

## Correspondence with endocrinologists

Dear Dr Baldeweg

It was kind of you to give me your time on Wednesday. It's such a great relief and help to be able to discuss my son's story with someone who has expert knowledge.

As you know, I've been writing newspaper articles. I realise after what you said that I need to be careful not to spread disinformation, and I would very much welcome your advice. I know your time is valuable and how busy you must be. I can only ask you to read this letter out of kindness.

Here are my thoughts.

### Can PTHP occur after a lapse of time?

I accept your point that Christopher's pituitary must have been functioning normally during puberty, at least as regards gonadotrophins. However, I have found a paper claiming that "Diminished pituitary hormone secretion, caused by damage to the pituitary and/or hypothalamus, may occur *at any time* after traumatic brain injury" [1]. I've also found a paper about a 14-year-old girl admitted with growth failure, found to have deficiency including TSH, gonadotrophins, and ACTH "which developed years after traumatic brain injury". [2] Thirdly, I found in a table of 15 survivors in a study by Benvenga [3] that three males who had head injuries aged 11, 10 and 10, were not diagnosed until ages 52, 45 and 40. (They were all deficient in FSH, LH and TSH and the first two were also deficient in ACTH.) It seems strange that their diagnosis would take 30-40 years if they had failed to go through puberty, so their pituitary trouble must have developed after that. Lisa Nachtigall writes "Longitudinal follow-up is necessary, as. . . some [patients] develop hypopituitarism as a late manifestation many years after the initial event" [4].

Can I rely on this? Is the research respectable? Can I legitimately write in articles "It is possible that our son suffered delayed pituitary dysfunction after his brain injury"?

### Can PTHP cause depression?

You explained that lack of growth hormone can cause "depression-like symptoms", but said that as Christopher grew to normal height it would not have been that. However am I right in thinking that if his pituitary dysfunction had happened after a time-lag, a GH deficiency could have occurred after he had reached full height?

It is established that head injury survivors are four times more likely than other people to commit suicide. [5]. Tate and Simpson's paper shows a third of their sample of 178 suffered 'clinically significant levels of hopelessness' and 17% attempted suicide in a mean of five years after TBI [7]. It does seem likely that Christopher's depression arose from his head injury.

The question is whether it is the endocrinological sequelae of TBI that cause depression, or some other factor. The Pituitary Foundation did a Needs Analysis Report on 28 patients with hypopituitarism in 2006, and found that 53% had clinical levels of anxiety and 35% had clinical levels of depression as measured by HADS. This refers to patients who are receiving treatment, so the figure would be even higher for those who are not. (The hypopituitarism of these patients was caused mainly by pituitary tumour, so their depression is clearly linked with hypopituitarism, not TBI.) An additional piece of circumstantial evidence is that depression can occur even after *mild* head injury, which perplexes those who see the depression as having a neurological source, but which would be explicable in endocrinological terms because hypopituitarism is also well documented to occur after mild head injury.

Several papers I've read contain statements like these: "Hypopituitarism impairs adaptation to stressful events and represents a negative risk factor for the prognosis of the traumatized patient." [3] "Fatigue, cognitive dysfunction and *depression* are known to limit rehabilitative progress and quality of life . . . such symptoms could potentially stem from or be compounded by a treatable, unrecognized pituitary hormone deficiency." [4]. "It is . . . reasonable to infer that PTHP may have an important contribution to the high physical and *neuropsychiatric* morbidity seen in patients with head injury." [6]

In view of all this, is it reasonable of me to write that head injury survivors who are depressed should press for a referral to an endocrinologist?

If you could give me your opinion on these two questions I would give you my heartfelt thanks! Can I also say that if you felt it was appropriate, I would be pleased to help raise funds for your research, as it is so important to me to raise awareness.

Yours sincerely

Joanna Lane

PS I read your article about the dog that needed its cup of tea during your consultation. I thought it was very charming!

[1] Hypopituitarism after traumatic brain injury, 2005, Bondanelli et al, European Journal of Endocrinology

[2] Delay in diagnosis of Hypopituitarism after Traumatic Brain Injury, Aug 2005, Neuro Endocrinology Lett

[3] Hypopituitarism Secondary to Head Trauma, 1985, Benvenga et al, Journal of Clinical Endocrinology and Metabolism.

[4] Brain Injury and Pituitary Dysfunction, 2005, Lisa B Nachtigall, Massachusetts General Hospital Neuroendocrine Clinical Center Bulletin

[5] Suicide after traumatic brain injury: A population study. Teasdale, Engbert, 2001 Journal of Neurology, Neurosurgery and Psychiatry

[6] Hypopituitarism following traumatic brain injury, 2007, Agha, Phillips, Thompson, British Journal of Neurosurgery.

