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TOURETTE'S SYNDROME (M SPECHT AND T ZEIGER, SECTION EDITORS)

A Review of Tics Presenting Subsequent to Traumatic Brain Injury

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Abstract

Purpose of Review This review summarizes case reports of patients with tics emerging subsequent to traumatic brain injury (TBI), with respect to demographics, post-TBI symptoms, tic onset latency and topography, clinical history, neuroimaging results, and treatment outcome.

Recent Findings Patients were 22 adults and 3 youth. Trauma onset appeared to fall mostly in adulthood. Two-thirds of patients were male and head trauma was related to motor vehicle accidents in most cases. Loss of consciousness was reported in just below half (48.0%) of cases. Associated physical and cognitive symptoms (e.g., impaired memory, reduced sensory perception, poor balance, muscle weakness, attention problems, aggression/impulsivity, obsessions and compulsions, depression, and anxiety) were commonly reported. The latency between head trauma and tic onset varied, but generally ranged from 1-day post-trauma to approximately 1-year post-trauma. Sole presentation of motor tics was common, with rostral to caudal development of motor tics in other cases. Simple and/or complex vocal tics were present in several cases, often emerging after motor tics. Post-trauma obsessive-compulsive symptoms were noted in five cases (20.0%). A personal or family history of tics was reported in four cases. Damage to the basal ganglia, ventricular system, and temporal region was observed across ten patients (40.0%). Pharmacological intervention varied, with tic symptoms deemed to have significantly or somewhat improved in 12 cases (48.0%). A comparison of post-TBI symptoms in youth with head trauma history relative to those with peripheral injury suggests tic symptoms are not a common post-TBI symptom in youth.

Summary Ultimately, there has been limited study on the link between traumatic brain injury and tic expression, and methodological issues preclude the ability to draw definitive conclusions regarding this relationship. Nevertheless, findings do suggest there may be heterogeneity in brain dysfunction associated with tic expression. Future case reports should utilize more systematic and thorough assessment of TBI and tics using validated measures, evaluate medication effects using single-case designs, and perform more longitudinal follow-up of cases with repeated neuroimaging.

Keywords Tics · Traumatic brain injury · Concussion; neuroimaging

Introduction

Tics are characterized by repeated, non-rhythmic, and sudden movements (i.e., motor tics) and/or vocalizations (i.e., vocal or phonic tics) [1]. Tics vary in complexity, with simple motor and vocal tics lasting a short duration and appearing or sounding purposeless (e.g., eye darting or blinking, shoulder shrugs, head jerks, throat clearing, humming, grunting), while complex tics involve multiple sequential movements and/or vocalizations, causing them to appear or sound more elaborate, orchestrated, and purposeful (e.g., chains of facial and head movements, tapping, jumping, writing tics, words, phrases, echolalia, coprolalia) [2]. Motor tics typically develop in a rostral-caudal manner, with tics involving the face/head emerging initially, and tics involving the torso and outer extremities developing as time progresses [3]. Additionally, both motor and vocal tics tend to increase in complexity over time, with initial tics involving simple movements and/or vocalizations, and subsequent tics often involving multiple chained movements or sounds. Further, tics typically follow a waxing and waning course, with symptoms increasing and decreasing over days, weeks, months, and years either spontaneously or in line contextual changes [3]. With up to 20% of school-aged

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children experiencing tics for at least some period of time [4], they are a relatively common occurrence among youth. Indeed, the onset of tics typically occurs during early childhood between the ages of 5 and 7 years on average [5, 6], with adult onset of tics considered to be rare [7]. Although most tics dissipate within 6 months of their initial onset, for individuals presenting with tics lasting longer than a year, a tic disorder diagnosis may be warranted.

The etiology of tic disorders has been proposed to be influenced by multiple factors. Genetic associations [8], dysfunction within brain structures (basal ganglia) [9] and circuits (cortico-striatal-thalamo-cortical loop) [10], and excess postsynaptic expression of dopaminergic receptor D2 [11] have consistently been implicated in the development and maintenance of tic disorders. However, tic disorders appear to onset spontaneously, and temporally related biological triggers are relatively less understood. Nevertheless, tics may present secondary to a range of other neurological, chemical, psychological, or external factors, including TBI [12]. Across 155 clinic-referred tic patients treated in a movement disorders clinic, tics were reported to occur or significantly worsen following head trauma in 2.5% of patients [12].

Traumatic brain injury (TBI) is a growing health concern, with the CDC estimating that 2.5 million US individuals present to the emergency room with TBI each year [13•]. Falls, blows to the head, motor vehicle accidents, and sports-related injuries are the leading causes of TBI [13•, 14]. TBIs are classed by severity (i.e., mild, moderate, severe) established through presence and degree of loss of consciousness, altered cognition, memory loss, and brain damage [15, 16]. Moderate and severe TBI is more likely to involve penetration of the skull and brain tissue resulting in damage and requiring intensive care or surgical intervention [15]. In contrast, mild TBI or concussion refers to a non-penetrating head injury caused by direct external force to the head, neck, face, or other body region. Mild TBI may or may not result in loss of consciousness, but often leads to short-term impairment in physical, cognitive, and/or emotional functioning [17, 18•]. Headache and dizziness are the most frequently reported complaints [19], with memory impairment, nausea, fatigue, irritability, depression, emotional lability, insomnia, and noise intolerance also occurring [15, 20].

