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Review

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Stroke syndromes and clinical management

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Summary

The knowledge of brain syndromes is essential for stroke physicians and neurologists, particularly those that can be extremely difficult and challenging to diagnose due to the great variability of symptom presentation and yet of clinical significance in terms of potential devastating effect with poor outcome. The diagnosis and understanding of stroke syndromes has improved dramatically over the years with the advent of modern imaging, while the management is similar to general care as recommended by various guidelines in addition to care of such patients on specialized units with facilities for continuous monitoring of vital signs and dedicated stroke therapy. Such critical care can be provided either in the acute stroke unit, the medical intensive care unit or the neurological intensive care unit. There may be no definitive treatment at reversing stroke syndromes, but it is important to identify the signs and symptoms for an early diagnosis to prompt quick treatment, which can prevent further devastating complications following stroke. The aim of this article is to discuss some of the important clinical stroke syndromes encountered in clinical practice and discuss their management.

Introduction

A stroke syndrome is a set of symptoms that helps to identify which part of the brain has been injured in stroke. The earliest classical syndromes were described in the 19th century and since then many new stroke syndromes have been discovered. Recent advances in neuroimaging have allowed many of the classical stroke syndromes previously described on clinical pathological basis or during autopsy to be confirmed.[1] As some of the syndromes are life-threatening, it is important that physicians are aware of the various individual clinical symptoms and signs arising from focal lesions and the complex or multiple clinical manifestations that could arise from the numerous vascular anatomical syndromes. There are a large number of well-described stroke syndromes (Box 1), but this review will focus on some rare, often being neglected but life-threatening syndromes with clinical significance encountered in clinical practice, that is, brain stem syndrome, thalamic syndrome, Horner's syndrome (HS), Alien hand syndrome (AHS) and acute spinal cord syndrome.

Brain stem syndromes

There are various subsets of brain stem syndromes, for example, dorsolateral medullary syndrome of

Box 1. Stroke syndromes arranged by vascular territory

Middle cerebral artery	Middle cerebral artery: complete
	Middle cerebral artery: superior division
	Middle cerebral artery: inferior division
	Gerstmann syndrome
	Ataxic hemiparesis
Posterior cerebral artery	Posterior cerebral artery: unilateral occipital
	Balint syndrome
	Cortical blindness (Anton syndrome)
	Weber syndrome
	Alexia without agraphia
	Thalamic pain syndrome (Dejerine–Roussy syndrome)
Anterior inferior cerebellar artery	Lateral pontine syndrome (Marie–Foix syndrome)
Posterior inferior cerebellar artery	Lateral medullary syndrome (Wallenberg syndrome)
Basilar artery	Locked-in syndrome
	Lateral pontine syndrome (Marie–Foix syndrome)
	Ventral pontine syndrome (Raymond syndrome)
	Ventral pontine syndrome (Millard–Gubler syndrome)
	Inferior medial pontine syndrome (Foville syndrome)
	Ataxic hemiparesis
	Cortical blindness (Anton syndrome)
	Medial medullary syndrome (Dejerine syndrome)
Vertebral artery	Medial medullary syndrome (Dejerine syndrome)
	Lateral medullary syndrome (Wallenberg syndrome)
Anterior spinal artery	ASAS
Posterior spinal artery	PSAS

Wallenberg, medial medullar syndrome of 'Dejerine', anterior inferior cerebellar artery syndrome (AICAS), superior cerebellar artery syndrome, the 'locked-in' syndrome and the 'top-of-the-basilar' syndrome.[2–8] As the brain stem controls some vital functions, for example, wakefulness, respiration, swallowing, circulation, patients with brain stem infarct (Figure 1) have a high early mortality rate.[9] Coma or loss of consciousness is commonly associated with brain stem syndromes such as the 'locked-in' syndrome and the 'top-of-the-basilar' syndrome.[2,5,6]

