Intensive Care Med (2008) 34:468–475
DOI 10.1007/s00134-007-0902-x

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Magnetic resonance imaging changes in the pituitary gland following acute traumatic brain injury

Received: 4 December 2006
Accepted: 20 September 2007
Published online: 29 November 2007

Descriptor: Neurology/Sedation — Neurotrauma

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Abstract *Objective:* The objective was to study the anatomical changes in the pituitary gland following acute moderate or severe traumatic brain injury (TBI). *Design:* Retrospective, observational, case-control study. *Setting:* Neurosciences Critical Care Unit of a university hospital. *Patients:* Forty-one patients with moderate or severe TBI who underwent magnetic resonance imaging (MRI) during the acute phase (less than seven days) of TBI. MRI scans of 43 normal healthy volunteers were used as controls. *Interventions:* None. *Measurements and main results:* Patient demographics, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Injury Severity Score (ISS), post-resuscitation Glasgow Coma Score (GCS), Glasgow Outcome Score (GOS), mean intracranial pressure (ICP), mean cerebral perfusion pressure (CPP), computed tomography (CT) data, pituitary gland volumes and structural lesions in the pituitary on MRI scans. The pituitary glands were significantly enlarged in the TBI group (the median and interquartile range were as follows: cases 672 mm^3 (range 601–783 mm^3) and controls 552 mm^3 (range 445–620 mm^3); p value < 0.0001). APACHE II, GCS, GOS and ICP were not significantly correlated with the pituitary volume. Twelve of the 41 cases (30%) demonstrated focal changes in the pituitary gland (haemorrhage/haemorrhagic infarction ($n = 5$), swollen gland with bulging superior margin ($n = 5$), heterogeneous signal intensities in the anterior lobe ($n = 2$) and partial transection of the infundibular stalk ($n = 1$). *Conclusions:* Acute TBI is associated with pituitary gland enlargement with specific lesions, which are seen in approximately 30% of patients. MRI of the pituitary may provide useful information about the mechanisms involved in post-traumatic hypopituitarism.

Keywords Traumatic brain injury · Hypopituitarism · Magnetic resonance imaging

Introduction

Traumatic brain injury (TBI) is the most common cause of death and disability in young adults [1]. Each year, in the United States 52,000 deaths can be attributed to TBI, with an additional 80,000 left with permanent and severe neurologic disabilities [2]. A significant proportion of survivors demonstrate cognitive and emotional deficits that prevent them from functioning at their pre-injury level. While these are substantially due to the direct effects of trauma to the

brain, it is important to detect and treat any correctable causes of such deficits.

Anterior pituitary dysfunction is known to occur during the acute phase of TBI [3–6]. Although the first reported case of post-traumatic hypopituitarism (PTHP) was in the early part of the 20th century [7], TBI has largely been ignored as a cause of hypopituitarism. However, there has been a growing body of literature over the last 6 years recognising the contribution of anterior pituitary dysfunction in TBI outcomes [8]. The neurobehavioral changes that occur in TBI are similar to those seen in hormone deficiencies in other settings [9–11] and some of these patients may show an improvement in cognitive function with hormone replacement [12].

Post-traumatic hypopituitarism could be secondary to the influence of drugs, cytokines or injury to the pituitary gland. Anatomical lesions like haemorrhage and necrosis have been well documented in post-mortem studies [13, 14]. While these post-mortem data provide robust evidence of pituitary involvement in fatal head injury, we have extremely limited imaging data on the pituitary gland in patients who survive. In particular, there are no reports of acute imaging studies of the pituitary following TBI, at a time when pituitary dysfunction is well documented. There is a clear need to define the spectrum of structural pituitary abnormalities in the wider population of patients who suffer TBI in order to begin to separate structural abnormalities from cytokine- and drug-induced mechanisms for hypopituitarism following TBI.

We reviewed the MRI scans of acute TBI patients in an attempt to define the structural changes in the pituitary following TBI.