In select cases, patients may develop involuntary movements following TBI, with tremor, dystonia, chorea, parkinsonism, and/or tics presenting subsequent to severe TBI in 13 to 66% of cases [21, 22]. The link between tics and TBI has been described in a number of case reports [23]. However, there is a paucity of literature on this phenomenon. In order to inform our understanding of the pathophysiology of tics, consideration should be given to the clinical characteristics, brain morphology, and tic symptom recovery among patients presenting with tics following TBI.

Patient Characteristics

This paper presents a review of case reports (see Table 1) describing three youth and 22 adult patients ranging in age from 6 to 55 years at the time of their visits, and presenting with tic symptoms following varying degrees of TBI. Age of trauma onset was reported to be early childhood in 4/25 (16.0%) cases [26, 34, 39, 41], adolescence in 2/25 (8.0%) cases [24], and 18 years and above in 5/25 (20.0%) cases [30, 32, 36, 38]. For most remaining cases, age of trauma was not clearly stated but is presumed to be in adulthood based on chronological age of the patient at the time of the report. Seventeen of the 25 patients (68.0%) were male and seven of the 25 (28.0%) patients were female, with sex going unreported in two cases. Incidents leading to head trauma included motor vehicle accidents in the majority (20/25; 80.0%) of cases, followed by falls in 2/25 (8.0%) cases [34, 35], being struck by an object in 1/25 (4.0%) cases, and unspecified injuries in 2/25 (8.0%) cases [37].

Post-traumatic Brain Injury Symptoms

Loss of consciousness following the concussion was reported in 12/25 patients (48.0%), with no loss of consciousness reported in 6/25 patients (24.0%). Physical and cognitive symptoms were reported across cases, and included memory problems [27, 29, 30, 38, 40•], poor impulse control [25, 30] and aggressive thoughts [24], reduced sensory perception [29, 30], poor balance [27, 30], hemiparesis or muscle weakness [26, 27], and impaired concentration [26, 27]. Further, at least one of the patients had a severe previous concussion, resulting in persistent short-term memory loss 2 years prior to the second one [30]. Emotional problems (i.e., depression, restricted affect, anxiety, irritability) were also noted [24, 29, 30, 38].

Tic Onset Latency and Topography

The latency between the head trauma and tic onset was reported in some cases. Tics presented within a few hours post-trauma in 1/25 (4.0%) case [32], 1 to about 4 days in 3/25 (12.0%) cases [29, 30], 2 to 3 weeks in 3/25 (12.0%) cases [29, 36], < 2 to 5 months in 6/25 (24%) cases [25, 30, 31, 38, 39, 41], and within about 1 year in 4/25 (16.0%) cases [26, 27, 29, 32]. On the higher end of the range, tics were reported to emerge a few years following the head trauma in one case [24] and 6 years in another [34]. In the majority of cases, patients presented with only simple motor tics, particularly involving the eyes, face, head, and neck. In some cases, simple motor tics evolved into more complex limb movements over time [34, 38, 41]. Simple and/or complex vocal tics were also present in several cases but were more likely to emerge after motor tics. Coprolalia and echolalia were present in each of five (out of 25) cases (20.0%) and often co-occurred. Further, the

Table 1 Summary of cases series and reports describing tics emerging subsequent to traumatic brain injury

Age, sex	Head trauma onset and description	Tic onset latency and topography	Other clinical observations	Laboratory testing	Clinical history	Treatment	Treatment outcome
50, F [24]	Age 13: motor vehicle accident with severe head trauma and multiple injuries, comatose for several days	Post-trauma: touching nose with fingertips, phonetic utterances, grimacing	Obsessive-compulsive symptoms: compulsive thoughts when holding sharp objects, restricted range of affect; anxiety and depressed mood with sleep problems, suicidal thoughts	NR	No history of mental or physical complaints	Since 2005: regularly attended psychiatric community practice, treated for obsessive-compulsive symptoms/behavioral problems/tics	NR
~ 55, M [24]	Age 16: motor vehicle accident, injuries, and head trauma resulting in coma	Few years' post-trauma: coprolalia, echolalia, other tics	Obsessive-compulsive thoughts, aggressive compulsive behaviors, homicidal thoughts, insecurity/fear/anxiety in crowds, restricted range of affect with insecurity, anxious and depressed mood with avoidance behavior	NR	No known history of neuropsychiatric disorders	Age 29: regularly attended psychiatric community practice for 5 years, medical treatment, cognitive behavioral therapy	Reduction in tic-related, physical, and mental complaints
Middle-aged, M [25]	Motor vehicle accident, head-on collision, severe closed head injury, multiple long bone, and pelvic fractures, 1-month coma	2-month post-trauma: severe motor tics: anterior flexion of right shoulder, right elbow and wrist extension, shoulder rotation movements, stomach tensing, platysma contractions, anterior dystonic-type neck flexion, occasional left neck movements, and eye tics; mild vocal tics: sniffing and throat clearing	Stability of movement location and topography over years with mild fluctuation in severity; partial tic suppression with rebound spike; premonitory urge in associated body regions; tic triggers: seat belts and tight shirts; non-distressing preference for ordering household items; developed behavioral disinhibition, impulsivity and recklessness leading to social impairment and divorce.	CT: unremarkable Lab testing for Wilson disease and inflammatory markers (erythrocyte sedimentation rate, C reactive protein and antinuclear antibodies), thyroid stimulating hormone, blood smear, ferritin, calcium, and magnesium levels: all normal	No family history of tics, OCD, or ADHD; no exposure to dopamine receptor-blocking agents prior to tic onset	Haloperidol, pimozide (led to renal failure); no improvement with trazodone, clonidine, sertraline, levodopa, and baclofen; mild subjective improvement with clonazepam. Botulinum toxin in neck and shoulder. Tetrabenazine showed clear benefit both subjectively and objectively (different dosing schedules in blinded fashion)	Eye tics improved spontaneously. Following tetrabenazine treatment YGTSS score improved by 24% on 12.5 mg twice daily and 45% on 12.5 mg three times daily. Side effects: sedation, impaired concentration, and mild parkinsonism. YGTSS: total decreased from 33 to 23 to 15. YGTSS: impairment decreased from 50 to 40 to 30. Subjective improvement was 50% and 70%, respectively. Rush video scores (masked) improved by 21% and 28.5%, respectively.
7.5, F [26]	Motor vehicle accident, struck by car resulting in severe head injury and requiring a week on ventilator	15-month post-trauma: over 3-week period developed blinking, shoulder and arm jerking, trunk flexing, loud and explosive grunts, tongue	Mild right hemiparesis (weakness), disinhibited verbal and physical behavior	CT (6-h post-trauma): hemorrhaging within left lateral ventricle and left internal capsule, diffuse cerebral edema	No tics prior to accident or in family history	Dramatic reductions in tic frequency and severity after higher doses of haloperidol; most vocalizations, including coprolalia, ceased;	7-year post-trauma: free of involuntary movements without medication for prior 3 years; below-average performance in a

