An anatomical study of the central myelin portion and transitional zone of the oculomotor and abducens nerves

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การศึกษาทางกายวิภาคของส่วนที่เป็นเซ็นทรัลไมอีลินและโซนเปลี่ยนผ่านของ เส้นประสาทสมองออกคิวโลมอเตอร์ และแอบดิวเซนส

น.ส.วิญาดา ขวัญเจริญทรัพย์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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วิญาดา ขวัญเจริญทรัพย์ : การศึกษาทางกายวิภาคของส่วนที่เป็นเซ็นทรัลไมอีลินและโซนเปลี่ยนผ่านของ เส้นประสาทสมองออกคิวโลมอเตอร์ และแอบดิวเซนส. (An anatomical study of the central myelin portion and transitional zone of the oculomotor and abducens nerves) อ.ที่ปรึกษาหลัก : ศ. ดร. พญ.วิไล ชินธเนศ

Neurovascular syndrome เป็นกลุ่มอาการที่มีการทำงานของเส้นประสาทสมองที่ผิดปกติ โดยเกิดจากหลอดเลือดกดทับเส้นประสาทสมอง ทำให้ผู้ป่วยมีอาการตามเส้นประสาทสมองนั้นๆ โรคที่รู้จักกันดี เช่น โรคปวดเส้นประสาทใบหน้า (Trigeminal neuralgia) โรคใบหน้ากระตุกครึ่งหน้า (Hemifacial spasm) และโรคปวดเส้นประสาทสมองคู่ที่ 9 (Glossopharyngeal neuralgia) ในกรณีที่มีหลอดเลือดกดทับเส้นประสาทออกคิวโลมอเตอร์และแอบดิวเซนส์ ก็จะทำให้เกิดโรค Ocular neuromyotonia และ abducens nerve plasy ซึ่งทำให้มีการกลอกตาที่ผิดปกติ บริเวณของรอยโรคยังเป็นที่ถกเถียงกันเนื่องจากคำจำกัดความไม่ชัดเจน เช่น คำว่า Root entry/ exit zone (REZ) ถูกนิยามหลากหลายในแต่ละการศึกษาและมีการใช้แทนกันกับคำว่าโซนเปลี่ยนผ่าน (Transitional zone) ทำให้ยากต่อการเปรียบเทียบระหว่างการศึกษา เมื่อมีการศึกษาเพิ่มเติม ทำให้ทราบว่าโซนเปลี่ยนผ่านคือจุดเชื่อมต่อระหว่างระบบประสาทส่วนกลางและส่วนปลาย ก่อนหน้านี้มีการศึกษาเซ็นทรัลไมอีลิน (Central myelin) และโซนเปลี่ยนผ่านของเส้นประสาทสมองคู่ที่ 5 (Trigeminal nerve) 7 (Facial nerve) และ 9 (Glossopharyngeal nerve) ด้วยคำจำกัดความที่ชัดเจน ในขณะที่ความรู้ทางจุลกายวิภาคเกี่ยวกับเส้นประสาทสมองออกคิวโลมอเตอร์และแอบดิวเซนส์ยังมีอยู่อย่างจำกัด จุดมุ่งหมายของการศึกษานี้คือเพื่อประเมินจุลกายวิภาคของเซ็นทรัลไมอีลินและโซนเปลี่ยนผ่านของเส้นประสาททั้งสอง

ในการศึกษานี้เก็บเส้นประสาทออกคิวโลมอเตอร์ 29 ตัวอย่างและเส้นประสาทแอบดิวเซนส์ 53 ตัวอย่างจากสมองของอาจารย์ใหญ่รวม 46 ร่าง แต่มีเพียงเส้นประสาท 10 เส้นในแต่ละชนิดที่สามารถนำมาศึกษาต่อได้ ตัวอย่างเหล่านี้จะถูกตัดให้มีความหนา 5 ไมครอน ย้อมสี ถ่ายภาพภายใต้กล้องจุลทรรศน์ และวัดระยะทางดังต่อไปนี้ เส้นผ่านศูนย์กลางของเส้นประสาทสมอง ความยาวของเซ็นทรัลไมอีลิน เส้นผ่านศูนย์กลางของโซนเปลี่ยนผ่าน ความลึกของโซนเปลี่ยนผ่าน และความยาวของเซ็นทรัลไมอีลินด้านที่ไกลจากสมอง ในการศึกษานี้พบว่ามีความยาวเซ็นทรัลไมอีลินในเส้นประสาทออกคิวโลมอเตอร์และแอบดิวเซนส์เท่ากับ 2.75 ± 0.83 มม.และ 1.66 ± 1.39 มม.ตามลำดับ ส่วนความยาวเซ็นทรัลไมอีลินที่ยาวที่สุดในเส้นประสาทออกคิวโลมอเตอร์และแอบดิวเซนส์ คือ 4.30 ± 1.26 มม. และ 1.88 ± 1.40 มม.ตามลำดับ ความลึกของโซนเปลี่ยนผ่านในเส้นประสาทออกคิวโลมอเตอร์และแอบดิวเซนส์ เท่ากับ 0.23 ± 0.07 มม.และ 0.16 ± 0.08 มม.ตามลำดับ ความยาวเซ็นทรัลไมอีลินด้านที่ไกลจากสมองในเส้นประสาทออกคิวโลมอเตอร์และแอบดิวเซนส์เท่ากับ 1.47 ± 0.90 มม.และ 1.42 ± 1.50 มม.ตามลำดับ นอกจากนั้นยังพบความสัมพันธ์ในเชิงบวกระหว่างความลึกของโซนเปลี่ยนผ่านและความยาวเซ็นทรัลไมอีลินของมัดเส้นประสาทแต่ละมัดในเส้นประสาทออกคิวโลมอเตอร์ (r +0.310, $p<0.05$) และเส้นประสาทแอบดิวเซนส์ (r +0.413, $p<0.05$) ความลึกของโซนเปลี่ยนผ่านมีความแตกต่างกันระหว่างเส้นประสาทและลำเส้นประสาทโดยอาจมีความยาวได้มากถึง 20% ของความยาวเซ็นทรัลไมอีลินทั้งหมด สำหรับเส้นประสาทออกคิวโลมอเตอร์จะพบเซ็นทรัลไมอีลินที่ยาวที่สุดที่เส้นประสาทลำแรก จากนั้นความยาวของเซ็นทรัลไมอีลินจะลดลงจากด้านข้าง (Lateral side) ไปตรงกลาง (Medial side) สำหรับเส้นประสาทแอบดิวเซนส์รูปแบบทางสัณฐานวิทยาแบ่งออกได้เป็นประเภท 4 ประเภทคือ A-D ซึ่งประเภท A และ B มีแนวโน้มที่จะมีเซ็นทรัลไมอีลินยาวกว่าประเภท C และ D นอกจากนี้เซ็นทรัลไมอีลินที่ยาวกว่ามีแนวโน้มที่จะมีโซนเปลี่ยนผ่านที่ยาวกว่าในเส้นประสาททั้งสอง

การศึกษานี้ได้ระบุรายละเอียดทางกายวิภาคของเซ็นทรัลไมอีลินและโซนเปลี่ยนผ่านได้ไว้อย่างชัดเจน ซึ่งจะช่วยในการระบุตำแหน่งรอยโรคได้อย่างแม่นยำและทำให้เข้าใจสาเหตุมากขึ้น นอกจากนี้เป็นที่ทราบกันว่าระบบประสาทส่วนปลายมีความทนทานต่อแรงกดมากกว่าเมื่อเทียบกับระบบประสาทส่วนกลาง ดังนั้นการรู้ลักษณะทางกายวิภาคของเส้นประสาทสมองจะช่วยให้การผ่าตัดปลอดภัยยิ่งขึ้น

สาขาวิชา	วิทยาศาสตร์การแพทย์	ลายมือชื่อนิสิต .....
ปีการศึกษา	2564	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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KEYWORD: Abducens nerve, Central myelin, Oculomotor nerve, Peripheral myelin, Transitional zone
Wiyada Quanchareonsap : An anatomical study of the central myelin portion and transitional zone of the oculomotor and abducens nerves. Advisor: Prof VILAI CHENTANEZ, M.D., Ph.D.

Neurovascular syndrome is a dysfunction of an individual cranial nerve which is compressed by vessels. Several neurovascular compression syndromes are well known such as trigeminal neuralgia, hemifacial spasm, and glossopharyngeal neuralgia. Having neurovascular conflicts at oculomotor nerves and abducens nerve cause ocular neuromyotonia and abducens nerve palsy. Site of compression is still controversial because of unclear definition. The term root entry/ exit zone (REZ) is defined variously and used interchangeably with transitional zone making it hard to compare between studies. It is generally thought to be at transitional zone which is defined as junction between central and peripheral nervous system. Lately, central myelin and transitional zone of trigeminal, facial, and glossopharyngeal nerves has been studied with clear definition. However, microanatomical knowledge about oculomotor and abducens nerves is limited. The aim of study was to evaluate microanatomy of central myelin and transitional zone of both nerves.

Twenty-nine oculomotor and 53 abducens nerves were obtained from 46 cadavers' brains but only 10 of each nerve were included. These specimens were serially sectioned with 5 μm thickness, stained, and photographed under the microscope. Five distances were measured: diameter of cranial nerve, extent of central myelin, diameter of transitional zone, depth of transitional zone, and length of central myelin on the far side of the brainstem. Length of central myelin was 2.75 ± 0.83 mm in oculomotor nerve and 1.66 ± 1.39 mm in abducens nerve. Longest central myelin length was 4.30 ± 1.26 mm in oculomotor nerve and 1.88 ± 1.40 mm in abducens nerve. Depth of transitional zone was 0.23 ± 0.07 mm in oculomotor nerve and 0.16 ± 0.08 mm in abducens nerve. Length of the central myelin portion on the far side of the brainstem was 1.47 ± 0.90 mm in oculomotor nerve and 1.42 ± 1.50 mm in abducens nerve. Positive weak correlation between depth of transitional zone and length of central myelin of each nerve bundle in oculomotor nerve (r +0.310, $p<0.05$) and abducens nerves (r +0.413, $p<0.05$) were found. Depths of transitional zone varied between nerves and nerves bundles. Transitional zone usually takes up to 20% of central myelin. For oculomotor nerve, longest central myelin was seen on first nerve bundles and then length of central myelin was gradually decreased from lateral to medial side. For abducens nerves, morphological patterns were classified into type A-D which type A and B tend to have longer segment of central myelin than type C and D. Also, longer central myelin tends to have longer transitional zone in both nerves.

Detail of microanatomy of central myelin and transitional zone is clearly stated. Clinicians could benefit from well-defined parameters which help to locate lesion precisely and understand etiology more. Moreover, it is previously known that peripheral nervous segment is more resistant to compression compared to central nervous segment so knowing microanatomy of cranial nerves could provide safer surgeries.

Field of Study:	Medical Sciences	Student's Signature .....
Academic Year:	2021	Advisor's Signature .....

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Wiyada Quanchareonsap

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A	Diameters of nerves where they exit from the brainstem
B	Diameters of transitional zone
C	Lengths of the central myelin portion on the far side of the brainstem
CNS	Central nervous system
COP	Cyclic oculomotor nerve palsy
F	Lengths of the central myelin portion
F*	Longest lengths of the central myelin portion
f	Depths of the transitional zone
MBP	Myelin basic proteins
OSP	Oligodendrocyte-specific protein
PLP	Proteolipid protein
PNS	Peripheral nervous system
REZ	Root entry/ exit zone

CHAPTER I

INTRODUCTION

Background and Rationales

Neurovascular syndrome is a dysfunction of an individual cranial nerve which is compressed by vessels.[1] Several neurovascular compression syndromes of cranial nerves including trigeminal neuralgia, hemifacial spasm, and glossopharyngeal neuralgia have been proved with successful surgical decompression of nerves.[2] Eye movements allow us to look at the objects and stabilize the images which are controlled by extraocular muscles. These muscles are innervated by oculomotor, trochlear, and abducens nerves.[3] Compression of these cranial nerves causes cyclic oculomotor nerve palsy, superior oblique myokymia, and abducens nerve palsy.[4] Neurovascular conflict of any of these nerves could cause ocular neuromyotonia.[5] Patient usually presents with horizontal diplopia when a lesion is at the abducens nerve.[5, 6] Cyclic oculomotor palsy causes abnormal eye movement and may also involve pupil contraction and involuntary lid lifting.[7] These symptoms impair quality of life and cause cosmetic concern. A diagnosis is made with the clinical manifestation. Magnetic resonance imaging is the investigation of choice to find neurovascular compression and exclude other causes such as a tumor, aneurysm.[1] The etiology is not fully understood but neurovascular compression has been proposed to be one of the causes. Also, successful microvascular decompression has been reported in ocular neuromyotonia and abducens nerve palsy.[8, 9]

The site of compression which causes the symptom is still controversial. Trigeminal neuralgia is generally thought to have a lesion at the root entry/ exit zone (REZ) which refers to the transitional zone.[10-12] Moller and Jannetta (1984) confirmed this hypothesis by results of intracranial recording that the neurovascular compression is located at REZ.[13] Nonetheless, the neurovascular press on the distal part other than REZ was explained by the traction of the nerve which had an indirect effect on the REZ.[14] The microanatomy of the central myelin portion and transitional zone of several cranial nerves including trigeminal, facial, glossopharyngeal, and vagus nerves have been clearly demonstrated.[2, 15, 16] However, knowledge of microanatomy of central myelin portion and transitional zone of the oculomotor and abducens nerves which involve in ocular neuromyotonia lacks.

Therefore, this study aims to provide microanatomical knowledge of the central myelin-peripheral myelin transitional zone and central myelin portion of the oculomotor and abducens nerves from human cadavers. Length of central myelin portion, diameter at the exit site, and the number of bundles will be determined.

Research Questions

Primary question

- What are the depths of the central myelin-peripheral myelin transitional zone of the oculomotor and abducens nerves?

Secondary question

- What are the lengths of the central myelin portion of the oculomotor and abducens nerves?
- What are the lengths of the central myelin portion on the far side of the brainstem of the oculomotor and abducens nerves?
- What are the diameters of oculomotor and abducens nerves where they exit from the brainstem?
- What are the diameters of the oculomotor and abducens nerves where the transitional zone begins?
- How many oculomotor and abducens nerve bundles are present in histology?
- What are the ratios of transitional zone-central myelin of the oculomotor and abducens nerves?
- Is there any correlation between the depth of transitional zone and length of central myelin of each nerve bundle?