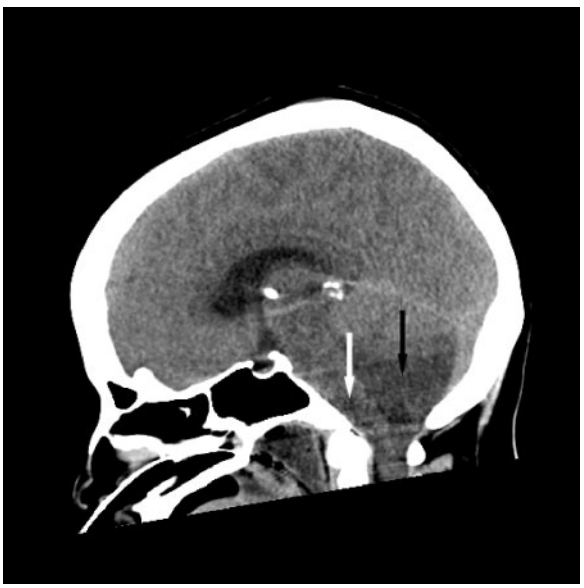

Figure 1. A CT image of brain infarct involving the brainstem (white arrow appointed) and left cerebellar hemisphere (black arrow appointed) with significant mast effect.

Dorsolateral medullary syndrome of Wallenberg

Dorsolateral medullary syndrome of Wallenberg's syndrome, also known as 'posterior cerebellar artery syndrome' or 'lateral medullary syndrome', is the commonest of the brain stem strokes (Figure 2a,b) with the middle medulla most frequently affected.[10] The syndrome results from spino- and trigeminothalamic systems injury with sparing of the lemniscal pathways and is characterized by vertigo, ipsilateral hemiataxia, dysarthria, ptosis, miosis and homolateral HS. Other defects include dysphonia and dysphagia (IX–X nerve palsies), as well as eye-movement disorders such as nystagmus, lateropulsion and skew deviation. This syndrome may also be associated with central pain, and cardiovascular abnormalities such as orthostatic hypotension and cardiac arrhythmias have been reported.[11] Lateral medullary ('Wallenberg') syndrome has been reported to be associated with chronic central

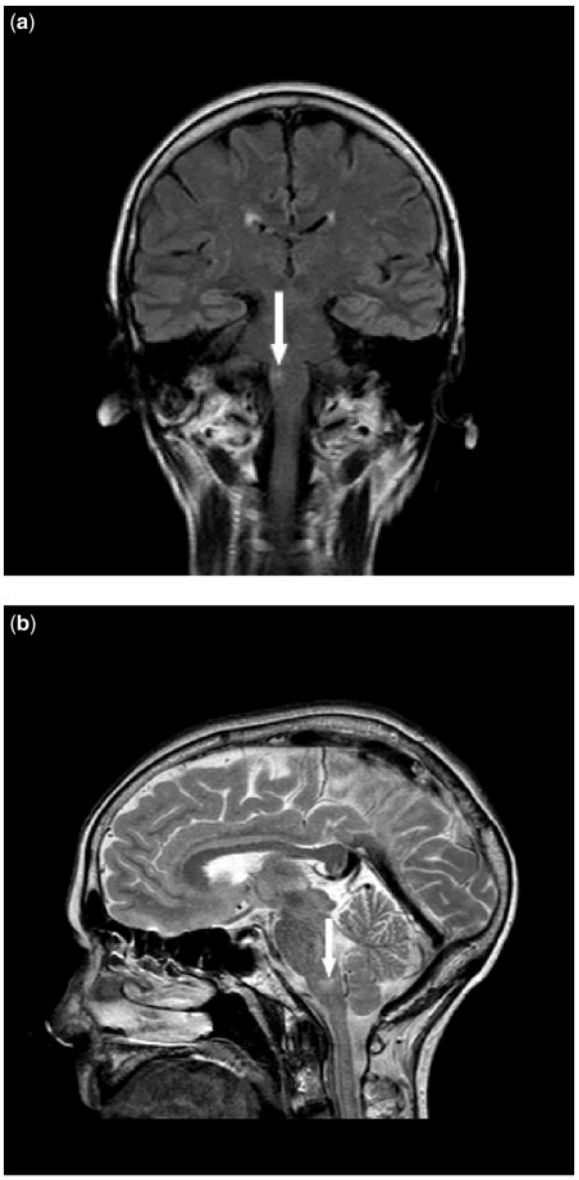

Figure 2. MRI Flair (a) and sagittal T2 (b) images showing established right lateral medullary infarct (white arrows appointed).

