Paediatric post-concussive symptoms: symptom clusters and clinical phenotypes

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ABSTRACT

Objective To assess the co-occurrence and clustering of post-concussive symptoms in children, and to identify distinct patient phenotypes based on symptom type and severity.

Methods We performed a secondary analysis of the prospective, multicentre Predicting and Preventing Post-concussive Problems in Pediatrics (5P) cohort study, evaluating children 5–17 years of age presenting within 48 hours of an acute concussion. Our primary outcome was the simultaneous occurrence of two or more persistent post-concussive symptoms on the Post-Concussion Symptom Inventory at 28 days post-injury. Analyses of symptom and patient clusters were performed using hierarchical cluster analyses of symptom severity ratings.

Results 3063 patients from the parent 5P study were included. Median age was 12.1 years (IQR: 9.2–14.6 years), and 1857 (60.6%) were male. Fatigue was the most common persistent symptom (21.7%), with headache the most commonly reported co-occurring symptom among patients with fatigue (55%; 363/662). Headache was common in children reporting any of the 12 other symptoms (range: 54%–72%). Physical symptoms occurred in two distinct clusters: vestibular-ocular and headache. Emotional and cognitive symptoms occurred together more frequently and with higher severity than physical symptoms. Fatigue was more strongly associated with cognitive and emotional symptoms than physical symptoms. We identified five patient groups (resolved/minimal, mild, moderate, severe and profound) based on symptom type and severity.

Conclusion Post-concussive symptoms in children occur in distinct clusters, facilitating the identification of distinct patient phenotypes based on symptom type and severity. Care of children post-concussion must be comprehensive, with systems designed to identify and treat distinct post-concussion phenotypes.

INTRODUCTION

Paediatric concussions are a major public health concern.[1–5] While the majority of children with a concussion will recovery completely within 4 weeks, nearly 30% will experience persistent post-concussive symptoms lasting 1 month or longer.[6–11] Prolonged symptoms can impact academic performance, participation in extra-curricular activities, and are associated with a lower quality of life.[12–14] Post-concussive symptoms are commonly categorised into physical, cognitive, emotional and sleep domains.[15 16] However, little is known about the relationships between individual symptoms, the co-occurrence of symptoms in each of these domains, or whether specific clinical phenotypes can be identified based on symptom clusters. By understanding the relationships between post-concussive symptoms and identifying distinct clinical phenotypes in children with concussion, clinicians will be better prepared to identify and address the entirety of patients' post-concussion symptomatology, which may reduce time to recovery.

We sought to evaluate the nature of persistent post-concussive symptoms in a prospective cohort of children diagnosed with concussion in the emergency department (ED). We sought to define the associations between symptoms persisting 28 days following concussion and between symptom domains (physical, cognitive and emotional). Finally, we sought to identify novel patient phenotypes based on symptom type and severity.

METHODS

Study population

This was a secondary analysis of the Predicting and Preventing Post-concussive Problems in Pediatrics (5P) study.[8 17] We evaluated patients from both the derivation and validation cohorts. Patients were included if they were 5–17 years old, had a concussion defined by the Zurich consensus statement,[10] suffered their head injury within 48-hours of ED presentation and were proficient in English or French.[17] Patients were excluded if they had a Glasgow Coma Score of ≤13, abnormal neuroimaging, required neurosurgery, intubation or intensive care, or experienced multisystem injuries requiring admission to the hospital or operating room, or had procedural sedation performed in the ED. Children with severe chronic neurodevelopmental delay with communication difficulties, children intoxicated at the time of ED presentation, children with no clear history of trauma and children with a previous history of enrolment in the study were also excluded.[17] Patients were screened and approached by research staff, and if willing were consented for study involvement.

Study design/setting

The parent study was a prospective cohort study from August 2013 to June 2015 at 9 Canadian

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paediatric hospitals in the Pediatric Emergency Research Canada Network.[17] All centres are academic, paediatric centres with a combined annual volume of approximately 500 000 ED visits. Neither patient nor public were involved in the design, conduct, reporting or dissemination of our research.

