MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA
NICOLAE TESTEMITANU
STATE UNIVERSITY OF MEDICINE AND PHARMACY

DEPARTAMENT OF NEUROLOGY NO. 2

ALEXANDRU GASNAȘ

THE BRAINSTEM: ANATOMIC AND CLINICAL CORRELATIONS FOR MEDICAL STUDENTS AND RESIDENTS

(Methodical recommendation)

CHISINAU, 2022

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The recommendations for the practical and theoretical (seminar) works on neurology correspond to the syllabus of the student curricula of faculties of Medicine, Pharmacy and Dentistry and residency program in Neurology

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ABBREVIATIONS

AAN – American Academy of Neurology
AICA – anterior inferior cerebellar artery
ANS – autonomic nervous system
ASA – anterior spinal artery
BA – basilar artery
CN – cranial nerve
CNS – central nervous system
CT – computed tomography
DWI – diffusion-weighted imaging
EEG – electroencephalography
ICVA – intracranial vertebral artery
INO – internuclear ophthalmoplegia
LGB – lateral geniculate body
LMI – lateral medullary infarction
MD – medial dorsal nucleus
MLF – medial longitudinal fasciculus
MMI – medial medullary infarction
MRI – magnetic resonance imaging
PCA – posterior cerebral artery
PICA – posterior inferior cerebellar artery
PPRF – paramedian pontine reticular formation
SCA – superior cerebellar artery
TIA – transient ischemic attack
VA – ventroanterior nucleus
VA – vertebral artery
VL – ventrolateral nucleus
VP – ventroposterior nucleus

INTRODUCTION

Neurology is medical specialty dealing with the inborn, developmental and acquired, acute and chronic diseases of the central and peripheral nervous system and skeletal muscle at all ages. Neurology covers their diagnosis, the understanding of underlying mechanisms and management. Neurology is a constantly evolving field parallel to the development of the neurosciences and overlaps with numerous other medical specialties, in particular neurosurgery, psychiatry, clinical genetics, pediatrics, rehabilitation, internal medicine and public health.

Current research has indicated an apparent pandemic of fear of the neural sciences, termed *neurophobia* [1-3], among medical students across the world. While the cause of this fear may be multifactorial, we seek to directly address the phenomenon of *neurophobia* in part by providing medical students as well as healthcare professionals a simplified approach to one of the most challenging topics in neurology: the brainstem anatomic and clinical correlations.

The focus in neurology is usually on the cortical areas that subserve movement, sensation, behavior, cognition, and mood. But, it is essential to also understand the roles of the brainstem for these domains, because it participates in a wide range of functions including control of movement, modulation of pain, autonomic reflexes, arousal, and consciousness. In spite of its role in these and many other essential bodily functions, the study of the brainstem has been neglected compared with research made on structures such as the cortex, hippocampus, cerebellum, retina, basal ganglia and spinal cord.

In the past few years, knowledge of brainstem circuitry has advanced greatly and it has become possible to investigate problems that previously seemed unapproachable, thanks to major technical advances.

This methodical recommendation will provide an overview of the anatomy, vascularization, causes of the various brainstem vascular syndromes emphasizing a simple approach for localizing the artery affected and brainstem death. With an abundance of easy to understand illustrations, we emphasize the clinical symptomatology, differentiating characteristics, and pertinent neuroanatomy of each described brainstem syndrome.

In conclusion, a working knowledge of the brainstem anatomy and semiology is essential for the assessment of patients with symptoms of cranial nerve deficits, motor, sensory, or cognitive/behavioral changes and the clinician needs to be familiar with how neuroanatomical functional units cluster in the brainstem.

I. INTERNAL ANATOMY OF THE BRAINSTEM

Learning objectives

After study of the assigned learning materials, the student will be able to:

1. Identify the major anatomical subdivisions of the brainstem, as seen in representative transverse cross-sections.
2. Recognize the principal features of the medulla oblongata as seen from the surface, including the attachments of cranial nerves VI-X and XII (and XI).
3. Recognize the principal features of the pons as seen from the surface, including the attachments of cranial nerves V and VI-VIII.
4. Recognize the principal features of the midbrain as seen from the surface, including the attachments of cranial nerves III & IV.

Form of training: practical, theoretical (seminar) and individual works, 1.5 hours.

Of chief importance in understanding the organization of the brainstem is knowledge of what is localized in each embryological subdivision and in any transverse section. This is a significant challenge for every student of neuroanatomy and we will now turn our attention progressively to this challenge. After working through this chapter, you should be able to recognize any transverse section through the brainstem in terms of what level is represented and what distinctive features may be present. But before proceeding, it will be worth again reminding yourself of the basic layout of sensory and motor neurons in the brainstem and spinal cord.

The CNS interacts with the outside world through primary sensory neurons, which convey information from the body or its environment into the brain and spinal cord, and motor neurons, which activate striated muscles and modulate the activity of cardiac and smooth muscles and glands (*Fig. 1*).

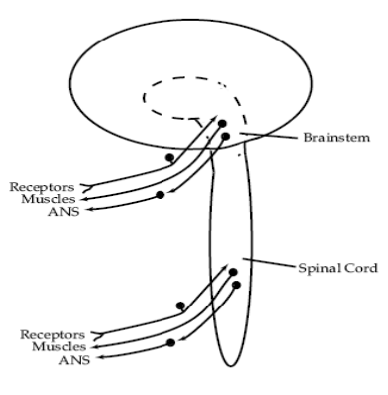

Fig. 1. Both the spinal cord and brainstem receive input from primary sensory neurons; the cell bodies of these neurons lie in sensory ganglia. In addition, both the spinal cord and brainstem give rise to motor output to striated muscles and to the autonomic ganglia (*ANS*, autonomic nervous system; synonymous with visceral motor system). (Illustration by N.B. Cant) [4]

The cell bodies of primary sensory neurons lie in the **dorsal root ganglia** or the **CN ganglia**. Each neuron gives rise to a peripheral process, which receives information either directly or through association with receptors, and a central process, which enters the CNS and forms synapses with second order neurons. The cell bodies of somatic motor neurons lie in clusters or **nuclei** within the CNS and give rise to axons that innervate striated muscles in the body or head. In this tutorial, you will be especially concerned with the organization of these second-order sensory neurons and somatic motor neurons. You will also be introduced to other motor neurons that are part of the visceral motor system (ANS) and are indirectly responsible for governing cardiac muscle, smooth muscle or glands. By the conclusion of this learning experience, you will learn how to locate:

1. nuclei that are the destination of all primary somatic sensory, visceral sensory, and special sensory *input* into the central nervous system (CNS) (i.e., the location of all of the second-order neuronal cell bodies that receive the primary sensory input), except for olfaction and vision. The olfactory nerve and the optic nerve are not included in this discussion; for several reasons they are atypical.

2. nuclei that are the origin of all of the somatic and visceral motor *output* of the CNS (i.e., the location of all of the alpha motor neurons and preganglionic visceral motor neurons).

From the viewpoint of clinical practice, the most important general principle of organization in the CNS is that each ***CNS function*** (e.g., perception of sensory stimuli, control of motor behavior) ***involves groups of neurons – interconnected through synapses – that are spatially distributed throughout several CNS subdivisions***. Groups of neurons that together subserve a particular function are called a „system"; for example, there are the visual, motor, and somatic sensory systems. The structures containing the neurons and axons of a particular system are collectively referred to as a „pathway". (The term „system" has a functional connotation, whereas the term „pathway" refers to the structures involved.) We will study several important sensory and motor pathways in detail in future tutorials.

If damage to the CNS at every level gave rise to exactly the same signs and symptoms, it would not be worthwhile for you to learn the details of neuroanatomy. However, as neurologists and neuroscientists recognized long ago, the neurons involved in specific functions occupy specific locations in the CNS. Even those systems that are represented in multiple subdivisions bear different physical relationships to one another from one subdivision to the next. Because neurons that subserve specific functions occupy specific locations, the combinations of neurological signs and symptoms exhibited by particular patients often provide detailed information about the location of damage in the CNS. These principals will guide our survey of the CN nuclei that are distributed across the three major subdivisions of the brainstem. Knowledge of their location and function will provide key information that will help you localize neurological injury and dysfunction in clinical patients.

The internal anatomy of the brainstem

The internal organization of the brainstem is considerably more complicated than that of the spinal cord. However, two factors work in your favor as you study its features. First, important general principles of

organization of the spinal cord also hold true for the brainstem. Second, much of the complexity of the brainstem is contributed by cell groups and axon tracts that will not be considered in this course. In the following discussion, the general plan of organization of the brainstem is presented first. Then, the prominent internal features that characterize each subdivision are identified.

It would be convenient if each subdivision of the brainstem were sufficiently homogeneous along its length that one cross-section could serve as a "typical" representative for the entire subdivision.

However, the brainstem changes continuously along its length – the subdivision into three parts is somewhat arbitrary.

As a compromise between examining three sections (one for each subdivision) and hundreds, seven sections of the brainstem are shown to serve as representatives (*Fig. 2).*

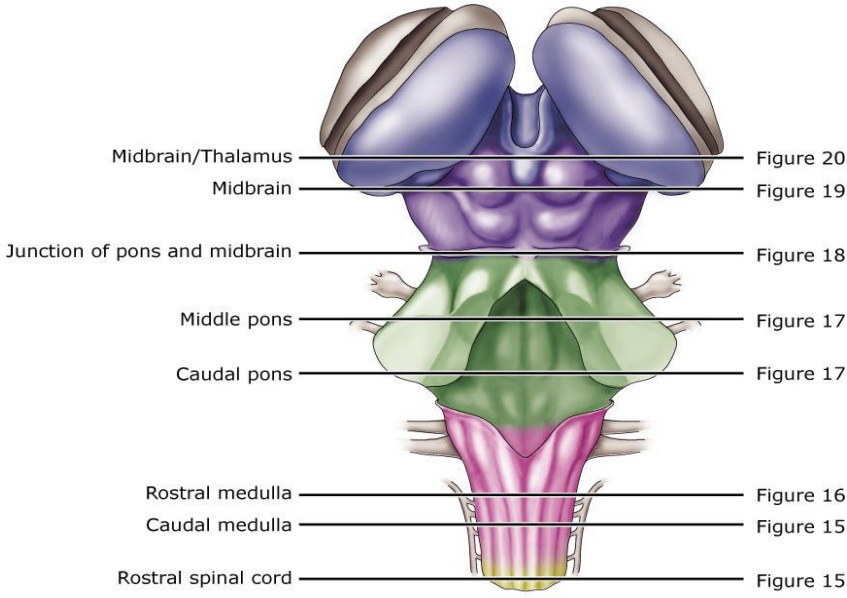

Fig. 2. **Drawing of the dorsal surface** of the brainstem with lines to indicate the seven levels that will be illustrated in the following pages. These same sections are also annotated in the Brainstem Cross Sectional Atlas in *Sylvius4 Online.* (*Illustration courtesy of Pyramis Studios, Durham NC*) [4]

Once you understand the organization of these seven levels and the way various pathways traverse them, you should be able to identify the location of any section through the brainstem and the important pathways represented in it.

An overview of the levels of the brainstem to be discussed is presented in *Fig. 3*. At this stage, it is not important to study the details. For now, three points should be taken from the figure. All of the sections are shown at the same magnification.

In most atlases (including ***Sylvius4 Online***), the smaller sections are magnified more than the larger ones, and it is easy to lose sight of the relative proportions of the different subdivisions. The CN nuclei lie in the tegmentum of the brainstem, as do many of the major ascending and descending tracts. Just as in the spinal cord, the nuclei that receive sensory inputs via the CNs are spatially separate from those that give rise to motor output.

The sensory nuclei are located laterally in the brainstem, whereas the motor nuclei are located medially. The spatial segregation of sensory and motor functions provides an important clue for localization of focal damage in the brainstem.

In Figures 4-9 on the following pages, major landmarks in each of the subdivisions are identified in sections prepared to enhance the appearance of myelin (again, it is conventional to prepare sections of the brainstem and spinal cord with stains that make the white matter appear dark). As usual, be sure to focus on the structures identified in the figure legends in **bold font**.

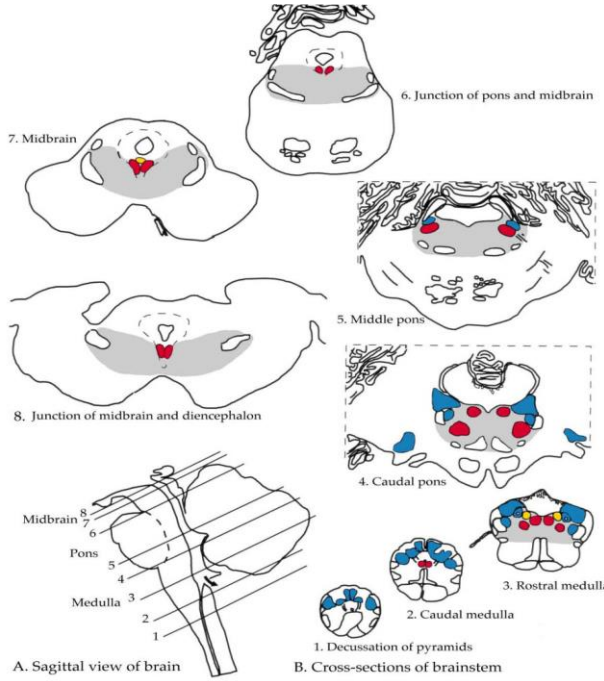

Fig. 3. A. **Sagittal view of the brainstem** to show the level of the sections in part B. (The small curved arrow indicates the location of the median aperture through which cerebrospinal fluid escapes from the ventricular system.) B. Sections through the brainstem. (These are not drawings of the sections illustrated in the following figures, but they are taken from approximately the same levels, with an additional section to illustrate midbrain structures.) The sections are all drawn at the same magnification (a little less than two times actual size). The tegmentum of the brainstem is indicated in gray. Note that although the sections themselves vary greatly in size, the tegmentum is approximately the same size in all of them. Much of the effort in this course will be spent on learning the organization of the structures in the tegmentum. The positions of the CN nuclei (and also the sensory nuclei known as the dorsal column nuclei, which will be covered in a later session of this course) are indicated. Motor nuclei are represented in red and yellow, indicating somatic motor and visceral motor nuclei, respectively; sensory nuclei are represented in blue; important tracts are represented in unfilled outline. Note that the tracts are external to the sensory and motor nuclei, as is the case in the spinal cord. (Only a portion of the cerebellum is included in the drawings of sections 4, 5 and 6). (*Illustration by N.B. Cant*) [4].