Materials and methods

Study design

This is a retrospective study involving a review of the scans and case notes of TBI patients undergoing imaging studies. The Local Research Ethics Committee approved the study.

The MRI scans of all patients with TBI admitted to our Neurosciences Critical Care Unit (NCCU) between the years 2002 and 2005 were reviewed. Patients who had a T1-weighted 3D spoiled gradient echo sequence (SPGR) in the acute phase of TBI were included in the study. This sequence was selected due to its suitability for volumetric measurements of the pituitary gland. The follow-up scans of these patients, if undertaken, were also reviewed. Patients with pre-existing pituitary pathology were excluded from the study. MRI scans of age- and sex-matched healthy volunteers were used as controls. All patients were managed according to Addenbrooke's Neurosciences Critical Care Unit (NCCU) cerebral perfusion pressure (CPP)/intracranial pressure (ICP) management algorithm [15].

The following data were extracted from the case notes: patient demographics, post-resuscitation Glasgow Coma Score (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, mean ICP for 12 h prior to scanning, ISS, GOS, extracranial injuries and hospital mortality. The admission CT scan was reviewed for skull fractures and midline shifts.

MRI analysis

The MRI scans were undertaken when the patient was considered stable for transfer to the MRI suite. All scans were undertaken at the Wolfson Brain Imaging Centre at Addenbrooke's Hospital, Cambridge, on a Bruker Medspec 3-Tesla actively shielded MRI scanner (Bruker Biospin MRI, Ettlingen, Germany). The images were obtained using a repetition time (TR) of 19.8 ms and an echo time (TE) of 5 ms. Pituitary volumes were measured using Analyze 7.0 software (Mayo Clinic, Rochester, MN, USA), using a technique described by Sassi et al. [16]. The margins of the pituitary gland were outlined in all the coronal slices. The infundibulum was excluded, but the hyperintensity of the posterior pituitary was included. Axial and sagittal views were used to confirm the borders if they were not clear in the coronal planes. Ten scans were selected randomly and pituitary volumes quantified repeatedly by two independent observers (BM, VN) to test the inter- and intra-observer variability of this technique. An experienced neuroradiologist (NA) reviewed all the scans for structural abnormalities.

Statistics

All statistical calculations were undertaken using Statview (SAS, Cary, NC, USA). Normally distributed continuous data were analysed using parametric statistical methods (t tests) and expressed as mean ± standard deviation. Non-parametric methods were applied for continuous data that were not normally distributed and data were expressed as median (interquartile range). Correlations between variables were assessed using Spearman's rank coefficient. A p value less than 0.05 was considered significant.

Results

Patient characteristics

During the study period a total of 306 patients were admitted to the NCCU with traumatic brain injury, of whom 64 patients underwent MRI scanning during the acute phase. The scans of 41 patients (28 males and 13 females; mean

age 35 ± 15 years) were considered suitable for our analysis. The median interval between the injury and the scans was 36 h (range 22–62). The majority of our patients suffered from high impact road traffic accidents (25 out of 41), while 13 had a low-impact injury (assault in 4 patients and a fall in 9). The scans of 43 healthy controls (24 males and 19 females; mean age 37 ± 13 years) were used for comparison. The demographic and clinical data are shown in Table 1.

The changes in the magnetic resonance imaging are summarised in Table 2.

Pituitary volumes

The pituitary glands were significantly enlarged in the TBI group (Fig. 1). The median (interquartile range) of pituitary volumes for cases and controls were as follows: cases 672 mm^3 (601–783) and controls 552 mm^3 (445–620), $p < 0.0001$. We did not find any significant difference ($p < 0.5$) between the volume of the gland in patients without focal pituitary lesions ($n = 29$) and those with focal abnormalities ($n = 12$). However, the difference remained significant between patients with-

Table 1 Demographic and clinical characteristics of 41 patients with moderate or severe traumatic brain injury

