

Permanent Hypopituitarism Is Rare after Structural Traumatic Brain Injury in Early Childhood

Natasha L. Heather, Craig Jefferies, Paul L. Hofman, José G. B. Derraik, Christine Brennan, Patrick Kelly, James K. M. Hamill, Rhys G. Jones, Deborah L. Rowe, and Wayne S. Cutfield

Liggins Institute (N.L.H., P.L.H., J.G.B.D., C.B., D.L.R., W.S.C.), University of Auckland; Te Kupenga Hauora Maori (R.G.J.), School of Population Health; and School of Nursing, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, 1020 Auckland, New Zealand; and Starship Children's Hospital (C.J., P.K., J.K.M.H.), Auckland District Health Board, Private Bag 92024, 1142 Auckland, New Zealand

Background: We sought to determine the incidence of permanent hypopituitarism in a potentially high-risk group: young children after structural traumatic brain injury (TBI).

Methods: We conducted a cross-sectional study with longitudinal follow-up. Dynamic tests of pituitary function (GH and ACTH) were performed in all subjects and potential abnormalities critically evaluated. Puberty was clinically staged; baseline thyroid function, prolactin, IGF-I, serum sodium, and osmolality were compared with age-matched data. Diagnosis of GH deficiency was based on an integrated assessment of stimulated GH peak ($<5 \mu\text{g/liter}$ suggestive of deficiency), IGF-I, and growth pattern. ACTH deficiency was diagnosed based on a subnormal response to two serial Synacthen tests (peak cortisol $<500 \text{ nmol/liter}$) and a metyrapone test.

Results: We studied 198 survivors of structural TBI sustained in early childhood (112 male, age at injury $1.7 \pm 1.5 \text{ yr}$ $6.5 \pm 3.2 \text{ yr}$ after injury). Sixty-four of the injuries (33%) were inflicted and 134 (68%) accidental. Two participants had developed precocious puberty, which is within the expected background population rate. Peak stimulated GH was subnormal in 16 participants (8%), in the context of normal IGF-I and normal growth. Stimulated peak cortisol was low in 17 (8%), but all had normal ACTH function on follow-up. One participant had a transient low serum T_4 . Therefore, no cases of hypopituitarism were recorded.

Conclusion: Permanent hypopituitarism is rare after both inflicted and accidental structural TBI in early childhood. Precocious puberty was the only pituitary hormone abnormality found, but the prevalence did not exceed that of the normal population. (*J Clin Endocrinol Metab* 97: 599–604, 2012)

Traumatic brain injury (TBI) is a common event in childhood. Incidence is best assessed by prospective population studies, such as the Christchurch Birth Cohort study, which reported that a third of the population had sustained TBI by 25 yr of age (1). The overall incidence was 1.75 per 100 per year, with 30% of injuries recurrent and 10% defined as moderate to severe (1). The New Zealand incidence of inflicted TBI (shaken baby syndrome) is conservatively estimated as 15–20 per 100,000 infants per year (2) but is likely to be greatly underreported.

The prevalence of hypopituitarism after TBI is poorly defined, particularly in childhood. A recent meta-analysis of adult TBI data reported the rate of long-term hypopituitarism as 27.5%, most commonly affecting GH or gonadotropins (3). The few childhood TBI studies have reported a highly variable rate of hypopituitarism (5–61%) (4–10). All have been small studies ($n < 50$) and used nonstandardized methods to assess and diagnose pituitary function. Routine pituitary assessment after moderate to severe TBI has been recommended for adult populations (11) and extrapolated to children as well (12).

The mechanism of traumatic hypopituitarism is proposed to be vascular. The pituitary gland is suspended on a stalk and potentially mobile. Long hypophyseal vessels traverse the stalk and supply the anterior pituitary via a latticework of portal vessels. These small perforating vessels may be vulnerable to shearing injury from sudden acceleration-deceleration forces. The pattern of anterior pituitary infarction, seen in up to a third of fatal head injuries, corresponds to areas supplied by portal vessels (13). Inflicted injuries can be caused by shaking or impact (or a combination of both), and either mechanism can produce identical pathological changes in the brain (14). The mechanisms by which inflicted TBI is produced, and the anatomy of the infant head and neck, may make infants particularly vulnerable to pituitary injury (14).