Data collection

After obtaining informed consent and assent, as appropriate, parents completed the Acute Concussion Evaluation (ACE), a validated tool to objectively diagnose concussion (as indicated by ≥1 symptoms on the ACE).[18] The following data were obtained from parents: demographics, medical history, presenting history and physical examination findings. Participant-reported ratings of current and pre-injury symptoms were obtained using the validated and reliable Post-Concussion Symptom Inventory (PCSI), where patients reported the presence and severity of each symptom relative to their pre-injury baseline.[15 16]

Patient follow-up

Research assistants contacted participating families at 4 weeks after their index ED visit. Automated follow-up surveys using the Research Electronic Data Capture (REDCap)[19] data collection tool and telephone follow-up survey were used to collect patient self-reported symptoms via the PCSI.

Outcome measures

Our primary outcome was the simultaneous occurrence of two or more post-concussive symptoms on the PCSI at 28 days post-injury. We chose to evaluate the 13 PCSI items common across all age groups (online supplemental table 1). PCSI scores for children aged 5–12 years, reported on a 0–2 scale, were multiplied by 3, so all scores were reported on the same (0–6) ordinal scale.[20] For initial analyses examining the co-occurrence of symptom pairs, we defined a post-concussive symptom as a dichotomous outcome (any positive difference between a patient-reported symptom at 28 days post-concussion minus their pre-injury symptom rating). For hierarchical cluster analyses, we analysed both the presence and severity (magnitude of the delta between pre-injury symptom rating score and patient-reported symptom severity) of symptoms.

Statistical analyses

We described the patient population using medians and interquartile ranges (IQRs) for continuous variables, and frequency and percentages for categorical variables. We analysed the relationship between post-concussion symptoms, describing their co-occurrence using conditional percentages (the portion of patients with symptom X who also have symptom Y). All usable PCSI data, including those from partially completed questionnaires, were included in this analysis.

We next analysed the relationship between post-concussive symptoms using hierarchal cluster analysis, reflecting clustering of post-concussive symptoms by type and severity. Because not all patients had data for all PCSI outcomes, we excluded those missing any PCSI data. We compared characteristics of included and excluded patients to ensure there were no significant differences.

To identify symptom and patient clusters (clinical phenotypes), hierarchical agglomerative cluster analysis (HCA) was applied in both dimensions to evaluate interrelationships among the 13 PCSI items, and to examine variations among patients based on their symptom profiles (ie, response patterns across PCSI items). Because of a relatively large number of unique patient symptom profiles, prior to HCA, an initial k-means clustering was performed on the patient dimension to reduce the number of observations to a manageable size (40 patient clusters).[21] Each of the 40 clusters contained varying numbers of patients that share similar symptom profiles. Cluster means were then computed (for each PCSI item) and applied to our HCAs using Ward's dissimilarity-based agglomerative algorithm (minimum variance method), where clustering criterion is based on squared Euclidean distances.[22 23]

To present our findings, two sets of dendrograms (tree diagrams) accompanied by an associated data heatmap were constructed. The two dendrograms represent an empirically derived 'classification' of symptoms and patients, respectively, based on the extent of (dis)similarity among constituents. The resulting heatmap provides an overview of study data summarised at the level of the initial patient clusters (n=40). 'Cutting' the dendrogram was performed to facilitate symptom and patients groups at a level of precision, which was determined a priori. For symptoms groups (composed of the 13 analysed symptoms), the dendrogram was 'cut' (based on tree height) to facilitate the emergence of four distinct groups, which was chosen to match the number of theoretical domains (physical, emotional, cognitive and fatigue) that originally conceptualised the PCSI.[15] Likewise, because of the large number of unique patient symptom profiles (40), prior to HCA, an initial k-means clustering was performed on patient dimension. We elected to 'cut' the patient dendrogram to identify five distinct patient groups.

