

# Disorders of the lower cranial nerves

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## ABSTRACT

Lesions of the lower cranial nerves (LCN) are due to numerous causes, which need to be differentiated to optimize management and outcome. This review aims at summarizing and discussing diseases affecting LCN. Review of publications dealing with disorders of the LCN in humans. Affection of multiple LCN is much more frequent than the affection of a single LCN. LCN may be affected solely or together with more proximal cranial nerves, with central nervous system disease, or with nonneurological disorders. LCN lesions have to be suspected if there are typical symptoms or signs attributable to a LCN. Causes of LCN lesions can be classified as genetic, vascular, traumatic, iatrogenic, infectious, immunologic, metabolic, nutritional, degenerative, or neoplastic. Treatment of LCN lesions depends on the underlying cause. An effective treatment is available in the majority of the cases, but a prerequisite for complete recovery is the prompt and correct diagnosis. LCN lesions need to be considered in case of disturbed speech, swallowing, coughing, deglutition, sensory functions, taste, or autonomic functions, neuralgic pain, dysphagia, head, pharyngeal, or neck pain, cardiac or gastrointestinal compromise, or weakness of the trapezius, sternocleidomastoid, or the tongue muscles. To correctly assess manifestations of LCN lesions, precise knowledge of the anatomy and physiology of the area is required.

**Key words:** Accessory, cranial nerves, glossopharyngeal, hypoglossal, infection, neoplasm, trauma, vagus, vascular

## Introduction

Lower cranial nerves (LCN) include the paired 9<sup>th</sup> (glossopharyngeal), 10<sup>th</sup> (vagal), 11<sup>th</sup> (accessory) and 12<sup>th</sup> (hypoglossal) cranial nerves.<sup>[1]</sup> Particularly the 9<sup>th</sup>, 10<sup>th</sup>, and 12<sup>th</sup> cranial nerves are involved in the execution of crucial physiological functions, such as swallowing, tasting, speech, heart rate and blood pressure control, and peristalsis. In addition to motor fibers, LCN carry sensory fibers and autonomic fibers. LCN are affected in a number of pathologic conditions. This review aims at summarizing and discussing diseases associated with LCN, its diagnosis, treatment, and outcome. Due to limitations in space, synaptic and postsynaptic neuromuscular transmission disease and disorders of the skeletal muscles supplied by LCN were excluded, and the discussion about treatment and outcome limited.

## Methods

Data for this review were identified by searches of MEDLINE, Current Contents, PubMed, and references from relevant articles using the search terms "glossopharyngeal nerve," "vagal nerve," "accessory nerve," "hypoglossal nerve," and "cranial nerves," in combination with "genetic," "hereditary," "motor neuron disease," "stroke," "vascular," "vasculitis," "trauma," "head injury," "iatrogenic," "infections," "immunologic," "immune neuropathies," "multiple sclerosis," "diabetes," "vitamin deficiency," "degeneration," "malformation," "neoplasm," and "carcinoma." Randomized (blinded or open-label) clinical trials, longitudinal studies, case series, and case reports were considered. Abstracts and reports from meetings were not included. Only articles published in English between 1966 and 2014 were considered. Appropriate papers were studied and discussed for their suitability to be incorporated in this review.

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## Anatomy and Physiology of Lower Cranial Nerves

To understand the complicated interplay between the four LCN and their anatomy and various functions,

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it is essential to realize the basics of anatomy and physiology.

#### **9<sup>th</sup> cranial (glossopharyngeal) nerve**

The ninth cranial nerve is a mixed nerve carrying motor efferents and sensory afferents. The nerve mediates five distinct functions: A branchial motor function providing voluntary control of the stylopharyngeal muscle (dilates and elevates pharynx during swallowing and speech); visceral motor functions to innervate the parotid gland via preganglionic fibers to the otic ganglion and postganglionic fibers to the parotid gland; visceral sensory functions providing visceral sensory input from the carotid sinus and carotid bodies, general somatic afferent functions providing sensory information for the skin of the external ear, the internal surface of the tympanic membrane, the upper pharynx, the soft palate, the tonsils, and the posterior third of the tongue; and a special sensory function providing taste sensation from the posterior third of the tongue.<sup>[2]</sup> Branches of the nerve include the tympanic, the pharyngeal, the lingual, the sinus caroticus, the tonsillar, and the stylopharyngeal branch. There is also a communicating branch to the vagal nerve.<sup>[2]</sup>

The branchial motor branch originates from the nucleus ambiguus in the reticular formation of the medulla, emerges from the lateral aspect of the medulla, exits the skull via the jugular foramen, and descends to the styloid process to innervate the target muscles.<sup>[3]</sup> The visceral (parasympathetic) motor branch of the nerve innervates the ipsilateral parotid gland. Preganglionic fibers originate from the inferior salivatory nucleus (receives afferents from the hypothalamus and the olfactory system) to exit the medulla between olive and inferior cerebellar peduncle. Together with other components of the nerve, parasympathetic fibers cross the two glossopharyngeal ganglia in the jugular foramen to form the tympanic nerve. The tympanic nerve ascends into the tympanic cavity to form a plexus, which provides the general sensation of the middle ear. Parasympathetic fibers leave the plexus as the lesser petrosal nerve, re-enter the middle cranial fossa to exit the skull via the foramen ovale along with the mandibular nerve and synapses in the otic ganglion. Postganglionic fibers travel with the auriculo-temporal branch of the mandibular nerve to enter the parotid gland. The visceral sensory component carries impulses from the baroreceptors of the carotid sinus and the chemoreceptors of the carotid body via the sinus nerve to join the 9<sup>th</sup> cranial nerve at the inferior glossopharyngeal ganglion. From there these projections reach the tractus solitarius to synapse in the caudal nucleus solitarius. Connections are made with the reticular formation and the hypothalamus to

mediate cardiovascular and respiratory reflex responses to changes of blood pressure or CO<sub>2</sub>/O<sub>2</sub>. The general sensory component originates from the skin of the external ear, the upper pharynx, and the posterior third of the tongue to travel via the pharyngeal branch and the tympanic nerve to the spinal trigeminal tract. Ascending neurons project to the thalamus. These sensory fibers mediate the afferent limb of the gag reflex, while the efferent impulse is carried by the branchial motor fibers of the vagal nerve. The 9<sup>th</sup> cranial nerve is also involved in the afferent side of the cough reflex.<sup>[4]</sup> Special sensory fibers carry taste sensation from the posterior third of the tongue to the inferior ganglion, and then pass the jugular foramen to ascend to the tractus solitarius and synapse with the nucleus solitarius.<sup>[1,2]</sup> Hiccups are due to a brief contraction of the inspiratory muscles plus a glottis adduction of the stylopharyngeal muscles.<sup>[4]</sup>

#### **10<sup>th</sup> cranial (vagal) nerve**

The vagal nerve is a mixed nerve carrying motor efferents and sensory afferents. The nerve conducts five distinct qualities, which are carried along general visceral efferent fibers (parasympathetic innervation of pharyngeal, laryngeal, bronchial, and gastrointestinal mucosa), general visceral afferent fibers (sensory information from the thoracic and abdominal viscera, the aortic body, aortic arch), special visceral afferent fibers (carry taste of the epiglottal region), general somatic afferent fibers (carry sensation from the external auditory meatus, outer tympanic membrane, back of the ear, part of meninges, pharynx), and along special visceral efferent fibers, which innervate skeletal muscles of the pharynx and larynx. Skeletal muscles innervated by the vagal nerve include the cricothyroid, levator veli palatini, salpingopharyngeus, palatoglossal, palatopharyngeus pharyngeal constrictor, and the laryngeal muscles (except cricothyroid). Innervation of these muscles is involved during speech or opening of the larynx during breathing. Efferent parasympathetic fibers control heart rate, peristalsis, and sweating. Stimulation of the efferent parasympathetic fibers lowers heart rate or blood pressure. 80–90% of the vagal fibers are afferent, only 10–20% are efferent fibers.<sup>[5]</sup>

