Analysis of Serum Cortisol to predict Recovery in Paediatric Sport-related Concussion

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ABSTRACT

Objectives: Acute neuroendocrine response has received little attention in paediatric sport-related concussion (SRC). This study aimed to determine whether there may be abnormal alterations in acute cortisol following paediatric SRC and to compare cortisol to outcome measures of symptom burden and length to return to sport.

Methods: In a prospective observational study, ice hockey players ages 11-12 were recruited prior to the hockey season. If players sustained a SRC they were assessed by a sports medicine physician and completed a child Sport Concussion Assessment Tool-3 (childSCAT3). Serum cortisol samples were collected and compared to length of time to return to sport, and symptom burden.

Results: Of 636 ice hockey players enrolled, 41 sustained a SRC. In total, 22 serum cortisol samples were collected, with 14 (63.6%) meeting inclusion criteria. Four players presented with abnormally low cortisol. Players with abnormally low cortisol experienced more symptoms (17.8±1.9 vs. 7.5±6.0) and more severe symptoms on the symptom portion of the ChildSCAT3 (28.5±5.8 vs. 10.2. ±8.8) and took longer return to sport (23±13.6 vs. 14.0.7±7.9.).

Conclusions: Paediatric ice hockey players following SRC with abnormally low cortisol may be more susceptible to experiencing increase symptom burden and take longer to return to sport than players with population-based normal cortisol.

Introduction

In the United States 1.1-1.9 million sport-related and recreational concussions (SRC) are estimated to occur annually in pediatric patients aged less than 18 years, with a doubling of the number of children aged 8-13 presenting to U.S. emergency rooms with SRC in 2007 as compared with 1997.[1,2] Current diagnosis of SRC is based on clinical assessment, which often includes using tools such as the Sport Concussion Assessment Tool-3 (SCAT3),[3] cognitive computerized testing, balance assessment, and neurological examination.[3] These clinical and functional measurements are often subject to interpretation. There is no current fluid biomarker available that quantitatively diagnoses SRC or predicts recovery following concussion. Previous studies have examined the neurometabolic response to SRC. These studies have examined alterations in tau protein,[4,5] s100B protein,[5–7] neuron specific enolase (NSE),[5,6] AMPAR peptide,[8] glial fibrillary acidic protein (GFAP),[9] prolactin levels,[10] plasma soluble prion protein (PrPC),[9] metabolites,[11] saliva cortisol[12] and metabolic markers of depression in an attempt to develop more accurate diagnostic and prognostic methods for concussion.[11] Interestingly, Hutchison et al. looked at changes in acute saliva cortisol levels post SRC. They did not correlate cortisol levels to prognosis, but did find that higher levels of saliva cortisol were related to a higher degree of perceived stress.[12] Though promising, no single metabolic biomarker has become an accepted method of prognosticating outcomes in SRC, particularly in children. However, a potential method of evaluating outcomes in SRC may be to examine acute anterior pituitary endocrine changes, specifically serum cortisol.

Endocrine dysfunction following traumatic brain injury (TBI) in the paediatric population is a relatively common source of morbidity, with prevalence cited between 16-61%.[13–15] To date, there has only been one published paper on neuroendocrine dysfunction in pediatric SRC. This

case report discussed anterior pituitary dysfunction in a 14 year old soccer player following SRC.[16] , In adults with mild TBI, a recent meta-analysis reported the prevalence of anterior hypopituitary dysfunction to be 16.8% .[17] , When looking specifically at adult with SRC, only two case report discussing post-traumatic diabetes insipidus and growth deficiency (GHD) and three studies on GHD in boxers suggest a link between pituitary dysfunction and SRC.[18–21]

The most common acute endocrine abnormality following head injury is a significant drop in serum cortisol. [22] Up to 50% of TBI patients (mild-severe) have a significant drop in serum cortisol in the acute phase following injury,[23] thought to be initiated by direct trauma to the hypothalamic-pituitary-adrenal (HPA) axis. The acute drop in serum cortisol within 1-7 days following TBI, has been linked to poorer outcomes and increased mortality.[23–26] To date, no studies have examined the acute response of cortisol following paediatric SRC.

This study will examine the response of serum cortisol following pediatric SRC and will explore whether an abnormal drop in cortisol is associated with a greater number of and more severe symptoms, as well as longer time to return to sport.