No.	Age (years)	Gender	APACHE II	ISS	Extra-cranial injury	Mean ICP	Mean CPP	GCS	GOS	ICU stay (days)	Mortality
1	33	Male	23	34	Major	19	76	4	4	6	Alive
2	53	Male	24	49	Minor	+	+	4	5	16	Alive
3	61	Male	15	48	Major	13	72	12	4	21	Alive
4	18	Male	23	25	Minor	10	67	6	4	23	Alive
5	41	Male	15	26	Minor	NA	NA	3	4	7	Alive
6	64	Male	12	10	Minor	12	91	13	4	20	Alive
7	39	Male	16	10	Minor	20	73	8	4	13	Alive
8	40	Female	20	10	None	18	77	3	4	25	Alive
9	37	Male	15	16	None	19	79	8	4	9	Alive
10	23	Female	23	50	Major	18	61	5	4	19	Alive
11	44	Male	18	38	Major	12	76	4	5	8	Alive
12	21	Female	19	17	Minor	15	69	7	5	15	Alive
13	21	Male	17	25	Minor	21	74	8	5	7	Alive
14	65	Female	23	9	None	23	76	3	3	29	Alive
15	29	Male	19	27	None	17	74	3	5	12	Alive
16	56	Male	16	25	None	16	77	3	1	10	Dead
17	21	Female	14	26	None	15	70	7	3	16	Alive
18	22	Male	13	14	Minor	12	65	9	1	17	Dead
19	38	Female	15	9	Minor	15	76	7	3	23	Alive
20	42	Female	19	21	NA	13	75	5	3	18	Alive
21	20	Male	20	16	None	17	76	7	3	22	Alive
22	31	Male	19	30	Minor	18	66	6	3	28	Alive
23	26	Male	23	25	Minor	NA	NA	5	1	10	Dead
24	48	Male	11	16	Minor	21	87	11	1	6	Dead
25	66	Male	22	17	None	23	65	11	1	5	Dead
26	18	Female	28	29	Minor	NA	NA	7	1	5	Dead
27	19	Male	16	21	Minor	25	72	8	4	12	Alive
28	39	Female	25	41	Major	+	+	3	5	16	Alive
29	19	Female	24	36	Major	14	76	5	3	28	Alive
30	54	Female	27	25	None	30	70	5	3	16	Alive
31	23	Male	15	16	None	NA	NA	4	1	7	Dead
32	17	Male	24	40	Major	NA	NA	4	3	25	Alive
33	32	Male	20	34	Major	16	69	3	3	26	Alive
34	16	Male	17	9	Minor	8	78	8	5	9	Alive
35	22	Male	22	38	NA	11	69	4	3	19	Alive
36	28	Male	23	38	Major	26	71	3	4	28	Alive
37	27	Male	17	25	Major	20	72	6	5	20	Alive
38	49	Male	27	16	None	17	50	6	1	2	Alive
39	47	Female	18	18	Major	15	64	7	3	30	Alive
40	23	Male	14	39	Minor	15	65	3	NA	22	Alive
41	58	Female	26	25	None	NA	NA	6	4	16	Alive

APACHE II, Acute Physiology and Chronic Health Evaluation II score; *ISS*, Injury Severity Score; *GCS*, post-resuscitation Glasgow Coma Scale; *GOS*, Glasgow Outcome Score at 6 months (1 = death, 2 = persistent vegetative state, 3 = severe disability, 4 = moderate disability, 5 = good recovery); *major extra cranial injury*, long bone fracture, thoracic or abdominal injury; *NA*, data not available; *ICP*, mean intracranial pressure 12 h prior to the scan; *CPP*, mean cerebral perfusion pressure 12 h prior to the scan; + No ICP bolt prior to scan; *Mortality*, hospital mortality

Table 2 Magnetic resonance imaging characteristics of anterior pituitary in 41 patients