TBI is a heterogeneous condition, and current methods of grading are poorly predictive of pituitary dysfunction. The Glasgow Coma Scale (GCS) is widely used to define severity (15), although a variety of factors such as interval to hospital presentation, prehospital interventions, and limited interobserver reliability can affect scores (16, 17). Scoring preverbal children presents further difficulty (18), and a single score may be less meaningful after the repeated injury commonly seen in inflicted TBI (19). Structural TBI is likely to be a more robust way to define significant head injury, and therefore predict pituitary damage, in young children.

There are no robust studies examining the prevalence of hypopituitarism in children after TBI. Thus, we aimed to determine the prevalence of hypopituitarism in a potentially high-risk group: young children after structural TBI.

Subjects and Methods

Starship Children's Hospital is the only hospital in New Zealand with a dedicated pediatric intensive care unit as well as being the regional neurosurgical pediatric center 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 yr of life and more than 12 months previously. Structural TBI was defined as the presence of skull fracture, intracranial hemorrhage (extradural, subdural, subarachnoid, or intraventricular), or cerebral injury (contusion, infarct, edema, 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 yr at assessment, or pituitary dysfunction that predated TBI.

All children with inflicted TBI met the following criteria: structural TBI, injuries incompatible with the history (20), careful evaluation by the multidisciplinary child protection team, and notification to the statutory authorities. Functional TBI severity was assessed as per GCS (15), whereas structural TBI was graded according to the Abbreviated Injury Scale (21).

Assessments were performed at the Liggins Institute, University of Auckland. Height was measured to the nearest 0.1 cm using a Harpenden stadiometer. Pubertal staging was assessed as per Marshall and Tanner (22). Reported or measured parental heights were recorded. Height and height velocity SD scores (SDS) were derived from Tanner/Whitehouse reference data (22), and body mass index (BMI) SDS according to British 1990 standards (23).

Baseline fasting serum samples were taken for analysis of IGF-I, IGF-binding protein 3 (IGFBP-3), TSH, free T₄, free T₃, prolactin, sodium, and osmolality. Dynamic tests were used to evaluate GH and ACTH sufficiency. Clonidine (150 µg/m²) was administered orally and GH samples drawn at 0, +30, +60, +90, and +120 min. Intravenous arginine (6.5 ml/kg of 10% solution) was then administered and additional samples drawn at +150 and +180 min. Low-dose Synacthen (1 µg as an iv push) was also given at baseline and cortisol measured at 0, +30, and +60 min. An additional gonadotropin stimulation test (GnRH, 100 µg) was performed in children with clinical evidence of precocious puberty, and LH and FSH measured at +30 and +60 min.

A Roche (Indianapolis, IN) E170 Modular laboratory analyzer using chemiluminescence was used for cortisol [coefficient of variation (CV) 6%], TSH (CV 5%), free T₄ (CV 7%), and free T₃ (7%). A Roche Modular ISE laboratory analyzer measured serum sodium and serum osmolality. A Siemens Immulite 2000 (Siemens, Los Angeles, CA) using immunochemiluminescence was used for GH (CV 5%), IGF-I (CV 8%), prolactin (CV 5%), LH (CV 13%), and FSH (CV 12%). A Bioclone RIA kit (Bioclone, Marrickville, NSW, Australia) measured IGFBP-3 (CV 8%) and 11-deoxycortisol (CV 20%).