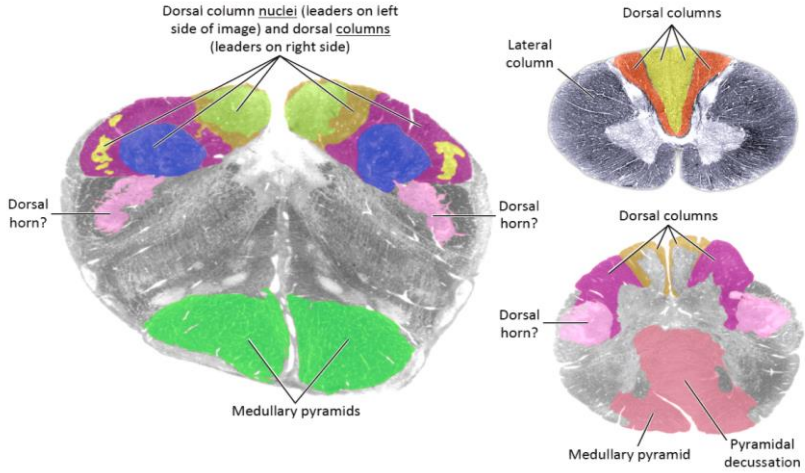

Fig. 4. **Section through the caudal medulla** (left picture; „11-medulla" in *Sylvius4 Online*). The shape is similar to that of the spinal cord (a section through the cervical cord is shown in top right picture; „14-Spinal Cord-cervical" in *Sylvius 4*). But, although the internal organization bears a resemblance to that of the spinal cord, there are some obvious differences. First, the medullary pyramids occupy the base of the caudal medulla; the anterior columns of the spinal cord do not contain so many fibers (and do not have the same pyramidal shape). On the other hand, the lateral columns are quite large in the cervical spinal cord, but there are relatively few myelinated axons in the lateral part of the caudal medulla. The bottom right picture is a photograph of the point of transition between the spinal cord and medulla („13-medulla" in *Sylvius4 Online*). [4]

Medulla oblongata

Dorsal column nuclei (leaders on left side of image) and dorsal columns (leaders on right side).

Here, at the level of the **pyramidal decussation**, the axons in the pyramids not only cross the midline, they also move laterally to enter the lateral columns of the spinal cord. This change in relative location of the axons explains why the anterior columns of the spinal cord are smaller in size and why the lateral columns are larger when the spinal cord is compared to the caudal medulla.

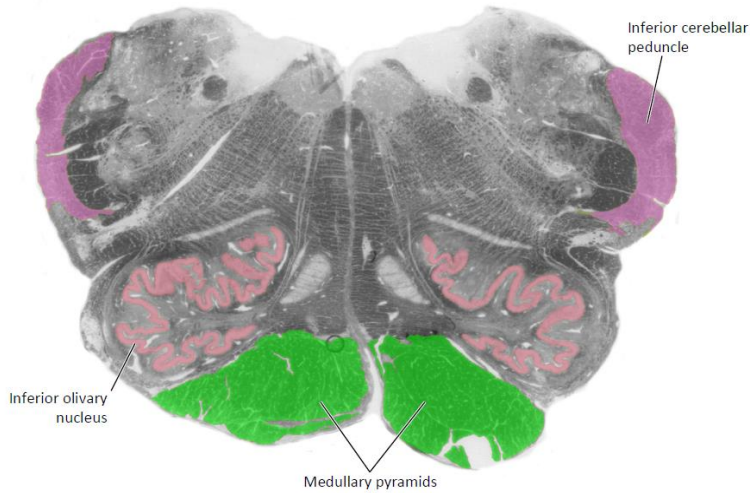

Fig. 5. **The rostral medulla** is easy to identify and is not likely to be confused with any other part of the brain (section shown is „9-medulla" in *Sylvius4 Online*). It features the large nuclei known as the paired inferior olivary nucleus (this is what accounts for the outward bulging seen superficially as the inferior olive). This nucleus is part of an extensive group of brainstem nuclei that project to the cerebellum. Together with the medullary pyramids, they form the base of the rostral medulla. A prominent fiber bundle on the lateral surface of the medulla is the incipient inferior cerebellar peduncle (not yet attached to the cerebellum at this point). [4]

A second difference between the spinal cord and lower medulla is that in the spinal cord, the dorsal columns are made up exclusively of white matter. In the caudal medulla, you can still see bundles of axons dorsally but now cell groups (the **dorsal column nuclei**) have appeared in the same location. These nuclei are second order sensory nuclei that will be discussed in a later session of this course. Finally, note that a cell group that resembles the dorsal horn is also present in the caudal medulla (it is labeled „dorsal horn?"). This is a nucleus known as the **spinal trigeminal nucleus**, and it is continuous with the dorsal horn of the spinal cord and serves comparable functions, except for representation of a different region of the body.

The thin roof of the fourth (IV) ventricle has been torn off of this specimen. It is made up of pia, ependyma, and blood vessels. You can see that the tegmentum of the medulla contains many different cell groups. They will be discussed later.

*With reference to Fig. 4 & 5 and the chart below, carefully inspect the internal features of the medulla from its caudal union with the spinal cord to the pons (Table 1). Spend some time browsing these medullary sections (and the sections in **Sylvius4 Online**), and find each of the internal features described in the chart below [4].*

Table 1

Internal features of the medulla

Subdivision	Surface feature	Internal structure
Caudal medulla (*Fig. 4*)	**Gracile tract** (dorsal surface) • pair of extended longitudinal bulges or columns on either side of a deep midline furrow; technically, this bulge is called the *tuberculum gracilis*, which is formed by the underlying gracile tract • continuation of the tract of the dorsal spinal cord	**Gracile tract & nucleus** • medial, superficial bundle of myelinated axons arising from the dorsal column of the spinal cord • just deep to the gracile tract is the **gracile nucleus**, a compact gray matter structure that receives the synapses made by gracile tract axons
	Cuneate tract (dorsal surface) • pair of extended longitudinal bulges or columns just lateral to the gracile tracts; technically, this bulge is called the *tuberculum cuneatus*, which is formed by the underlying cuneate tract • continuation of the tract of the dorsal spinal cord	**Cuneate tract & nucleus** • just lateral to the gracile tract, superficial bundle of myelinated axons arising from the dorsal column of the spinal cord • at the superior „head" of the cuneate tract is the **cuneate nucleus**, a compact gray matter structure that receives the synapses made by cuneate tract axons
	Pyramidal decussation (ventral surface) • see **Medullary pyramids** below	**Pyramidal decussation** • see **Medullary pyramids** below • midline crossing of dense bundles of myelinated axons

	• apparent "stitching" of fibers that cross the midline	that run the longitudinal extent of the ventral brainstem • accounts for the formation of the **lateral** and **ventral** (**anterior**) **corticospinal tracts** of the spinal cord
Middle to rostral medulla (*Fig. 5*)	**Medullary pyramids** (ventral surface) • pair of extended longitudinal bulges or columns on either side of a deep midline furrow	**Medullary pyramids** • dense bundle of myelinated axons that run the longitudinal extent of the ventral brainstem; these axons are also known as the **corticospinal tract** • these same axons are present in the **internal capsule**, **cerebral peduncles**, basilar pons, and about 90 % are present in the **lateral columns** of the spinal cord
	Inferior olive (ventral-lateral surface) • pair of elongated bulges just lateral to the pyramids; a shallow furrow separates the pyramid and olive on each side	**Inferior olivary nucleus** • prominent nucleus of the ventral-lateral medulla just dorsal to the medullary pyramids • note the highly convoluted bands of gray matter that account for the superficial, ventral-lateral bulge
	Hypoglossal nerve (XII) (ventral-lateral surface) • exits through ventral-medial surface	**Hypoglossal nerve roots & nucleus** • nerve roots emerge between the **medullary pyramid** and the **olive** • trace these nerve roots dorsally to their origin in the **hypoglossal nucleus**, located along the dorsal midline

Pons

With reference to *Fig. 6 & 7* and the chart below, carefully inspect the internal features of the pons.

Spend some time browsing these pontine sections (and the sections in ***Sylvius4 Online***), and find each of the internal features described in the chart below.

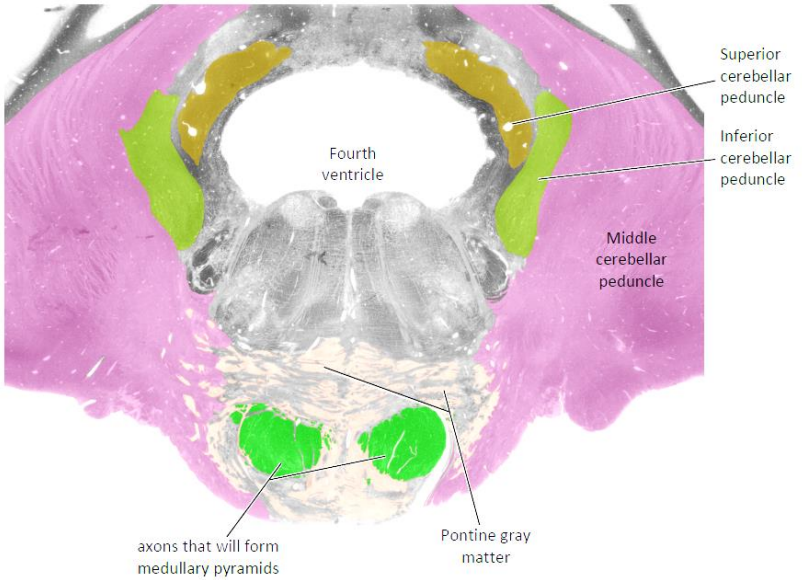

Fig. 6. **The caudal and middle pons** (upper and lower sections, respectively; „7-pons" & „6-pons" in *Sylvius4 Online*) look very similar at first inspection. We need two levels to represent the pons because there are different groups of CN nuclei at the two levels. These sections are attached to the cerebellum (a dead giveaway that we are in the pons) by the massive middle cerebellar peduncles (cut on the lateral edge of the sections). The base of the pons is made up of a mix of cells – the pontine gray matter and transversely coursing fibers – fibers that arise from the cells in the pontine gray matter and travel into the cerebellum via the middle cerebellar peduncle. Not all the fibers in the base of the pons are running transversely. Note that some appear to be traveling perpendicular to the plane of section. These will emerge on the base of the medulla as the medullary pyramids. The tegmentum of the pons looks similar at both levels, but the nuclei contained at each level are different. [4]

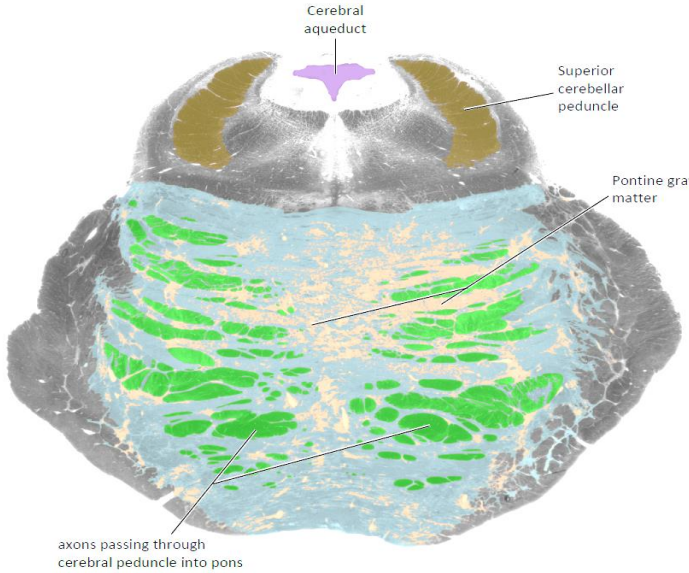

Fig. 7. At the **junction of the pons and midbrain**, the brainstem looks relatively simple. The massive pontine base is about to give way to the cerebral peduncles. Dorsal to the base, the brainstem is reduced to the tegmentum. The fourth ventricle, which you saw in the sections through the pons, is disappearing to be replaced by the cerebral aqueduct. (Table 2) (Section is „4-pons" in *Sylvius4 Online*) [4]

Table 2

Internal features of the pons

Subdivision	Surface feature	Internal structure
Caudal pons (Fig. 6, upper)	***Gracile tract*** *(dorsal surface)* *• pair of extended longitudinal bulges or columns on either side of a deep midline furrow; technically, this bulge is called the tuberculum gracilis, which is formed by the underlying gracile tract* *• continuation of the tract of the dorsal spinal cord*	***Gracile tract & nucleus*** *• medial, superficial bundle of myelinated axons arising from the dorsal column of the spinal cord* *• just deep to the gracile tract is the* ***gracile nucleus****, a compact gray matter structure that receives the synapses made by gracile tract axons*

	Cuneate tract (dorsal surface) • pair of extended longitudinal bulges or columns just lateral to the gracile tracts; technically, this bulge is called the *tuberculum cuneatus*, which is formed by the underlying cuneate tract • continuation of the tract of the dorsal spinal cord	**Cuneate tract & nucleus** • just lateral to the gracile tract, superficial bundle of myelinated axons arising from the dorsal column of the spinal cord • at the superior „head" of the cuneate tract is the **cuneate nucleus**, a compact gray matter structure that receives the synapses made by cuneate tract axons
	Pyramidal decussation (ventral surface) • see **Medullary pyramids** below • apparent „stitching" of fibers that cross the midline	**Pyramidal decussation** • see **Medullary pyramids** below • midline crossing of dense bundles of myelinated axons that run the longitudinal extent of the ventral brainstem • accounts for the formation of the **lateral** and **ventral** (**anterior**) **corticospinal tracts** of the spinal cord
Middle of pons (*Fig. 6*, lower)	**Medullary pyramids** (ventral surface) • pair of extended longitudinal bulges or columns on either side of a deep midline furrow	**Medullary pyramids** • dense bundle of myelinated axons that run the longitudinal extent of the ventral brainstem; these axons are also known as the **corticospinal tract** • these same axons are present in the **internal capsule**, **cerebral peduncles**, basilar pons, and about 90 % are present in the **lateral columns** of the spinal cord
	Inferior olive (ventral-lateral surface) • pair of elongated bulges just lateral to the pyramids; a shallow furrow separates the pyramid and olive on each side	**Inferior olivary nucleus** • prominent nucleus of the ventral-lateral medulla just dorsal to the medullary pyramids • note the highly convoluted bands of gray matter that

		account for the superficial, ventral-lateral bulge
	Hypoglossal nerve (XII) (ventral-lateral surface) • exits through ventral-medial surface	**Hypoglossal nerve roots & nucleus** • nerve roots emerge between the **medullary pyramid** and the **olive** • trace these nerve roots dorsally to their origin in the **hypoglossal nucleus**, located along the dorsal midline

Midbrain

With reference to *Fig. 8 & 9* and the chart below, carefully inspect the internal features of the midbrain. Spend some time browsing these pontine sections (and the sections in ***Sylvius4 Online***), and find each of the internal features described in the chart below.