Vagal nerve fibers originate from or converge to four medullar nuclei, which include the dorsal nucleus of the vagal nerve (responsible for parasympathetic output to viscera), nucleus ambiguus (origin of branchial efferent motor fibers and of preganglionic parasympathetic to the heart), solitary nucleus (receives taste information and afferents from viscera), and the spinal trigeminal nucleus (receives sensory input from the outer ear, dura, posterior cranial fossa, and mucosa). The vagal nerve leaves the medulla between the pyramid and

inferior cerebellar peduncle, crosses the jugular foramen, and passes into the carotid sheath down to the neck, chest and abdomen. It splits into the auricular, pharyngeal (innervates palate and pharynx), superior laryngeal (innervates constrictor and cricothyroid), and recurrent laryngeal nerves, the anterior and posterior vagal trunk, and provides superior and inferior cervical cardiac branches and thoracic cardiac branches to the heart and the esophageal and pulmonary plexus (vagus nerve branches). The superior laryngeal nerve divides into the internal and external laryngeal nerves. The external laryngeal branch supplies the inferior constrictors. The vocal cord is also innervated by the superior laryngeal nerve and the external and internal rami of the inferior laryngeal nerve.<sup>[5]</sup>

The right vagus crosses anteriorly of the subclavian artery, runs posterior of the superior vena cava, descends posterior to the right main bronchus to form the cardiac, pulmonary and esophageal plexus. Distally, the right vagal nerve passes over into the posterior vagal trunk, which crosses the diaphragm through the esophageal hiatus. The right recurrent laryngeal nerve deviates from the right vagal nerve and hooks around the right subclavian artery and ascends to the neck. From the left vagal nerve deviates the left recurrent laryngeal nerve, which hooks around the aortic arch to ascend back to the neck. After having contributed to the esophageal, cardiac, and pulmonary plexus, the left vagal nerve forms the anterior vagal trunk, which enters the abdomen via the esophageal hiatus. The right vagal nerve innervates the sinusnode, whereas the left vagal nerve innervates the atrioventricular-node. One of the most important reflexes mediated by the vagal nerve is the gag reflex. Also, the cough reflex is partially mediated via general visceral afferent parasympathetic fibers.<sup>[4]</sup> The cough reflex is initiated by cough receptors. Vagal sensory fibers together with trigeminal and glossopharyngeal fibers carry information from the cough receptors to the cerebral cough center (nucleus tractus solitarius). From there efferent fibers of the phrenic nerve, spinal nerves, and laryngeus recurrens nerve project to the diaphragm, abdominal, intercostal, and laryngeal muscles.<sup>[4]</sup> Parasympathetic compensation of sympathetic overstimulation in response to pain, carotid sinus massage, the Valsalva manoeuvre, or gastrointestinal illness, may cause a vasovagal syncope.

### **11<sup>th</sup> cranial (accessory) nerve**

The accessory nerve is anatomically split into a spinal and a cranial portion. Fibers of the spinal portion originate from the upper spinal cord (spinal accessory nucleus located in the postero-lateral aspect of the anterior horn). The cranial portion originates from the nucleus

ambiguus, which is continuous with the lateral horn of the cervical segments. The spinal roots form the spinal accessory component, which enters the skull through the foramen magnum. The cranial part descends from the medulla oblongata to connect with the spinal accessory component. The nerve then courses along the skull to the jugular foramen through which it exits together with the 9<sup>th</sup> and 10<sup>th</sup> cranial nerve. The 10<sup>th</sup> cranial nerve lies most medial in the foramen. The 9<sup>th</sup> cranial nerve exits together with the inferior petrosal sinus through the anterior compartment of the foramen. Vagus and accessory nerves exit via the middle compartment of the foramen. The sigmoid sinus exits via the posterior compartment of the foramen. Shortly before crossing the foramen, the cranial component branches off the accessory nerve to join the vagal nerve (the 11<sup>th</sup> cranial nerve is a transitional nerve). In the neck, the nerve crosses the internal jugular vein anteriorly (80% of cases) or posteriorly (20% of cases) to enter the target muscles shortly afterwards. Due to this unique anatomic course, the accessory nerve is the only cranial nerve which enters and exits the skull and is thus sometimes not regarded as a true cranial nerve.<sup>[6]</sup> Physiologically, the accessory nerve is a mixed or transitional nerve conducting general somatic qualities (innervation of the sternocleidomastoid and trapezius muscles) originating from the cranial portion and a distinct modality originating from the spinal portion.<sup>[7]</sup> Anastomoses between the spinal component of the accessory nerve and the dorsal roots of the cervical nerves exist below level C1.<sup>[8,9]</sup>

### **12<sup>th</sup> cranial (hypoglossal) nerve**

The hypoglossal nerve innervates the muscles of the tongue and is involved in tongue movements during speech, food manipulation, and swallowing.<sup>[1]</sup> The nerve is pure motor.<sup>[10]</sup> The nerve directs not only voluntary activities of the tongue, but also involuntary functions, such as clearing the mouth of saliva by swallowing. The nerve is also involved in adjusting the tongue to new movements to create desired sounds when learning a new language.<sup>[10]</sup> The nerve originates from the hypoglossal nucleus.<sup>[1]</sup> It leaves the medulla oblongata between the olive and the pyramid to pass through the hypoglossal canal. Immediately after leaving the skull it gives off a meningeal branch and unites with a branch of the anterior root C1, which innervates the geniothyroid and thyrohyoid muscles. The nerve then winds behind the 10<sup>th</sup> cranial nerve and passes between internal carotid artery and internal jugular vein to the posterior belly of the digastric muscle to continue to the submandibular region lateral to the hypoglossal muscle and inferior of the lingual nerve to finally reach the tongue. All muscles of the tongue are supplied except for the palatoglossal muscle, which is innervated by the 9<sup>th</sup> cranial nerve.

There are anastomoses between the hypoglossal nerve and other caudal cranial nerves and the cervical plexus.

## Classification of Lower Cranial Nerve Lesions

Lesions of the LCN may be classified according to various aspects. According to the number of nerves affected they may be categorized as either single nerve lesions or as multiple nerve lesions. According to the impaired function, they may be qualified as motor (muscle or visceral) or sensory (visceral, general somatic, special). LCN lesions may be also classified whether the nerves are involved individually or whether other cranial nerves, the brain, the spinal cord or the spinal nerves are additionally affected. Another categorization is based on the cause of the lesion, which may be genetic, vascular, traumatic, iatrogenic, infectious, immunologic, metabolic, nutritional, degenerative, or neoplastic.

## Symptoms of Lower Cranial Nerve Lesions

Symptoms arising from lesions of LCN correlate with the various functions of the four nerves. Thus, symptoms of LCN lesions include dysphagia, dysarthria, hoarse voice, choking during ingestion of fluids, taste disturbances (posterior third of tongue), sensory disturbances (posterior third of the tongue, soft palate, throat, external auditory meatus), palpitations, tachycardia, bradycardia, tachypnea, bradypnea, dyspnea, arterial hypotension, arterial hypertension, fainting, syncope, dizziness, pain in the posterior oral cavity, the face, the neck, the head, obstipation, or diarrhoea. Affection of the 11<sup>th</sup> cranial nerve may lead to weakness of head rotation, head anteflexion, or shoulder elevation, to scapular winging or to shoulder pain. Affection of the 12<sup>th</sup> cranial nerve may lead to slurring of speech and the feeling of a thick, heavy, or clumsy tongue. If additional neural or nonneural structures are involved, symptomatology may be even broader.