Hypopituitarism was defined as deficiency in one or more pituitary hormones. Baseline hormone values were compared with age-, sex-, and (where appropriate) pubertal stage-adjusted normal reference ranges provided by Auckland Healthcare Laboratory Services. All participants with abnormal results underwent further comprehensive review. The diagnosis of GH deficiency was based on the integrated assessment of stimulated GH peak, IGF-I, IGFBP-3, and growth parameters. Growth velocity was monitored over a minimum of 6 months among participants with peak stimulated GH below 5 µg/liter, which is New Zealand's adopted cutoff for possible childhood GH deficiency based on current assay (24). Estrogen priming was reserved for repeat GH tests in prepubertal participants (ethinyl estradiol 40 µg/m² orally taken for 2 d before assessment). The diagnosis of ACTH deficiency was based on consistently subnormal results. Participants with peak stimulated cortisol below 500 nmol/liter underwent a second low-dose Synacthen test, and those with a second subnormal response underwent a short metyrapone test (oral metyrapone 30 mg/kg, maximum of 2 g, taken at 2300 h). Blood samples were obtained the following morning, and a normal response was defined as the sum of cortisol plus 11-deoxycortisol higher than 450 nmol/liter and ACTH higher than 20 pmol/liter (25). Possible precocious puberty was defined in girls as Tanner stage 2 breast development at under 8 yr or onset of menstruation at under 9.5 yr and in boys as testicular volume of at 4 ml or more at under 9 yr of age. Confirmation was obtained via pubertal level of sex steroids and stimulated LH peak higher than 10 IU/liter.

Data are presented as mean ± SD. Two-tailed χ^2 tests with Yates correction were used to assess whether the frequency of precocious puberty among boys and girls who suffered TBI was greater than normal, based on reference data from the Danish national database (26).

This study was approved by the hospital (Auckland District Health Board) and regional (Northern X) ethics committees.

Written informed consent was obtained from guardians of all participants.

Results

This study identified 770 TBI admissions of children under 5 yr of age. A total of 156 children had no structural TBI, 42 were deceased, and an additional 127 were excluded due to either young age or geographical distance from the testing center. A total of 175 could not be contacted, and 270 were invited to participate. Sixty-seven declined, the most common reason being no concern about the child's health or development. Five others were excluded because secure venous access could not be obtained. As a result, 198 participants were studied, whose baseline characteristics are outlined in Table 1.

Sixty-four participants (32%) sustained inflicted and 134 (68%) accidental TBI. Computerized tomography reports were available for all but three participants and magnetic resonance imaging scans for 34%. Intracerebral hemorrhage (66%), cerebral injury (66%), and skull fractures (70%) occurred in most. Most subjects had severe to critical structural TBI, although just under half had moderate to severe injury by GCS (Table 1). Specific pituitary abnormality (posterior hemorrhage) was reported in only one case and was associated with transient diabetes insip-

idus. Average length of stay in hospital was 10.5 d, and 40% were admitted to intensive care (Table 1).

Endocrine evaluation

Patients were assessed 6.5 ± 3.2 yr after injury, at an age of 8.3 ± 3.3 yr. A total of 170 participants (85%) were Tanner stage 1–2, 22 (11%) stage 3–4, and six (3%) stage 5. Chronic illness included asthma (eight participants reported taking low-dose inhaled steroids), medically treated ADHD, congenital cardiac disease, and achondroplasia (height SDS -4.8 , omitted from auxological analysis). Endocrine assessment was complete in 191; four participants declined GH stimulation tests, and one additionally declined the Synacthen test. Thyroid function was not available in three cases.

GH-IGF-I axis

Peak GH response to arginine-clonidine was 14.4 ± 7.8 $\mu\text{g/liter}$. GH peak was under 10 $\mu\text{g/liter}$ in 65 subjects (33%) and under 5 $\mu\text{g/liter}$ in 16 (8%). Among subjects with GH under 5 $\mu\text{g/liter}$ (with apparent GH deficiency), mean height SDS was 1.0 ± 1.2 and BMI SDS 2.8 ± 0.8 , whereas both IGF-I and IGFBP-3 were within the normal range for all subjects (Table 2). This group was followed in growth clinics for a period of 6–36 months, and all demonstrated normal height velocity (Table 2). Repeat arginine-clonidine tests were performed in five cases. Repeat GH was more than 5 $\mu\text{g/liter}$ in all but one case, likely confounded by severe obesity (BMI SDS 4.2). None of the subjects with short stature or who were short for their parents' heights had low GH or IGF-I levels. There were six subjects (3%) who had height below -2 SDS at assessment and seven (4%) with height corrected for genetic potential below -2 SDS. Only two subjects had short stature as assessed by both measures: one with achondroplasia and another with spastic quadriplegia.