The study's sample size was determined by the number of patients in the parent 5P study. All analyses were performed using R version 4.0.3.[24]

RESULTS

Patient population

Screening was performed on 8046 patients (5229 from the derivation cohort and 2817 from the validation cohort), of whom 3063 (38%) were enrolled; all of whom we included. Median patient age was 12.1 years (IQR: 9.2–14.6 years), and 1857 (60.6%) were male. Sports and recreational injuries accounted for the majority (68.1%) of included concussions, followed by falls (28.6%). Characteristics of the included population are summarised in table 1. For purposes of evaluating symptom and patient clusters, 2355 (76.9%) patients without any missing data from the PCSI at 28 days post-concussion were included (table 1). Differences between included and excluded patients in this analysis are summarised in online supplemental table 2.

Co-occurrence of post-concussive symptoms

The co-occurrence of post-concussive symptoms 28 days post-injury is described in table 2. Fatigue was the most commonly reported symptom (21.7%) and was reported as a concurrent symptom in 62%–76% of patients reporting any other post-concussive symptom. Among patients reporting fatigue (N=665), only headache was reported in more than 50% of patients. Headache was the second most commonly reported symptom (19.3%) and was reported as a concurrent symptom in 54%–72% of patients reporting any other post-concussive symptom. Among patients with headache (N=593), fatigue (62%) and difficulty concentrating (50%) were the most commonly reported co-occurring post-concussive symptoms. Difficulty concentrating was reported by 488 (15.9%) patients and was reported as a concurrent symptom in 49%–72% of patients reporting any other post-concussive symptom. Vision problems were the least commonly reported post-concussive symptom (6.7%) but occurred with a high frequency (39%) among those with balance problems, and were present among 22%–35% of patients reporting any other post-concussive symptom.

Table 1 Patient characteristics of included children with a concussion

Characteristic	Patients included in bivariate symptom analyses N=3063	Patients included in hierarchical symptom analyses N=2553
Age (years), median (IQR)	12.0 (9.2–14.6)	12.0 (9.3–14.6)
Male sex, n/total (%)	1857/3062 (60.6%)	1416/2354 (60.2%)
Time from Injury to ED triage (hours), median (IQR)	2.9 (1.5–11.3)	3.0 (1.5–12.6)
Mechanism of injury, n/total (%)		
Sports/recreation	2075/3049 (68.1%)	1614/2353 (68.6%)
Fall	871 (28.6%)	659 (28.0%)
Motor vehicle crash	57 (1.9%)	45 (1.9%)
Assault	43 (1.4%)	32 (1.4%)
Other	3 (0.1%)	3 (0.1%)
Loss of consciousness, n/total (%)	395/2712 (14.6%)	304/2084 (14.6%)
Post-injury seizure, n/total (%)	57/3041 (1.9%)	41/2348 (1.7%)
Glasgow Coma Score, median (IQR)	15 (15–15)	15 (15–15)
History, n/total (%)		
Prior treatment for headache	518/3049 (17.0%)	400/2353 (17.0%)
Personal history of migraine	392/3038 (12.9)	310/2342 (13.2%)
Learning disability	243/3039 (8.0%)	179/2347 (7.6%)
Attention deficit hyperactivity disorder	268/3036 (8.8%)	195/2345 (8.3%)
Anxiety	237/3045 (7.8%)	188/2349 (8.0%)
Depression	87/3047 (2.9%)	62/2350 (2.6%)
Sleep disorder	62/3040 (2.0%)	47/2348 (2.0%)
Other psychiatric disorders	32/3016 (1.1%)	24/2327 (1.0%)
Family history of migraine, n/total (%)	1436/2981 (48.2%)	310/2342 (13.2%)
BESS number of tandem stance errors, median (IQR)	3 (1–8)	3 (1–8)
BESS number of double leg stand errors, median (IQR)	0 (0–1)	0 (0–1)
PCSI scores at index ED visit, median (IQR)		
Physical	1.5 (0.9–2.5)	1.5 (0.9–2.4)
Fatigue	2.0 (0.7–3.7)	2.0 (0.7–3.7)
Emotional	0.5 (0.0–1.5)	0.5 (0.0–1.5)
Cognitive	0.8 (0.0–2.0)	0.6 (0.0–2.0)

PCSI scores represent item averages for each domain.
BESS, Balance Error Scoring System; ED, emergency department; PCSI, Post-Concussion Symptom Inventory.