No.	Interval 1 (hours)	Pituitary volume, acute scan (mm^3)	Fracture skull	Acute MRI	Interval 2 (months)	Pituitary volume, follow-up scan (mm^3)	Follow-up MRI
1	73	521	No	Normal	11	379	LSI in atrophic gland
2	7	702	No	Normal	14	473	Normal
3	NA	653	Vault	HSI in the anterior lobe	25	487	Atrophic gland
4	66	538	Vault	Normal	8	558	Normal
5	NA	672	No	Normal	18	612	Normal
6	109	879	Vault	Normal	9	646	Normal
7	25	817	Basal skull	Normal	17	663	Normal
8	28	784	No	Normal	8	678	Normal
9	60	740	Vault	Normal	14	679	Normal
10	16	641	No	Normal	5	688	Normal
11	84	749	No	Normal	14	729	Normal
12	25	960	No	Normal	8	769	Normal
13	53	725	No	Normal	16	811	Normal
14	28	546	No	Normal	12	616	Normal
15	15	700	No	Normal	7	708	Normal
16	32	763	Basal skull	Normal			
17	48	686	No	HSI anterior lobe			
18	22	905	Pituitary fossa	Partial disruption of infundibular stalk			
19	36	625	Vault	Normal			
20	27	842	Pituitary fossa	Swollen gland[a]			
21	39	645	Vault	Normal			
22	62	625	Vault	Normal			
23	NA	721	No	Normal			
24	63	793	Vault	Normal			
25	20	642	Basal skull	Normal			
26	60	634	Pituitary fossa	Swollen gland[a]; heterogeneous signal intensity			
27	43	584	Vault	Swollen gland[a] and infundibulum			
28	17	650	Vault	HSI posterior to infundibulum			
29	21	782	Vault	Normal			
30	39	560	Basal skull	Normal			
31	19	778	No	Heterogeneous signal in anterior lobe			
32	24	549	No	HSI of anterior lobe; swollen infundibulum			
33	120	488	No	Normal			
34	63	576	Vault	Normal			
35	51	853	No	Swollen gland[a]			
36	57	580	Vault	Normal			
37	67	450	Vault	HSI in anterior lobe			
38	20	789	No	Normal			
39	22	650	No	Normal			
40	165	607	No	Normal			
41	13	1010	Pituitary fossa	Swollen gland[a]			

Interval 1, interval between injury and scan; *Interval 2*, time between the first and the follow-up scan; *HSI*, high signal intensity; *LSI*, low signal intensity; *NA*, more specific data not available
[a] Convex upper border of the gland

out focal lesions ($n = 29$) and the controls ($p < 0.0001$). APACHE II ($p < 0.16$), GCS ($p < 0.13$), mean ICP ($p < 0.15$), GOS ($p < 0.12$) and length of stay in the ICU ($p < 0.09$) were not correlated with pituitary volumes.

Structural changes

Twelve out of 41 cases (30%) showed focal abnormalities in the pituitary gland. The abnormalities were as follows: haemorrhage/haemorrhagic infarction ($n = 5$), swollen

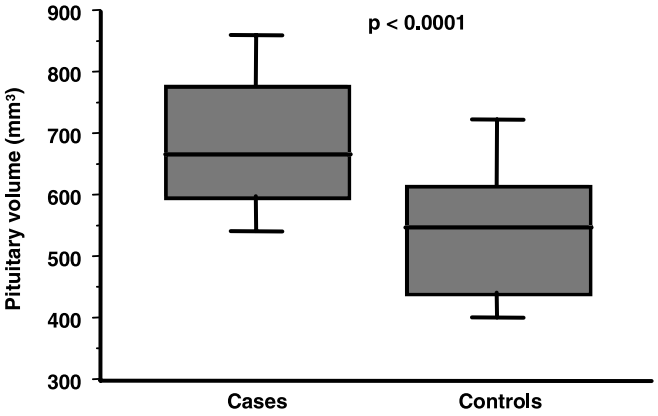

Fig. 1 Box plot showing increased pituitary volume after acute traumatic brain injury. The *central line* of the boxes represents the median, the *upper and lower lines* of the boxes represent the 75th and the 25th percentiles respectively, and the *short horizontal bars* at the ends represent the 90th and the 10th percentiles

