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Neurological conditions associated with spinal cord injury

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A B S T R A C T

Background: Comorbid neurological conditions associated with spinal cord injury (SCI) significantly affect an individual's quality of life, yet they are often underrated. Recent reports suggest that SCI may predispose patients to develop other neurological disorders. We aim at providing an overview of the evidence of neurological conditions which are or seem resultant of SCI.

Methods: We conducted a literature review using PUBMED and GOOGLE SCHOLAR to evaluate the occurrence of different neurological disorders in people with SCI.

Results: Individuals with SCI seem at an increased risk of stroke, cognitive impairment, dementia, multiple sclerosis, Parkinson's disease, restless leg syndrome, and seizures. The co-occurrence of Guillain-Barré syndrome, and myasthenia gravis, were also reported.

Conclusion: Neurological comorbidities in individuals with SCI may lead to poor long-term outcomes, which could be minimized by early diagnosis and treatment of these conditions.

1. Introduction

Spinal cord injury (SCI) is a devastating condition with a worldwide incidence of 3.6–195.4 patients per million [1]. It has been shown that SCI have a significant financial impact on individuals and the healthcare system: the estimated lifetime cost of a 25 year-old with a new SCI may be as high as US$ 4.7 million [2]. Those with SCI may develop several complications and neurological comorbid conditions which may significantly impact their quality of life. In clinical care, neurological comorbidities are often underrated. We conducted a narrative review to establish what is known about the association.

2. Method

A full search of PUBMED and GOOGLE SCHOLAR up to March 2019 identified any report in which the presence of neurological disorders in people with SCI was examined. Reviews were excluded. The search and revision was independently conducted by two authors (MA and MS). Only articles in English were reviewed. Search items included "spinal cord", "SCI", "comorbidity", "stroke" "cerebrovascular disease", "cardiovascular disease", "cognit*" "dementia", "alzheimer's disease", "multiple sclerosis", "Parkinson's disease", "restless leg syndrome", "Willis-Ekbom disease", "autonomic dysreflexia", "autonomic hyperreflexia", "dysautonomia", "autonomic dysregulation", "seizure", "epilep*", "myasthenia gravis", and "Guillain-Barré syndrome". After identification of each relevant article, the reference list was reviewed for further references. Gray literature was not searched.

3. Results

Different studies indicated that individuals with SCI are at an increased risk of stroke, dementia, multiple sclerosis, Parkinson's disease, restless leg syndrome, and seizures. The co-occurrence of Guillain-Barré syndrome, and even myasthenia gravis, was also reported.

3.1. Stroke

We found six studies investigating the correlation between SCI and stroke occurrence (Table 1). A study with approximately 9000 veterans with SCI showed that almost one-third of the subjects had at least one macro-vascular complication including coronary artery disease and stroke [3]. Over half of the deaths among this population were due to macro-vascular events. Advanced age (odds ratio (OR: 5), diabetes (OR: 2), more than one physical comorbidity (OR: 1.8), and serious mental illness (OR: 1.2) increased the odds of macro-vascular events in patients with SCI. Three studies with SCI cases and controls investigated the correlation between SCI and stroke occurrence. It was reported that up to 10% of individuals with SCI had a stroke [4,5]. The incidence of stroke in SCI patients was approximately 6 per 1000 person-years, with a cumulative incidence rate of 2.4%, which was threefold greater than

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Table 1

Study	Year of publication	Country	Design	No of cases/ controls	Age	gender	Stratifications	OR/HR/RR	Other results
Banerjea et al. [3]	2008	USA	Retrospective cohort	1333 case 7436 control	median age was 55 with 25% over the age of 65	98% of all individuals were males	Age/diabetes/ physical comorbidity/serious mental illness/ marital status/the place of living/ Duration of SCI/level of injury	Adjusted OR (diabetes): 2.04	Age, diabetes, physical comorbidity, serious mental illness are the risk factors of macrovascular events
Wu et al. [6]	2012	Taipei	Retrospective cohort	2806 case 28,060 control	Case: 40.48 (12.74) Control: 42.87 (10.78)	Case: 76.4% Male Control: 73.1% Male	Hypertension/ arrhythmia/coronary heart disease/ exposure to aspirin/ lipid profile/ diabetes/exposure to anticoagulant	Adjusted HR: 2.93 Hemorrhagic HR: 1.91 Ischemic HR: 3.13	The cumulative incidence of stroke was 2.4% among SCI and 0.8% among controls
Cragg et al. [4]	2013	Canada	Cross sectional	356 case 60,675 control	Both group median age: 40-44	Case:51.8% Male Control: 50.6% Male	Sex/age	Adjusted OR: 3.72	The prevalence of stroke was 5.7% in cases compared to 1.1% in control
LaVela et al. [5]	2012	USA	Cross sectional	794 SCI case 13,528 general veterans 6105 general poulation	Mean SCI and general veterans: 74 (10.3) General population: 73.1 (8.2)	All 100% Male	Education/blood pressure/smoking/ past smoking/chronic drinking/cholestrol level/marital status	Adjusted OR: 1.44 vs. general veteran No difference vs. general population	Smoking, low educated, high blood pressure, and high cholestrol are the risk factors of stroke in SCI people
Chikuda et al. [7]	2014	Japan	Retrospective cohort	2363 cervical fracture without SCI 7359 SCI without fracture 1283 with both SCI and fracture	63.5 (18)	Male to female in groups:2.70	Age/sex/spinal surgery/diabetes/ coronary heart disease/diabetes/ arrhythmia	–	Risk of stroke was similar between groups but the mortality was higher in SCI and fracture cases followed by SCI cases without fracture
De Heredia et al. [8]	2015	UK	Cross sectional	98 cases	46 (18)	81% Male	–	–	Post circulation infarct occurred in 7% of cases