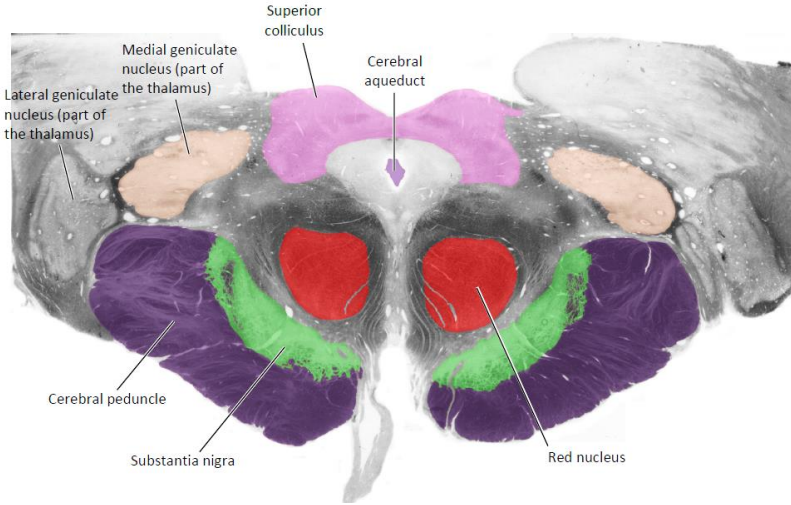

Fig. 8. **This section is through the rostral midbrain** and so it cuts through the superior colliculus. The space between the colliculi is the cerebral aqueduct. The cerebral peduncles form the base of the midbrain. Two very large nuclei lie dorsal to them. These are the substantia nigra and the red nucleus; they are discussed in a later session. (A small part of the dorsal thalamus, including the medial and lateral geniculate nuclei, are also included in this section.) (Section is „2-midbrain" in *Sylvius4 Online*) [4] (Table 3)

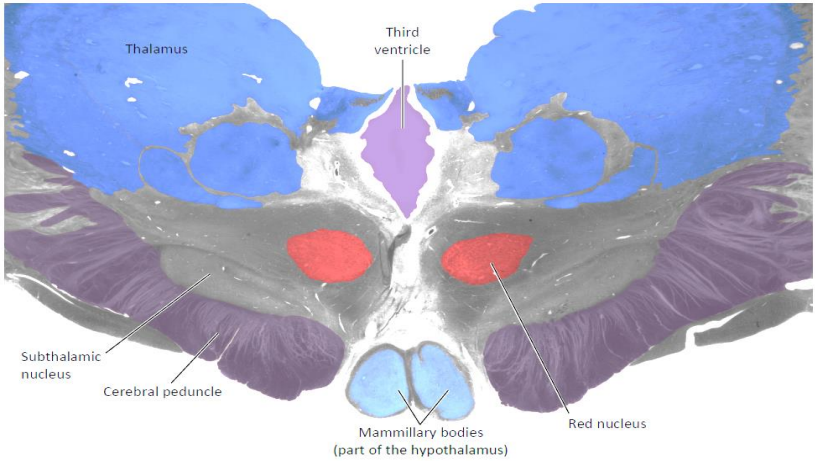

Fig. 9. The last section in the series through the brainstem is cut through the junction of the midbrain and diencephalon. **Structures of the midbrain** are seen medially, but laterally the diencephalon has appeared. The cerebral peduncles will become continuous with the internal capsule a little rostral to this level. Likewise, the cerebral aqueduct will become continuous with the third ventricle. Note the presence of the subthalamic nucleus on the dorsal aspect of the cerebral peduncle (in the place where the substantia nigra is located a centimeter inferior to this level; cf. *Fig. 8*). (Section is „1-midbrain-diencephalon junction" in *Sylvius4 Online*) [4]

Table 3

Internal features of the midbrain

Subdivision	Surface feature	Internal structure
Midbrain (*Fig. 8*)	**Cerebral peduncles** (ventral surface) • large, longitudinal „stalks" (peduncle means stalk) that occupy the ventral midbrain	**Cerebral peduncles** • technically, „cerebral peduncle" refers to the entire ventral midbrain, including the midbrain tegmentum and the fiber systems that run through the stalks; however, it is common to use the term „cerebral peduncle" to refer specifically to these fiber systems (the proper term for these ventral portions of the peduncles – where the fibers are – is *pes* or *basis pedunculi*)

		• the cerebral peduncles comprise efferent fibers of the cerebral cortex that terminate in the brainstem and spinal cord; these fibers are referred to collectively as the **corticobulbar/corticospinal fibers**; this compound terms indicates that the some of these fibers terminate among brainstem nuclei ("bulbar" refers to the brainstem and CN nuclei), while other fibers continue and terminate in the spinal cord • it is important to recognize the course of these fibers from their origin in the cerebral cortex through brainstem: cerebral cortex → subcortical white matter → **internal capsule** → **cerebral peduncle** → basilar pons → **medullary pyramids** → **lateral** and **anterior** (**ventral**) **corticospinal tract** • there are about 20 million axons in each cerebral peduncle; can you guess how many axons are present in medullary pyramid by simply noting the difference in size of these two structures? (the majority of these axons never reach the spinal cord) • now consider the tegmentum of the midbrain; just dorsal to the cerebral peduncles (pes pedunculi) there is an important gray matter nucleus called the **substantia nigra**, and in a similar position but just a bit more rostral is the **subthalamic nucleus**; you will learn much more about these nuclei when we study the basal ganglia • just dorsal to the substantia nigra, is a spherical gray matter structure called the **red nucleus**, which modulates cerebellar function
	Oculomotor nerve (III) (ventral surface) • exits through ventral surface just medial to cerebral	**Oculomotor nerve roots & nuclear complex** • trace these nerve roots dorsally to their origin in the nuclei of the oculomotor complex along the midline of the dorsal tegmentum; here you will find two

	peduncles (in the interpeduncular fossa)	divisions: the **oculomotor nucleus** and the **Edinger-Westphal nucleus** • this nuclear complex is embedded within gray matter that surrounds the **cerebral aqueduct**, termed the **periaqueductal** (or **central**) **gray**
	Inferior colliculi (dorsal surface) • inferior pair of the four bumps that are visible in brainstem model/illustration, but are normally covered by the cerebellum	**Inferior colliculi** • in the caudal midbrain, the inferior colliculi are gray matter structures that occupy a position just dorsal and lateral to the periaqueductal gray (see section „3 - Midbrain") • together with the superior colliculi, they form the „roof" of the midbrain (above the cerebral aqueduct); for this reason, these four bumps are also called the **tectum** (*tectum* means *roof*) • the **trochlear nerve** exits the dorsal surface of the brainstem just caudal to the inferior colliculus (see **Brainstem Model** in **Surface Anatomy** module) • although that nerve is not visible in section 3 – Midbrain, you can see the small **trochlear nuclei** where you should expect to find somatic motor nuclei, along the midline of the dorsal tegmentum
	Superior colliculi (dorsal surface) • superior pair of the four bumps that are visible in brainstem model/illustration	**Superior colliculi** • in the rostral midbrain, the superior colliculi are laminated gray matter structures that occupy a position just dorsal and lateral to the periaqueductal gray matter (see section labeled „2 - Midbrain") • together with the inferior colliculi, they form the „roof" (tectum) of the midbrain (above the cerebral aqueduct)

After-study test

Q1. What is the **brainstem nucleus** that accounts for the outward bulge just lateral to the nerve roots of the CN (CN) XII (hypoglossal nerve)?

A. gracile nucleus

B. cuneate nucleus

C. inferior olivary nucleus
D. facial motor nucleus
E. spinal trigeminal nucleus

Q2. Which of the following is a defining feature of the **pons**?
A. medullary pyramids
B. cerebral peduncles
C. inferior olivary nucleus
D. pontocerebellar fibers forming the middle cerebellar peduncle
E. dorsal column nuclei

Q3. Which of the following CN nuclei is found in the **midbrain**?
A. abducens nucleus
B. hypoglossal nucleus
C. oculomotor nucleus
D. facial motor nucleus
E. red nucleus

Q4. Which of the following is NOT part of the brainstem?
A. Medulla oblongata
B. Cerebellum
C. Pons
D. Midbrain
E. Basal ganglia

Q5. Which cranial nerves arise from the midbrain?
A. 1, 2 and 3
B. 3 and 4
C. 3, 4 and 6
D. 9, 10, 11 and 12
E. 5, 6, and 7

II. BRAINSTEM VASCULAR SYNDROMES

Learning objectives

After study of the assigned learning materials, the student will be able to:

1. List common brainstem syndromes and correlate them with their anatomic locations.
2. Understand and apply the "rule of 4".
3. Recognize the clinical manifestations, distinguishing features, and relevant neuroanatomy for each major vascular syndrome.

Form of training: practical, theoretical (seminar) and individual works, 1.5 hours.

Current research has indicated an apparent pandemic of fear of the neural sciences, termed neurophobia, among medical students across the world. While the cause of this fear may be multifactorial, we seek to directly address the phenomenon of neurophobia in part by providing medical students as well as healthcare professionals a simplified approach to one of the most challenging topics in neurology; brainstem vascular syndromes.

This article will provide an overview of the causes of the various brainstem vascular syndromes emphasizing a simple approach for localizing the artery affected. „The rule of 4" is discussed and then applied to each of the brainstem vascular syndromes highlighting the distinguishing features of each specific syndrome. With an abundance of easy-to-understand illustrations and pictorials, we emphasize the clinical symptomatology, differentiating characteristics, and pertinent neuroanatomy of each brainstem vascular syndrome.

Recently, it has been reported that medical students and trainee doctors perceive neurology as one of the more difficult disciplines of medicine [1-3, 5-11]. Furthermore, it has been found that medical students and physician residents feel less confident in the field of neurology than other specialties of medicine [12]. The fear of the neural sciences and clinical neurology, termed „neurophobia", is a common problem among students and trainee doctors worldwide [1-3, 7, 8, 10-12].

Traditionally, a difficult topic to grasp in clinical neurology is brainstem vascular syndromes [12-14].

This methodic recommendation provides a brief overview of the etiology of brainstem vascular syndromes and a simplified approach for medical students and trainee doctors to localize the vascular territory affected [15].

We discuss „the rule of 4" and then provide a basic overview of each of the major vascular syndromes emphasizing clinical manifestations, distinguishing features, and relevant neuroanatomy for each syndrome. The aim of this recommendation is to be used as a supplement to neuroscience textbooks used by medical students and healthcare professionals.

The Rule of 4

„The rule of 4" is a simplified method to localize brainstem vascular syndromes specific to a vascular territory. Utilizing the rule of 4 as well as distinguishing clinical signs specific to each vascular syndrome, the vascular territory affected can be quickly and accurately localized. There are 4 basic rules to this schema [16, 17]:

1. First Rule: There are 4 midline structures that begin with the letter M
2. Second Rule: There are 4 lateral structures that begin with the letter S
3. Third Rule: There are 4 CNs below the pons, 4 in the pons, and 4 above the pons

a. Medulla: glossopharyngeal, vagus, spinal accessory, hypoglossal (CN 9–12, respectively)
b. Pons: trigeminal, abducens, facial, vestibulocochlear (CN 5–8, respectively)
c. Midbrain: oculomotor, trochlear (CN 3–4, respectively)

4. Fourth Rule: There are 4 midline CN motor nuclei (the nuclei of CNs 3, 4, 6, and 12)

Within each of the 4 rules are 4 additional guidelines necessary to understand in order to localize the site of vascular occlusion [17]. (*Fig. 10*):

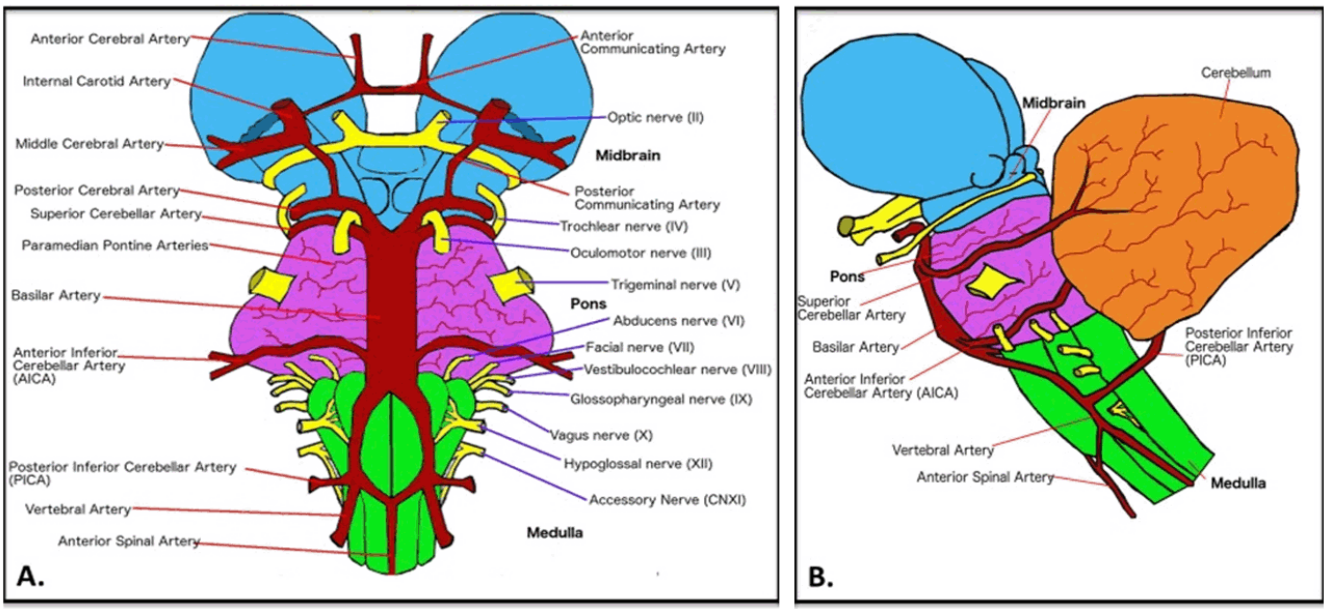

***Fig. 10**:* **Brainstem vasculature and emerging CNs** (A) Ventral view of the brainstem, (B) Lateral view of the brainstem. The brainstem is organized into three divisions. Caudal to cranial they are the medulla oblongata, pons, and midbrain. At the level of the medulla, four CNs emerge including the glossopharyngeal, vagus, accessory, and hypoglossal nerves. At the level of the pons, four CNs emerge including the trigeminal, abducens, facial, and vestibulocochlear nerves. At the level of the midbrain, two CNs emerge including the oculomotor and trochlear nerves. The trochlear nerve is the only nerve to exit via the dorsal surface of the brainstem as well as immediately decussate. The olfactory and optic nerves emerge above the level of the midbrain. [18].

Vascular Syndromes of the Medulla Oblongata

Lateral Medullary Syndrome

Lateral medullary syndrome, also known as Wallenberg syndrome, is usually due to infarction of the posterior inferior cerebellar artery (PICA) **(***Fig. 11***)** [19, 20].

