Increasing severity of traumatic brain injury in early childhood is associated with a progressive reduction in long-term serum thyroid-stimulating hormone concentrations

Structural traumatic brain injury (TBI) can result in late-occurring health sequelae, consisting mainly of neuroendocrine dysfunctions.[1,2] Studies have suggested that hypopituitarism is relatively common following TBI in childhood, but recent evidence suggests that the incidence appears to be frequently overestimated.[3] We recently showed that permanent hypopituitarism is rare after both inflicted and accidental structural TBI in early childhood.[3]

However, subtle disturbances in pituitary function have been reported after TBI, including abnormalities in thyroid function.[2] Niederland and colleagues found that concentrations of peripheral thyroid hormones were lower in children with TBI history than in control subjects, even though their levels were in age-related normal ranges.[4] A recent small pilot study reported a subtle reduction in overnight thyroid-stimulating hormone (TSH) surge in children following moderate-to-severe inflicted TBI.[1] Thus, it is unclear whether injury severity can be responsible for more subtle long-term effects on thyroid function in the absence of hypopituitarism. Therefore, we assessed whether severity of TBI was associated with changes in circulating thyroid hormone concentrations in childhood in a cross-sectional study.

Ethics approval was provided by the Northern X Regional Ethics Committee. This study covers a previously reported cohort of children who suffered TBI in Auckland (New Zealand).[3] 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. Structural TBI was graded according to the Abbreviated Injury Scale for the head region (AIS-HR).[5] AIS-HR is an anatomical scoring system, where injuries are ranked on a 'threat to life' scale of 1–6 (1 – mild, 2 – moderate, 3 – serious, 4 – severe, 5 – critical and 6 – not survivable).[5] All participants had structural TBI with AIS-HR ≥2.

Participants underwent a single clinical assessment at the Maurice and Agnes Paykel clinical research unit at the Liggins Institute (University of Auckland). All assessments were carried out between 8:00 and 10:00 am, after a 15-min period of rest.[6] Assays were performed as previously described.[6]

One hundred and ninety-eight (112 males) survivors of structural TBI sustained in early childhood [age at injury 1·7 years (SD = 1·5)] were assessed 6·5 years (SD = 3·2) after injury. No participants had significant abnormalities in thyroid function. Three participants had slightly elevated TSH concentrations that were 0·8–1·5 mIU/l above the normal range (0·50–4·70 mIU/l), but all displayed normal fT3 (1·5–9·2 pmol/l), fT4 (10–26 pmol/l) and prolactin (40–600 mIU/l) concentrations.

Greater AIS-HR scores (i.e. increasing TBI severity) were correlated with decreasing TSH concentrations ($\rho = -0{\cdot}20$; $P = 0{\cdot}004$), but not with free triiodothyronine (fT3; $P = 0{\cdot}10$) or free thyroxine (fT4; $P = 0{\cdot}49$) concentrations. Multivariate analyses (adjusting for important confounders) showed that increasing TBI severity was associated with a progressive reduction in serum TSH concentrations ($P = 0{\cdot}004$; Fig. 1). Thus, children with an AIS-HR score of 2 had a mean TSH concentration of 2·09 (95% CI 1·78–2·45) mIU/l compared to 1·44 (95% CI 1·20–1·74) mIU/l for those with an AIS-HR of 5 ($P = 0{\cdot}002$), that is TSH concentrations were 31% lower in the most severe TBI cases.

Overall, increasing TBI severity was not associated with changes in fT3 ($P = 0{\cdot}17$) or fT4 ($P = 0{\cdot}77$) concentrations. However, the most severe TBI cases (AIS-HR = 5) had lower fT3 concentrations than the rest of the cohort: 6·29 (95% CI 5·95–6·64) *vs* 6·64 (95% CI 6·47–6·82) pmol/l ($P = 0{\cdot}046$).

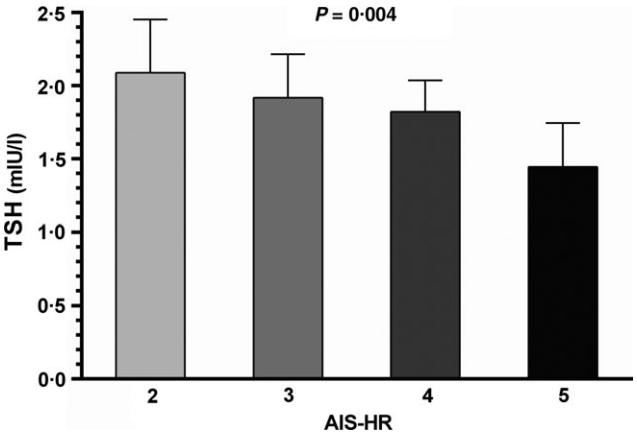

Fig. 1 The association between severity of structural traumatic brain injury (TBI) and thyroid-stimulating hormone (TSH) levels in 198 children. Data are means and 95% confidence intervals adjusted for confounding factors in the multivariate models: sex, pubertal status, ethnicity, age at assessment, time lag between injury and assessment, BMI SDS and TBI class (accidental *vs* inflicted). Higher Abbreviated Injury Scale for the head region (AIS-HR) scores represent more severe injury. *P*-value shown is for a continuous association.

© 2015 John Wiley & Sons Ltd

There were no observed associations between injury severity and cortisol or prolactin levels.

This study shows that increasing TBI severity is associated with a progressive reduction in serum TSH concentrations in children in the long term, but which remained within the normal range. Although no clinically significant abnormalities in thyroid function were observed in this cohort after structural TBI in early childhood,[3] these findings suggest subclinical effects on thyroid function that are related to the severity of TBI. Overt endocrinological abnormalities following TBI in children are uncommon,[3] but our study suggests that with increasing severity there is a greater but apparently subtle impact on the neuroendocrine system that has not been previously described. Note that a single sample was collected from each participant for TSH measurement, which may not incorporate subtle short-term TSH pulsatility.