ACTH axis

Basal cortisol was 270 ± 150 nmol/liter and peak 695 ± 152 nmol/liter. Suboptimal cortisol response (<500 nmol/liter) was seen in 17 (9%) participants (range 304–487 nmol/liter). None of these had hyponatremia, fasting hypoglycemia, or postural hypotension suggestive of adrenal insufficiency. Three reported regular low-dose inhaled steroids. Interim stress steroid precautions were advised in all cases. All 17 underwent repeat Synacthen tests, 13 of which achieved peak cortisol above target. Four remained low, one declined additional assessment (peak cortisol 490 nmol/liter), and three responded appropriately to metyrapone. None were considered to have significant ACTH deficiency.

TABLE 1. Baseline characteristics of participants (n = 198)

Characteristic	Data
Age at injury (yr)	1.7 ± 1.5
Gender (M/F)	116/82
Cause of injury	
Fall	72 (36%)
Abuse	64 (32%)
Motor vehicle accident	43 (22%)
Other	19 (10%)
GCS at time of injury	
13–15 (mild)	109 (55%)
9–12 (moderate)	35 (18%)
3–8 (severe)	54 (27%)
Structural TBI (assessed by AIS)	
Moderate-serious (AIS 2–3)	78 (39%)
Severe-critical (AIS 4–5)	120 (61%)
Intensive care admission	77 (40%)
Acute surgical intervention ^a	47 (24%)
Duration of hospitalization (d)	10.5 ± 12.2
Time since TBI (yr)	6.5 ± 3.3
Age at assessment (yr)	8.3 ± 3.2
BMI SDS	0.9 ± 1.3
Height SDS	0.5 ± 1.3
Height SDS – MPH SDS	0.3 ± 1.4

Data are mean \pm SD, n (percent), or ratio. AIS, Abbreviated Injury Scale; F, female; M, male; MPH, mean parental height.

^a Mass evacuation or drain inserted.

TABLE 2. Hormonal and growth profile of study participants with GH peak under 5 $\mu\text{g/liter}$

Subject	Gender	Age (yr)	Tanner stage	GH peak ($\mu\text{g/liter}$)	IGF-I ($\mu\text{g/ml}$)	Height (cm)	Height SDS	BMI (kg/m^2)	BMI SDS	HV (cm/yr)	HV SDS	HV interval (months)
GH1	F	14	5	2.0 (6) ^a	385	167.8	1.0	30.2	2.5	ND ^b	ND ^b	ND ^b
GH2	M	8	1	2.1 (8.6) ^a	134	134	1.5	30.4	3.8	6.8	1.6	9
GH3	M	7	1	2.2 (5.6) ^a	100	122	-0.8	23.9	3.1	4.7	-0.8	31
GH4	M	12	1	2.3	144	159	1.2	34.5	3.4	8.5	2.9	6
GH5	F	9	1	2.5	123	131	2.3	30.8	3.5	7.6	2.8	6
GH6	F	6	1	3.0	143	124	1.3	25	3.3	7.2	2.1	36
GH7	M	7	1	3.1	127	128	0.5	24.4	3.1	5.9	0.6	17
GH8 ^c	F	8	4	3.4 (7.6) ^a	240	124	-0.9	26	2.9	3.9	-2.1	8
GH9	F	10	1	3.8	206	139	0.1	20.8	1.3	7.1	0.5	12
GH10	M	11	1	4.6	143	163.3	2.3	26.5	2.6	4.9	-0.1	6
GH11	M	7	1	4.6	142	132	0.8	23	2.8	5.5	0.1	36
GH12	F	8	1	4.7	196	132	0.6	22.3	2.2	5.9	0.6	12
GH13	M	6	1	4.8 (4.2) ^a	151	139.5	3.6	29	4.2	5.9	0.2	6
GH14	M	6	1	4.8	231	123	1.4	19.2	2.2	6.1	0.1	7
GH15	M	10	1	4.9	221	140	0.1	22.9	2.2	5.5	0.1	18
GH16	M	12	1	4.9	180	157.3	1.2	23.8	2.2	5.5	0.8	6