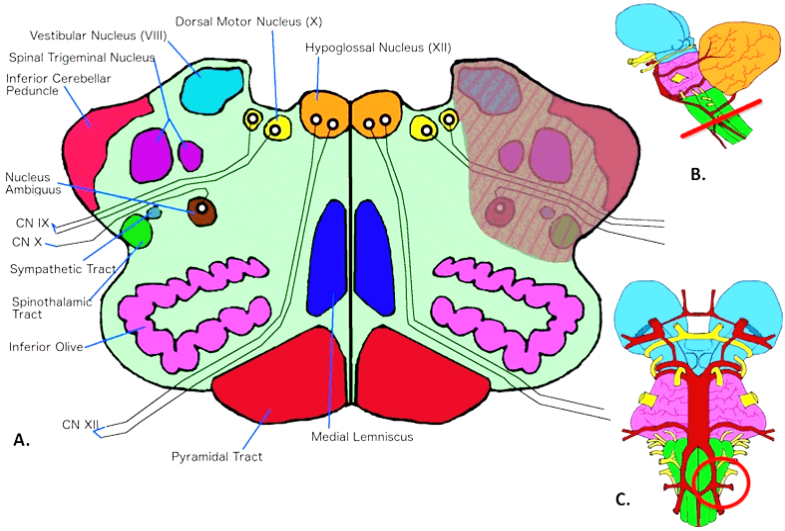

Fig. 11*:* **Structures affected in lateral medullary syndrom**e (A) Transverse view of nuclei affected in the left lateral medullary syndrome. The posterior inferior cerebellar artery (PICA) originates from the vertebral arteries and supplies the lateral most aspect of the medulla. The PICA supplies vestibular nucleus, spinal trigeminal nucleus, and nucleus ambiguus. Furthermore, the inferior cerebellar peduncle, sympathetic tract, and spinothalamic tract can also be affected as these structures extend through the dorsolateral aspect of the medulla, (B) Lateral view of the brainstem level affected in lateral medullary syndrome. The red line indicates the level being described is the medulla in this syndrome. (C) Ventral view of the brainstem level affected in lateral medullary syndrome. The red circle indicates that the PICA is affected in this syndrome. [18]

PICA supplies the lateral territory of the medulla. With the lateral medulla affected, the second rule of 4 applies to this vascular syndrome. Patients with lateral medullary syndrome present with **(***Fig. 12***)**:

• loss of pain and temperature of the contralateral arm and leg (spinothalamic tract)
• ataxia of the ipsilateral arm and leg (spinocerebellar tract)
• Horner's syndrome of the ipsilateral eye (sympathetic pathway)
• loss of pain and temperature of the ipsilateral face (sensory nucleus of trigeminal nerve).

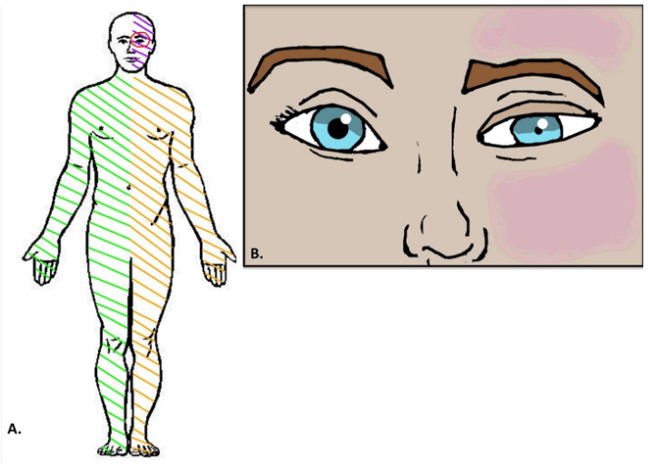

***Fig. 12*: Clinical manifestations of lateral medullary syndrome** (A) Body representation of the clinical manifestations of left lateral medullary syndrome. The green lines indicate loss of pain and temperature of the contralateral arm and leg (spinothalamic tract). The yellow lines represent ataxia of the ipsilateral arm and leg (spinocerebellar tract). The purple lines on the left face indicate loss of pain and temperature of the ipsilateral face (sensory nucleus of trigeminal nerve). The red circle represents Horner's syndrome of the ipsilateral eye (sympathetic pathway). Furthermore, patients may experience vertigo and nystagmus (vestibular nucleus), loss of the gag reflex (vagus nerve), and dysphagia (nucleus ambiguus and glossopharyngeal nerves), (B) Horner's syndrome. The left eye exhibits ptosis (drooping of the upper eyelid), anhidrosis (lack of sweat in response to heat), and miosis (constriction of the pupil). [18]

Distinguishing features of lateral medullary syndrome

The third rule indicates that CNs 9-12 may be affected in medullary infarcts. The fourth rule excludes CN 12 from being affected in this particular syndrome, as CN 12 is a midline structure. This leaves CNs 9,

10, and 11 as possible CNs affected by a lateral medullary infarct. CNs 9 and 10 are affected in this particular syndrome as CN 11 is usually not affected in medullary infarcts. Differentiating features specific to lateral medullary syndrome are loss of function of CNs 9 and 10 (glossopharyngeal and vagus nerve, respectively) resulting in hoarseness and dysphagia [19, 20]. A simple pneumonic to remember these distinguishing features as well as the artery affected is „Never pick a (PICA) horse (hoarseness) that cannot eat (dysphagia)" [21, 22].

Medial Medullary Syndrome

Medial medullary syndrome, also known as Dejerine syndrome, is most commonly due to infarction of the vertebral artery (VA) *(Fig. 13)* [23-25].

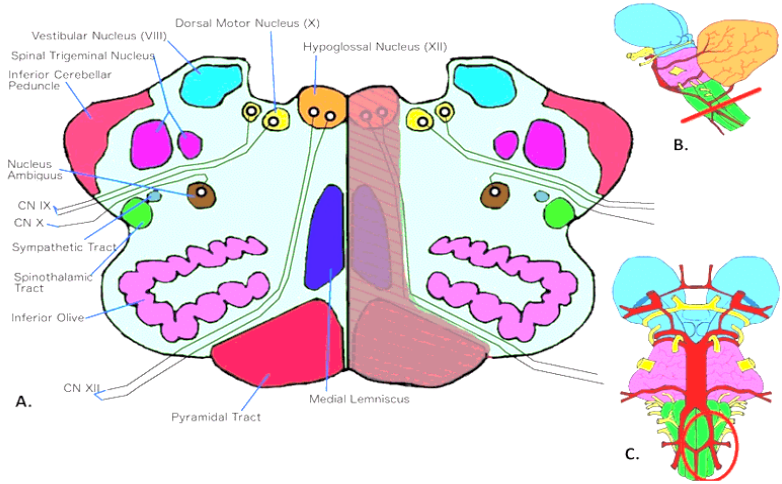

Fig. 13: **Structures affected in medial medullary syndrome** (A) Transverse view of nuclei affected in left medial medullary syndrome. The anterior spinal artery (ASA) is a single midline structure that receives blood from the bilateral vertebral arteries. This artery supplies the medial aspect of the medulla. ASA supplies the pyramidal tracts, medial lemniscus, MLF, and hypoglossal nucleus, (B) Lateral view of the brainstem level affected in medial medullary syndrome. The red line indicates the level being described is the medulla in this syndrome, (C) Ventral view of the brainstem level affected in medial medullary syndrome. The red circle indicates that the ASA is affected in this syndrome. [18].

VA supplies the medial territory of the medulla. As the medial medulla is affected, the first rule of 4 applies to this vascular syndrome. Patients with medial medullary syndrome present with *(Fig. 14):*

- weakness of the contralateral arm and leg (corticospinal tract),
- loss of vibration and proprioception of the contralateral arm and leg (medial lemniscus),
- internuclear ophthalmoplegia (INO) of the ipsilateral eye (medial longitudinal fasciculus, MLF),
- loss of function of midline ipsilateral CN 12.

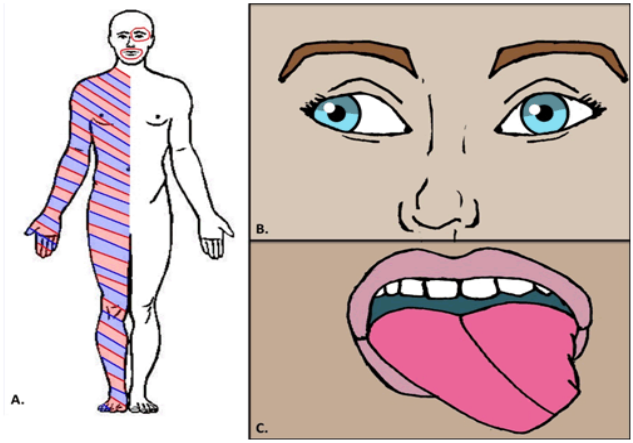

Fig. 14: Clinical manifestations of medial medullary syndrome (A) Body representation of the clinical manifestations of left medial medullary syndrome. The red lines represent weakness of the contralateral arm and leg (corticospinal tract). The blue lines indicate loss of vibration and proprioception of the contralateral arm and leg (medial lemniscus). The red circle around the eye represents internuclear ophthalmoplegia (INO) of the ipsilateral eye, via MLF. The red circle around the mouth indicates deviation of the tongue towards the side of the lesion (hypoglossal nerve), (B) Internuclear ophthalmoplegia (INO). With respect to left medial medullary syndrome, when an attempt is made to look to the right, the left eye will adduct to a minimal extent whereas the right eye will abduct with nystagmus, (C) Deviation of tongue towards side of lesion. With respect to left medial medullary syndrome, infarction of the hypoglossal nucleus will cause the tongue to deviate to the left. [18].

Distinguishing features of medial medullary syndrome

The third rule indicates that CNs 9-12 may be affected in medullary infarcts. The fourth rule indicates that CN 12 is the only CN affected in this syndrome because it is the only CN that arises midline and from the medulla. A differentiating feature specific to medial medullary syndrome is loss of function of CN 12 (hypoglossal nerve) resulting in deviation of the hypoglossal nerve to the ipsilateral side (side of the infarction) [23]. A simple pneumonic to remember that the tongue deviated to the ipsilateral side when the hypoglossal nerve is affected is „lick your wounds" – referring to the tongue deviating towards the side of the „wound" (infarct) [22].

Vascular Syndromes of the Pons

Lateral Pontine Syndrome

Lateral pontine syndrome usually results from infarction of the anterior inferior cerebellar artery (AICA) *(Fig. 15)* [26, 27].

AICA supplies the lateral territory of the pons. With the lateral pons affected, the second rule of 4 applies to this vascular syndrome.

Patients with lateral pontine syndrome present very similar to patients with lateral medullary syndrome, except for different distinguishing CN features. Patients with lateral pontine syndrome present with *(Fig. 16):*

- loss of pain and temperature of the contralateral arm and leg (spinothalamic tract)
- ataxia of the ipsilateral arm and leg (spinocerebellar tract)
- Horner's syndrome of the ipsilateral eye (sympathetic pathway) [28]
- loss of pain and temperature of the ipsilateral face (sensory nucleus of trigeminal nerve)

Distinguishing features of lateral pontine syndrome

The third rule indicates that CNs 5–8 may be affected in pontine infarcts. The fourth rule excludes CN 6 from being affected in this particular syndrome, as CN 6 is a midline structure.

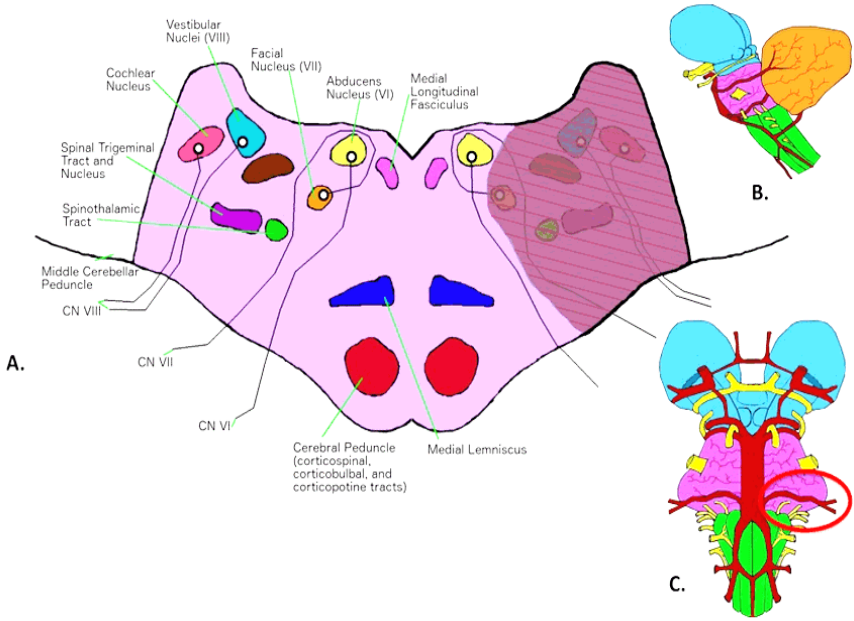

Fig. 15: **Structures affected in lateral pontine syndrome** (A) Transverse view of nuclei affected in left lateral pontine syndrome. The anterior inferior cerebellar artery (AICA) branches from the early basilar artery (BA). This artery supplies the lateral aspect of the pons. The AICA supplies the cochlear nucleus, vestibular nucleus, facial nucleus, spinal trigeminal nucleus, and spinothalamic tract, (B) Lateral view of the brainstem level affected in lateral pontine syndrome. The red line indicates the level being described is the pons in this syndrome, (C) Ventral view of the brainstem level affected in lateral pontine syndrome. The red circle indicates that the AICA is affected in this syndrome. [18]

This leaves CNs 5, 7, and 8 as possible CNs affected by a lateral pontine infarct. A differentiating feature specific to lateral pontine syndrome is loss of function of CN 7 (facial nerve) resulting in facial paralysis [26, 27].

A simple mnemonic to remember that facial nucleus effects are specific to AICA lesions is „facial droop means AICA is pooped” [22].

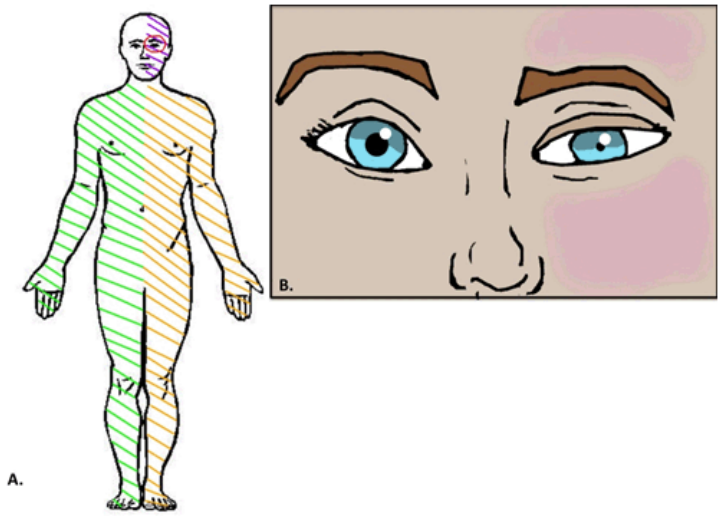

Fig. 16: Clinical manifestations of lateral pontine syndrome (A) Body representation of the clinical manifestations of left lateral pontine syndrome. The green lines indicate loss of pain and temperature of the contralateral arm and leg (spinothalamic tract). The yellow lines represent ataxia of the ipsilateral arm and leg (spinocerebellar tract). The purple lines on the left face indicate loss of pain and temperature of the ipsilateral face (sensory nucleus of trigeminal nerve). The red circle represents the Horner's syndrome of the ipsilateral eye (sympathetic pathway). Furthermore, patients may experience facial muscle weakness (facial nucleus) as well as vertigo and nystagmus (vestibular nucleus), (B) Horner's syndrome. The left eye exhibits ptosis (drooping of the upper eyelid), anhidrosis (lack of sweat in response to heat), and miosis (constriction of the pupil). [18].