Clusters and phenotypes of post-concussive symptoms

Analysis of patient and symptom clusters by symptom severity using HCA is seen in figure 1. Overall, this analysis revealed that physical, emotional, cognitive and fatigue symptoms clustered together, consistent with the proposed structure of the PCSI. Physical symptoms further differentiated into a vestibular-ocular cluster (balance problems, dizziness, vision problems and nausea) and a headache cluster (headache, sensitivity to light and sensitivity to noise). Fatigue was more closely related to cognitive and emotional symptoms than to physical symptoms.

The k-means analysis identified the initial 40 clusters of post-concussive patients. The largest cluster of patients (1371 (44.8%)) was asymptomatic at 28 days. The next largest cluster (96 (4.1%)) reported mild fatigue as their only post-concussive symptom. One cluster of 9 (0.4%) children reported a high symptom burden across all domains. Overall, the analysis yielded five broad groups of clusters that varied by symptom type and severity (table 3). Group 1 (clusters 1–17) was fully recovered or were minimally symptomatic. Group 2 (clusters 18–23) was mildly symptomatic, but had higher symptom burden in the cognitive/emotional and fatigue domains. Group 3 (clusters 24–32) was moderately symptomatic, and was further divided into those with a higher burden of balance, dizziness and headache symptoms (clusters 24–27) and those with more headache, cognitive and fatigue symptoms (clusters 28–32). Group 4 (clusters 33–35) was highly symptomatic, largely across cognitive, emotional and fatigue domains, with minimal physical symptoms. Group 5 (clusters 36–40) was profoundly symptomatic with high symptom burden across all domains, with only one cluster of patients (cluster 36) reporting low symptom burden in the vestibular-ocular domain. Clusters of patients reporting a high burden of vestibular-ocular symptoms (clusters 38–40) had the highest cumulative symptom burden. Overall, symptom severity was higher in clusters of patients reporting cognitive and emotional symptoms than in those reporting physical symptoms.

DISCUSSION

In this multicentre, prospective study of children with concussion, we found important overlap between post-concussive symptoms at 28 days and describe novel clinical phenotypes of post-concussion patients. Fatigue was the most common persistent post-concussive symptom and was more closely related to cognitive and emotional symptoms than to physical symptoms, with implications for how this common symptom is treated. Additionally, we found that physical symptoms divided into vestibular-ocular and headaches clusters, while cognitive and emotional symptoms clustered together, and were associated with a higher symptom burden. Finally, we identified novel patient phenotypes and groups of post-concussive patients based on symptom type and severity. Together, these results support the need for clinicians to assess the entirety of a patient's symptomatology, and identify phenotypes of patients who may require distinct treatments. Furthermore, these data underscore the importance of multidisciplinary treatment approaches, with the goal of accelerating time to recovery.

While our post-concussion patient phenotypes were identified quantitatively, they reflect previously reported patient groupings.[25–33] A prior analysis evaluating symptoms in adolescents identified four novel symptom clusters, including cognitive–fatigue–migraine, affective, somatic and sleep.[26] Another analysis in a sports medicine clinic identified 3 clusters of symptoms: neurocognitive, somatic and emotional, with a higher burden of emotional symptoms.[28] Finally, the headache, vestibular-ocular and emotional symptom clusters we identified are congruent with other proposed symptom classification phenotypes.[25 29 34 35] Our study augments these previous works through its large sample size, prospective design, and incorporation of both the presence and severity of symptoms. Finally, this work builds on our prior latent class analyses of the 5P data, which identified distinct phenotypes of acute parent-reported symptoms, and assessed the association between these phenotypes and the diagnosis of post-concussion symptoms.[36] It is still not known how these acute

Table 2 Bivariate comparison of the presence of individual post-concussion symptoms at 28 days