F, Female; HV, height velocity; M, male.

^a Values in parentheses refer to repeat arginine-clonidine GH tests, sex-steroid priming used for subjects GH2, GH3, and GH13.

^b No data (ND) because subject GH1 had reached final adult height before the study.

^c Subject GH8 has spastic quadriplegia with flexion contractures as well as precocious puberty and advanced bone age (+3 SDS), which collectively are growth limiting independently of GH status.

Precocious puberty

One male aged 7 yr had previously been diagnosed with precocious puberty (Tanner G3P3 with 6- to 8-ml testes, stimulated LH peak 21.4 IU/liter, testosterone 8.9 nmol/liter, and bone age +2 SDS), and was treated with regular depot injections of leuprorelin acetate. One female was diagnosed with precocious puberty at the time of assessment, with a history of breast development at 5–6 yr and menses from 7.5 yr. She had been seen by her general practitioner and reassured that her pubertal development was normal. At 8 yr, she was Tanner B4 and had stimulated LH peak 28.1 IU/liter, bone age +3 SDS advanced, and predicted final height 142 cm. Both had sustained severe TBI as assessed by GCS, structural injury, and clinical progress. The incidence of precocious puberty among boys was one in 116 and among girls was one in 82. Incidence among girls was no different ($P = 0.42$) from that of the general population (~ 20 in 10,000), but there was a trend for increased incidence among boys (*vs.* about four in 10,000; $P = 0.063$).

Other pituitary deficiencies

One female had possible mild central hypothyroidism on initial assessment, free T_4 of 10.6 pmol/liter (11–22 pmol/liter), free T_3 of 6.8 pmol/liter (3–10 pmol/liter), and TSH of 1.1 mU/liter (1.6 mU/liter). She was clinically well, and thyroid function normalized a month later (free T_4 of 13.3 pmol/liter and TSH of 1.4 mU/liter). No participants had hypernatremia or high serum osmolality. One female had a history of transient posttraumatic diabetes insipidus and had been off treatment and asymptomatic for 3 yr at

the time of assessment. Seven subjects had mildly elevated prolactin levels (range 370–750 mIU/liter) that were not considered clinically significant. In one case, this was attributed to risperidone, and repeat prolactin was normal in all three cases where it was reassessed.

Discussion

We show that permanent hypopituitarism is rare after structural TBI in early childhood in the largest such pediatric study performed to date. There were two cases of precocious puberty, but the prevalence did not exceed that of the normal childhood population. All other apparent pituitary hormone deficiencies were shown to be erroneous, when tests were repeated or considered as part of comprehensive assessments.

Importantly, there were no cases of GH deficiency. This finding contrasts to high rates reported by many previous TBI studies, showing a prevalence of 11–31% among adults (27–30) and 16–42% in small pediatric studies (5, 7, 10). Whereas earlier studies have based the diagnosis of GH deficiency entirely on GH stimulation tests, we performed detailed assessments of GH, IGF-I, and growth pattern, with recognition of obesity.