control able-bodied individuals. The odds of stroke was about 1.5 to 4-fold higher than controls [4,5] with the hazard risk ratio of 2.9 [6]. Persons with SCI were more likely to have hemorrhagic and ischemic strokes, but the incidence rate of ischemic stroke was more than three-fold higher than that of hemorrhagic stroke [6]. One study investigating the association between cervical spine trauma and ischemic stroke found that the risk of ischemic stroke was similar among people with cervical fracture/dislocation without SCI, those with SCI without cervical fracture/dislocation, and individuals with fracture/dislocation and SCI [7] but the individuals with both conditions had the highest mortality rate after stroke, followed by SCI patients without fracture/dislocation. Overall, stroke had a significant negative impact on clinical outcomes and increased the in-hospital mortality rates in this population.

People with SCI are at an increased risk of various physical comorbidities (e.g. diabetes, hypertension) due to their sedentary lifestyle which may increase the risk of cardiovascular disorders. A nationwide study with over 30,000 individuals (2,806 SCI cases and 28,060 controls) reported greater risk of stroke after SCI, even after appropriate adjustment for confounders such as age, gender, hypertension, diabetes, arrhythmia, and use of medicines [6]. Vascular injury after SCI can also increase the risk of stroke. A prospective study of 100 participants with traumatic cervical SCI indicated that about 7% of them had significant posterior circulation infarcts and 13% had vertebral artery injury [8]. This occurred in only two individuals, and no association between stroke and vertebral artery injury was found. Other underlying mechanisms including neuroinflammation or alterations of the autonomic cerebrovascular control were also discussed [9], although sufficient evidence for confirmation is lacking.

3.2. Cognitive impairment and dementia

A high prevalence of cognitive impairment was reported among people with SCI. About 10%–60% of SCI individuals were reported to have some degree of cognitive dysfunction [10–13]. In a recent case-control study with 150 SCI participants, it what reported that approximately one third of individuals with SCI experienced varying degrees of cognitive dysfunction [14]. Patients with SCI were at a 13 times greater risk for having impaired cognition as compared with controls [14]. Different forms of cognitive impairment, such as difficulty processing information and abstract thinking, inability to learning new skills, and impaired concentration and memory, were reported in SCI patients [15].

Improving cognitive deficits due to SCI has been the aim of some clinical trials, one of which investigated the effect of 12-week anti-inflammatory diet on verbal learning and memory. The results showed no significant cognition improvement after the intervention, despite a considerable decrease in pro-inflammatory cytokine levels [16]. Phillips et al. reported that low blood pressure (BP) in individuals with

high-level SCI may partially mediate cognitive dysfunction. They observed the effect of midodrine in 10 individuals with SCI higher than the T6 spinal segment, showing that retaining BP to 85 ± 10 mmHg was associated with approximately 15% improvement in cognitive function ($P < 0.05$), which was also proportional to the increase of the resting BP as a result of midodrine [17].

Dementia is a term used to describe symptoms associated with progressive loss of cognitive function. Alzheimer's disease (AD) is by far the most common type of dementia. Two recent studies investigated the association between SCI and dementia [18,19]. One study enrolled 941 SCI individuals and 5,060 controls and reported an increased risk of dementia in the SCI group (crude hazard ratio (HR): 1.91 (95% confidence interval (CI): 1.38–2.63)). The higher risk of dementia was still observed after adjusting for age, sex, diabetes mellitus, hyperlipidemia, hypertension, autoimmune disorders, affective psychosis, coronary heart disease, stroke, traumatic brain injury, and Parkinson's disease (HR: 1.94 (95%CI: 1.41–2.67, P-value<0.001)). However, no statistically significant difference was noted for specifically developing AD (adjusted HR: 1.78 (95%CI: 0.69–4.48)) [19]. However, another study included 9,257 SCI patients and 555,390 controls, and the results indicated an increased risk of developing AD in individuals with SCI (HR: 1.71 (95%CI: 1.06–2.76)) [18].