Symptoms, N (%) of total patients reporting this symptom	Headache	Nausea	Problem with balance	Dizziness	Sensitivity to light	Sensitivity to noise	Vision problems	Fatigue	Irritability	Sadness	Nervousness	Difficulty concentrating	Difficulty remembering
Headache, N=593 (19.4%)	100%	34%	33%	44%	45%	46%	25%	62%	41%	27%	28%	50%	37%
Nausea, N=296 (9.7%)	68%	100%	43%	53%	48%	51%	31%	68%	52%	35%	36%	53%	42%
Problem with balance, N=294 (9.6%)	67%	43%	100%	68%	55%	56%	39%	71%	53%	41%	37%	65%	42%
Dizziness, N=358 (11.7%)	72%	44%	56%	100%	52%	54%	35%	72%	50%	38%	34%	62%	46%
Sensitivity to light, N=382 (12.5%)	69%	37%	43%	49%	100%	64%	32%	68%	49%	34%	34%	61%	45%
Sensitivity to noise, N=412 (13.5%)	66%	37%	40%	47%	60%	100%	30%	68%	53%	32%	37%	63%	47%
Vision problems, N=205 60.7%)	70%	45%	56%	60%	60%	60%	100%	75%	50%	43%	42%	68%	55%
Fatigue, N=665 (21.7%)	55%	30%	32%	39%	39%	42%	23%	100%	47%	31%	30%	49%	36%
Irritability, N=462 (15.1%)	54%	33%	34%	39%	41%	47%	22%	68%	100%	41%	38%	55%	41%
Sadness, N=272 (8.9%)	60%	38%	44%	50%	48%	47%	32%	76%	69%	100%	53%	60%	48%
Nervousness, N=276 (8.9%)	59%	39%	40%	45%	47%	55%	31%	73%	64%	52%	100%	62%	47%
Difficulty concentrating, N=488 (15.9%)	61%	32%	38%	45%	48%	53%	29%	67%	52%	33%	35%	100%	52%
Difficulty remembering, N=354 (11.6%)	62%	35%	45%	47%	48%	53%	32%	68%	52%	37%	36%	72%	100%

Percentages represent the proportion of patients with the symptom in column 1 who are concurrently reporting the additional symptoms in the top row.
Colours correspond to the frequency of co-occurence of post-concussion symptoms, ranging from green to red, with green corresponding to the lowest co-occurence and red the highest co-occurence of symptoms.