Affection of the LCN may go along with pain, such as neuralgias, dysesthesias, paresthesias, muscle pain, or pain with swallowing. Neuralgias are characterized by paroxysmal painful attacks of electric shock-like sensation, occurring spontaneously or evoked by innocuous stimuli in specific trigger areas.<sup>[11]</sup> Pain is usually experienced in the distribution of one or several nerves. Neuralgias of the LCN are the rare glossopharyngeal neuralgia and the even more rare neuralgia of the laryngeal nerve. Glossopharyngeal neuralgia is characterized by excruciating pain attacks

of the short duration of the ear, pharynx, neck, tonsil, or base of the tongue. Pain may be triggered by contact of the tongue with the teeth<sup>[12]</sup> or with the back of the tongue.<sup>[13]</sup> Glossopharyngeal neuralgia may be associated with syncope (fainting) in 10% of the cases due to reflex bradycardia (efferent limb of reflex via vagal nerve) or occasionally induced by swallowing. Glossopharyngeal neuralgia is most frequently primary (compression of the nerve by adjacent vessel loop)<sup>[14]</sup> or secondary to an intrinsic brain lesion such as in multiple sclerosis<sup>[13,15]</sup> or in the Eagle-syndrome.<sup>[16]</sup> Neuralgia of the laryngeal nerve is a rare condition and may be due to a deviated hyoid bone,<sup>[17]</sup> due to previous acute laryngitis,<sup>[18]</sup> a pharyngeal diverticulum,<sup>[19]</sup> or idiopathic.<sup>[20]</sup> Patients present with paroxysmal, lancing pain located to the area of the thyrohyoid membrane, which can be induced or worsened by swallowing.<sup>[17]</sup>

## Investigations to Diagnose Lower Cranial Nerve Lesions

### Clinical exam (signs of lower cranial nerve lesions) *Neurological*

Examination of the 9<sup>th</sup> cranial nerve includes asking the patient to swallow or cough. In addition, taste and a general sensation of the posterior third of the tongue and the throat can be evaluated. The bitter taste (posterior third of the tongue) is used to test for this nerve. There may also be hypoesthesia of the soft palate or reduced palatal or pharyngeal reflexes. Physical exam of the 10<sup>th</sup> cranial nerve includes eliciting the gag reflex, to look if the uvula is deviated from the side of the lesion, if there is failure of palate elevation upon phonation, and evaluation of speech impairment. In case of bilateral vagal nerve lesions, heart rate and breath rate may be increased. The somatic sensory function can be assessed by testing the sensibility of the external auditory meatus. The 11<sup>th</sup> cranial nerve is tested by assessing strength, mass, and spontaneous activity of the trapezius and sternocleidomastoid muscle. The patient is asked to shrug the shoulders with and without resistance. The sternocleidomastoid is tested by asking the patient to turn the head to the left or right or to anteflect the head against resistance. Inspection of the muscles may reveal wasting or fasciculations. The 12<sup>th</sup> cranial nerve is tested by asking the patient to stick the tongue out straight. If there is a lesion of the nerve, the tongue will deviate toward the affected side or there may be wasting and fasciculations if the lesion is not acute. The strength of the tongue can be tested by pressing it toward the cheek against the finger of the examiner outside. Weakness of the tongue will also manifest as slurred speech. Practical bedside testing is used to identify lesions in the anterior part of the oral

cavity ("B"), the oral cavity in particular the tongue ("T") and the posterior part of the oral cavity ("G").

Lower cranial nerve lesions may occur in particular distributions giving rise to various syndromes, such as Horner-syndrome, Tapia-syndrome, Collet-Sicard-syndrome, Vernet-syndrome, Jugular-foramen-syndrome, Garcin-syndrome, Schmidt-syndrome, or Villaret's-syndrome [Table 1]. These syndromes are usually case-based descriptions, which are useful, to summarize, the findings, but usually lack accuracy.<sup>[21-24]</sup> Vernet-syndrome manifests with dysphonia, hoarseness, drop of soft palate, deviation of the uvula, dysphagia, hypoesthesia of the posterior third of the tongue, reduced parotid gland secretion, loss of gag reflex, and weakness of the sternocleidomastoid and trapezius muscles. Jugular-foramen-syndrome is characterized by

acute onset dysphagia, dysphonia, and accompanied or preceded by cranial, cervical, or pharyngeal pain.<sup>[25]</sup> The most frequent cause of jugular-foramen-syndrome is herpes zoster oticus with herpetic eruptions of the skin or the mucosa. Magnetic resonance imaging (MRI) may reveal contrast enhancement around the jugular foramen, suggesting inflammation of the glossopharyngeal or vagal nerve ganglia.<sup>[25]</sup> Imaging may also show erosions of bones or metastasis. The diagnosis is confirmed by demonstration of varicella-zoster virus (VZV)-DNA or VZV antibodies in the cerebro-spinal fluid (CSF).<sup>[25]</sup>

#### *Oto-rhino-laryngological*

Clinical exam by the oto-rhino-laryngologist may be helpful to detect oto-rhino-laryngological causes of LCN lesions. The oto-rhino-laryngologist may assess morphology and function of the oral cavity and the larynx.

**Table 1: Syndromes of lower cranial nerve lesions**

Syndrome	Definition	Causes
Tapia-syndrome	Hypoglossal nerve palsy and deficit of the laryngeal branch of the vagal nerve resulting in unilateral tongue palsy and unilateral vocal cord palsy	Anterior or posterior cervical spine surgery, airway manipulation, cervical laminoplasty, trauma during bullfights, or inflammatory pseudotumor of the neck
Collet-Sicard-syndrome	Palsy of the 9 <sup>th</sup> , 10 <sup>th</sup> , 11 <sup>th</sup> , and 12 <sup>th</sup> cranial nerve	Glomus tumor jugulotympanicum, base of skull metastasis, neck fibrosarcoma, multiple myeloma, hypoglossal Schwannoma, jugular foramen neurinoma, jugular foramen metastatic melanoma, hemangiopericytoma, carotid or vertebral artery dissection, panarteritis nodosa, closed head trauma, necrotising otitis externa, occipital condyle fracture, traumatic atlas fracture, skull-based osteomyelitis, sinus thrombosis, carotid fibromuscular dysplasia, pseudoaneurysm of maxillary artery, cardiac surgery, Jefferson fracture
Vernet-syndrome	Palsy of the 9 <sup>th</sup> , 10 <sup>th</sup> and 11 <sup>th</sup> cranial nerve	Malignancy, aneurysm, zoster meningitis, osteolytic metastasis of the petrous pyramid, or base of the skull fracture
Jugular-foramen-syndrome	Acute onset dysphagia, dysphonia, accompanied or preceded by cranial, cervical, or pharyngeal pain, due to affection of the 9 <sup>th</sup> , 10 <sup>th</sup> , and 11 <sup>th</sup> cranial nerve	Herpes zoster oticus
Schmidt-syndrome	Ipsilateral palsy of the 9 <sup>th</sup> , 10 <sup>th</sup> , 11 <sup>th</sup> , and 12 <sup>th</sup> cranial nerves with contralateral hemiparesis	Stroke, multiple sclerosis
Villaret's-syndrome	Unilateral palsy of 9 <sup>th</sup> , 10 <sup>th</sup> , 11 <sup>th</sup> , and 12 <sup>th</sup> nerve and ipsilateral Horner's sign	Carotid artery dissection, local metastasis
Wallenberg-syndrome	Lateral medullary syndrome (dysphagia, slurred speech, vertigo, double vision, palatal myoclonus, ipsilateral ataxia, hemifacial hypoesthesia, nystagmus, Horner-syndrome, vocal cord paresis+contralateral impairment of pain, temperature, and lemniscal sensation, lateropulsion to side of lesion)	Stroke
Avellis-syndrome	Ipsilateral paralysis of soft palate and vocal cord+contralateral loss pain and temperature sensation	Stroke
Jackson-syndrome	Ipsilateral hypoglossal palsy and contralateral hemiparesis	Stroke
Opalski-syndrome	Ipsilateral hemiparesis, lemniscal sensation loss, hypoglossus nerve palsy	Stroke
Cestan-Chenais syndrome	Contralateral hemiplegia, hemihypoesthesia, paralysis of the larynx and soft palate, and Horner-syndrome	Stroke, multiple sclerosis, tumor
Dejerine syndrome	Ipsilateral hypoglossal palsy, contralateral hemiplegia and loss of proprioception	Occlusion of anterior spinal artery
Garcin-syndrome	Unilateral palsy of cranial nerves 5-12 or all cranial nerves	Base of the skull inflammation, neoplasm, base of the skull metastasis