Methods

Subjects

We enrolled 636 hockey players aged 11-12 years in the 2013-2014 hockey season as part of a larger study called “Safe to Play”. Safe to Play, is a longitudinal cohort study including multiple clinical, psychosocial, and functional measurements aimed at understanding, identifying, treating, and preventing paediatric SRC. Baseline biographical information was collected.

Inclusion criteria included 11 and 12-year-old ice hockey players enrolled in the Pee Wee Hockey league of Hockey Calgary, Calgary, Alberta, Canada prior to the 2013-2014 hockey season. Exclusion criteria included players with a past medical history of neurological disorders such as stroke, epilepsy, brain tumours, movement disorders, or a history of moderate to severe traumatic brain injury, and any player taking medication with a steroid component. Ice hockey players were followed throughout the 2013-2014 hockey season using previously validated injury surveillance methods.[27] All athletes thought to sustain a SRC during the season were examined by a certified sports medicine physician. Concussions were diagnosed based on current International Consensus on Sport Concussion recommendations;[3] completed ChildSCAT-3, neurological examination including balance assessment, brief cognitive assessment, motor examination, reflexes, and cranial nerve examination. Players diagnosed with SRC were asked to provide serum cortisol samples. Players were then followed through their recovery by a sport medicine physician until cleared to return to sport. This study was approved by the conjoint ethics board at the University of Calgary. All players and parent/guardian provided informed consent prior to participation in the "Safe to Play" study.

Cortisol collection

Serum Cortisol samples were drawn and analyzed by Calgary Laboratory Services (CLS). Samples were collected between 0730 and -1400. Physiological cortisol in human have a specific circadian rhythm in which cortisol peaks between 7-10 am. It is often recommended a morning cortisol samples, be drawn "upon awakening" or "between 7-10 am" as this is the physiological peak. Due to logistical reasons, such as access to CLS, it was difficult for participants to visit the

laboratory during the ideal early morning period. Therefore, we allowed participants to have blood drawn between 730-1400. Because we allowed athletes to have blood samples drawn during a larger time period we may find far greater variability in cortisol values and were forced to exclude any low samples taken after 10 am. However, interestingly, in our dataset no samples taken after 10 am were abnormally low. As well, a recent study Llompart-Pou et al. revealed there was a loss of cortisol circadian rhythms in patient with TBI suggesting that timing of sample may not be as important in SRC as in a healthy population[28].

Blood samples were collected from the antecubital fossa of each athlete and processed using the Elecsys Cortisol assay (Roche Diagnostics, Rotkreuz, Switzerland). During the first incubation period, endogenous cortisol that had been released from binding proteins within the sample competed with exogenous cortisol labelled with ruthenium complex for binding to a polyclonal antibody. A second incubation period involved addition of streptavidin-coated particles to bind the complex to the solid phase. Aspiration onto a measuring cell allowed magnetic capture of bound microparticles on an electrode, while unbound particles were removed with Pro Cell/Pro Cell M. Voltage through the electrode caused chemiluminescent emission that was measured by a photomultiplier and calibrated using a 2-point calibration and master curve. Cortisol reference ranges were determined by CLS internal studies and were derived from 300 self-reported healthy individual's age and sex matched (exclusion criteria were pregnancy, lactation, use of oral contraceptives and medication with cortisone/cortisol). Serum cortisol was considered normal if reported between 200-500 nmol/litre and abnormal if below 200 nmol/litre. Other laboratories across Canada and the United States may use different assays for analysis thus reflecting different population-based normative values. Of note, it is known that there is a large

intra-individual variability in cortisol measurements[29] that can be influenced by various types of stress[12,30],seasonal variation[31] and other factors, therefore using conventional population-based reference ranges as described above may not always reflect clinically significant alterations in individual subjects.

Statistical analysis

We completed an observational case series on pediatric hockey players who sustained a SRC. Pre-season biographical information including concussion modifiers (based on the current concussion guidelines – previous history of attention deficit disorder, migraines, learning disabilities, neck pain and family history of migraines) and concussion history was collected. Post-injury information including position played, Glasgow coma scale, length of loss of consciousness, length of post-traumatic amnesia, length of return to sport and childSCAT3. All data was collected and analysed with SPSS V.18. Post-injury symptom severity scores and number of symptoms based on the childSCAT3, as well as number of days to return to sport, were collected. Mean and standard deviations were calculated for all the players that sustained a SRC with an abnormally low cortisol and were compared to those with population-based normal cortisol.