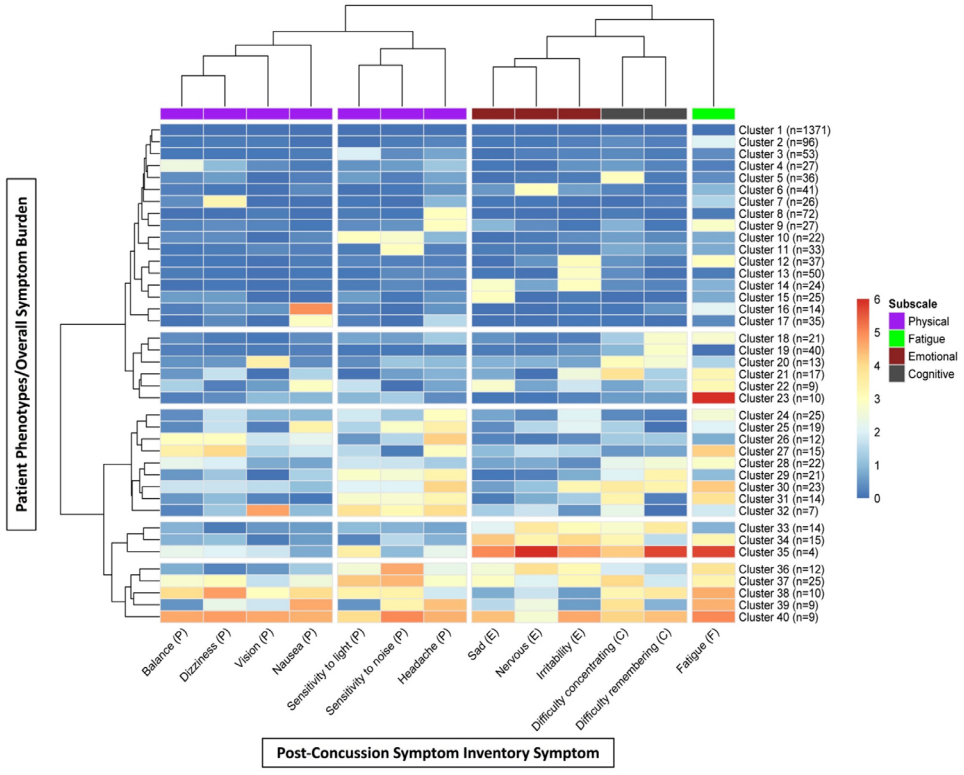

Figure 1 Clusters of post-concussive symptoms in paediatric patients.

patient symptom phenotypes predict patient symptomatology and phenotypes at 28 days post-concussion.

Symptom co-occurrence, clusters and novel patient phenotypes

We uncovered important findings regarding the co-occurrence of post-concussive symptoms. Fatigue and headache were the most commonly described symptoms. However, among patients reporting fatigue or headache, few other symptoms were commonly reported. Furthermore, while vision problems were the least commonly reported symptom, those with vision problems had an overall higher symptom burden. These data suggest some symptoms may be more likely to occur in isolation, while others, such as vision problems, sadness and problems with balance, may be an indicator of higher overall symptom burden. By being aware of symptoms which represent an overall high symptom burden, clinicians may identify those children more likely to benefit from earlier or more aggressive therapies or interventions. Furthermore, our results emphasise that while some symptoms may occur with less frequency than others, the lowest co-occurrence of symptoms (irritability and vision problems) still occurred together in more than 1 in 5 children, emphasising the importance of comprehensive symptom assessment.[37]

Table 3 Groupings of patient phenotypes by symptom type and severity

Group	Clusters	Name	Description
1	1–17	Resolved or minimally symptomatic	No symptoms (cluster 1) or minimal symptoms (clusters 2–16) reported across all domains
2	18–23	Mildly symptomatic	Mildly symptomatic with higher symptoms severity in fatigue and cognitive emotional domains
3	24–32	Moderately symptomatic	Moderately symptomatic and further divided into: balance, dizziness and headache subgroup (clusters 24–27) and headache, cognitive and fatigue subgroup (clusters 28–32)
4	33–35	Highly symptomatic	Highly symptomatic but largely across cognitive/emotional and fatigue domains with minimal physical symptoms
5	36–40	Profoundly symptomatic	Profoundly symptomatic with a high symptom burden across all domains with exception of cluster 36 reporting few vestibular-ocular symptoms

The clusters of patients and symptoms we identified have important implications for treating children following a concussion. First, and reassuringly, the largest group (group 1) of patients based on symptom type and severity was of those who were asymptomatic or minimally symptomatic at 28 days. Second, these results highlight the importance of addressing fatigue, the most common post-concussive symptom, which commonly coexists with other symptoms, and if not properly addressed could potentially prolong overall symptoms duration. Aetiologies for fatigue following concussion are multifactorial.[38–40] Addressing sleep issues is one possible focus for clinicians treating fatigue in concussed children.[41–43] Importantly, fatigue was more strongly associated with cognitive and emotional than physical symptoms, suggesting it may represent a mental rather than physical phenomenon by 4 weeks post-injury, with critical implications for how it is best treated.[44 45] Third, while moderately symptomatic patients were more troubled by headache, among those patients with severe symptom burden, the severity and burden of cognitive and emotional symptoms often exceeded those of physical symptoms. These results highlight the importance of recognising and treating the often difficult to manage cognitive and emotional post-concussion symptoms.[46] Fourth, we found that

physical symptoms further differentiated into vestibular-ocular and headache clusters. While the most symptomatic patients may have higher severity symptoms in both physical domains, patients with more mild and moderate symptoms tend to have a predominance of either headache or vestibular-ocular symptoms but not both. Fifth, a high burden of vestibular-ocular symptoms was associated with an overall high symptom burden across all domains.[47] Previous literature has suggested therapies targeted at improving vestibular-ocular symptoms may improve patient outcomes.[48] Finally, among the most severely symptomatic children, the severity of vestibular-ocular, headache, cognitive, emotional and fatigue symptoms varied. These results demonstrate the heterogeneity in symptoms that are characteristic even among the most severely affected patients and underscore the need for clinicians to develop specific treatment strategies for individual patients.