pain in 25% of cases within 6 months of the infarct.[4] The ipsilateral cheek alone or in combination with the contralateral limbs is the area most commonly affected by the pain, which is constant, burning and frequently exacerbated by cold and mechanical stimuli.[4]

Anterior inferior cerebellar artery syndrome (lateral pontine syndrome)

AICAS is the second most common brain stem stroke.[7] It is characterized by ipsilateral facial weakness, gait and limb ataxia, vertigo and unilateral ipsilateral deafness from labyrinthine artery ischaemia.[7] The combination of ipsilateral hearing loss, facial paralysis and loss of facial sensation is a very typical feature of AICAS, and a combination of vomiting, ataxia, nystagmus and ipsilateral fifth, seventh and eighth nerve dysfunction typically suggests AICAS.[12]

Medial medullar syndrome of Dejerine

This syndrome is as a result of infarction of the paramedian region of the medulla due to occlusion of the vertebral or anterior spinal artery or their small branches.[13] The high prevalence of motor dysfunction in patients with this syndrome has been attributed to the lesions mostly located in the rostral medulla or upper medulla.[10,14] Other deficits could include upbeat nystagmus, vertigo/dizziness and respiratory disturbances, especially in extensive medullar lesions, with bilateral medial medullary infarction (MMI) or combined MMI and lateral medullary infarction (LMI).[14] Breathing difficulties in MMI probably relate to an impairment of voluntary respiratory control secondary to the corticospinal lesions.[11] Contralateral pharyngeal paralysis is another rare association.[15] Similarly, bladder disturbances in the form of retention or uninhibited contractions could be a form of presentation with bilateral MMI lesion.[11] In contrast to lateral medullary syndrome, the medial medullary syndrome has a higher incidence of bilateral involvement and a worse prognosis.[13]

Hemimedullary (Reinhold's) syndrome

Hemimedullary syndrome is a rare syndrome in which both medial and lateral medullary lesions occur together with few reported cases.[16–18] It is characterized by simultaneous infarction of median, paramedian lateral and dorsal areas of the medulla oblongata.[18] It can occur occasionally in associations with multiple brain stem strokes, but rarely in isolation either simultaneously or consequently.[11] Hemimedullary syndrome usually presents with respiratory disturbances.[14]

Superior cerebellar artery syndrome

Superior cerebellar artery syndrome is characterized by ipsilateral cerebellar ataxias, nausea and vomiting, slurred (pseudobulber) speech and contralateral loss of pain and temperature. Other reported features include partial deafness, tremor of the upper extremity, an ipsilateral HS and palatal myoclonus.[8]

The 'locked-in' syndrome (ventral pontine syndrome)