Objectives

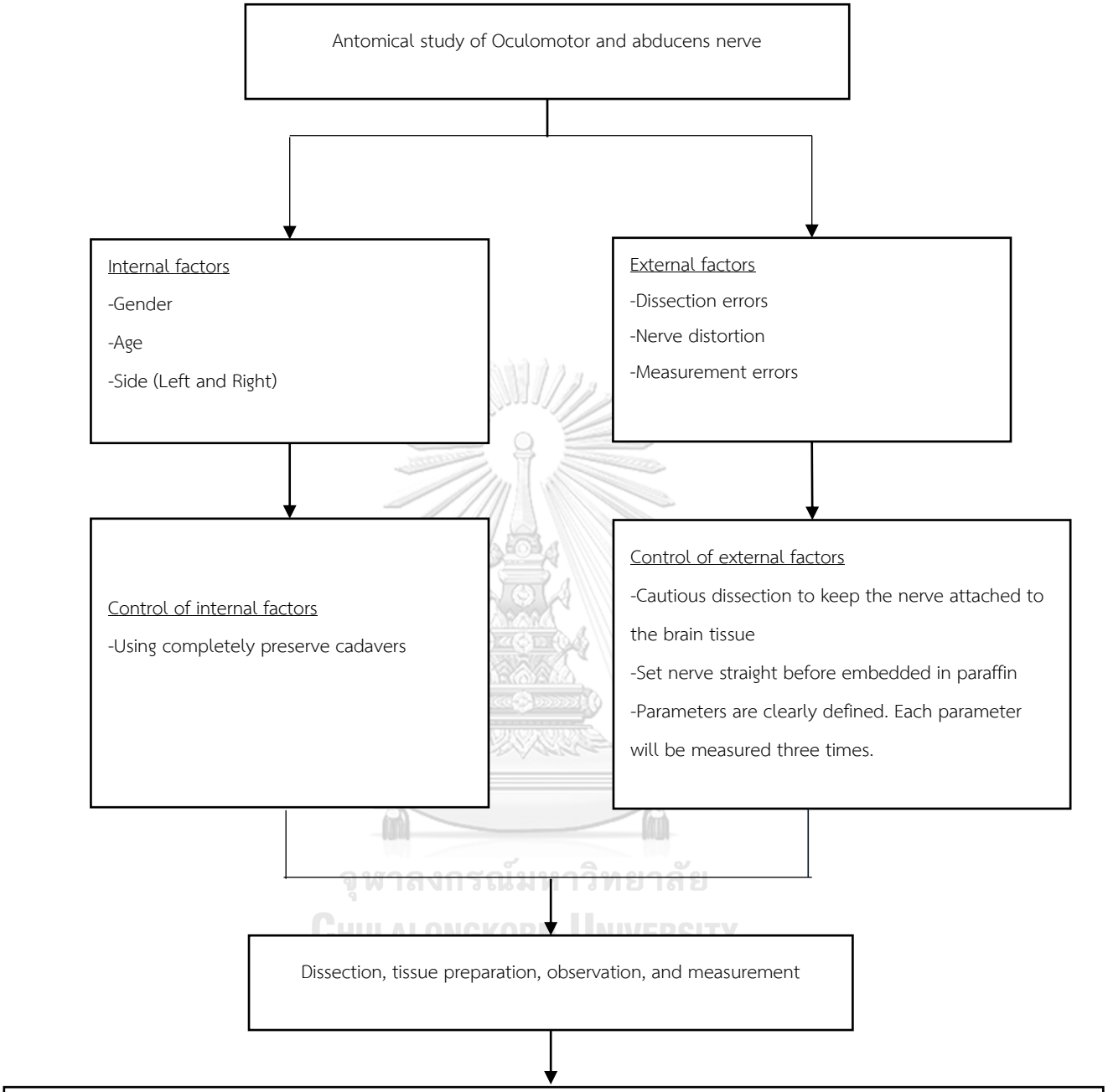
Primary objective

- To evaluate the depth of the central myelin-peripheral myelin transitional zone of the oculomotor and abducens nerves from human cadavers

Secondary objective

- To evaluate the length of the central myelin portion of the oculomotor and abducens nerves from human cadavers
- To evaluate the length of the central myelin portion on the far side of the brainstem of the oculomotor and abducens nerves from human cadavers
- To determine the diameter of the oculomotor and abducens nerves where they exit the brainstem
- To determine the diameter of the oculomotor and abducens nerves where the transitional zone begins
- To determine the number of oculomotor and abducens nerve bundle(s) in histology
- To determine the ratios of transitional zone-central myelin of the oculomotor and abducens nerves
- To determine if there is any correlation between the depth of transitional zone and length of each nerve bundle

Conceptual framework



Keywords

Oculomotor nerve, abducens nerve, cranial nerve, central myelin, transition zone

Study design

Descriptive study

CHAPTER II

Literature Reviews

Microanatomy of oculomotor and abducens nerves

Neurovascular compression syndrome is described as direct contact with mechanical irritation of cranial nerves by blood vessels.[17] A cranial nerve is consists of a central nervous system and peripheral nervous system connected by the transitional zone.[18] The glial cells in the central nervous system project distally making well defined dome-shaped transitional zone that consists of both central and peripheral nervous tissue (Figure 1).[19] The former is composed of astrocyte, oligodendrocyte, and microglia cells. The latter is formed by Schwann cells and endoneurium.[18] The length of the central glial segment varies between nerves and differs between each rootlets of the same nerve.[20] The transitional zone is considered a vulnerable part since the junction contains myelin sheaths in the central part which are produced by oligodendrocytes and the supporting issues and myelin sheaths in the peripheral part which is produced by Schwann cells.[21] The myelin sheath which is made up of protein and lipid functions as an insulating layer allowing faster nerve conduction and provides metabolic support to its axon.[22, 23] Myelin is the multilayered membranous formation with alternating electron-dense (major dense line) and light layer (intraperiod line) which is seen on electron microscopy.[23] The phospholipid membrane has two parts which are the hydrophilic heads and hydrophobic tails.[24] The major dense line is stabilized by various structures, especially the myelin basic protein (MBP) creating dense myelin membrane formation. The cationic side chain of myelin basic proteins (MBP) is neutralized with phosphate anions of the head of the lipid membrane, allowing other forces to bond. Meanwhile, the interaction in the intraperiod line is not well understood.[23] Transmembrane proteins and Proteolipids in the intralipid line are hydrophobic so they are present in the hydrophobic tails of the membrane which is believed to help with tight apposition (Figure 2).[23, 24] The difference in the origin of central and peripheral myelin explains the difference in molecular components which contributes to structural difference (Table 1). Luxol fast blue is used for staining myelin sheath in the paraffin-embedded section. The blue anionic dye is soluble in a water-insoluble organic cation. The myelin will appear blue to green since the dye is bound to

phospholipids and basic amino acids of the proteins of myelin. Whereas neurons will appear pink to violet after counterstaining with violet or red cationic dye colors[24] (Figure 3).

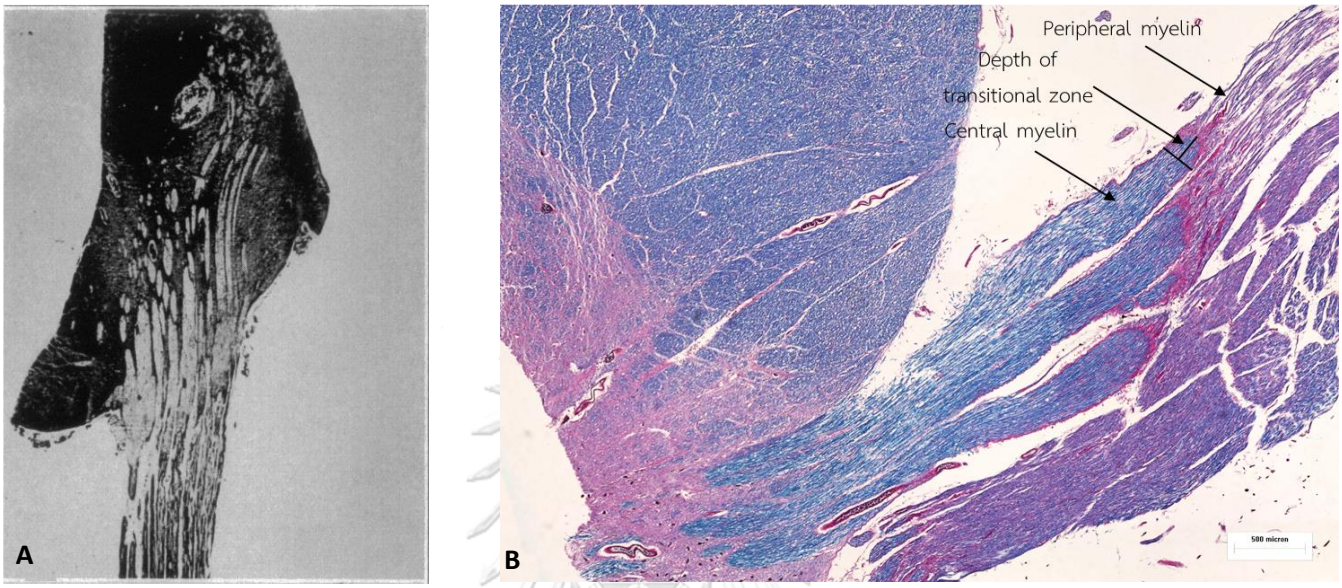


Figure 1 A Photomicrograph of a section of the oculomotor nerve stained with silver carbonate, showing glial cells extend into the peripheral nervous system.[19] **B** Photomicrograph of a section of the oculomotor nerve from our pilot study, showing the dome-shaped transitional zone and the various length of the central glial segment of each rootlets.

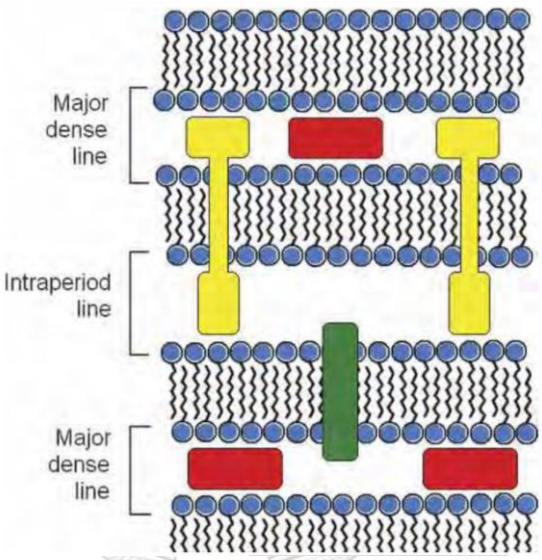


Figure 2 Diagram demonstrating the arrangement of lipids and proteins in myelin. The phospholipid molecules of the membrane have two parts which are the hydrophilic heads (blue) and hydrophobic tails (black zigzag lines). The phosphate anions of the head of the lipid membrane are neutralized by the cationic side chain of myelin basic proteins (red) in a major dense line. Transmembrane proteins (yellow) and Proteolipids (green) are hydrophobic so they are present in the hydrophobic tails of the membrane. (Diagram from Kiernan, 2007)[24]

Table 1 Comparison between central myelin and peripheral myelin[24, 25]

	Central myelin	Peripheral myelin
Embryologic origin of myelin-producing cells	Neural tube	Neural crest
myelin-producing cells	Oligodendrocyte	Schwann cell
Protein in myelin	-Myelin basic protein (MBP) -Claudin-11 (oligodendrocyte-specific protein, OSP) (basic) -Proteolipid protein (PLP)	-MBP -P2 protein (basic) -P0 protein (transmembrane) -Peripheral myelin protein, PMP-22 (proteolipid)
Myelination pattern	One Oligodendrocyte gives myelin to several axons	One Schwann cell forms one internodal myelin

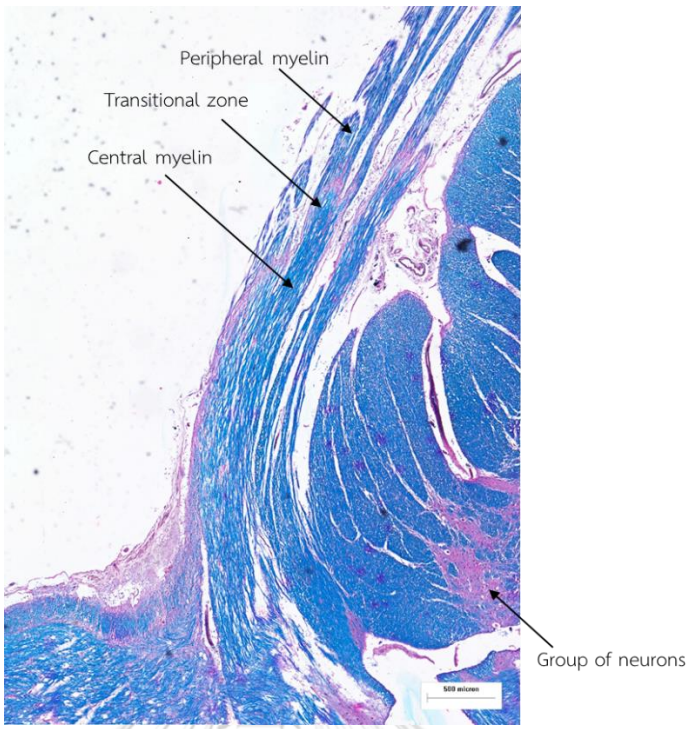


Figure 3 Photomicrograph of a section of the abducens nerve from our pilot study stained with Luxol fast blue and hematoxylin and eosin showing blue to green myelin and pink to violet neurons.

Different sites of neurovascular compression causing the symptoms have been proposed. Jannetta (1980) reviewed 684 patients with hyperactive dysfunction of cranial nerves and concluded that the abnormalities are at the REZ causing the symptoms.[17] However, it has been suggested that vascular contact anywhere along the side of the CNS segment can cause a symptom. Leclercq et al. (1980) showed that the compression could be located anywhere between the brainstem and internal auditory meatus in 10 patients who have the eighth cranial nerve compression.[26] Also, De Ridder et al. (2002) studied five patients with clinical manifestations of cochleovestibular compression syndrome undergoing surgical decompression which was found at the level of the CNS segment and not REZ.[21] Furthermore, Sindou et al. (2002) observed during the microvascular decompression and found that the location of neurovascular conflict was at the root entry zone in 52.3% of the patients, in the mid-third of the nerve in 54.3%, and at the exit of the nerve from Meckel cave in 9.8% for 579 idiopathic trigeminal neuralgia patients.[14]

There is no clear definition of the root exit/entry zone (REZ). Tomii et al. (2003), Peker et al. (2006), and Liang et al. (2009) agreed that REZ is an anatomic junction between a nerve and brain stem [15, 16, 27] For the transitional zone, it is defined as the region where the myelin sheath is composed of both central glial and Schwan cell myelin.[16, 28] While, Glucu et al. (2011) stated that the term REZ consists of the transitional zone, the central myelin portion of the root, and the adjacent surface of the brainstem (Figure 4).[2] Thus, we define the transitional zone as the junction between central and peripheral myelin and central myelin portion starts from where the nerves exit the brainstem to the tip of the arc-shaped transitional zone and in this study.

