, as children in the inflicted group were slimmer and had a proportionally greater ratio of girls than the accidental group, both of which were shown to be associated with increased stimulated cortisol concentrations.

There are a number of potential explanations for the lower stimulated cortisol levels observed in TBI_I children. Firstly, inflicted TBI may lead to greater incidence of traumatic ACTH deficiency, which may in turn lead to the observed cortisol differences between groups. Inflicted TBI is typically severe and is likely to involve repeated events, so that abused children may be a group particularly at risk of pituitary damage. However, although hypopituitarism has a reported prevalence of 10–60% after childhood brain injury, we recently showed that this is likely to have been greatly overestimated.[17] In addition, we show in this study that the observed differences in cortisol responses between TBI_I and TBI_A children were not associated with injury severity. Further, we did not observe any differences between groups in the thyroid axis. Thus, the blunted cortisol responses in TBI_I children were most likely associated with other environmental stressors, rather than a direct result of the head injury itself.

Another possible explanation is HPA programming, as inflicted TBI is a marker of abuse in early childhood. The strongest evidence for environmental programming of the HPA axis comes from rodent studies, where maternal separation in the early postnatal period led to an increased cortisol response to subsequent stressors.[26] This occurs in part through methylation of glucocorticoid receptors and a subsequent decrease in negative feedback.[27–29] In humans, maternal depression and anxiety during the third trimester have both been associated with increased basal salivary cortisol levels in offspring.[30,31] Within our TBI_I cohort, violence during pregnancy was reported in over half of the cases. Although we found no cortisol differences associated with this history, synacthen tests do not provide a

sensitive assessment of cortisol negative feedback. Therefore, although domestic violence would likely lead to perinatal programming of the HPA axis, its impact within out cohort is unclear.

It is also possible that attenuation of stimulated cortisol reflects a greater level of day-to-day environmental stressors amongst TBI_I subjects. Although stress is classically associated with increased cortisol production, low levels are increasingly recognized in conditions of chronic stress.[32] For example, cortisol levels are low in association with post-traumatic stress disorder despite increased CRH, and there is exaggerated feedback sensitivity.[33] Similarly, low basal levels of salivary cortisol have been observed in young children exposed to institutional neglect[14] or raised by depressed mothers in extreme poverty.[34] Although we found no differences in either basal or stimulated cortisol when subjects were grouped according to their current living situation (i.e. foster placement), it may be that living arrangements are not a good predictor of a stable environment. Further, although the majority of subjects lived in the most deprived quintile, deprivation scores did not affect cortisol levels in this study. It is nonetheless conceivable that ongoing environmental adversity might have influenced the HPA axis and be responsible for the observed differences.

We acknowledge that there are possible limitations associated with our study. We conducted a cross-sectional rather than a prospective study, which ideally should have commenced from early pregnancy and included mothers with and without risk factors for physical abuse. A limitation inherent to any study of this kind is the difficulty in obtaining accurate and complete information about domestic violence and details regarding ongoing child abuse. A major challenge for this study was recruitment, mostly owing to difficulty in obtaining up-to-date case contact details. This was particularly challenging amongst children with inflicted injuries and as the interval from TBI increased. Although we managed to achieve a high rate of acceptance amongst those contacted (73%), in practice, we could only achieve a 44% rate of recruitment amongst the eligible TBI subjects. Finally, there are a range of different techniques to assess aspects of HPA axis function, but we have chosen a single gold standard technique for this study.

It should be noted that our data corroborate previous evidence showing a high concurrence between child abuse and interparental violence, which often escalates during pregnancy.[35,36] In our study, children who suffered inflicted TBI were over sixfold more likely to have a mother who suffered domestic violence. Thus, one intervention to prevent abusive TBI in children might be through measures to prevent interparental violence.

In conclusion, our study provides new evidence on HPA axis alterations in children who have been abused in childhood. We observed that children who suffered abusive TBI in early childhood had a blunted cortisol response to synacthen stimulation, possibly as a result of ongoing chronic stress during childhood. This study is part of a growing body of work documenting that child abuse is associated with long-term alterations to the HPA axis. However, in the absence of longitudinal data, the significance of our findings is unclear, and robust longitudinal studies are warranted.

Acknowledgements

We thank participants and our advisory Kaitiaki group. We also thank Rangi Dansey (Auckland City Hospital) for his assistance with the Starship Trauma database. The study was supported by grants from the Health Research Council of New Zealand and the Australasian Paediatric Endocrine Group. Natasha Heather was supported by the Starship Fellowship Foundation. The authors have no financial or nonfinancial interests to declare that may be relevant to this submitted work. We acknowledge the Paykel Trust for long-term funding of the Maurice & Agnes Paykel Clinical Research Unit at the Liggins Institute.

Disclosure statement

The authors have nothing to disclose.

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