Plum and Posner first defined locked-in syndrome in 1966 as quadriplegia, lower cranial nerve paralysis and mutism with preservation of consciousness, vertical gaze and upper eyelid movement.[19] However, to clarify that mutism could imply unwillingness to speak, it was later redefined as quadriplegia and anarthria with preservation of consciousness.[20] This syndrome is caused by occlusion of the corticospinal and corticobulbar pathways in the pons causing quadriplegia and paralysis of all cranial nerve muscles except for those controlling eye movements.[21] The lips, tongue and soft palate are usually weakened, as a consequence preventing coordination of breathing, voluntary vocalization or swallowing.[22] Anarthria is due to bilateral facioglossopharyngo-laryngeal paralysis, which also causes dysphagia and limits the use of facial expression in communication.[23] However, because the supranuclear ocular motor pathways of the mid-brain tectum, which allows communication, are spared, patients can move their eyes and blink.[24] Many patients with locked-in syndrome (LIS) retain some other voluntary movements such as horizontal gaze, facial expression, limb, head or tongue movements. Respiration is often affected when the lateral tegmentum of the pons or medulla is involved and patients may require assistance with ventilation. In addition, there may be abnormalities of rapid eye movement (REM) and non-REM Sleep.[22] Patients may remain comatose for some days or weeks, needing artificial respiration and then gradually wake up but remain paralysed and speechless with the eyes often directed laterally and downwards.[5,6,25] Other features include vertigo, insomnia[25] and emotional lability.[5] In contrast to 'vegetative state', patients with LIS have both visual and audible signals and are able to understand speech and respond to lid movement. Usually hearing may recover before eye opening.[26] The diagnosis of LIS can be missed if voluntary vertical eye movement is not assessed in unresponsive stroke patients. Therefore, observation and examination of eye movements in unresponsive stroke patients is crucial for making the diagnosis of LIS.[22,24] However, in some cases, the diagnosis can be difficult and often, especially in cases where the patients emerge from coma into a locked-in state after a variable delay.[24] In a case series involving 44 patients, the mean time to diagnosis of LIS was reported to be 79 days after onset due to the inherent difficulty with the diagnosis.[5] Pulmonary complications such as pneumonia, pulmonary embolism and respiratory compromise compounded by reduced vital capacity are the leading cause of death as well as sepsis and extension of brain stem lesions, and sepsis.[22,24] The mortality rate from LIS has been reported to be around 60% from the largest published review of 139 cases, with most of the deaths (87%) occurring within the first 4 months.[27]

The 'top-of-the-basilar' syndrome

The 'top-of-the-basilar' syndrome (also known as rostral brain stem infarction) is most often due to an embolus leading to the thalami ischaemia bilaterally because of occlusion of perforator vessels and multiple infarcts in the territory of the basilar artery.[2] The syndrome manifests clinically as numerous combinations of abnormalities of alternating unresponsiveness, hypersomnolence, disorientation, hallucination and behavioural abnormalities as well as visual, oculomotor deficits and cortical blindness.[2,28–30]

Ondine's syndrome

Ondine's (curse) syndrome occurs from damage to the brain stem centres responsible for automatic breathing but with intact voluntary corticospinal pathways,[31] and usually result from a distal vertebral artery occlusion. It is characterized by complete failure of breathing during sleep with normal awake ventilation.[31,32] This condition could be a life-threatening condition leading to major respiration impairment, convulsions and even death, when asleep,[33] thus the need to closely monitor stroke patients with lower brain stem involvement as they could suffer from respiratory arrest during sleep.

Clinical management

The acute management of brain stem syndromes is similar to that for patients with other brain stem insults, with initial emphasis on maintaining patent airways and adequate oxygenation. Pulmonary complications could be reduced through chest physiotherapy such as deep breathing exercises, frequent positional changes, postural drainage and suctioning. This is in addition to preventing complications that could arise from immobility, swallowing difficulties and other cranial neuropathies.

Corneal ulceration, due to impaired eye closure in patients with LIS, can be treated by lateral tarsorrhaphy or botulinum therapy. Electronic devices may be used to facilitate communication.[24]

There has been a case report of significant recovery with the use of sildenafil in a patient with LIS.[34] Patients with Ondine's syndrome may require

assisted ventilation. Ondine' curse is generally treated with mechanical ventilation during sleep.[31]

Thalamic syndromes

Thalamic infarcts account for 11% of vertebrobasilar infarcts and are generally classified into anterior, paramedian, inferiolateral and posterior territory infarcts (Figure 3).[35] As the thalamus pays a role in sensation, thalamic stroke is the most common source of pure sensory stroke.[35]

The thalamic pain syndrome (Dejerine–Roussy syndrome)