Table 1 (continued)

Age, sex	Head trauma onset and description	Tic onset latency and topography	Other clinical observations	Laboratory testing	Clinical history	Treatment	Treatment outcome
		clicking, and vocalizations (e.g., coprolalia, echolalia, echopraxia)		EEG video telemetry: frequent slow wave activity without spiking from left frontotemporal region MRI (16-month post-trauma): tissue death in left putamen, globus pallidus, head of the caudate, and internal capsule; subtle reduction in the size of left frontoparietal cortex compared with right and a 3–4-mm cystic lesion in the left brainstem at the level of the superior colliculi.		echolalia decreased but persisted; movements persisted infrequently; haloperidol dose reduced 9 months after tic onset and withdrawn 3 months later; psychiatric input at 3 and 6 months after discontinuation of haloperidol; further therapy declined due to patient's sustained improvement	mainstream school, impaired concentration and disinhibited verbal behavior, minimal weakness in right hand.
19, M [27]	Motor vehicle accident, sustained traumatic brain injury, intubated, and ventilated for 1 week, 2 tonic-clonic seizures 2 weeks apart	1-year post-trauma: closure of eyelids, facial grimacing, sniffing, fist-clenching, grunting, throat clearing	Attention, memory and information processing problems, ataxia (poor muscle control and balance), and left hemiparesis (body weakness)	MRI (initial): multiple petechial hemorrhages in corpus callosum and basal ganglia, diffuse cerebral atrophy MRI (2-month post-trauma): small subdural fluid collection over right hemispheres, but no significant mass; mild atrophy; a few lesions of high T2 signal within right basal ganglia GRE: multiple lesions of low signal within body of corpus callosum, right putamen, and gray/white matter interface over convexity of the brain MRI (13-month post-trauma): resolution of prior subdural fluid collection; GRE: persistence of lesions of low signal	No history of obsessive-compulsive behavior or any other neurological or psychiatric problems prior to trauma; no family history of tics or any movement disorders	Attended community brain injury rehabilitation program	18-month post-trauma: motor and vocal tics persisted; 24-month post-trauma: tic frequency and intensity significantly decreased
33, M [28]	Motor vehicle accident with head trauma	Multiple motor and vocal tics in the neck, arms, and larynx	NR	NR	No family history of tic disorders	Carbamazepine and clonazepam	No benefit; stable and persistent tics

Table 1 (continued)

Age, sex	Head trauma onset and description	Tic onset latency and topography	Other clinical observations	Laboratory testing	Clinical history	Treatment	Treatment outcome
41, M [28]	Motor vehicle accident	Motor and vocal tics involving the face, neck, arms	NR	NR	No family history of tic disorders	Botulinum toxin	Tics improved over time
33, F [29]	Motor vehicle accident, pain in neck, right-sided weakness next day	Few days post-trauma: multiple motor tics of the face, left arm jerks, and startle induced loud high pitched screams; 3-year post-trauma: coprolalia, kissing tics, high-pitched yelping, grimacing, pouting, shoulder and arm jerking	Triggers: bright lights, startle, stress, anger, stress; no clear premonitory urge; auditory startle response (stimulus 90 dB tone) testing: isolated response in orbicularis oculi muscle (latency 48.6 ms) followed by complex, variable muscle activation with mean latencies from 113 ms (mentalis/lip-chin muscle) to 250 ms (forearm muscles); percussion of left side of body: complex patterns of muscle activation and vocalization, latency of 80 to 500 ms in different muscles	EEG, MRI, and blood tests: normal	No family history of tics or obsessive-compulsive behavior	Tetrabenazine, sulpiride	Considerable improvement in tics following tetrabenazine
32, F [29]	Knocked down by car, unconscious for 3 days followed by anterograde amnesia for seconds and post-traumatic amnesia for several months	1-year post-trauma: vocalizations with wheezing and facial grimacing, head movements, eye closure, left arm and shoulder raising, eye darting upwards	Post-trauma: slightly slurred speech, mild right-sided weakness and sensory loss, anxiety, panic attacks, forgetfulness	MRI: bilateral frontal high signal change consistent with head injury		Clonazepam	Clonazepam ineffective
33, F [29]	Motor vehicle accident, pain in the neck, right-sided weakness next day	Few days post-trauma: multiple motor tics of the face, left arm jerks, and startle induced loud high pitched screams; 3-year post-trauma: coprolalia, kissing tics, high-pitched yelping, grimacing, pouting, shoulder and arm jerking	Triggers: bright lights, startle, stress, anger, stress; no clear premonitory urge; auditory startle response (stimulus 90 dB tone) testing: isolated response in orbicularis oculi muscle (latency 48.6 ms) followed by complex, variable muscle activation with mean latencies from 113 ms (mentalis/lip-chin muscle) to 250 ms	EEG, MRI, and blood tests: normal	No family history of tics or obsessive-compulsive behavior	Tetrabenazine, sulpiride	Considerable improvement in tics following tetrabenazine