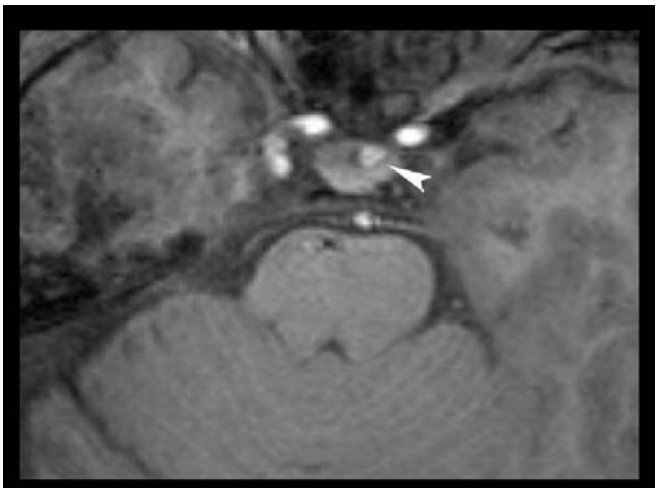

Fig. 2 Axial view (case 3) showing haemorrhage in the anterior lobe of the pituitary gland (*white arrowhead*)

gland with bulging superior margin ($n = 5$), heterogeneous signal in the anterior lobe ($n = 2$; Fig. 2) and partial transection of the infundibular stalk ($n = 1$).

Twenty-two patients sustained skull fractures; in 8 the fracture involved the base of the skull. Four of these 8 patients (case nos. 18, 20, 26 and 41) had fracture lines through the sella turcica. All these patients had pituitary changes that were visible on MRI. Six of the 41 patients showed evidence of a midline shift on the admission CT scan. Only 1 of these 6 patients had structural changes in the gland.

Follow-up scans

Fifteen patients underwent follow-up scans at varying time intervals after the first admission scan (median 12 (range 8–15 months); Fig. 3). The pituitary gland volumes were significantly reduced compared with the acute scans

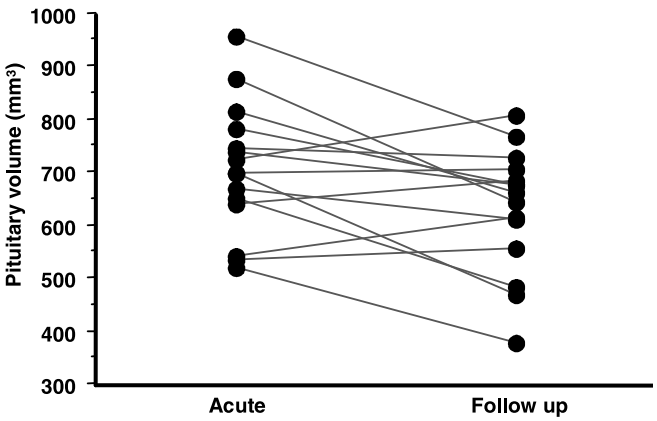

Fig. 3 Changes in pituitary volumes in individual cases between acute and follow-up scans ($n = 15$; $p = 0.03$)