Medial Pontine Syndrome

Medial pontine syndrome most commonly results from infarction of the paramedian branches of the basilar artery (BA) *(Fig. 17)* [29].

The paramedian branches of the BA supply the medial territory of the pons. As the medial pons is affected, the first rule of 4 applies to this vascular syndrome.

Patients with medial pontine syndrome present very similar to the patients with medial medullary syndrome, except for different distinguishing CN features.

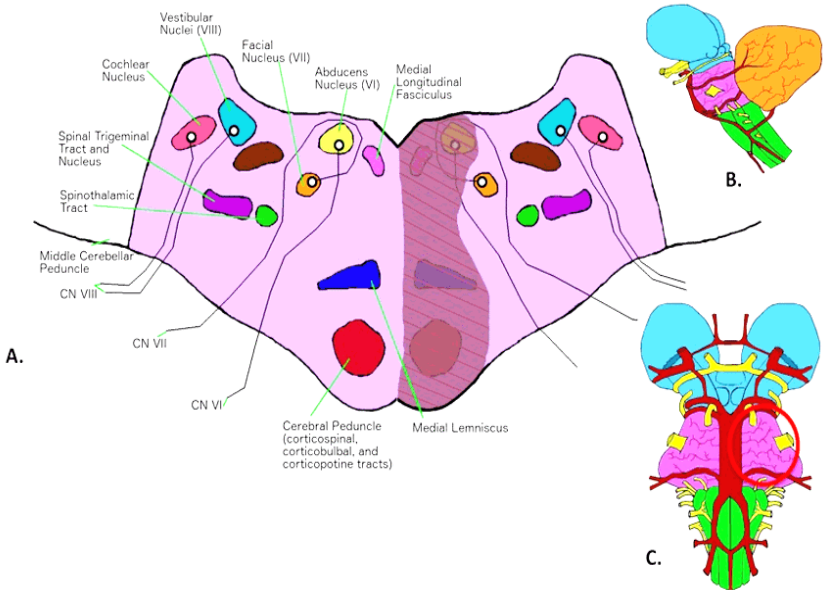

Fig. 17: **Structures affected in medial pontine syndrome** (A) Transverse view of nuclei affected in left medial pontine syndrome. The paramedian pontine arteries are branches originating from the basilar artery (BA). These branches supply the medial aspect of the pons. These branches supply the abducens nucleus, facial nucleus, medial longitudinal fasciculus (MLF), medial lemniscus, and corticospinal tracts. However, rarely are all these structures affected with a single infarction due to the numerous branches anastomosing in the pons, (B) Lateral view of the brainstem level affected in medial pontine syndrome. The red line indicates the level being described is the pons in this syndrome, (C) Ventral view of the brainstem level affected in medial pontine syndrome. The red circle indicates that the paramedian pontine arteries are affected in this syndrome. [18]

Patients with medial pontine syndrome present with *(Fig. 18)*:

- weakness of the contralateral arm and leg (corticospinal tract)
- loss of vibration and proprioception of the contralateral arm and leg (medial lemniscus)
- INO of the ipsilateral eye (MLF)
- loss of function of midline ipsilateral CN 6

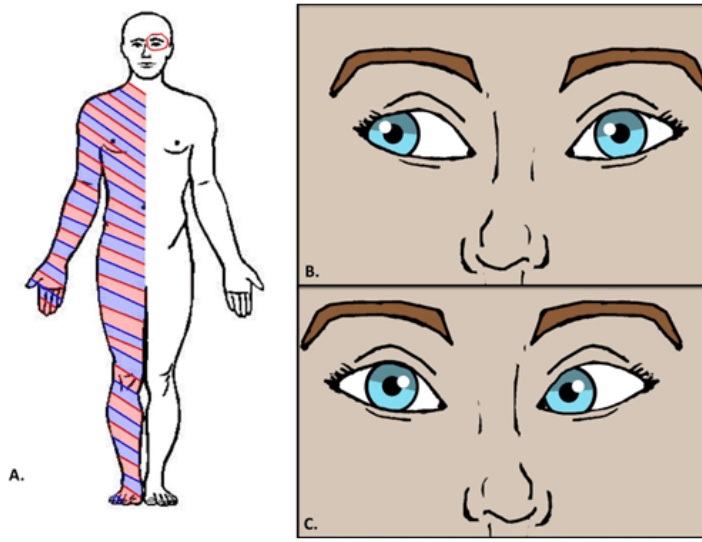

Fig. 18: **Clinical manifestations of medial pontine syndrome** (A) Body representation of the clinical manifestations of left medial pontine syndrome. The red lines represent weakness of the contralateral arm and leg (corticospinal tract). The blue lines indicate loss of vibration and proprioception of the contralateral arm and leg (medial lemniscus). The red circle around the eye represents internuclear ophthalmoplegia (INO) of the ipsilateral eye (medial longitudinal fasciculus, MLF), (B) Internuclear ophthalmoplegia (INO). With respect to left medial pontine syndrome, when an attempt is made to look to the right, the left eye will adduct to a minimal extent whereas the right eye will abduct with nystagmus, (C) Abducens nerve palsy. With respect to right medial pontine syndrome, when an attempt is made to look to the right, the right eye will be unable to look to the right due to dysfunction of the right abducens nerve. [18].

Distinguishing features of medial pontine syndrome

The third rule indicates that CNs 5-8 may be affected in pontine infarcts. The fourth rule indicates that CN 6 is the major CN affected in this syndrome, as CN 6 is a midline structure. A differentiating feature specific to medial pontine syndrome is loss of function of CN 6 (abducens nerve) resulting in strabismus [29]. Strabismus is characterized as ipsilateral paralysis of the lateral rectus muscle (the eye that is affected will look inferior and towards the nose).

Ventral Pontine Syndrome

Ventral pontine syndrome, also known as cerebromedullospinal disconnection, or locked-in syndrome, is caused by infarction of the BA *(Fig. 19)* [30].

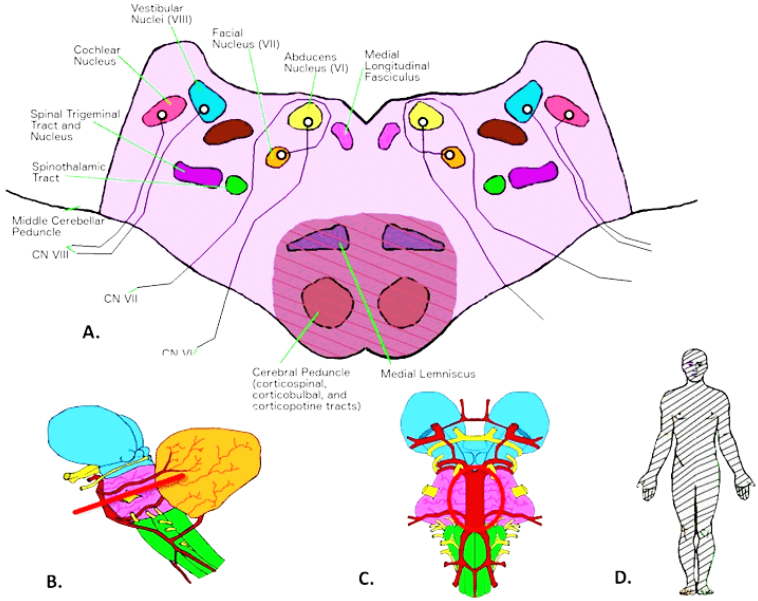

***Fig. 19*: Structures affected and clinical manifestations in ventral pontine syndrome** (A) Transverse view of nuclei affected in ventral pontine syndrome. The basilar artery (BA) supplies the pons. Although there is variability in presentation, extensive bilateral destruction is seen in the corticospinal, corticopontine, and corticobulbar tracts. The medial lemniscus may or may not also be affected, (B) Lateral view of the brainstem level affected in ventral pontine syndrome. The red line indicates the level being described is the pons in this syndrome, (C) Ventral view of the brainstem level affected in ventral pontine syndrome. The red circle indicates that the BA is affected in this syndrome, (D) Body representation of the clinical manifestations of ventral pontine syndrome. Black lines represent quadriplegia (complete body paralysis) and numbness. Usually, the only function spared in ventral pontine syndrome is that of eye movement and blinking. [18].

BA supplies the pons. The first and second rule of 4 applies to this vascular syndrome. Ventral pontine syndrome is easy to identify as a

collection of bilateral long tract signs (motor and sensory) sometimes supplemented by signs of CNs 5-8 dysfunctions. This results in the quadriplegia and aphasia. However, patients with this syndrome usually do not exhibit paralysis of the eyes. Individuals with „locked-in syndrome" may be able to communicate by moving their eyes or blinking [31, 32].

Vascular Syndromes of the Midbrain

Medial Midbrain Syndrome

Medial midbrain syndrome, also known as Weber's syndrome, is usually due to infarction of the penetrating branches of the posterior cerebral artery (PCA) *(Fig. 20)* [33, 34].

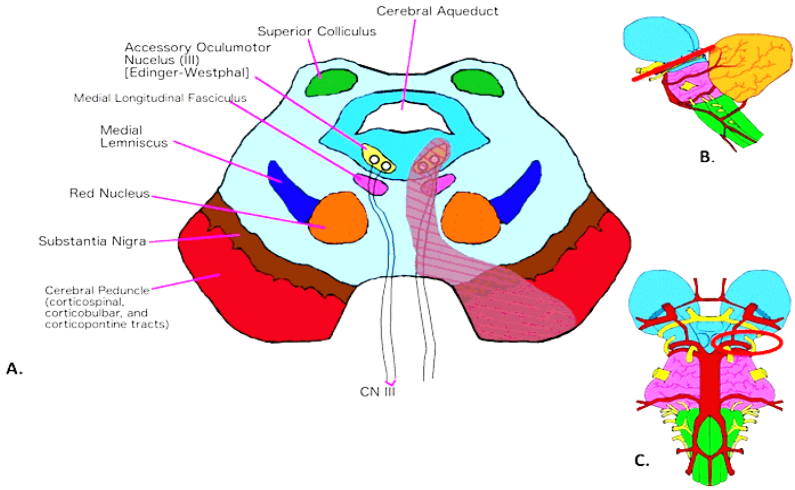

Fig. 20: **Structures affected in medial midbrain syndrome** (A) Transverse view of nuclei affected in left medial midbrain syndrome. The proximal penetrating branches of the posterior cerebral artery (PCA) supply the most medial aspect of the midbrain. These branches supply the corticospinal and corticobulbar tracts as well as the oculomotor nucleus, (B) Lateral view of the brainstem level affected in medial midbrain syndrome. The red line indicates the level being described is the midbrain in this syndrome, (C) Ventral view of the brainstem level affected in medial midbrain syndrome. The red circle indicates that PCA (proximal branches) is affected in this syndrome. [18]

The penetrating branches of PCA supply the midbrain [35, 36]. Unlike the medulla and pons, vascular syndromes of the midbrain do not exactly follow the rule of 4. Occlusion of these branches in this syndrome results in *(Fig. 21)*:

- ipsilateral eye „down and out" with dilation, and an unresponsive pupil (oculomotor nerve)
- weakness of the contralateral face (corticobulbar tract)
- weakness of the contralateral arm and leg (corticospinal tract).

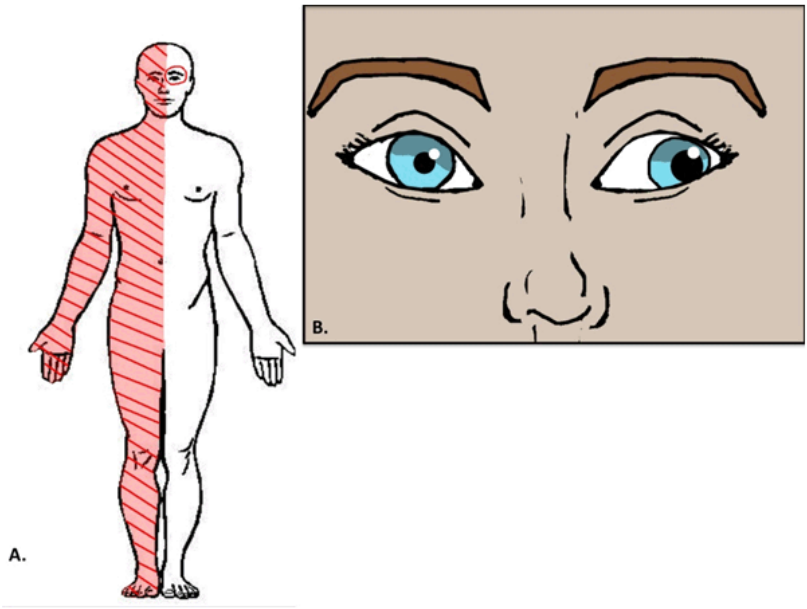

Fig. 21: **Clinical manifestations of medial midbrain syndrome** (A) Body representation of the clinical manifestations of left medial midbrain syndrome. The red lines represent weakness of the contralateral arm and leg (corticospinal tract) and contralateral face (corticobulbar tract). The red circle around the eye indicates an ipsilateral eye that is „down and out" with dilation and an unresponsive pupil (oculomotor nucleus), (B) Oculomotor nerve palsy. With respect to left medial midbrain syndrome, the left eye will be „down and out" in position, exhibit dilation, and the pupil will be unresponsive to light. [18]

Lateral Midbrain Syndrome

Lateral midbrain syndrome, also known as Benedikt syndrome, is most commonly due to penetrating branches of PCA *(Fig. 22)* [37].

The penetrating branches of PCA supply the midbrain [35, 36].

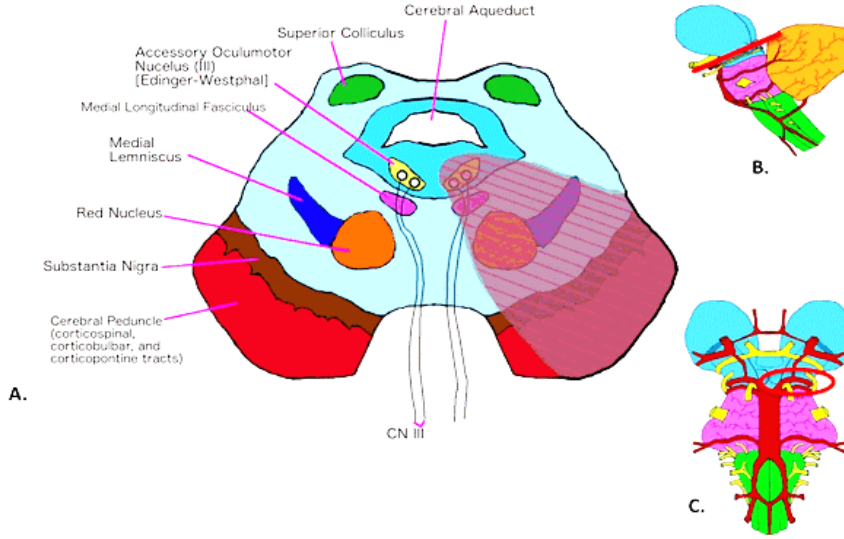

Fig. 22: **Structures affected in lateral midbrain syndrome** (A) Transverse view of nuclei affected in left lateral midbrain syndrome. The distal penetrating branches of the posterior cerebral artery supply the lateral aspect of the midbrain. These branches supply the oculomotor nucleus, medial longitudinal fasciculus (MLF), medial lemniscus, red nucleus, and cerebral peduncles, (B) Lateral view of the brainstem level affected in lateral midbrain syndrome. The red line indicates the level being described is the midbrain in this syndrome, (C) Ventral view of the brainstem level affected in lateral midbrain syndrome. The red circle indicates that the PCA (distal branches) is affected in this syndrome. [18].