Results

In total, 636 Pee Wee ice hockey players were enrolled in the study in the 2013-2014 ice hockey season. Baseline characteristics are summarized in Table 1. Forty-six SRC were sustained in 41 players during the ice hockey season. Of these, only twenty-two (53.7%) players had cortisol levels drawn due to a weak compliance rate amongst injured players with their blood work appointments. Those athletes with SRC that did not have blood drawn did not differ from athletes with SRC that did have blood drawn, in terms of age, sex and past medical history.

Further, the time to return to play for athletes with SRC that did not have serum cortisol drawn was 16.6±19.3, similar to athletes with normal cortisol (14.0±7.9). Seven of the 22 players were excluded from analysis as their serum samples were not collected within the appropriate timeframe, while another player was excluded due to asthma medication containing a steroid component. This left fourteen samples for analysis. In total, four (28.6%) of fourteen eligible samples had abnormally low cortisol compared to population-based standardized normal values. The remaining ten samples were all within the normal range (Table 2).

Players that sustained a SRC with abnormally low cortisol (17.8±1.9) experienced on average 10.3 more symptoms out of a possible 22 symptoms on the childSCAT3 than players with population-based normal cortisol (7.5±6.0). Players with abnormally low cortisol (28.5±5.8) had on average 18.3 more severe symptoms compared to players with normal cortisol (10.2±8.8). Players with SRC with low cortisol took 9 days longer to return to play (23±13.6) than their counterparts with normal cortisol (14.0±7.9). There appeared to be no trend for athletes with an abnormally low cortisol to have longer length of consciousness, longer post-traumatic amnesia, greater concussion history or concussion modifiers, however we were unable to retrieve a complete dataset for all these parameters.

Discussion

To the authors' knowledge, this is the first study to report measurements of serum cortisol following paediatric sport-related concussion (SRC). In total, 28.6% (4 out of 14 athletes) of paediatric ice hockey players sustaining a SRC had abnormally low acute serum cortisol. These

athletes on average had more symptoms and more severe symptoms on the childSCAT3 and took longer to return to sport compared to athletes with population-based normal cortisol.

Pathophysiology of low cortisol in brain injury

Evidence of abnormally low cortisol response acutely following brain injury is an important finding as we would expect the opposite; an immediate increase in cortisol following injury which would reflects an appropriate stress response and act as a protective mechanism for the body. From a pathophysiological perspective, elevated cortisol promote peripheral insulin resistance, stimulating the glycogenolysis and gluconeogenesis pathways. This provides much needed energy at the time of injury for the brain and other end organs. As well, cortisol has the ability to act as a vasopressor, promoting adequate perfusion to the brain and end organs, which in turn encourages an appropriate immune response.[30] If the hypothalamic-pituitary axis (HPA) is disrupted secondary to trauma, cortisol cannot increase and these protective mechanisms do not occur, most likely leading to increase symptoms and prolonged recovery.

Association between acute cortisol and traumatic brain injury

Our results are similar to studies that have examined acute neuroendocrine changes following mild, moderate and severe paediatrics TBI. [22-24] Srinivas et al. (2010) examined cortisol and ACTH levels over the first seven days following moderate and severe TBI in pediatric patients.[32] Patients with abnormally low cortisol at day 3 and 7 had more severe head injuries and increased morbidity compared to those that had normal cortisol. Other studies have found a nearly identical cortisol-TBI severity trend in adult mild-severe TBI population [33,34], while Dupuis et al. found 36% of paediatric patients with severe TBI admitted to the critical care unit had acutely

abnormal low cortisol after day 3 of injury.[26] In addition, the inability for cortisol levels to normalize within seven days following injury has been linked to increase mortality and morbidity.[35] Finally, a more recent study has shown that patients with severe TBI have a loss of cortisol circadian rhythms in the first week of injury suggesting injury to the hypothalamic-pituitary axis can cause impaired cortisol release throughout the day.