Using provocative GH tests alone and conservative international criteria (peak GH <10 $\mu\text{g/liter}$) (31), up to 33% of our study population might have been incorrectly diagnosed with GH deficiency. All these subjects were overweight or obese but had normal height, height veloc-

ity, and IGF-I level. It is common for normally growing children to display low GH responses that may falsely suggest deficiency (32). Stimulated GH levels are inversely associated with BMI in childhood (33), and misleadingly low GH levels (suggestive of deficiency) are especially common in obese children. Nonetheless, previous childhood TBI studies have not adjusted for confounding adiposity. In addition, GH tests are poorly reproducible; individuals who undergo repeated tests have highly variable results (34). In our study, 80% of low GH responses were normal when tests were repeated, and the remainder had normal IGF-I and growth velocity. Similarly, in contrast to what is usually reported in TBI studies, we found no cases of ACTH deficiency: 5–27% for adults (27–30) and 18–34% for children (5, 7, 10). Once again, retesting of subnormal ACTH results showed that these were false positives (*i.e.* apparent ACTH deficiency in normal children).

Given the high-risk group we studied, it is surprising that we observed no cases of hypopituitarism. Young children are thought to be particularly vulnerable to the effects of acceleration-deceleration on the brain and cerebral vasculature (14). Our study population was a clearly defined homogeneous group of young children with structural TBI. It was apparent within our cohort that significant structural injury can be associated with mild GCS impairment. The relationship between TBI severity as defined by GCS and hypopituitarism has been weak and may reflect the indirect nature of GCS as an assessment tool for pituitary damage. In addition, a high-risk subgroup was included, children after inflicted TBI. Inflicted brain injuries are typically repeated and severe and affect very young infants, yet no hypopituitarism was found. Note that these findings may not be applicable to adolescents, whose physical characteristics and types of injury more closely resemble those seen in adults.

Our data on precocious puberty were within the expected prevalence for girls. There was a trend toward a significant increase for boys, although this was also within the expected range. The population prevalence of precocious puberty is not well described, and our reference data were derived from the Danish national registry (26). The authors stressed that their estimates were conservative, particularly because they relied upon referrals to pediatricians. The pathogenic mechanism of precocious puberty is loss of normal childhood hypothalamic inhibition of pituitary gonadotropins and could be anticipated to increase after TBI. However, our study shows that the rate of precocious puberty after TBI is unlikely to exceed that of the normal population. Nonetheless, not all subjects in our study had reached the normal age of pubertal onset, so that our prevalence data might also have been an underestimate. Thus, although precocious puberty appears to be

rare after TBI, prevalence should ideally be assessed by longitudinal follow-up of a large population.

The major challenge for this study was recruitment, mostly due to difficulty in obtaining up-to-date case contact details. This was particularly challenging among children with inflicted injuries and as the interval from TBI increased. Overall, the rate of acceptance among those contacted was high (75%), with probable selection bias toward children with chronic disability, who would be expected to be at greater risk of hypopituitarism. Another potential limitation was the variable timing of assessments. However, because the purpose of this study was to assess the rate of permanent pituitary hormone deficiency, all assessments were performed at least 1 yr after injury (beyond which point the occurrence of new hypopituitarism is rare) (35). It is possible that some of our subjects had already recovered from transient hormone deficiency, but the significance of this would be unclear.

In conclusion, permanent hypopituitarism after TBI appears to be a very rare event. Given that all subjects with initial tests suggestive of ACTH deficiency were normal when reassessed, significant abnormality that would require treatment is likely to be rare, but further evaluation of ACTH status within a larger cohort will help to clarify this issue. In our cohort, precocious puberty was the only pituitary abnormality present. We found no cases of GH deficiency that met comprehensive assessment criteria, even though it is generally reported to be common after TBI. Because both precocious puberty and GH deficiency can be detected on clinical assessment during childhood, a pragmatic approach would be for family physicians to monitor growth and development in children after TBI. Invasive assessments should be reserved for selected cases where there is slow growth or other clinical suspicion of hypopituitarism.

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Address all correspondence and requests for reprints to: Wayne S. Cutfield, Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand. E-mail: w.cutfield@auckland.ac.nz.