Occlusion of these branches in this syndrome results in *(Fig. 23)*:

- ipsilateral eye „down and out" with dilation, and an unresponsive pupil (oculomotor nerve)
- ataxia of the contralateral body (red nucleus)
- tremor (dentatorubrothalamic tract)

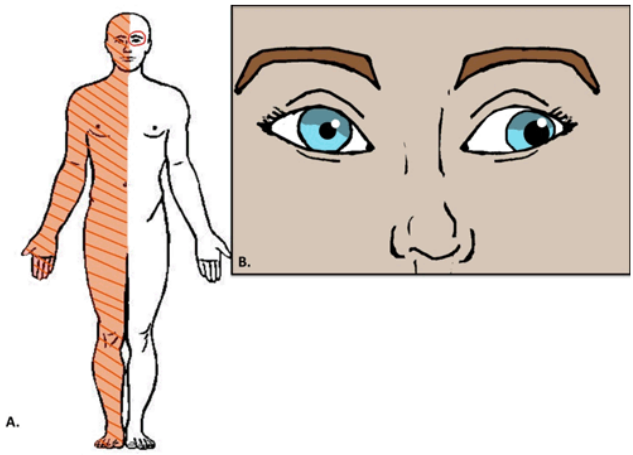

***Fig. 23*: Clinical manifestations of lateral midbrain syndrome** (A) Body representation of the clinical manifestations of left medial midbrain syndrome. The orange lines represent contralateral ataxia and tremor (red nucleus). The red circle around the eye indicates an ipsilateral eye that is „down and out" with dilation and an unresponsive pupil (oculomotor nucleus), (B) Oculomotor nerve palsy. With respect to left medial midbrain syndrome, the left eye will be „down and out" in position, exhibit dilation, and the pupil will be unresponsive to light. [18]

Dorsal Midbrain Syndrome

Dorsal midbrain syndrome, also known as Parinaud's syndrome and vertical gaze palsy, is most commonly caused by a pinealoma, which compresses the superior colliculus at the rostral interstitial nucleus of MLF *(Fig. 24)* [38, 39].

This syndrome can also result from multiple sclerosis and stroke of the upper brainstem [40]. It should be noted that case reports in the medical literature have demonstrated that occlusion of the posterior thalamo-subthalamic paramedian artery can also cause this syndrome [41]. Nevertheless, the classic etiology of Parinaud's syndrome, caused by a pinealoma, results in:

- paralysis of upward gaze (rostral interstitial nucleus of medical longitudinal fasciculus)
- collier's sign (retraction of the eyelids).

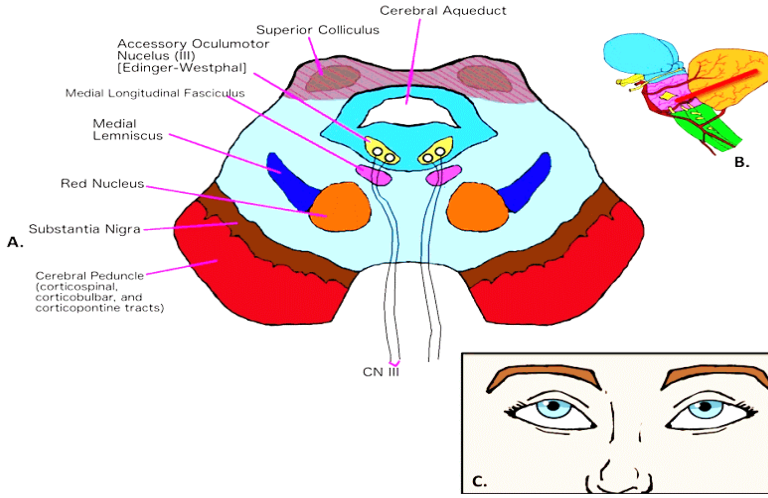

Fig. 24: **Structures affected and clinical manifestations in dorsal midbrain syndrome** (A) Transverse view of nuclei affected in dorsal midbrain syndrome. Dorsal midbrain syndrome most commonly results from superior colliculi compression due to mass effect from a pinealoma. Although extremely rare, this syndrome can also be a result of an infarct to the posterior thalamo-subthalamic paramedian artery (not shown), (B) Lateral view of the brainstem level affected in dorsal midbrain syndrome. The red line indicates the level being described is the midbrain in this syndrome, (C) Physical representation of the clinical manifestations of dorsal midbrain syndrome. Compression of the superior colliculus at the rostral interstitial nucleus of medical longitudinal fasciculus results in patients experiencing paralysis of upward gaze. [18]

In summary, if one can remember the rule of 4 and the distinguishing CN feature(s) of each vascular syndrome then one will be able to identify the presenting syndrome and localize the stroke to a vascular territory.

After-study test

Q1. Which of the following midline brainstem structures will result in an internuclear ophthalmoplegia if damaged?

A. Corticospinal tract

B. Medial lemniscus

C. Medial longitudinal fasciculus

D. Cranial nerve 6 motor nucleus

E. Lateral lemniscus

Q2. Which of the following descriptions most accurately describes Weber's syndrome?

A. Ipsilateral 3rd palsy, contralateral weakness of limbs

B. Ipsilateral 3rd palsy with contralateral choreoathetosis and ataxia

C. Ipsilateral 3rd palsy, contralateral limb ataxia

D. Contralateral 3rd palsy, ipsilateral weakness of limbs

E. Contralateral 3rd palsy, ipsilateral weakness of limbs and ataxia

Q3. Occlusion of which artery can result in „locked-in syndrome"?

A. Anterior communicating artery

B. Anterior choroidal artery

C. Middle cerebral artery

D. Recurrent artery of Heubner

E. Basilar artery

Q4. With respect to a brainstem stroke, what is locked-in syndrome?

A. A condition where the person cannot move anything but the eye muscles, and is devoid of the ability to think but is still conscious.

B. A condition where the person cannot move anything but the eye muscles, and is devoid of consciousness but not thinking.

C. A condition where the person cannot move the eye muscle, despite retaining consciousness and thinking.

D. A condition where the person cannot move anything but the eye muscles, despite retaining consciousness and thinking.

E. A condition where the person cannot move the eye muscles and is unconscious.

III. CLINICAL STROKE SYNDROMES

Learning objectives

After study of the assigned learning materials, the student will be able to:

1. Identify the presenting clinical syndrome of the brainstem and localize the stroke to a vascular territory.
2. Revise and explain each brainstem's segment vascularization.

Form of training: practical, theoretical (seminar) and individual works, 1.5 hours.

The main mechanism of stroke in patients who have extracranial atherosclerosis is artery to artery embolism, occasionally associated with hemodynamic disturbances. Although these mechanisms are also important in patients with intracranial atherosclerosis, branch occlusion and in-situ thrombotic occlusion play a relatively more important role in these patients. Accordingly, clinical stroke syndromes differ between extracranial atherosclerosis and intracranial atherosclerosis. In anterior circulation, middle cerebral artery atherosclerosis frequently produces subcortical infarction by way of branch occlusion. [42-46]

The clinical syndromes are similar to lacunar syndromes classically associated with small perforator artery diseases, although a larger size infarction can be accompanied by cortical dysfunction [47] such as aphasia or neglect. In-situ thrombotic occlusion of the large intracranial anterior circulation arteries leads to larger infarction that results in cortical symptoms – however, parts of the cortex are usually spared due to relatively well-developed collateral circulation associated with prolonged perfusion impairment. In the posterior circulation, intracranial atherosclerosis is common in the distal VA and BA that often causes medullary and pontine infarction syndromes, mostly by way of branch occlusion. PCA atherosclerosis produces pure midbrain or thalamic infarction through branch occlusion. Artery to artery embolisms from posterior fossa intracranial atherosclerosis lead to cortical infarction – cerebellar or temporo-occipital lobe infarction, producing ataxic

syndromes, and visual field defects and associated neurobehavioral syndromes, respectively.

Posterior Circulation Disease

In the posterior circulation, atherosclerosis is prone to occur in the proximal VA, distal intracranial VA, lower-middle portion of the BA, and proximal PCA [48]. Thrombus formed within the intracranial VA occasionally extends into the proximal BA [49]. Within the BA, atherosclerotic stenosis is common in the proximal 2 cm of the vessel, more often seen on the ventral than in the dorsal side [50]. Intracranial (distal VA, BA and PCA) atherosclerosis leads to stroke or transient ischemic attack (TIA) by way of artery-to-artery embolism, branch occlusion, hypoperfusion and in situ atherothrombotic occlusion.

Intracranial Vertebral Artery (ICVA) Diseases. Clinical Features Lateral Medullary Infarction (LMI) Syndrome.

Dizziness and gait instability, attributed either to vestibular or cerebellar system dysfunction, occur in more than 90 % of the patients. Whirling vertigo occurs in approximately 60 %, usually accompanied by nystagmus and nausea/vomiting [51, 52].

Gait ataxia is usually more severe than limb incoordination [53]. The nystagmus is mostly horizontal-rotational to the side opposite to the lesions [51, 52]. Skew deviation, with the ipsilateral eye going down, is also frequent. Ptosis and meiosis (components of a Horner's syndrome), is caused by involvement of the descending sympathetic fibers in the lateral reticular substance, occurs in about 90 % of patients [28]. Involvement of the nucleus ambiguous results in dysphagia, dysarthria and hoarseness. Dysphagia is present in approximately 2/3 of lateral medullary infarction (LMI) patients, among whom about 60% require nasogastric tube feeding [21]. Dysphagia is distinctly more severe in patients with rostral than in caudal lesions [54]. Approximately 1/4 of patients develop hiccup [55, 56], often days after the stroke onset. Headache, most often occurring in the ipsilateral occipital or upper nuchal area, occurs in approximately a half of the patients [57-59].

Prominent and persistent neck pain may be a manifestation of arterial dissection [60]. Facial palsy, usually mild and upper neuron type, is present in 1/5 to 1/4 of patients [61]. Sensory symptoms/signs are common, and sensory function remains intact in only 4 % of the patients [62, 63]. A selective loss of spinothalamic sensation is a rule [64]. Crossed (ipsilateral trigeminal-contralateral limb/body) sensory changes are characteristic, but recent studies have identified more diverse sensory pattern [64]. In one study [53], the patterns included ipsilateral trigeminal-contralateral limb/body in 26 %, contralateral trigeminal-contralateral limb/body in 25 %, bilateral trigeminal-contralateral limb/body in 14 %, limb/body involvement without trigeminal involvement in 21 % and trigeminal involvement without limb/body involvement in 10 %. In addition, approximately 7 % of LMI patients have additional ipsilateral tingling sensation often associated with lemniscal sensory deficits [63] due to involvement of yet uncrossed lemniscal sensory fibers in the caudal medulla.

Medial Medullary Infarction (MMI) Syndrome.

Dejerine proposed a triad of medial medullary syndrome: contralateral hemiplegia sparing the face, contralateral loss of deep sensation, and ipsilateral hypoglossal paralysis [24, 25]. Recent studies using magnetic resonance imaging (MRI) showed that medial medullary infarction (MMI) lesions are mostly unilateral, located in the rostral medulla, and usually present with relatively benign, sensori- motor stroke [65, 66]. Definite ipsilateral hypoglossal paresis is rare [67].

Contralateral hemiparesis sparing the face is the most characteristic sign of MMI, quadriparesis occurs in less than 10 % of patients [68]. Facial paresis, usually slight, occurs in 1/4 to 1/2 of the patients [69]. In patients with quadriparesis, dysarthria and dysphagia are severe while in those with unilateral lesion, a nasogastric tube is required in less than 10 %.

Sensory dysfunction is the second most important symptom/sign of MMI. Unlike LMI patients, MMI patients typically complain of tingling sensation from the onset, and show decreased perception of position and vibration due to selective involvement of the lemniscal sensory fibers.

The involved area is usually hemibody/ limbs below the ear or neck sparing the face. Limb incoordination is occasionally observed [70].

Vertigo/dizziness, nystagmus and ocular motor disturbances are closely related to involvement of dorsal medulla [59, 71], that contain vestibular nuclei and the nucleus prepositus hypoglossi.[72]

In contrast to LMI, nystagmus is mostly ipsilesional, and ocular lateropulsion is to the contralateral side (contrapulsion) [73]. Upbeat nystagmus is found in 1/10 to 1/5 of patients [74].

Significance of Intracranial Vertebral Artery (ICVA) Disease in Medullary Syndromes.

The medulla is mainly supplied by a number of penetrating arteries arising from the intracranial vertebral arteries (ICVAs). The dorsal area is also supplied by branches arising from the PICA. The most rostral part is also supplied by branches from the BA or AICA. The caudal part of the anterior medulla is supplied by penetrating arteries arising from the ASA. Atherothrombosis occurring in the ICVA or its penetrators is the most important cause of medullary infarction. Wallenberg initially considered PICA disease as a cause of lateral medullary infarction [75]. Half a century later, Fisher et al. [76] identified sole involvement of the PICA in only two of their 17 cases of lateral medullary infarction; 14 patients showed ICVA steno-occlusion. Since then, the most common cause of LMI has been recognized as occlusion of penetrating branches associated with ICVA steno-occlusive disease [76]. In a large series investigating 123 LMI patients [53], ipsilateral VA steno-occlusive disease was present in 83 (67 %) (33, ICVA disease, 34, whole VA disease and 5 proximal VA disease) and PICA disease in 12 (10 %) patients. Atherothrombosis is the dominant pathology, while dissection of the VA or PICA is the cause of steno-occlusive lesion in approximately 14–33 % of patients [28, 77].

In patients with normal angiographic findings, atherothrombotic occlusion of a perforating artery itself seems to be the mechanism of infarction. Embolic occlusion of the PICA or ICVA from diseased heart or a proximal vessel (e.g., extracranial VA) atherosclerosis may also

produce LMI [78, 79], but concomitant brainstem or cerebellar infarcts are usually present in these patients.

Regarding the medial medullary syndrome, ASA occlusion was initially considered an important stroke mechanism [80]. However, more recent studies reported that MMI is most often caused by occlusion of penetrating branches associated with atherosclerotic ICVA or VA and BA junction steno-occlusion [81]. In one series, relevant VA atherosclerotic disease was present in 62 % of patients while perforator occlusion without VA disease (small artery disease) occurred in 28 % patients [82]. Dissection of the ICVA may result in MMI, but is less common than in LMI.