Implications for concussion care and research

This work has important implication for clinicians caring for children with post-concussion symptoms. These data inform clinicians about other symptoms to be assessed for when patients report a specific symptom. Additionally, by identifying novel phenotypes of patients, clinicians can understand how symptoms travel together. Failure to address co-occurring symptoms may lead to prolonged recovery, despite addressing the patient's primary complaint. Furthermore, the high burden of cognitive and emotional symptoms among the most severely symptomatic patients stresses the importance of a multidisciplinary, biopsychosocial approach to treatment.[49] In addition, future studies evaluating concussion and targeting interventions for specific post-concussion symptoms such as headache should take into account the co-occurrence of symptoms when designing outcome assessments.

Methodologic considerations and limitations

Our study must be interpreted in the context of its limitations. First, all participants were recruited after presenting to the ED for evaluation, and may be more severely concussed than children presenting to other clinical settings. Therefore, our results may not be applicable to patients presenting with concussion to other clinical settings. However, recent data suggest this assumption about site of initial concussion care and sevrity of injury may not be correct.[50 51] Second, we were missing follow-up symptom data for some patients, requiring us to eliminate them from our HCA. However, we found few clinically meaningful differences between those patients for whom all data were available and those with missing data. Third, we included patients over a range of ages. Clinical phenotypes and co-occurrence of symptoms may vary by age and sex. Furthermore, we multiplied symptom scores for the youngest to normalise symptom scales. While this method has been previously reported, the validity of this approach is not known. Fourth, sleep problems are commonly reported post-concussion, but we could only report on fatigue, as it was the only common element across all age groups in PCSI. Fifth, we included any increase in symptom severity over baseline for our analysis of the co-occurrence. In doing so, a patient with even a minor increase from their pre-injury state would be classified similarly to a patient with a marked increase in symptomatology. However, this methodology has been previously described,[52–55] and the magnitude of symptom change on the PCSI was accounted for in our HCA. Finally, we only report patient clusters and phenotypes at 28 days post-injury. Prior data have suggested changes in the types and severity of symptoms at various intervals post-recovery.[11] However, the early identification of clinical phenotypes could allow for targeted interventions. Further work is needed to understand how these symptom clusters and clinical phenotypes evolve over time as well as how patient-level factors such as age and gender impact symptom type and severity.

CONCLUSIONS

In this prospective, multicentre study, we identified the frequency with which post-concussive symptoms occur together, and described clusters of post-concussive symptoms and novel patient phenotypes at 28 days post-concussion. These data underscore the need for comprehensive, multidisciplinary treatment programmes and individualised management plans based on symptomatology. They also highlight the need to address the high burden of cognitive, emotional and fatigue symptoms among the most symptomatic patients. Care systems designed to treat these distinct post-concussion phenotypes are needed, with the goal of reducing time to recovery.

Key messages

What is already known on this topic?

⇒ Post-concussive symptoms are commonly categorised into physical, cognitive, emotional and sleep domains.

What this study adds?

⇒ In this study of more than 3000 children with a concussion, the relationships between post-concussion symptoms at 28 days were examined, and novel phenotypes of patients with post-concussion symptoms were empirically defined.

How this study might affect research, practice or policy?

⇒ These data underscore the need for comprehensive, multidisciplinary treatment programmes and individualised management plans for patients following concussion.

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Competing interests GG is an author of the Post-Concussion Symptom Inventory (PCSI) used in this study. The PCSI is freely available and he receives no financial benefit from its use.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The ethics committees of each participating centre approved this study with permission for data sharing. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. Data for this manuscript are stored and available online in BrainCode and are available upon reasonable request.

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