3.3. Multiple sclerosis (MS)

Multiple sclerosis is considered a chronic immune-mediated neurological disorder that results in the destruction of both white and gray matter. Lin et al. performed a cohort study investigating the association between SCI and MS [19]. The study included 11,913 participants with SCI and over 59,565 controls matched for sex, age, pre-existing comorbidities (diabetes mellitus, hypertension, and dyslipidemia), and socioeconomic status (geographical region, level of urbanization, and income level). Within the median follow-up time of 30 months, 5 MS events were reported among the SCI group (0.041%) compared to 4 events in the non-SCI group (0.006%). The incidence rate of MS in SCI patients was approximately 18 per 100,000 person-years (vs. 2.82 per person-years in non-SCI individuals). They also reported an over eightfold-increased risk of developing MS among patients with SCI (HR: 8.33, 95%CI: 1.99–34.87,$P < 0.05$).

The co-occurrence of SCI and MS can be a great dilemma for clinicians. On one side, SCI manifestations can mask the typical symptoms of MS which lead to a significant delay in MS diagnosis. On the other side, this co-existence can considerably affect the patient's quality of life. To date, the number of human studies regarding this correlation is limited and the underlying mechanisms are unclear. It can be speculated that neuroinflammation due to SCI may increase the risk of MS, but there is scarce evidence to support this supposition thus far.

3.4. Parkinson's disease (PD)

Parkinson's disease is the most common neurodegenerative movement disorder, and is caused by the degeneration and death of dopaminergic neurons. One study evaluated the occurrence of PD in persons with SCI, comparing 10,125 participants in the SCI group versus 10,125 non-SCI individuals [20]. It was found that within 30 months of follow-up, 99 persons in SCI group (0.98%) and 59 in non-SCI group (0.58%) developed PD. The incidence rate of PD among SCI cases was approximately 4 per 1000 person-years (versus 2.5 per 1000 person-years among non-SCI persons). After adjustment for sex, age, comorbidities (including diabetes, hypertension, dyslipidemia, stroke, and coronary heart disease), as well as socioeconomic status (including income, geographical region, and levels of urbanization), it was found that the risk of PD occurrence among SCI patients within the first year of follow-up was 1.39-fold higher than controls, although it was not statistically correlated (95%CI: 0.87–2.29). However, after the first year, risk of PD was statistically associated with SCI (hazard risk (HR), 95%CI: 2.05, 1.19–3.55). The overall risk of PD was 1.65-fold greater among SCI participants (95%CI: 1.16–2.33).

It is now recognized that α-synuclein, a small presynaptic neuronal protein with 140 amino acids, is a central component to the pathogenesis of PD [21]. The structural changes in this protein may lead to autoimmune responses targeting dopaminergic neuronal cells and cause PD. Synuclein expression can be induced due to SCI, which may justify this correlation [22,23]. Further studies should investigate this association and the possible underlying mechanisms for this correlation.

3.5. Restless leg syndrome (RLS)

Restless leg syndrome or Willis-Ekbom disease is a chronic progressive movement disorder of the limbs which is characterized by an urge to move the legs accompanied by unpleasant sensations at rest. About 2%–3% of people in the US suffer from RLS [24]. Some prior studies with a small number of SCI patients reported the co-occurrence of RLS and SCI [25–28]. A case survey of 195 individuals with SCI showed that RLS occurs frequently (17.9%) in SCI patients, and RLS usually responds well to dopaminergic treatment [29]. It was also appreciated that RLS developed within the first year following SCI in most of the cases. Moreover, it appeared mostly in people with lumbosacral lesions. In line with this study, another study consisting of 162 SCI cases reported a similar prevalence of RLS, but it was found that RLS developed in most cases with both cervical and thoracic SCI [30].

The diagnosis of RLS in patients with SCI could be confusing. Differentiation between neuropathic pain and RLS is challenging and the treatment-resistant sensory motor symptoms of SCI patients could be the signs of RLS [27]. Overall, the main complaint of SCI patients with RLS was reported to be tingling in the legs, followed by burning and sense of an electric shock. In those who were not able to move their legs, symptoms could be relieved by rubbing, massage, or washing the legs with cold water. Passive movement of lower extremities or moving the trunk back and forth was also found to be useful [27,29]. It was reported that Pramipexole, as a dopamine agonist, can significantly improve RLS symptoms in SCI cases [27,28].