## Instrumental investigations

Most helpful in the work-up of LCN lesions is the application of static or dynamic imaging methods, such as X-ray (base of the skull, styloid process, deglutition), video-cinematography (dynamic), computed tomography, MRI, angiography (static), or ultrasound [Figure 1]. A useful tool to investigate lesions of the tongue is an ultrasound. Muscle MRI may show atrophy as an indirect sign of a lesion of the supplying nerve by bone erosion or metastases. Oto-rhino-laryngological techniques, such as fiber-optic endoscopy can be helpful to detect causes of LCN lesions. Electrophysiological techniques, such as nerve conduction studies,<sup>[26]</sup> electromyography (larynx muscles (cricothyroid, thyroarytenoid muscles), sternocleidomastoid, trapezius muscles), electrical nerve root stimulation, or trans-cranial magnetic stimulation (accessory, hypoglossal nerve) are helpful for localizing the level of a nerve lesion and to determine whether it is axonal or demyelinating in nature. Intra-operative electrophysiological monitoring of LCN functions can be helpful to avoid iatrogenic damage of the LCN during surgery. Blood chemistry can be useful to assess inflammatory markers, antibodies against viruses, vasculitis parameters, vitamin levels, tumor-markers, etc. CSF investigations may be helpful to detect infections (meningitis), neoplastic (carcinosis), or immunologic disease (radiculitis) as a cause of LCN lesions. To assess parasympathetic functions autonomic testing by means of the Valsalva maneuver, heart rate variability, tilt test, gastric emptying tests, the sympathetic

skin response, the quantitative sudomotor axon reflex test, or the thermoregulatory sweat test is available.

## Disorders of Lower Cranial Nerves

Isolated affection of a single cranial nerve is rare [Table 2]. In the majority of the cases, multiple LCN are simultaneously affected. Causes of LCN lesions can be genetic, vascular, traumatic, iatrogenic, infections, immunologic, metabolic, nutritional, degenerative, or neoplastic.

### Genetic causes

The most frequent genetic disorders associated with LCN involvement are the motor neuron disorders (MNDs). They include amyotrophic lateral sclerosis (ALS), spinal muscular atrophy, bulbospinal muscular atrophy (BSMA), and unclassified MNDs (Sandhoff disease, triple-A-syndrome, Brown-Vialetto-Van Lare-syndrome). Among these, LCN are affected in ALS, BSMA, triple-A-syndrome, and Brown-Vialetto-Van Lare-syndrome. More rarely, cranial nerves are involved in hereditary neuropathy.

### Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is the most common among the MNDs.<sup>[27-29]</sup> ALS is sporadic in the majority of the cases but hereditary in an increasing number of patients with sporadic ALS.<sup>[29]</sup> More details are thus presented in the chapter about degenerative causes.

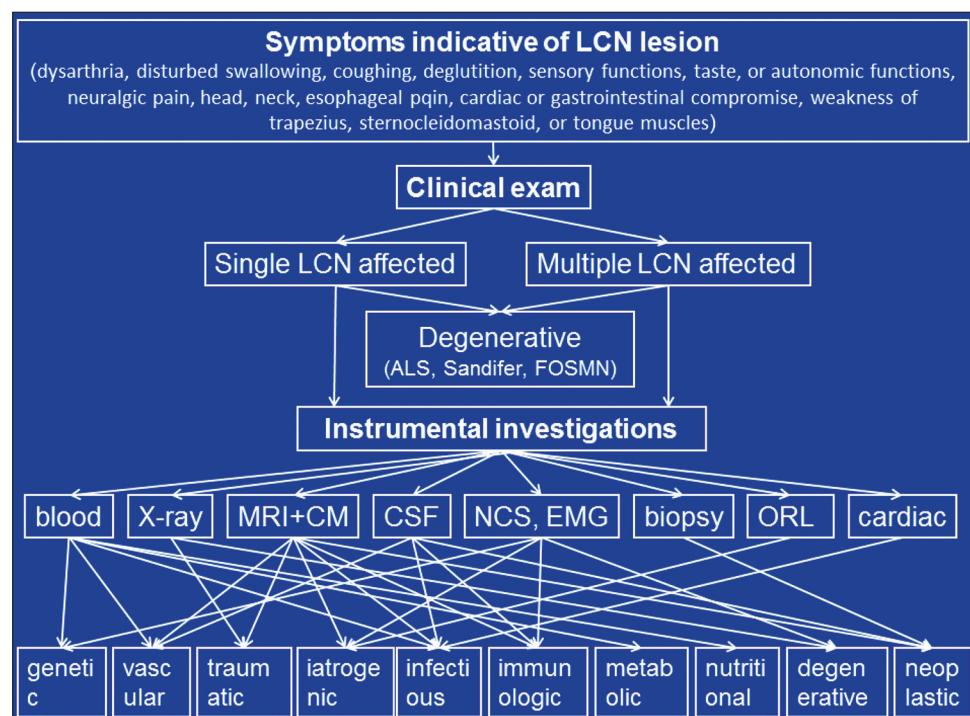


Figure 1: Work-up in case of symptoms indicating lower cranial nerves lesion

**Table 2: Lower cranial nerve lesions**

Category of disease	Disorders affecting lower cranial nerves	SLCNA	Cranial nerves involved
Genetic	Familial ALS	No	Multiple
	BSMA	No	Multiple
	Brown-Vialetto-Van Laere syndrome	No	Multiple
	Triple-A-syndrome	No	Multiple
Vascular	Stroke	Rarely	Multiple
	Aneurysm	No	Multiple (IX, X, XI, XII)
	Dissection	No	Multiple
Traumatic	Vasculitis	No	Multiple
	Skull base fracture	Yes	Multiple
	Atlas fracture	No	Multiple
	Fracture of the styloid process	Yes	IX
Iatrogenic	Traumatic brain injury	No	Multiple
	Surgical recanalization of carotid artery	Yes	IX, X, XII
	Laryngeal mask	Yes	IX
Infectious	Thyroid surgery (recurrents nerve)	Yes	X
	Diphtheria	No	Multiple
	Poliomyelitis	No	Multiple
	Tetanus	No	Multiple
	Sarcoidosis	No	Multiple
	Borreliosis	No	Multiple
	Ramsey Hunt syndrome	No	Multiple
	Tuberculous meningitis	Yes	Multiple
Immunologic	Glossopharyngeal neuralgia (multiple sclerosis)	Yes	IX
	Pharyngo-cervical-brachial variant of GBS	No	Multiple
	Multiple cranial nerve neuropathy (GBS)	No	Multiple
Metabolic	Diabetes	Yes	X
Nutritional	Vitamin B12-deficiency	Yes	X
Degenerative	Eagle-syndrome (elongated styloid process)	Yes	IX
	Sporadic ALS	No	Multiple
	FOSMN	No	Multiple
	Sandifer's syndrome	No	Multiple
Neoplastic	Intra and extracranial neoplasms	Yes	Multiple

SLCNA: Single lower cranial nerve affected, FOSMN: Facial-onset sensory and motor neuronopathy, ALS: Amyotrophic lateral sclerosis, BSMA: Bulbo-spinal muscular atrophy, GBS: Guillain-Barre-syndrome