Basilar Artery (BA) Diseases. Clinical Features.

The lower/middle portion of the BA is relatively common site for advanced atherosclerosis. In some patients atherostenosis in the distal portion of the ICVA near the BA origin leads to clot formation that propagates into the BA from the ICVA. The most important clinical syndromes associated with BA disease are those caused by pontine infarction.

Pontine Infarction Syndromes. Clinical Features.

Pontine infarct may occur in isolation or in association with other posterior fossa infarction [83-85]. Hospital registry studies showed that the patients with isolated pontine infarcts account for 2.6–3 % of ischemic strokes and 12–15 % of patients with posterior circulation infarcts [86]. One study from Asia showed a higher prevalence; 7.6 % of cerebral infarcts and 28 % of vertebrobasilar artery territory infarcts [87].

Motor Dysfunction (Including Dysarthria and Ataxia). The pontine base contains fibers regulating motor function including descending corticospinal, corticopontocerebellar, and corticobulbar tracts [88]. Although limb weakness is the most common symptom/sign, the clinical features depend upon the degree of involvement of each fiber tract and may manifest as pure motor stroke [89], ataxic-hemiparesis [90], and dysarthria clumsy hand syndromes [91].

Sensory Dysfunction. Tegmental pontine infarcts involving the sensory tracts (medial lemniscus and spinothalamic tract) produce a hemisensory deficit [92, 93]. Small infarcts often produce sensory symptoms in restricted body parts, most frequently in the pattern of cheiro-oral syndrome [94].

Ocular Motor Dysfunction. Structures related to ocular motor function are located in the dorsal paramedian pontine tegmentum that include: abducens nucleus/fascicles, paramedian pontine reticular formation (PPRF) and medial longitudinal fasciculus (MLF). Lesions affecting these structures produce various ocular motor dysfunctions than include 6th nerve palsy, INO: paralysis (or slowing) of adduction of the ipsilateral eye for conjugate eye movements, and nystagmus in the contralateral eye when this eye is in abduction [95, 96]. A unilateral pontine lesion involving the PPRF would produce ipsilateral gaze paresis. If the lesion involves both PPRF and the MLF on the same side, the patient has ipsilateral conjugate gaze palsy and paralysis of adduction of the ipsilateral eye on conjugate gaze to the opposite side (one-and-a-half syndrome) [97-99].

Bilateral Infarction Syndrome. As the bilateral lesions almost always involve the ventral part, involving the corticospinal tracts, quadriparesis is usual [83, 100]. The quadriparesis may start from the beginning; more often, the initial motor dysfunction is lateralized to one side and then progresses [101]. Unless successful therapy (such as recanalization) is immediately performed, asymmetrical motor disturbances often progress to severe quadriplegia [102-104]. The progression usually occurs within 24 h, but may be delayed up to several days.

Ataxia or incoordination is another common finding, observed in the limbs that are not severely paretic. Dysarthria and dysphagia due to bilateral bulbar muscles paresis are also common and severe. Some patients become totally unable to speak, open their mouth, or protrude their tongue. Somatosensory abnormalities should also be common, but they are usually overshadowed by motor dysfunction. Because large bilateral pontine infarcts frequently involve the dorsal tegmental area,

ocular motor dysfunction is also common, including an INO and one-and-a-half syndrome.

Extensive lesions involving the abducens nucleus and PPRF produce paralysis of all horizontal eye movements. Vertical gaze is usually spared because it is mediated at a more rostral level. Ocular bobbing, ptosis and pinpoint pupils may be observed. Symptoms such as tinnitus, hearing loss and auditory hallucination are related to involvement of the central auditory tracts/nuclei or to ischemia of the 8th nerves/fascicles. Some patients develop delayed-onset palatal myoclonus.

Altered consciousness is an important sign in patients with sudden BA occlusion and is related to bilateral medial tegmental pontine ischemia. Consciousness usually improves overtime. Patients may show pathological crying and laughing spells that are triggered by minimal social-emotional stimuli. When all voluntary movements are lost, the deficit is referred to as the „locked-in" syndrome. Intact vertical eye movements may be used in simple communications.

Significance of Basilar Artery (BA) Atherosclerosis in Pontine Infarction Syndromes

The majority of pathology leading to pontine infarction is BA atherothrombosis or perforator disease. Dissection is an uncommon etiology compared to medullary infarction. Branch occlusion associated with BA stenosis is an important stroke mechanism of pontine base infarction [105]; BA stenosis is present in 39–50 % of patients having lesions extending to the basal surface [106]. Even in patients without angiographically identified BA stenosis, small plaques that obliterate the orifice of perforating branches are seen occasionally if high resolution vessel wall MRI is used [107, 108]. Therefore, branch occlusion is actually more common than previously realized. Pontine infarcts limited to the tegmental area are mostly caused by small artery disease (lipohyalinosis), and are seldom associated with BA stenosis [109].

In patients with bilateral pontine infarction, significant BA steno-occlusion is usually present [110, 111]. This may result from either embolism (from diseased heart or proximal artery (e.g., VA) diseases) or

intrinsic BA thrombosis. Embolism is usually associated with infarcts in other parts of the brain, and is an uncommon cause of isolated pontine infarction. The clinical presentation of intrinsic BA diseases is less abrupt than embolism; patients often present with fluctuating or gradually progressing symptoms.

Posterior Cerebral Artery (PCA) Disease. Clinical Syndromes

The posterior cerebral arteries (PCAs) supply the midbrain, thalamus, medial temporal area, a part of the parietal lobe and the occipital lobe. Clinical syndromes are quite different according to the location of infarction.

Midbrain Infarction. In the largest series assessed by MRI [112, 113], clinical manifestations included gait ataxia (68 %), dysarthria (55 %), limb ataxia (50 %), sensory symptoms (43 %), third nerve palsy (35 %), definitive limb weakness (≤ IV/V) (23 %), and INO (13 %). Although third nerve palsy has been considered a clinical hallmark of midbrain infarction, it occurs in only 35 % to 50 % of patients with pure midbrain infarction [114, 115]. Third nerve palsy can be caused by involvement of either the third nerve fascicles or the third nerve nucleus due to lesions involving paramedian structures. Paramedian, dorsal lower midbrain lesions involving the MLF can produce INO. Antero-lateral lesions involving the cerebral peduncle will produce various motor syndromes, i.e., pure motor stroke, ataxic-hemiparesis, dysarthria clumsy hand syndrome. Generally, ataxia is prevalent because there are both descending (the cortico-ponto-cerebellar tract at the cerebral peduncle) and ascending (cerebello- rubro-thalamic tract, around the red nucleus) cerebellar fibers that are vulnerable to ischemic insults. Paramedian lesions may produce bilateral ataxia due to involvement of bilateral cerebello-rubro-thalamic tracts bilaterally.

These patients usually have long-standing gait ataxia and dysarthria. Some patients have persistent tremor like symptoms, that may be related to concomitant involvement of cerebellar tracts and nigro-lenticular dopaminergic fibers. Tremor most often develops after a delay and is rarely evident at stroke onset. Because the trochlear nerve fascicles exit dorsally after decussation around the aqueduct, they are spared in patients

with ventral midbrain lesions. Therefore, 4th nerve palsy is extremely uncommon in patients with pure midbrain infarcts [114, 115]. It may be present in patients who have superior cerebellar artery (SCA) infarction that involve both the dorsolateral midbrain and the cerebellum.

Thalamic Infarction. The arteries that supply the thalamus branch from the P1 and P2 portions of the PCA and the posterior communication artery. Thalamic infarction generally follows the topography according to four major thalamic vascular territories: the inferolateral, tuberothalamic, paramedian, and posterior choroidal arteries [116].

(a) Inferolateral (Thalamogeniculate) Artery Territory Infarction. The inferolateral (thalamogeniculate) arteries generally arise from the P2 portion of the PCA [117]. These arteries mainly supply the ventrolateral thalamus, which includes the ventrolateral (VL) and ventroposterior (VP) nuclear groups. Inferolateral artery territory infarction is the most common type of thalamic infarction [118-120].

The most frequent and important symptom/ sign of inferolateral artery infarction is hemisensory disturbance [121-123]. Small lateral thalamic infarcts that selectively involves the VP nucleus are the most common etiology of pure sensory stroke [123, 124]. A relatively large lesion that concomitantly involves the adjacent internal capsule can result in sensorimotor stroke, and additional involvement of the cerebellothalamic fibers at the VL nucleus may result in a „hypesthetic ataxic hemiparesis" syndrome.

(b) Tuberothalamic (Polar) Artery Territory Infarction.

The tuberothalamic artery originates from the middle-third of the posterior communicating artery or occasionally from the P1 portion of the PCA [125]. The tuberothalamic arteries (also often called the polar arteries) mainly supply the ventroanterior nucleus (VA), rostral part of the VL, and the ventral pole of the medial dorsal nucleus (MD). The main clinical syndromes include neuropsychological deficits [126]. Patients have fluctuating levels of alertness and impaired recent memory formation [127]. Some patients become abulic with decreased spontaneity and delayed, brief

responses to queries and conversation [128]. Language disturbances also occur in patients with left-side infarction.

(c) Paramedian (Thalamic-Subthalamic) Artery Territory Infarction. The paramedian arteries supply the paramedian parts of the upper midbrain and thalamus, including the intralaminar nuclear group and most of the dorsomedial nucleus.

Involvement of the paramedian territory is very common in patients with occlusion of the top of BA) [129, 130]. Somnolence and fluctuating levels of consciousness are a conspicuous feature during the early stages, and can last for hours or days [131, 132]. Confusion, agitation, aggression, and apathy may be present [133, 134]. Ocular motor disturbances are also found, that include vertical gaze palsy (upgaze, downgaze or both), convergence failure, pseudo-sixth-nerve palsy, pupillary changes, and ocular tilt reaction [135, 136], due to involvement of rostral midbrain structures. Difficulty making new memories is another common component of the syndrome.

(d) Posterior Choroidal Artery Territory Infarction. The posterior choroidal arteries arise from the P2 segment of the PCA distal to the origin of the posterior communicating artery. These arteries supply the lateral geniculate body (LGB), the inferolateral region of the pulvinar, the lateral dorsal nucleus, and the lateral posterior nucleus. Infarction limited to posterior choroidal artery territory area is uncommon [137, 138]. The two most prominent clinical manifestations are visual field defects and hemisensory deficits. Visual field defects include homonymous hemianopia (either congruent or incongruent), quadrantanopia, and sectoranopia [139, 140]. Hemisensory dysfunction is attributed to involvement of the VP nucleus, which is often supplied by the lateral posterior choroidal artery at least its caudal section [141].

Cortical (Superficial) Infarction. Hemispheric infarction due to PCA occlusion involves the occipital, posterior temporal, and parietal lobes, and clinical manifestations vary according to the location and extent of infarction [142, 143]. The most frequent clinical finding is a visual field defect, which occur in > 90 % of patients with cortical PCA territory infarction [144, 145].

Various types of cognitive abnormalities have been described. According to a study on patients with only cortical PCA infarction, memory impairment and aphasia affect 18 and 15 % of patients, respectively [146]. Although the cognitive deficits associated with visual dysfunction have been intensively studied, they are actually uncommon in clinical practice. In the cited study, the following frequencies were reported: visual hallucination (10 %), visual neglect (9 %), visual agnosia (8.5 %), prosopagnosia (5.5 %), color dysnomia (5 %), palinopsia (3 %), and color agnosia (3 %) [147].

Significance of PCA Atherosclerosis as a Cause of PCA Territory Infarction

The role of PCA atherosclerosis as a cause of PCA territory infarction remains uncertain, even though the proximal PCA is a predilection site of atherosclerosis [148]. Previous studies report a low (<10 %) prevalence of intrinsic PCA disease in patients with PCA territory infarction [144, 149]. Recent studies from Turkey [150] and Korea [151], where angiograms was performed on all the patients, identified PCA atherosclerosis as a cause of PCA territory infarction in 20–25 % of cases. Racial differences and the inclusion of isolated deep infarction in their studies may also explain the different prevalence of PCA disease among studies. PCA atherosclerosis also results in either branch occlusion or artery-to-artery embolism (from the proximal PCA to distal branches) that leads to deep (midbrain or thalamus) infarction and cortical (temporo-occipital) infarction, respectively. In the aforementioned Koreans study [151], authors found that among 38 patients with PCA atherosclerosis, diffusion-weighted imaging (DWI) identified infarcts were located in deep structures in 53 %, superficial structures in 13 and 34 % had the combination. The most often affected area was the lateral thalamus (58 %) followed by parieto-occipital area (45 %), temporal area (26 %) and midbrain (21 %). For midbrain infarction, the midbrain is mainly supplied by branches arising from the PCA, upper BA and the SCA.

It is often affected in patients with embolic stroke occurring in the posterior circulation usually with the concomitant involvement of other

structures such as the pons, thalamus, cerebellum and occipital lobe [152]. Infarcts limited to the midbrain are rare, accounting for 0.2-2.3 % of admitted ischemic stroke [114, 115]. Approximately 2/3 of pure midbrain infarction is caused by large artery atherosclerotic disease occurring in the proximal PCA or rostral BA. Small artery disease explains stroke in approximately 1/4 of the patients who have deep-seated lesions. Cardiac embolism is rare in patients with isolated midbrain infarction. The frequency of PCA atherosclerosis as a cause of pure thalamic infarction is not well known. However, previous studies have shown that underlying PCA atherosclerosis was the cause of 7-22 % of lateral thalamic infarcts [153, 154]. Patients with lateral thalamic infarction associated with underlying PCA disease tend to have larger lesions, symptoms in addition to sensory deficits and worse clinical outcome than in those without PCA disease [154].

Cerebellar Artery Diseases. Cerebellar Infarction Syndromes

Cerebellar infarcts are uncommon, accounting for 1-4 % of stroke [155-157], and usually follow the vascular topography, i.e., SCA, PICA and AICA territories, or their combination. In studies using computed tomography (CT) or MRI [158-160], PICA infarction is slightly more common than SCA infarction.

AICA infarction is distinctly uncommon. In patients with cerebellar infarction the most common symptoms are dizziness (or less commonly vertigo). Nausea/vomiting is usually accompanied by dizziness/vertigo and occurs in more than half of the patients) [161, 162]. Nystagmus is present in about half of the patients, usually horizontal, and occasionally vertical [163-166].

Headache occurs usually in the ipsilateral nuchal occipital area in 30–50 % of patients [167-169], presumably related to acute distention or stretch on the intracranial pain sensitive structures including cerebral vessels. Increasing severity of headache is a sign suggesting expanding edema or hemorrhagic transformation. Severe headache localized at the nuchal area may indicate VA or PICA dissection. Limb incoordination is an important sign, occurring in 60–70 % of the patients [161, 170-172].