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Age, sex	Head trauma onset and description	Tic onset latency and topography	Other clinical observations	Laboratory testing	Clinical history	Treatment	Treatment outcome
			(forearm muscles); percussion of left side of body: complex patterns of muscle activation and vocalization, latency of 80 to 500 ms in different muscles				
26, M [30]	Age 21: motor vehicle accident, with car striking passenger side of another vehicle; struck forehead on front windshield; no loss of consciousness, dizziness for several hours	1-day post-trauma: head jerking, contractions of anterior neck muscles; 3-month post-trauma: lower lip retracting, lip-smacking, facial grimacing	Mild atrophy left leg weakness, minimal left arm weakness	X-ray: normal CT (1-month post-trauma): cavum septi pellucidi, otherwise normal MRI (2-year post-trauma): normal EMG: right C5 to C7 radiculopathy (pinched nerve)	Family history negative for movement disorders, denied abnormal movements prior to accident, no history of obsessive-compulsive behavior, hyperactivity, abnormal vocalizations, mild left hemiparesis, or hemiatrophy	Baclofen, cyclobenzaprine, carbamazepine, haloperidol, and buspirone not effective; some improvement with trihexyphenidyl and clonazepam but led to sedation; tetrabenazine showed tic improvement but discontinued due to insomnia.	Marked reduction in intensity and frequency of neck tics after injection of botulinum toxin into right and left sternocleidomastoid muscles
33, M [30]	Age 23: motor vehicle accident with severe head trauma, comatose for 2 weeks	Within months post-trauma: picking and rubbing nose, rubbing eyes, opening mouth, intermittent leg twitching with abduction and adduction of thighs, sniffing, hand wringing	Within months post-trauma: obsessive-compulsive behaviors; demented, disoriented, stuttering speech, broad-based (wide) gait, difficulty with tandem gait (walking with toes of back foot touching heel of front foot), increased irritability and distractibility, depressed, low self-esteem, social introversion	MRI: cerebral atrophy with panventricular dilation and widened convexity sulci and cerebellar fissures; bilateral subcortical and periventricular leukoencephalopathic changes of frontal and right temporoparietal white matter, no focal lesions of basal ganglia or brainstem	Family history negative for movement disorders; age 21: motor vehicle accident with severe closed head injury, immediate loss of consciousness, and 3-week coma; recovered completely over next years except for short-term memory impairment	Patient and family unconcerned about movements; no treatment initiated; prescribed fluoxetine for his depression 20 mg four times daily	Follow-up (4 months later): improved mood
21, M [31]	Motor vehicle accident, car struck by other vehicle, knocked unconscious for few minutes, no significant injuries and discharged; dull neck and back pain later that day	5-month post-trauma: right eye twitching, shoulder shrugging, and head turning or tilting, back arching	Movements subsided completely with distraction; all movements suppressible, but with increased neck stiffness and tension; movements increased post-suppression with relief of neck stiffness once suppression stopped	CT (head) and MRI (cervical spine): normal	Grade school: hyperactive, very distractible, and inattentive; long history of engaging in checking behavior and rituals; no family or personal history of tics, drug exposure, OCD, or ADHD	Clonazepam ineffective and led to excessive sedation; trial of clonidine;	Chronic dull neck and back pain persisted
38, M [32]	Working under automobile that was hit by other vehicle and knocked off the jack, pinning patient	Few hours post-trauma: lower right face began twitching;	Few hours post-trauma: right facial droop	Facial nerve conduction testing: decreased amplitude of motor action potential on right	No family or personal history of tics or associated behavioral disorders	Clonazepam improved twitching but caused sedation	After 9 months: movements decreased to near absent levels spontaneously; when patient was

Table 1 (continued)