[7] Suicidality after traumatic brain injury, Simpson, Tate, 2002, Psychological Medicine



**london medical**

49 Marylebone High Street  
London W1U 5HJ  
Tel: +44 (0)20 7467 5470  
Fax: +44 (0)20 7467 5471  
E-mail: [info@londonmedical.co.uk](mailto:info@londonmedical.co.uk)  
Web: [www.londonmedical.co.uk](http://www.londonmedical.co.uk)

18<sup>th</sup> March 2009

Ms Joanna Lane  
28 Southwood Avenue  
Coulsdon  
CR5 2DT

Dear Ms Lane

Many thanks for your letter dated 17<sup>th</sup> March 2009. I have read this with interest. You have clearly have undertaken a large amount of research trying to get answers not only for your son but for anyone who might be in a similar position following head injury.

Your first paragraph says PTHP occurs after a lapse of time. I think the research is somewhat scanty on this but I agree that there are case reports on this, I think, the sentence you would like to write saying that it is possible that your son suffered late pituitary dysfunction after his brain injury is legitimate and that wording would fit into what we find in the literature and note from our experience.

Regarding your second paragraph on PTHP and depression, I think it is reasonable to write that in head injury survivors who are depressed endocrinological followup should be considered.

I hope this is helpful both for you in trying to come to terms with what has happened to your son Christopher as well as in the long run to raise awareness for this important topic. At the pituitary foundation next week we are planning to discuss a possible collaboration with Headway.

Many thanks also for offering to help fund raising for my research; it is much appreciated.

With kind regards

Yours sincerely

**Dr Stephanie E. Baldeweg MD FRCP**  
**Consultant Physician in Diabetes and Endocrinology**

# The Leeds Teaching Hospitals

Dr Robert D Murray BSc FRCP  
Dr Steve Orme MD, FRCP

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Joanna Lane  
28 Southwood Avenue  
Coulston  
CR5 2DT

The Department of Endocrinology  
The General Infirmary at Leeds

Great George Street  
Leeds  
West Yorkshire  
LS1 3EX

Tel: 0113 392 3232  
Fax: 0113 392 2431

[www.leedsteachinghospitals.com](http://www.leedsteachinghospitals.com)

Dear Mrs Lane

Thank you for your letter of 7th March 2009, which has been passed on to me as Dr Belchetz retired from the NHS over two years ago. After a little modification I have essentially taken over his NHS practice. My condolences go out to you for the loss of your son.

The data linking traumatic brain injury and hypopituitarism has been around for a long time and has only resurged with widespread popularity by newer studies showing evidence of hypopituitarism in around 10% of individuals. This again has been because of the ability to replace growth hormone in adults, and which was not undertaken routinely until the mid nineteen-nineties. Growth hormone deficiency is the most common permanent hormone deficit to occur following traumatic brain injury (TBI). Although I quote a figure on 10% based on published studies many of these have used biased populations and inadequate tests of pituitary hormone reserve, such that the real incidence is probably a lot lower. One study performed in Oxford has failed to find any evidence of hypopituitarism in survivors of TBI, and I do wonder if this is nearer the truth, but remain open to the true incidence. The data you enclosed from Chris Thompson and Amar Agha, who are good friends of mine, was based on a slightly biased group as many of the individuals in their series were referred because of problems that could represent hypopituitarism (i.e. impaired well-being, sexual dysfunction). Those who remained well were not referred for assessment and therefore not accounted for. Their studies do, however, remain the benchmark for others to follow.

This being said, even more importantly the incidence quoted is for TBI occurring during adulthood. Data concerning children who experience TBI imply the incidence is much less than in adults. Given that growth hormone is the commonest deficit to occur after TBI we do not see children that fail to grow after the vast majority of TBI events. This suggests TBI-induced hypopituitarism is rare if the injury is sustained in childhood as per your son.

I agree that the message regarding the possibility of hypopituitarism post TBI has not been as well disseminated as it could be, but suspect that is in part because of the high prevalence quoted of 'roughly one in four', which we truly do not see. I work on the neurosurgical wards along with my Neurosurgeon colleagues and truly believe this incidence is exaggerated due to study biases. Until we are more realistic about the true incidence of hypopituitarism in TBI cases I do not think this finding will be believed or acted upon.

Regarding the issue of gender identity and TBI, I am unaware of any recognized association, and thinking of my patients I am unaware of any of those with gender dysphoria who have had significant TBI in the past. I admit I have not specifically asked them however. I do not know, however, of any individual with both hypopituitarism and gender dysphoria. All patients with gender dysphoria would have their reproductive hormones assessed from which hypopituitarism would be easily detected, so I suspect there is not a link.


I do have an interest in this area, and we hope to set up a study to examine the incidence of hypopituitarism in TBI survivors which go through our Unit. A database has recently been established to record all instances of TBI that we see. Furthermore we hope to examine the beneficial effects of hormone replacement in those found to be deficient in growth hormone. We have some funding to do this in association with the Manchester Neurosurgical Unit, but unfortunately it all comes down to time. If we can achieve further funding it would be hoped to get a Research Fellow in to place to take this on and speed up this process. Once we have the data, and assuming we do find a significant rate of hypopituitarism (>5%), I would hope to set up a pathway in Leeds to make sure we screen for TBI-induced hypopituitarism in the future.