Dysarthria in cerebellar infarction is mainly due to involvement of the superior paravermal lesion. Therefore, dysarthria is more common and prominent in patients with SCA infarction than in PICA infarction [173-176]. The clinical syndrome of AICA occlusion, first described by Adams [177] is distinct from that caused by SCA or PICA occlusion. Aside from vertigo, vomiting, ataxia and dysarthria, patients have tinnitus, ipsilateral facial palsy, hearing loss, tinnitus, trigeminal sensory loss, and Horner's syndrome. Sensory loss or hemiparesis in the contralateral limbs may occur when lateral pons is involved [178].

Significance of Intracranial Atherosclerosis as a Cause of Cerebellar Infarction Amarenco et al. [179] reviewed 88 pathologically proven cerebellar infarcts, and found that presumed causes include a cardiac embolism in 38 (43 %) patients and atherosclerosis in the vertebrobasilar artery in 31 (35 %) patients.

PICA infarction is caused by occlusion of the ICVA or PICA itself. According to previous studies, PICA occlusions are equally divided between in situ atherothrombosis and cardioembolism [5, 180]. Other less common causes include dissection (either VA or PICA). Most SCA territory infarction is caused by embolism from atrial fibrillation, and less commonly from large artery atherosclerosis [181, 182]. Atherosclerosis in the proximal part of the SCA as a cause of cerebellar infarction is uncommon [183]. Dissection and fibromuscular dysphasia of the SCA are even less common [184]. For AICA territory infarction, atherothrombotic BA steno-occlusion seems to be the most common stroke mechanism [185, 186].

When BA atherostenosis is the cause invariably other areas of the posterior circulation are involved along with the AICA territory. Embolism is distinctly uncommon for isolated AICA territory infarction. According to Kumral et al. [187], large artery disease was the cause of stroke in 52 %, cardiac embolism in 4 % while 17 % had both etiologies.

Because AICA territory infarction is often associated with significant lower BA atherosclerosis, it should be kept in mind that this may herald massive BA thrombotic infarction [186]. In patients who

showed deterioration of neurological function, early reperfusion therapy and rehabilitation may have to be considered to prevent worsening of the symptoms. [42-44, 188-190].

Top of the Basilar Artery (BA) Syndrome

Infarction of the rostral brainstem and cerebral hemispheral regions fed by the distal BA causes a clinically recognizable syndrome characterized by visual, oculomotor, and behavioral abnormalities, often without significant motor dysfunction. Caplan [191] described this as „the top of the BA syndrome". Typically, there are bilateral multiple infarcts in the paramedian midbrain, medial thalamus, medial temporal areas and occipital lobes. However, the clinical features vary greatly depending on the damaged brain [192, 193]. BA Atherosclerosis as a Cause Top of Basilar Syndrome Atherosclerosis is generally most severe in the proximal BA, and occlusions of the BA tip are usually embolic [191, 194], more often from the diseased heart than proximal atherothrombosis. Although atherothrombosis occurring in the distal BA can also result in TOB [195], this is distinctly uncommon [196].

After-study test

Q1. A 65-year-old African American man presents to the emergency department with 6 hours history of left hemiplegia and tongue deviation to the right. His past medical history is significant for atrial fibrillation. On examination, there is a loss of proprioception on the left side of the body. His vitals are stable. Which of the following artery is affected?

A. Left vertebral artery

B. Right vertebral artery

C. Posterior inferior cerebellar artery

D. Anterior inferior cerebellar artery

E. Medullary artery

Q2. A 65-year-old man comes to the office due to dizziness, abnormal gait, and double vision for the past few days. Her previous history is positive for type 2 diabetes mellitus and hypertension, for which she is on regular medication. Family history is positive for

ischemic heart disease in father. His pulse is 67 beats/min, blood pressure is 128/76 mmHg. On physical examination of the visual system, her right eye abducts and exhibits horizontal nystagmus, but her left eye doesn't move. When asked to look left, both eyes appear normal. Convergence appears normal in both eyes. Which of the following is the most likely site for her lesion?

A. Edinger-Westphal nucleus
B. Occulomotor nerve (CN III)
C. Trochlear nerve (CN IV)
D. Abducens nerve (CN VI)
E. Medial longitudinal fasiculus

IV. BRAINSTEM DEATH

Learning objectives

After study of the assigned learning materials, the student will be able to:

1. Outline current recommendations and guidelines pertaining to the diagnosis of brain stem death.
2. Identify specific prerequisites that are mandatory before initiation of evaluation for brain stem death.
3. Summarize confounding factors and the pitfalls that can erroneously jeopardize the protocol in diagnosing brain stem death.
4. Explain the role of an interprofessional team in performing brain stem death evaluation.

Form of training: practical, theoretical (seminar) and individual works, 1.5 hours.

The revised memorandum in 1979 correlated the brain stem death with death itself. This chapter outlines current recommendations set for diagnosing brain stem death and highlights mandatory prerequisites to be rigorously adopted prior to initiating the process of evaluating brain stem integrity and reviews the potential pitfalls and shortcomings during the

steps in assessing brain stem reflexes, the apnea test, and the ancillary tests to avoid complications.

Mollart and Goulon first coined the term „coma depasse," meaning a state beyond coma, for brain death [197, 198].

The Conference of Royal Medical Colleges in 1976 came to the consensus that brainstem death constitutes brain death. The revised memorandum in 1979 correlated brainstem death with death itself [199].

The American Academy of Neurology (AAN) has postulated brain death as a „coma, absence of brainstem reflexes, and apnea." [200].

Academy of Medical Royal Colleges Working Party has defined brainstem death as „the irreversible loss of the capacity for gaining consciousness, and the capacity to spontaneously breathe." [201].

Persistent vegetative state – loss of only cortical functions with intact brain stem functions

Brain-stem death – absent brain stem reflexes but the presence of few cortical as well as hypothalamic integrity such as osmoregulation

Whole Brain death – biological death with absent cortical and brainstem functions

Death – Whole-brain death along with the cardiopulmonary arrest

Brainstem reflexes

The following brainstem reflexes should be carried out for evaluating the clinical integrity of the brainstem [200, 202, 203]:

- The corneal reflex: The blinking of eyelids after touching the cornea with a cotton wisp or small jet of water.
- The pupillary light reflex This constitutes brisk constriction of the pupils after exposure to bright light. However, precautions are necessary to rule out any previous eye surgeries, concurrent cataract, and use of drugs such as atropine.
- Oculocephalic reflex: Turning of the eyes in the opposite direction of head movement when the head is turned from the mid position to both sides. This should not be attempted in patients with concern for cervical cord injuries.

- Oculovestibular reflex: Lack of eye movements after 50 ml of ice-cold water is instilled into the external auditory meatus over one minute after assuring patency of the tympanic membrane.
- Gag reflex: Pharyngeal contraction after stimulating the pharynx with a spatula or tongue depressor.
- Cough reflex: Presence of cough after stimulation of the carina by a bronchial catheter.
- Response to noxious stimuli along the distribution of CNs. For-example facial grimace after noxious stimulus applied on the supraorbital ridge supplied by the trigeminal nerve.

However, following confounding factors that can impede upon correct evaluation of the brainstem function must first be ruled out [200]:

- No concurrent use of CNS depressant drugs or neuromuscular blocking agents
  - ✓ Must wait for at least five half-lives of the drug to attempt valid evaluation if such agents have been used
- Normal core body temperature
- Normal systolic blood pressure
- No severe electrolyte, acid-base or endocrine disturbances

If the patient fulfills the above criteria and evaluation reveals the absence of brainstem reflexes, the clinician should perform apnea testing per the AAN recommendation [204, 205].

Apnea Test:

- Connect a pulse oximeter, pre-oxygenate with 100 % oxygen (O2), and disconnect the ventilator.
- Deliver 100 % O2 at 6 L/min through a cannula placed at the level of the carina.
- If respiratory movements are absent despite arterial partial pressure of carbon dioxide (PCO2) of greater than or equal to 60 mmHg or a 20 mmHg increase in PCO2 over a normal baseline is noted, the apnea test is considered concluded.

The test is terminated in instances wherein there is hypotension, hypoxemia, or cardiac arrhythmias.

The absence of brainstem reflexes and an apnea test negative for spontaneous respirations validate the brain death of the patient.

Ancillary tests:

that can be used to diagnose brain death include:

- Flat electrical activity on at least a 30-minute electroencephalography (EEG) [206]
- Absence of cerebral flow beyond the circle of Willis during angiography
- No uptake of isotope within the blood vessel or brain parenchyma during a nuclear scan
- Small systolic peaks in early systole without diastolic flow or reverberating flow on a transcranial Doppler. [207]

These tests are only justified when apnea testing is inconclusive, or patients are too unstable to proceed with apnea testing, or when brainstem reflexes cannot be carried out (vestibulo-ocular reflex in cervical spine injuries).

Issues of Concern

Brainstem death is a clinical diagnosis made by an examiner. Ancillary tests are not essential for confirming brain death [208, 209]. Brainstem death has to be **certified by** certified board members, which include:

- Medical superintendent– in-charge of the hospital
- The treating medical or critical care specialist
- A neurologist or a neurosurgeon
  - ✓ Members from the organ donation or the transplantation team cannot be involved in this certification.

The clinical diagnosis of brain death should take place in **three steps**:

- Establishing the etiology
- Excluding possible reversible syndromes that may produce signs similar to brain death
- Demonstration of clinical signs of brain death including coma, brainstem areflexia, and apnea

However, when planning for organ donation, separate complete examinations by two physicians is recommended [197, 202, 203].

Ethical morality - justifying the use of limited medical resources, adding up the financial burden, and maximizing emotional toll to relatives in a hopeless clinical scenario

The whole-brain death concept – It is more prudent for the application of brainstem death rather than the whole brain death concept. It requires emphasis that though the brain stem is dead, there may still be some cortical and the hypothalamic functions (osmoregulation) intact in the patient. It is also distinct from cortical death (persistent vegetative state) wherein the brainstem functions are intact.

Concerns with the apnea test - There are inherent confounding clinical factors that can invalidate the apnea test, such as hypoxia, hypotension, cervical cord injuries. Moreover, hypercarbia by causing cerebral vasodilation can further impede upon the cascade of impending cerebral herniation, thereby further complication the clinical scenario.

Public belief in brain death and organ procurement - There can be a significant concern among the relatives and the public that organ donation occurs when the patient heart is still beating, and the person is not entirely dead. There can be looming fear that death will be declared prematurely for the sake of organ and tissue retrieval [210, 211].

Is the brain-dead person really dead? - Issues in defining biological death - certain pitfalls merit consideration while evaluating for brainstem death confirmation [212-215]:

- **The inexperience** of the performing physician
- **Potential confounders** - such as hypothermia, drugs, alcohol
- **Inadequate consideration during apnea test -** such as low pCO2, ventilator trigger settings
- **False Positive Brain Death Determination** in scenarios such as barbiturate coma, baclofen toxicity
- **False Negative Brain Death Determination -** spinal reflexes and automatisms, ventilator auto-triggering during the apnea test

- **Brain Death in Children** - from 37 weeks of gestational age to 30 days, two examinations 24 hours apart whereas in 30 days to 18 years' child, two examinations 12 hours apart
- **Limitations of Ancillary Tests** - artifacts in EEG
- **Concerns relating to families and potential Organ donation** such as personal and religious beliefs
- **Failure to Maintain adequate environment for Organ donation** - systolic blood pressure of 100 mm Hg, urine output of at least 0.5 ml/kg/h; normal serum electrolytes and a tidal volume, not more than 8 ml/kg.

Clinical Significance

The diagnosis of brain death is primarily derived clinically [202, 203]. The first step in determining brainstem death is to notify the next of kin about the process. The interval observation period of 6-hour period is usually considered sufficient in adults and children over one-year age. A reliable interval period has not been established for children less than seven days old. For children between 7 days to two months, two examinations and EEGs should be separated by at least 48 hours. In contrast, in children between two months to one year, two examinations and EEGs should be separated by at least 24 hours.

Repeat the clinical assessment of brain stem reflexes. The steps and all examinations require full documentation. Confirmatory testing [216] should only take place out when deemed necessary and include:

- Angiography: the absence of intracerebral filling at the level of the carotid bifurcation or circle of Willis.
- Electroencephalography: absent electrical activity during at least 30 minutes of recording [206]
- Nuclear brain scan: the absence of uptake of isotope („hollow skull phenomenon")
- Somatosensory evoked potentials: Brain death confirmed by the bilateral absence of N20-P22 response with median nerve stimulation.

- Transcranial Doppler ultrasonography: small systolic peaks confirm brain death in early systole without diastolic flow or reverberating flow. [207].

Medical Record Documentation should include:

- Etiology and irreversibility of coma
- Absent motor response to pain
- Absent brainstem reflexes during two separate examinations separated by at least 6 hours
- Absent respiration with pCO2 greater than or equal to 60 mmHg
- Justification for, and result of, confirmatory tests if applicable.

Other Issues

Clinical instances that can be observed but compatible with the diagnosis of brain death [202, 203]:

- Spontaneous movements other than pathologic flexion or extension response
- Respiratory-like movements
- Autonomic features such as sweating, flushing, tachycardia
- Normal or sudden increases in blood pressure
- Absence of diabetes insipidus
- Deep tendon reflexes; superficial abdominal reflexes; triple flexion response
- Babinski reflex.

Enhancing Healthcare Team Outcomes

Because of differences in the definition of death owing to different cultural and religious grounds, it is challenging to obtain equivocal consensus for declaring brainstem death [213-215].

The diagnosis of brainstem death requires meticulous and verifiable testing and evaluation. In most intensive care settings, the initial examination is performed by the critical care provider. The critical care nurse assists the clinician to make this diagnosis by verifying and documenting the neurological status of the patient before and during the

brainstem evaluation. The critical care nurse also assists the medical team by monitoring the patient, especially during the apnea testing, to ensure the test is terminated if unstable vital signs develop. The bedside nurse, social worker, and the clinical providers can educate the family about the process of brainstem death evaluation and the meaning of the results to help the family understand this difficult concept. A collaborative inter-professional team can help accurately and efficiently diagnose the patient with brainstem death. This will help avoid unnecessary testing and provide timely family support when the diagnosis is confirmed.

After-study test

Q1. Brainstem death:

A. Can be diagnosed in a spontaneously ventilating patient.

B. Can be diagnosed by any consultant acting alone.

C. Is impossible to diagnose in a sedated patient.

D. Cannot be diagnosed after hypoxic brain injury.

E. Is confirmed after one set of 'brainstem tests'.

Q2. Regarding brainstem tests:

A. The pupillary reflexes examine the function of the facial nerve and the trigeminal nerve.

B. Oculo-vestibular reflexes are examined by injecting warm saline into the middle ear.

C. A plasma potassium of less than 4.0 mmol litre−1 should be corrected before brainstem death testing.

D. Apnoea testing need only be completed once.

E. Motor response in the arms in response to nail bed pressure excludes brainstem death.

Q3. A 20-year-old male patient intubated and ventilated on ICU following a head injury requires brainstem death testing for potential organ donation. Which of the following statements is true?

A. The pupils must be fixed and dilated

B. Lack of limb movement is essential
C. Two consultants must perform the tests
D. Caloric tests must be performed bilaterally
E. There must be no EEG activity

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