3.6. Seizures

Provoked seizures may occur in SCI individuals in the context of autonomic dysreflexia occurrence. Prior studies investigating the clinical features of autonomic dysreflexia in patients with SCI indicated that about 1% of this population had acute seizures [31,32]. However, no characteristic aspects of seizures were reported in these studies. Four case-reports also described the co-occurrence of convulsive/focal seizures and autonomic dysreflexia in SCI individuals [33–36]. Posterior reversible encephalopathy syndrome (PRES) could be the cause of the seizure. PRES is a condition characterized by transient and sudden onset of seizures, headaches, and visual loss accompanied by abnormalities on T2 fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) in the brain. Severe hypertensive episodes are correlated with increased risk of PRES. The concomitance of SCI, PRES, autonomic dysreflexia, and convulsion has been reported [35,36].

Long-term outcomes in patients experiencing seizures due to autonomic dysreflexia were reported to be poor. One clinical review evaluated life-threatening outcomes associated with autonomic dysreflexia and demonstrated that 39% of those complications were seizure or convulsions, which was the second most frequent CNS-related complication after hemorrhage [37].

Seizure was also reported in SCI patients without autonomic dysreflexia. Two case-reports described the presence of epilepsy in SCI subjects. Bu et al. [38] reported a male with old odontoid fracture and atlantoaxial dislocation and spinal cord compression experienced grand mal seizures and Lavy et al. [39] described a case with clonic convulsions of the upper limbs and grand mal attacks after a high thoracic traumatic spinal cord lesion. No symptom of autonomic dysreflexia was

Table 2

Study identifier	Year of publication	Country	No of case	Age (year)	Gender	Results
Grant et al. [40].	2011	Canada	1	31	Male	After sepsis occurrence the patient developed flaccidity and facial diplegia and paraclinical tests showed GBS which get treated by IVIg
Scozzafaya et al. [41]	2008	Canada	1	28	Male	After SCI and shortly after admission due to injury marked autonomic instability, fluctuating temperature and severe hypotension occurred which accompanied by lower weakness and new weakness in face and upper extremities. Six months after GBS treatment the patient weakness in face got better.
Son et al. [42]	2011	South Koreas	1	50	Male	After admission due to SCI patient first, suffered abdominal pain; followed by numbness in hands, chest discomfort, dyspnea, facial weakness and areflexia which GBS was diagnosed. IVIg was used and in two months neurological dificits got treted
Gounden et al. [43]	2016	Australia	1	61	Male	A patient with tetraplegia due to SCI had sudden onset of diplopia and bilateral ptosis. Acetylcholine receptor antibody was negative but EMG showed muscle fatigue. Ocular signs respond to pyridostygmine.
Lin et al. [44]	2008	Taiwan	1	N/A	Male	Previous case of myasthenia gravis had SCI and later, due to pneumonia and urinary tract infection the signs and symptoms of myasthenia gravis returned which got treated
Kolli et al. [45]	2011	UK	1	54	Male	A paralyzed person for 40 years admitted for surgery of sacral pressure sore. During admission diplopia, fluctuating dysphagia, and slurred speech occurred. EMG and response to pyridostigmine confirmed MG diagnosis. The patient died in six weeks due to cardiorespiratory arrest.
Kaux et al. [46]	2009	Belgium	1	92	Male	Major swallowing disorder occurred in a quadriplegic patient which MG diagnosis was achieved after performance of EMG.

recognized in these cases and the underlying mechanisms were unclear.

3.7. Other neurological disorders

The occurrence of Guillain-Barré syndrome (GBS) and myasthenia gravis (MG) in individuals with SCI have been reported in case reports [40–46] (Table 2). The presence of pre-existing neurological manifestations of SCI, such as paraplegia/tetraplegia and paresis, may mask typical patterns of skeletal muscle impairment of MG and GBS and cause significant delay for the diagnosis of these disorders.

4. Conclusion

Spinal cord injury is associated with an increased risk of different neurological disorders. However, there is a paucity of evidence specifically evaluating these associations. The occurrence of these neurological comorbidities along with SCI can considerably impact the quality of life of patients and increase the economic burden. The underlying mechanisms of these correlations are unclear. One speculation is that immune system dysfunction due to SCI may play a critical role in the occurrence of these neurological conditions [47]. Future human studies should focus on the neurological comorbidities of SCI, while animal studies should investigate the possible underlying mechanisms of this correlation.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical statement

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