### Bulbospinal muscular atrophy

Bulbospinal muscular atrophy (Kennedy disease) is a rare X-linked MND with onset in adolescence or early adulthood. BSMA is caused by a CAG-triplet repeat expansion in the androgen-receptor gene.<sup>[30]</sup> Clinically, BSMA is characterized by slowly progressive weakness and wasting of all muscles with a predominance of the limb muscles, impairment of speech and swallowing, and muscle cramps. In addition to motor neuropathy, there is also sensory neuropathy, and postural and intention tremor. Nonneurological manifestations include gynecomastia, loss of masculinisation, and erectile dysfunction. Motor manifestations may be asymmetric. Lifespan is usually normal. Leuprorelin and symptomatic therapy is available.<sup>[30]</sup>

### Brown-Vialetto-Van Lare-syndrome

Brown-Vialetto-Van Lare-syndrome is a rare, hereditary disorder characterized by bulbar palsy, respiratory

compromise, and sensorineural hearing loss.<sup>[31]</sup> Brown-Vialetto-Van Lare-syndrome is due to mutations in the SLC52A1 gene encoding the human riboflavin transporter-1.<sup>[31]</sup> Substitution of riboflavin has a beneficial effect and prolongs life expectancy.<sup>[31]</sup>

### Triple-A-syndrome

Triple-A-syndrome is a rare condition mimicking MND. It follows an autosomal recessive trait of inheritance and is due to mutations in the ALADIN gene, which encodes a nuclear pore complex component.<sup>[32]</sup> Clinically, triple-A-syndrome is characterized by esophageal achalasia, alacrimia, adrenal insufficiency, and progressive bulbar spinal muscular atrophy with the involvement of upper and lower motor neurons.<sup>[32]</sup>

### Hereditary neuropathies

Rarely, mononeuropathy of the accessory nerve may be a manifestation of hereditary neuropathy with liability to pressure palsies (HNPP).<sup>[33]</sup> Another LCN involved

**Table 3: Differentials of LCN lesions (disorders which indirectly affect LCN or are associated with LCN lesions)**

Neuropathies
HMSN
CIAP
Sensory ataxic neuropathy with bulbar onset (GD1a, GT1b, GM3)
Transmission disorders
Myasthenia
Lambert-Eaton myasthenic syndrome
Myopathies
Faciocapulohumeral muscular dystrophy
LGMD
Myotonic dystrophy type I
Myotonic dystrophy type II
Oculopharyngeal muscular dystrophy
Oculopharyngodistal muscular dystrophy
Distal myopathy (VCPDM, matrin 3 mutation)
Mitochondrial disorders (POLG1 mutations)
CNS disorders
Supranuclear palsy
Dystonia
Others
Alcohol intoxication
Pharmacological sedation
Amyloidosis of the tongue

HMSN: Hereditary motor and sensory neuropathy, CIAP: Chronic idiopathic axonal polyneuropathy, LGMD: Limb girdle muscular dystrophy, VCPDM: Vocal cord and pharyngeal weakness with distal myopathy, POLG: Polymerase gamma, CNS: Central nervous system, LCN: Lower cranial nerves

in HNPP is the hypoglossal nerve.<sup>[34]</sup> The affection of the hypoglossal nerve has been also reported in other types of hereditary neuropathy.<sup>[35]</sup> Dysarthria may be a feature of hereditary motor and sensory neuropathy Lom.<sup>[36]</sup> In X-linked Charcot-Marie-Tooth disease due to mutations in the GJB1 gene, neuropathy may be associated with vocal cord paralysis.<sup>[37]</sup> Vocal cord paralysis has been also reported in congenital hypomyelination.<sup>[38]</sup>

## Vascular

### Stroke

Ischemic stroke is a frequent cause of LCN affection, particularly if nuclei or fascicles of any of the four LCN are affected (nuclear or fascicular cranial nerve lesions). Additionally, LCN may be secondarily affected in case of supranuclear vascular lesions [Table 3]. According to the location of the ischemic lesion in the brain stem, a dorsal, lateral, paramedian, or median location of the vascular lesion is delineated. In addition, short, long, or circumferential arteries may be involved. Various syndromes are differentiated of which the Wallenberg-syndrome (lateral medullary syndrome) is the most common [Table 1]. More rare ischemic medullary stroke syndromes include the Avellis-syndrome, the Jackson-syndrome, and the Opalski-syndrome [Table 1].

### Aneurysm

Internal carotid artery aneurysm directly underneath the base of the skull may affect the 9<sup>th</sup>, 10<sup>th</sup>, 11<sup>th</sup>, or 12<sup>th</sup> cranial nerves.<sup>[39]</sup> These nerve lesions may result in impaired swallowing or dysarthria but also tongue weakness.<sup>[39]</sup> Treatment of such aneurysms by parent vessel occlusion may result in shrinkage of the aneurysm and consecutive improvement of the neurological deficits.<sup>[39]</sup> Additionally, aneurysms of the intracranial vertebral artery may be associated with LCN neuropathy.<sup>[40]</sup> Aneurysms of the posterior inferior cerebellar artery (PICA) may affect the glossopharyngeal, the vagal, or the accessory nerve.<sup>[41]</sup>

### Artery dissection

Quite frequently internal carotid artery dissection can lead to compression of the hypoglossal nerve.<sup>[11,42]</sup> Also, dissection of the vertebral artery may go along with hypoglossal palsy.<sup>[43]</sup> Dissection of the internal carotid artery may even lead to Villaret's-syndrome<sup>[44]</sup> or Collet-Sicard-syndrome. Vertebral artery dissection may cause Tapia-syndrome [Table 1].<sup>[45]</sup> Dissection of the internal carotid artery may result in dysphonia and homolateral shoulder paralysis due to palsy of the vagal and accessory nerves.<sup>[46]</sup> Horner-syndrome may be another manifestation of a carotid artery dissection, which usually is painful.

### Vasculitis

Rarely, Takayasu vasculitis may lead to injury of the LCN, particularly the glossopharyngeal or the hypoglossal nerves.<sup>[47]</sup> There is one report about a patient who developed glossopharyngeal neuralgia following an arteritis temporalis.<sup>[48]</sup> Another patient developed Vernet-syndrome [Table 1] from giant cell arteritis.<sup>[49]</sup> Collet-Sicard-syndrome [Table 1] has been reported in a single patient with panarteritis nodosa.<sup>[50]</sup>

### Ischemia of lower cranial nerves

Since LCN receive their arterial supply from a network of tributaries originating from the internal carotid, external carotid and the vertebro-basilar arteries, it is conceivable that impaired blood supply via these networks results in ischemia of the supplied nerves.<sup>[51]</sup> Small vessel disease, as well as macroangiopathy, may affect the vasa nervorum of LCN and may thus lead to ischemia causing LCN dysfunction.<sup>[51]</sup> The vascular supply of LCN is also of relevance for the base of the skull surgery<sup>[51]</sup> and an issue in interventions by artery embolization in tumor therapy.