Age, sex	Head trauma onset and description	Tic onset latency and topography	Other clinical observations	Laboratory testing	Clinical history	Treatment	Treatment outcome
	underneath; the head was turned to the left, and right face and chest pinned down for 8 min; no significant head injury; two fractured ribs	6-month post-trauma: facial twitching, nose twitching, sniffing, vocal tic		side suggesting right facial axonal neuropathy Blink reflex test: normal			nervous/stressed movements returned in same location and pattern to a much lesser extent
34, M [32]	Age 31: motor vehicle accident, towing trailer that came loose and smashed into back of vehicle at highway speed, minor neck injury with stiffness and pain most notable 2 days after accident	1-year post-trauma: involuntary forceful neck movements to the right with breath-holding		MRI (cervical): normal	Past medical and family history unremarkable	Few weeks post-trauma: chiropractor and physical therapy; clonidine started but discontinued after 2 weeks due to adverse side effects (vivid dreams, light headedness, and fatigue)	Follow-up: continued occurrence of neck movements with no change in location or character
35, M [33]	Motor vehicle accident caused trauma to the head, neck, back; no loss of consciousness; herniated lumbar disc; headaches, neck pain, radiating lower back pain	~2-week post-trauma: developed twitching of the anterior cervical musculature (tic-like movements of the platysma bilaterally of moderate to large amplitude, rapid, and irregular)	NR	NR	No family or personal history of movement disorders	Clonidine and valium associated with some reduction in symptoms, discontinued due to sedating effects	2-year follow-up: no changes in syndrome
24, F [34]	Age 5: fell down stairs, sustained head injury	6-year post-trauma: involuntary forehead, neck, and right hand movements 11-year post-trauma: scream-like sounds; 13-year post-trauma: echolalia 19-year post-trauma: scream-like sounds, jerky movements of extended upper limbs	Hesitant gait	EEG (age 17): abnormal and showed diffusional changes, irregular alpha rhythms, and slowing of electrical activities in left temporoparietal region X-ray (age 24): cranial nerves and skull/chest normal CT (age 24): normal Blood work and lumbar puncture (age 24): normal	Post-head trauma: convulsive seizure affecting right side of body; no family history of chronic tics	Age 14: cartalan and benztropine, stopped due to visual disturbance, later took promazine; Age 17: haloperidol and rivoltril, taken for ~3 years with tetrabenazine, tics improved, haloperidol discontinued when patient developed dystonia and oculogyric crises; Age 21: metoclopramide improved symptoms, developed galactorrhea and oculogyric crises controlled with benztropine, started on piracetam	Chronic tics persisted
33, M [35]	Fell from third-story fire escape, hit shoulder and		NR	CT: normal	Chin "twitching" since high school; no family history	Over course of 22 months of post-trauma	

Table 1 (continued)

Age, sex	Head trauma onset and description	Tic onset latency and topography	Other clinical observations	Laboratory testing	Clinical history	Treatment	Treatment outcome
	head upon impact, no loss of consciousness	2-week post-trauma: involuntary head and neck movements			of tics or similar movements; no family or personal history of obsessive-compulsive behaviors	follow-up: tics were controlled with haloperidol and later pimozide due to sedating effects of haloperidol	Tic severity waxed and waned based on anxiety, but tics improved overall
27, M [36]	Age 25: motor vehicle accident, front-seat passenger in van hit on passenger side by front end of tractor, right femur and cerebral fracture, concussion with 45-min loss of consciousness	~2–3-weeks post-trauma: eye blinking, right-sided facial tics, head and neck rotation toward the right side, forward head thrusting, anterior rotational right shoulder movements	NR	CT and EEG: normal	No evidence of prior use of neuroleptics or drugs; no family history of motor/vocal tics or similar movement disorders	Lorazepam, haloperidol, and clonidine had no effect on tics.	2 years after tic onset: no change in symptoms
NR, NR [37]	Closed head trauma	Post-trauma: simple tics emerged	NR	NR	NR	NR	NR
NR, NR [37]	Head trauma	Post-trauma: Marked worsening in prior mild tic symptoms	NR	NR	Mild tics	NR	NR
18, M [38]	Age 18: struck in face by steel girder and thrown backwards hitting head against wall, lost consciousness for few minutes, hospitalized for 2-week post-trauma	Within 3-month post-trauma: abnormal twitching movements of face and limbs mostly on right side; 2-year post-trauma: grunting sounds; increased twitching movements 4-year post-trauma: complex shrugging, complex facial tics, sniffing, snorting, throat-clearing, coughing, eye blinking; 6-year post-trauma: grunting, sniffing, throat-clearing, coughing, eye blinking, whistling, grimacing, head flexion, rapid movement of right arm, elbow flexion, right leg rotation, right shoulder twitches	2-year post-trauma: compulsive behaviors 4-year post-trauma: simple myoclonic jerks 6-year post-trauma: memory impairments, emotional problems, depression, inability to maintain job	NR	NR	2-year post-trauma: acute dystonic reaction upon trial with chlorpromazine, trihexphenidyl, and haloperidol; then treated with diphenhydramine; 2 later trials linked to successful reduction in involuntary movements but caused akathisia; 4-year post-trauma: clonazepam, with relief 2 years later;	6-year post-trauma: Clonazepam, persistent tics, but suppressible in public
6, F [39]	March 30th, 1978: ran out in front of oncoming car	43-day post-trauma: involuntary movement of right upper extremity	Complete left-side hemiplegia (paralysis), scalp bruising on left of	X-ray: normal	NR	33-day post-trauma: right frontotemporal craniotomy performed	Discharged on July 24, 1979, to attend a special school

Table 1 (continued)