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N.L.H. and W.S.C. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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References

- McKinlay A, Grace RC, Horwood LJ, Fergusson DM, Ridder EM, MacFarlane MR 2008 Prevalence of traumatic brain injury among children, adolescents and young adults: prospective evidence from a birth cohort. *Brain Inj* 22:175–181
- Kelly P, Farrant B 2008 Shaken baby syndrome in New Zealand, 2000–2002. *J Paediatr Child Health* 44:99–107
- Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, Agha A 2007 Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. *JAMA* 298:1429–1438
- Einaudi S, Matarazzo P, Peretta P, Grossetti R, Giordano F, Altare F, Bondone C, Andreo M, Ivani G, Genitori L, de Sanctis C 2006 Hypothalamo-hypophysial dysfunction after traumatic brain injury in children and adolescents: a preliminary retrospective and prospective study. *J Pediatr Endocrinol Metab* 19:691–703
- Niederland T, Makovi H, Gál V, Andréka B, Abrahám CS, Kovács J 2007 Abnormalities of pituitary function after traumatic brain injury in children. *J Neurotrauma* 24:119–127
- Poomthavorn P, Maixner W, Zacharin M 2008 Pituitary function in paediatric survivors of severe traumatic brain injury. *Arch Dis Child* 93:133–137
- Khadr SN, Crofton PM, Jones PA, Wardhaugh B, Roach J, Drake AJ, Minns RA, Kelnar CJH 2010 Evaluation of pituitary function after traumatic brain injury in childhood. *Clin Endocrinol (Oxf)* 73:637–643
- Kaulfers AM, Backeljauw PF, Reifschneider K, Blum S, Michaud L, Weiss M, Rose SR 2010 Endocrine dysfunction following traumatic brain injury in children. *J Pediatr* 157:894–899
- Moon RJ, Sutton T, Wilson PM, Kirkham FJ, Davies JH 2010 Pituitary function at long-term follow-up of childhood traumatic brain injury. *J Neurotrauma* 27:1827–1835
- Norwood KW, Deboer MD, Gurka MJ, Kuperminc MN, Rogol AD, Blackman JA, Wamstad JB, Buck ML, Patrick PD 2010 Traumatic brain injury in children and adolescents: surveillance for pituitary dysfunction. *Clin Pediatr (Phila)* 49:1044–1049
- Ghigo E, Masel B, Aimaretti G, León-Carrión J, Casanueva FF, Dominguez-Morales MR, Elovic E, Perrone K, Stalla G, Thompson C, Urban R 2005 Consensus guidelines on screening for hypopituitarism following traumatic brain injury. *Brain Inj* 19:711–724
- Acerini CL, Tasker RC 2007 Traumatic brain injury induced hypothalamic-pituitary dysfunction: a paediatric perspective. *Pituitary* 10:373–380
- Dusick JR, Wang C, Cohan P, Swerdloff R, Kelly DF 15 May 2008 Chapter 1: pathophysiology of hypopituitarism in the setting of brain injury. *Pituitary* 10.1007/s11102-008-0130-6
- Case ME, Graham MA, Handy TC, Jentzen JM, Monteleone JA; National Association of Medical Examiners Ad Hoc Committee on Shaken Baby Syndrome 2001 Position paper on fatal abusive head injuries in infants and young children. *Am J Forensic Med Pathol* 22:112–122
- Teasdale G, Jennett B 1974 Assessment of coma and impaired consciousness. A practical scale. *Lancet* 2:81–84
- Marion DW, Carlier PM 1994 Problems with initial Glasgow Coma Scale assessment caused by prehospital treatment of patients with head injuries: results of a national survey. *J Trauma* 36:89–95
- Gill MR, Reiley DG, Green SM 2004 Interrater reliability of Glasgow Coma Scale scores in the emergency department. *Ann Emerg Med* 43:215–223
- Simpson DA, Cockington RA, Hanich A, Raftos J, Reilly PL 1991 Head injuries in infants and young children: the value of the Paediatric Coma Scale. *Childs Nerv Syst* 7:183–190