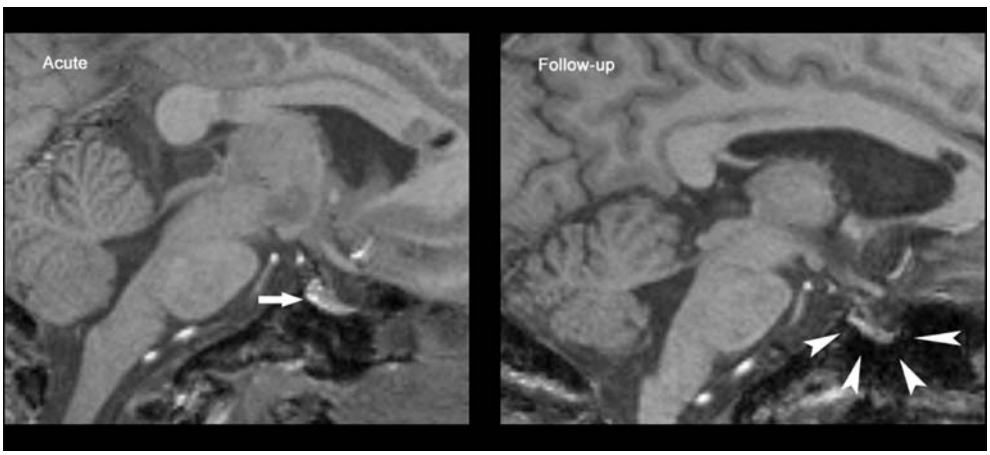

Fig. 4 Acute and follow-up scans (11 months post-injury) of case 1. The follow-up images show an atrophic pituitary gland (*white arrowheads*) compared with the acute scan (*white arrow*)

(acute, median 723 (range 656–809); follow-up, median 678 (range 572–724); $p = 0.03$). There was no significant difference in the gland volume between the follow-up scans and age- and sex-matched controls ($p < 0.25$). Two of the 15 follow-up cases demonstrated pituitary changes on MRI. The first case showed high intensity signal on the acute scan, but a small atrophic anterior lobe in the follow-up scan (Fig. 4), while the second case had a normal acute scan, but an atrophic anterior lobe with hypointense areas at follow-up (likely to be due to a previous infarction).

Discussion

We retrospectively reviewed MRI scans following acute TBI. The data showed an increased pituitary volume that tended to normalize over time. Thirty percent of patients had focal lesions in the pituitary gland. We believe these data provide important clues regarding the anatomical substrates for post-traumatic hypopituitarism.

Neuroendocrine dysfunction has been demonstrated during both the acute and chronic phases of TBI [3, 17]. The severity of these abnormalities may be correlated to the degree of injury, as well as outcome [4]. Several mechanisms have been described to explain hypopituitarism in acute TBI. These include direct or indirect trauma to the gland or its blood supply, leading to haemorrhage and/or infarction, lesions in the hypothalamus, effects of inflammatory mediators and drugs used for sedation and anaesthesia.

Structural changes in the pituitary gland during the acute phase of TBI have been demonstrated in several post-mortem case series. The predominant changes that have been described include oedema, necrosis and haemorrhage. Oedema was the most common finding in a series of 102 cases described by Ceballos [13]. This is consistent with our study, where we found a significant increase in the size of the gland during the acute phase of TBI. The enlarged gland is more likely to be secondary to oedema than hyperplasia since the majority of the scans were obtained within 48 h, a time frame too short for hyperplasia to result in the enlargement of the gland. This is further confirmed by the absence of hyperplasia in autopsies [13]. Although we did not find a correlation between gland size and ICP, Kelly et al. [17] have shown diffuse brain swelling on CT scans in patients with pituitary dysfunction. This may suggest that pituitary gland oedema reflects changes occurring in rest of the brain. The oedema could potentially contribute to pituitary dysfunction. The pituitary gland sits in a bony compartment, the sella turcica, with a rigid fold of dura, the diaphragm sellae forming its roof. As the gland swells, a part of it may herniate through the opening in the diaphragm and compress the portal vessels against the dural fold, resulting in infarction of a part of the anterior lobe [14]. One can also hypothesize that interstitial oedema may interfere with the transport of releasing/inhibiting factors and hormones across the capillary walls that separate the nerve endings from the sinusoids.

Infarction of the anterior pituitary was the second most common finding demonstrated in autopsy studies with histological evidence of necrosis seen in 4–22% of cases [13, 14, 18]. Similar changes have also been reported in several case reports [19, 20]. We noted high signal intensities on T1-weighted images in five cases. This could represent either haemorrhage or a haemorrhagic infarction. Pituitary infarction may appear hyperintense or isointense on T1-weighted imaging, depending on the presence of haemorrhagic transformation [21]. Our series may have missed some cases of infarction for two reasons. First, the majority of scans were obtained within 48 h, which may have been too early to reveal a pituitary infarct on imaging. Ceballos [13], in his series of 102 autopsies, demonstrated ischaemic infarction on histopathology as early as 2 days, but the infarct was more established at between 3 and 8 days. Second, by examining T1-weighted images only, we may have missed patients with non-haemorrhagic infarction.