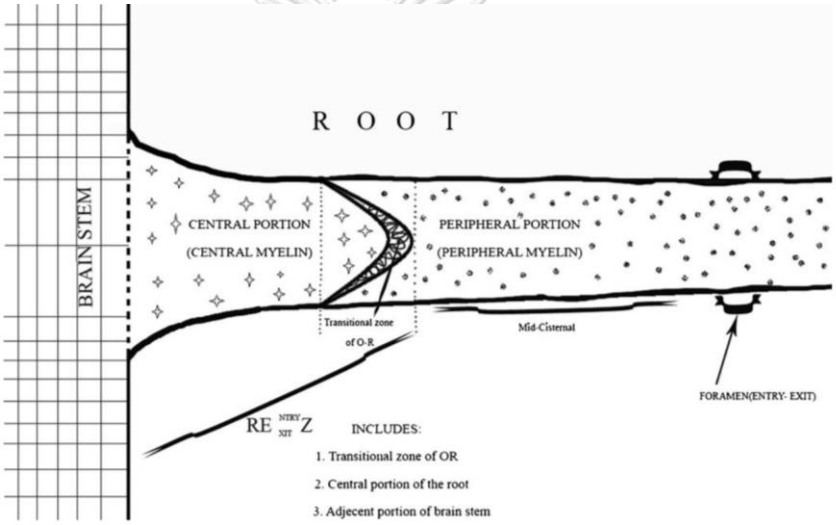


Figure 4 Diagram showing root exit/entry zone (REZ) which consists of the transitional zone, the central myelin portion of the root, and the adjacent surface of the brainstem. (Diagram from Glucu et al.,2011)[2]

For the oculomotor nerve, the nucleus is found in the tegmentum of the midbrain at the level of the superior colliculus and the nerve emerges from the inner side of the cerebral peduncle of the midbrain. The nerve travels through the cavernous sinus and reaches the orbit via superior orbital fissure. For the abducens nerve, the nucleus is found at dorsal pons and the nerve emerges caudally from the pons and travels along the upper edge of the tip of the petrous. It later enters the cavernous sinus and comes to orbit via superior orbital fissure.[3]

The microanatomy of cranial nerves has been studied. Skinner (1931) and Tarlov (1937) showed that there is an outgrowth of glial cells from the brain to cranial nerves. The length of the glia is longer in the sensory nerve than the motor nerve. The difference is thought to be from development.[19, 20] The ends of the glial tissue always form domes that represent each bundle of fibers.[19] De Ridder et al. (2002) supported the PNS segment is more resistant to external compression than the CNS segment confirmed by histological data and neurophysiological data from intraoperative monitoring. PNS segment is abundant in connective tissue and regular myelin sheaths around the axons which gives it elasticity.[21] Tomii et al. (2003) obtained 75 facial nerves with the attached brainstem and associated vessels from the cadavers without knowing the clinical conditions. More than 80% of the case were found vascular compression at the central myelin portion which was measured 8 ± 2.79 mm for the lateral side and 9.9 ± 3.03 mm for the medial side.[16] Peker et al. (2006) examined 100 trigeminal nerves from cadavers and recorded that the length of the central myelin was 2.47 mm for the lateral side and 1.13 mm for the medial side.[15] Guclu et al. (2011) evaluated the anatomy of the trigeminal, facial, and vago-glossopharyngeal nerve and their association with the incidences of the hyperactive dysfunctional syndromes. The length and volume of these nerves starting from the longest and the maximum volume to the least are trigeminal, facial, and glossopharyngeal nerve which have a positive correlation with the incidences of corresponding diseases.[2]

There were only two previous studies about the central myelin portion of the nerves responsible for eye movement. Skinner (1931) is the first to demonstrated that the length of the glial part of the oculomotor and abducens nerve are 1.2 and 0.5 mm respectively.[19] Tarlov (1937) showed that the length of the glial part of the oculomotor and abducens nerve are 0.6 and 0.5 mm respectively.[20] The number of subjects is not noted in both studies. The larger sample size would give the measurement more accurate and representative samples for the population.

Clinical correlation

The ocular movement is controlled by the oculomotor, trochlear, and abducens nerve. The oculomotor nerve not only innervates medial rectus muscle, superior rectus muscle, inferior rectus muscle, and inferior oblique muscle but also gives a branch to levator palpebrae muscle elevating the upper eyelid. Additionally, it carries the parasympathetic fibers to the ciliary ganglion which plays a role in pupillary function and accommodation. The actions of muscles mentioned above are adduction, elevation, and depression including intorsion and extorsion of the eye. Next, the trochlear nerve innervates the superior oblique muscle. The primary action is the intorsion movement. It is also responsible for the depression and abduction of the eye. Last, the abducens nerve innervates the lateral rectus muscle which controls abduction movement.[3]

Cyclic oculomotor nerve palsy (COP) is characterized by episodic contraction and relaxation of the muscles innervated by the oculomotor nerve. Localization of lesion is in disagreement between peripheral oculomotor nerve and oculomotor nerve nucleus in the midbrain. However, Loewenfelf and Thompson (1975) suggested that the symptoms can be explained by the combination of central and peripheral nerve damage.[7] For treatment, baclofen, a central muscle relaxant, failed to control the cyclic movement.[29] In a review of the 35 cases of levator transposition procedure to correct ptosis and abnormal movement of the eyelid, three patients with COP had satisfactory outcomes and no further surgery was needed.[30] Bansal and Das (2017) described using tarsofrontal silicone sling surgery as an effective method for controlling cyclic movements.[31] Additionally, Liang et al. (2009) studied anatomy in neuroimaging and cadavers. From the cadaveric study, the REZ of the oculomotor nerve is located in the interpeduncular cistern. On magnetic resonance imaging, the length of the intracisternal segment of the oculomotor nerve is 14.61 ± 2.33 mm. The study demonstrated that 231, 216, 7 out of 392 nerves (196 normal volunteers) had asymptomatic vascular contact with superior cerebellar artery, posterior cerebral artery, posterior communicating artery respectively. For the basilar artery, it was contacted in 80 out of 196 cases.[27]

Ocular neuromyotonia (ONM) is characterized by intermittent, tonic spasms of one or more of the extraocular muscles. Clinical presentations are strabismus and transient

diplopia.[5] The mechanism is unknown but it has been proposed to be related to cranial radiation[32-38], neurovascular compression[39, 40], and autoimmune disorder.[41-43] In the literature review of 49 ocular neuromyotonia cases, abducens and oculomotor nerve are affected by 65.3% and 32.6% respectively.[5] The vascular compression cause accounts for 4 out of 49 patients;[9, 39, 40, 44] one was compressed from the internal carotid aneurysm.[44] The location of neurovascular conflict was the oculomotor nerve root exit zone[39] and the proximal cisternal portion of the oculomotor nerve.[40] Carbamazepine was effective in 1 out of 3 patients.[40] If failed medical treatment, surgical microvascular decompression would be a choice.[9]

Abducens nerve palsy is the most common ocular motor paralysis presented with diplopia. It usually results from neoplasm, trauma, and microvascular ischemia.[45] It is very rare if considered vascular compression as a cause. Until now, only 11 cases have been reported with 4 cases that had a vascular conflict at the root entry zone.[6, 46] Only one out of four needed eye muscle surgery.[47] Most of the cases remain stable or spontaneously recover with no treatment. Some were treated with spectacle prism.[6, 46]

The study will provide the depth of the transitional zone and length of the central myelin portion of these nerves with a clear definition. Also, the detailed anatomy about the diameter where nerves leave the brainstem and where the transitional zones begin have not been reported. The information could be compared to the neuroimaging study and may help understand the mechanism of the diseases and better treatment approaches in the future.

CHAPTER III

RESEARCH METHODOLOGY

Target population

Removed brains of adult cadavers used in teaching medical student year 2 in Department of Anatomy, Faculty of Medicine, Chulalongkorn University

Approach to participant

We request permission to approach the removed brains of adult cadavers used in teaching medical student year 2 in the Department of Anatomy, Faculty of Medicine, Chulalongkorn University

Inclusion and Exclusion criteria

Inclusion criteria

- All removed brains of adult cadavers used in teaching medical student year 2 in Faculty of Medicine, Chulalongkorn University
- At least one of the oculomotor or abducens nerve is intact with the brainstem

Exclusion criteria

- The brain is poor preservation
- The sections are damaged during tissue processing, sectioning, and staining

Sample size calculation

For oculomotor nerves

From the pilot study, 4 of the oculomotor nerves are collected, the standard deviation (SD) of the depth of the transitional zone was 46.49 μm. This current study will use the formula to calculate the sample size with a confidence interval set as 95% as shown below:

$$n = \frac{z_{\alpha/2}{}^2 \sigma^2}{d^2}$$

When $z_{\alpha/2} = z_{0.05/2} = 1.96$ (two tail)

σ = variance = SD= 46.49 μm for the oculomotor nerves.

d = acceptable error = 30 μm

n= 9.22

For abducens nerves

From the pilot study, 4 of the abducens nerves are collected, the standard deviation (SD) of the depth of the transitional zone was 47.38 μm. This current study will use the formula to calculate the sample size with a confidence interval set as 95% as shown below:

$$n = \frac{z_{\alpha/2}{}^2 \sigma^2}{d^2}$$

When $z_{\alpha/2} = z_{0.05/2}$= 1.96 (two tail)

σ= variance = SD= 47.38 μm for the abducens nerves.

d = acceptable error = 30 μm

n= 9.58

The estimated sample size is 10 and 10 nerves for oculomotor and abducens nerves, respectively.

Materials and equipment

Materials

- Dissection instruments i.e. blade, forceps
- Microtome blades
- Paraffin wax
- Absolute alcohol
- Luxol fast blue stain
- Hematoxylin and eosin stains
- Positive charge slides

Equipment

- Axiocam 506 color microscope camera with 5X microscope objective lens
- IMAGE-PRO plus program version 6.0

Research framework

Cadaveric selection -Completely preserved
-Cranial nerve III and VI can be identified

↓

Dissection -Small piece of brainstem tissue is cut along with the cranial nerve

↓

Tissue preparation

1. 10% neutral buffered formalin is used for the tissue fixation
2. Each tissue block is embedded in paraffin
3. Each tissue block is serially sectioned (the thickness of the sections is 5 μm)
4. The tissue ribbons placed in a diluted alcohol solution then a warm water bath are taken up with the charged slides
5. The sections which the nerve is integral and connected to the brainstem under the microscopic examination will be chosen.
6. Deparaffinization of paraffin-embedded sections before staining.
7. Luxol fast blue and hematoxylin and eosin are used for tissue Staining

↓

Selection of appropriate sections for image analysis

The sections that are damaged during the tissue processing, sectioning, and staining will be excluded. Only the sections which the cranial nerve connected to the brainstem will be measured.

↓

Photographing selected sections

We use Axiocam 506 color microscope camera with 5X microscope objective lens to take a photomicrograph and IMAGE-PRO plus program version 6.0 for measurement.

↓

Observation- For the oculomotor and abducens nerves, we will observe the number of nerve bundles microscopically.

↓

Measurements

Measurements on the longest central myelin section*

- Measurements for the longest myelin

1.The diameters of the nerves where they exit brainstem (A)
2.Identify and measure the length of the central myelin portion (F) of the longest central myelin in each section
3. The average value of central myelin length from each micrograph will be compared and the longest one will be chosen for measuring the other two parameters
   3.1The diameters where the transitional zone begins (B)
   3.2The depth of the transitional zone (f)

Measurements for other nerve bundles *

The section which is most clearly seen for each nerve bundle will be measured four parameters
(F, B, f, C)

*Each distance will be measured three times

Methods

Dissection and tissue preparation

1. Selecting the removed brains of the cadavers which the cranial nerve III and VI is still attached
2. The small piece of brainstem tissue is cut along with the cranial nerve.
3. 10% neutral buffered formalin is used for tissue fixation.
4. Each tissue block which consists of the cranial nerve and brainstem is embedded in paraffin.
5. Each tissue block is serially sectioned. The thickness of the sections is 5 μm.
6. After sectioning, the tissue ribbons are placed in a diluted alcohol solution then a warm water bath. We use charged slides to take up the sections.
7. All sections are collected. The sections at the beginning and the end of each tissue block are excluded because the cranial nerve is not entirely seen. The remaining sections which the cranial nerve is integral and connected to the brainstem under the microscopic examination will be chosen for staining.
8. Deparaffinization of paraffin-embedded sections before staining.
9. Luxol fast blue and hematoxylin and eosin are used for tissue staining.

Selection of appropriate sections for image analysis

The sections that are damaged during the tissue processing, sectioning, and staining will be excluded. Only the sections which the cranial nerve connected to the brainstem will be selected for image analysis.

Photographing selected sections

We use Axiocam 506 color microscope camera with a 5X microscope objective lens to take a photomicrograph via ZEN 3.3 (blue edition) and IMAGE-PRO plus program version 6.0 for measurement.

Observation

For the oculomotor and abducens nerves, we will observe the number of nerve bundles microscopically.

Measurements

1. Measurements on the longest central myelin section
    1.1. Measurements for the longest central myelin of each cranial nerve
        1.1.1. Measure the diameters of the nerves where they exit from the brainstem, a line is drawn between the junction where the nerve met the brainstem (A) (Figure 6).
        1.1.2. Identify and measure the length of the central myelin portion of the longest central myelin in each selected section. The central myelin portion is defined as a line drawn from the tip of the arc-shaped transitional zone continues at the middle of the nerve bundles until it meets with segment A (F) (Figure 6).
        1.1.3. The average value of central myelin length from each micrograph will be compared and the longest one will be chosen for measuring the other two parameters as follow;
            1.1.3.1. The diameters where the transitional zone begins, a line is drawn between the junction of the central and peripheral myelin (B) (Figure 6).
            1.1.3.2. The depth of the transitional zone, a line is drawn from the middle of segment B to the tip of the arch (f) (Figure 6).
2. Measurements for other nerve bundles
    2.1. The section which is most clearly seen for each nerve bundle will be measured four parameters, F, B, f, as mentioned above and the length of central myelin on the far side of the brainstem, a line is drawn from the nerve-brainstem junction to the central myelin-peripheral myelin junction on the far side of the brainstem (C) (Figure 6).

Each parameter will be measured three times.