### Rare vascular causes

A rare vascular cause of LCN compromise is brainstem cavernoma.<sup>[52]</sup> Lesion of the LCN may persist despite surgery.<sup>[53]</sup> A further rarity of a vascular cause is transient

dysarthria due to compression of the hypoglossal nerve by a calcified persistent hypoglossal artery.<sup>[54]</sup>

## Trauma

### *Base of the skull fracture*

The base of the skull fractures frequently affect the LCN, particularly if the occipital condyles are involved.<sup>[55]</sup> The outcome of the base of the skull fractures is poor particularly if LCN are affected.<sup>[56]</sup> Isolated palsies of the LCN may occur in case of occipital condyle fractures.<sup>[57,58]</sup> Ipsilateral<sup>[59]</sup> or contralateral<sup>[60]</sup> hypoglossal nerve palsy is the most frequent isolated LCN injury from condyle fractures. Early full recovery of these lesions has been reported,<sup>[57]</sup> but in other cases, palsy persisted for months. Traumatic LCN lesions may not only manifest immediately after the trauma, but with a delay of several days.<sup>[61]</sup> Prognosis of traumatic LCN lesions is poor if the carotid artery is additionally damaged.<sup>[62]</sup>

### *Atlas fractures*

Atlas burst fractures rarely cause neurological deficits because of an enlarged opening of the spinal canal at this level and a tendency of the lateral masses to move centrifugally away from the cord posttraumatically.<sup>[63]</sup> In case of atlas fracture and congenital basilar invagination, however, LCN may be also damaged.<sup>[63]</sup> Though cranial nerve lesions from atlas fractures are rare, they occasionally occur and affect the 9<sup>th</sup> through 12<sup>th</sup> cranial nerve.<sup>[64]</sup> The most frequent clinical manifestation of cranial nerve involvement is dysphagia, which resolves upon Halo-fixation.<sup>[65]</sup>

### *Traumatic brain injury*

Traumatic brain injury (TBI) is a leading cause of death or disability, particularly in the younger population.<sup>[66]</sup> LCN lesions may be a complication of TBI.<sup>[67]</sup> Decompression of injured cranial nerves improves the outcome of TBIs.<sup>[67]</sup> Injury of the vagal nerve may increase vagal tone, which consecutively may diminish the anti-inflammatory capacity of patients with TBI. In the acute phase of TBI patients are thus more vulnerable to infectious disease due to decreased immune response.<sup>[66]</sup>

### *Fracture of the styloid process*

Fracture of the styloid process may lead to compromise of the 9<sup>th</sup> cranial nerve.<sup>[68]</sup> The glossopharyngeal nerve is compromised because it crosses the gap between the process and the first cervical vertebra.<sup>[68]</sup> Clinical manifestations of a styloid fracture include neck pain or painful dysphagia.<sup>[68]</sup> Not only bone fractures, but also traumatic soft tissue lesions may cause LCN dysfunction.

## Iatrogenic

### *Carotid surgery*

Carotid surgery may go along with the iatrogenic

injury of a single or multiple LCN.<sup>[69]</sup> Local pressure may lead to impairment of various functions of the 9<sup>th</sup> or 12<sup>th</sup> cranial nerves. Particularly during the open restoration of the internal carotid artery, LCN may be iatrogenically injured.<sup>[69]</sup> In a retrospective study of 543 patients undergoing carotid surgery the glossopharyngeal nerve was damaged in 2 cases (0.4%), the vagal nerve in 9 cases (1.8%), and the hypoglossal nerve in 7 cases (1.4%).<sup>[69]</sup> Most of these lesions recovered spontaneously and completely.<sup>[69]</sup> In a retrospective study of 752 patients undergoing reconstructive surgery of the supra-aortic arteries damage of the glossopharyngeal nerve occurred in 16 cases with complete recovery during a period of 1–6 months.<sup>[70]</sup>

### *Neck dissection*

Neck dissection refers to a surgical procedure in which the fibro-fatty contents of the neck including cervical lymph nodes are removed for the treatment of cervical lymphatic metastases. It is also applied to malignancies of the skin (head, neck), the thyroid, or the salivary glands. Complications of the procedure affecting LCN include damage of the hypoglossal or accessory nerve. To avoid damage of the accessory nerve from neck dissection, monitoring of accessory function during surgery is increasingly performed.<sup>[71]</sup>

### *Rare iatrogenic causes*

Rare iatrogenic causes of LCN lesions include unilateral taste disturbance due to local pressure of a classical laryngeal mask onto the nerve,<sup>[72]</sup> glossopharyngeal or hypoglossal nerve palsy after tonsillectomy, or vagal nerve palsy after obesity treatment.<sup>[73]</sup> During bariatric surgery the vagal may be accidentally compromised without severe consequences.<sup>[74]</sup> Thyroid surgery may be complicated by injury of the accessory and recurrent nerve.<sup>[75]</sup> Rhinoplasty may be complicated by Tapia-syndrome.<sup>[76]</sup>

## Infectious

### *Varicella-zoster virus*

Varicella-zoster virus infection involving the LCN may manifest as Ramsey-Hunt-syndrome, Garcin-syndrome, or Jugular-foramen-syndrome. Ramsey-Hunt-syndrome is caused by infection with the virus of the geniculate ganglion of the facial nerve.<sup>[77]</sup> Clinically, it is characterized by 7<sup>th</sup> cranial nerve palsy, otic pain, and herpetic vesicles around the auricle and external auditory canal.<sup>[77,78]</sup> Occasionally, LCN may be additionally involved, particularly the vagal nerve which may manifest with transient dysphagia.<sup>[77,78]</sup> Jugular-foramen-syndrome is characterized by acute onset dysphagia, dysphonia, and accompanied or preceded by cranial, cervical, or pharyngeal pain.<sup>[13]</sup> The most frequent cause of

Jugular-foramen-syndrome is herpes zoster oticus with herpetic eruptions of the skin or the mucosa. MRI may reveal contrast enhancement around the jugular foramen, suggesting inflammation of the glossopharyngeal or vagal nerve ganglia.<sup>[13]</sup> The diagnosis is confirmed by demonstration of VZV-DNA or VZV-antibodies in the CSF [Figure 1].<sup>[13]</sup> If there is unilateral herpes zoster infection of the larynx, ipsilateral LCN may be affected.<sup>[79]</sup> In rare cases VZV-infection may present as Garcin-syndrome.<sup>[80]</sup>

#### Diphtheria

Diphtheria is characterized by initial infection of the upper airway tract with *Corynebacterium diphtheriae*, which later is secondarily complicated by systemic radiculoneuropathy also affecting the 9<sup>th</sup> or 10<sup>th</sup> cranial nerve. Clinically, these patients present with paralyzed accommodation, palatal paralysis, tongue weakness, and sensory > motor polyneuropathy. Diphtheria is frequently associated with cardiomyopathy and arrhythmias. Paralysis of the diaphragm occurs in 1/3 of the cases. In severe cases laryngospasm may develop. Autonomic involvement includes sinus tachycardia, bladder dysfunction, or arterial hypotension. Occasionally, there may be facial weakness, ophthalmoparesis, or optic atrophy.

#### Poliomyelitis

Poliomyelitis is caused by an RNA-enterovirus and occurs in only 5–10% of the infected patients. It starts with fever, myalgia, and nonspecific gastrointestinal symptoms. 4–20 days after the infection patients develop meningitis with headache and stiff neck followed by weakness of limb muscles.<sup>[81]</sup> In 20% of the cases, poliomyelitis is associated with bulbar involvement.<sup>[81]</sup> Cranial nerves are variably affected. If the 7<sup>th</sup> cranial nerve is affected, hemifacial atrophy may ensue.<sup>[82]</sup> In other cases, the 5<sup>th</sup>, 9<sup>th</sup>, 10<sup>th</sup>, and 11<sup>th</sup> cranial nerves may be involved.<sup>[83]</sup> Skeletal muscles supplied by these nerves become atrophic.<sup>[83]</sup>

#### Tetanus

Tetanus is an infection caused by the endotoxins of *Clostridium tetani*, which block the presynaptic SNARE protein. It may occur focally or generalized. Entry of the toxin into the body is in 75% of the cases an acute wound. Despite modern medicine, mortality still ranges between 15% and 30%. Among the cranial nerves, the facial nerve is most commonly affected. Others are the nerves supplying the extra-ocular muscles, or the hypoglossal nerve. Rarely, the 9<sup>th</sup> or 10<sup>th</sup> cranial nerve is affected.<sup>[81]</sup>