Thalamic pain syndrome, also known as central post-stroke pain (CPSP), occurs after infarcts of the ventroposterolateral thalamus, subcortical, capsular, lower brain stem infarcts,[36,37] LMI (Wallenberg's syndrome),[4] and after anterior spinal artery syndrome (ASAS) referred to as 'pseudo-thalamic' pain.[37] The prevalence of CPSP has been estimated to be between 1 and 12% in all stroke patients, while ~18% of stroke patients with a somatosensory disturbance develop CPSP.[36,38,39] The onset time for symptoms to develop is variable, ranging from days to years, but symptoms usually occur several months later.[39] The infarcts are characterized by involvement of the spinothalamic system anywhere in its course and sparing of the lemniscal pathways, as evidenced by the normal somatosensory evoked potentials in patients with CPSP.[4] The pain of thalamic pain syndrome has been described as 'burning', 'shooting', 'stabbing', 'squeezing', 'lacerating', 'freezing', 'cutting sensation' or 'throbbing' and may be aggravated by several stimuli such as touch (even clothing brushing against the skin), movement, changes in temperature or stress.[36,39,40,41] Allodynia, dysaesthesia and hyperalgesia are commonly associated with most patients with CPSP and have been considered as important and perhaps essential parts of CPSP syndrome.[42,43] CPSP is common with left-sided stroke and the pain can be felt in the face, arm, leg, trunk on the stroke side, sometimes the pain may involve the whole of one side of the body.[36,40] CPSP can reduce quality of life in patients who have had stroke,[39] compromise rehabilitation,[40] interfere with sleep,[36,39] lead to self-mutilation[4] and even push patients to suicide due to the intensity and unremitting nature of the pain.[44]

Clinical management

It is important to distinguish different types of post-stroke pain from CPSP, as it may result in different treatment strategies. Despite numerous guidelines for treatment of neuropathic pain there are few guidelines for the treatment of CPSP. However, amitriptyline and lamotrigine have been recommended as first line and mexiletine, fluvoxamine and gabapentin as second-line drugs.[45,46] For short-term pain relief in intractable pain patients with CPSP, lidocaine and propofol have been recommended.[45] No significant prophylactic effect of CPSP was found with amitriptyline in patients with acute thalamic infarct.[47] Neurostimulation therapy has been used in pharmacoresistant CPSP patients.[48] Surgical ablation of the affected part of the thalamus by stereotactic thalamotomy has been shown to provide relief.[49] As with all chronic pain syndromes, psychological factors may play a major role in the intensity of the pain. Thus, psychological treatment such as training in coping strategies and behavioural therapy might be of benefit to patients with CPSP. The prognosis for central pain syndromes is poor with no spontaneous resolution of symptoms.

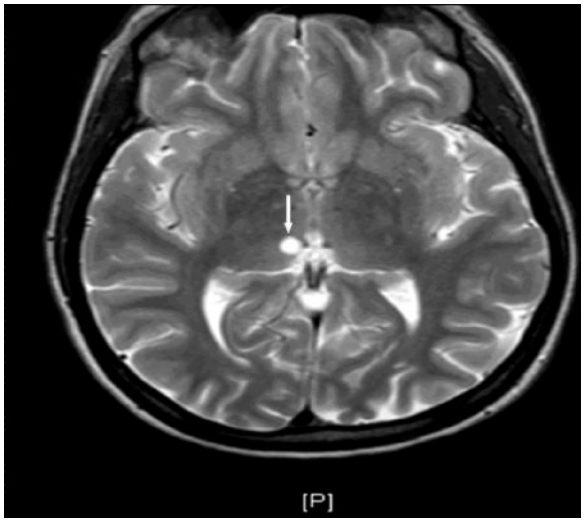

Figure 3. A MRI image showing small focal area of acute infarction involving the medial aspect of the right midbrain and extending into the medial thalamus on the right (white arrow pointed).