Age, sex	Head trauma onset and description	Tic onset latency and topography	Other clinical observations	Laboratory testing	Clinical history	Treatment	Treatment outcome
			forehead, able to open eyes 3-month post-trauma	CT (19-day post-trauma): massive hemorrhage in right basal ganglia CT (53-day post-trauma): enlargement of lateral ventricles R1-cisternography (61-day post-trauma): ventricular reflux which persisted 48 h later		and about 20 ml of dark brown fluid was aspirated; 35 days after the first operation: V-P shunt was performed, convalescence was remarkable, was able to sit up by herself, rehabilitation of about 6-month duration enabled her to walk with aid of leg brace and assistance	
32, M [40•]	Motor vehicle accident, after ~ 24 h regained semi-consciousness, developed extreme motor restlessness	Coprolalia, echolalia of meaningless phrases or words, shouting, coughing, barking, echolalia, and eye-related tic	9-day post-trauma: exaggerated reflexes on left side, left supranuclear facial paresis, intermittent positive Babinski sign on left side, marked bilateral optic disc swelling. 46-day post-trauma: optic disc swelling subsided; trigeminal hypesthenia, slight central facial weakness, arm deep reflexes slightly above average on left side, reduced synkinetic movements of left arm, short attention span, Korsakoff's syndrome with few brief periods of memory left, rambling confabulations, lack of adequate emotional response to own circumstances, in addition to themes and events	Right carotid angiogram (within first 9 days): normal EEG (1-month post-trauma): bitemporal delta activity prominent on left side EEG (4-month post-trauma): normal AEG: slight dilation of left lateral ventricle and more dilated pear-shaped 3rd ventricle with diameter of 12 mm	NR	1-month post-trauma: Diazepam, chlordiazepoxide, nicotinic acid, vitamin B, biperiden, and thioridazine for motor restlessness and wandering; but only slight improvement of flat affect and amnesia; L-dopa post-carbon monoxide poisoning to improve memory, L-tryptophan to prevent L-dopa side-effects, ascorbic acid, biperiden, diazepoxide, amitriptyline.	L-Dopa for 3 days; 16 days after stopping suddenly developed marked restlessness with aggression, shouting, coprolalia, echolalia, and eye-related tics; tics gradually decreased 3 days after stopping L-dopa; causal connection between symptoms and administration of L-dopa was confirmed with follow-up trial
15, M [41]	Age 3: knocked down by motor cycle, no immediate signs of concussion	< 2-month post-trauma: eye, facial, and shoulder tics Age 12: limb movements, biting and chewing cheek Severe relapse: loud bellowing, continuous cheek and tongue biting,	2-month post-trauma: tics worse when patient tired, irritated, or tense Age 12: anxiety, admitted to hospital for infection related to biting mouth	X-ray (age 3): depressed fracture in right temporal region EEG (age 12): suspiciously sudden non-specific sporadic activity, most	2 paternal uncles with facial tics, Jactatio capitis (i.e., rhythmic movement disorder) in childhood	Age 12: sedatives and psychotherapy for 1 month dramatically reduced symptoms; Severe relapse: heavy sedation via levomepromazine	After ~ 4 days on phenytoin and diazepam w/occasional barbiturates, attacks and tics stopped

Table 1 (continued)

Age, sex	Head trauma onset and description	Tic onset latency and topography	Other clinical observations	Laboratory testing	Clinical history	Treatment	Treatment outcome
		attacks of severe generalized muscular tics	Severe relapse: attacks including restlessness, twisting, and turning in bed.	intense mainly in left temporal region		temporarily reduced attacks; spent ~4 days on phenytoin and diazepam w/occasional barbiturates	

F, female; *M*, male; *NR*, none reported; *CT*, computerized tomography; *YGTSS*, Yale Global Tic Severity Scale; *EEG*, electroencephalography; *MRI*, magnetic resonance imaging; *GRE*, gradient echo imaging; *EMG*, electromyography; *AEG*, air encephalography; *L-dopa*, levodopa

presence of obsessive-compulsive symptoms was reported post-concussion in 20% (5/25) of cases [24, 25, 30, 38].

Clinical History

In most cases (60.0%; 15/25), personal and family history were negative for both tics and/or related conditions (e.g., obsessive-compulsive symptoms, attention-deficit/hyperactivity disorder). However, 4/25 (16%) patients reported a family or personal history of tics. For example, a 15-year-old who had experienced a concussion at age 3, with tics emerging less than 2 months following the head trauma, and had two paternal uncles with facial tics [41]. A 33-year-old adult, who had presented with head and neck movements 2 weeks after hitting her head and shoulders during a fall, revealed she had engaged in repetitive chin movements since high school [35]. Another patient reported a possible prior sniffing tic [30]. In another case, severe worsening of pre-existing tic symptoms was observed following head trauma [37]. Finally, in a separate case, although the patient denied a family or personal history of tics, he reported childhood hyperactivity, distractibility and inattention, suggestive of attention-deficit/hyperactivity disorder (ADHD), and ongoing checking behavior, implying a history of obsessive-compulsive symptoms predating the trauma [31]. Personal and family history were not reported in the remaining 4/25 (16%) cases.