Although the changes noted above may occur following a direct insult to the pituitary gland, they may also follow injury to the vascular supply of the anterior pituitary lobe [22, 23].

It is debatable whether fractures of the skull are directly responsible for pituitary damage. Daniel et al. [20] found fractures of skull in all 6 of their cases of pituitary necrosis. Ceballos [13] found a similar incidence of necrosis irrespective of the presence or absence of a skull fracture. Kelly et al. [17] did not find an increased incidence of fractures in patients with pituitary dysfunction. It may be that patients with basal skull fractures have been subjected to greater forces, which are associated with fronto-occipital displacements of the brain over the skull base. This can result in a jarring effect on the stalk, resulting in pituitary damage. In our series, 8 patients suffered from basal skull fractures, with the fracture line extending through the sella turcica in 4 of them. All 4 patients demonstrated changes in the pituitary gland morphology. Although high-speed injuries like road traffic accidents are more likely to lead to PTHP compared with low impact injuries, there are no data in the literature suggesting any particular form of injury (high-speed/low-impact or blunt/penetrating) is more commonly associated with PTHP [24].

The prevalence of pituitary dysfunction in patients with previous TBI varies from 28 to 68% [17, 25–29]. MRI data of 15 follow-up cases were examined for evidence of structural changes. The gland volumes in the follow-up scans were significantly smaller compared with the acute scans ($p = 0.03$). This probably suggests an increased gland volume following acute TBI, with subsequent normalisation in the long term. This is confirmed by a significantly smaller size of the gland in controls

compared with the acute TBI patients. Moreover, we found similar gland volumes in follow-up scans of cases compared with age- and sex-matched healthy controls. Two of the 15 follow-up cases demonstrated pituitary changes on MRI. These findings may explain some of the cases of hypopituitarism with a previous history of TBI. One of the follow-up patients who showed abnormalities in the anterior lobe had a normal acute scan. It may be that the scan was obtained before the possible infarction was established or that the scanning protocol was not sensitive enough to detect changes in the acute scan. Lorenzo et al. [30] postulate that the injury sustained in the acute phase may trigger an inflammatory response that may result in subsequent neuronal death. This may explain some cases of late onset hypopituitarism.

This study has several limitations that need to be noted. First, we had no data on the functional status of the pituitary gland. All lesions may not have been clinically significant since a large area of the anterior lobe may need to be destroyed before pituitary dysfunction can be demonstrated clinically [31]. Second, as these images were obtained as a part of other studies, the imaging protocols were not sensitive enough to detect the full range of pituitary lesions. We feel that spin-echo sequences and T2-weighted imaging may have detected more lesions and also provided more information about the nature of the lesions. Third, in order to study the rate and extent of repair of pituitary damage it is important to study the progress of these changes with follow-up scans. In our study, less than half the patients had undergone a follow-up scan. Only one of the patients who had a follow-up scan demonstrated a lesion on the acute scan. This made it difficult to study the natural progression of the lesions. Prospective studies that correlate the functional data with more detailed imaging will provide us with a better understanding of this common condition.

Conclusion

Although PTHP is increasingly being recognised as a factor in determining outcomes following TBI, its mechanism remains uncertain. We believe magnetic resonance imaging data may provide answers to some of the mechanisms involved in its pathogenesis.

Acknowledgements. This research was supported within the framework of a grant from the Medical Research Council. V. Newcombe is supported by the Gates Cambridge Trust and an Overseas Research Studentship. J. Nortje was supported by a British Journal of Anaesthesia/Royal College of Anaesthetics Research Fellowship. P. Hutchinson is supported by an Academy of Medical Sciences Health Foundation Senior Surgical Scientist Fellowship.

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