- Jenny C, Hymel KP, Ritzen A, Reinert SE, Hay TC 1999 Analysis of Missed Cases of Abusive Head Trauma. *JAMA* 281:621–626
- Bechtel K, Stoessel K, Leventhal JM, Ogle E, Teague B, Laviates S, Banyas B, Allen K, Dziura J, Duncan C 2004 Characteristics that distinguish accidental from abusive injury in hospitalized young children with head trauma. *Pediatrics* 114:165–168
- Association for the Advancement of Automotive Medicine 2001 The abbreviated injury scale, 1990 revision, update 98. Barrington, IL: Association for the Advancement of Automotive Medicine
- Tanner JM, Whitehouse RH 1976 Clinical longitudinal standards for height, weight, height velocity and stages of puberty. *Arch Dis Child* 51:170–179
- Cole TJ, Freeman JV, Preece MA 1995 Body mass index reference curves for the UK, 1990. *Arch Dis Child* 73:25–29
- Barth JH, Sibley PEC 2008 Standardization of the IMMULITE systems growth hormone assay with the recombinant IS 98/574. *Ann Clin Biochem* 45:598–600
- Berneis K, Staub JJ, Gessler A, Meier C, Girard J, Müller B 2002 Combined stimulation of adrenocorticotropin and compound-S by single dose metyrapone test as an outpatient procedure to assess hypothalamic-pituitary-adrenal function. *J Clin Endocrinol Metab* 87:5470–5475
- Teilmann G, Pedersen CB, Jensen TK, Skakkebaek NE, Juul A 2005 Prevalence and incidence of precocious pubertal development in Denmark: an epidemiologic study based on national registries. *Pediatrics* 116:1323–1328
- Agha A, Rogers B, Sherlock M, O'Kelly P, Tormey W, Phillips J, Thompson CJ 2004 Anterior pituitary dysfunction in survivors of traumatic brain injury. *J Clin Endocrinol Metab* 89:4929–4936
- Aimaretti G, Ambrosio MR, Di Somma C, Fusco A, Cannavo S, Gasperi M, Scaroni C, De Marinis L, Benavente S, degli Uberti EC, Lombardi G, Mantero F, Martino E, Giordano G, Ghigo E 2004 Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. *Clin Endocrinol (Oxf)* 61:320–326
- Klose M, Juul A, Poulsen L, Kosteljanetz M, Brennum J, Feldt-Rasmussen U 2007 Prevalence and predictive factors of post-traumatic hypopituitarism. *Clin Endocrinol (Oxf)* 67:193–201
- Schneider HJ, Schneider M, Kreitschmann-Andermahr I, Tuschy U, Wallaschofski H, Fleck S, Faust M, Renner CI, Kopczak A, Saller B, Buchfelder M, Jordan M, Stalla GK 2011 Structured assessment of hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage in 1242 patients; the German Interdisciplinary Database. *J Neurotrauma* 28:1693–1698
- Growth Hormone Research Society 2000 Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 85:3990–3993
- Ghigo E, Bellone J, Aimaretti G, Bellone S, Loche S, Cappa M, Bartolotta E, Dammacco F, Camanni F 1996 Reliability of provocative tests to assess growth hormone secretory status: study in 472 normally growing children. *J Clin Endocrinol Metab* 81:3323–3327
- Loche S, Guzzetti C, Pilia S, Ibba A, Civolani P, Porcu M, Minerba L, Casini MR 2011 Effect of body mass index on the growth hormone response to clonidine stimulation testing in children with short stature. *Clin Endocrinol (Oxf)* 74:726–731
- Tassoni P, Cacciari E, Cau M, Colli C, Tosi M, Zucchini S, Cicognani A, Pirazzoli P, Salardi S, Balsamo A 1990 Variability of growth hormone response to pharmacological and sleep tests performed twice in short children. *J Clin Endocrinol Metab* 71:230–234
- Tanriverdi F, Ulutabanca H, Unluhizarci K, Selcuklu A, Casanueva FF, Kelestimur F 2008 Three years prospective investigation of anterior pituitary function after traumatic brain injury: a pilot study. *Clin Endocrinol (Oxf)* 68:573–579