Laboratory Testing of Neural Structure and Functioning

Laboratory testing results describing neural structure and function were included in two-thirds of the case reports (16/25; 64%), with most tests including various forms of imaging (most commonly X-ray, computerized tomography (CT), magnetic resonance imaging (MRI)), and/or electroencephalography (EEG). Among these cases, testing results were unremarkable in 6/16 (37.5%) patients [29–32, 35, 36]. Among the remaining 10/16 (62.5%) patients, testing revealed several reports (5/16; 6.3%) of damage or dysfunction within the temporal region, with right temporal region fracture via x-ray [41], abnormal activity in the left temporal, frontotemporal, bitemporal and parietotemporal regions via EEG [26, 34, 40•, 41], and damage to the frontal and right temporoparietal white matter via MRI [30]. Decreased activation in the temporal region has been linked with increased tic severity [42]. Research suggests activation within the right temporoparietal junction in adults with TS is linked with premonitory urges to tic, repetition of others' speech and movements, and impulse control deficits, and activation in the left temporoparietal junction was linked to increased socially inappropriate symptoms [43]. Further, cortical thinning in the temporal, frontal, and parietal regions is associated with increased tic severity [44].

Basal ganglia damage was reported in 3/16 (18.8%) cases, with hemorrhaging found across the basal ganglia [27], right basal ganglia [39], and left internal capsule [26]; tissue death noted in the left putamen, globus pallidus, head of the caudate, and internal capsule [26]; and lesions present in the right basal ganglia and right putamen [27]. Indeed, the basal ganglia has been most frequently implicated in TS, with studies showing reduced basal ganglia volumes in patients with TS [45••, 46]. Another brain region reported to be damaged across several cases (4/16; 25.0%) was the ventricular system, with reports suggesting enlargement of lateral ventricles [30, 35, 39], ventricular reflux [39], and hemorrhaging within the left lateral ventricle [26]. Findings are mixed with respect to ventricular abnormalities in individuals with TS. Research has shown no significant differences in ventricular size between youth and adults with TS and healthy controls [36, 47••]. However, an analysis of psychiatric outcomes in 6-year-old children of low birthweight showed neonatal ventricular enlargement increased odds for any psychiatric disorder, tic disorders, and ADHD [48]. Further, in monozygotic twins with discordant tic severity, the left lateral ventricle was reduced in the twin with greater symptom severity, which may have suggested organic differences or medication effects [49].

Treatment of Tics Subsequent to Traumatic Brain Injury

Treatments described in these case reports often involved combined medication regimens or a series of medication trials. Often, patients reported adverse side effects, most commonly sedation [30–35], resulting in their discontinuation or substitution for a more promising medication in several cases. With respect to final reported treatment outcomes, tics were reported to have significantly improved in 7/21 (33%) cases [25–27, 29, 30, 41]. Across these cases the only or final medication attempted varied greatly, with phenytoin (anticonvulsant) and diazepam (anxiolytic and sedative) with intermittent barbiturate administration [41], botulinum toxin [30], tetrabenazine [25, 29], and haloperidol [26] included. Tics were deemed to have improved somewhat in 5/21 (23.8%) cases [24, 28, 32, 35, 38], for example, decreasing, but occasionally re-emerging during stressful situations [32], waxing and waning but generally improving [35], or persisting but becoming suppressible in public settings [38]. Among these patients who experienced some improvement, medications used were antipsychotics (i.e., haloperidol, pimozide [35], clonazepam [32, 38], and botulinum toxin [28].

In four cases, no information on tic outcomes was provided [24, 37, 39]. In 3/21 (14.3%) cases, tics improved slightly over the course of treatment, but with no change in status by the final follow-up [30, 33, 34]. In several other cases (5/21; 4.8%), medications were ineffective or discontinued due to adverse side effects [28, 29, 31, 32, 36]. In one case, neither the patient nor family were concerned about the movements or interested in receiving treatment for them [30], highlighting that tic symptoms post-concussion may not be bothersome enough to warrant treatment for all patients. And finally, in one case involving a trial of levodopa (a dopamine agonist) to aid memory, tics emerged following administration of the medication and diminished 3 days after stopping the medication. A later re-trial of the medication confirmed that levodopa was the likely culprit [40•].

Validity of Mild Traumatic Brain Injury Symptoms Including Tics

Mild TBI or concussion typically resolves within 3 months, however, in individuals with symptoms that persist beyond this window, a diagnosis of post-concussion syndrome may be warranted [15]. However, some have called into question the validity of post-concussion syndrome. One study [50] compared the frequency of parent endorsement of child health complaints, including tics among 102 youth ages 4 to 15 years with a history of isolated mild TBI to 102 control youth with a history of mild peripheral bodily injury matched on age, sex, and date of trauma-related admission. This study was performed through a two-stage survey process to reduce expectancy bias. First, in the absence of any direct reference to the prior trauma, parents were mailed and asked to complete surveys regarding their child's demographics, medical history, and presence and severity of health-related/physical symptoms. Second, upon receiving initial survey responses, parents were mailed an additional survey regarding history of mild TBI, which the researchers used to confirm the assignment of the survey responses to the head trauma group and exclude any cases in which additional head trauma occurred since the initial patient visit.