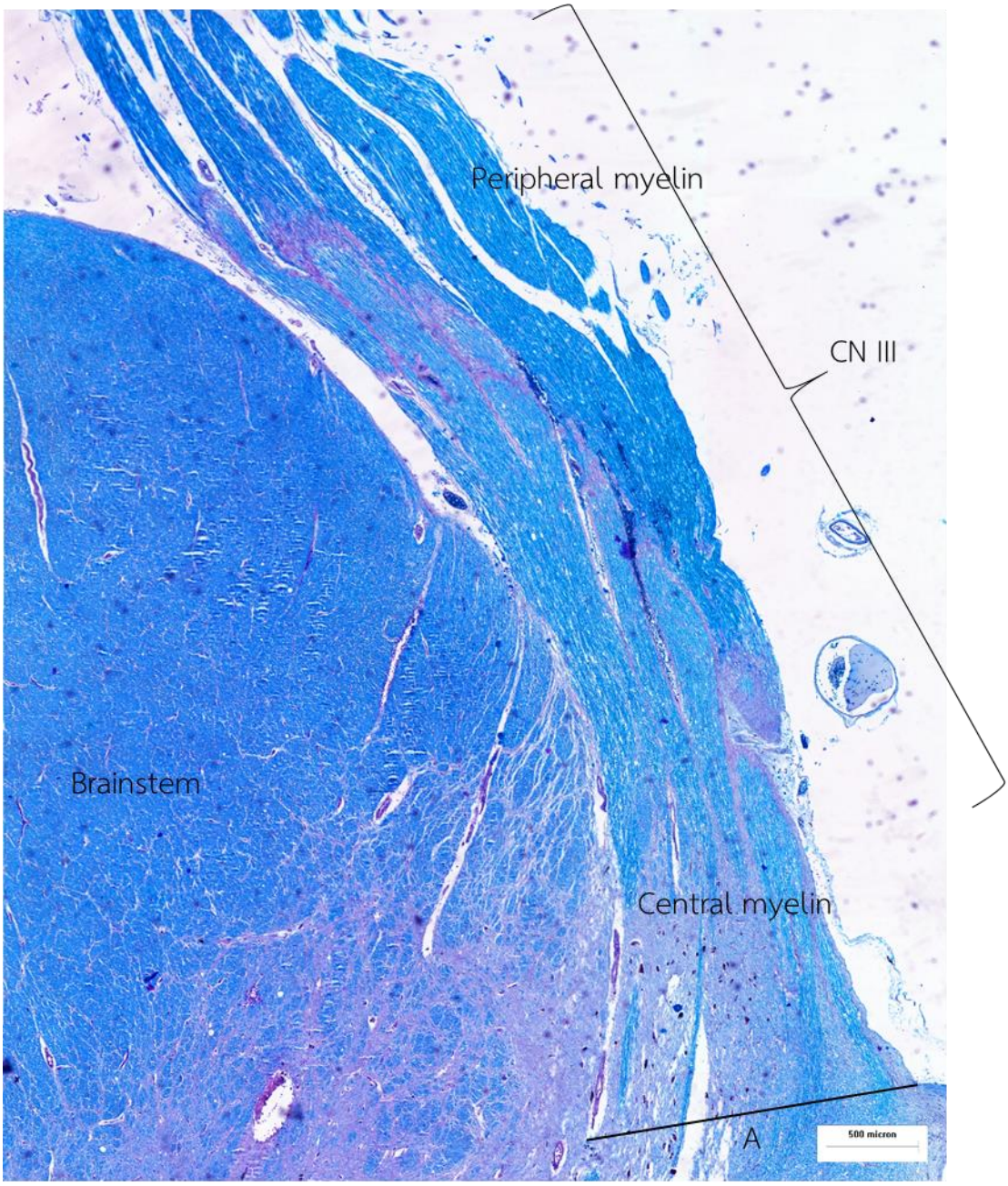


Figure 5 Photomicrograph of a section of the oculomotor nerve (CN III) stained with Luxol fast blue and hematoxylin and eosin showing central myelin and peripheral myelin. (A) is the diameter of the nerves where they exit from the brainstem.

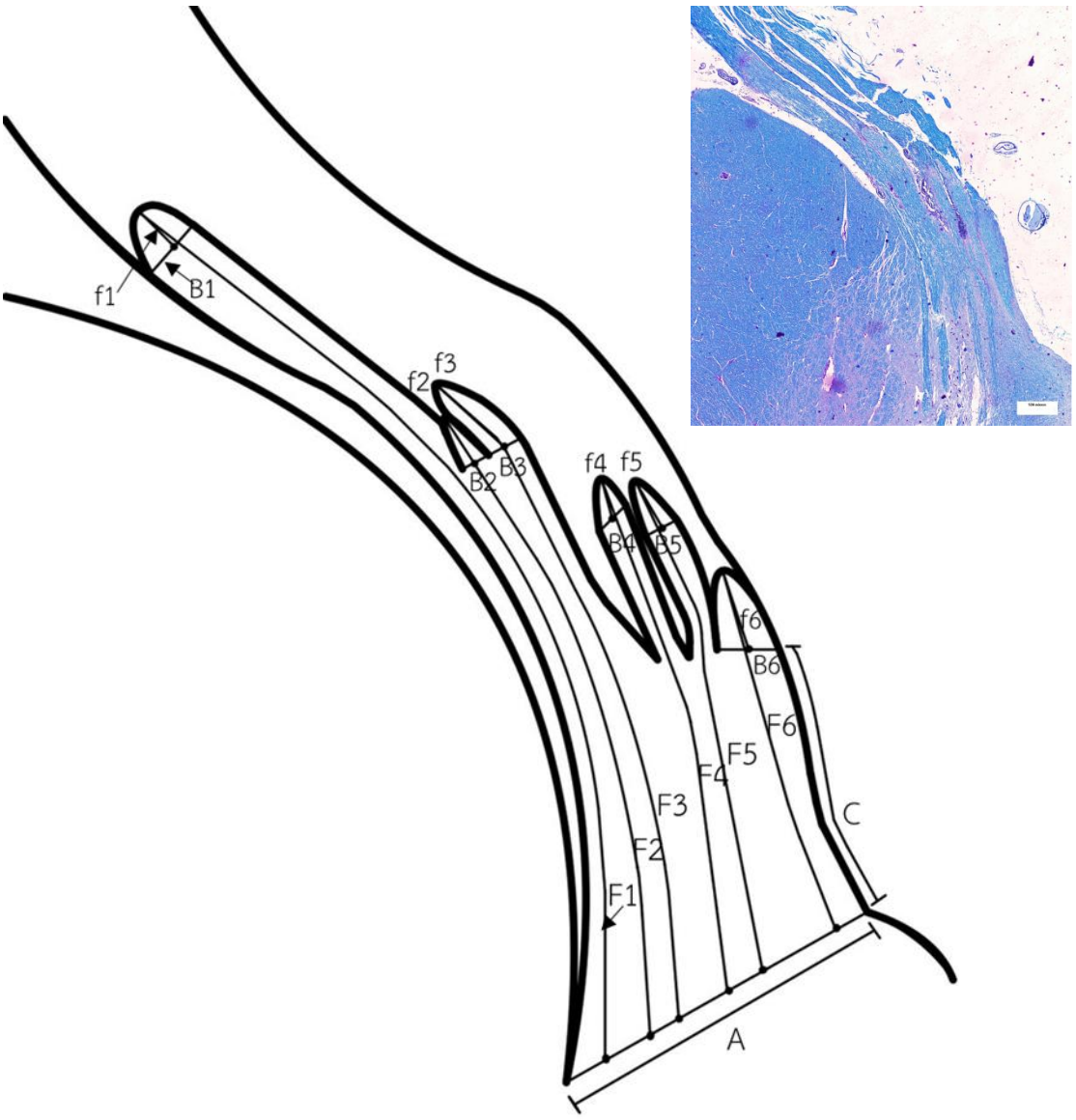


Figure 6 On the top right: Photomicrograph of a section of oculomotor nerve, **In the center**: Drawing demonstrating **(A)** is diameter of the nerves where they exit from the brainstem, a line is drawn between the junction where nerve met the brainstem. **(F)** is length of central myelin of nerve bundle, a line drawn from the tip of the arc-shaped transitional zone continues at the middle of the nerve bundles until it meets with segment A. **(B)** is diameter of transitional zone of nerve bundle, a line is drawn between the junction of the central and peripheral myelin. **(f)** is the depth of transitional zone of nerve bundle, a line is drawn from the middle of segment B to the tip of the arch. The numbers, 1 to 6, represent the sequence of each nerve bundle. **(C)** is the length of central myelin on the far side from the brainstem, a line drawn from nerve-brainstem junction to central myelin-peripheral myelin junction on the far side from the brainstem.

Data collection

All the information will be recorded in the case record form.

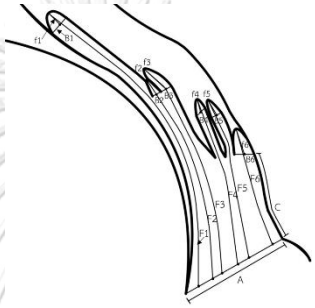
Case record form

Brain No._____

Cranial nerve ☐ Oculomotor nerve ☐ Abducens nerve

Side ☐ Left ☐ Right

Drawing demonstration of nerve



A= The diameters of the nerves where they exit from the brainstem, F=The length of the central myelin portion, B=The diameters where the transitional zone begins, f=The depth of the transitional zone, C= The length of central myelin on the far side from the brainstem

Parameters	nerve bundle 1 (section no.____)	nerve bundle 2 (section no.____)	nerve bundle 3 (section no.____)	nerve bundle 4 (section no.____)	nerve bundle 5 (section no.____)
A in μm	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____
F in μm	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____
B in μm	1)_____	1)_____	1)_____	1)_____	1)_____

	2)_____ 3)_____	2)_____ 3)_____	2)_____ 3)_____	2)_____ 3)_____	2)_____ 3)_____
f in μm	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____

Parameters	nerve bundle 6 (section no.____)	nerve bundle 7 (section no.____)	nerve bundle 8 (section no.____)	nerve bundle 9 (section no.____)	nerve bundle 10 (section no.____)
A in μm	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____
F in μm	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____
B in μm	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____
f in μm	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____	1)_____ 2)_____ 3)_____

C in μm 1)_____

2)_____

3)_____

Data analysis and Statistics

The length of central myelin, depth of the central myelin-peripheral myelin transitional zone, the length of central myelin on the far side of the brainstem, the diameter of the nerve at the brainstem exit, diameter at the transitional zone, and the ratio of transitional zone-central myelin are considered as the continuous numerical data which will be presented as mean and standard deviation. To determine the correlation between depth of transitional zone and length of central myelin of each bundle, Pearson's correlation coefficient and scatter plot will be used. The number of nerve bundles of oculomotor and abducens nerves is considered as categorical data which will be presented with the percentage of each type. The significant level was set at a p-value <0.05.

Ethical consideration

In respect of the person, we will request permission from the director of King Chulalongkorn Memorial Hospital to dissect adult cadavers in this research. All of the information will be confidential. In the beneficence aspect, adult cadavers in this research will not directly have benefits or risks. However, we hope that the result of this research will provide more information about the central myelin portion and transitional zone of the oculomotor and abducens nerves which could be applied to the microvascular compression syndromes. In the justice aspect, inclusion and exclusion criteria are well-defined.

Expected or Anticipated Benefit Gain

Information about the central myelin portion and transitional zone of the oculomotor and abducens nerves could help understanding the mechanism of cyclic oculomotor nerve palsy, ocular neuromyotonia, and abducens nerve palsy respectively. Moreover, the anatomical knowledge could be used for neuroimaging interpretation and precisive surgical decompression.

Challenges

- Dissect error; therefore, we will be cautious during dissection to keep the cranial nerve attached to the brainstem.
- The measurement error; therefore, the parameters are clearly defined. Each parameter will be measured three times.
- The distortion of the nerves after dissection will cause measurement errors; therefore, we will set the cranial nerve straight before embedded in paraffin.

Risk and Investigator's Responsibility

No

Timeline

1 year

Venue of the study

Department of Anatomy, Faculty of Medicine, Chulalongkorn University, Bangkok 10330

Tabulation of Research Activities and Timeline

	Procedures	Duration (month)					
		1-2	3-4	5-6	7-8	9-10	11-12
1.	Data collection	←	→				
2.	Analyze data			←	→		
3.	Write a report					←	→

Budgets

Materials for dissection and tissue preparation

Operative knife	x1	1,200	Baht
Surgical blade	x1	750	Baht
Forceps	x1	125	Baht

Microtome blades	x1	3,500	Baht
Paraffin wax	x1	1,350	Baht
Absolute alcohol	x3	3,600	Baht
Positive charge slides	x15	5,250	Baht
Hematoxylin stain	x1	5,000	Baht
Eosin stain	x1	5,000	Baht
Luxol fast blue	x1	3,520	Baht
Total		29,295	Baht

CHAPTER IV

RESULTS

Twenty-nine oculomotor nerves and 53 abducens nerves were obtained from 46 cadavers' brains. Only 10 of each cranial nerve were included, the rest were excluded due to poor fixation and disconnection of the brainstem and cranial nerve. The total number of the nerve bundles for observation and measurement was 63 for oculomotor nerve and 32 for abducens nerve.

Numbers of nerve bundles

Oculomotor nerve

The number of nerve bundles of each oculomotor nerve was between 5 to 7. The prevalence of 5,6, and 7 nerve bundles in each oculomotor nerve was 20%, 30%, and 50% respectively. The total number of nerve bundles was 63 nerve bundles. The longest central myelin was appeared on the first nerve bundle which is counted from the lateral side in all 10 oculomotor nerves. The length of central myelin of the nerve bundle was gradually decreased from lateral to medial side (Figure 7). The details of nerve bundles are shown in Table 2.

Table 2 The number of nerve bundles and the order of nerve bundle with the longest central myelin

Nerve		Nerve No.										
		1	2	3	4	5	6	7	8	9	10	Total
Oculomotor nerve	No. of nerve bundles	5	6	7	7	5	6	7	6	7	7	63
	Nerve bundle order with longest central myelin	1	1	1	1	1	1	1	1	1	1	-
Abducens nerve	No. of nerve bundles	1	3	3	3	5	3	4	4	3	3	32
	Nerve bundle order with longest central myelin	1	3	3	2	2	1	3	3	1	2	-

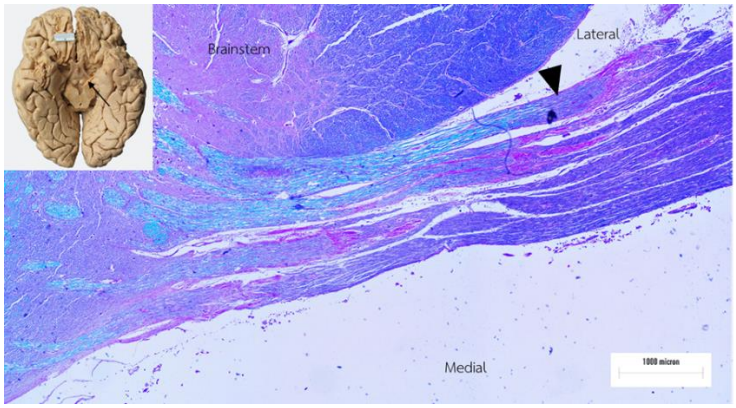


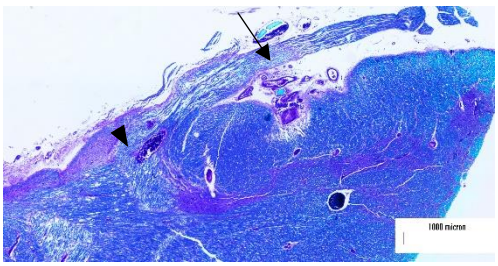
Figure 7 On the top left: the photo of the brain from inferior view with some part of the brainstem cut at midbrain level, left oculomotor nerve (arrow) is emerging from the medial aspect of the cerebral peduncle. **In the center:** The photomicrograph of the oculomotor nerve stained with luxol fast blue demonstrated that the longest central myelin was seen on the first nerve bundle (arrowhead) and then the length of central myelin of the nerve bundle is gradually decreased from lateral to the medial side.

Abducens nerve

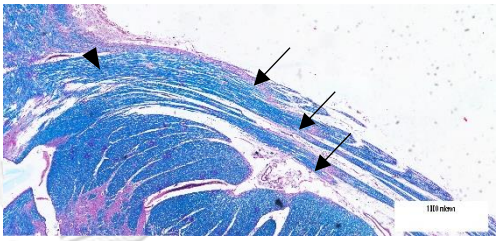
The number of nerve bundles of each abducens nerve was between 1 to 5. The prevalence of 1,3,4 and 5 nerve bundles in each abducens nerve was 10%, 60%, 20%, and 10% respectively. The total number of nerve bundles was 32 nerve bundles. The longest central myelin was found between the first to third nerve bundle. The prevalence of first, second, and third nerve bundle being the longest central myelin was 30%, 30%, and 40% respectively. The abducens nerve was classified into 4 types based on the number of nerve rootlet originated from the brainstem and the number of nerve bundles; Type A single nerve rootlet with one nerve bundle; Type B single nerve rootlet with more than one nerve bundle; Type C more than one nerve rootlet originated from different origins with one nerve bundle in each nerve rootlet; Type D more than one nerve rootlet originated from different origins with the most caudal nerve rootlet having more than one nerve bundle (Figure 8). The number of abducens nerves of type A, B, C, and D was 1 (10%), 4 (40%), 3 (30%), and 2 (20%) respectively. In addition, the vessels passing through the nerve bundles and glial layer covering the root of the abducens nerve were noted (Figure 9).