Horner's syndrome

HS (Bernard–Horner syndrome) results from an interruption of the sympathetic nerve supply to the eye and is characterized by pupillary miosis (constricted pupil), partial ptosis and hemifacial anhidrosis (absence of sweating).[50,51] Other clinical findings may include apparent enophthalmos, increased amplitude of accommodation, paradoxical contralateral eyelid retraction, transient decrease in intraocular pressure and changes in tear viscosity.[52] HS

may be associated with brain stem stroke, Wallenberg lateral medullary syndrome,[4] superior cerebellar artery syndrome,[8] carotid artery ischaemia and dissecting carotid aneurysm.[53] Painful HS has been associated with carotid artery dissection.[53] Thus, HS in the presence of acute onset, ipsilateral facial or neck pain or transient monoocular visual loss may indicate carotid artery dissection.[53] Although HS is commonly an incidental finding, its presence may be a manifestation of a serious and life-threatening disorder.

Clinical management

In general, the treatment for HS will depends upon the underlying aetiology or cause. There is no definitive treatment at reversing this syndrome, but is important to identify the signs and symptoms for an early diagnosis to prompt quick treatment which can prevent a devastating ocular or hemispheric stroke. In addition, the ocular complications associated with the syndrome merits ophthalological referral. Possible surgical care includes neurosurgical and vascular surgical care for aneurysm-related HS carotid artery dissection/aneurysm, respectively. Similarly, surgery may be indicated for drooping of the upper eyelid in HS.[51,52]

Alien hand syndrome

AHS is a rare complication post-stroke characterized by involuntary and uncontrollable motor behaviour, usually of an arm or hand. It is not life-threatening, however, it is an important condition because of its disabling impact on daily activities, and potentially causes self-injurious behaviours, such as the alien hand's grasping dangerous objects.[54] Patients experience involuntary, uncontrollable and purposeless movement of the affected limb, with associated denial of self-ownership of the limb without visual guidance.[54,55] The affected limb is perceived as being controlled by an external force.[54] Most commonly, AHS is associated with lesions of the left mediofrontal cortex (frontal type AHS) or corpus callosum (callosal type AHS). However, some cases have been reported involving lesions of the basal ganglia, right thalamus, right occipital or inferior parietal lobe.[54–56] Bartolo *et al.* have recently described a patient who presented posterior AHS after a left hemisphere infarction with posterior thalamus involvement.[57] Alien hand behaviours may be aggravated by fatigue, stress or anxiety and are usually elicited by nearby objects.[55–59] The prognosis of right hemispheric AHS is reported to be better compared with left hemispheric AHS.[60,61]

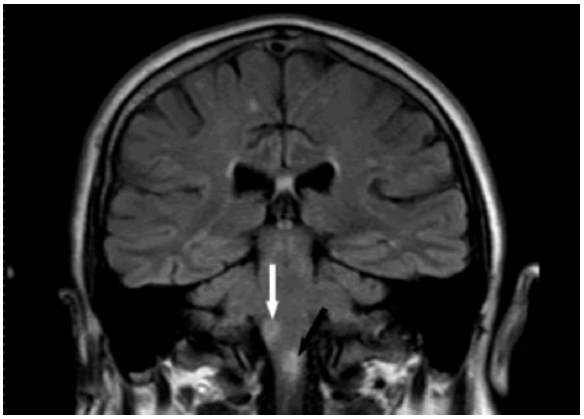

Figure 4. A MRI image of right lateral medullary (white arrow appointed) and upper spinal cord (black arrow appointed) infarcts secondary to intra and extra cranial right vertebral artery dissection.

Clinical management

Although there is no known evidenced-based pharmacological treatment for AHS, medical treatment involves the use of anti-platelet drug ticlopidine in some case reports.[54,56,62] Similarly, amantadine has been reported to be of use in treatment of utilization behaviour, especially in the frontal alien hand variant.[63] There has been limited evidence from the use of methylphenidate up to 30 mg per day in a double-blind, placebo-controlled fashion.[64] The patient's environment should be modified to reduce fatigue, nearby distractors and the risk of injury.[54,58]