I was interested to see you live in CR5, which I don't know well, but some of my family live in CR8. On this basis I was wondering about the link with Leeds? Or if it was specifically Dr Belchetz you were trying to chase?

I hope the above has been of help,

Best wishes,

Yours sincerely



**Robert D Murray**  
Consultant Endocrinologist & Honorary Senior Lecturer

28 Southwood Avenue  
Coulson  
CR5 2DT

Dr Robert D Murray BSc FRCP  
The Department of Endocrinology  
The General Infirmary at Leeds  
Great George Street  
Leeds  
LS1 3EX

20 April 2009

Dear Dr Murray

Thank you so much for giving your time to answering my letter. You can imagine how helpful it is to me to be able to discuss PTHP with someone who has expert knowledge, especially as I have been communicating with the media (eg Guardian, Woman's Hour), and I know there's a risk I may spread disinformation. I recognise the tendency for people to react to tragedy by reading the internet, in my case with great intensity, but with no underpinning of specialist knowledge, and a limited 'feel' for how much to rely on each source.

Having said this, I'd like to set before you what I have concluded from my reading, with my sources, in the hope that you may find time to 'shoot me down' – or at least, reassure me about which studies I can rely on and where I should be cautious.

#### **What percentage of head injury survivors have pituitary damage?**

I don't remember which Thompson/Agha paper I sent you. Was it the 2006 paper (High Risk of Hypogonadism etc)? Perhaps a better one would have been the 2008 systematic review by Behan, Phillips, Thomson and Agha [1]. This is an overview of 12 sets of data collected in different projects (measuring anterior HP in TBI survivors) and covers 961 patients. On average 25% show damage. I take your point that some of the series may be biased, but equally, one has to accept that specifically testing for pituitary function must have brought to light cases that could not be diagnosed with the naked eye. Many studies stress how symptoms of HP can be masked by neurological sequelae. I would like to know where you get your 10% figure from, and would also be interested to read the Oxford study you mention.

#### **Can children be affected?**

I confess we have no proof that our son had hypopituitarism. Although we discovered about PTHP before his cremation, the pathologist said there were no tests we could do. All we know is that his ex-girlfriend confirmed that he never managed full sex in the four years they were together, and of course, he did have a serious brain injury aged seven. The research that made us believe PTHP might be the cause was a paper by Acerini, Tasker et al [2]. Since then I've read Poomthavorn's study (2007) of 54 paediatric survivors [3] where 9 out of the 54 had pituitary dysfunction (12.5%), and Einaudi and Bondone's paper (2007)[4] which stresses the risk for children and adolescents and calls for 'careful follow-up of growth and pubertal development'. Also Baldelli, Bellone et al (2006) [5] say that "Unlike other problems in pediatrics, studies suggest that the younger a child is when severe brain injury occurs, the worse the prognosis is in the long run," which challenges your own view.

The real crux of what you say is the common observation that children in general do not fail to grow after the brain injury, and therefore must have escaped pituitary damage. But this presupposes that the pituitary dysfunction, if it is to happen at all, occurs immediately. There is some evidence to show that this is not so. For example, in a table of 15 survivors in a study by Benvenga, [6] three males who had head injuries aged 11, 10 and 10, were not diagnosed until ages 52, 45 and 40. (They were all deficient in FSH, LH and TSH and the first two were also deficient in ACTH.) It seems unlikely that their diagnosis would take 30-40 years if they had failed to go through puberty, so their pituitary trouble must have developed after that. Lisa Nachtigall writes [7] "Longitudinal follow-up is necessary, as . . . some [patients] develop hypopituitarism as a late manifestation many years after the initial event." Bondanelli [8] says "Diminished pituitary hormone secretion, caused by damage to the

pituitary and/or hypothalamus, may occur *at any time* after traumatic brain injury.” There are also interesting individual case studies which are examples of this [9], [10].

To turn to the rest of your letter, I am delighted that you are hoping to set up a study examining the incidence of hypopituitarism in TBI survivors who go through your unit. I have learned that Dr Tara Kearney at the Salford Royal is also doing a study on this topic, and Dr Deshpande at the Wolfson Rehabilitation Centre in Wimbledon is setting up a pathway I believe, so it is all happening!

I hope that even if you do find the risk is less than 5% you may still feel you can set up a pathway. After all, all babies are screened for PKU even though the risk is one in 10,000 -15,000 i.e. less than 0.0001%!

I am interested that your family live in Purley. My mother-in-law lives in Downlands Road where my husband grew up. My Leeds link is that our son lived in Skipton, and my sister and her husband live in Guiseley (before he retired he lectured in Biochemistry at Leeds University).

Once again, my heartfelt thanks for replying to my letter and laying yourself open to this screed,

With best regards

Joanna Lane

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5. Traumatic Brain Injury-Induced Hypopituitarism in Adolescence, R Baldelli, S Bellone, G Corneli, S Savastio, A Petri and G Bona *Official Journal of the Pituitary Society*, 2006
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