A

Caudal Rostral



B



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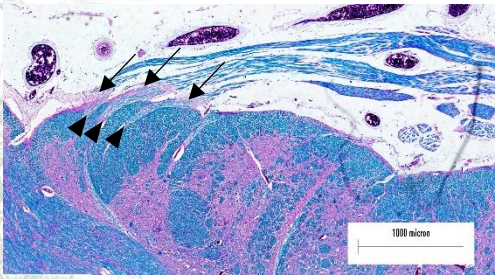
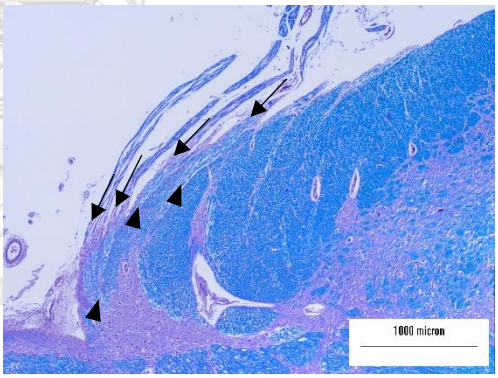
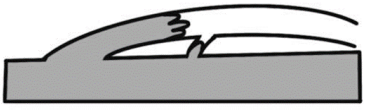


D





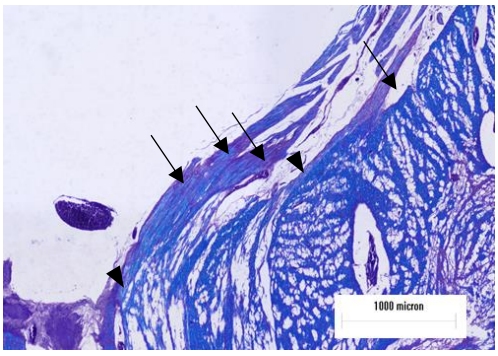


Figure 8 Morphological patterns of abducens nerves. Schematic diagram (on the left) and photomicrograph of abducens nerves stained with luxol fast blue (on the right) showing different morphology of abducens nerves. **A** single nerve rootlet (arrowhead) with one nerve bundle (arrow); **B** single nerve rootlet (arrowhead) with more than one nerve bundle(arrows); **C** more than one nerve rootlet (arrowheads) originated from different origins with one nerve bundle (arrow) in each nerve rootlet; **D** more than one nerve rootlet (arrowheads) originated from different origins with the most caudal nerve rootlet having more than one nerve bundle (arrows). Central nervous tissue: shaded; peripheral nervous tissue: unshaded.

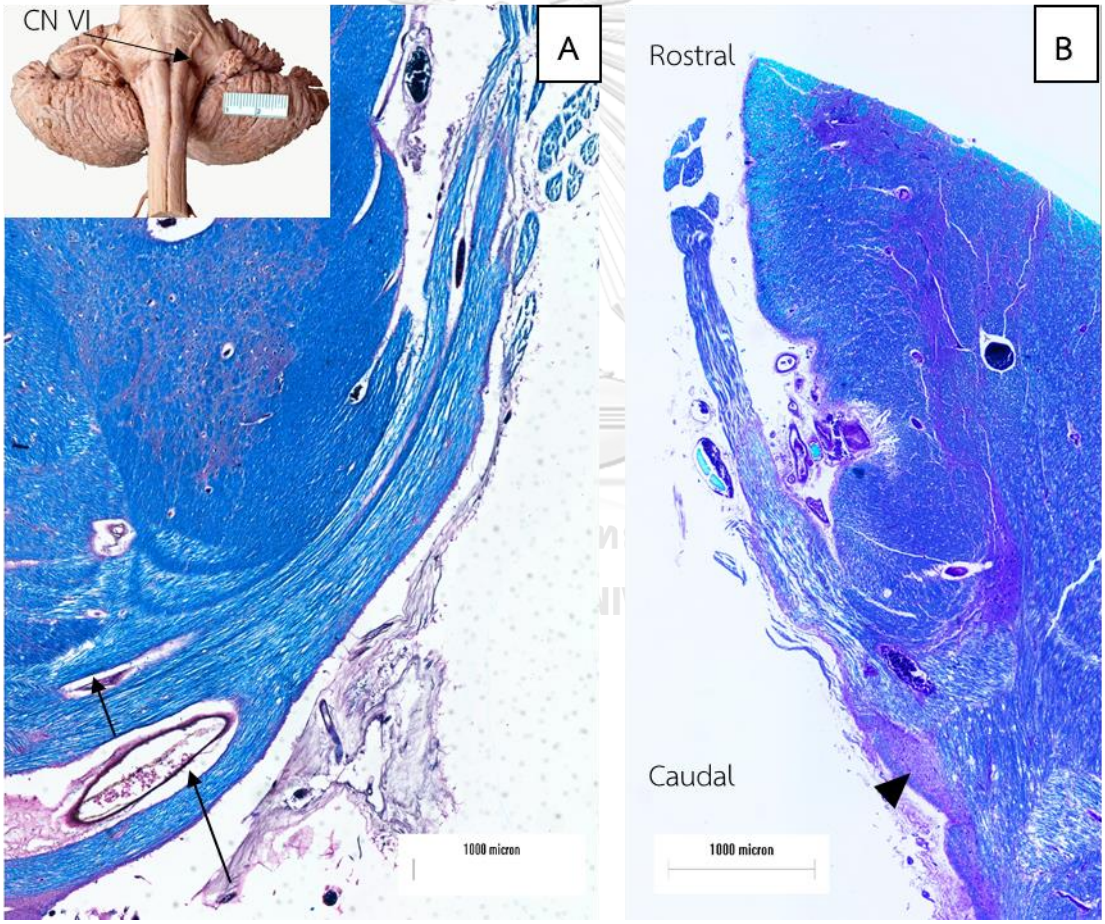


Figure 9 On the top left: the photo of the abducens nerve emerging from the pontomedullary junction. **A** Abducens nerve stained with luxol fast blue shows the vessels (arrows) passing through the nerve. **B** The photomicrograph shows the glial layer covering the abducens nerve (arrowheads)

Diameters where they exit from the brainstem (A)

The mean diameter of oculomotor and abducens nerves where they exit from the brainstem (A) was 2.18 ± 0.44 (1.36-2.97) and 1.21 ± 0.60 (0.19-2.38) mm, respectively. Diameters of oculomotor and abducens nerves where they exit from the brainstem are shown in Table 3. 80% of the oculomotor nerves had the diameter where they exit from the brainstem between 2.01-3.00 mm. while 90% of the abducens nerves had the diameter where they exit from the brainstem below 2.00 mm. Distribution diameters of oculomotor and abducens nerves where they exit from the brainstem are shown in Table 4. The average measure intraclass correlation coefficient (ICC) was 0.999 (0.996-1.000) for oculomotor nerve measurement and 0.999 (0.998-1.000) for abducens nerve measurement.

Table 3 Diameters of nerves where they exit from the brainstem (A)

Nerve No.	Mean (mm)										Mean±SD (Range) mm
	1	2	3	4	5	6	7	8	9	10	Average
Oculomotor nerve	2.10	2.01	1.72	2.29	1.37	2.10	2.53	2.55	2.15	2.95	2.18±0.44 (1.36-2.97)
Abducens nerve	1.72	1.06	2.34	0.71	1.56	1.25	1.21	1.37	0.20	0.68	1.21±0.60 (0.19-2.38)

Table 4 Distribution diameters of nerves where they exit from the brainstem (A)

Oculomotor nerves		Abducens nerve	
Diameter (mm)	Number of nerves	Diameter (mm)	Number of nerves
≤1.00	0	≤1.00	3
1.01-2.00	2	1.01-2.00	6
2.01-3.00	8	2.01-3.00	1

Lengths of the central myelin portion (F)

For the oculomotor nerve, the mean length of central myelin (F) was 2.75 ± 0.83 (0.36-6.10) mm (Table 5) with 92% had the mean length of central myelin below 5.00 mm (Table 7). The longest central myelin length was 4.29 ± 1.26 (2.76-6.10) mm (Table 6) and 90% had the mean longest length of central myelin between 3.01-7.00 mm (Table 7).

For the abducens nerve, the mean length of central myelin (F) was 1.66 ± 1.39 (0.13-5.01) mm (Table 5) with 88% of nerve bundles had the length of central myelin of each nerve below 3.00 mm (Table 7). The longest central myelin length was 1.88 ± 1.40 (0.28-5.01) mm (Table 6) and 80% of nerve bundles had the longest length of central myelin below 3.00 mm (Table 7). The details of lengths and longest lengths of central myelin are shown in Table 5 and 6 respectively. The distribution of lengths and longest lengths of the central myelin portion are shown in Table 7. The average measure intraclass correlation coefficient (ICC) was 1.000 (0.999-1.000) for oculomotor nerve measurement and 1.000 (1.000-1.000) for abducens nerve measurement.

Table 5 Lengths of the central myelin portion of each nerve (F)

		Nerve No.										Summary
		1	2	3	4	5	6	7	8	9	10	
Oculomotor nerve	Number of nerve bundles	5	6	7	7	5	6	7	6	7	7	Total =63
	Mean ±SD (Range) mm	2.23± 0.75 (1.28-3.01)	2.24± 1.06 (0.64-3.22)	1.57± 0.97 (0.51-2.76)	3.33± 1.05 (2.14-5.11)	1.95± 0.96 (1.18-3.37)	3.99± 1.59 (2.12-6.10)	2.67± 0.91 (1.54-3.76)	3.78± 1.07 (2.33-5.21)	2.34± 1.57 (0.36-4.28)	3.44± 1.60 (1.92-6.10)	2.75± 0.83 (0.36-6.10)
Abducens nerve	Number of nerve bundles	1	3	3	3	5	3	4	4	3	3	Total =32
	Mean ±SD (Range) mm	2.00	2.26± 0.03 (2.23-2.29)	4.76± 0.28 (4.46-5.01)	0.36± 0.21 (0.13-0.53)	2.80± 0.28 (2.31-3.01)	0.63± 0.33 (0.37-1.00)	0.35± 0.32 (1.03-1.73)	0.62± 0.23 (0.37-0.86)	1.56± 0.68 (0.79-2.03)	0.21± 0.06 (0.16-0.28)	1.66± 1.39 (0.13-5.01)

Table 6 Longest lengths of the central myelin portion of each nerve

Nerve No.	Mean (mm)										Mean±SD (Range) mm
	1	2	3	4	5	6	7	8	9	10	Average
Oculomotor nerve	3.01	3.22	2.76	5.11	3.37	6.10	3.76	5.21	4.28	6.10	4.29±1.26 (2.76-6.10)
Abducens nerve	2.00	2.29	5.01	0.53	3.01	1.00	1.73	0.86	2.03	0.28	1.88±1.40 (0.28-5.01)

Table 7 Distribution of lengths and longest lengths of the central myelin portion

Oculomotor nerves		Abducens nerve	
Length (mm)	Number of nerve bundles	Length (mm)	Number of nerve bundles
Central myelin			
≤2.00	17	≤1.00	14
2.01-3.00	22	1.01-2.00	6
3.01-4.00	12	2.01-3.00	8
4.01-5.00	7	3.01-4.00	1
5.01-6.00	3	4.01-5.00	2
6.01-7.00	2	5.01-6.00	1
Length (mm)	Number of nerves	Length (mm)	Number of nerves
Longest central myelin			
1.01-3.00	1	≤1.00	4
3.01-5.00	5	1.01-3.00	4
5.01-7.00	4	3.01-5.00	1
		5.01-7.00	1

Diameters of transitional zone (B)

The mean diameter of where the transitional zone (B) begins was 0.28 ± 0.05 (0.12-0.58) and 0.22 ± 0.06 (0.09-0.39) mm for oculomotor and abducens nerves respectively. Diameters, where the transitional zone begin, are shown in Table 8. 93% of the oculomotor nerves had the diameter of transitional zone below 0.40 mm. For abducens nerves, 97% had the diameter of transitional zone between 0.11-0.40 mm Distribution diameters of nerves where the transitional zone begin are shown in Table 9. The average measure intraclass correlation coefficient (ICC) was 0.992 (0.988-0.995) for oculomotor nerve measurement and 0.991 (0.984-0.995) for abducens nerve measurement.

Table 8 Diameters of transitional zone (B)

		Nerve No.										Summary
		1	2	3	4	5	6	7	8	9	10	
Oculomotor nerve	Number of nerve bundles	5	6	7	7	5	6	7	6	7	7	Total =63
	Mean ±SD (Range) mm	0.22± 0.09 (0.16-0.35)	0.28± 0.05 (0.18-0.34)	0.24± 0.06 (0.15-0.32)	0.21± 0.08 (0.13-0.34)	0.34± 0.17 (0.19-0.58)	0.31± 0.12 (0.14-0.48)	0.37± 0.05 (0.31-0.42)	0.28± 0.13 (0.12-0.44)	0.26± 0.05 (0.23-0.35)	0.27± 0.10 (0.16-0.39	0.28± 0.05 (0.12-0.58)
Abducens nerve	Number of nerve bundles	1	3	3	3	5	3	4	4	3	3	Total =32
	Mean ±SD (Range) mm	0.26	0.34± 0.06 (0.27-0.39)	0.21± 0.07 (0.16-0.26)	0.21± 0.08 (0.16-0.30)	0.16± 0.05 (0.09-0.20)	0.21± 0.15 (0.12-0.38)	0.20± 0.07 (0.14-0.29)	0.18± 0.02 (0.15-0.18)	0.27± 0.14 (0.11-0.38)	0.14± 0.01 (0.12-0.15)	0.22± 0.06 (0.09-0.39)

Table 9 Distribution of diameters of transitional zone (B)

Oculomotor nerves		Abducens nerve	
Diameter (mm)	Number of nerve bundles	Diameter (mm)	Number of nerve bundles
≤0.20	17	≤0.10	1
0.21-0.30	20	0.11-0.20	18
0.31-0.40	15	0.21-0.30	6
0.41-0.50	4	0.31-0.40	5

Depths of the central myelin-peripheral myelin transitional zone (f)

The mean depth of the central myelin-peripheral myelin transitional zone (f) was 0.23 ± 0.07 (0.07-0.58) and 0.16 ± 0.07 (0.05-0.40) mm for oculomotor and abducens nerve

respectively. The depths of the transitional zone of each nerve are shown in Table 10. Out of 63 nerve bundles of oculomotor nerves, 7 nerve bundles were excluded because the transitional zones were not clearly seen. 93% of nerve bundles had the depth of transitional zone of oculomotor nerve below 0.40 mm. For the abducens nerve, there were 32 nerve bundles with 2 nerve bundles were excluded because the transitional zones were not clearly seen. 97% had the transitional zone of abducens nerve below 0.30 mm. The distribution of depths of the transitional zone is shown in Table 11. Figure 10 demonstrates the mean values of the length of central myelin and transitional zone of each nerve. 80% of oculomotor nerves had the mean length of central myelin of each nerve more than 2.00 mm and abducens nerve type A and B tend to have a longer segment of central myelin than type C and D. The average measure intraclass correlation coefficient (ICC) was 0.992 (0.987-0.995) for oculomotor nerve measurement and 0.995 (0.991-0.997) for abducens nerve measurement.