#### Botulinism

Concerning the entrance of the bacterium into the body, foodborne botulism and wound botulism

are differentiated. Concerning age at onset, infant botulism (in one fifth of the cases via ingestion of honey) and adult intestinal toxæmia are differentiated. Accidentally, botulism may be caused by overdosing therapeutic botulinum toxin. In rare cases *Clostridium botulinum* infection may involve cranial nerves.<sup>[84]</sup> Particularly hemorrhage within the vagal nerve has been reported.<sup>[84]</sup>

#### Borreliosis

Borreliosis and Lyme disease are due to an infection with the spirochete *Borrelia burgdorferi*. In the majority of the cases it is transmitted from ticks to humans. Occasionally, the central nervous system (CNS) is affected manifesting as headache, sleep disturbance, papilledema, meningitis, meningo-radiculitis, myelitis, affection of the cranial nerves, ataxia, chorea, and altered mental state. LCN are rarely involved.<sup>[85]</sup> Manifestations attributable to LCN involvement resolved upon adequate antibiotic treatment in a single patient.<sup>[85]</sup>

#### Tuberculous meningitis

Affection of the LCN by tuberculous meningitis is rare and usually has a poor outcome.<sup>[86]</sup> Involvement of the LCN in tuberculous meningitis may manifest clinically as speech disturbance (slurring).<sup>[86]</sup> If tuberculous spondylitis involves the craniocervical junction, affected patients may present with isolated hypoglossal nerve palsy.<sup>[87]</sup>

#### Immunological

##### Sarcoidosis

Sarcoidosis is an inflammatory, granulomatous, systemic disease. In about 25% of the cases involvement of the nervous system occurs (neurosarcoidosis).<sup>[88]</sup> Involvement of the cranial nerves is the most common abnormality in neurosarcoidosis and most frequently affects the 7<sup>th</sup> and second most frequently the 2<sup>nd</sup> cranial nerve. Only rarely, the 8<sup>th</sup>, 9<sup>th</sup>, or 10<sup>th</sup> cranial nerves are being affected. In a retrospective study of 54 patients with neurosarcoidosis, those with LCN involvement had a slightly better outcome than those with optic nerve involvement.<sup>[88]</sup> Clinical manifestations of neurosarcoidosis usually resolve upon administration of steroids.<sup>[89]</sup>

#### Multiple cranial nerve neuropathy

Multiple cranial nerve neuropathy is the pharyngo-facial variant of Guillain-Barre-syndrome (GBS).<sup>[90]</sup> Affected patients present with facial swelling, bilateral facial palsy, and bulbar palsy with dysphagia or aspiration.<sup>[90]</sup> There may also be weakness of the neck, the upper limbs, the hips, or the facial muscles. In 70% of the cases, an upper respiratory tract infection and in 30% diarrhea or other gastrointestinal problems precede the immune neuropathy. Infectious

agents are the campylobacter jejunii or the cytomegaly virus. Intravenous immunoglobulins have a beneficial effect. In a case of Miller-Fisher-syndrome associated with Bickerstaff encephalitis, the patient presented with ophthalmoplegia, bilateral facial palsy, dysphagia, dysarthria, neck weakness, distal quadripareisis, and ataxia.<sup>[91]</sup> These abnormalities improved gradually upon intravenous immunoglobulins.<sup>[91]</sup>

#### *Pharyngo-cervical-brachial variant of Guillain-Barre-syndrome*

This GBS variant manifests with dysphagia, weakness of facial muscles, neck flexors, and proximal upper limb muscles, ophthalmoplegia, ataxia, and autonomic dysfunction (heart rate, bladder). Laboratory and electrophysiological investigations are similar to those in GBS.

#### *Chronic inflammatory demyelinating polyneuropathy*

Rarely, LCN are involved in chronic inflammatory demyelinating polyneuropathy (CIDP) manifesting as hypogeusia due to the involvement of the glossopharyngeal nerve.<sup>[92]</sup> Much more frequently than the glossopharyngeal nerve, the hypoglossal nerve may be affected in CIDP patients.<sup>[93]</sup>

#### *Multiple sclerosis*

Neuropathic pain, manifesting as cranial neuralgia, is a frequent feature of multiple sclerosis.<sup>[94]</sup> The most well-known LCN neuralgia is the one of the glossopharyngeal nerve. Demyelination in the centrally myelinated part of the cranial nerve roots is held responsible for the development of pain.<sup>[94]</sup> The most frequent neuralgia of the LCN in multiple sclerosis is glossopharyngeal neuralgia.<sup>[15]</sup>

#### *Metabolic*

##### *Diabetes*

Autonomic neuropathy from diabetes may also affect the vagal nerve and its branches and may be associated with cardiovascular and gastrointestinal compromise.<sup>[95]</sup> In humans or animals with severe hyperglycemia, impairment of the cardiac autonomic nervous system may occur.<sup>[96,97]</sup> Diabetic gastroparesis is well-known but poorly understood phenomenon, which may also be due to affection of the autonomic innervation by the vagal nerve.<sup>[98]</sup>

#### *Nutritional*

##### *Vitamin B<sub>12</sub> deficiency*

Rarely, Vitamin-B<sub>12</sub> deficiency may be the cause of unilateral vocal cord palsy.<sup>[99]</sup> Among cranial nerves, the optic nerve is the one most frequently affected in B<sub>12</sub>-deficiency.<sup>[99]</sup> Folate deficiency has not been reported

as a cause of LCN lesions. Autonomic dysfunction with vagal withdrawal and defective sympathetic activation has been reported in patients with cobalamin deficiency.<sup>[100]</sup>

#### *Degenerative*

##### *Amyotrophic lateral sclerosis*

Usually, ALS manifests clinically in adulthood as a continuum between the exclusive affection of the upper motor neurons and exclusive affection of lower motor neurons.<sup>[29]</sup> The affection of the LCN leads to a bulbar syndrome including slurred and dysarthria and dysphagia. LCN may be affected already at the onset of the disease (bulbar-onset ALS), or following the affection of the limb muscles (limb-onset ALS). In ALS with bulbar involvement, a dynamic collapse of the airway due to the gravitational pull of the mandible (mandibula ptosis) may occur in the supine position.

#### *Facial onset sensory and motor neuronopathy*

Facial onset sensory and motor neuronopathy is a rare, slowly progressive neurodegenerative disorder clinically characterized by numbness and paresthesias initially in a trigeminal nerve distribution followed by spreading to the scalp, neck, upper trunk, and upper limbs.<sup>[101]</sup> Later in the course, patients develop muscle cramps, fasciculations, muscle weakness and wasting, dysphagia, and dysarthria.<sup>[101]</sup> Nerve conduction studies reveal a caudally descending sensorimotor neuropathy.<sup>[101]</sup> An autopsy may show loss of motoneurons in the hypoglossal nucleus and cervical anterior horns.

#### *Sandifer's syndrome*

Sandifer's syndrome is a gastrointestinal disorder characterized by reflex torticollis following deglutition in patients with gastro-esophageal reflux or hiatal hernia.<sup>[102]</sup> Sandifer's syndrome is regarded as a vagal reflex triggered by afferent impulses transmitted via general visceral afferents to the nucleus tractus solitarii and from there to the nucleus ambiguus and the nucleus dorsalis nervi vagi. From the latter, visceral efferents reach the accessory nerve via hypothetical anastomoses to innervate the trapezius and sternocleidomastoid muscles.<sup>[102]</sup>

#### *Eagle-syndrome*

Eagle-syndrome, also known as syndrome of the elongated styloid process, is characterized by cervical pain, which can be enhanced by head rotation, chewing, or head extension.<sup>[103]</sup> Neck or throat pain usually radiates to the ipsilateral ear. Other symptoms include foreign body sensation, dysphagia, or facial pain.<sup>[104]</sup> Symptoms are due to an elongated styloid process or an ossified stylohyoid ligament. The ossification of the ligament leads to throat symptoms due to the affection of the glossopharyngeal nerve.<sup>[103]</sup>

### **Chiari malformation**

In rare cases, Chiari-I malformation may be associated with the affection of the hypoglossal nerve.<sup>[105]</sup> More frequently, Chiari-I malformation causes glossopharyngeal neuralgia.<sup>[106]</sup> Chiari-I malformation may also compromise the vagal nerve. Chiari-I malformation may lead to compression of the LCN between the PICA and the herniated cerebellar tonsil.<sup>[107]</sup>

### **Neoplasms**

A number of benign or malignant intra- or extra-cranial neoplasms are associated with lesions of the LCN (base of the skull syndromes). Also, bone metastases of the skull base may damage LCN.<sup>[108]</sup> Intra-cranial neoplasms may be further divided into those located intra-cerebrally and those located extra-cerebrally. Among the extracranial neoplasms, those located just below the skull and those of the neck are differentiated. Intrinsic brain tumors may affect the nuclei or intra-parenchymatous nerve tracts. Malignant spread within the CSF space affects cranial nerves and nerve roots. Tumors affecting the cranial nerves outside the bony skull may spread in an antero- or retrograde fashion.