Our results suggest that those athletes with SRC and low cortisol were more at risk for increase symptom burden and prolong recovery. However, as alteration in cortisol following TBI is quite prevalent we could hypothesize that all the athletes that sustained a SRC had a drop in cortisol following concussion compared to their own pre-injury values. Previous research has shown a large intra-individual variability in cortisol suggesting that population-based normative ranges may not accurately reflect important clinical fluctuations in cortisol in individual subjects[29,31]. This would suggest that SRC may affect pituitary function acutely, reflected in a decline in cortisol, but those athletes with a greater drop in cortisol (below population-based normative values) may be more affected in terms of symptom burden and length of return to activity. Unfortunately, we can cannot investigate this within the parameters of this study, but further research would include sampling athletes pre-season, prior to injury and then daily following SRC until symptom resolution.

Neuroendocrine dysfunction following sport concussion

Few studies have evaluated acute neuroendocrine changes following SRC. To date, only one case study has described chronic neuroendocrine dysfunction in paediatric sport participants.[16] This case report describes a 14-year-old soccer player that sustained four concussions over a four-

month period. Following the last SRC he became symptomatic with decreased energy, poor concentration, weakness and decline in growth. He was diagnosed with hypopituitarism and subsequently treated for hypothyroidism, adrenal insufficiency and growth hormone deficiency. The authors suggested that multiple concussions over a short period of time increase the risk of persistent pituitary dysfunction following SRC. Similar to this report, others studies in adults have shown *chronic* pituitary dysfunction following multiple SRC.[18–20,36] These studies describe alterations in pituitary function that caused diabetes insipidus and growth hormone deficiency.[19,21,36,37] Further, two studies have examined *acute* pituitary changes following adult SRC. La Fountaine et al. reported acute prolactin was significantly decreased in collegiate football players with SRC and gradual increase in prolactin mirrored recovery.[10] Prolactin is released by the anterior pituitary and an acute decline in prolactin may reflect direct damage to the HPA following SRC. Most recently a study by Hutchison et al. examined saliva cortisol lin ice hockey players with SRC.[12] They found no difference between post-SRC acute saliva cortisol and return to play cortisol. However, there was a significant relationship between perceived stress severity and saliva cortisol but not mood, sleep quality or symptom severity.

Limitations

Aspects of this study limit us from making definitive conclusions, but the results suggest the need for future studies. First, we had a small sample size (n=14). Despite having baseline assessment on 636 players, and 46 SRC during the season, only 22 athletes had post-concussion blood work of which 14 met the inclusion/exclusion criteria. This is due to lack of compliance from athletes who understandably did not want to participate in a painful test (needle poke) or found it

inconvenient to go to a lab for blood draws. A smaller sample size increases the risk of a type II error, but it is hopeful this study will inform future studies with larger sample sizes. We suggest future studies might use a less invasive method of cortisol sampling, such as saliva sampling methods that can be done on the field or at the clinician bedside.

Other limitations include the variable timing of sample collection. All samples were taken within 7 days, but we know from previous studies in paediatric TBI that there is a fluctuation in cortisol from day 1 through to day 7 and potentially beyond following injury.[25] Therefore, we may have missed variations in cortisol levels because we were only taking one sample post injury and not on the same day. Future studies should sample cortisol pre-season and then daily and at the same time of day in all subjects to observe fluctuations in cortisol following SRC.

Finally, the variability in time of day which serum cortisol samples were collected presented us with an analytical problem because of the diurnal pattern exhibited by serum cortisol. Cortisol levels peak between 7-10 am and it is often recommended to sample during this time. However, due to logistical reasons we were unable to do so. Any player with low cortisol levels measured after 10 am had to be excluded because their peak levels could have been above the threshold for low if measured earlier in the day. Players with a normal cortisol level taken after 10 am could be included because their peak levels would still have exceeded the threshold for low if measured between the recommended timeframe. Future studies using serum cortisol samples should sample strictly between the hours of 7 and 10 am to reduce inter- and intra- sample variability.

Conclusion

The results of this small observational study provide preliminary evidence that serum cortisol can be abnormally low compared to population-based normal values following pediatric SRC. We found paediatric ice hockey players with abnormally low cortisol where are at risk of experiencing more symptoms and more severe symptoms, and tended to show a delayed return to sport. Further studies are needed, with larger samples size, consistent sampling time, and more frequent sampling to better characterize the alterations in acute cortisol following sport-related concussion.

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Declaration of interest

The authors report no declaration of interest.

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