Table 10 Depths of the transitional zone of each nerve (f)

		Nerve No.										Summary
		1	2	3	4	5	6	7	8	9	10	
Oculomotor nerve	Number of nerve bundles	5	6	7	7	5	6	7	6	7	7	Total =63
	Mean ±SD (Range) mm	0.16± 0.03 (0.13-0.20)	0.14± 0.04 (0.11-0.21)	0.19± 0.04 (0.13-0.23)	0.18± 0.06 (0.09-0.26)	0.34± 0.17 (0.19-0.58)	0.33± 0.11 (0.24-0.53)	0.27± 0.05 (0.20-0.32)	0.24± 0.13 (0.11-0.43)	0.20± 0.07 (0.09-0.28)	0.25± 0.14 (0.07-0.50	0.23± 0.07 (0.07-0.58)
Abducens nerve	Number of nerve bundles	1	3	3	3	5	3	4	4	3	3	Total =32
	Mean ±SD (Range) mm	0.14	0.21± 0.02 (0.20-0.24)	0.23± 0.02 (0.22-0.24)	0.13± 0.13 (0.05-0.27)	0.10± 0.05 (0.06-0.17)	0.17± 0.03 (0.15-0.20)	0.15± 0.06 (0.08-0.22)	0.10± 0.02 (0.08-0.13)	0.30± 0.10 (0.23-0.41)	0.07± 0.01 (0.06-0.07)	0.16± 0.07 (0.05-0.40)

Table 11 Distribution of depths of the transitional zone (f)

Oculomotor nerves		Abducens nerve	
Length (mm)	Number of nerve bundles	Length (mm)	Number of nerve bundles
≤0.10	3	≤0.10	12
0.11-0.20	24	0.11-0.20	9
0.21-0.30	20	0.21-0.30	8
0.31-0.40	5	0.31-0.40	0
0.41-0.50	2	0.41-0.50	1
0.51-0.60	2		

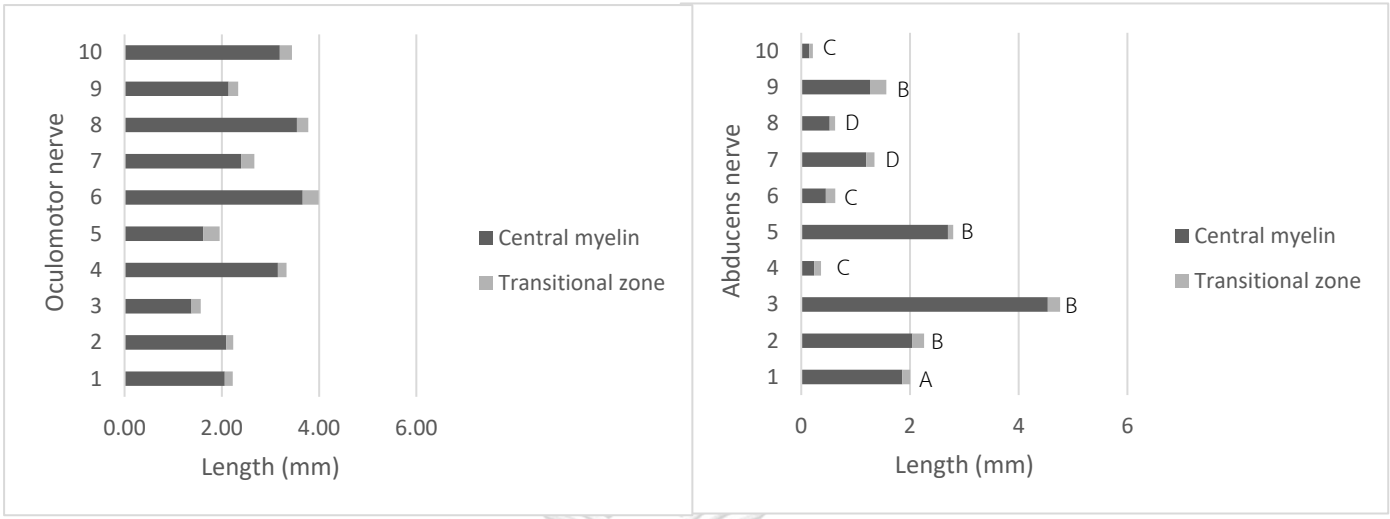


Figure 10 The mean values of the length of central myelin (black) and transitional zone (grey) of 10 oculomotor and 10 abducens nerves. Each bar represents each nerve. The letters at the end of the graph of abducens nerves represent the morphological pattern of abducens nerves.

Ratios of transitional zone-central myelin (f:F)

The average ratio of transitional zone-central myelin (f:F) was 0.10 ± 0.04 (0.03-0.45) and 0.18 ± 0.12 (0.02-0.52) for oculomotor and abducens nerves respectively. The ratios of transitional zone-central myelin of each nerve are shown in Table 12. 98% of oculomotor nerve bundles had the transitional zone-central myelin ratio below 0.3 while 90% of abducens nerves bundles had the transitional zone-central myelin ratio below 0.4. The distribution of ratios of transitional zone-central myelin is shown in Table 13.

Table 12 Ratios of transitional zone-central myelin (f:F)

		Nerve No.										Summary
		1	2	3	4	5	6	7	8	9	10	
Oculomotor nerve	Number of nerve bundles	5	6	7	7	5	6	7	6	7	7	Total =63
	Mean ±SD (Range) mm	0.08± 0.03 (0.05-0.11)	0.09± 0.06 (0.04-0.21)	0.15± 0.09 (0.05-0.28)	0.06± 0.02 (0.04-0.09)	0.16± 0.03 (0.12-0.18)	0.09± 0.04 (0.04-0.17)	0.09± 0.03 (0.05-0.13)	0.07± 0.06 (0.03-0.18)	0.15± 0.14 (0.03-0.45)	0.08± 0.05 (0.03-0.16)	0.10± 0.04 (0.03-0.45)
Abducens nerve	Number of nerve bundles	1	3	3	3	5	3	4	4	3	3	Total =32
	Mean ±SD (Range) mm	0.07	0.09± 0.01 (0.09-0.11)	0.05± 0.00 (0.05-0.05)	0.34± 0.20 (0.12-0.51)	0.03± 0.02 (0.02-0.06)	0.32± 0.14 (0.16-0.41)	0.12± 0.06 (0.05-0.20)	0.17± 0.03 (0.13-0.21)	0.26± 0.23 (0.11-0.52)	0.33± 0.07 (0.26-0.38)	0.18± 0.12 (0.02-0.52)

Table 13 Distribution of ratios of transitional zone-central myelin (f:F)

Oculomotor nerves		Abducens nerve	
Ratios	Number of nerve bundles	Ratios	Number of nerve bundles
≤0.10	38	≤0.10	10
0.11-0.20	14	0.11-0.20	11
0.21-0.30	3	0.21-0.30	2
0.31-0.40	0	0.31-0.40	4
0.41-0.50	1	0.41-0.50	1
		0.51-0.60	2

Lengths of the central myelin portion on the far side of the brainstem (C)

The length of the central myelin portion on the far side of the brainstem (C) was 1.47 ± 0.90 (0.12-2.63) and 1.42 ± 1.50 (0.09-5.11) mm for oculomotor and abducens nerves respectively. The lengths of the central myelin portion on the far side of the brainstem of each nerve are shown in Table 14. All of the oculomotor and 90% of the abducens nerves had the length of central myelin on the far side of the brain stem below 3.00 mm. The distribution of lengths of the central myelin portion on the far side of the brainstem of each nerve is shown in Table 15. The average measure intraclass correlation coefficient (ICC) was 0.999 (0.997-1.000) for oculomotor nerve measurement and 1.000 (1.000-1.000) for abducens nerve measurement.

Table 14 Lengths of the central myelin portion on the far side of the brainstem (C)

Nerve No.	Mean (mm)										Mean±SD (Range) mm
	1	2	3	4	5	6	7	8	9	10	Average
Oculomotor nerve	1.34	0.52	0.47	2.52	1.06	1.77	2.21	2.61	0.13	2.05	1.47±0.90 (0.12-2.63)
Abducens nerve	1.02	2.47	5.09	0.18	2.18	0.76	0.99	0.81	0.57	0.11	1.42±1.50 (0.09-5.11)

Table 15 Distribution of lengths of the central myelin portion on the far side of the brainstem (C)

Oculomotor nerves		Abducens nerve	
Length (mm)	Number of nerves	Length (mm)	Number of nerves
≤1.00	3	≤1.00	6
1.01-2.00	3	1.01-2.00	1
2.01-3.00	4	2.01-3.00	2
		3.01-4.00	0
		4.01-5.00	0
		5.01-6.00	1

Correlation between the depth of transitional zone and length of central myelin

We found a positive weak correlation between the depth of transitional zone and length of central myelin of each nerve bundle in the oculomotor nerve by Pearson's correlation coefficient (r +0.310, $p<0.05$) which means there is a linear correlation. While using Spearman's rank correlation coefficient, we found a positive weak correlation between the depth of transitional zone and length of central myelin of each nerve bundle in the abducens nerves (r +0.413, $p<0.05$) which means there is a monotonic relationship. Scatter plots between central myelin and transitional zone of each nerve bundle of oculomotor nerves and abducens nerves are shown in Figure 11.

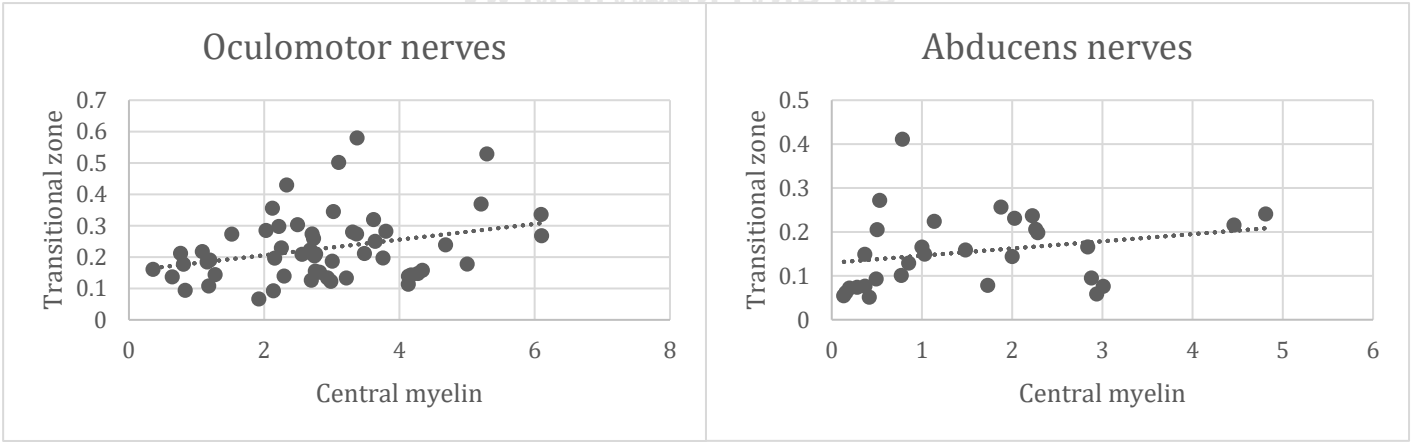


Figure 11 Scatter plot showing a correlation between central myelin and transitional zone of each nerve bundle of oculomotor nerves and abducens nerves.

CHAPTER V

DISCUSSIONS

Ocular neuromyotonia is defined as uncontrollable spasms of one or more of the extra-ocular muscles. Patients usually present with diplopia and strabismus. While abducens nerve palsy is dysfunction of the sixth cranial nerve resulting in horizontal diplopia. Both conditions have a common cause which is neurovascular compression. The site of compression is still puzzled, but the combination of the anatomical knowledge of the oculomotor and abducens nerve and clinical study could provide the solution to this question. In the literature review of 49 ocular neuromyotonia cases, three were caused by vascular compression and 1 out of 3 was successfully treated with microvascular decompression.[5] The location of neurovascular conflict was the oculomotor nerve root exit zone[39] which in clinical studies refers to where the nerve exits the brainstem and the proximal cisternal portion[9, 40] of the oculomotor nerve. Even though abducens nerve palsy is the most common ocular motor paralysis, vascular compression is considered a rare cause. 11 cases had been reported so far; 7 cases had the conflict at root exit zone[47-53], 2 cases had the conflict at nerve portion[8, 54], 1 case had a conflict at cisternal space[55] and 1 case was not seen.[6] Moreover, De Ridder and Menovsky (2007) reported abducens nerve palsy with successfully microvascular decompression and the site of compression was close to the Dorello canal which is distal from the root exit zone.[8] This would support the hypothesis that having the neurovascular compression at the distal site also has an indirect effect on the transitional zone. It is hard to decide where the compressed sites were because the distances were not measured.

Number of nerve bundles

The number of nerve bundles varies between nerves, but the exact number has not been reported. In our study, we demonstrated oculomotor nerve having nerve bundles between 5 to 7 of each and abducens nerve having the nerve bundles between 1 to 5 of each.

Morphological pattern of oculomotor and abducens had never been described before. In this study, the longest central myelin of oculomotor nerve was appeared on the first nerve bundle which is counted from the lateral side in all 10 oculomotor nerves. The

length of central myelin of the nerve bundle was gradually decreased from lateral to medial side. However, Fraher (1992) who studied the type of transitional zone showed the similar central myelin pattern and multiple nerve bundles in schematic diagram of oculomotor nerves.[56] For abducens nerve, 4 types of morphological pattern, based on the number of nerve rootlet originated from the brainstem and the number of nerve bundles, were observed. Fraher (1992) also showed the same schematic diagram of abducens nerves having more than one nerve bundles as type C pattern mentioned above.[56] The different position of transitional zone could be explained by the CNS and PNS tissue migration during development.[56]

We also observed the glial part covering the abducens nerve root which had been mentioned previously in facial nerves.[57, 58] The extension of the glial part did not go beyond the length of central myelin which is consistent with this study.[57] The function is believed to be a physical barrier.