Acute spinal cord syndromes

Spinal cord ischaemic strokes due to vertebral body infarctions could lead to acute spinal cord syndromes and vertebral body infarction may serve as the only confirmatory sign of spinal cord ischaemic stroke (Figure 4).[65] Spinal cord infarction is much less frequent than cerebral infarction accounting for ~1% of all strokes,[66] but they are usually associated with an unfavourable prognosis.[67] The various subsets of spinal cord syndromes include ASAS, posterior spinal artery syndrome (PSAS), Brown Sequard syndrome (BSS) and complete spinal cord transection (CSCT) with ASAS and CSCT having worse prognosis.[37,68,69]

Anterior spinal artery syndrome

ASAS is an extremely rare cause of acute ischaemic cord infarction and is most commonly associated with aortic dissection or as complication of aortic surgery, thrombosis or embolism that accounts for

the increased incidence.[37,70,71] ASAS is characterized by complete paralysis with hyperesthesia and hypoalgesia below the level of the lesion, whereas vibration and position sense are intact because of the preservation of the posterior columns (dissociated sensory impairment).[37] ASAS carries a poor prognosis for functional recovery, with only 10–20% chance of muscle recovery, and even in those with some recovery, there is poor muscle power and coordination.[69] Neurogenic pain is a problem with anterior spinal infarct, which develops in the hypoesthetic area after a few months.[37,72] The pain can be diffuse, radicular or girdle-like and is usually severe.[37] Autonomic dysfunction may be present and can manifest as orthostatic or frank hypotension and with bowel or bladder dysfunction.[38] Similarly, breathing dysfunctions and sleep breathing disorders are rare presentations associated with ASAS.[73] When the cervical spine is involved, breathing disorders may be observed.[74] ASAS carries a poor prognosis for functional recovery, with only 10–20% chance of muscle recovery, and even in those with some recovery, there is poor muscle power and coordination.[69]

Posterior spinal artery syndrome

PSAS is the least of the spinal cord syndromes as infarction of the posterior spinal artery is rare.[37,68] This is because the presence of an anastomotic network of vessels directly penetrating the spinal cord and a plexus of pial vessels fed by the paired posterior spinal arteries.[37] The clinical findings consists of loss of sensation at the level of the injury with loss of associated segmental reflexes and decreased appreciation of proprioceptive and vibratory stimuli below the level of the involvement.[67] There may be some degree of motor paralysis and sphincter dysfunction when the ischaemia extends to the posterior part of the anterolateral columns.[75]

Brown Sequard syndrome

BSS is defined as a lesion that produces ipsilateral proprioceptive and motor loss and contralateral loss of sensitivity to pain and temperature below the level of the lesion.[69] Patients with BSS usually have a favourable outcome with good neurological improvement over time.[69]

Complete spinal cord transection

Total infarction of the spinal cord segment presents with flaccid paralysis or tetraplegia, bladder and bowel dysfunction and complete loss of sensation below the lesion.[76] Autonomic dysfunction may be present and can lead to cardiovascular collapse, pulmonary oedema and bowel pseudo-obstruction with diffuse pain, as well as to dysfunction of thermoregulation and sweating.[76] CSCT generally carries a poor prognosis with risk of secondary disabling complications.[76]

Clinical management

There are no clear guidelines for the treatment of spinal cord syndromes.[77] General medical care will depend on the severity of spinal cord ischaemia. Patients with high thoracic or cervical infarction should be admitted to intensive care for close monitoring of vital signs and neurological status.[68] In addition to rehabilitative measures, thorough care should be given to bowel and bladder function as well as to skin care.

Conclusion

Stroke syndromes are of clinical importance as they could represent the clinical manifestation and consequences of stroke. It is imperative that clinicians are aware of the various stroke syndromes, particularly those with potential devastating effect which could lead to significant disability and even death. Even if they are not life-threatening they could pose a great challenge for post-stroke treatment and recovery and may delay or prevent aggressive rehabilitation. Patient with stroke syndromes should be managed on specialized stroke units with facilities for continuous monitoring of vital signs including mechanical ventilation and invasive monitoring, particularly for those at risk of respiratory compromise. Early mobilization (when clinical condition permits) will improve clinical outcome and reduce the risk complications such as aspiration pneumonia, urinary tract infections and deep venous thrombosis.

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