Intra-cerebral neoplasms affecting nuclei of LCN include the posterior fossa ependymoma,<sup>[109]</sup> choroid plexus papilloma,<sup>[110]</sup> primary CNS lymphoma,<sup>[111]</sup> or rarely metastasis.<sup>[112]</sup> Extra-axial neoplasms affecting the LCN include cisternal meningomas,<sup>[113]</sup> extra-axial cavernomas,<sup>[114]</sup> choroid plexus papillomas,<sup>[115]</sup> intracranial Schwannomas,<sup>[116]</sup> or metastasis.<sup>[117]</sup> Leptomeningeal carcinomatosis involving the LCN is less frequent than involvement of upper cranial nerves.<sup>[118]</sup> Suspected leptomeningeal carcinomatosis may not always be confirmed at autopsy. Usually, however, an autopsy in meningeal carcinomatosis may show squamous-type carcinoma cells scattered in the cerebro-spinal leptomeninges and perineurium of almost all spinal and cranial nerve roots, causing severe axonal degeneration.<sup>[119]</sup> Involvement of the leptomeninges in lymphomatoid granulomatosis may also damage LCN.<sup>[120]</sup> Bone metastases of the base of the skull, which are usually painful, are a frequent cause of LCN dysfunction including Collet-Sicard-syndrome.<sup>[108,121]</sup>

The most frequent neoplasms of the jugular foramen are the paragangliomas,<sup>[113]</sup> followed by Schwannomas,<sup>[122]</sup> neuroendocrine carcinoma,<sup>[123]</sup> and meningomas.<sup>[124]</sup> Paraganglioma accounts for <1% of neoplasms in the head-neck region. Traditionally, paragangliomas are considered as benign, slowly growing, locally invasive, encapsulated and highly vascularised tumors.<sup>[22]</sup> Paragangliomas of the neck may even cause Collet-Sicard-syndrome.<sup>[22]</sup> Neoplasms originating from

one of the LCN include the hypoglossal Schwannoma,<sup>[125]</sup> the vagal nerve Schwannoma,<sup>[126]</sup> and the neurilemmoma of the vagal nerve.<sup>[127]</sup> The base of the skull neoplasms affecting LCN include the hemangiopericytoma,<sup>[128]</sup> the glomus tumor,<sup>[129]</sup> chordomas,<sup>[130]</sup> osteosarcoma, or metastasis. Neoplasms of the neck may also injure LCN. Recurrent squamous carcinoma metastatic to the neck may directly infiltrate the glossopharyngeal or vagal nerves.<sup>[131]</sup> Neck fibrosarcoma as well as multiple myeloma, hypoglossal Schwannoma, jugular foramen neurinoma, jugular foramen metastatic melanoma, or hemangiopericytoma may cause Collet-Sicard-syndrome. Tonsillar carcinoma invading the parapharyngeal space may lead to hypersensitivity of the carotid sinus coupled with glossopharyngeal neuralgia.<sup>[132]</sup> LCN lesions may also originate from perineural spread of a facial squamous

**Table 4: Disorders specifically affecting a LCN and disorders with LCN involvement but diagnosed upon systemic manifestations**

Disorder	Affected LCN nerve
Disorders specifically affecting LCN	
Hereditary neuropathies	12 <sup>th</sup>
PICA-aneurysm	9 <sup>th</sup> , 10 <sup>th</sup> , 11 <sup>th</sup>
Artery dissection	10 <sup>th</sup> , 11 <sup>th</sup>
Ischemia of CN	9 <sup>th</sup> through 12 <sup>th</sup>
Calcified persisting hypoglossal artery	12 <sup>th</sup>
Condyle fracture	12 <sup>th</sup>
Atlas fracture	9 <sup>th</sup> through 12 <sup>th</sup>
Styloid fracture	9 <sup>th</sup>
Carotid surgery	9 <sup>th</sup> , 10 <sup>th</sup> , 12 <sup>th</sup>
Neck dissection	11 <sup>th</sup> , 12 <sup>th</sup>
Poliomyelitis	9 <sup>th</sup> through 11 <sup>th</sup>
Tetanus	9 <sup>th</sup> , 10 <sup>th</sup> , 12 <sup>th</sup>
Botulinism	10 <sup>th</sup>
Tuberculous meningitis	12 <sup>th</sup>
Neuralgia	9 <sup>th</sup>
Eagle-syndrome	9 <sup>th</sup>
Chiari malformation	9 <sup>th</sup> , 10 <sup>th</sup>
Schwannoma	10 <sup>th</sup> , 12 <sup>th</sup>
Tonsillar carcinoma	9 <sup>th</sup>
Metastasis	9 <sup>th</sup> , 10 <sup>th</sup>
Disorders with LCN involvement diagnosed upon systemic manifestations	
ALS	All
Borreliosis	All
GBS	All
CIDP	9 <sup>th</sup> , 12 <sup>th</sup>
Multiple sclerosis	All
Sarcoidosis	All
Diabetes	All
Vitamin deficiency	All
FOSMN-syndrome	12 <sup>th</sup>
Sandifer's syndrome	11 <sup>th</sup>

LCN: Lower cranial nerves, CN: Cranial nerve, ALS: Amyotrophic lateral sclerosis, GBS: Guillain-Barre-syndrome, FOSMN: Facial-onset sensory and motor neuropathy, CIDP: Chronic inflammatory demyelinating polyneuropathy, PICA: Posterior inferior cerebellar artery

cell carcinoma.<sup>[133]</sup> In a report of 3 cases, super-selective arterial embolization of paragangliomas with ethylene vinyl alcohol resulted in damage of the 10<sup>th</sup>, 11<sup>th</sup>, or 12<sup>th</sup> cranial nerve with recovery in only one patient.<sup>[134]</sup>

## Conclusions

This review about disorders of the LCN shows that causes of LCN lesions are heterogeneous. Causes of LCN lesions may be classified as genetic, vascular, traumatic, iatrogenic, infectious, immunologic, nutritional, metabolic, degenerative, or neoplastic. LCN may be affected as a single nerve or as multiple LCN. LCN may be affected together with more proximal cranial nerves, together with CNS disease, or together with nonneurological disorders. There are disorders which specifically affect LCN and multisystem disorders with nondominant LCN involvement [Table 4]. If LCN lesions are suspected upon typical symptoms and signs, specific instrumental investigations may confirm the suspected LCN lesion [Figure 1]. Affection of multiple LCN is much more frequent than the affection of a single LCN. Treatment of LCN lesions depends on the underlying cause. An effective treatment is available in the majority of the cases but the requirement for complete recovery is the prompt and correct diagnosis. To correctly assess complaints resulting from LCN lesions, precise knowledge about the anatomy and physiology of the area is a prerequisite.

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