Diameters where they exit from the brainstem (A)

Comparison of the diameter of cranial nerves where they exit the brainstem revealed that trigeminal nerve had the greatest diameter and vagus nerve was the least (Table 16).[2, 59] The diameter of abducens nerve was larger than glossopharyngeal nerve but smaller than facial nerve. The diameter of oculomotor nerve was smaller than vestibulocochlear nerve. Having the larger diameter would increase the volume of central myelin portion of the trigeminal, facial, glossopharyngeal and vagus nerves which had been reported a positive correlation with the incidences of the trigeminal neuralgia, hemifacial spasm, and vago-glossopharyngeal neuralgia respectively.[2]

Table 16 Comparisons of diameters where they exit from the brainstem between cranial nerves (A)[2, 59]

Author	Year	Cranial nerve	n	Diameters where they exit from the brainstem (mm) Mean ± SD (Range)
This study	2021	CN III	10	2.18±0.44 (1.36-2.97)
		CN VI	10	1.21±0.60 (0.19-2.38)
Glucu et al.[59]	2012	CN VIII	10	2.31± 0.68 (1.21-3.16)
Glucu et al.[2]	2011	CN V	10	3.11±0.83 (2.02-4.43)
		CN VII	8	1.60±0.66 (0.87-3.11)
		CN IX	7	0.93±0.17 (0.62-1.11)
		CN X	8	0.90±0.19 (0.62-1.16)

Lengths of the central myelin portion (F)

The central myelin portion of the nerves responsible for eye movement were reported in two previous studies (Table 17).[2, 15, 16, 19, 20, 57, 59] Skinner (1931) is the first to demonstrate that the length of the glial part of the oculomotor and abducens nerve from humans, dogs, cats, and rabbits were 1.2 and 0.5 mm respectively.[19] Tarlov (1937) examined the human cranial nerve and showed that the length of the glial part of the oculomotor and abducens nerve are 0.6 and 0.5 mm respectively.[20] While our study found that the length of central myelin (F) was 2.75 ± 0.83 mm and the longest central myelin length was 4.29 ± 1.26 mm in oculomotor nerves. For the abducens nerve, the length of central myelin (F) was 1.66 ± 1.39 mm and the longest central myelin length was 1.88 ± 1.40 mm. If considered postfixation shrinkage[60], the length of central myelin would be 3.31-7.32 mm for the oculomotor nerve and the length of central myelin would be 0.34-6.01 mm for the abducens nerve. The oculomotor having the greater length of central myelin when compared to abducens nerve is consistent with Skinner and Tarlov.[19, 20] However, the exact lengths cannot be compared because the definition of the glial part was not mentioned and some of the nerve specimens were from animals. The longest central myelin length were used to compare with other cranial nerve rather than the mean central myelin because most of the cranial nerve reported one central myelin length with draw from the base to the tip of the arch-shaped transitional zone.[2, 59] The results of this study showed that abducens nerves having a longer central myelin portion

than glossopharyngeal and vagus nerves and oculomotor nerve having a central myelin portion greater than the facial nerve and trigeminal nerve (Table 17).[2, 15, 16, 19, 20, 57, 59] Glucu et al. (2011) proved that having the greater length of central myelin of trigeminal, facial, glossopharyngeal and vagus nerves would be at greater risk of having the trigeminal neuralgia, hemifacial spasm, and vago-glossopharyngeal neuralgia respectively.[2]

Table 17 Comparisons of lengths of the central myelin portion between cranial nerves[2, 15, 16, 19, 20, 57, 59]

Author	Year	Cranial nerve	n	Lengths of the central myelin portion (mm) Mean ± SD (Range)
This study	2021	CN III	10	Mean length 2.75±0.83 (0.36-6.10)
				Longest length 4.29±1.26 (2.76-6.10)
		CN VI	10	Mean length 1.66±1.39 (0.13-5.01)
				Longest length 1.88±1.40 (0.28-5.01)
Nomura et al.[57]	2020	CN VII	134	Anterior side 8.06 (4.62-12.6)
				Posterior side 1.68 (0.00-4.58)
Glucu et al.[59]	2012	CN VIII	10	11.50± 1.56 (9.28-13.84)
Glucu et al.[2]	2011	CN V	10	4.19±0.81 (3.24-5.65)
		CN VII	8	2.86±1.19 (1.18-5.93)
		CN IX	7	1.51±0.39 (0.97-2.09)
		CN X	8	1.63±1.15 (0.45-4.22)
Peker et al.[15]	2006	CN V	100	Medial side 1.13 (0.1-2.5)
				Lateral side 2.47 (0.17-6.75)
Tomii et al.[16]	2003	CN VII	75	Medial side 0.284 ± 0.338 (-0.127-1.379)
				Lateral side 8.00 ± 2.79 (1.78-17.66)
Tarlov[20]	1937	CN I	-	0.5
		CN III		0.6
		CN IV		0.6
		CN V		Sensory root 2.2 Motor root 0.5
		CN VI		0.5
		CN VII		0.8
		CN VIII		Vestibular division 8.0 Cochlear division 8.3

		CN IX		Sensory root 1.1 Motor root <0.1
		CN X		Sensory root 1.3 Motor root <0.1
		CN XI		<0.1
		CN XII		<0.1
Skinner[19]	1931	CN III	-	1.2
		CN IV		1.9
		CN V		3.0
		CN VI		0.5
		CN VII		2.5
		CN VIII		Vestibular division 9.0 Cochlear division 8.2
		CN IX		1.3
		CN X		1.0

Diameters of transitional zone (B)

The diameter of where the transitional zone (B) begins was lesser in abducens and oculomotor nerves when compared to other cranial nerves in previous reports (Table 18).[2, 59] The ascending order of the diameter of where the transitional zone begins was vagus, glossopharyngeal, facial, and vestibulocochlear nerve respectively. Trigeminal nerve had the greatest diameter (Table 18).[2, 59] Although sites of compression have been reported variously, the transitional zone is still the common site.[28] Thus, having greater diameter means having greater space to be compressed.

Table 18 Comparisons of diameters of transitional zone between cranial nerves (B)[2, 59]

Author	Year	Cranial nerve	n	Diameters of transitional zone (mm) Mean ± SD (Range)
This study	2021	CN III	10	0.28±0.05 (0.12-0.58)
		CN VI	10	0.22±0.06 (0.09-0.39)
Glucu et al.[59]	2012	CN VIII	10	1.44±0.38 (1.07-2.21)
Glucu et al.[2]	2011	CN V	10	3.08±0.39 (2.26-3.67)
		CN VII	8	1.42±0.41 (1.01-2.34)
		CN IX	7	0.78±0.26 (0.39-1.10)
		CN X	8	0.73±0.15 (0.50-0.86)

Depths of the central myelin-peripheral myelin transitional zone (f)

Previous studies demonstrated that the depth of transitional zone was greatest in the trigeminal nerve.[2] The descending order of the depth of transitional zone was facial nerve, vestibulocochlear, vagus, and glossopharyngeal nerve respectively (Table 19).[2, 16, 57, 59] The depth of transitional zone (f) was least in abducens and oculomotor nerves respectively. The estimated postfixation shrinkage has been reported up to 20%[60], so the transitional zone from this study would range from 0.08 mm to 0.70 mm for the oculomotor nerve. The mean transitional zone of the abducens nerve would be between 0.06-0.48 mm. The transitional zone started from 3.03 (1.65-4.39) and 1.79 (0.17-5.44) mm distal to where the cranial nerve exits the brainstem for oculomotor and abducens nerves respectively (After postfixation shrinkage correction, starting point of transitional zone was calculated by the depth of transitional zone subtracted from the length of central myelin). Knowing starting point of the transitional zone could be useful in localization of compressed site in neuroimaging.

Table 19 Comparisons of depths of the transitional zone between cranial nerves (f)[2, 16, 57, 59]

Author	Year	Cranial nerve	n	Depths of transitional zone (mm) Mean ± SD (Range)
This study	2021	CN III	10	0.23±0.07 (0.07-0.58)
		CN VI	10	0.16±0.07 (0.05-0.40)
Nomura et al.[57]	2020	CN VII	134	1.51 (0.00-2.76)
Glucu et al.[59]	2012	CN VIII	10	0.81±0.27 (0.56-1.28)
Glucu et al.[2]	2011	CN V	10	1.53±0.45 (0.89-2.38)
		CN VII	8	1.03±0.55 (0.46-1.82)
		CN IX	7	0.36±0.08 (0.25-0.44)
		CN X	8	0.42±0.22 (0.22-0.82)
Tomii et al.[16]	2003	CN VII	75	Medial side 0.58 ± 0.32 (0.14-2.08) Lateral side 1.90 ± 1.14 (0.14-5.60)

Ratios of transitional zone-central myelin (f:F)

Comparisons of proportions of transitional zone-central myelin between cranial nerves revealed that the proportion was smallest in vestibulocochlear nerve (Table 20).[2, 59] The ascending order of the proportion of transitional zone-central myelin was oculomotor, abducens, glossopharyngeal, vagus, and trigeminal nerve respectively (Table 20).[2, 59] The largest percentage was found in the facial nerve.[2] Using ratios to compare between nerves would be more accurate than using the length since some papers already applied the postfixation shrinkage correction and some did not apply. The ratios of transitional zone-central myelin do not depend on the length of central myelin or the diameter. Moreover, if future studies measure the length of the nerve from the brainstem to the foramen that the nerve exits (cisternal portion) and determine the ratio of central myelin portion-cisternal portion, the f:F ratio could be applied for the transitional zone localization.

Table 20 Comparisons of proportions of transitional zone-central myelin between cranial nerves (f:F)[2, 59]

Author	Year	Cranial nerve	n	Proportions of transitional zone-central myelin (%)
This study	2021	CN III	10	10.11±3.54 (2.74-44.78)
		CN VI	10	18.03±12.42 (1.98-52.31)
Glucu et al.[59]	2012	CN VIII	10	7.23± 3.10 (4.5-13.8)
Glucu et al.[2]	2011	CN V	10	31.42±4.86 (24.6-39.7)
		CN VII	8	38.79±10.14 (20.4-57.8)
		CN IX	7	25.34±7.45 (13.7-35.4)
		CN X	8	30.48±12.36 (17.8-49.6)

Lengths of the central myelin portion on the far side of the brainstem (C)

The length of the central myelin portion on the far side of the brainstem (C) had been reported in trigeminal and facial nerves.[15, 16, 57] The mean value of the length of the central myelin portion on the far side of abducens and oculomotor nerves was the shortest. The mean length of the central myelin portion on the far side of the brainstem

(C) was 1.47 ± 0.90 and 1.42 ± 1.50 mm for oculomotor and abducens nerves respectively. After postfixation shrinkage correction[60], mean central myelin on the far side of brainstem would be 0.14-3.16 mm for oculomotor nerve. The mean central myelin on the far side of brainstem would be 0.11-6.13 mm for abducens nerves. While the mean value of length of the central myelin portion on the far side of trigeminal nerve was 2.47 mm, the facial nerves had the longest length which was 8.00-8.06 mm (Table 21).[15, 16, 57] The length of the central myelin portion on the far side of the brainstem is ended at the junction between central myelin and transitional zone of the farthest nerve bundles. It is a bare area which could be a possible site of compression and would be at greater risk to pressure effect.

Table 21 Comparisons of diameters of central myelin portion on the far side of the brainstem between cranial nerves (C)[15, 16, 57]

Author	Year	Cranial nerve	n	Lengths of the central myelin portion on the far side of the brainstem (mm) Mean ± SD (Range)
This study	2021	CN III	10	1.47 ± 0.90 (0.12-2.63)
		CN VI	10	1.42 ± 1.50 (0.09-5.11)
Nomura et al.[57]	2020	CN VII	134	8.06 (4.62-12.6)
Peker et al.[15]	2006	CN V	100	2.47 (0.17-6.75)
Tomii et al.[16]	2003	CN VII	75	8.00 ± 2.79 (1.78-17.66)

Correlation between the depth of transitional zone and length of central myelin

Glucu et al (2011) demonstrated a positive correlation between the length of central myelin of trigeminal, facial, glossopharyngeal and vagus nerves and the incidence of the trigeminal neuralgia, hemifacial spasm, and vago-glossopharyngeal neuralgia respectively.[2] In cases of ocular neuromyotonia and abducens nerve palsy, the neurovascular compression is not the sole explanation. Instead, we found a positive weak correlation between the depth of transitional zone and length of central myelin of each nerve bundle in the oculomotor nerve and abducens nerves which means the greater the

central myelin, the greater the depth of transitional zone. This could be additional knowledge to f:F ratio. Even though the f:F ratios are wide-ranging but at least we know that the length of central myelin and depth of transitional will always be in the same direction. To our knowledge, this is the first to report the relationship between these two parameters.

Benefit of this study

This study provides the details of microanatomical knowledge of oculomotor and abducens nerve. Knowing the length of central myelin and depth of transitional zone would be helpful in localization of compressed site in neuroimaging. Moreover, this might help understanding the etiology of the ocular neuromyotonia and abducens nerve palsy from neurovascular compression.

Limitation

First, the cranial nerves we studied were selected from the brain collection, so the age, sex, underlying disease, and cause of death of the cadavers are unknown. Second, this study only evaluated the cranial nerves, which were connected with the brain stem and were not damaged during the fixation or staining, causing the sample selection bias. Also, we couldn't analyze the difference between sides due to a small number of specimens.

Suggestion

Further studies should increase the number of samples and freshly preserved cadavers with known age, sex, race to discover whether there is a statistically significant between these factors. Future studies in the neurovascular syndrome of oculomotor and abducens nerve could combine this anatomical knowledge to help understand the etiology of the disease and clarify the site of compression.

CHAPTER VI

CONCLUSIONS

This study provided morphometric measurements and morphological pattern of oculomotor and abducens nerves as follow.

1. For morphological pattern in oculomotor nerves, the longest central myelin was seen on the first nerve bundle at the most lateral side and the length of glial segment decreased medially. For the abducens nerve, the morphologies of the nerve bundle were classified into 4 types based on the number of nerve rootlet originated from the brainstem and the number of nerve bundles. Furthermore, abducens nerve types A and B tend to have a longer segment of mean central myelin than types C and D.
2. All parameters are shown in the table below

	Oculomotor nerve	Abducens nerve
Number of nerve bundles (bundles)	5-7	1-5
A (mm)	2.18±0.44 (1.36-2.97)	1.21±0.60 (0.19-2.38)
F (mm)	2.75±0.83 (0.36-6.10)	1.66±1.39 (0.13-5.01)
F* (mm)	4.29±1.26 (2.76-6.10)	1.88±1.40 (0.28-5.01)
B (mm)	0.28±0.05 (0.12-0.58)	0.22±0.06 (0.09-0.39)
f (mm)	0.23±0.07 (0.07-0.58)	0.16±0.07 (0.05-0.40)
f:F	0.10±0.04 (0.03-0.45)	0.18±0.11 (0.02-0.52)
C (mm)	1.47±0.90 (0.12- 2.63)	1.42±1.50 (0.09- 5.11)

A= diameter where nerve exits brainstem; B= diameter where transitional zone begins; C= length of central myelin on the far side of brainstem; F= length of central myelin; F*= longest central myelin; f= depth of transitional zone

3. Transitional zone started from 3.03 (1.65-4.39) and 1.79 (0.17-5.44) mm distal to where the cranial nerve exits the brainstem for oculomotor and abducens nerves respectively which could help localize compressed sites in neuroimaging.
4. A positive weak correlation between the depth of transitional zone and length of central myelin of each nerve bundle in the oculomotor nerve (r +0.310, $p<0.05$)

and abducens nerves (r +0.413 $p<0.05$) were found which could imply that the greater the central myelin, the greater the transitional zone depth.