Findings revealed tics were endorsed at respective rates of 28.4% in parents of youth with concussion history and 31.4% in parents of youth with a history of peripheral bodily injury, with no significant group differences observed. Essentially, there were no significant differences between groups for all symptoms except for parental concerns regarding the possibility of brain damage, which parents of youth with a history of concussion endorsed at higher rates. The presence of headache, learning difficulty, and sleep disorder symptoms significantly predicted the increased likelihood of concern [50]. As there was no excess of tic symptom occurrence in the head trauma group, this suggests tics are not a common post-concussion symptom at least in children and younger adolescents. The authors also question the likelihood of physical symptoms being directly linked to concussion and suggest that they may be a product of psychological factors or stress related to the traumatic incident. In general, findings were concordant with a previous similarly designed study performed in adults, although no questions on tics were included in that

study [51]. However, this study has some limitations. We lack information on the children's health status prior to their head or peripheral body trauma. Further, parents were asked to rate general health status without regard for links with the trauma. This was important to reduce expectancy bias. However, as such, the degree to which physical symptoms can be attributed to the trauma is unclear. Additionally, the age range of the sample (i.e., 4 to 15) overlaps with the period of average age of tic onset (i.e., 5 to 7) [6]. Therefore, it is possible that tics may have emerged for these school-aged children even without head trauma.

Conclusion

The present review summarizes case reports and series describing tics emerging or worsening following TBI. With respect to demographics, patients described in the reports were predominantly male. This is in line with the higher preponderance of TS in males relative to females (with a ratio of 3:1) [52]. As such, the higher incidence of males among these cases is likely reflective of male sex being a risk factor for tic occurrence. Additionally, in several of the patients, there was a family history of tics or common co-occurring symptoms, which is in line with research demonstrating the heritability of TS. Further, mild tics were present or suspected prior to the head trauma in three cases; and a history of obsessive-compulsive disorder (OCD) and ADHD symptoms was present in a separate patient. This raises the question as to whether additional patients may have had a personal history of tics prior to TBI that went undetected. Age of head trauma onset was reported or presumed to be in adulthood in most cases. However, in four of 25 cases (16.0%), it was reported to be in early childhood (i.e., ages 3, 5, and < 6 years, < 7.5 years). This raises challenges related to the attribution of tics to TBI. Since tics typically onset during early childhood, it cannot be determined whether tics would have emerged naturally in these children even without a history of TBI. Relatedly, the study evaluating the validity of physical complaints presenting following mild TBI showed no significant differences in parent-report of tics in youth between those with head trauma history versus peripheral injury history [50]. This suggests that tics emerging post-TBI are relatively uncommon in youth. Further, latency between head trauma and age of onset varied widely across cases. Whether this variation holds clinical significance (e.g., links between latency and trauma severity or affected brain region) cannot be ascertained from these few case reports.

With respect to tic topography, presentation of motor tics involving the face, head, and neck was common, with motor tics increasing in complexity to involve the extremities over time in several other cases. Vocal tics were also common but often developed following motor tics. This pattern of tic emergence mirrors the rostral to caudal and motor to vocal development of tics in TS [3]. Obsessive-compulsive symptoms emerged post-TBI in 20% of cases. Obsessive-compulsive disorder and TS commonly co-occur, overlap with respect to patterns of brain dysfunction, and have symptoms (e.g., complex tics and compulsions) that are difficult to discern at times [53]. The presence of obsessive-compulsive symptoms presenting post-trauma in these cases is also in line with the common co-occurrence between TS and OCD.

Among patients who had undergone neuroimaging, findings most often revealed damage to the basal ganglia, ventricular system, and temporal region, with damage sometimes present across multiple regions within the same patient. Neural abnormalities noted in these reports are consistent with extant knowledge regarding neural sequelae within TS and other persistent tic disorders However, given the lack of pre-TBI data, it is difficult to know if abnormal imaging findings were pre-existing. Nevertheless, broadly speaking, case report findings suggest there may be broad heterogeneity in neural dysfunction implicated in tic expression.

With respect to treatment outcome, tics appeared to improve significantly in seven cases and somewhat in five cases, with various medications trialed. However, the degree to which tics may have remitted without pharmacological intervention is unclear. More longitudinal follow-up and repeat neuroimaging of these patients are needed to address this important question.

Although informative, these case reports and series provide limited information for several reasons. First, the inconsistency across cases in reporting of patient demographics, clinical features, neuroimaging results, and timing of follow-up visits poses a challenge for identifying clinical patterns across similar cases. Second, causative links between TBI and tics cannot be determined and are more questionable in certain cases (e.g., tic onset observed 6-years post-head trauma in a child [34], and tic onset emerging following levodopa administration post-head trauma in an adult [41]). Further, with respect to pharmacological intervention, the open trial administration used in most cases limits the ability to discern the relative effectiveness of these medications on tic symptoms. Further, objective measurement of tics was lacking, with only one case report [25] including clinician-rated tic interview and video assessment of tics. In the future, patient assessments should be performed more thoroughly and systematically. Details regarding age of onset, clinical history, and neuroimaging results and treatment outcome should be included more consistently to allow for drawing of inferences across cases. There should also be greater use of standardized and validated measures of tic symptoms including the Yale Global Tic Severity Scale, a clinician-rated interview, subjective measures, and video-based observation of tics (See Cohen et al., 2013 for a review of tic assessment) [54]. Further, as utilized in two cases, single case designs [55] should be incorporated to more systematically test medication effects.

Ultimately, given the limited systematic study of the link between TBI and tics and the aforementioned methodological issues in the extant literature, there is presently no definitive evidence to support that brain trauma is causative for tics. Given these findings, should tics emerge around the same time as a TBI, typical treatments for tics should be pursued first (as needed). This remains an area ripe for examination, and this important line of research should be carried out in larger scale, systematic investigations that employ more rigorous methodology.

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Compliance with Ethical Standards

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer The conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute of Mental Health.

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- • Of importance
- •• Of major importance

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