Short-term impact of TBI on thyroid function has been previously shown. Data on 45 patients (15–70 years) showed that, within 24 h of severe TBI, serum TSH concentrations progressively decreased with increasing injury severity as per Marshall computerized tomography scores.[7] A small adult study ($n = 18$) also showed opposite TSH responses in mild *vs* severe TBI.[8] Early disturbances in thyroid function following TBI have also been reported in children. In a paediatric cohort involving survivors of moderate or severe TBI, most children showed fT4 levels at the low end of the normal range early after injury, and both low TSH and fT4 levels have been found in one participant.[2] Interestingly, in the same study, a TSH elevation was observed in two patients (one and 2–3 months post-TBI).[2] This increase early after injury could result from low TSH biological activity due to altered glycosylation of alpha and beta TSH subunits.[9]

Regarding long-term outcomes, the published data seem to be entirely related to more severe effects on thyroid function, with incidence of TSH deficiency one year after TBI reported as 5–12% in paediatric TBI studies.[4,9] Kaulfers and colleagues found that 2 of 21 (9%) survivors of moderate/severe TBI were diagnosed to have central hypothyroidism 1 year post-TBI.[2] Similarly, a decrease in concentrations of fT4 and fT3 has been detected in a cohort of 26 children with history of hospitalization due to mild to severe TBI, although both fT4 and fT3 were within the normal range.[4] Notably, in both previous studies, the degree of pituitary dysfunction was found to be independent from the severity of TBI. Conversely, in a cohort of 14 children with moderate-to-severe inflicted TBI, 12 children (86%) showed at least one endocrine or growth alteration, with abnormal thyroid function in 33% of them.[1] The specific mechanisms leading to long-term changes in thyroid function following TBI are unclear. Autopsy results suggest that vascular injury is common.[10] In our study, the lack of association between injury severity and either cortisol or prolactin levels argues for direct pituitary injury rather than diffuse CNS or hypothalamic damage.

These previous data suggest that subtle changes in thyroid function in children with moderate-to-severe inflicted TBI may be more common than expected. Similar evidence is provided by the present study, which provides the first report of an association between TBI severity and subtle long-term effects on thyroid function. This raises the possibility that subtle changes in TSH may commonly occur following TBI, without overt abnormalities in thyroid function. The clinical significance of our findings is unclear and should be explored in future prospective studies. This subtle TSH reduction could possibly reflect minor hypothalamic-pituitary damage, which may include vascular insults to the small perforating vessels that supply the anterior pituitary gland.

Funding

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.

Disclosure statement

The authors have no financial or nonfinancial conflicts of interest to disclose that may be relevant to this work. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of this manuscript.

Author contributions

N.L.H., W.S.C., P.L.H. and J.G.B.D. conceived and designed the study. N.L.H. collected the data. J.G.B.D. carried out the statistical analyses. J.G.B.D., V.C. and N.L.H. wrote the manuscript with input from W.S.C. and P.L.H.

Natasha L. Heather, José G.B. Derraik, Valentina Chiavaroli, Paul L. Hofman and Wayne S. Cutfield
Liggins Institute, University of Auckland, Auckland, New Zealand
E-mail: w.cutfield@auckland.ac.nz

N.L.H. and J.G.B.D. contributed equally to this work.

doi: 10.1111/cen.12961

References

1 Auble, B.A., Bollepalli, S., Makoroff, K. *et al.* (2014) Hypopituitarism in pediatric survivors of inflicted traumatic brain injury. *Journal of Neurotrauma*, **31**, 321–326.
2 Kaulfers, A.M., Backeljauw, P.F., Reifschneider, K. *et al.* (2010) Endocrine dysfunction following traumatic brain injury in children. *Journal of Pediatrics*, **157**, 894–899.
3 Heather, N.L., Jefferies, C., Hofman, P.L. *et al.* (2012) Permanent hypopituitarism is rare after structural traumatic brain injury in early childhood. *Journal of Clinical Endocrinology and Metabolism*, **97**, 599–604.
4 Niederland, T., Makovi, H., Gal, V. *et al.* (2007) Abnormalities of pituitary function after traumatic brain injury in children. *Journal of Neurotrauma*, **24**, 119–127.
5 Association for the Advancement of Automotive Medicine (2001) The Abbreviated Injury Scale, 1990 Revision, Update 98.

© 2015 John Wiley & Sons Ltd

Association for the Advancement of Automotive Medicine, Barrington, IL.
6 Heather, N.L., Derraik, J.G.B., Brennan, C. *et al.* (2012) Cortisol response to synacthen stimulation is attenuated following abusive head trauma. *Clinical Endocrinology*, **77**, 357–362.
7 Olivecrona, Z., Dahlqvist, P. & Koskinen, L.O. (2013) Acute neuro-endocrine profile and prediction of outcome after severe brain injury. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, **21**, 33.
8 Cernak, I., Savic, V.J., Lazarov, A. *et al.* (1999) Neuroendocrine responses following graded traumatic brain injury in male adults. *Brain Injury*, **13**, 1005–1015.
9 Rose, S.R. & Auble, B.A. (2012) Endocrine changes after pediatric traumatic brain injury. *Pituitary*, **15**, 267–275.
10 Schneider, H.J., Kreitschmann-Andermahr, I., Ghigo, E. *et al.* (2007) Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. *JAMA*, **298**, 1429–1438.

© 2015 John Wiley & Sons Ltd