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APPENDIX

1. Depths of the central myelin-peripheral myelin transitional zone (f)

Oculomotor nerve	Nerve bundle No. Mean (mm)						
	1	2	3	4	5	6	7
Nerve 1	0.19	0.13	0.20	0.14	NA		
Nerve 2	0.13	0.12	0.15	0.21	0.11	0.14	
Nerve 3	0.21	0.13	0.23	0.18	0.18	0.21	NA
Nerve 4	NA	0.16	0.21	0.15	0.09	0.20	0.26
Nerve 5	0.58	0.30	0.27	0.19	NA		
Nerve 6	0.27	0.53	0.24	0.31	0.27	0.36	
Nerve 7	0.20	0.32	0.27	NA	NA	NA	0.30
Nerve 8	0.37	0.11	0.14	0.14	0.43	0.22	
Nerve 9	0.15	0.28	0.28	0.21	0.22	0.09	0.16
Nerve 10	0.34	0.18	0.25	0.50	0.14	0.07	0.28

Abducens nerve	Nerve bundle No. Mean (mm)				
	1	2	3	4	5
Nerve 1	0.14				
Nerve 2	0.24	0.21	0.20		
Nerve 3	0.22	0.24	NA		
Nerve 4	0.05	0.27	0.05		
Nerve 5	0.06	0.08	0.17	0.09	NA
Nerve 6	0.16	0.15	0.20		
Nerve 7	0.08	0.22	0.16	0.15	
Nerve 8	0.08	0.09	0.13	0.10	
Nerve 9	0.23	0.26	0.41		
Nerve 10	0.07	0.07	0.06		

NA=Not available due to poorly defined transitional zone

2. Diameters of transitional zone (B)

Oculomotor nerve	Nerve bundle No. Mean (mm)						
	1	2	3	4	5	6	7
Nerve 1	0.35	0.21	0.17	0.16	NA		
Nerve 2	0.26	0.31	0.18	0.34	0.26	0.29	
Nerve 3	0.30	0.26	0.15	0.22	0.22	0.32	NA
Nerve 4	NA	0.14	0.34	0.18	0.13	0.22	0.23
Nerve 5	0.19	0.25	0.12	0.14	NA		
Nerve 6	0.48	0.14	0.39	0.30	0.23	0.31	
Nerve 7	0.31	0.34	0.42	NA	NA	NA	0.41
Nerve 8	0.44	0.12	0.18	0.19	0.32	0.40	
Nerve 9	0.30	0.24	0.23	0.35	0.25	0.23	0.25
Nerve 10	0.39	0.16	0.36	0.22	0.20	0.17	0.36

Abducens nerve	Nerve bundle No. Mean (mm)				
	1	2	3	4	5
Nerve 1	0.26				
Nerve 2	0.36	0.27	0.39		
Nerve 3	0.16	0.26	NA		
Nerve 4	0.16	0.30	0.17		
Nerve 5	0.09	0.15	0.20	0.18	NA
Nerve 6	0.12	0.12	0.38		
Nerve 7	0.15	0.29	0.23	0.14	
Nerve 8	0.18	0.18	0.15	0.18	
Nerve 9	0.11	0.33	0.38		
Nerve 10	0.14	0.15	0.12		

NA=Not available due to poorly defined transitional zone

3. Ratios of transitional zone-central myelin (f:F)

Oculomotor nerve	Nerve bundle No. Mean						
	1	2	3	4	5	6	7
Nerve 1	0.06	0.05	0.09	0.11	NA		
Nerve 2	0.04	0.04	0.05	0.08	0.09	0.21	
Nerve 3	0.08	0.05	0.10	0.16	0.22	0.28	NA
Nerve 4	NA	0.04	0.06	0.06	0.04	0.07	0.09
Nerve 5	0.17	0.12	0.18	0.16	NA		
Nerve 6	0.04	0.10	0.05	0.10	0.10	0.17	
Nerve 7	0.05	0.09	0.08	NA	NA	NA	0.13
Nerve 8	0.07	0.03	0.03	0.03	0.18	0.08	
Nerve 9	0.03	0.07	0.08	0.08	0.20	0.11	0.45
Nerve 10	0.06	0.04	0.07	0.16	0.06	0.03	0.14

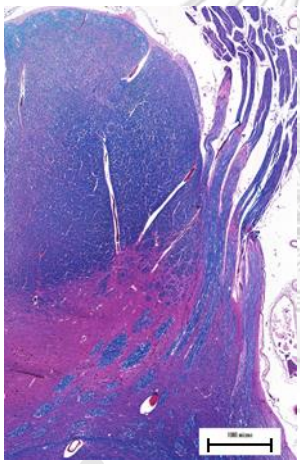
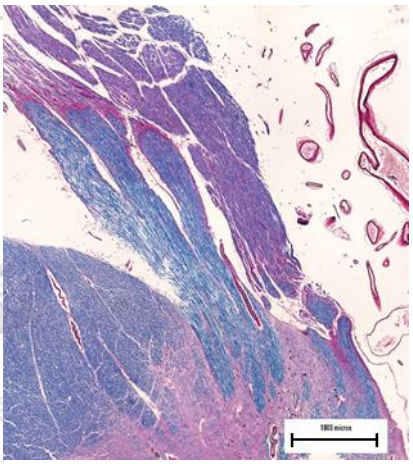
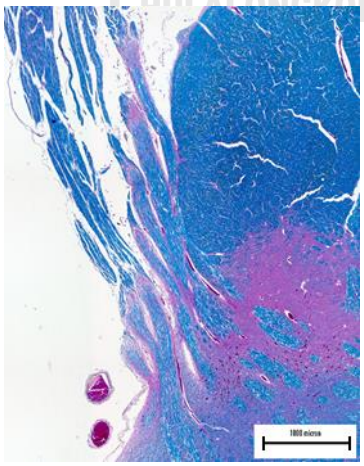
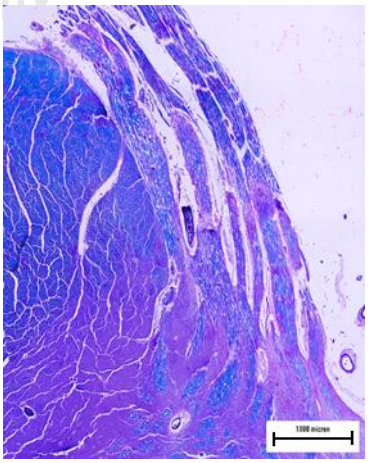
Abducens nerve	Nerve bundle No. Mean				
	1	2	3	4	5
Nerve 1	0.07				
Nerve 2	0.11	0.09	0.09		
Nerve 3	0.05	0.05	NA		
Nerve 4	0.12	0.51	0.40		
Nerve 5	0.02	0.03	0.06	0.03	NA
Nerve 6	0.16	0.40	0.41		
Nerve 7	0.05	0.20	0.11	0.14	
Nerve 8	0.21	0.19	0.15	0.13	
Nerve 9	0.11	0.14	0.52		
Nerve 10	0.36	0.26	0.38		

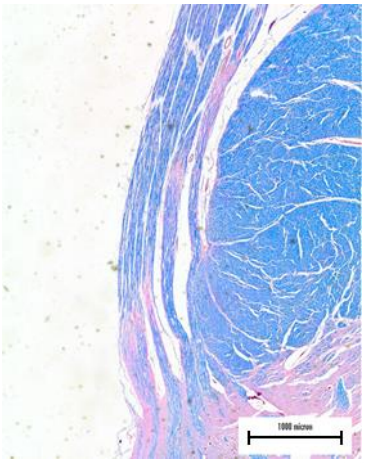
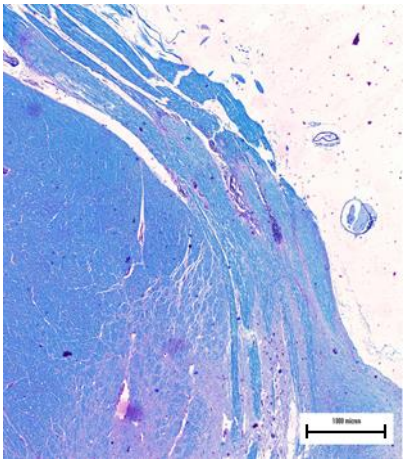
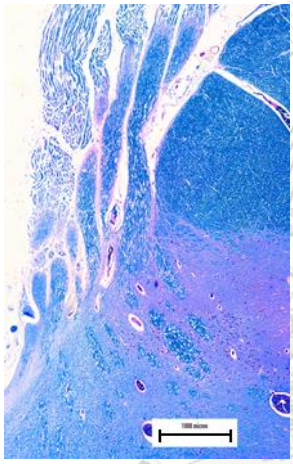
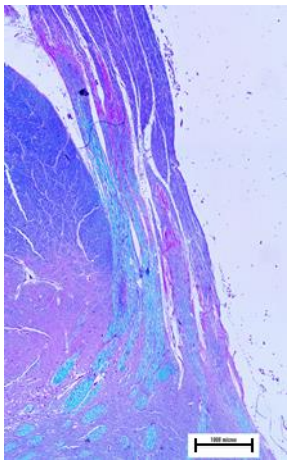
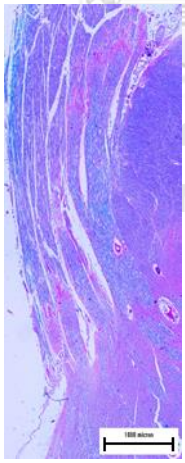
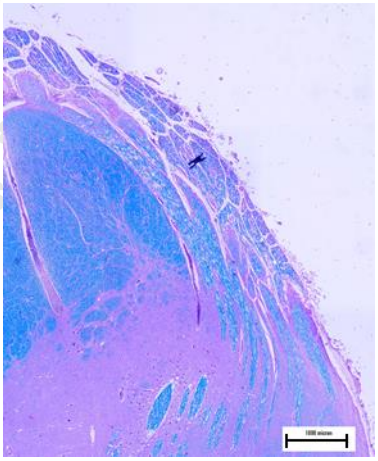
NA=Not available due to poorly defined transitional zone

4. Correlation between the depth of transitional zone and length of central myelin

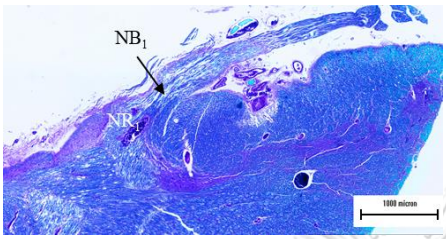
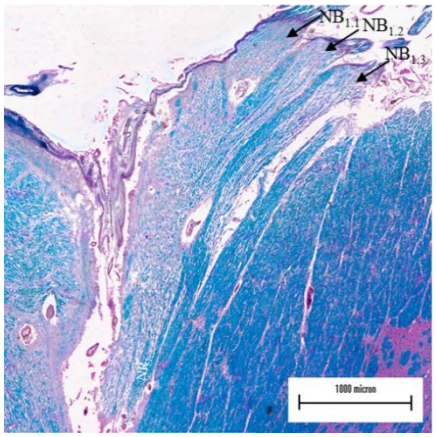
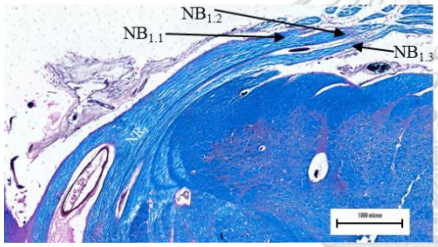
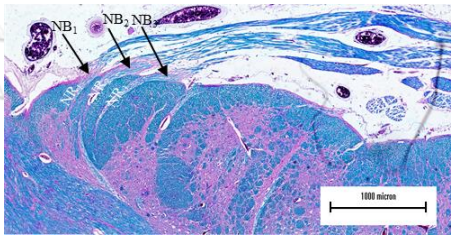
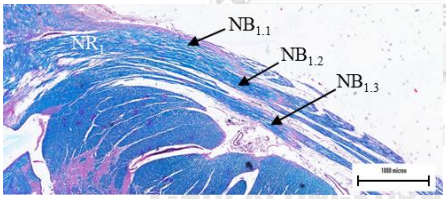
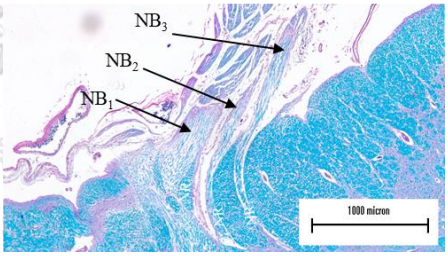
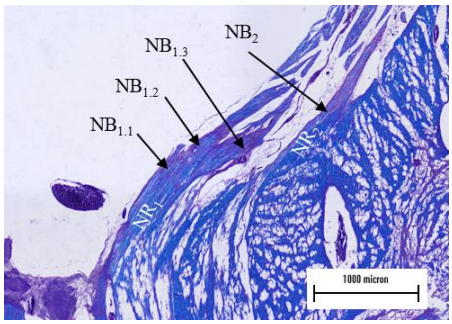
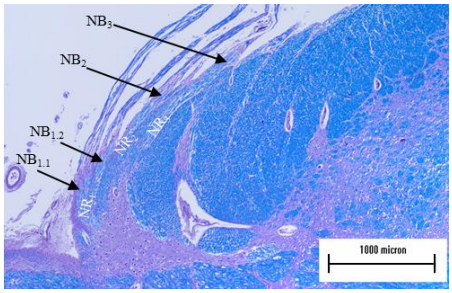
Cranial nerve	Correlation		Nonparametric correlation	
	Pearson's Correlation	Sig (2-tailed)	Spearman's rho	Sig (2-tailed)
Oculomotor nerve	0.310	0.020	0.250	0.063
Abducens nerve	0.243	0.196	0.413	0.023

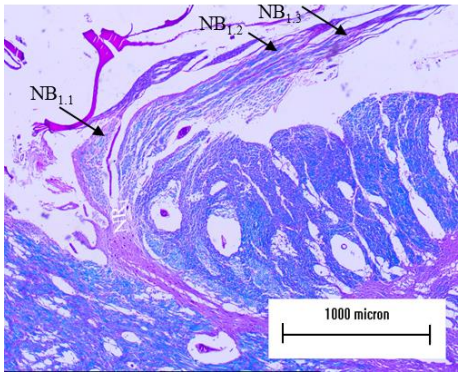
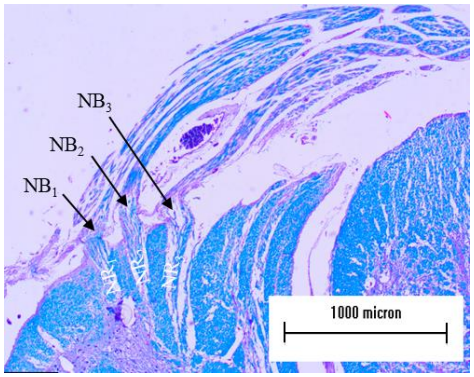
5. Photomicrograph of 10 oculomotor nerves stained with luxol fast blue

Nerve No.	Photomicrograph	Nerve No.	Photomicrograph
1		2	
3		4	

5		6	
7		8	
9		10	

6. Photomicrograph of 10 abducens nerves stained with luxol fast blue

Nerve No.	Photomicrograph	Nerve No.	Photomicrograph
1		2	
3		4	
5		6	
7		8	

9		10	

NR1, the first nerve rootlet emerging from the ventral surface of brainstem; NR2 and NR3, the second and third nerve rootlets emerging from the ventral surface of brainstem; NB1, NB2 and NB3, nerve bundle in the first, second and third nerve rootlets, respectively; NB1.1, NB1.2, NB1.3, number of nerve bundle in the first nerve rootlet.

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